Brain functional and structural changes in adult ADHD and their relation to long-term stimulant treatment

By

José Salavert Jiménez

THESIS

PhD in Psychiatry

Department of Psychiatry and Legal Medicine

Universitat Autònoma de Barcelona

Supervisors:

Dr. Edith Pomarol-Clotet

FIDMAG Research Foundation
Germanes Hospitalàries

Dr. Xavier Caseras Vives

Cardiff University

Tutor:

Dr. Rafael Torrubia Beltri

Universitat Autònoma de Barcelona

May 2015

Dr. Edith Pomarol-Clotet and Dr. Xavier Caseras Vives as thesis supervisors,

Dr Rafael Torrubia Beltri as thesis tutor,

Certify

That José Salavert Jiménez has completed the research corresponding to the thesis entitled "Brain functional and structural changes in adult ADHD and their relation to long-term stimulant treatment" which was developed in the Department of Psychiatry and Legal Medicine at the *Universitat Autònoma de Barcelona* and may attain the academic title of Ph.D. in Psychiatry.

May 2015

Signed:

PhD: José Salavert Jiménez

Dr. Edith Pomarol-Clotet Dr. Xavier Caseras Vives Dr. Rafael Torrubia Beltri

For Teresa, Tomàs and Guim, thanks for your love.

This thesis is dedicated to the memory of my friend and mentor Dr. Lluís Perisé, psychiatrist who spent many years touching people's lives through his work and implication. He is deeply missed.

“Freud was right on the mark when he described consciousness as the tip of the mental iceberg.”

Joseph Ledoux*. The Emotional Brain: The Mysterious Underpinnings of Emotional Life.*

AKNOWLEDGMENTS

A heartfelt thank to my supervisors Dr. Edith Pomarol-Clotet and Dr. Xavier Caseras for their continued assistance, hard work, patience, knowledge and motivation.

I am deeply grateful to Drs. Ana Moreno, Quim Radua and Raymond Salvador, who have made an enormous contribution to this thesis. Very special thanks to Drs. Peter J. McKenna, Gloria Palomar, Rosa Bosch and Pilar Salgado.

A special mention and appreciation to Dr. Josep Antoni Ramos-Quiroga and Prof. Miquel Casas, pioneers in the field of adult ADHD in our country and co-leaders of the study's scientific team.

I am specially appreciative of the support and belief in this thesis project of my tutor Prof. Rafael Torrubia.

I appreciate the members of the annual evaluation academic tribunal, Profs. Adolf Tobeña, Antoni Bulbena and Ferran Balada, for their advice and valuable comments during the annual review of the thesis project, from which I definitively benefited.

I want to thank Dr. Nicolás Ramírez for helping me not to give up and finish this project.

Thanks so much to my parents, Dr. Agustí Salavert and Dr. María Isabel Jiménez, for their encouragement to be confident, humble, cooperative and respectful to myself and others.

Thanks to Dr. Mariano Trillo, Dr. Lluís San and Dr. Maria Lluïsa Tiffon for their example, guidance and mentorship and for believing in me. Thank you Mariano for all your support and teaching.

Thanks to all my colleagues and coworkers in Hospital Sant Rafael, Hospital Universitari Vall d'Hebron and FIDMAG Research Foundation.

I thank very much all the participants who volunteered to take part in the study; they made a huge effort collaborating with the lengthy and exhausting data collection procedures.

A special thanks goes to my brother Paco beside whom I grew personally and musically; he is and has been always an inmense support at important moments of my life.

This project was supported by the Catalonian Government (2009SGR211 to the Research Unit of FIDMAG Germanes Hospitalàries) and several grants from the Plan Nacional de I +D+i and co-funded by the Instituto de Salud Carlos III-Subdirección General de Evaluación y Fomento de la Investigación and the European Regional Development Fund (FEDER): Miguel Servet Research Contracts (CP10/00596); Río Hortega Research Contract (CM11/00024) and Research Project Grant (PI11/01766). The funding organizations played no role in the study design, data collection and analysis, or manuscript approval.

TABLE OF CONTENTS

INDEX OF TABLES

INDEX OF FIGURES

ABBREVIATIONS

ADHD: Attention-Deficit Hyperactivity Disorder

ACC: Anterior Cingulate Cortex

ALFF: Amplitude of Low Frequency Fluctuations

ANTS: Advanced Normalization Tools software

APA: American Psychiatric Association

BA: Brodmann Area

BET: Brain Extraction Tool

BOLD: Blood Oxygenation Level-Dependent

CAADID: Conners Adult ADHD Diagnostic Interview for DSM-IV

CAARS: Conners Adult ADHD Rating Scale

CPT: Continuous Performance Test

DLPFC: Dorsolateral Prefrontal Cortex

DMN: Default-Mode Network

DSM: Diagnostic and Statistical Manual of Mental Disorders

EEG: Electroencephalography

EF: Executive Functions

EPI: Echo-Planar Imaging

FEAT: fMRI Expert Analysis Tool software

fcMRI: functional connectivity Magnetic Resonance Imaging

Fig.: Figure

FILM: FMRIB's Improved Linear Modelling

FLAME: FMRIB's Local Analysis of Mixed Effects software

FLIRT: FMRIB's Linear Image Registration Tool software

fMRI: Functional Magnetic Resonance Imaging

FOV: Field Of View

FSL: FMRIB's Software Library software

FWE: Familywise Error correction

FWHM: Full Width At Half Maximum

GBC: Global brain connectivity

GE: General Electrics

GLMs: General Linear Models

GM: Grey/gray Matter

HCG: Healthy Comparison Group

IAPS: International Affective Picture System

ICD: International Classification of Diseases

IFC: Inferior Frontal Cortex

IQ: Intelligence Quotient

IPFC: Inferior Prefrontal Cortex

MCFLIRT: Motion Correction FMRIB's Linear Image Registration Tool software

MELODIC: Multivariate Exploratory Linear Optimized into Independent Components

MNI: Montreal Neurological Institute

MPFC: Medial Prefrontal Cortex

MPH: Methylphenidate

MRI: Magnetic Resonance Imaging

NIRS: Near-infrared Spectroscopy

OFC: Orbitofrontal Cortex

PCC: Posterior Cingulate Cortex

PET: Positron Emission Tomography

PFC: Prefrontal Cortex

ROI: Region of Interest

SCID-I: Structured Clinical Interview for Axis I

SCID-II: Structured Clinical Interview for Axis II

SD: Standard Deviation

SMA: Supplementary Motor Area

SMC: Supplementary Motor Complex

SyN: Symmetric Normalization

TAP: Test de Acentuación de Palabras

TE: Echo Time

TFCE: Threshold-Free Cluster Enhancement

TR: Repetition Time

VBM: Voxel-based Morphometry

VLPFC: Ventrolateral Prefrontal Cortex

VMPFC: Ventromedial Prefrontal Cortex

WM: Working Memory

WURS: Wender Utah Rating Scale

1. INTRODUCTION

1.1. Neurobiological conceptualizations of Attention-Deficit Hyperactivity Disorder (ADHD)

Attention-Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder characterized by childhood onset of age-inappropiate levels of inattention, hyperactivity and impulsivity. Although some adverse environmental factors have been linked with ADHD, its high heritability and the early age of onset of the disorder, suggest strong genetic underpinnings (Faraone and Biederman 1998) (Faraone and Doyle 2001). It is estimated to affect about 5 % of child and adolescent population (Polanczyk, de Lima et al. 2007), with around 50 % of those carrying the disorder into adulthood (Biederman, Monuteaux et al. 2006). A meta-analysis of 32 follow-up studies showed a pooled persistence rate of 15 % applying the full childhood criteria, although another 65 % fulfilled adult ADHD partial remission criteria, with only about 20 % of childhood cases undergoing spontaneous remission (Faraone, Biederman et al. 2006).

ADHD's core symptoms involve clusters of inattention, hyperactivity and impulsivity (APA 2000). Whereas symptoms of hyperactivity, impulsivity and deficit of attention are well characterized in children, these symptoms can be expressed in adult life in the form of inner restlessness, inability to relax, impatience, difficulty to make decisions, affective instability and stress intolerance, with the attentional deficit cluster of symptoms being

usually the most functionally impairing in adults and closely related to executive impairment (Barkley 2003) (Kooij, Bejerot et al. 2010).

Several research articles have discussed potential conceptualizations of attention-deficit hyperactivity disorder, though none has yet produced sufficient conclusive evidence in support of any of the different proposed causal theories. Taking into account the heterogeneity of the disorder, it is more likely that a combination of factors underlies its manifestation, each to different degrees within individuals and ADHD types or presentations (predominantly inattentive, predominantly hyperactive-impulsive and combined). Main postulated theories emphasize:

- Underlying deficits in Executive Functions (Barkley 1997) (Barkley, Murphy et al. 2001) (Willcutt, Doyle et al. 2005) (Doyle 2006), with generalized difficulties in cognitive processes that encompass organizing and planning and the execution of complex responses requiring the implication of sustained attention, working memory, time tracking, attentional shifting, self-monitoring and above all, cognitive inhibitory control. A dysfunction of the prefrontal-dorsal-striatal and prefrontal-parieto-cerebellar neuronal pathways would explain this cognitive deficits (Nigg and Casey 2005) (Doyle 2006). Executive impairment constitutes a core feature of adult ADHD, persisting from childhood into adulthood even in ADHD individuals whose other symptoms of the disorder have remitted (Barkley, Murphy et al. 2007) (Miller, Ho et al. 2012).

- Dysfunctional Reward Processing or altered Motivation, in relation to a steeper delayed reinforcement gradient (delay-discounting gradient), impaired reward prediction errors

(neural signals that indicate violations of expectations) and a negative emotional response to reward delay (delay aversion), with poorer derived decision making as a consequence (Luman, Oosterlaan et al. 2005) (Hauser, Iannaccone et al. 2014). In other words, a deficit in behavioral inhibition during the expectation of a reinforcer that would result in a pattern of impulsive behavior, with more impulsive responses to reward and a prioritization of small but immediate incentives over larger but delayed rewards, due to altered processing of incentives and rewards as a consequence of hyporesponsivity of the dopaminergic neurons that project from the midbrain to striatal and prefrontal areas (Modesto-Lowe, Chaplin et al. 2013) (Hauser, Iannaccone et al. 2014). This is supported by the evidence of dysfunction in the activation of brain areas associated with reward processing, mainly the mesolimbic (medial-prefrontal and orbitofrontal) and ventral striatal circuitry, with nucleus accumbens in the ventral striatum as its core component (Luman, Oosterlaan et al. 2005) (Luman, Tripp et al. 2010) (Modesto-Lowe, Chaplin et al. 2013) (Hauser, Iannaccone et al. 2014).

- Deficit in Arousal and Activation, conceptualized as the “cognitive-energetic” model (Sergeant 2005). Arousal (slow or innacurate processing of perceptual input) has been mainly associated with the mesencephalic reticular formation and the amygdala and activation (inadequate response output) with the basal ganglia, principally involving striatum (Sergeant 2005). Little evidence has been found in studies for arousal deficits while there is greater evidence for activation deficits in terms of difficulties in self-mobilization and task initiation (Luman, Oosterlaan et al. 2005).

- Emotional Regulation deficits have also emerged as a prevalent feature of the disorder (Herrmann, Schreppel et al. 2009) (Marx, Domes et al. 2011). Emotional impulsiveness has recently been proposed as a central feature of ADHD contributing to impairment beyond the two classical ADHD dimensions of inattention and hyperactivity-impulsivity (Barkley and Fischer 2010) with symptoms of emotional dysregulation (temper, affective lability, and emotional overreactivity) having been found in one third of ADHD patients in the absence of anxiety or depressive disorder diagnosis (Reimherr, Marchant et al. 2005), and a recent study showing a pattern of inheritance of ADHD with deficient emotional self-regulation suggesing that this could be a familial subtype of ADHD (Surman, Biederman et al. 2011). Brain dysfunctions would be dependent on interactions between orbitofrontal and ventromedial prefrontal cortex, anterior cingulate (ACC), amygdala, hippocampus and ventral striatum (Plessen, Bansal et al. 2006) (Herrmann, Biehl et al. 2010).

- Models based in Multiple Pathways, including different patterns of deficit (executive dysfunction, altered reward/reinforcement sensitivity, emotional regulation deficits and cognitive-energetic factors), each of them affecting different patients to varying degrees. Multiple pathway models explain ADHD in terms of the participation of different dysfunctional neurobiological pathways that may not be incompatible, but rather may represent more complete, alternate conceptualizations in order to capture ADHD's heterogenity (Sonuga-Barke 2003) (Sonuga-Barke, Sergeant et al. 2008) (Sonuga-Barke, Bitsakou et al. 2010), provided that neural circuits underlying the processes mentioned above, are made up of overlapping networks.

1.2. Neuroimaging studies in Attention-Deficit Hyperactivity Disorder

Neuroimaging studies constitute one of nowadays most important techniques examining the biological basis for ADHD, with studies of brain structure and brain functioning potentially supporting the implication of certain brain regions and networks in the pathophysiology of the disorder.

1.2.1. Current state of Structural Neuroimaging studies in Attention-Deficit Hyperactivity Disorder.

Structural neuroimaging research relating to ADHD is reviewed including English language articles, covering the major databases (PubMed, Scopus, EMBASE, PsycINFO and Web of Knowledge), selecting as eligible those studies which used structural neuroimaging (MRI) to compare ADHD diagnosed subjects to healthy controls. The population of interest was composed by children, adolescents and adults diagnosed with ADHD according to recognised criteria: Diagnostic and Statistical Manual of Mental Disorders (DSM; versions: -IV-R, -IV, -III or -III R), or International Classification of Diseases 10 (ICD-10). No limits were placed on gender nor age of the study populations. Databases were searched to January 2012 and search terms included: “ADHD and neuroimaging”, “ADHD and structural neuroimaging”, “ADHD and MRI”, “ADHD and cortical thickness”. A permanent hand search of relevant original, review and meta-analytic papers was also performed to january 2015.

Results of the review:

The two most commonly used analytical techniques in volumetric studies with magnetic resonance imaging (MRI) are voxel based morphometry (VBM) and manual segmentation or tracing, drawing regions of interest (ROIs). A disadvantage of the latter type of analysis is that the non-selected areas of the brain are not evaluated. Voxel-based morphometry (VBM) allows the simultaneous assessment of whole-brain cortical and subcortical structures without selecting a priori a specific set of regions (Hoekzema, Carmona et al. 2012), segmenting the brain automatically and therefore minimizing experimenter's bias in comparison to manually segmenting a ROI. A third analytical technique, complementary to the two previous anatomical analyses, is cortical thickness measurement, which has only recently become possible by means of MRI computational implementations, and has not been carried out on ADHD datasets until the last ten years. Nowadays, different algorithms are widely available for computing cortical thickness accurately from MRI scans (Fischl and Dale 2000).

a. Conventional Volume Measurement Studies

The two most consistently reported and replicated brain structure alterations in studies using segmentation methods in ADHD include total cerebral volume reduction (using morphometric analyses calculating volumes for each hemispheric region en bloc or obtaining volumetric measurements of the whole brain) and reduced volume in the right caudate (analyses using ROIs). Other consistently reported alterations with manual

segmentation using ROIs are reduction in total volume of the cerebellum and cerebellar regions (total vermis, superior vermis and posterior inferior vermis, lateral surface of the left anterior and the right posterior cerebellar hemispheres) and volume reduction of the splenium of the corpus callosum (Valera, Faraone et al. 2007) (Mackie, Shaw et al. 2007) (Ivanov, Murrough et al. 2014). Further regions with significant volume reductions relative to controls in some studies are frontal lobes, principally prefrontal and medial paralimbic regions, especially ACC (Valera, Faraone et al. 2007) (Makris, Seidman et al. 2010) (Seidman, Valera et al. 2006) (Makris, Seidman et al. 2010) (Johnston, Mwangi et al. 2014), inferior parietal lobule, putamen (Johnston, Mwangi et al. 2014) and left hippocampus (reduced hippocampal volumes correlated with the severity of comorbid depressive symptoms) (Posner, Siciliano et al. 2014).

b. Voxel-Based-Morphometry (VBM) Studies

More recent studies using VBM have confirmed as prominent findings, total cerebral volume reduction, cerebellum volume reduction and volume reduction in basal ganglia regions, mainly in components of the right corpus striatum: right globus pallidus, right putamen and right caudate (Ellison-Wright, Ellison-Wright et al. 2008) (Nakao, Radua et al. 2011) (Johnston, Mwangi et al. 2014). However, these studies have also found evidence of significant volume reductions in other regions relative to controls, principally frontal lobes (with superior and inferior frontal gyrus and dorso-lateral and ventromedial/orbitofrontal prefrontal regions as the most replicated by studies), but also in parietal lobes (Ellison-Wright, Ellison-Wright et al. 2008) (Shaw and Rabin 2009) (Nakao, Radua et al. 2011) (Pironti, Lai et al. 2014) (Kessler, Angstadt et al. 2014). Findings of volumetric changes in

other areas have been less consistent, with more evidence for volume reduction in temporal lobes (mainly superior and medial gyri and temporal poles), occipital lobes and ACC, posterior cingulate (PCC), amygdala, splenium and mid-corpus callosum (Brieber, Neufang et al. 2007) (Kobel, Bechtel et al. 2010) (Sasayama, Hayashida et al. 2010) (Makris, Seidman et al. 2010) (Ahrendts, Rusch et al. 2011) (Amico, Stauber et al. 2011) (Cubillo, Halari et al. 2012) (Makris, Liang et al. 2013) (Kessler, Angstadt et al. 2014).

Volume reductions seem to be more pronounced in non-treated populations, diminishing over time from child to adulthood (Frodl and Skokauskas 2012) (Makris, Liang et al. 2013). Chronic stimulant treatment is likely to be associated with attenuation of brain structure abnormalities in ADHD, with more normative volumes under treatment mainly for striatum, some cerebellar subregions (principally inferior vermis), corpus callosum, ACC and prefrontal regions (Semrud-Clikeman, Pliszka et al. 2006) (Bledsoe, Semrud-Clikeman et al. 2009) (Nakao, Radua et al. 2011) (Frodl and Skokauskas 2012) (Spencer, Brown et al. 2013) (Ivanov, Murrough et al. 2014), in spite of variability in study designs and in anatomical regions of interest examined.

c. Cortical Thickness Studies

Cortical thickness studies constitute a very interesting complement to VBM techniques, influenced by area and thickness, thus facilitating the study of these two measures separately. These implementations in scanning techniques and image analysis facilitate the presentation of prospective data determining whether there are changes in cortical thickness across time and make it easier to track disease progression and to study how

the normal brain develops and ages (Hutton, De Vita et al. 2008). Longitudinal data in this type of studies point out that ADHD in childhood could be characterized by a delay in cortical maturation and that different clinical outcomes may be associated with different developmental trajectories in adolescence and adulthood (Shaw and Rabin 2009). When using a brain maturation index, maturation process has been shown to progress in a way regionally similar in children with ADHD and controls in the early childhood phase of cortical increase. However, a significant delay in reaching the cortical thickness peak over most of the brain (especially in the frontal lobe) has been observed in children with ADHD (10 years) in comparison to controls (7.5 years), which documents a regional cortical maturation delay in ADHD (2,5 year lag in brain development with respect to controls) (Shaw, Eckstrand et al. 2007). Main findings have been of global thinning of cerebral cortex during childhood in ADHD when compared to typically developing controls (mean reductions about -0.1 mm), mostly in the superior and medial prefrontal/orbitofrontal regions, and in the precentral area, and across parietal and anterior temporal cortex (Castellanos, Lee et al. 2002) (Shaw, Lerch et al. 2006) (Fernandez-Jaen, Lopez-Martin et al. 2014). A slower velocity rate in the phase of cortical thinning in early adolescence has been shown, with cortical assimetries with respect to typically developing controls normalizing with time (mainly in posterior cortical regions and right parietal cortex), but continuing to be maintained with respect to frontal lobe during adolescence (mainly superior prefrontal and ACC) and adulthood (mainly medial and dorso-lateral prefrontal) (Shaw, Lerch et al. 2006) (Shaw, Lalonde et al. 2009) (Narr, Woods et al. 2009) (Shaw, Malek et al. 2013). Children with ADHD with a more similar developmental trajectory of cortical thickness to that of typically developing children, would seem to have a better functional outcome than children with greater thickness reductions at baseline, specifically

for fixed nonprogressive deficits of the medial prefrontal and cingulate regions (Shaw, Lerch et al. 2006), suggesting that a pattern of delayed cortical development that doesn't catch up to levels seen in typically developing population may be central to the pathophysiology of adult ADHD. However, a recent 33-year longitudinal follow-up study, shows that cortical thickness reductions are observable in adults with childhood ADHD, regardless of the remission or persistence of the diagnosis, with findings of decreased overall mean cortical thickness and, beyond this global difference, with greatest cortical thinning affecting regions related to top-down regulation of cognitive executive functions (frontal poles, bilateral parietal lobes, right precuneus, left medial occiptal cortex, cerebellar hemispheres) and motivational and emotional processes (thalamus, temporal poles, insula, subgenual ACC, parahippocampus, caudate). Exploratory analyses suggested that diagnostic remission may result from compensatory maturation of prefrontal, cerebellar, and thalamic circuitry (Proal, Reiss et al. 2011).

These maturational changes may be repaired to some extent with stimulant treatment, with positive research findings in different brain areas, mainly for right motor area, left middle/ inferior frontal area (including DLPFC and VLPFC) and right parietal and occipital cortex, although longitudinal within-subject studies that track changes from childhood to adulthood are still needed to confirm this (Shaw, Sharp et al. 2009) (Spencer, Brown et al. 2013).

d. Volumetric Studies in ADHD Adult population: State of the Question

Whereas volumetric neuroimaging studies in children and adolescents are plentiful, there are fewer studies in adults with ADHD and their results are more inconsistent. Structural

studies in ADHD adults have focused on evaluating if these patients share grey matter (GM) abnormalities in fronto-striato-cerebellar circuits that sustain cognitive control, as the proposed neurobiological basis of deficits that persist through the course of the disorder, but results have been inconclusive.

Most of these adult studies applied a VBM procedure and didn't find significant differences between patients and controls (Seidman, Valera et al. 2006) (Seidman, Biederman et al. 2011) (Amico, Stauber et al. 2011) (Pironti, Lai et al. 2014) (Onnink, Zwiers et al. 2014), except for the studies of Ahrendts et al. (2011) and Almeida et al. (2010). Ahrendts et al. did show that ADHD adult patients presented a significant reduction in GM volume bilaterally in the occipital lobes (Ahrendts, Rusch et al. 2011); and Almeida et al. showed reductions in the right caudate (Almeida Montes, Ricardo-Garcell et al. 2010). Recently, Makris et al. reported volume reductions in cerebellum, ACC and caudate and volume increases for DLPFC, OFC and inferior parietal lobe; however these findings appeared to be significant only for the finding of cerebellum volume decrease, after corrections for multiple comparisons (Makris, Liang et al. 2013). Alternatively, in some of these VBM studies, authors carried out an exploratory ROI analysis, and were then actually capable of reporting deficits compared to healthy controls, in different regions within the frontal lobe (including the orbito-frontal and dorso-lateral cortices and the inferior frontal gyrus), in the ACC, the parietal and occipital lobes, the cerebellum, and the caudate and putamen nuclei (Hesslinger, Tebartz van Elst et al. 2002) (Seidman, Valera et al. 2006) (Almeida Montes, Ricardo-Garcell et al. 2010) (Seidman, Biederman et al. 2011) (Amico, Stauber et al. 2011) (Pironti, Lai et al. 2014) (Makris, Liang et al. 2013) (Onnink, Zwiers et al. 2014). Two of these studies however, have reported an increase of GM volume in regions within some of

the same areas, specifically in occipital and parietal lobes and the DLPFC, and in other regions as the dorsal and mid cingulated cortex in ADHD participants relative to controls (Seidman, Biederman et al. 2011) (Pironti, Lai et al. 2014) (Onnink, Zwiers et al. 2014). The inability of these VBM studies in adult ADHD to demonstrate smaller volumes of total brain and subcortical regions, consistently reported in child and adolescent studies, gives support to the possibility of a delayed maturation in childhood (Shaw and Rabin 2009), and to the hypothesis of developmental structural brain differences in ADHD normalizing into adulthood (Onnink, Zwiers et al. 2014). As stated above, stimulant medication appears to modulate the brain volume in patients with ADHD as shown in a meta-analysis, reporting that treatment with stimulants may be positively associated with more normative brain structures (Frodl and Skokauskas 2012), but these results need to be replicated in larger samples of ADHD adults because the majority of the analysed studies were undertaken in children.

The discrepancy in adult vs. child/adolescent literature could be explained by smaller sample sizes, inclusion rate of comorbid conditions, lack of uniformity in terms of medication status and no-discrimination between ADHD subtypes (Cortese, Kelly et al. 2012) (Cortese and Castellanos 2012) (Spencer, Brown et al. 2013).

Therefore, little is known about structural neurobiological substrates of adult ADHD and more research is needed to understand the disorder at this stage of life.

e. Structural Neuroimaging - Summary -

In summary, **structural imaging studies** using manual segmentation ROI approaches and VBM in children/adolescents and less consistently in adults with ADHD, have shown atypical neural structure in the brain, with total cerebral volume reduction and specific regions which have been found principally to be slightly smaller in ADHD patients compared to controls. These brain regions are: the prefrontal cortex (PFC) and other regions with reciprocal connections with PFC, including the striatum, cerebellum, parietal regions, temporal regions, occipital cortex and cingulate (mainly ACC). All of these areas play an important role in attention and cognitive processes, as well as emotional and motivational processes, functions that are impaired in ADHD. In relation to cortical thickness studies, significant global cortex thinning maintained along time has most prominently been shown in the medial prefrontal (including ACC), superior prefrontal and dorso-lateral prefrontal regions. These studies show a neurological development delay which tends to normalize with advancing age. Volume reductions and differences in cortical thickness between patients and controls could be attenuated by longterm stimulant treatment, although more studies are needed to confirm this.

A summary of the findings of the reviewed brain structure studies in ADHD can be found in **Tables 1.1.** (Children and Adolescents) and **1.2.** (Adults).

References of the revised articles selected through hand search of relevant original Structural Neuroimaging studies performed from february 2012 to january 2015 can be found in **Table 1.3.**

Table 1.1. *Structural changes observed in ADHD studies with Children and Adolescents*

Study and year	Neuroimaging technique	Sample number ADHD (by type: I inattentive, C combined, HI hyperactive-impulsive, NOS not otherwise specified)/ Controls	Main findings Volume reduction (VR), Cortical thickness reduction (CTR) or Cortical maturation delay (CMD)	Other observations
(Aylward, Reiss et al. 1996)	Manual Segmentation	10 (types not specified)/ 11	VR: -Right caudate	
(Baumgardner, Singer et al. 1996)	Manual Segmentation	13 (types not specified)/ 27	VR: -Splenium	
(Berquin, Giedd et al. 1998)	Manual Segmentation	46 (DSM-III-R ADHD diagnosis : no correspondence with either DSM-IV types)/ 47	VR: -Cerebellar vermis volume reduction	-Posterior inferior vermis volume reduction
(Bledsoe, Semrud-Clikeman et al. 2009)	Manual Segmentation	32 (C)/ 15	VR: - Cerebellar vermis volume reduction in treatment-naïve ADHD children (N=14) compared to ADHD children treated with stimulant medication (N=18) and controls	
(Brieber, Neufang et al. 2007)	VBM	15 (types not specified)/ 15	VR: -Left medial temporal lobe	-Left inferior parietal cortex volume increase
(Bussing, Grudnik et al. 2002)	Manual Segmentation	5 (C)/ 19	VR: -Total cerebral volume -Right caudate	-Posterior inferior vermis volume reduction
(Carmona, Vilarroya et al. 2005)	VBM	25 (5 I, 5 HI, 15 C) / 25	VR: -Total cerebral volume -Right orbitofrontal region -Left motor, premotor and somatosensory cortex	-Cerebellum (bilateral posterior) volume reduction

(Castellanos, Giedd et al. 1996)	Manual Segmentation	57 (DSM-III-R ADHD diagnosis : no correspondence with either DSM-IV types)/ 55	VR: -Total cerebral volume -Right caudate -Prefrontal region	-Cerebellum volume reduction
(Castellanos, Giedd et al. 2001)	Manual Segmentation	50 (C)/ 50	VR: -Right caudate -Prefrontal region	-Cerebellum volume reduction -Cerebellar vermis volume reduction -Posterior inferior vermis volume reduction
(Castellanos, Lee et al. 2002)	Manual Segmentation	152 (C)/ 139	VR: -Total cerebral volume	
(Durston, Hulshoff Pol et al. 2004)	Manual Segmentation	30 (21 C, 4 HI, 5 I)/ 30	VR: -Splenium -Prefrontal cortex	-Cerebellum volume reduction -Occipital lobe reduction
(Filipek, Semrud-Clikeman et al. 1997)	Manual Segmentation	15 (C; close correspondence between DSM-III ADD/H type and the DSM-IV combined type)/ 15	VR: -Total cerebral volume -Right caudate -Frontal lobe (Right>Left): posterior prefrontal cortex, motor association area, ACC and midcingulate cortex	
(Giedd, Castellanos et al. 1994)	Manual Segmentation	18 (DSM-III-R ADHD diagnosis : no correspondence with either DSM-IV types)/ 18	VR: -Splenium	
(Hill, Yeo et al. 2003)	Manual Segmentation	23 (types not specified)/ 24	VR: -Total cerebral volume -Right caudate -Splenium	-Cerebellum volume reduction -Posterior inferior vermis volume reduction
(Hynd, Semrud-Clikeman et al. 1990)	Manual Segmentation	10 (C; close correspondence between DSM-III ADD/H type and the DSM-IV combined type)/ 10	VR: -Total cerebral volume	
(Hynd, Semrud-Clikeman et al. 1991)	Manual Segmentation	7 (DSM-III-R ADHD diagnosis : no correspondence with either DSM-IV types)/ 10	VR: -Splenium	

(Hynd, Hern et al. 1993)	Manual Segmentation	11 (DSM-III-R ADHD diagnosis : no correspondence with either DSM-IV types)/ 11	VR: -Left caudate	
(Kates, Frederikse et al. 2002)	Manual Segmentation	13 (9 C, 4 I)/ 13	VR: -Total cerebral volume -Frontal lobes (especially prefrontal region)	
(Kobel, Bechtel et al. 2010)	VBM	14 (types not specified)/ 12	VR: -Right superior temporal gyrus (extending anteriorly to the medial temporal gyrus)	
(Lyoo, Noam et al. 1996)	Manual Segmentation	25 (DSM-III-R ADHD diagnosis : no correspondence with either DSM-IV types)/ 20	VR: -Total cerebral volume -Splenium	
(Mackie, Shaw et al. 2007)	Manual Segmentation	36 (35 C, 1 HI)/ 36	VR: -Superior cerebellar vermis	-Right and left inferiorposterior cerebellar lobes reduction (in worse outcome ADHD subjetcs)
(Mataro, Garcia-Sanchez et al. 1997)	Manual Segmentation	11 (DSM-III-R ADHD diagnosis : no correspondence with either DSM-IV types)/ 19	VR: -Total cerebral volume	
(McAlonan, Cheung et al. 2007)	VBM	28 (5 HI, 9 I, 14 C)/ 31	VR: -Right corpus striatum (especially globus pallidus) -Right frontal lobe	-Cerebellum volume reduction -Right parietal lobe volume reduction
(Mostofsky, Reiss et al. 1998)	Manual Segmentation	12 (10 DSM-III-R ADHD diagnosis, 2 DSM-IV I)/ 23	VR: -Cerebellar vermis	-Posterior inferior vermis volume reduction
(Mostofsky, Cooper et al. 2002)	Manual Segmentation	12 (4 I, 8 C)/ 12	VR: -Total cerebral volume -Frontal lobes (especially prefrontal region)	
(Overmeyer, Bullmore et al. 2001)	VBM	18 (C: correspondence with ICD-10 hyperkinetic disorder)/ 16	VR: -Right superior frontal gyrus -Basal ganglia bilaterally (especially right globus pallidus and putamen)	-Right posterior cingulate volume reduction

(Pineda, Restrepo et al. 2002)	Manual Segmentation	30 (15 C, 15 I)/ 30	No group differences	
(Plessen, Bansal et al. 2006)	Manual Segmentation	51 (C)/ 63		-Bilateral volume increase of the hippocampus (mainly head enlargement) -No significant differences in volume of the amygdala with conventional measures (VR of bilateral amygdalar basolateral complex with surface analyses)
(Qiu, Ye et al. 2011)	Manual Segmentation and Cortical Thickness Mapping	15 (I)/ 15	VR: -All brain structures except for the putamen and globus pallidus CTR: - Focal thinning in bilateral frontal regions and the right cingulate cortex	
(Sasayama, Hayashida et al. 2010)	VBM	18 (10 C, 6 I, 2 HI)/ 17	VR: -Bilateral temporal polar cortices -Bilateral amygdala -Left middle frontal gyrus	-Right occipital cortex reduction -Right superior temporal sulcus reduction
(Semrud-Clikeman, Filipek et al. 1994)	Manual Segmentation	15 (C; close correspondence between DSM-III ADD/H type and the DSM-IV combined type)/ 15	VR: -Splenium	
(Semrud-Clikeman, Pliszka et al. 2006)	Manual Segmentation	30 (C) / 21	VR: -Bilateral caudate	- Right ACC volume reduction only for treatment-naïve ADHD children (N=16)
(Shaw, Lerch et al. 2006)	Cortical thickness mapping	163 (157 C, 4 I, 2 HI)/ 166	CTR: -Global cortex thinning -Medial prefontal (left side: initial thinning associated with worse outcome) -Superior prefrontal	-Thinning of precentral regions

(Shaw, Eckstrand et al. 2007)	Cortical thickness mapping	223 (types not specified; same ADHD cohort than Shaw et al. 2006)/ 223	CMD: -Frontal regions (most prominent in Prefrontal regions)	
(Shaw, Lalonde et al. 2009)	Cortical thickness mapping	218 (types not specified; same ADHD cohort than Shaw et al. 2006)/ 358	CTR: - loss of prefrontal evolving assymetry	-Intact posterior (occipital) evolving assymetry
(Schnoebelen, Semrud-Clikeman et al. 2010)	Manual Segmentation	25 (C) / 15	VR: -Splenium (in treatment-naïve ADHD patients; N = 13)	
(Sobel, Bansal et al. 2010)	Manual Segmentation	47 (C) / 57	VR: - Putamen - Caudate and globus pallidus (only for treatment naïve ADHD subjects N=16)	
(Sowell, Thompson et al. 2003)	Manual Segmentation	27 (types not specified)/ 46	VR: -Inferior portions of dorsal prefrontal cortices -Anterior temporal cortex	-Inferior parietal lobe volume increase -Posterior temporal lobe volume increase
(Tremols, Bielsa et al. 2008)	Manual Segmentation (method for semi-automatic caudate head and body segmentation)	39 (8 I, 7 HI, 24 C)/ 39	VR: -Right caudate (head and body)	
(van 't Ent, Lehn et al. 2007)	VBM	High-low concordant twin pairs (types not specified): 6/34	VR: -Orbitofrontal cortex	- Posterior corpus callosum volume reduction
(van 't Ent, Lehn et al. 2007)	VBM	Discordant twin pairs (types not specified): 10/10	VR: Right inferior dorsolateral prefontal cortex	

(Wang, Jiang et al. 2007)	VBM	12 (types not specified)/ 12	VR: -Right prefrontal -Right basal ganglia (especially right putamen)	-Right medial temporal volume reduction -Left parietal lobe volume reduction -Right occipital lobe volume increase -Left posterior lateral ventricle volume increase
(Yang, Wang et al. 2008)	VBM	57 (types not specified)/ 57	VR: -Total cerebral volume -Caudate -Cerebellum	

VBM: Voxel Based Morphometry; ACC: Anterior cingulate cortex; ADD/H: Attention-deficit disorder with hyperactivity.

Table 1.2. *Structural changes observed in ADHD studies with Adults*

Study and year	**Neuroimaging technique**	**Sample number** ADHD (by type: I inattentive, C combined, HI hyperactive-impulsive, NOS not otherwise specified)/Controls	**Main findings** Volume reduction (VR), Cortical thickness reduction (CTR) or Cortical maturation delay (CMD), Volume increase (VI)	**Other observations**
(Ahrendts, Rusch et al. 2011)	VBM	31 (C)/ 31	VR: -bilateral occipital lobes (especially located in bilateral BA 17 and 18, corresponding to visual cortex areas V1/V2)	
(Almeida Montes, Ricardo-Garcell et al. 2010)	VBM	20 (C)/ 20	VR: -Right caudate -Right superior frontal gyrus	
(Amico, Stauber et al. 2011)	VBM	20(types not specified)/ 20	VR: -Right and left ACC	

(Depue, Burgess et al. 2010)	VBM	31 (C)/ 21	VR: -Inferior prefrontal regions (especially right inferior frontal gyrus [negatively correlated with response inhibition and response variability])	- Anterior insula reduction (correlated with slower speed processing) -Superior parietal lobe reduction (negatively correlated with response variability)
(Frodl, Stauber et al. 2010)	Manual Segmentation	20 (types not specified)/20	VR: -Amygdala (bilateral)	
(Hesslinger, Tebartz van Elst et al. 2002)	Manual Segmentation	8 (C)/ 17	VR: -Left orbitofrontal cortex	
(Makris, Biederman et al. 2007)	Cortical thickness mapping	24 (types not specified)/ 18	CTR: -Global cortex thinning -Prefrontal regions bilaterally (dorsolateral prefrontal cortex and orbitofrontal cortex) -Right ACC -Left posterior cingulate	- Thinning of lateral inferior parietal cortex - Thinning of right angular gyrus
(Makris, Seidman et al. 2010)	Manual Segmentation	26 (types not specified)/ 22	VR: -Left ACC (in treatment-naive patients) -Right ACC (in treated patients)	
(Perlov, Philipsen et al. 2008)	Manual Segmentation	27 (C)/ 27	-No significant differences in hippocampus and amygdala volumes	
(Proal, Reiss et al. 2011)	Cortical Thickness Mapping	59 (26 Remitting ADHD; 17 Persistent ADHD: 7 I, 6 HI, 4 C; 16 NOS) / 80	CTR: *Probands with remitting and persisting ADHD: -multiple regions, including dorsal attentional network, limbic areas, right caudate, right thalamus, bilateral cerebellar hemispheres *Only probands with persisting ADHD: medial occipital cortex, insula, parahippocampus, and prefrontal regions	
(Seidman, Valera et al. 2006)	Manual Segmentation	24 (9 I, 2 HI, 12 C, 1 data missing)/ 18	VR: -Total cerebral volume -Frontal lobes (especially dorsolateral prefrontal cortex) -Medial paralimbic regions: (especially ACC)	-Nucleus accumbens volume increase -Greater white matter volumes

(Seidman, Biederman et al. 2011)	VBM	74 (types not specified)/ 54	VR: -Caudate -Putamen -Dorsolateral prefrontal cortex -ACC VI: -Orbitofrontal cortex -Dorsolateral prefrontal cortex -Visual areas (BA 19/18)	-Cerebellum volume reduction -Inferior parietal lobule volume reduction

VBM: Voxel Based Morphometry; BA: Brodmann area; ACC: Anterior cingulate cortex; ADD/H: Attention-deficit disorder with hyperactivity.

Table 1.3. *Results of hand search of original Structural Neuroimaging articles performed from february 2012 to january 2015*.

Studies with Children and Adolescents		
VBM studies	**Manual Segmentation studies**	**Cortical Thickness studies**
(Kessler, Angstadt et al. 2014)	(Ivanov, Murrough et al. 2014) (Johnston, Mwangi et al. 2014)	(Fernandez-Jaen, Lopez-Martin et al. 2014) (Shaw, Malek et al. 2013) (Shaw, De Rossi et al. 2014)
Studies with Adults		
VBM studies	**Manual Segmentation studies**	**Cortical Thickness studies**
(Makris, Liang et al. 2013) (Pironti, Lai et al. 2014) (Onnink, Zwiers et al. 2014)		

f. Structural Neuroimaging - Limitations of the studies -

Several limitations of the structural neuroimaging studies revised lead to potential problems of confounding and bias:

- 43 of the studies included child and adolescents while only 12 studies focused on adult population. Results of the hand search of articles performed from february 2012 to january 2015 also reveales a disparity between 6 studies with children and adolescents and 3 adult studies (see **Table 1.3.**). Whether structural brain abnormalities observed in childhood persist into adult ADHD remains poorly understood in the light of the current literature, with more research needed in adult ADHD.
- Sample sizes were relatively small (N ≤ 20 in 47% of the reviewed studies; N ≤ 30 in 69% of studies).
- Only 20 studies used fully automated volumetric techniques versus 35 studies using manual segmentation. It is known that manual tracing by ROI analyses, with voxel-by-voxel comparison assessment and no cluster thresholding favours findings of significant differences in many regions (type I error). Results of the hand search of articles performed from february 2012 to january 2015 indicate a shift in the balance in favor of fully automated volumetric techniques (7 studies versus 2 using manual segmentation) in the last two years.
- Different ways of establishing an ADHD diagnosis were detected between studies, with participants undergoing either clinical assesments, structured interviews, semi-structured interviews, or simply retrospective reports of childhood symptoms.

- Discrimination between ADHD subtypes was lacking for most of the studies, thus not considering the effect of different underlying brain neurophysiology for the different presentations of the disorder.
- There was not a uniform assessment of comorbid conditions across studies, with the majority of studies not adressing the effects of comorbidity in brain structural findings.
- Misclassification in terms of medication status and wash-out periods prior and during the acquisition of the scans was the norm. The majority of studies didn't specify if participants were washed out before the scans, and for most of the studies that did wash out medicated subjects, the length of washout wasn't provided. Treatment histories if assessed, were based on self-reports, with no studies considering different treatment doses.

1.2.2. Current state of Functional Neuroimaging studies in Attention-Deficit Hyperactivity Disorder.

Functional neuroimaging research relating to ADHD is reviewed including English language articles, covering the major databases (PubMed, Scopus, EMBASE, PsycINFO and Web of Knowledge), selecting as eligible those studies which used functional neuroimaging (PET, fMRI, fcMRI) to compare ADHD diagnosed subjects to healthy controls. The population of interest was composed by children, adolescents and adults diagnosed with ADHD according to recognised criteria: Diagnostic and Statistical Manual of Mental Disorders (DSM; versions: -IV-R, -IV, -III or -III R), or International Classification of Diseases 10 (ICD-10). No limits were placed on gender nor age of the study populations. Databases were searched to January 2012 and search terms included:

“ADHD and neuroimaging”, “ADHD and functional neuroimaging”, “ADHD and fMRI”, “ADHD and PET” and “ADHD and functional connectivity”. A permanent hand search of relevant original, review and meta-analytic papers was also performed to january 2015.

Results of the review:

The revised studies use techniques such as positron emission tomography (PET) or more frequently functional magnetic resonance imaging (fMRI), due to its superior temporal and spatial resolution and lesser invasiveness (Bush 2008). Functional brain imaging techniques use indirect methods for detecting changes in neural activity. They can study changes in brain blood flow directly via injection of a radioactive tracer (PET) or indirectly analysing changes in the blood oxygenation level dependent (BOLD) signal (fMRI) (Frith and Frith 2008). These accounts of neural activity can be detected at baseline (resting state) or using experimental paradigms that employ cognitive, emotional, sensorial or motor tasks or stimuli. Novel functional connectivity studies involve correlation between BOLD signal fluctuations in different brain areas during rest or under task demands. These studies permit testing the hypothesis that interacting brain regions, rather than isolated regions of interest, are the cortical substrate for performance. Finally, we also found one study using Near-infrared spectroscopy (NIRS), neuroimaging approach with relatively poor temporal resolution as compared to (EEG) and relatively poor spatial resolution as compared to fMRI, but with minor susceptibility to movement artefacts (Ehlis, Bahne et al. 2008) (especially of interest in psychiatric patients which often find it difficult to remain still during fMRI studies).

Most fMRI studies with experimental paradigms in ADHD have looked at executive functions such as response inhibition (the most studied), working memory (WM), planning and sustained attention. The more frequently used experimental paradigms to explore executive functions in ADHD have been: 1) response inhibition tasks such as go/no-go tasks and stop-signal tasks; 2) cognitive interference/working memory tasks such as task-switching paradigms, digit span tasks, delay tasks and N-back task; and 3) attention tasks such as sustained attention tasks with continuous performance feedback and Stroop tasks. Fewer research has studied impaired time tracking in ADHD by means of time processing tasks such as sensorimotor synchronization tasks, time estimation tasks and temporal discounting tasks. Recently more attention has been payed to reward and motivational processes in functional neuroimaging in ADHD population, using reward-related tasks such as delay-discounting or incentive delay tasks. In spite of the high rate of emotional dysregulation in ADHD there are very few functional neuroimaging emotion processing studies in this population (see ^ in Tables 2.1. and 2.2.); these studies employ tasks involving the regulation of emotion by including the presentation of emotional stimuli such as viewing emotionally aversive slides or facial expressions of emotion i.e..

In relation to more recent functional connectivity studies in psychiatric disorders (mainly with resting state fMRI) that have identified various large-scale intrinsic networks (Sporns 2014), we have to mention the growing interest of some brain regions referred to as the *default mode network* (DMN) since 2001 (Raichle, MacLeod et al. 2001). This network describes a functionally connected set of brain regions that is more active at rest than under externally oriented cognitive tasks, during which, its activation decreases, contrary to *task-positive* networks (usually regions of interest in functional brain imaging studies

using experimental paradigms) with increased activation during performance of goal-directed cognition tasks that demand attention or mental control (Fox, Snyder et al. 2005) (Kelly, Uddin et al. 2008) (Uddin, Kelly et al. 2009). Regions of DMN are often anticorrelated with regions of task-positive networks (Fox, Snyder et al. 2005) (Whitfield-Gabrieli and Ford 2012). DMN regions include: the medial prefrontal cortex, the posterior cingulate cortex/precuneus and parts of the parietal and temporal lobe cortex and also the hippocampus (Buckner, Andrews-Hanna et al. 2008). DMN is implicated in internally directed mentation (self-referential processing and autobiographical recollection) and mind wandering (Gusnard, Akbudak et al. 2001) (Raichle, MacLeod et al. 2001) (Buckner, Andrews-Hanna et al. 2008), and deficits in attention to tasks have been linked to inadequate suppression of the DMN during task performance in different psychiatric populations (Broyd, Demanuele et al. 2009), therefore, recent studies have been looking at DMN in ADHD (see ** in Tables 2.1. and 2.2.).

a. Brain Regional Activity Studies

a.1. Studies using Experimental Paradigms (Task Activation Studies)

Looking at brain regional activity studies, most frequently reported alterations have been found in studies using experimental paradigms.

These studies have found consistent evidence of hypoactivation of the prefrontal regions (especially dorsolateral prefrontal cortex (DLPFC) and inferior prefrontal cortex (IPFC) – containing ventrolateral prefrontal cortex (VLPFC) -, the caudate nucleus (principally right

caudate), the ACC, the parietal lobes (especially superior and inferior parietal), temporal regions, right cerebellum and the supplementary motor area (SMA) for Response Inhibition tasks (Dickstein, Bannon et al. 2006) (Paloyelis, Mehta et al. 2007) (Cubillo and Rubia 2010) (Cubillo, Halari et al. 2010) (Bush 2011) (Cubillo, Halari et al. 2012) (Hart, Radua et al. 2013) (Hart, Chantiluke et al. 2014) (Chantiluke, Christakou et al. 2014) (Fan, Gau et al. 2014) (Morein-Zamir, Dodds et al. 2014). Stimulant medication would attenuate hypoactivity in the prefrontal, parietal, striatal and supplementary motor regions during this type of tasks in child and adolescent ADHD population (Rubia, Halari et al. 2011) (Spencer, Brown et al. 2013) (Cubillo, Smith et al. 2014), with inconsistent findings for ADHD adults (Congdon, Altshuler et al. 2014).

Frontal cortex (especially lPFC and DLPFC), occipito-parietal cortices, striatum and cerebellum hypoactivations, have been the more replicated findings for Working Memory tasks (Paloyelis, Mehta et al. 2007) (Silk, Vance et al. 2008) (Cubillo and Rubia 2010) (Valera, Brown et al. 2010) (Bush 2011) (Brown, Biederman et al. 2011) (Prehn-Kristensen, Krauel et al. 2011). Specifically in relation to lPFC hypoactivation, this has been probably the most consistently observed finding and proposed to be disorder-specific compared with other disorders, such as conduct disorder or obsessive–compulsive disorder (Cubillo and Rubia 2010). Stimulant treatment with methylphenidate (MPH) would have shown a normalizing effect for this frontal-striatal hypoactivity (McCarthy, Skokauskas et al. 2014). A recent double-blind, placebo-controlled, cross-over study in medication-naive ADHD boys, under a WM N-back task showed normalization effects under atomoxetine (significant upregulation of right DLPFC activation) and MPH (significantly normalized left lPFC underactivation) (Cubillo, Smith et al. 2014).

In relation to tasks involving Attentional Processes, hypoactivation of temporal, insular, parietal, cingulate and frontal regions (especially IPFC, DLPFC and SMA) are the most replicated findings (Paloyelis, Mehta et al. 2007) (Cubillo and Rubia 2010) (Bush 2011) (Cubillo, Halari et al. 2011) (Rubia, Smith et al. 2005) (Orinstein and Stevens 2014). Stimulant medication has been associated with greater PFC activation during attentional tasks (Spencer, Brown et al. 2013).

With regard to Reward-Related tasks, hypoactivation of the ventral striatum during reward anticipation seems to be the more consistent finding (Plichta and Scheres 2014); reduced activation in posterior cingulate during reward outcome and in fronto–striato–cerebellar networks during reward delay have also been found (Cubillo and Rubia 2010) (Plichta, Vasic et al. 2009) (Chantiluke, Christakou et al. 2014). Studies tend to show an attenuation of PFC, striatal and cerebellar dysfunction during rewarded paradigms under stimulant medication (Spencer, Brown et al. 2013).

Among studies dealing with Temporal Processing experimental paradigms, differences in activation compared to controls have been principally located in regions of the prefrontal cortex (mainly IPFC and DLPFC), parietal cortices, cingulate, striatum and cerebellum (Rubia, Halari et al. 2009) (Hart, Marquand et al. 2014) (Chantiluke, Christakou et al. 2014) and in a lesser extent in primary motor cortex and premotor areas in studies with Sensorimotor Synchronization tasks (Castellanos and Proal 2011).

Finally, with respect to the processing of emotional stimuli and expected differences in brain activity to affective negative stimuli i.e., divergent findings have been reported in relation to the amygdala and other areas, and no clear picture can be discerned for ADHD from Emotional Processing studies (Brotman, Rich et al. 2010) (Herpertz, Huebner et al. 2008) (Marsh, Finger et al. 2008).

In relation to the DMN, studies using experimental paradigms have identified a reduced task-related deactivation of this network in ADHD, particularly in medial PFC (Fassbender, Schweitzer et al. 2011); this inadequate suppression of the DMN has been shown to normalise under high incentivating conditions and on medication with MPH (Peterson, Potenza et al. 2009) (Liddle, Hollis et al. 2011) (Cubillo, Smith et al. 2014) and atomoxetine (Cubillo, Smith et al. 2014). Brown et al. however, found greater deactivation in the DMN in ADHD adults while performing a 2-back task, contrary to the previously mentioned findings, pointing to the fact that the task demands dindn't surpass the expected attentional or difficulty threshold, as a plausible explanation for the unexpected results (Brown, Biederman et al. 2011); this argument however doesn't seem very convincing since the N-back task is recognised as difficult even for healthy subjects from a 2-back level of difficulty onwards (Gevins, Smith et al. 1998).

The vast majority of studies looking at potential brain functional effects of exposure to stimulant treatment are cross-sectional studies with naturalistic dosing of the patients, with the exception of three randomized drug/placebo studies, which however, lacked a control group (Bush, Spencer et al. 2008) (Cubillo, Smith et al. 2014) (Cubillo, Smith et al. 2014). With regards to MPH effects on altered brain regional activity, an overview of these studies

up to date, suggests a positive acute effect in normalising brain function in ADHD patients (Peterson, Potenza et al. 2009) (Liddle, Hollis et al. 2011) (Rubia, Halari et al. 2011) (Rubia, Halari et al. 2011) (Rubia, Alegria et al. 2014) (Cubillo, Smith et al. 2014), whereas long lasting or trait effects of the medication rather than acute effects, remain undocumented.

a.2. Task Activation Studies of Working Memory in ADHD Adult population: State of the Question

Deficits in executive functions have been replicated in numerous neuropsychological studies both in child and adolescents and in adults with ADHD (Hervey, Epstein et al. 2004) (Willcutt, Doyle et al. 2005). Impairment of WM in particular has been one of the most replicated findings in child and adolescents ADHD research studies, being consistently observed to persist into adulthood, with WM deficits as a core characteristic of adult ADHD in comparison to the general population (Seidman, Doyle et al. 2004) (Alderson, Kasper et al. 2013), being also found in ADHD adults with high intelligence quotient (IQ ≥ 120) (Brown, Reichel et al. 2009), and being proposed as an endophenotype of adult ADHD (Castellanos and Tannock 2002) (Jacob and Lesch 2006) (Finke, Schwarzkopf et al. 2011).

Although these cognitive deficits were initially associated with reduced fMRI responses in the prefrontal cortex (Rubia, Overmeyer et al. 1999) (Ernst, Kimes et al. 2003) (Valera, Faraone et al. 2005), latter neuroimaging studies have shown a widespread of neurofunctional abnormalities in other brain regions subserving executive functions, as

well as alterations in the connectivity between those regions (Cubillo and Rubia 2010) (Cortese and Castellanos 2012).

During performance of WM paradigms, children and adolescents with ADHD have consitently shown reduced activity in frontal cortices (mainly dorso- and ventro-lateral prefrontal cortex), occipito-parietal cortices, striatum and cerebellum (Rubia, Overmeyer et al. 1999) (Smith, Taylor et al. 2006) (Kobel, Bechtel et al. 2009) (Fassbender, Schweitzer et al. 2011) (Massat, Slama et al. 2012) (Cubillo, Smith et al. 2014) and increased activity in right mediotemporal areas (mainly hippocampus) (Li, Li et al. 2014). In contrast, findings in adult ADHD have been inconsistent, with reports of reduced activity in frontal cortices (dorso- and ventro-lateral, but also medial prefrontal cortex), occipito-parietal cortices, striatum, cerebellum, anterior cingulate and insula (Valera, Faraone et al. 2005) (Wolf, Plichta et al. 2009) (Valera, Brown et al. 2010) (Cubillo and Rubia 2010) (Bayerl, Dielentheis et al. 2010) (McCarthy, Skokauskas et al. 2014), but also reports of increased activity in the same prefrontal areas, occipito-parietal cortices and cerebellum (Schweitzer, Lee et al. 2004) (Hale, Bookheimer et al. 2007) (Dibbets, Evers et al. 2010).

This discrepancy in the adult literature relative to children and adolescents research could be explained by smaller sample sizes, elevated inclusion rate of comorbid conditions, lack of uniformity in terms of medication status and presence and length of wash-out periods prior and during the acquisition of the scans, no-discrimination between ADHD subtypes and inaccurate diagnoses due to reliance on retrospective reports of childhood symptoms (Cortese, Kelly et al. 2012) (Cortese and Castellanos 2012) (Spencer, Brown et al. 2013).

Moreover, no prior studies have examined the potential effects of long-term treatment with methylphenidate (MPH) especifically on brain activity within the working memory network in adult ADHD (Rubia, Alegria et al. 2014).

Since 2001, it has been recognized that some brain regions de-activate rather than activate during performance of attention-demanding cognitive task (Gusnard, Akbudak et al. 2001) (Raichle, MacLeod et al. 2001). These regions integrate the DMN (default mode network: medial prefrontal cortex, posterior cingulate cortex/precuneus, parts of the parietal and temporal cortices and of the hippocampus (Buckner, Andrews-Hanna et al. 2008)). Changed patterns of de-activation during task performance in the default mode network have been found in a range of psychiatric disorders ranging from schizophrenia (Pomarol-Clotet, Salvador et al. 2008) (Whitfield-Gabrieli, Thermenos et al. 2009) (Dreher, Koch et al. 2012) and major affective disorders (Grimm, Boesiger et al. 2009) (Sheline, Barch et al. 2009) (Allin, Marshall et al. 2010) (Pomarol-Clotet, Moro et al. 2012) (Fernandez-Corcuera, Salvador et al. 2013) to autistic spectrum disorder (Kennedy, Redcay et al. 2006) and neuropsychiatric disorders such as mild cognitive impairment (see (Broyd, Demanuele et al. 2009)). De-activation changes have also been replicated in children with ADHD, with findings of a reduced task-related de-activation of the default mode network, particularly in medial prefrontal cortex (Fassbender, Zhang et al. 2009) (Peterson, Potenza et al. 2009) (Fassbender, Schweitzer et al. 2011) (Liddle, Hollis et al. 2011). As stated above, this inadequate suppression of the default mode network has been shown to normalise under high incentivating conditions and on acute medication with methylphenidate (Peterson, Potenza et al. 2009) (Liddle, Hollis et al. 2011) (Cubillo, Smith et al. 2014) and atomoxetine (Cubillo, Smith et al. 2014). However, de-activation of the

default mode network in ADHD adults while performing WM tasks could be much stronger than in ADHD children as reported by Brown et al. in a study with ADHD adults while performing an N-back task (Brown, Biederman et al. 2011), with more studies needed to understand the link between this neural network and adult ADHD symptoms.

b. Brain Connectivity Studies

b.1. Resting State Connectivity

More recent connectivity studies suggest that ADHD is characterized by abnormal patterns of functional connectivity. These novel type of studies use resting state functional connectivity MRI (fcMRI) as the standard technique for the analysis of functional connectivity patterns in brain networks and the temporal dynamics of their activity fluctuations. Resting state fcMRI examines the temporal coherence of neural activity across disparate brain regions (Posner, Park et al. 2014). Those brain regions presenting a positive temporal correlation of their activity fluctuations over time are “functionally connected” and are believed to be components of distributed neural networks termed large-scale intrinsic functional networks (Damoiseaux, Rombouts et al. 2006) (Posner, Park et al. 2014) (Sporns 2014). An incresing volume of research is documenting that the brain is organized into large-scale networks that structure communication between distributed brain regions, that exhibit coherent activity, to accomplish different tasks and objectives (Fox, Corbetta et al. 2006) (Shehzad, Kelly et al. 2009) (Sporns 2014). Altered connectivity between these large-scale brain networks would underlie the pathophysiology of psychiatric disorders (Menon 2011) (Sporns 2011).

On the one hand, with these resting state approaches, the main findings in ADHD have been of disrupted functional connectivity within different networks, especially the DMN. In relation to it, decreases in functional connectivity (reduced correlations) between key regions inside the network have been found in ADHD, principally between ACC/medial prefrontal cortices, precuneus and posterior cingulate cortex regions (Cao, Zang et al. 2006) (Castellanos, Margulies et al. 2008) (Uddin, Kelly et al. 2008) (Fair, Posner et al. 2010) (Qiu, Ye et al. 2011) (Tomasi and Volkow 2011) (Fair, Nigg et al. 2012) (Sokunbi, Fung et al. 2013) (Sripada, Kessler et al. 2014) (Elton, Alcauter et al. 2014) (Mattfeld, Gabrieli et al. 2014) (Kessler, Angstadt et al. 2014), with less consistent findings (increased and decreased functional connectivity) within other regions of the network (McCarthy, Skokauskas et al. 2013). Interestingly, the only study comparing adults with persistent ADHD vs. adults with remitted ADHD and healthy comparison adults, showed reduced positive posterior cingulate cortex - medial prefrontal cortex connectivity only for the persistent ADHD group, but not for the remitted ADHD and control groups, indicating that intrinsic functional dysconnectivity within the DMN would be a more specific neurobiological trait in persistent adult ADHD (Mattfeld, Gabrieli et al. 2014).

Findings related to other networks in resting state fcMRI studies have been mainly of decreased connectivity within ventral and dorsal attention networks (Tomasi and Volkow 2011) (McCarthy, Skokauskas et al. 2013) (Ou, Lian et al. 2014) (Kessler, Angstadt et al. 2014), frontal-parietal-cerebellar executive control network (Li, He et al. 2014) (Kessler, Angstadt et al. 2014) and visual network (Kessler, Angstadt et al. 2014), and of increased connectivity within motivational-reward systems (ventral striatum and orbito-frontal cortex -

OFC-) (Tomasi and Volkow 2011); although findings of lowered connectivity between ventral striatum and medial prefrontal cortex have also been reported (Hauser, Iannaccone et al. 2014). Other studies analysing connectivity have revealed increased connectivity within affective networks (ventral ACC, amygdala, nucleus accumbens, hypothalamus, anterior insula, hippocampus, and OFC with reciprocal connections to autonomic, visceromotor, and endocrine systems) (McCarthy, Skokauskas et al. 2013), with greater positive intrinsic functional connectivity between the amygdala and ventral ACC, specifically shown in ADHD youths with high ratings of emotional lability (Hulvershorn, Mennes et al. 2014). Reduced connectivity between the left hippocampus and the left OFC has also been observed (Posner, Siciliano et al. 2014). These findings suggest increased emotional sensitivity and emotional impulsivity in ADHD along with a liability for anxiety and depressive symptoms. Finally, connectivity alterations in sensory networks have also been found (Tian, Jiang et al. 2006) (Wang, Zhu et al. 2009).

In relation to functional connectivity across networks in ADHD subjects, the more consistent findings have been localized at the DMN‘s interrelationship with task-positive networks, with increased extrinsic functional connectivity (reduced anticorrelations = reduced “effective” connectivity = reduced segregation) during resting state found between:

1) DMN/medial prefrontal cortex and frontoparietal network (including DLPFC, VLPFC and ACC), pointing to inappropriate DMN - frontal cognitive control signaling during rest (Castellanos, Margulies et al. 2008) (Sun, Cao et al. 2012) (Hoekzema, Carmona et al. 2014) (Kessler, Angstadt et al. 2014). This finding has been associated with greater

severity of hyperactive/impulsive symptoms (Elton, Alcauter et al. 2014), but has also been replicated in adults with remitted ADHD and not only in those with symptom persistence (Mattfeld, Gabrieli et al. 2014).

2) the DMN and sensory brain regions (Tian, Jiang et al. 2008) (McCarthy, Skokauskas et al. 2013) (Elton, Alcauter et al. 2014).
3) DMN and ventral attention network ("salience network"), specifically between posterior cingulate cortex and right anterior insula and supplementary motor area (Sripada, Kessler et al. 2014).

Other altered internetwork relations different from DMN - Task-positive networks connectivity, have been reported in recent studies examining resting state functional connectivity in the context of neural large-scale network organization of the entire brain of children with ADHD compared to typically developing children, showing functional low connectivity for: 1) networks within the "functional rich-club organization" of the brain (dense structural neural connections linking highly connected network hubs said to form a "rich club" (Sporns 2014): midline frontal and midline posterior areas, insula, inferior temporal and cingulate cortex), explained in part by reduced fractional anisotropy (Ray, Miller et al. 2014); 2) between dorsal attention netwok and somatomotor network (Kessler, Angstadt et al. 2014); 3) between dorsal and ventral attention networks and frontoparietal network; and 4) between visual network and dorsal attention network, also with findings of between network hyperconnectivity in this case (Kessler, Angstadt et al. 2014).

Resting state connectivity studies in ADHD thus far haven't looked at stimulant treatment effects, with the majority of studies based in medication-naïve samples.

As a whole, however, resting state connectivity studies in ADHD still reveal apparent inconsistencies, with findings of reduced connectivity within large-scale networks (Castellanos, Margulies et al. 2008) (Cao, Zang et al. 2006) (Fair, Posner et al. 2010) (Qiu, Ye et al. 2011) (Tomasi and Volkow 2011) (Uddin, Kelly et al. 2008) (Sokunbi, Fung et al. 2013) (Sripada, Kessler et al. 2014) (Elton, Alcauter et al. 2014) (Mattfeld, Gabrieli et al. 2014) (Kessler, Angstadt et al. 2014) and between large-scale networks (McCarthy, Skokauskas et al. 2013) (Elton, Alcauter et al. 2014) (Sripada, Kessler et al. 2014) (Hoekzema, Carmona et al. 2014) (Mattfeld, Gabrieli et al. 2014) (Kessler, Angstadt et al. 2014), but also of increased connectivity (Tian, Jiang et al. 2006) (Tomasi and Volkow 2011), with differing locations for atypical connectivity from one study to another and different proposals for the reasons of dysconnectivity. Overall, evidence suggests disrupted functional connectivity with difusse alterations both inside and outside different brain networks in ADHD, but the altered network patterns remain unclear.

On the other hand, there is a paucity of studies measuring amplitude of low frecuency fluctuations (ALFF) in the resting state (Zang, He et al. 2007). Measures of the ALFF (< 0.08 Hz) in the variance of the observed BOLD signal for a given brain region are interpreted as a measure of local spontaneous neuronal activity during a resting state session (Zou, Zhu et al. 2008) and are of interest to investigate the baseline brain neural activity in ADHD. Regions with greater ALFF may have greater baseline neural activity than regions with lower ALFF (Posner, Park et al. 2014). ALFF patterns have been also proposed as a possible basal scaling factor, accounting for baseline individual variability, as a marker of neural activity different from the resting state signal (ALFF) (Di, Kannurpatti

et al. 2012) (Yuan, Di et al. 2013), but this still remains speculative. To date, all studies computing ALFF have focused exclusively in children and adolescent ADHD population, and have reported inconsistent findings. These studies have shown significantly different ALFF at different brain regions, including findings of contrary results between studies for some of those brain regions. For example, while Zang et al. found increased ALFF in the ACC of their ADHD participants (Zang, He et al. 2007), Yang et al. found the exact opposite, reporting reduced ALFF in the ACC (Yang, Wu et al. 2011). Both studies did show however greater ALFF in the sensorimotor cortex (Zang, He et al. 2007) (Yang, Wu et al. 2011). Li et al. also found regional differences in ALFF between 33 boys with ADHD (of different subtypes but without comorbidity) and 32 healthy controls, notably: lower ALFF in the left OFC and the left ventral superior frontal gyrus and higher ALFF in bilateral globus pallidus and the right dorsal superior frontal gyrus (Li, He et al. 2014). In relation to frontal cortex, previous studies with children and adolescents have reported reduced ALFF in right VLPFC (Zang, He et al. 2007) and right DLPFC (Yang, Wu et al. 2011) and increased ALFF in the left superior frontal gyrus (Yang, Wu et al. 2011). Sato et al. however, reported limited accuracy to discriminate ADHD participants from typically developing controls for ALFF maps in their study based on extensive data acquired by the ADHD-200 Consortium which provided public release of 929 resting state scans of children and adolescents with ADHD and typical controls (Sato, Hoexter et al. 2012). Similar results have been found by Alonso et al. in a study with a sample of 23 children with ADHD (of the inattentive and hyperactive-impulsive subtypes) and 23 controls, were the ALFF analysis presented no differences between groups (Alonso Bde, Hidalgo Tobon et al. 2014); and by An et al. in a study with 19 ADHD patients (of different subtypes and with important comorbidity issues) and 23 controls, with significant differences found only

for one region, the right occipital cortex, in which ADHD participants exhibited a higher ALFF (An, Cao et al. 2013). These negative findings are in contrast with the previous studies presented above, and would represent that ADHD didn't influence the function of different brain regions at rest to a significant extent.

b.2. Task Dependent Connectivity

On the other hand, connectivity studies using experimental paradigms have identified: 1) hypoconnectivity between DMN areas (ventral ACC) and lateral prefrontal cortex during a Stroop task, with stimulant treatment improving their connectivity to control comparable levels (Peterson, Potenza et al. 2009); 2) reduced connectivity between left DLPFC and DMN (left midcingulate cortex and posterior cingulate cortex) for a high-load N-back WM task (Bedard, Newcorn et al. 2014), and strengthened connectivity of the frontoparietal executive network (consistently identified as hypoactivated in fMRI studies using functional executive tasks) following the administration of stimulant medication in comparison to placebo during a Sternberg WM task (Wong and Stevens 2012); 3) increased connectivity between amygdala and lateral PFC under negative valenced stimuli (fearful faces) during an emotional Stroop, being attenuated by stimulant treatment (Posner, Maia et al. 2011); and 4) hypoconnectivity between frontal, striatal and cerebellar regions during a rewarded Continuous Performance Test (CPT), also normalised under stimulant treatment with MPH (Rubia, Halari et al. 2009).

b.3. Connectivity Studies in ADHD Adult population: State of the Question

While the great majority of studies have looked at brain connectivity in child and adolescent ADHD population, these studies are lacking for adult ADHD, so alterations in brain network connectivity are not well defined nor understood in ADHD persisting into adulthood. In fact, all of the revised connectivity articles included children and/or adolescent samples with only five exceptions that studied adult population, producing inconsistent findings but mainly pointing to dysfunction of functional interacctions within DMN and between DMN and frontoparietal/WM and sensory networks (Castellanos, Margulies et al. 2008), (McCarthy, Skokauskas et al. 2013), (Sokunbi, Fung et al. 2013), (Mattfeld, Gabrieli et al. 2014) (Hoekzema, Carmona et al. 2014). Moreover, to our knowledge, there are no studies to date analysing new emerging network measures like ALFF in adults with ADHD.

c. Functional Neuroimaging - Summary -

In summary, **functional brain imaging studies** using experimental paradigms have found functional alterations in structures implicating more importantly fronto-parietal cortices, frontostriatal-cerebellar loops and the limbic system (mainly ACC and striatum), all of them structures mediating cognitive control and the regulation of emotion and response inhibition. More recent studies show decreased deactivation of the DMN during task performance. With respect to intranetwork functional connectivity studies, a reduced connectivity within DMN regions would be the main finding. Functional connectivity studies across networks have found preliminary evidence of reduced effective connectivity

between the DMN and sensorimotor, attentional and cognitive networks. Acute stimulant treatment would seem to normalise activation and connectivity but future studies are needed to confirm such improving effects.

A summary of the findings of the reviewed functional brain imaging studies in ADHD can be found in **Tables 2.1.** (Children and Adolescents) and **2.2**. (Adults)

Table 2.1. *Functional changes observed in ADHD studies with Children and Adolescents*

Study	**Neuroimaging technique**	**Sample number** ADHD (by type: I inattentive, C combined, HI hyperactive-impulsive, NOS not otherwise specified)/ Controls	**Task**	**Main findings**
(Anderson, Polcari et al. 2002)	fMRI	10 (C)/ 6	Resting state (on MPH vs. placebo)	-Hypoactivation in cerebellar vermis under MPH compared to placebo in ADHD subjects with more hyperactivity symptoms -Hyperactivation in cerebellar vermis under MPH for less hyperactive ADHD subjects
(Booth, Burman et al. 2005)	fMRI	12 (8 C, 4 I)/ 12	Go/No-Go	-<u>During response inhibition:</u> Hypoactivation of inferior, middle and superior frontal gyri as well as caudate nucleus and globus pallidus
(Braet, Johnson et al. 2011)	fMRI	high risk DAT1 genotype (types not specified): 6/15 low risk DAT1 genotype (types not specified): 11/16	Go/No-Go	-<u>Succesful inhibition:</u> Hypoactivation in left inferior parietal cortex, right cuneus and prefrontal regions (left superior frontal gyrus and ACC) * *High risk DAT1 genotype subjects:* Hyperactivation of ACC, MPFC, caudate, middle temporal gyrus and middle occipital gyrus -<u>Error response:</u> Hypoactivation in the left superior frontal gyrus, the ACC and right insula * *High risk DAT1 genotype subjetcs:* Hypoactvation of parahippocampal gyrus

(Brotman, Rich et al. 2010) ^	fMRI	18 (types not specified)/ 37	Viewing facial expressions of emotion (Pictures of Facial Affect series/Ekman faces and NimStim set of facial expressions)	-Left amygdala hyperactivation while rating subjective fear of neutral faces
(Cao, Zang et al. 2006) **	fMRI	29 (15 I, 8 C, 4 comorbid oppositional defiant disorder, 2 comorbid conduct disorder)/ 27	Resting state	Reduced DMN deactivation (decreased regional homogeneity in the frontal-striatal-cerebellar circuits; specifically in regions that included bilateral inferior frontal gyrus, right inferior ACC, left caudate, bilateral pyramis and left precuneus)
(Durston, Tottenham et al. 2003)	fMRI	7 (3 I, 4 C)/ 7	Go/No-Go	-Controls: Activation of VLPFC, ACC and caudate nucleus -ADHD patients: More diffuse activation pattern of other regions (including more posterior and dorsolateral prefrontal regions).
(Epstein, Casey et al. 2007)	fMRI	9 (4 I, 1 HI, 4 C)/ 9 Children/ Adolescents 9 (4 I, 5 C)/ 9 Adults *This study included an Adults sample too*	Go/No-Go	Children/Adolescents: -Hypoactivation of bilateral middle frontal gyrus, right IFC, right inferior parietal lobule, ACC and bilateral caudate nucleus Adults: -Hypoactivation of bilateral IFC and left caudate -Hyperactivation of left ACC, left inferior parietal lobe, striatum and cerebellum
(Fair, Posner et al. 2010) **	fMRI	23 (types not specified)/ 23	Resting state	- Hypoconnectivity within the DMN
(Fassbender, Zhang et al. 2009) **	fMRI	12 (C)/ 13	Working memory and control tasks: Visual Serial Addition Task (VSAT) Addition Task Matching-to-Sample Task	-Attenuated deactivation with increased working memory load in frontal DMN regions (mainly medial prefrontal cortex – including VMPFC-) *(less deactivation in ADHD subjects with greatest reaction time variability -distractibility index-)*
(Herpertz, Huebner et al. 2008) ^	fMRI	13 (types not specified)/ 13	Viewing of negative, positive and neutral scene pictures (IAPS)	-Hypoactivation of insula without abnormalities in amygdala activation in pure ADHD patients
(Kobel, Bechtel et al. 2009)	fMRI	14 (C)/ 12	N-back task	-Hypoactivation in left frontal cortex, bilateral parietal lobe and right cerebellum
(Konrad, Neufang et al. 2006)	fMRI	16 (9 C, 6 I, 1 HI)/ 16	Modified version of the Attention Network Test	-Hypoactivation: Right-sided in ACC during alerting Fronto-striatal for executive control -Hyperactivation: Fronto-striatal-insular during reorienting

(Liddle, Hollis et al. 2011) **	fMRI	18 (C)/ 18	Go/No-Go + variable motivational incentive (on and off MPH)	-Off MPH + low task incentive: Event-related DMN deactivation significantly attenuated compared to controls -Off MPH + high task incentive: No significant differences in DMN deactivation -On MPH: No differences with controls (no attenuation in either motivational condition)
(Marsh, Finger et al. 2008) ^	fMRI	12 (types not specified)/ 12	Viewing facial expressions of emotion (Pictures of Facial Affect series/Ekman faces)	- No differences in amygdala activity to negative facial expressions
(Mostofsky, Rimrodt et al. 2006)	fMRI	11 (2 I, 9 C)/ 11	Self-paced sequential finger tapping	-Hypoactivation in contralateral primary motor cortex during simple motor tapping -Hyperactivation in right parietal cortex during simple motor tapping
(Passarotti, Sweeney et al. 2010) ^	fMRI	15 (C)/ 14	Emotional Stroop	-For negative versus neutral words: * Hyperactivation in DLPFC and parietal cortex * Hypoactivation of VLPFC -During cognitive control of emotion processing: * Decreased VLPFC engagement
(Peterson, Potenza et al. 2009) **	fMRI	16 (C)/ 20	Color and Word Stroop (on and off MPH)	-Attenuated task-related DMN deactivation in ADHD (mainly ventral anterior cingulate) during the inhibitory control task, normalised by MPH
(Pliszka, Glahn et al. 2006)	fMRI	17 (C)/ 15	Go/No Go (Stop signal task)	-Failure to activate the ACC and the left VLPFC after unsuccessful inhibition -Treatment with MPH associated with ACC activity attenuation; no effect in VLPFC
(Posner, Maia et al. 2011) ^	fMRI	15 (13 C, 2 I)/ 15	Cognitive and emotional Stroop (on and off MPH)	-Atypical activity in the MPFC during the emotional Stroop task: *Greater deactivation in billateral MPFC under negatively valenced stimuli *Greater activation in left MPFC under positively valenced stimuli *Increased connectivity between amygdala and lateral PFC under negative valenced stimuli (fearful faces) *-Effects normalised by MPH*
(Prehn-Kristensen, Krauel et al. 2011)	fMRI	12 (C)/ 12	Delayed match-to-sample task with face distractor	-Hypoactivation in frontal, ACC and temporo-parieto-occipital regions -Hyperactivation in right insula - If the delay was interrupted by a distractor, only healthy controls showed activation of the caudate - MPH enhances prefrontal activity during the delay in ADHD patients when no distractor is present. MPH did not enhance caudate activity with or without distractor presence.
(Qiu, Ye et al. 2011) **	fMRI	15 (I) / 15	Resting State	- Decreased functional connectivity in the ACC, posterior cingulate cortex, lateral prefrontal cortex,left precuneus and thalamus - Increased functional connectivity in bilateral posterior medial frontal cortex in the DMN

(Rubia, Overmeyer et al. 1999)	fMRI	7 (types not specified but all C or HI)/ 9	Stop task and Delay task/ Motor timing task	-Hypoactivation in the right mesial prefrontal cortex during both tasks -Hypoactivation in the right inferior prefrontal cortex and left caudate during the stop task
(Rubia, Smith et al. 2005)	fMRI	16 (C)/ 21	Stop task	-Hypoactivation in the right inferior prefrontal cortex during successful motor response inhibition -Hypoactivation in the precuneus and posterior cingulate gyrus during inhibition failure
(Rubia, Halari et al. 2009)	fMRI	12 (C)/ 12	Time discrimination task	-Hypoactivation in bilateral OFC, IPFC, MPFC, ACC, caudate, and in right cerebellum. -Hyperactivation in left middle frontal gyrus, superior temporal gyrus, occipital region and cerebellum. -On medication with MPH group activation differences were normalized
(Rubia, Halari et al. 2009)	fMRI	13 (C)/ 13	Rewarded Continuous Performance Test on MPH vs placebo	<u>ADHD patients on placebo:</u> -Hypoactivation in right IPFC, VMPFC, OFC, hyppocampus, left basal ganglia, left and right insula/parahippocampal gyrus and cerebellum -Underconnectivity in fronto-striatal-cerebellar circuits <u>ADHD patients on MPH:</u> -Hyperactivation in right DLPFC, inferior cerebellar vermis, bilateral inferior parietal and right superior parietal lobe, and superior temporal gyrus -Underconnectivity in fronto-striatal-cerebellar circuits normalized
(Rubia, Halari et al. 2011)	fMRI	12 (C) /13	Simon Oddball Task on MPH vs placebo	<u>ADHD patients on placebo:</u> -Hypoactivation in right IPFC, left VMPFC, supplementary motor area, superior parietal lobe, superior and middle temporal gyri, basal ganglia, thalamus and occipital lobe. <u>ADHD patients on MPH:</u> -Hypoactivation in left supplementary motor area, ACC, precuneus, superior and middle temporal gyri, inferior parietal lobe, occipital lobe. -Normalized underactivity in IPFC, VMPFC and striatum

(Rubia, Halari et al. 2011)	fMRI	12 (C)/ 13	Stop task on MPH vs placebo	ADHD patients on placebo/ Unsuccesful inhibition: -Hypoactivation in left IPFC, posterior cingulate cortex, precuneus, rigt premotor cortex, pre-supplementary motor area, inferior and superior parietal lobe, pulvinar, inferior temporal lobe, cerebellum, bilateral dorsal-medial PFC, occipital lobe ADHD patients on placebo/ Succesful inhibition: -Hypoactivation in left IPFC, right medial temporal lobe, occipital lobe, lyngual gyrus, inferior parietal lobe, posterior cingulate cortex, precuneus, ACC, pre-supplementary motor area, pulvinar, cerebellum and bilateral insula ADHD patients on MPH: -No significant differences with controls -Normalized underactivity in IPFC, VMPFC and striatum
(Scheres, Milham et al. 2007)	fMRI	11 (types not specified)/ 11	Monetary incentive delay task	-Hypoactivation of ventral striatum
(Schulz, Fan et al. 2004)	fMRI	10 (C)/ 9	Go/No-Go	-Hyperactivation of the left ACC, bilateral frontopolar regions, bilateral VLPFC, and left medial frontal gyrus, during inhibition
(Shafritz, Marchione et al. 2004)	fMRI	19 (C)/ 14	Divided Attention Task ans Selective Attention Task on MPH vs placebo	ADHD patients on placebo: -Hypoactivation in middle temporal gyrus and dorsal striatum ADHD patients on MPH: -Hypoactivation in middle temporal gyrus persisted, dorsal striatum underactivity normalized for divided attention task (not for selective attention)
(Silk, Vance et al. 2008)	fMRI	12 (C)/ 12	Raven's Standard Progressive Matrices task	-Hypoactivation of VLPFC, right lateral prefrontal cortex, ACC, bilateral occipito-parietal cortices, bilateral temporal cortex, cerebellum and striatum
(Smith, Taylor et al. 2006)	fMRI	19 (C)/ 27	Go/No-Go Motor-Stroop Switch task	Go-No Go: -Hypoactivation in left rostral mesial frontal cortex Motor Stroop: -No significant differences Switch task: -Hypoactivation in bilateral prefrontal and temporal lobes and right parietal lobe
(Spinelli, Joel et al. 2011)	fMRI	13 (10 C, 3 I)/ 17	Go/No-Go (looking at brain activation patterns immediately preceding errors)	- Comparing pre-error with pre-correct trials: * Activation in the cerebellum, DLPFC and basal ganglia - Between-group comparison for the pre-error versus pre-correct contrast: * Hyperactivity in the cerebellum, DLPFC and VLPC - Results of region-of-interest analysis : * Precuneus/posterior cingulate cortex less active in ADHD children

(Suskauer, Simmonds et al. 2008)	fMRI	25 (17 C, 6 I, 2 HI)/ 25	Go/No-Go	-Intra-subject variability (ISV) positively related to pre-supplementary motor area (pre-SMA) activation in children with ADHD, whereas in healthy controls variability was inversely related to pre-SMA activation -Children with ADHD with less ISV showed greater prefrontal activation, whereas controls with more prefrontal activation demonstrated more ISV
(Tamm, Menon et al. 2004)	fMRI	10 (C)/ 12	Go/No-Go	<u>During response inhibition:</u> -Hypoactivation of ACC extending to SMA -Hyperactivation of left temporal gyrus
(Teicher, Anderson et al. 2000)	fMRI	11 (C)/ 6	Resting state on MPH vs placebo	<u>ADHD patients on placebo:</u> - Hyperactivity in putamen <u>ADHD patients on MPH:</u> - Attenuation of hyperactivity in putamen for more hyperactive ADHD subjects
(Tian, Jiang et al. 2006) **	fMRI	12 (10 I, 2 C)/ 12	Resting state	Increased DMN deactivation (increased resting state functional connectivity of DMN with dorsal ACC and within DMN itself)
(Tian, Jiang et al. 2008)	fMRI	12 (10 I, 2 C)/ 12	Resting state	Increased resting-state activities in basic sensory and sensory-related cortices
(Tomasi and Volkow 2011) **	fMRI	255 (148 HI, 5 I, 102 C)/ 304 (from a public magnetic resonance imaging database)	Resting state	-Increased connectivity within reward-motivation regions : * Ventral striatum and OFC -Decreased connectivity within regions from the DMN (precuneus) and dorsal attention networks (superior parietal cortex) and cerebellum -OFC (region involved in salience attribution) had higher connectivity with reward-motivation regions (striatum and ACC) and lower connectivity with superior parietal cortex(region involved in attention processing)
(Vaidya, Austin et al. 1998)	fMRI	10 (8 C, 2 I)/ 6	Go/No-Go with and without MPH	<u>-With MPH:</u> Frontal hyperactivation in patients and controls and striatal hyperactivation only in patients <u>-Without MPH:</u> Greater frontal activation on one task and reduced striatal activation on the other task
(Vaidya, Bunge et al. 2005)	fMRI	10 (C)/ 10	Modified Eriksen Flanker + Go-No Go	<u>Interference suppression:</u> -Hypoactivation of left inferior frontal gyrus (including insula and thalamus) <u>Successful Response inhibition:</u> -Hypoactivation of left inferior frontal and premotor area -Hyperactivation of right superior temporal gyrus
(Wang, Zhu et al. 2009)	fMRI	19 (types not specified but all I or C)/ 20	Resting state	-Decreased network nodal efficiency in multiple brain regions involving prefrontal, temporal and visual cortex regions

(Wong and Stevens 2012)	fMRI	18 (C) on and off stimulant medication (MPH or dextroamphetamine /amphetamine combination)	Sternberg working memory task	-Independent component analysis: identification of six frontoparietal networks with hemodynamic responses to encoding maintenance or retrieval phases of the Sternberg task On medication: three of these networks significantly increased activation - Functional connectivity analyses on medication: Led to recruitment of additional brain regions that were not engaged into the networks when participants were on placebo Strengthened connectivity of some frontoparietal regions Regional functional connectivity changes following medication in structures previously implicated as abnormal in ADHD, such as ACC, VLPFC cortex and precuneus
(Yang, Wu et al. 2011)	fMRI	17 (5 I, 12 C)/ 17	Resting state	Measure of amplitude of low frequency fluctuations (ALFF) in the BOLD signal: -Reduced ALFF in bilateral ACC, bilateral middle cingulate cortex and right middle frontal gyrus -Increased ALFF in the left superior frontal gyrus and sensorimotor cortex
(Zang, Jin et al. 2005)	fMRI	9 (6 I, 3 C)/ 9	Stroop	-Interference conditions: Hypoactivation in prefrontal cortex, cingulate cortex, basal ganglia, insula and cerebellum -Neutral conditions: *Hyperactivation in basal ganglia, insula and cerebellum *Hypoactivation in prefrontal cortex
(Zang, He et al. 2007) **	fMRI	13 (10 I, 3 C)/ 12	Resting state	Measure of amplitude of low frequency fluctuations (ALFF) in the BOLD signal: -Reduced ALFF in right inferior frontal cortex, bilateral cerebellum and vermis -Increased ALFF in the right ACC, left lateral cerebellum, left fusiform gyrus, right inferior temporal gyrus, left sensorimotor cortex and bilateral brain stem
(Zhu, Zang et al. 2008) **	fMRI	9 (types not specified)/ 11	Resting state	Fisher discriminative analysis on regional homogeneity measures of resting state brain activity: -Correct classification rate of 85% using leave-one-out cross validation, and a sensitivity and specificity of 78% and 91%, respectively -Highly discriminative brain regions were the prefrontal cortex, ACC and thalamus

ACC: anterior cingulate cortex; CPT: continuous performance task; DMN: default-mode network; DLPFC: Dorsolateral prefrontal cortex; fMRI: functional magnetic resonance imaging; IAPS: International Affective Picture System; IFC: inferior frontal cortex; MPFC: medial prefrontal cortex; MPH: methylphenidate; NIRS: near-infrared spectroscopy; OFC: orbitofrontal cortex; SMA: supplementary motor atea; VLPFC: ventrolateral prefrontal cortex; VMPFC: vetromedial prefrontal cortex.

Table 2.2. *Functional changes observed in ADHD studies with Adults*

Study	Neuroimaging technique	Sample number ADHD (by type: I inattentive, C combined, HI hyperactive-impulsive, NOS not otherwise specified)/ Controls	Task	Main findings
(Banich, Burgess et al. 2009)	fMRI	23 (C)/ 23	Colour-Word Stroop	-Hypoctivation in right DLPFC for sustained attentional control -Hyperactivation in right IFC for transient aspects of attentional control
(Brown, Biederman et al. 2011) **	fMRI	53 (17 C, 18 I, 1 HI; 17 remitted ADHD)/ 38	N-back task	-Task positive network: Hypoactivation of right DLPFC, SMA and middle cingulum -DMN: *Greater suppression of medial prefrontal cortex (ACC, OFC, superior medial frontal region) in DAT1 genotype *Relationship of task-related suppression of DMN to inattentive ADHD symptoms
(Bush, Frazier et al. 1999)	fMRI	8 (types not specified)/ 8	Counting Stroop	-Failure to activate the ACC -Compensatory activation of frontostriatal-insular network instead
(Bush, Spencer et al. 2008)	fMRI	21 (C) (Double blind randomized placebo-controlled study: 10 patients on MPH and 11 patients on placebo)	Multi Source Interference Task	Treatment with MPH associated with - Hyperactivity in ACC, right DLPFC and left and right superior parietal region - Greater hyperactivity in dorsal anterior midcingulate cortex for treatment responders than for nonresponders
(Carmona, Hoekzema et al. 2012)	fMRI	19 (C) / 19	Go-No Go Monetary incentive delay task	-No differences during response inhibition -Hypoactivation in bilateral ventral striatum during reward anticipation
(Castellanos, Margulies et al. 2008) **	fMRI	20 (C)/ 20	Resting state	Disrupted functional connectivity between ACC and regions of the DMN (mainly precuneus/posterior cingulate cortex regions and VMPFC)
(Cubillo, Halari et al. 2010)	fMRI	11(5 C, 6 HI)/ 14	Stop task	-Successful inhibition: Hypoactivation in right and left IFC, premotor cortex, ACC, SMA, right basal ganglia and right thalamus -Inhibition failure: Hypoactivation in right IFC and right striatum
			Cognitive Switch task (modified version of the Meiran Switch task)	-Hypoactivation in right and left IFC, insula, right and left striatum, and left inferior parietal lobe

(Cubillo, Halari et al. 2011)	fMRI	11 (5 C, 6 HI)/ 15	Simon task (interference inhibition)	-Hypoactivation in IFC (left OFC, left MPFC) and left ACC -Hypoactivation of left striatum
			Oddball task (perceptual attention allocation)	-Hypoactivation in left IFC and DLPFC
(Dibbets, Evers et al. 2009)	fMRI	16 (C)/ 13	Modified Go/No-Go with presentation of negative feedback	-<u>During response inhibition:</u> *Hyperactivation in inferior frontal gyrus and putamen -<u>During feedback-related processes:</u> *Hypoactivation in IFC/OFC, hippocampus/ nucleus accumbens and caudate nucleus *Hyperactivation in inferior frontal gyrus
(Dibbets, Evers et al. 2010)	fMRI	15 (C)/ 14	Task-switching paradigm	-<u>ADHD patients:</u> Hyperactivation of dorsal ACC, middle temporal gyrus, precuneus, lingual gyrus, precentral gyrus and insula -<u>Controls:</u> Hyperactivation of putamen, posterior cingulate gyrus, medial frontal gyrus, thalamus, OFC and postcentral gyrus
(Dillo, Goke et al. 2010)	fMRI	15 (5C, 7I, 3 HI)/ 15	Go/No-Go	-Hyperactivation in parietal regions
(Ehlis, Bahne et al. 2008)	NIRS	13 (C: correspondence with ICD-10 hyperkinetic disorder)/ 13	N-back task	-Hypoactivation of right and left IFC/VLPFC
(Epstein, Casey et al. 2007)	fMRI	9 (4 C, 5 I)/ 9	Go/No-Go	-Hypoactivation in bilateral IFC and left caudate -Hyperactivation in left parietal lobe and ACC
(Ernst, Kimes et al. 2003)	PET	10 (6 C, 4 I)/ 12	Gambling task	-Hypoactivation of left insula, left temporal lobe and left occipital cortex -Hyperactivation of right ACC, right temporal lobe and left parietal gyri
(Hale, Bookheimer et al. 2007)	fMRI	10 (7 I, 3 C)/ 10	Digit span	-Hypoactivation of bilateral superior parietal lobe, right inferior parietal lobe, left temporal lobe and left occipital cortex -Hyperactivation of right DLPFC, right IFC, right medial superior parietal lobule, right precuneus, left cingulate gyrus, left posterior temporal-occipital border and occipital cortex.
(Mulligan, Knopik et al. 2011)	fMRI	12 (C)/ 12	Go/No-Go	-Hypoactivation of right PFC and pre-SMA, left precentral gyrus, bilateral inferior parietal lobe
(O'Gorman, Mehta et al. 2008)	fMRI	9 (C)/ 11 on and off MPH	Resting state	-Hyperactivation in left caudate, lPFC, ACC, precuneus, middle frontal gyrus, postcentral gyrus, parahippocampal gyrus and supramarginal gyrus -Treatment with MPH attenuates hyperactivity in frontal and parietal regions and in caudate
(Plichta, Vasic et al. 2009)	fMRI	14 (C)/ 12	Temporal discounting task	-<u>Immediate rewards:</u> Hypoactivation of ventral striatum/nucleus accumbens and bilateral amygdala -<u>Delayed rewards:</u> Hyperactivation of dorsal caudate and bilateral amygdala

(Schweitzer, Lee et al. 2004)	PET	10 (C)/ 11	Paced Auditory Serial Addition Task (PASAT)	-Hypoactivation of left IFC and insula, ACC and left temporal and parietal lobes -Hyperactivation of MPFC, right midbrain and right caudate and cerebellar vermis
(Stoy, Schlagenhauf et al. 2011)	fMRI	23 (C)/ 12	Monetary Incentive Delay Task	During gain anticipation -Hypoactivity in bilateral inferior frontal gyrus During gain outcome -No differences between groups During loss anticipation -Hypoactivity in right middle frontal gyrus During loss outcome -Hypoactivity in insula and right precentral gyrus
(Strohle, Stoy et al. 2008)	fMRI	10 (4 I, 2 HI, 4 C)/ 10	Monetary incentive delay task	-During anticipation of gain: Hypoactivation in the left ventral striatum/ nucleus accumbens -In response to gain outcomes: Hyperactivation of the right OFC, right DLPFC, left IFC and right basal ganglia
(Uddin, Kelly et al. 2008) **	fMRI	20 (C)/ 20	Resting state	Reduced DMN network homogeneity (mainly altered precuneus connectivity)
(Valera, Faraone et al. 2005)	fMRI	20 (types not specified)/ 20	N-back	-Hypoactivation of left cerebellum (posterior lobe) and left inferior occipital gyrus
(Valera, Brown et al. 2010)	fMRI	44 (13 C, 17 I, 1 HI)/ 49	N-back	-Hypoactivation of bilateral MPFC and left ACC
(Valera, Spencer et al. 2010)	fMRI	21 (5 C, 12 I, 4 NOS)/ 19	Paced and unpaced finger tapping	-Hypoactivation in different regions associated with sensorimotor timing, including prefrontal and precentral gyri, basal ganglia, cerebellum, inferior parietal lobe, superior temporal gyri and insula
(Wolf, Plichta et al. 2009)	fMRI	12 (9 C, 2 I, 2 HI)/ 12	Delay task	-Hypoactivation in left VLPFC/IFC, right cerebellum, right occipital regions, right MPFC and right insula
(Zametkin, Nordahl et al. 1990)	PET	25 (C; close correspondence between DSM-III ADD/H type and the DSM-IV combined type)/ 50	CPT	-Hypoactivation of ACC, premotor and somatosensory areas

ACC: anterior cingulate cortex; CPT: continuous performance task; DMN: default-mode network; DLPFC: Dorsolateral prefrontal cortex; fMRI: functional magnetic resonance imaging; IAPS: International Affective Picture System; IFC: inferior frontal cortex; MPFC: medial prefrontal cortex; MPH: methylphenidate; NIRS: near-infrared spectroscopy; OFC: orbitofrontal cortex; SMA: supplementary motor area; VLPFC: ventrolateral prefrontal cortex; VMPFC: vetromedial prefrontal cortex.

Table 2.3. *Results of hand search of original Functional Neuroimaging articles performed from february 2012 to january 2015.*

Studies with Children and Adolescents		
Task Activation studies	**Resting State Connectivity studies**	**Task Dependent Connectivity studies**
(Chantiluke, Christakou et al. 2014)	(Sato, Hoexter et al. 2012)	(Wong and Stevens 2012)
(Cubillo, Smith et al. 2014)	(Sun, Cao et al. 2012)	(Bedard, Newcorn et al. 2014)
(Cubillo, Smith et al. 2014)	(Fair, Nigg et al. 2012)	
(Fan, Gau et al. 2014)	(An, Cao et al. 2013)	
(Hart, Chantiluke et al. 2014)	(Alonso Bde, Hidalgo Tobon et al. 2014)	
(Hart, Marquand et al. 2014)	(Elton, Alcauter et al. 2014)	
(Orinstein and Stevens 2014)	(Hulvershorn, Mennes et al. 2014)	
(Rubia, Alegria et al. 2014)	(Li, He et al. 2014)	
	(Ou, Lian et al. 2014)	
	(Posner, Siciliano et al. 2014)	
	(Ray, Miller et al. 2014)	
	(Sripada, Kessler et al. 2014)	
	(Kessler, Angstadt et al. 2014)	
Studies with Adults		
Task Activation studies	**Resting State Connectivity studies**	**Task Dependent Connectivity studies**
(Congdon, Altshuler et al. 2014)	(McCarthy, Skokauskas et al. 2013)	
(Morein-Zamir, Dodds et al. 2014)	(Sokunbi, Fung et al. 2013)	
	(Mattfeld, Gabrieli et al. 2014)	
	(Hoekzema, Carmona et al. 2014)	

d. Functional Neuroimaging - Limitations of the studies -

Limitations of the functional neuroimaging studies revised that may lead to potential confounding factors and bias are:

- 47 of the studies included in our first systematic review of the literature to January 2012, studied child and adolescents, while only 27 studies focused on adult population. The result of the hand search of articles performed from february 2012 to january 2015 also reveales a disparity between 23 studies with children and adolescents and 6 adult studies (*see* **Table 2.3.**). As there is a considerable variability between children and adult studies, more adult studies are needed to better characterize adult ADHD neural functioning.
- Sample sizes were small for the majority of the studies revised (N ≤ 20 in 89% of the studies), thus implicating insufficient statistical power and increasing the risk of type II errors.
- Matching procedures were often inappropriate (not considering IQ i.e.).
- Different ways of establishing ADHD diagnosis were used between studies with very few using structured interviews and a number of them relying on retrospective reports of childhood symptoms involving unreliable memory issues.
- No distiction was made between ADHD subtypes in some of the studies, with other studies including all of the subtypes (predominantly inattentive, predominantly hyperactive-impulsive and combined). This clinical heterogeneity may account for inconsistent findings due to physiological group differences.

- The assessment of comorbid conditions was not uniform across the revised studies with some of the studies not even considering or reporting the exclusion of comorbid conditions. Comorbidity assessment and adequate adressing of its effects is very important in adult ADHD, provided that up to 50% of cases present a co-ocurring anxiety or depressive disorder (Kessler, Adler et al. 2006) (McIntosh, Kutcher et al. 2009), besides other frequent comorbid disorders such as substance use disorders and personality disorders (Asherson, Chen et al. 2007).
- In terms of medication status, presence and length of wash-out periods prior and during the acquisition of the scans weren't clearly stated in all the studies, with predominance of wash-out periods of only 48 hours, which could explain to some extent group differences due to rebound effects as a result of short discontinuation periods of stimulant treatment.

2. GENERAL OBJECTIVES of the THESIS

The aim was to investigate brain structural and functional changes of a large sample of ADHD adults and to explore to what extent these changes could be corrected by long-term exposure to methylphenidate (MPH).

To this end a group of adults with a positive diagnosis of ADHD-Combined subtype (as a means to select a more neurophysiologically homogeneous sample) and a matched group of healthy volunteers were recruited. Anatomical MRI images were carried out to explore regional brain differences in grey matter using voxel-based morphometry (VBM). fMRI images from participants were obtained to examine brain activations and deactivations during performance of a well-validated working memory task (N-back task). And resting state fMRI was carried out to look at the levels of brain activity at rest quantified by the Amplitude of Low Frequency Fluctuations (ALFF) and to evaluate the general levels of functional connectivity measured by the Global Brain Connectivity maps (GBC).

To investigate the potential corrective effect of long-term exposure to MPH, our adult ADHD group was subdivided in a group of patients who had been treated with this drug in the long term and a group of patients naïve to stimulant treatment.

3. SPECIFIC OBJECTIVES of the THESIS

3.1. STUDY 1: Structural Neuroimaging

In order to shed some light on the volumetric neurobiological correlates and potential neuro-structural effects of MPH in adult ADHD, the present study aimed to:

1) evaluate changes in whole-brain analysis in a large sample of adults with ADHD with the combined presentation and no other psychiatric comorbid conditions, compared with a healthy comparison group (HCG),

2) assess the association between ADHD symptom severity and volumetric abnormalities,

3) and investigate the potential volume corrective effect of long-term exposure to methylphenidate (MPH).

3.2. STUDY 2: Functional Neuroimaging

3.2.1. Sequence during Task Performance of a Working Memory paradigm (N-back task)

In order to address potential confounders and to shed light on adult ADHD neural activity literature, the present study aimed to:

1) investigate brain activity (activations and deactivations) in a larger sample than in most previous studies, of ADHD-Combined presentation adults (either naïve to pharmacological treatment or chronically, but exclusively, treated with MPH) during performance of the N-back working memory task (that has shown the ability to activate the dorso-lateral prefrontal cortex (DLPFC) along with other brain areas associated with working memory and executive function in general), compared to a sample of healthy comparison participants,

2) assess the association between ADHD symptom severity and brain functional alterations,

3) and investigate the potential attenuation effect of functional abnormalities of long-term exposure to methylphenidate (MPH).

3.2.2. Sequence during Resting State

To fill the gap in adult literature looking at functional connectivity in ADHD, the aim was to:

1) investigate the presence of abnormalities in the levels of intrinsic activity in the different parts of the brain of the ADHD participants by means of ALFF images,

2) evaluate potential ADHD related alterations in brain connectivity by means of maps of Global Brain Connectivity (GBC). Individual GBC maps summarize the connectivity levels at each location of the brain by portraying the average correlation of each grey matter voxel with the remaining voxels of the brain (Cole, Pathak et al. 2010) allowing

the quantification of overall connectivity in a single image. Once areas of abnormal GBC are located, a more standard seed based connectivity analysis may be applied to identify the specific connections that are affected;

3) and study the potential corrective effect in both ALFF and GBC alterations of long-term exposure to methylphenidate (MPH)

4. HYPOTHESIS

Based on previous research, the hypotheses of the thesis are:

4.1. STUDY 1: Structural Neuroimaging

1) Reduced volume in frontal, striatal and cerebellar brain areas will be found in adult ADHD participants when compared with healthy controls.

2) The magnitude of these differences in volume will be associated with ADHD symptoms intensity.

3) Chronic treatment with MPH will have a normalising effect on the above structural differences.

4.2. STUDY 2: Functional Neuroimaging

During the performance of the working memory paradigm:

1) ADHD participants will show reduced activation in prefrontal (mainly dorso- and ventro-lateral prefrontal cortex) and in parietal cortices, compared to healthy participants.

2) Failure of DMN regions de-activation is also predicted to be seen.

3) In line with an expected 'normalization' effect due to long-term treatment with MPH, ADHD participants chronically treated with MPH will sit in between healthy participants and ADHD medication-naïve participants with regards of functional differences in brain activity.

During resting state:

1) ADHD participants will show abnormal levels of amplitude of fluctuations (ALFF) and of global connectivity (GBC) in DMN regions, specially in the precuneus/PCC, medial PFC and ACC and lateral prefrontal cortex.

2) ADHD participants under long-term stimulant treatment with MPH will show a tendency to normalization of these pathological patterns in comparison to medication-naïve participants.

5. METHODS

5.1. Subjects

Forty-six right-handed adult ADHD-Combined type (30 men and 16 women) participiants were recruited from the Hospital Universitari Vall d'Hebron and from private practice.

Forty-six healthy controls were recruited from non-medical staff working in the hospital, their relatives and acquaintances, plus independent sources in the community. They were selected to be age, sex and IQ (current and premorbid) matched to the patients.

ADHD clinical diagnosis was obtained from a full clinical interview by an experienced psychiatrist and based on the assessment of ADHD on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revised (DSM-IV-TR) (APA 2000). Additional assessment instruments applied to confirm the diagnosis were the Conners' Adult ADHD Diagnostic Interview for DSM-IV (CAADID) (Epstein, Johnson et al. 2001) (Ramos-Quiroga, Bosch et al. 2012), the Wender Utah Rating Scale (WURS) (Ward, Wender et al. 1993), the ADHD Rating Scale (DuPaul, Power et al. 1998) and the Conners Adult ADHD Rating Scale (CAARS) (Conners, Erhardt et al. 1999). Also, all subjects were evaluated to exclude comorbidity with other psychiatric or personality disorders applying the Structured Clinical Interview for Axis I (SCID-I) (First, Spitzer et al. 2002) and Axis II (SCID-II) (First, Gibbon et al. 1997).

The healthy comparison samples consisted of right-handed healthy individuals with no personal or family (1st degree) history of mental disorders. ADHD diagnosis was ruled out in the comparison group by means of a checklist including DSM-IV criteria for ADHD and all subjects in the group were also assessed to exclude other psychiatric or personality disorders administering the Structured Clinical Interview for Axis I (SCID-I) (First, Spitzer et al. 2002) and Axis II (SCID-II) (First, Gibbon et al. 1997).

On the full sample, premorbid IQ was estimated using the Word Accentuation Test (Test de Acentuación de Palabras, TAP (Del Ser, Gonzalez-Montalvo et al. 1997)); a test requiring pronunciation of Spanish words with removed accents. Scores can be converted into IQ estimates (Gomar, Ortiz-Gil et al. 2011). Current IQ was also evaluated with two subtests of the Wechsler Adult Intelligence Scale III (Wechsler 1997): vocabulary and block design.

Other exclusion criteria that applied to the entire sample were: (a) age younger than 18 or older than 65 years, (b) history of brain trauma or neurological disease and (c) drug or alcohol use meeting diagnostic criteria for abuse/dependence.

Two ADHD participants were excluded from the analyses in STUDY 1 - Structural sequence; five were excluded from STUDY 2 - Functional sequence during Task (N-back); and ten from STUDY 2 - Functional sequence during Resting State, respectively, due to excessive movement in the fMRI images (see fMRI data acquisition section). Therefore, the final sample included 44 ADHD participants (15 medication-naïve and 29 stimulant-treated) and 44 matched controls for STUDY 1 - Structural sequence; 41 ADHD participants (15 medication-naïve, 26 stimulant-treated) and 41 matched controls for

STUDY 2 - Functional sequence during Task; and 36 ADHD participants (13 medication-naïve, 23 stimulant-treated) and 36 matched controls for STUDY 2 - Functional sequence during Resting State (demographic data for the samples is shown in **Table 3.**).

Table 3. *Demographic Data for ADHD participants and Controls.*

STUDY 1 - Structural sequence	ADHD N = 44 Mean (SD)	Controls N = 44 Mean (SD)
Age (years)	31.61 (11.38)	32.57 (10.63)
Sex (male/female)	29/15	29/15
TAP scores (premorbid IQ)	22.42 (4.49)	23.10 (3.88)
Current IQ (WAIS-III)	105.00 (7.53)	105.97 (11.38)
STUDY 2 - Functional sequence during Task	**ADHD N = 41 Mean (SD)**	**Controls N = 41 Mean (SD)**
Age (years)	31.00 (10.85)	31.73 (9.59)
Sex (male/female)	28/13	28/13
TAP scores (premorbid IQ)	22.40 (4.54)	22.97 (3.92)
Current IQ (WAIS-III)	104.87 (7.48)	106.06 (11.53)
STUDY 2 - Functional sequence during Resting State	**ADHD N = 36 Mean (SD)**	**Controls N = 36 Mean (SD)**
Age (years)	31.86 (10.73)	32.75 (10.07)
Sex (male/female)	23/13	23/13
TAP scores (premorbid IQ)	23.06 (4.37)	23.56 (4.19)
Current IQ (WAIS-III)	106.19 (7.23)	105.25 (12.53)

ADHD stimulant-treated participants had a history of pharmacological treatment only with MPH and were medicated with the following relative daily doses and treatment duration (**Table 4**):

Table 4. *MPH relative daily doses and treatment duration*

	Relative daily doses (mg/day) Mean ± SD	Treatment duration (months) Mean ± SD
STUDY 1 Structural	42.24 ± 16.17	25.20 ± 24.41
STUDY 2 Functional during Task	41.15 ± 16.98	23.55 ± 22.63
STUDY 2 Functional during Resting State	42.31 ± 15.73	27.91 ± 25.56

The methylphenidate-treated ADHD patients were discontinued from medication at least 4 days prior to the MRI hence avoiding short-term withdrawal effects. ADHD medication-naïve participants had never received pharmachological treatment for their psychiatric condition.

The study was approved by the Ethics Committee of Hospital Universitari Vall d'Hebron and FIDMAG Research Foundation Germanes Hospitalàries and all participants gave written informed consent.

5.2. Procedure

During a single fMRI session per participant the following sequences were acquired:

- High-resolution T1 sequence for volumetric analysis (VBM).

- Functional resting state sequence taken with open eyes.

- Functional during task sequence taken while participants performed a blocked designed verbal N-back task (Gevins and Cutillo 1993) with two-memory load conditions (i.e. 1 and 2-back).

5.2.1. STUDY 1 - Structural Neuroimaging -

a. Structural magnetic resonance imaging (MRI) data acquisition

All participants were scanned in the same 1.5-T GE Signa scanner (General Electric Medical Systems, Milwaukee, WI, USA) at Sant Joan de Déu Hospital in Barcelona (Spain). The high-resolution structural T1 MRI data were obtained with the following parameters: 180 axial slices, 1 mm slice thickness with no gap, 512×512 matrix size, 0.5×0.5×1mm3 voxel resolution, 4 ms echo time (TE), 2000 ms repetition time (TR), 15° flip angle.

b. Structural MRI image processing

Raw structural images had the non-brain matter removed with the 'brain extraction tool' (BET) (Smith 2002) and were segmented into gray matter and other tissues with FSL (Zhang, Brady et al. 2001).

Normalization of the gray matter segments to a common template was conducted with the 'advanced normalization tools' (ANTS) high-resolution diffeomorphic symmetric normalization (SyN) based on directly manipulated free form deformation (Avants, Epstein et al. 2008) (Avants, Yushkevich et al. 2010), which has shown to substantially improve the accuracy of other methods (Klein, Andersson et al. 2009). Normalization steps were as follows: a) affine registration of the native-space GM images to a Montreal Neurological Institute (MNI) GM template (voxel-size: 1.5x1.5x1.5mm3); b) creation of a template using the registered GM images; c) non-linear registration of the native-space gray matter images to the template; and d) four extra iterations of the steps b and c.

Modulated and non-modulated images were Gaussian-smoothed with a σ=4mm (FWHM=9.4mm) kernel, which has shown to yield increased sensitivity as compared to narrower kernels (Radua, Canales-Rodriguez et al. 2014). Note that the non-linear registration is able to capture gross differences such as brain shape abnormalities, but not more subtle differences such as fine cortical thinning. Thus, unmodulated images may better detect mesoscopic (i.e. between microscopic and macroscopic) differences not captured by the non-linear registration, as in that case the modulation would only introduce macroscopic noise, ultimately reducing the statistical power (Radua, Canales-Rodriguez et

al. 2014). Conversely, modulated images may better detect macroscopic differences captured by the non-linear registration, as a great part of these differences might be removed during the non-linear registration but re-introduced with the modulation (Ashburner and Friston 2001).

c. Structural MRI statistics

Voxel-based anatomical differences between patients and controls were fitted with a general linear model with sex, age and cumulated stimulant dose as regressors. The 'threshold-free cluster enhancement' (TFCE) was used due to its increased sensitivity as compared to voxel- or cluster-based statistics (Smith and Nichols 2009) (Salimi-Khorshidi, Smith et al. 2011) (Radua, Canales-Rodriguez et al. 2014). Statistical significance was assessed with the permutation test included in FSL.

Maps were thresholded twice, once using a FWE corrected $p < 0.05$ and once using an uncorrected $p<0.001$ (in both cases excluding clusters with less than 10 voxels), with the understanding that the former minimized false positive results whilst the latter minimized false negative results (Durnez, Moerkerke et al. 2014).

GM volume within clusters of statistically significant difference between patients and controls was extracted for further analysis within the patients' sample (note that these analyses did not include the patient-control comparison and thus were not circular). Specifically, we correlated these volumes with the cumulated stimulant dose, the ADHD Rating Scale scores and the inattentive, hyperactive-impulsive and ADHD total subscales of the CAARS.

5.2.2. STUDY 2 - Functional Neuroimaging -

For task sequence, the participants performed a sequential-letter version of the N-back task (Gevins and Cutillo 1993). Two levels of memory load (1-back and 2-back) were presented in a blocked design manner. Each block consisted of 24 letters that were shown every 2 s (1 s on, 1 s off) and all blocks contained five repetitions (1-back and 2-back depending on the block) located randomly within the blocks. Individuals had to indicate repetitions by pressing a button. Four 1-back and four 2-back blocks were presented in an interleaved way, and between them a baseline stimulus (an asterisk flashing with the same frequency as the letters) was presented for 16 s. To identify which task had to be performed, characters were shown in green in 1-back blocks and in red in the 2-back blocks. All participants first went through a training session outside the scanner. This task has already been effectively used to show the neural correlates of cognitive deficiencies in several disorders (Madre, Pomarol-Clotet et al. 2013).

The behavioural measure used was the signal detection theory index of sensitivity, d‘ (Green and Swets 1966/1974). Higher values of d’ indicate better ability to discriminate between targets and distractors. If subjects showed negative d’ values in either or both of the 1-back and 2-back versions of the task, which suggests that they were not performing it, they were not included in the study.

For resting state sequence, participants received no other special instructions, except to try to remain still with their eyes open to avoid falling asleep and to try to remain quiet and as relaxed as possible.

a. Functional magnetic resonance imaging (fMRI) data acquisition

In each individual scanning session during task sequence 266 volumes were acquired from a 1.5-T GE Signa scanner. A gradient echo echo-planar imaging (EPI) sequence depicting the blood oxygenation level-dependent (BOLD) contrast was used. Each volume contained 16 axial planes acquired by descending order with the following parameters: TR=2000 ms, TE=20 ms, FOV=20, flip angle=70°, section thickness=7 mm, section skip=0.7 mm, in-plane resolution=3×3 mm. The first 10 volumes were discarded to avoid T1 saturation effects.

Resting state fMRI data was obtained using a gradient echo EPI sequence depicting the BOLD contrast. Each volume contained 16 axial planes acquired with the following parameters: TR = 2000 ms, TE = 20 ms, flip angle = 70°, section thickness = 7 mm, section skip = 0.7 mm, in-plane resolution = 3.125 x 3.125 mm. The first 10 of a total of 266 volumes acquired were discarded to avoid T1 saturation effects.

b. Functional MRI image processing

fMRI image analyses during task sequence were performed with FEAT (fMRI Expert Analysis Tool) Version 5.98, included in FSL (FMRIB's Software Library) (Smith, Jenkinson et al. 2004). At a first level, images were corrected for movement using MCFLIRT (Jenkinson, Bannister et al. 2002), brain-extracted using BET (Smith 2002), spatial smoothed using a Gaussian kernel of FWHM 5mm, normalized to the grand-mean intensity and filtered with a high-pass temporal Gaussian-weighted least-squares straight line fitting (sigma=65.0s). To minimize unwanted movement-related effects, individuals with an estimated maximum absolute movement >3.0 mm or an average movement >0.3 mm were excluded from the study.

General linear models (GLMs) including the 1- and 2-back blocks, their temporal derivatives, and the six motion parameters were fitted using FILM with local autocorrelation correction (Woolrich, Ripley et al. 2001) to generate individual activation maps for the 1-back vs. baseline and 2-back vs baseline contrasts. Individual statistical images were then co-registered to a common stereotactic space (Montreal Neurological Institute template) using FLIRT (Jenkinson and Smith 2001) (Jenkinson, Bannister et al. 2002).

For processing of individual resting state fMRI images, prior to the calculation of global brain connectivity (GBC) and amplitude of low frequency fluctuations (ALFF) images, a common preprocessing pipeline based on FSL functions (Smith, Jenkinson et al. 2004)

and inhouse C programs, was applied to the fMRI volumes. This included sequentially: 1) extraction of non-brain signal (FSL BET), 2) volume coregistration (FSL MCFLIRT), 3) checking of movement levels (allowed thresholds of maximum movement > 3.0 mm and a mean movement > 0.3 mm), 4) minimization of movement artifacts by regressing independent components with clear edge effects (FSL MELODIC), 5) removal of linear and quadratic trends in time series, 6) normalization to MNI template (FSL FLIRT), 7) spatial filtering with Gaussian kernel (σ = 3 mm) and finally 8) regression of spurious trends characterized by the signal from a region of interest (ROI) in the lateral ventricles and six spherical ROIs located in white matter locations.

Resting state images were used to calculate both GBC maps and the images of ALFF. Prior to their calculation, a common preprocessing pipeline was applied to them. In the GBC calculations, following Cole et al. (Cole, Pathak et al. 2010) the correlation between each gray matter voxel and the remaining gray matter voxels was calculated, assigning the mean (of the absolute value) of these correlations to that voxel. Such quantity is an indicator of the average levels of functional connectivity of the voxel with the rest of the brain. To lower the computational burden of these calculations, normalized images were resampled to a 4 x 4 x 4 mm3 voxel size. Before calculating correlations time series were filtered to remove patterns outside the 0.01 – 0.1 Hz interval. A second spatial filter (σ = 7 mm) was applied to the 4 x 4 x 4 mm3 resolution GBC images, before group comparisons. For the ALFF images, which relate to the levels of spontaneous brain activity occurring at each voxel, the original resolution of the normalization template was kept (2 x 2 x 2 mm3). Periodograms (estimates of power spectra) were obtained for each voxel using the function spec.pgram implemented in the R statistical package

(R_Development_Core_Team 2011) and averages of these periodograms in the 0.01 – 0.1 Hz interval were given as outputs. Finally, a second spatial Gaussian filter (σ = 3 mm) was applied to these ALFF images.

c. Functional MRI statistics

Group comparisons of the BOLD response to 1- and 2-back between ADHD participants and the healthy comparison group during task performance were performed within FLAME (FMRIB's Local Analysis of Mixed Effects) stage 1 (Beckmann, Jenkinson et al. 2003) (Woolrich, Behrens et al. 2004). Z (Gaussianised T) statistic images were thresholded using clusters determined by $Z>2.3$ and a cluster parametric significance threshold of $p<0.05$, corrected for multiple comparisons (Worsley 2001).

In a first analysis we compared all ADHD participants (including both medication-naïve and stimulant-treated) and the healthy comparison group. Also, to explore the possible influence of long-term use of MPH we performed additional separate analyses for the ADHD treated (n = 26) and never-treated patients (n = 15).

For ADHD participants only, Pearson correlations were performed to examine the relationship between BOLD response to 1- and 2-back and the ADHD Rating Scale scores and inattentive, hyperactive-impulsive and total ADHD subscales of the CAARS.

For group comparisons during resting state, for the two variables of interest (GBC and ALFF) images of ADHD participants were compared with images of healthy comparison

subjects by means of nonparametric permutation tests. Specifically, the “randomise” FMRIB Software Library function (Smith, Jenkinson et al. 2004) using the threshold-free cluster enhancement method was used. To reduce the intrinsic levels of variability and the residual movement effects in the GBC and ALFF images, the average amount of movement and the average value of each variable were considered as covariates in the models. A threshold of $p < 0.05$ corrected for multiple comparisons was applied in all statistical tests, and reported p values were always corrected.

In a first analysis we compared all ADHD participants (including both medication-naïve and stimulant-treated) and the healthy comparison group. Secondly, to explore the possible influence of long-term use of MPH we performed additional separate analyses for the ADHD treated (n = 23) and never-treated patients (n = 13).

6. RESULTS

6.1. STUDY 1 - Structural Neuroimaging -

a. Demographic and clinical data

As **Table 3** shows (p. 79), ADHD participants were not significantly different than the healthy comparison group on the matching variables of age, sex, premorbid IQ and IQ scores. Clinical data for the ADHD sample are presented in **Table 5**.

Table 5. *Clinical data for ADHD participants (N = 44)*

	Mean (SD)
WURS	51.95 (11.09)
ADHD Rating Scale	32.15 (9.12)
CAARS	
Inattention	22.29 (7.68)
Hyperactivity	20.80 (8.45)
Impulsivity	18.56 (7.84)
Problems with self-concept	9.51 (4.32)
DSM-IV inattentive symptoms	17.49 (4.88)
DSM-IV hyperactivity-impulsivity symptoms	15.80 (6.64)
DSM-IV total ADHD symptoms	33.29 (9.85)
ADHD Index	21.61 (6.08)

b. Modulated analysis

Compared to the healthy comparison group, individuals with ADHD showed three clusters of macroscopic GM reduction. A cluster was situated in the right supplementary motor area (SMA), extending to superior frontal lobe (cluster size: 889 voxels; $p<0.001$; MNI x=8 y=24 z=64). A second cluster was located in the subgenual ACC (cluster size: 53 voxels; $p<0.001$; MNI x=6 y=18 z=-14) and the last cluster was found in the right middle frontal lobe (corresponding to DLPFC) (cluster size: 16 voxels; $p<0.001$; MNI x=48 y=18 z=44). There were no cortical or subcortical regions where ADHD patients showed more GM volume macroscopically than controls (see **Table 6** and **Fig. 1**).

c. Unmodulated analysis

ADHD patients did not show any brain region with less GM relative to the healthy comparison group at the mesoscopic level. Conversely, ADHD participants showed a cluster of mesoscopic GM increase relative to the healthy comparison group situated in the basal ganglia, specifically in the left caudate and putamen nuclei (cluster size: 15 voxels; $p=0.001$; MNI x=-8 y=12 z=-2) (see **Table 6** and **Fig. 1**).

d. Correlation analysis

The cluster analysis showed a positive correlation between cumulated stimulant dose and the clusters of macroscopic GM reduction in right SMA (extending to superior frontal) and

in right DLPFC (see **Table 6**). Specifically, a higher cumulated dose was associated to a greater (i.e. more normative) volume of these areas. There were no other statistical significant correlations, included correlations between the volume of these clusters and clinical measures.

Table 6. *Gray matter volumetric differences between patients with ADHD and healthy controls.*

	Peak		Cluster size	Effects of cumulated stimulant dose
	MNI	P (a)		
Macroscopic changes (modulated data)				
Increases of volume (ADHD > Controls)				
(none)				
Decreases of volume (ADHD < Controls)				
Right SMA, extending to superior frontal	8,24,64	<0.001 (b)	889	r = 0.451 (p = 0.002)
Subgenual ACC	6,18,-14	<0.001	53	n.s.
Right dorsolateral prefrontal cortex	48,18,44	<0.001	16	r = 0.407 (p = 0.006)
Mesoscopic changes (unmodulated data)				
Increases of volume (ADHD > Controls)				
Left caudate and putamen	-8,12,-2	0.001	15	n.s.
Decreases of volume (ADHD < Controls)				
(none)				

Analyses covaried by age, sex and cumulated stimulant dose.
(a) p < 0.001 uncorrected for multiple comparisons, 10 voxels extent threshold.
(b) This result was also significant (p < 0.05) after correction for multiple comparisons.

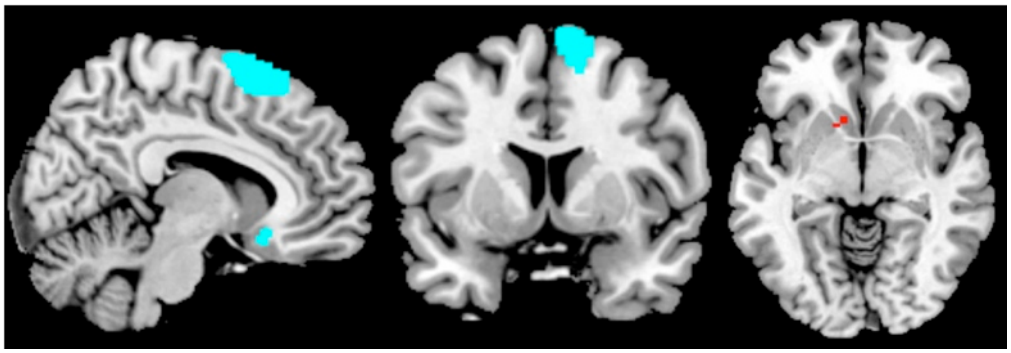

Fig.1. *Volumetric differences in patients with ADHD relative to the healthy comparison group*. Areas in blue indicate a significant grey matter volume reduction in patients relative to controls; areas in red indicate a significant grey matter density increase in ADHD compared to controls.

6.2. STUDY 2 - Functional Neuroimaging -

a. Demographic and clinical data

As **Table 3** shows (p. 79), ADHD participants weren't significantly different from the healthy comparison group on the matching variables of age, sex, premorbid IQ and IQ.

By subgroups of patients, both stimulant-treated and non-treated patients obtained similar scores in the clinical variables and presented no significant differences in sex, age and IQ between them (see **Table 7**).

Table 7. *Demographic and clinical data for ADHD medicated and ADHD non medicated participants.*

	Non-med ADHD N= 15 Mean (SD)	Med ADHD N= 26 Mean (SD)
Age (years)	32.19 (11.07)	30.24 (10.86)
Sex (male/female)	12/5	16/8
Current IQ (WAIS-III)	102.88 (5.93)	106.32 (8.26)
WURS	51.69 (9.71)	49.18 (9.89)
ADHD Rating Scale	31.63 (6.60)	31.24 (10.47)
CAARS		
Inattention	22.64 (4.92)	22.68 (8.50)
Hyperactivity	20.71 (8.40)	21.82 (7.58)
Impulsivity	17.50 (6.91)	20.00 (7.85)
Problems with self-concept	10.86 (3.90)	8.86 (4.46)
DSM-IV inattentive symptoms	19.00 (4.00)	16.50 (4.84)
DSM-IV hyperactivity-impulsivity symptoms	14.26 (6.54)	17.55 (5.66)
DSM-IV total ADHD symptoms	33.29 (8.52)	34.05 (9.18)
ADHD Index	22.29 (5.15)	22.45 (5.39)

b. Behavioural performance

There were no significant differences between the healthy comparison group and ADHD participants on either the 1-back or the 2-back versions of the task (d' 1-back: 4.36 ± 0.59 vs 4.43 ± 0.68, t=-0.44;p=0.66; d' 2-back: 3.44 ± 1.07 vs 3.18 ± 0.71; t=1.31; p=0.19).

c. fMRI comparisons

c.1. Sequence during Task Performance

Overall, the task produced activation within the expected brain network. Both healthy comparison group and ADHD participants showed similar patterns of positive activation during the 1-back and 2-back conditions in the frontal, parietal and temporal cortices (see **Fig. 2**). These areas show a substantial overlap with the 'working memory network' identified in a meta-analysis of fMRI studies in normal subjects (Owen, McMillan et al. 2005). Patterns of de-activation (areas where the task led to a decrease in the BOLD response) were also similar in ADHD participants and healthy comparison subjects at the 1-back level, whilst a general pattern of less de-activation was seen in the ADHD participants anteriorly, in the medial frontal cortex (orbitofrontal/ventromedial frontal cortex), in the 2-back vs. baseline contrast (see **Fig. 3**).

Average (within-group) task-related activations and deactivations for the entire sample are shown in **Table 8** (1-back vs. baseline contrast) and **Table 9** (2-back vs. baseline contrast).

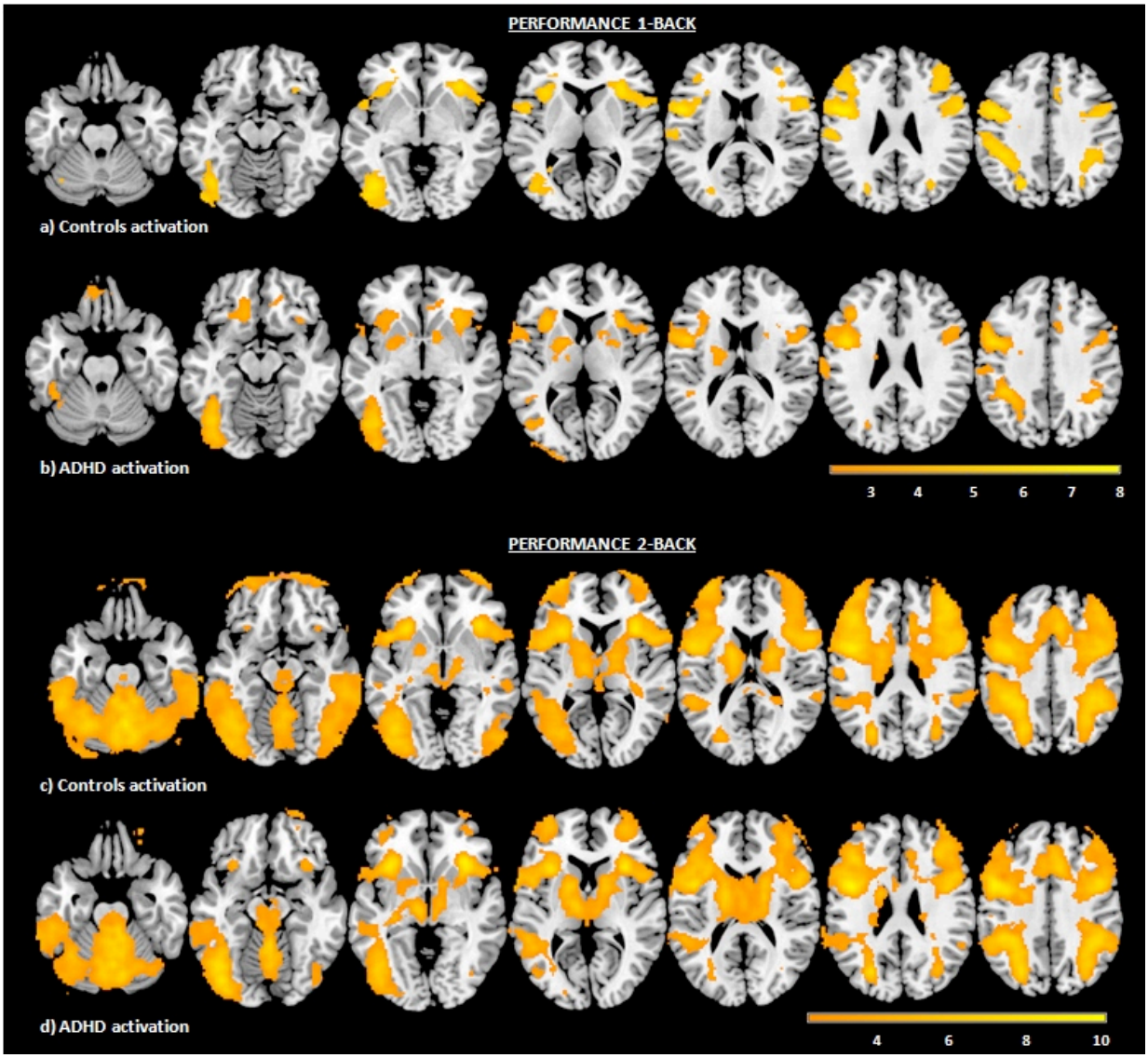

Fig. 2. *Average of activation of the groups during the performance of the N-back task*. Images a and b show the activation patterns for the healthy comparison and ADHD groups during the performance of the 1-back respectively. Images c and d show the activation patterns for both groups during the performance of the 2-back. Colour bars indicate z scores from the group-level analysis. The right side of each image represents the left side of the brain.

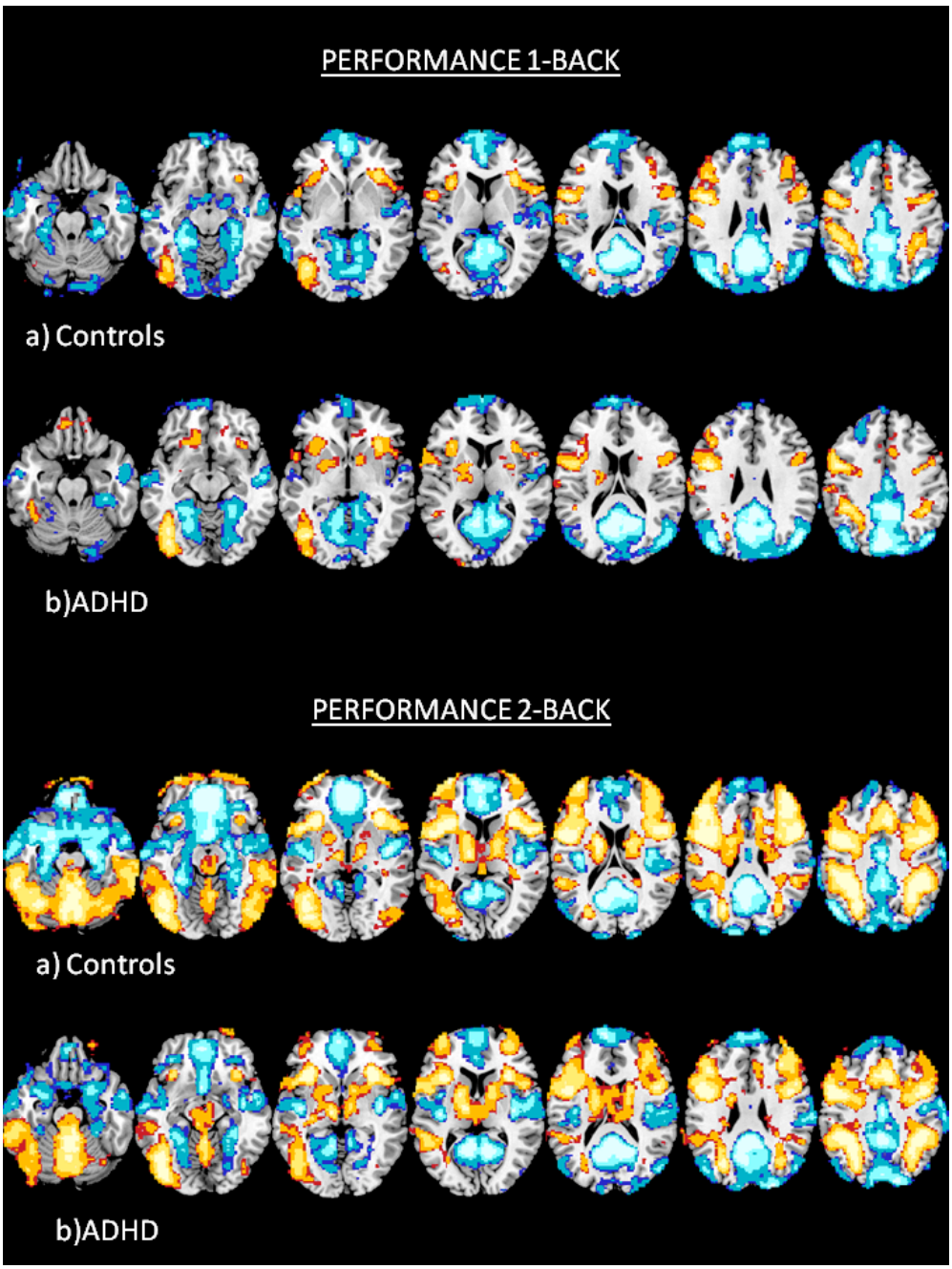

Fig. 3. *Average of activation/deactivation of the groups during the performance of the N-back task*. Brain regions showing a significant effect in the 1-back vs. baseline and in the 2-back vs. baseline contrast in controls (a) and in ADHD participants (b). Yellow indicates a positive association (activation) with the task. Blue indicates areas where the task led to a decrease in the BOLD response (de-activation). The right side of each image represents the left side of the brain.

Table 8. *Clusters of significant activation/de-activation in the ADHD participants and healthy comparison subjects in the 1-back vs. baseline contrast*

	Local Peaks			Cluster size (voxels)	Brodmann Areas
	MNI (x,y,z)	Z value	P value		
Mean Activations					
ADHD participants					
SMA, L DLPFC, L middle temporal, L superior parietal, mid cingulate, L insula	-4,6,54	7.48	<0.0001	13526	6,7,21,32,44,47
R DLPFC, R precentral gyrus	36,2,64	5.26	<0.0001	3281	6
L middle occipital, L inferior occipital, L inferior temporal, L fusiform gyrus	-42,-72,0	6.12	<0.0001	2371	19,37
R inferior and R superior parietal, R angular gyrus	40,-46,42	4.75	<0.0001	1816	7,40
Controls					
SMA, DLPFC, precentral gyrus	-46,2,32	6.74	<0.0001	11537	6,32
L inferior and L superior parietal, L inferior and L superior occipital	-42,-72,-2	6.08	<0.0001	5437	7,19,40
R inferior and R superior parietal, R angular gyrus, R middle temporal	48,18,44	5.28	0.0002	2086	7,37,40
Mean Deactivations					
ADHD participants					
precuneus, cuneus, mid cingulum, calcarine	4,-46,40	8.33	<0.0001	27118	17,23
superior frontal medial	-8,70,14	4.63	<0.0001	3291	10
L middle occipital, L middle temporal, L angular gyrus	-40,-82,30	6.37	<0.0001	1817	19,37,39
R middle temporal, R superior temporal, R Heschl's gyrus, R postcentral	56,-10,-12	5.34	0.006	1317	3,21,22,48
L middle temporal, L inferior temporal, L temporal pole	-68,-14,-16	5.2	0.04	881	20,21
Controls					
posterior cingulum, middle occipital, middle temporal, precuneus, cuneus	2,-52,30	7.93	<0.0001	41823	19,20,21,23,48
orbito-frontal medial, superior frontal medial, anterior cingulum	-2,56,-2	6.17	<0.0001	8602	10,11,32

R: right L: left

Table 9. *Clusters of significant activation/de-activation in the ADHD participants and healthy comparison subjects in the 2-back vs. baseline contrast*

	Local Peaks			Cluster size (voxels)	Brodmann Areas
	MNI (x,y,z)	Z value	P value		
Mean Activations					
ADHD participants					
DLPFC, insula, inferior parietal, SMA	-44,4,26	9.04	<0.0001	58766	6,40,44,47
Controls					
DLPFC, insula, inferior parietal, supramarginal gyrus, SMA, superior frontal medial	-44,4,28	9.19	<0.0001	71547	6,31,40,44,48
Mean Deactivations					
ADHD participants					
precuneus, cuneus, posterior cingulum, R middle temporal	-4,-54,14	8.51	<0.0001	43972	17,23,30
L middle temporal, L middle occipital	-50,-68,22	4.84	0.02	1022	19,39
Controls					
medial frontal, orbito-frontal medial, precuneus, posterior cingulum, middle temporal	0,46,–8	8.51	<0.0001	50234	11,23,25,30

R: right L: left

Between-group comparisons: No clusters of significant difference between the groups were seen in the 1-back condition. In the 2-back condition group differences were detected in the orbitofrontal/ventro-medial prefrontal cortex (VMPFC) (size 1479 voxels, peak activation MNI (14x 40y -6z), z score=3.7, p=0.002). As shown in the boxplot in **Fig. 4**, these differences were due to a greater deactivation in controls compared to ADHD participants (mean deactivation: control group=-24.79±18.64; ADHD group=-12.92±18.64, *t*=-2.88, *p*=0.005).

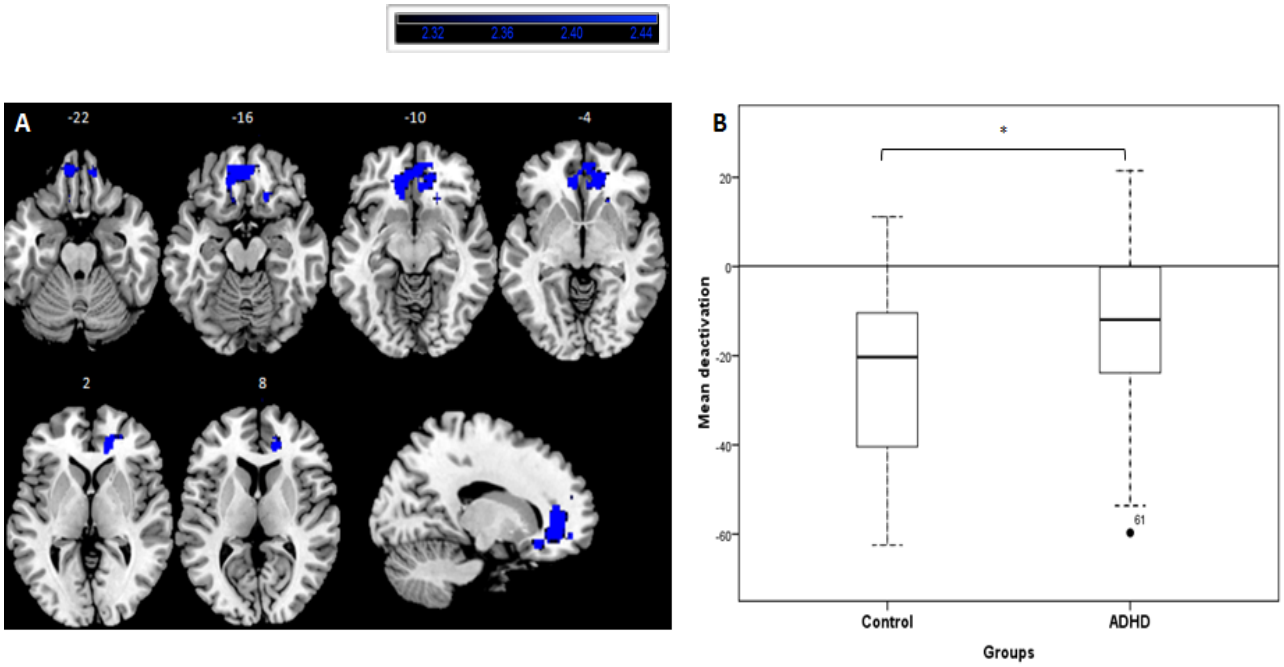

Fig. 4. *Failure of de-activation in ADHD participants versus the healthy comparison group*. **A)** Ventral medial prefrontal region showing significant differences between ADHD patients and healthy controls in the 2-back versus baseline contrast. Numbers refer to Montreal Neurological Institute (MNI) z coordinates of the slice shown. Colour bars indicate z scores from the group-level analysis.The right side of each image represents the left side of the brain. **B)** Bloxplot showing the levels of deactivation in ADHD participants and controls average across the cluster where there are significant differences in the comparison between groups.

Influence of stimulant treatment: To asses the potential effects of stimulant treatment we compared the BOLD response in the above deactivation cluster between the 26 patients who had received stimulant treatment with MPH and the 15 patients who had never received treatment. As shown in **Fig. 5** there were no significant differences between the two patient groups during the 2-back performance (mean deactivation: treated group= -13.41±18.01, never-treated = -12.92±18.64, t=0.22, p=0.82).

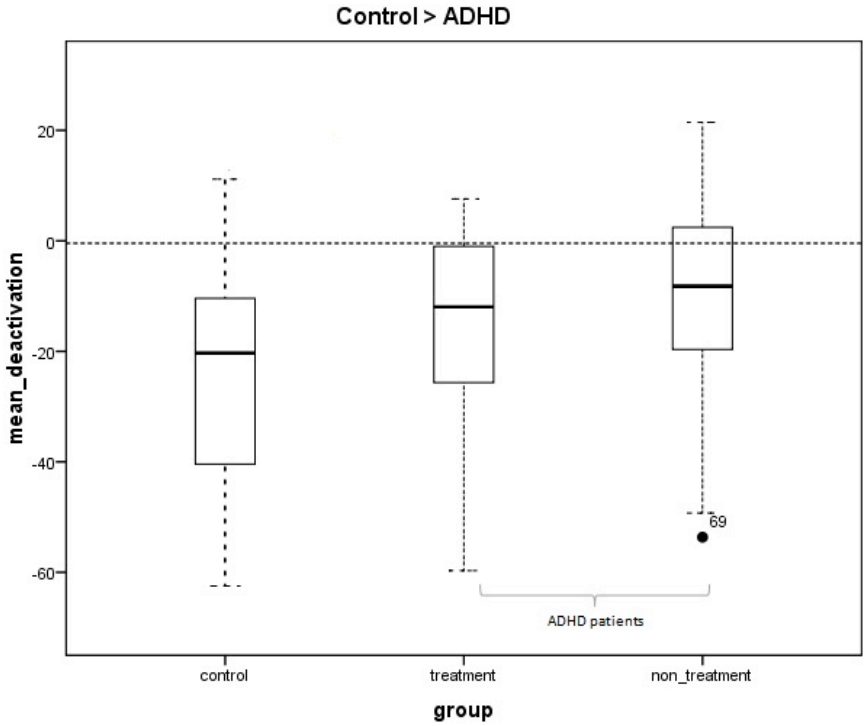

Fig. 5. *Levels of deactivation in the two subgroups of ADHD participants compared to healthy controls.* Bloxplot showing the levels of deactivation in the two subgroups of ADHD patients (medicated and non-medicated) compared to controls average across the cluster where there are significant differences in the comparison between groups.

Correlations with performance and clinical variables: There were no significant correlations between mean activations in the above ROI and performance on the 1-back and 2-back versions of the task [d'1: r=-0.11, p=0.49; d'2: r=0.15, p=0.34]. Examination of the ADHD Rating Scale scores and the symptom measures of the different subscales of the CAARS revealed no significant correlations with this ROI.

c.2. Sequence during Resting State

Compared with the healthy comparison group, participants with ADHD did not differ significantly in global brain connectivity (GBC) in any area of the brain. Thus, no connectivity abnormality was detected in areas conforming the major large-scale brain networks underlying cognitive, motor nor affective control. Likewise, ALFF analyses showed no significant increases nor reductions in amplitudes between groups, suggesting the absence of relevant differences in the intrinsic brain activity as measured by ALFF. Finally, the connectivity voxelwise analysis between the 23 ADHD medicated participants and the 13 ADHD medication-naïve participants showed no significant differences on functional connectivity in any large-scale brain network either.

7. DISCUSSION

7.1. STUDY 1 - Structural Neuroimaging -

The aim of this study was to evaluate volumetric differences between adults with ADHD and healthy subjects. A modulated VBM analysis showed a macroscopic reduction of GM volume in the right SMA, the subgenual ACC and the right DLPFC. Using the unmodulated approach we found a mesoscopic increase of GM density in the left caudate and putamen nuclei. Our study did not find statistically significant alterations in brain regions reported in other studies such as the orbitofrontal cortex, the occipital and parietal lobes and the cerebellum (Hesslinger, Tebartz van Elst et al. 2002) (Seidman, Valera et al. 2006) (Seidman, Biederman et al. 2011) (Ahrendts, Rusch et al. 2011) (Pironti, Lai et al. 2014).

These results support the findings of Amico et al. (2011) and Seidman et al. (2006, 2011), showing a smaller volume in ACC and the DLPFC in adult patients with ADHD. According to previous literature in childhood, our findings are also consistent with the observation of significant reductions in these structures (De La Fuente, Xia et al. 2013). On the one hand, ACC is associated with different roles, i.e. the projections from the ACC to the motor cortex and spinal cord seem to implicate this region in motor control (Frodl and Skokauskas 2011), dorsal ACC plays a role in conflict monitoring and attention functioning (Bush 2011) and subgenual ACC is considered to be part of the affective network, involved in processing and regulation of emotional information, and in fear control and autonomic and visceral regulation (Whalen, Bush et al. 1998) (Bush, Luu et al. 2000), and has been considered a component of DMN (Whitfield-Gabrieli and Ford 2012) (Kessler, Angstadt et

al. 2014), being specific to the DMN of depressed patients (Broyd, Demanuele et al. 2009). Relative to the DLPFC, this structure constitutes an important region involved in executive functions, which are highly affected in ADHD patients. Actually, anatomical studies in children have shown volume reductions in this structure relative to healthy controls and functional studies have shown underactivation of the DLPFC during different cognitive and motor tasks. Therefore, many investigators hypothesize that DLPFC dysfunction plays a central role in the etiology of the disorder (Seidman, Valera et al. 2006) (Cubillo, Halari et al. 2012).

Our data do not replicate the results of Seidman et al. (2011) and Almeida et al. (2010) of volume reduction in the putamen and caudate nuclei. On the contrary, our results showed a cluster of GM increase relative to the healthy comparison group in the basal ganglia (left caudate and putamen nuclei), supporting a positive association in ADHD patients between age and GM increase in this regions. Caudate and putamen integrate the fronto-striato-thalamo-cortical circuit, mediating cognitive executive functions and motor activity, typically impaired in ADHD. Volumetric reductions in basal ganglia typically reported in childhood ADHD, would not only seem to diminish over time from childhood to adulthood, but the size of these structures in adult ADHD could actually increase in relation to healthy controls, as a compensatory striatal overgrowth of frontal deficits to prevent cognitive and motor behavioral inhibitory output impairment. These data support the results found in the meta-analyses by Nakao et al. (2011) and Frodl et al. (2012), reporting a positive association between age and GM increase in the basal ganglia in ADHD patients. Our results of basal ganglia volume increase toward adulthood, are also in accordance with a very recent study looking at developmental changes in shape in the basal ganglia from

childhood (age 4) to late adolescence (age 19 years) with comparison of two MRI scans acquired in both development stages, in 220 individuals with ADHD compared to healthy controls (Shaw, De Rossi et al. 2014). This finding may be clinically relevant as caudate and putamen nuclei are associated with motor activity, and there is frequently a relative reduction in hyperactivity symptoms later in development stages, which might be explained as a function of this normalization in striatal volume.

This is the first volumetric study in adult population that has shown smaller GM in an important region involved in ADHD as the SMA. SMA plays a role in motor response inhibition (Hart, Radua et al. 2013) (Hart, Chantiluke et al. 2014) (Chantiluke, Christakou et al. 2014), acting as a motor executive to the motor cortex, preparing it to perform complex volitional bodily action, but not actually triggering the action itself (Tanji, Taniguchi et al. 1980) (Jurgens 1984) or in other words, rehearsing proposed motor actions before they are executed. The results are relevant, because several psychological theories have proposed that ADHD symptoms follow from a primary deficit in inhibitory control (Barkley 1997), and no previous study had found structural alterations in the SMA in adult ADHD population. Similar results have been found in a study with pediatric population that detected the left supplementary motor complex (SMC) emerging as the most anomalous frontal lobe region in patients with ADHD (Mahone, Ranta et al. 2011).

The correlation analysis showed no correlation between clinical measures and volumetric abnormalities, but it did find a positive correlation between cumulated stimulant dose and volumes of the right SMA and the right DLPFC. Since there has been a scarce attention in long-term effects of stimulant treatment on brain structure in patients with adult ADHD, our

results cannot be compared with previous literature. Only some studies conducted in pediatric population using a ROI approach showed that patients who had a history of previous medication with psycho-stimulants did not show volume reductions in regions like the ACC, the pulvinar nucleus of the thalamus, the posterior inferior region of the cerebellum and the corpus callosum, compared with typically developing children and children with ADHD who had not been treated with stimulants (Schweren, de Zeeuw et al. 2013) (Rubia, Alegria et al. 2014), suggesting a neuroprotective effect of psycho-stimulants on ADHD brain development (Rubia, Alegria et al. 2014). Also, studies using cortical thickness techniques suggest that long-term stimulant treatment with psycho-stimulants reduces the rate of cortical thinning in frontal and parieto-occipital regions during adolescence (Schweren, de Zeeuw et al. 2013). In a recent meta-analysis, the authors carried out a meta-regression analysis and reported that long-term stimulant medication was associated with more normal basal ganglia structure (Nakao, Radua et al. 2011), however, in our study we did not find a correlation with this cluster.

In summary, our results in a large sample of ADHD adults in a whole brain VBM analysis show that patients with ADHD have a GM volume reduction in the right SMA, the subgenual ACC and the right DLPFC and an increase of GM density in the left caudate and putamen relative to the healthy comparison group. All these regions mediate cognitive and motoric functions such as motor response and interference inhibition, cognitive flexibility, temporal foresight, selective and sustained attention, working memory, motor and timing processes which are dysfunctional in ADHD patients (Castellanos, Sonuga-Barke et al. 2006) (Cubillo, Halari et al. 2012). These findings of GM reduction circumscribed to frontal regions only, with no siginificant findings for cerebellar, occipital,

temporal nor parietal regions in our adult ADHD sample, give support to the hypothesis of a posterior-anterior brain volume normalization with increasing age in ADHD subjects, with maintenance of volume reduction only with respect to frontal lobe during adulthood.

7.2. STUDY 2 - Functional Neuroimaging -

The present study aimed to compare brain activity during the performance of a well-validated WM task and functional connectivity at rest between adult ADHD participants (chonically treated with MPH and medication-naïve) and a healthy comparison group. We hypothesised that ADHD participants would show 1) decreased activity within the WM brain network, mainly dorso- and ventro-lateral prefrontal regions and the parietal cortex; 2) failure of de-activation of the DMN and 3) decreased connectivity specially between DMN regions and dorso- and ventro-lateral prefrontal cortex compared with the healthy comparison group. We expected that chronic treatment with MPH would somehow moderate these differences between ADHD and the HCG.

Despite our N-back paradigm showed to activate the WM network (Owen, McMillan et al. 2005) across all participants, reduced activations in ADHD participants within this network were not found. Instead the patients showed a failure to deactivate in the medial frontal cortex, an area that forms part of default mode network.

Hypoactivations have been regularly reported in studies using working memory tasks in children and adolescents with ADHD, particularly in dorso- and ventrolateral prefrontal cortex and the parietal cortex (Silk, Vance et al. 2008) (Kobel, Bechtel et al. 2009)

(Massat, Slama et al. 2012) (Cubillo, Smith et al. 2014) (McCarthy, Skokauskas et al. 2014). However, this has previously been a somewhat inconsistent finding in studies of adult patients with the disorder. Thus, Valera et al. (2005) found no differences between 20 adult ADHD participants and 20 healthy controls in prefrontal or parietal cortices while performing the 2-back task (Valera, Faraone et al. 2005). Later, however, the same group reported group differences in these areas in a larger sample of 44 patients and 49 controls (Valera, Brown et al. 2010). In another study using the N-back task, Hale et al. (2007) found that 12 adult ADHD patients showed greater activation in the frontal and parietal cortex than 12 controls at low task demands, but reduced parietal activation at higher task demands (Hale, Bookheimer et al. 2007). Recently, a study using the N-back task also found increased activity in frontal cortex in 20 ADHD adults compared to 20 controls in the 2-back task, by contrast this study did find less activity in ADHD participants in left frontoparietal cortices at very high working memory demands (3-back condition) (Ko, Yen et al. 2013).

One obvious interpretation of our failure to find task-related hypoactivations is that a degree of normalization of working memory function takes place with increasing age in ADHD. In this respect it is interesting to note that previous longitudinal cortical thickness studies have found evidence that brain structures supporting attention and cognitive control in ADHD show a neurological development delay in reaching peak cortical thickness but tend converge to normal trajectories of development with aging (Castellanos, Lee et al. 2002) (Shaw, Eckstrand et al. 2007). It may also be relevant here that in adult ADHD patients impairment on tests of executive function may not be detectable (Hervey, Epstein et al. 2004) (Kooij, Bejerot et al. 2010) (Rosler, Casas et al.

2010), even while executive-type cognitive failures in everyday life (such as difficulties organizing their work and daily task completion, excessive procrastination, inconsistent effort, forgetfulness, challenges with attentional focus and time management, and impaired emotional regulation) are present. It could be argued however that the choice of a 2-back task as the high working memory load condition wasn't particularly demanding for ADHD adults to perform, which might explain the lack of significant differences in task-positive activity between ADHD participants and the healthy comparison group, making it possible for positive findings to occur at a more challenging WM load such as 3-back task. Yet, as stated above, the N-back task is recognised as difficult even for healthy adult subjects from a 2-back level of difficulty onwards (Gevins, Smith et al. 1998) (Kitzbichler, Henson et al. 2011).

On the other hand, we did find evidence of brain functional changes in adult ADHD, in the form of reduced de-activation in the medial frontal cortex, which in turn could imply default mode network dysfunction considering that this area forms part of DMN and the type of cognitive task performed during the scanning session (N-back). Some recent studies in children with ADHD have identified an attenuated task-related deactivation of the default mode network during performance of working memory tasks, as well as tasks requiring response inhibition and sustained attention. Interestingly, this failure has been found to normalize under high incentivising conditions and on treatment with methylphenidate and atomoxetine (Peterson, Potenza et al. 2009) (Liddle, Hollis et al. 2011) (Cubillo, Smith et al. 2014). It is also possible that some of the hyperactivations reported in childhood ADHD, actually reflect default mode network dysfunction. For example, the largest meta-analysis up to date, of 55 functional imaging task-based studies, found that most of the brain

regions that showed hyperactivation in ADHD when compared to controls corresponded to regions in the default mode network (Cortese, Kelly et al. 2012). It is accepted that brain regional hyperactivity can actually represent a failure to deactivate because of ‘reverse subtraction’ from a high baseline (Gusnard and Raichle 2001). To our knowledge, there have been no previous studies especifically examining de-activations in adult ADHD.

Extra-executive circuitry based explanations of our findings of medial prefrontal cortex blunted de-activation could implicate reward/motivation and emotion regulation circuits. One plausible hypothesis could be that of a compensating hyperactivation of the ventromedial prefrontal cortex in ADHD participants in order to control impulsive responses, as this brain structure has been widely related with impulse regulation (Davidson, Putnam et al. 2000) (Best, Williams et al. 2002) (Potenza, Leung et al. 2003). However underactivation or a stronger deactivation of the VMPFC would be the expected finding in our study population if we were to explain an impulsive decision making style (Bechara, Damasio et al. 1999) (Bechara 2001), contrary to our findings. On the other hand, decreased activity/increased deactivations in the medial prefrontal cortex along with other findings such as increased activity in amygdala and medial temporal lobes would be our prior expectation if we were to consider altered emotional experiences in our ADHD participants during the task due to challenges with emotional self-regulation as a relatively common trait of the disorder (Davidson 2002) (Etkin, Egner et al. 2006) (Urry, van Reekum et al. 2006) (Posner, Nagel et al. 2011). Conversely, VMPFC overactivity due to reduced deactivation with no other co-activations/deactivations was what we found. Anyhow, activations of medial prefrontal cortex have also been associated with emotional valence, although direction of these activity alterations have varied considerably across different

studies, with reports of under- and hyper-activation (Wager, Phan et al. 2003) (Posner, Russell et al. 2009). The monotonous nature of the N-back task however doesn't seem a specially encouraging or motivating challenge to increase hedonic coding reflected by hyperactivation or blunted deactivation of the VMPFC in ADHD adults, with demonstrated dysfunctions in the brain reward system (Sonuga-Barke 2003). Moreover and the more important, in spite of recent models emphasizing different non-executive deficits in ADHD population, findings of functional deficits in medialprefrontal-limbic circuitries have been hoewever less consistent, not showing to survive in meta-analytic studies and confounded by frequent comorbidities in ADHD such as conduct disorder and depression which explain these deficits to a larger extent (Dowson 2008) (Rubia 2011) (Arnsten and Rubia 2012). So with that said, and in the search of the more plausible relation of our findings to the studied task (N-back), the identification of medial prefrontal cortex reduced deactivation as ineffective deactivation of the DMN's anterior node constitutes the most likely scenario.

In healthy subjects there is clear evidence that the default mode network activity varies with cognitive function, with increased activity being associated with lapses of attention during task performance and reduced activity being associated with better performance (see Buckner et al (Buckner, Andrews-Hanna et al. 2008) and Anticevic et al (Anticevic, Cole et al. 2012). Default mode dysfunction, specifically failure to de-activate during task performance due to an alteration of the reciprocal exchanges or "give and take" coactivation patterns between the DMN and its anti-correlated networks (Pomarol-Clotet, Salvador et al. 2008) (He and Raichle 2009) (Raichle 2009), therefore provides a plausible basis for one of the key areas of symptomatology in ADHD: inattentiveness. This has been argued by several authors (Sonuga-Barke and Castellanos 2007) (Cortese, Kelly et al.

2012) (Cortese and Castellanos 2012). Our finding supports the idea that while brain task-positive networks specifically specialized for WM such as the frontoparietal could be quite neurodevelopmentally normalized in ADHD adults, a failure to de-activate the DMN during WM tasks due to blunted coupling of brain regions normally implicated in WM performance, would rather account for inefficient WM. This would imply a difficulty to allocate attention toward task execution, predicting greater lapses of inattention and the need to exert greater mental effort to achieve a normal level of individual WM performance. Medial prefrontal cortex represents a region increasingly shown to be impaired in ADHD, both during rest and during cognitive tasks. However, it is important to note that we found no significant association between the level of de-activation in the medial frontal cortex in the patients and either N-back task performance or the inattentiveness subscale of the CAARS. Even so, there is evidence that findings from brain functional imaging studies cannot be mapped directly to the behavioral manifestations of a disorder, but should be mapped to abnormalities in specific neurocognitive processes that are thought to underlie the bevavior, explaining why compared individuals may show the same performance on behavioral tests but different patterns of brain activation, corresponding to different ways of performing the cognitive task (Frith and Frith 2008).

ADHD groups defined by history of medication treatment (i.e. chronically treated with MPH or medication-naïve) did not show any different pattern of activation during the task. We also failed to find significant de-activation differences between ADHD participants who were on chronic treatment with MPH and those who were medication-naïve. At first sight this goes against previous findings that methylphenidate has normalizing effects on brain functional changes in the disorder (Peterson, Potenza et al. 2009) (Liddle, Hollis et al.

2011) (Rubia, Alegria et al. 2014) (Cubillo, Smith et al. 2014). However, it needs to be borne in mind that medicated patients in our study underwent a washout period of at least 4 days prior to scanning, which could have been long enough for acute effects of treatment to disappear. What can probably be inferred with more confidence from our results is that stimulant medication does not exert long-lasting changes on brain function. In fact all of the studies mentioned above looked at acute effects of MPH in normalising brain function in ADHD patients but not in the long-term (Peterson, Potenza et al. 2009) (Liddle, Hollis et al. 2011) (Rubia, Halari et al. 2011) (Rubia, Halari et al. 2011) (Rubia, Alegria et al. 2014) (Cubillo, Smith et al. 2014).

Finally, our findings don't support growing evidence that network dysconnectivity is a central feature of ADHD, or at least not the case when it comes to adults. Prior studies of ADHD, basically focused on samples of children with the disoder, have shown altered connectivity within brain networks underlying cognitive, motor and affective control (Posner, Park et al. 2014) (Kessler, Angstadt et al. 2014). Functional connectivity studies in adult ADHD have found reduced connectivity within default mode network regions (Castellanos, Margulies et al. 2008) (Mattfeld, Gabrieli et al. 2014) and reduced connectivity between default mode network and sensory and cognitive networks (DLPFC and parietal cortices) (Hoekzema, Carmona et al. 2014) (Mattfeld, Gabrieli et al. 2014). Our findings with a large sample of adult ADHD participants differed from those prior studies. One probable explanation is that different resting state fMRI methods have been used in prior studies, with seed-based approaches as the most applied in resting state fcMRI studies of ADHD, with a greater susceptibility to investigator biases influencing final resting state fcMRI findings (Posner, Park et al. 2014). The resting state study comprised

in this thesis uses a whole-brain multimodal analysis methodology, without using a priori selected regions, thus avoiding this important limitation. Another plausible explanation for the lack of significant connectivity abnormalities could be in relation to increased functional segregation throughout development into adulthood in ADHD population as has been well documented in typical development in healthy population (Fair, Dosenbach et al. 2007) (Fair, Cohen et al. 2009) (Anderson, Ferguson et al. 2011), with abnormal connectivity being more likely in ADHD children due to modification by maturational delay of the developing brain in contrast to ADHD adults with plausibly more normalized connections through ontogenetic evolution. In fact, functional connectivity between medial prefrontal cortex and posterior cingulate cortex (major nodes of the DMN) is completely absent in newborn babies (Fransson, Skiold et al. 2007), probably due to a lack of development of anterior-posterior white matter fiber tracts as revealed by diffusion tensor MRI studies in infants (Hermoye, Saint-Martin et al. 2006) (Dubois, Dehaene-Lambertz et al. 2008). As has been confirmed by recent research, functional and structural connectivity between the DMN's main nodes and between the DMN and other brain networks with reciprocal exchanges, develops and matures throughout development (Eluvathingal, Hasan et al. 2007) (Fair, Cohen et al. 2008) (Kelly, Di Martino et al. 2009).

In summary, this study finds that adult ADHD patients have a defficient deactivation during WM task performance in the medial prefrontal cortex, part of the DMN. Since failure of de-activation is linked to lapses of attention, our findings suggest difficulty to allocate attentional resources away from self-oriented thoughts and toward extrinsic task execution, predicting greater lapses of inattention during complex problem-solving performance in adult ADHD patients. In contrast to what has been suggested, we failed to find reduced prefrontal activation and reduced resting state connectivity in the WM network

and other large-scale brain networks, despite examining a relatively large sample of patients and controls. Nor did we find a relationship between failure of de-activation and stimulant treatment, although this may have been due to the fact that we employed a washout period before scanning in the treated patients.

Taken together our findings provide further evidence for the importance of the DMN in relation to adult ADHD. The adult ADHD brain would be vulnerable to “getting distracted” because its function of “turning off” the DMN during goal-directed cognition would be insufficient, suggesting reduced suppresion of DMN as the main potential link to adult ADHD symptomatology.

7.3. LIMITATIONS and STRENGTHS of the Studies

The main strength of the studies comprising the thesis is the large homogeneous sample, including only carefully and solidly diagnosed Combined presentation patients, ruling out active Axis I and Axis II comorbid disorders, and with clearly stablished medication status and presence and length of wash-out period. All these aspects make the generalizability of the findings very reliable. Combined presentation of the disorder was chosen for the study because it is the most commonly represented subtype and the more prevalent in clinical services due to likeliness to being referred (Wilens, Biederman et al. 2002) (Willcutt 2012). Moreover, predominantly Inattentive subtype in adults, can often represent a more subtle presentation of a previous Combined subtype in childhood for the same individual due to age dependent changes in the presentation of ADHD symptoms, with fewer overt symptoms of hyperactivity and impulsivity as the patient ages, while symptoms of

inattention and executive disfunction tend to remain (Kooij, Bejerot et al. 2010) (Willcutt 2012)). Another strength of the studies comprising the thesis is that patients and controls are matched by sex, age, premorbid and current IQ, so these variables will not skew the final results. Particularly as regards gender, in spite of the uneven gender distribution of the samples, gender wasn't a bias to the results of the study because the samples were matched for gender. Moreover, previous research in adult ADHD has shown no evidence that gender moderates the phenotypic expression of the disorder nor its level of cognitive and psychosocial functioning (Biederman, Faraone et al. 1994) (Biederman, Faraone et al. 2004). Finally, one more of the study's strong points is that different brain measures could be made during a single MRI session, making it possible to integrate findings across multimodal imaging.

Although our study represents one of the largest neuroimaging investigations in adult ADHD, some limitations should be noted. Firstly, the relatively small sample of ADHD medication-naïve participants may limit our ability to find differences between the ADHD medication-naïve group and the ADHD group on chronic treatment with MPH, due to a possible lack of power to detect activation and structural differences. Secondly, the cross-sectional design cannot provide the temporal association to confirm a causal relationship with the hypothesized normalising effects of MPH. Thirdly, whilst differences in treatment extent and duration were precisely controlled in the structural neuroimaging study (Study 1), by means of the inclusion of the *cumulated dose* variable as a regressor in a regression model (which took treatment duration time and dose into account), we didn't proceed in the same way in the analyses of the functional study (Study 2), looking like this could have compromised our ability to test betweengroup treatment effect differences due to different

treatment doses and treatment times of exposure for the group of medicated ADHD subjects. Not to covariate for treatment dose or time in treatment in the functional neuroimaging study (Study 2), was the preferred option because despite the loss of accuracy for not covariating, it is considered for functional studies (for which obtaining patients is much more difficult), that it is right to separate between treated and untreated subjects, using treatment as a binary variable, which simplifies the statistical analysis. Furthermore, the fact that the sample of treated patients would include very different treatment duration times (mean ± SD: 23.55 ± 22.63 months), was favorable for this type of analysis, making it unlikely to confound the study findings. One final limitation of the study could have been that the untreated ADHD sample may represent a possibly less severely affected ADHD subgroup, not representative of the ADHD population, but ADHD non-medicated participants were not significantly different than the ADHD medicated group on any of the clinical assesment scales for adult ADHD used (WURS, ADHD Rating Scale and CAARS), so we therefore ensured that our findings were not biased by the ADHD subgroup regarding treatment (medicated vs. non-medicated).

8. CONCLUSIONS

8.1. ADHD participants showed three clusters of GM reduction corresponding to 1) the right SMA, extending to superior frontal lobe; 2) the subgenual ACC; and 3) the right DLPFC. All these regions are key regions in cognitive executive regulation, specially for WM and cognitive and motor response inhibition, found to be dysfunctional in ADHD patients. These findings of GM reduction circumscribed to frontal regions, with no siginificant findings for cerebellar, occipital, temporal nor parietal regions, give support to the hypothesis of a posterior-anterior brain volume normalization with increasing age in ADHD subjects.

8.2. ADHD participants showed a cluster of GM increase relative to the healthy comparison group in the left striatum (left caudate and putamen nuclei). These data would support a positive association in ADHD patients between age and GM increase in the basal ganglia. These structures are typically reduced in GM volume in ADHD children but would show a progressive volume normalization as children mature towards adulthood, with ADHD adults showing similar, or even larger striatal volumes than healthy adults as a possible compensatory overgrowth to prevent cognitive and motor inhibitory output impairment. This finding may be clinically relevant as there is frequently a relative reduction in hyperactivity symptoms later in development, which might be explained as a function of this volumetric normalization in motoric regulation regions.

8.3. ADHD participants showed failure of de-activation in the medial frontal cortex under a WM 2-back task, which in turn implies default mode network dysfunction. This finding supports the idea that while brain networks specifically specialized for WM such as the frontoparietal could be quite neurodevelopmentally normalized in ADHD adults, a failure to deactivate the DMN during WM tasks would rather account for inefficient WM, due to a difficulty to allocate attentional resources away from self-oriented thoughts and toward extrinsic task execution, predicting greater lapses of inattention and the need to exert greater mental effort to achieve a normal level of individual WM performance. Default mode network reduced deactivation during task performance would be mainly due to an impairment in the process of recruitment of different brain areas under task demand and therefore of coactivation/deactivation between them for the purpose of executing specific tasks or mental functions like WM. DMN dysfunction provides a plausible basis for one of the key areas of symptomatology in adult ADHD: inattentiveness.

8.4. Our results showed greater GM volume with higher MPH cumulated dose in right SMA and right DLPFC. These findings suggest evidence for long-term MPH associated effects on brain structure, in the direction of an attenuation in GM volume reduction in key brain regions for WM and response inhibition with reduced volumes in ADHD adults, specifically DLPFC and the SMA.

8.5. The study yielded no significant differences in brain activity between ADHD participants chronically medicated with MPH and those medication-naïve. Our and previous findings would support that MPH has a positive acute effect in normalising brain function in ADHD patients, but these acute effects seem to dissipate as the drug is washed out of the system, not leading to long-lasting changes on brain function, in a contrary way as it is the case for brain structure. This interpretation is speculative, but it could be tested in longitudinal studies.

8.6. The study found no significant differences on resting state functional connectivity between ADHD participants and the healthy comparison group in any large-scale brain network. These finding doesn't support network dysconnectivity as a central feature of adult ADHD, probably due to functional segregation throughout development into adulthood in ADHD population as in typical development in healthy population.

8.7. This study supports the conceptualization of ADHD as a developmental disorder with related measurable changes in brain structure and function across the lifespan, susceptible of improvement with therapeutical interventions such as pharmacological treatment with MPH.

9. SUMMARY

Introduction: Attention-Deficit Hyperactivity Disorder is a neurodevelopmental disorder affecting about 5 % of child and adolescent population, with around 50 % of those carrying the disorder into adulthood. Structural and functional neuroimaging studies in ADHD adults however, have been inconsistent.

Objectives: Our aim was to investigate the strucutural and functional brain changes in adult ADHD. To what extent these changes could be corrected by long-term exposure to methylphenidate was also examined.

Methods: We recruited a large sample of adults with a positive diagnosis of ADHD-Combined subtype and a matched group of healthy volunteers. We obtained fMRI images from participants while performing a well-validated working memory task (N-back), anatomical MRI images using voxel-based morphometry (VBM) and resting state fMRI to look at functional connectivity within the working memory network and other brain networks in the resting brain.

Results: Relative to the healthy comparison group ADHD participants showed: 1) a smaller grey matter volume in the right supplementary motor area, the subgenual anterior cingulate cortex and the right dorsolateral prefrontal cortex; 2) a higher grey matter density in the left caudate and putamen; 3) a defficient deactivation of the medial prefrontal cortex during the 2-back task; and 4) long-term corrective effects of methylphenidate treatment for brain structure but not for brain activations.

Conclusions: Structural and functional neuroanatomy of working memory is impaired in ADHD adults, showing structural abnormalities in key regions of working memory and cognitive control (including the supplementary motor area, the anterior cingulate cortex and the dorsolateral prefrontal cortex) and dysfunctional brain deactivation of the medial prefrontal cortex during high-load working memory performance (leading to an excessive processing of irrelevant internal information that is detrimental to working memory itself). Chronic exposure to methylphenidate normalizes brain structural deficits in the long-term, exerting no longer changes in brain activity. Developmental structural and functional brain differences in ADHD seem to normalize into adulthood to a large extent.

10. REFERENCES

Ahrendts, J., N. Rusch, et al. (2011). "Visual cortex abnormalities in adults with ADHD: a structural MRI study." World J Biol Psychiatry **12**(4): 260-70.

Alderson, R. M., L. J. Kasper, et al. (2013). "Attention-deficit/hyperactivity disorder (ADHD) and working memory in adults: a meta-analytic review." Neuropsychology **27**(3): 287-302.

Allin, M. P., N. Marshall, et al. (2010). "A functional MRI study of verbal fluency in adults with bipolar disorder and their unaffected relatives." Psychol Med **40**(12): 2025-35.

Almeida Montes, L. G., J. Ricardo-Garcell, et al. (2010). "Clinical correlations of grey matter reductions in the caudate nucleus of adults with attention deficit hyperactivity disorder." J Psychiatry Neurosci **35**(4): 238-46.

Alonso Bde, C., S. Hidalgo Tobon, et al. (2014). "A multi-methodological MR resting state network analysis to assess the changes in brain physiology of children with ADHD." PLoS One **9**(6): e99119.

Amico, F., J. Stauber, et al. (2011). "Anterior cingulate cortex gray matter abnormalities in adults with attention deficit hyperactivity disorder: a voxel-based morphometry study." Psychiatry Res **191**(1): 31-5.

An, L., Q. J. Cao, et al. (2013). "Local synchronization and amplitude of the fluctuation of spontaneous brain activity in attention-deficit/hyperactivity disorder: a resting-state fMRI study." Neurosci Bull **29**(5): 603-13.

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

Anderson, J. S., M. A. Ferguson, et al. (2011). "Connectivity gradients between the default mode and attention control networks." Brain Connect **1**(2): 147-57.

Anticevic, A., M. W. Cole, et al. (2012). "The role of default network deactivation in cognition and disease." Trends Cogn Sci **16**(12): 584-92.

APA (2000). Diagnostic and statistical manual of mental disorders Washington DC, American Psychiatric Association

Arnsten, A. F. and K. Rubia (2012). "Neurobiological circuits regulating attention, cognitive control, motivation, and emotion: disruptions in neurodevelopmental psychiatric disorders." J Am Acad Child Adolesc Psychiatry **51**(4): 356-67.

Ashburner, J. and K. Friston (2001). "Why voxel-based morphometry should be used." Neuroimage **14**(6): 1238-1243.

Asherson, P., W. Chen, et al. (2007). "Adult attention-deficit hyperactivity disorder: recognition and treatment in general adult psychiatry." Br J Psychiatry **190**: 4-5.

Avants, B. B., C. L. Epstein, et al. (2008). "Symmetric diffeomorphic image registration with cross-correlation: evaluating automated labeling of elderly and neurodegenerative brain." Med Image Anal **12**(1): 26-41.

Avants, B. B., P. Yushkevich, et al. (2010). "The optimal template effect in hippocampus studies of diseased populations." Neuroimage **49**(3): 2457-66.

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

Banich, M. T., G. C. Burgess, et al. (2009). "The neural basis of sustained and transient attentional control in young adults with ADHD." Neuropsychologia **47**(14): 3095-104.

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

Barkley, R., K. Murphy, et al. (2001). "Time perception and reproduction in young adults with attention deficit hyperactivity disorder." Neuropsychology **15**(3): 351-360.

Barkley, R., K. Murphy, et al. (2007). ADHD in adults: What the science says. New York, Guilford Press.

Barkley, R. A. (2003). "Issues in the diagnosis of attention-deficit/hyperactivity disorder in children." Brain Dev **25**(2): 77-83.

Barkley, R. A. and M. Fischer (2010). "The unique contribution of emotional impulsiveness to impairment in major life activities in hyperactive children as adults." J Am Acad Child Adolesc Psychiatry **49**(5): 503-13.

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

Bayerl, M., T. F. Dielentheis, et al. (2010). "Disturbed brain activation during a working memory task in drug-naive adult patients with ADHD." Neuroreport **21**(6): 442-6.

Bechara, A. (2001). "Neurobiology of decision-making: risk and reward." Semin Clin Neuropsychiatry **6**(3): 205-16.

Bechara, A., H. Damasio, et al. (1999). "Different contributions of the human amygdala and ventromedial prefrontal cortex to decision-making." J Neurosci **19**(13): 5473-81.

Beckmann, C., M. Jenkinson, et al. (2003). "General multilevel linear modeling for group analysis in FMRI." Neuroimage **20**(2): 1052-1063.

Bedard, A. C., J. H. Newcorn, et al. (2014). "Reduced prefrontal efficiency for visuospatial working memory in attention-deficit/hyperactivity disorder." J Am Acad Child Adolesc Psychiatry **53**(9): 1020-1030 e6.

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

Best, M., J. M. Williams, et al. (2002). "Evidence for a dysfunctional prefrontal circuit in patients with an impulsive aggressive disorder." Proc Natl Acad Sci U S A **99**(12): 8448-53.

Biederman, J., S. V. Faraone, et al. (2004). "Gender effects on attention-deficit/hyperactivity disorder in adults, revisited." Biol Psychiatry **55**(7): 692-700.

Biederman, J., S. V. Faraone, et al. (1994). "Gender differences in a sample of adults with attention deficit hyperactivity disorder." Psychiatry Res **53**(1): 13-29.

Biederman, J., M. C. Monuteaux, et al. (2006). "Young adult outcome of attention deficit hyperactivity disorder: a controlled 10-year follow-up study." Psychol Med **36**(2): 167-79.

Bledsoe, J., M. Semrud-Clikeman, et al. (2009). "A magnetic resonance imaging study of the cerebellar vermis in chronically treated and treatment-naive children with attention-deficit/hyperactivity disorder combined type." Biol Psychiatry **65**(7): 620-4.

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

Braet, W., K. Johnson, et al. (2011). "fMRI activation during response inhibition and error processing: the role of the DAT1 gene in typically developing adolescents and those diagnosed with ADHD." Neuropsychologia **49**(7): 1641-1650.

Brieber, S., S. Neufang, et al. (2007). "Structural brain abnormalities in adolescents with autism spectrum disorder and patients with attention deficit/hyperactivity disorder." J Child Psychol Psychiatry **48**(12): 1251-8.

Brotman, M. A., B. A. Rich, et al. (2010). "Amygdala activation during emotion processing of neutral faces in children with severe mood dysregulation versus ADHD or bipolar disorder." Am J Psychiatry **167**(1): 61-9.

Brown, A. B., J. Biederman, et al. (2011). "Relationship of DAT1 and adult ADHD to task-positive and task-negative working memory networks." Psychiatry Res **193**(1): 7-16.

Brown, T. E., P. C. Reichel, et al. (2009). "Executive function impairments in high IQ adults with ADHD." J Atten Disord **13**(2): 161-7.

Broyd, S. J., C. Demanuele, et al. (2009). "Default-mode brain dysfunction in mental disorders: a systematic review." Neurosci Biobehav Rev **33**(3): 279-96.

Buckner, R. L., J. R. Andrews-Hanna, et al. (2008). "The brain's default network: anatomy, function, and relevance to disease." Ann N Y Acad Sci **1124**: 1-38.

Bush, G. (2008). "Neuroimaging of attention deficit hyperactivity disorder: can new imaging findings be integrated in clinical practice?" Child Adolesc Psychiatr Clin N Am **17**(2): 385-404.

Bush, G. (2011). "Cingulate, frontal, and parietal cortical dysfunction in attention-deficit/hyperactivity disorder." Biol Psychiatry **69**(12): 1160-7.

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

Bush, G., P. Luu, et al. (2000). "Cognitive and emotional influences in anterior cingulate cortex." Trends Cogn Sci **4**(6): 215-222.

Bush, G., T. J. Spencer, et al. (2008). "Functional magnetic resonance imaging of methylphenidate and placebo in attention-deficit/hyperactivity disorder during the multi-source interference task." Arch Gen Psychiatry **65**(1): 102-14.

Bussing, R., J. Grudnik, et al. (2002). "ADHD and conduct disorder: an MRI study in a community sample." World J Biol Psychiatry **3**(4): 216-20.

Cao, Q., Y. Zang, et al. (2006). "Abnormal neural activity in children with attention deficit hyperactivity disorder: a resting-state functional magnetic resonance imaging study." Neuroreport **17**(10): 1033-6.

Carmona, S., E. Hoekzema, et al. (2012). "Response inhibition and reward anticipation in medication-naive adults with attention-deficit/hyperactivity disorder: a within-subject case-control neuroimaging study." Hum Brain Mapp **33**(10): 2350-61.

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

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

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

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

Castellanos, F. X., D. S. Margulies, et al. (2008). "Cingulate-precuneus interactions: a new locus of dysfunction in adult attention-deficit/hyperactivity disorder." Biol Psychiatry **63**(3): 332-7.

Castellanos, F. X. and E. Proal (2011). "Large-scale brain systems in ADHD: beyond the prefrontal-striatal model." Trends Cogn Sci **16**(1): 17-26.

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

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

Chantiluke, K., A. Christakou, et al. (2014). "Disorder-specific functional abnormalities during temporal discounting in youth with Attention Deficit Hyperactivity Disorder (ADHD), Autism and comorbid ADHD and Autism." Psychiatry Res **223**(2): 113-20.

Cole, M. W., S. Pathak, et al. (2010). "Identifying the brain's most globally connected regions." Neuroimage **49**(4): 3132-48.

Congdon, E., L. L. Altshuler, et al. (2014). "Neural activation during response inhibition in adult attention-deficit/hyperactivity disorder: preliminary findings on the effects of medication and symptom severity." Psychiatry Res **222**(1-2): 17-28.

Conners, C., D. Erhardt, et al. (1999). CAARS Conners' Adult ADHD Rating Scales. North Tonawanda, NY: Multi-health Systems, Inc.

Cortese, S. and F. X. Castellanos (2012). "Neuroimaging of attention-deficit/hyperactivity disorder: current neuroscience-informed perspectives for clinicians." Curr Psychiatry Rep **14**(5): 568-78.

Cortese, S., C. Kelly, et al. (2012). "Toward Systems Neuroscience of ADHD: A Meta-Analysis of 55 fMRI Studies." Am J Psychiatry **169**(10): 1038-1055.

Cubillo, A., R. Halari, et al. (2010). "Reduced activation and inter-regional functional connectivity of fronto-striatal networks in adults with childhood Attention-Deficit Hyperactivity Disorder (ADHD) and persisting symptoms during tasks of motor inhibition and cognitive switching." J Psychiatr Res **44**(10): 629-39.

Cubillo, A., R. Halari, et al. (2011). "Fronto-striatal underactivation during interference inhibition and attention allocation in grown up children with attention deficit/ hyperactivity disorder and persistent symptoms." Psychiatry Res **193**(1): 17-27.

Cubillo, A., R. Halari, et al. (2012). "A review of fronto-striatal and fronto-cortical brain abnormalities in children and adults with Attention Deficit Hyperactivity Disorder (ADHD) and new evidence for dysfunction in adults with ADHD during motivation and attention." Cortex **48**(2): 194-215.

Cubillo, A. and K. Rubia (2010). "Structural and functional brain imaging in adult attention-deficit/hyperactivity disorder." Expert Rev Neurother **10**(4): 603-20.

Cubillo, A., A. B. Smith, et al. (2014). "Drug-specific laterality effects on frontal lobe activation of atomoxetine and methylphenidate in attention deficit hyperactivity disorder boys during working memory." Psychol Med **44**(3): 633-46.

Cubillo, A., A. B. Smith, et al. (2014). "Shared and drug-specific effects of atomoxetine and methylphenidate on inhibitory brain dysfunction in medication-naive ADHD boys." Cereb Cortex **24**(1): 174-85.

Damoiseaux, J. S., S. A. Rombouts, et al. (2006). "Consistent resting-state networks across healthy subjects." Proc Natl Acad Sci U S A **103**(37): 13848-53.

Davidson, R. J. (2002). "Anxiety and affective style: role of prefrontal cortex and amygdala." Biol Psychiatry **51**(1): 68-80.

Davidson, R. J., K. M. Putnam, et al. (2000). "Dysfunction in the neural circuitry of emotion regulation--a possible prelude to violence." Science **289**(5479): 591-4.

De La Fuente, A., S. Xia, et al. (2013). "A review of attention-deficit/hyperactivity disorder from the perspective of brain networks." Front Hum Neurosci **7**: 192.

Del Ser, T., J. I. Gonzalez-Montalvo, et al. (1997). "Estimation of premorbid intelligence in Spanish people with the Word Accentuation Test and its application to the diagnosis of dementia." Brain Cogn **33**(3): 343-56.

Depue, B. E., G. C. Burgess, et al. (2010). "Behavioral performance predicts grey matter reductions in the right inferior frontal gyrus in young adults with combined type ADHD." Psychiatry Res **182**(3): 231-7.

Di, X., S. S. Kannurpatti, et al. (2012). "Calibrating BOLD fMRI activations with neurovascular and anatomical constraints." Cereb Cortex **23**(2): 255-63.

Dibbets, P., E. A. Evers, et al. (2010). "Differential brain activation patterns in adult attention-deficit hyperactivity disorder (ADHD) associated with task switching." Neuropsychology **24**(4): 413-23.

Dibbets, P., L. Evers, et al. (2009). "Differences in feedback- and inhibition-related neural activity in adult ADHD." Brain Cogn **70**(1): 73-83.

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

Dillo, W., A. Goke, et al. (2010). "Neuronal correlates of ADHD in adults with evidence for compensation strategies--a functional MRI study with a Go/No-Go paradigm." Ger Med Sci **8**: Doc09.

Dowson, J. H. (2008). "Characteristics of adults with attention-deficit/hyperactivity disorder and past conduct disorder." Acta Psychiatr Scand **117**(4): 299-305.

Doyle, A. E. (2006). "Executive functions in attention-deficit/hyperactivity disorder." J Clin Psychiatry **67 Suppl 8**: 21-6.

Dreher, J. C., P. Koch, et al. (2012). "Common and differential pathophysiological features accompany comparable cognitive impairments in medication-free patients with schizophrenia and in healthy aging subjects." Biol Psychiatry **71**(10): 890-7.

Dubois, J., G. Dehaene-Lambertz, et al. (2008). "Asynchrony of the early maturation of white matter bundles in healthy infants: quantitative landmarks revealed noninvasively by diffusion tensor imaging." Hum Brain Mapp **29**(1): 14-27.

DuPaul, G., T. Power, et al. (1998). ADHD Rating Scale IV: checklists, norms, and clinical interpretation. New York, Guilford.

Durnez, J., B. Moerkerke, et al. (2014). "Post-hoc power estimation for topological inference in fMRI." Neuroimage **84**: 45-64.

Durston, S., H. Hulshoff Pol, et al. (2004). "Magnetic resonance imaging of boys with attention-deficit/hyperactivity disorder and their unaffected siblings." J Am Acad Child Adolesc Psychiatry **43**(3): 332-340.

Durston, S., N. Tottenham, et al. (2003). "Differential patterns of striatal activation in young children with and without ADHD." Biol Psychiatry **53**(10): 871-878.

Ehlis, A. C., C. G. Bahne, et al. (2008). "Reduced lateral prefrontal activation in adult patients with attention-deficit/hyperactivity disorder (ADHD) during a working memory task: a functional near-infrared spectroscopy (fNIRS) study." J Psychiatr Res **42**(13): 1060-7.

Ellison-Wright, I., Z. Ellison-Wright, et al. (2008). "Structural brain change in Attention Deficit Hyperactivity Disorder identified by meta-analysis." BMC Psychiatry **8**: 51.

Elton, A., S. Alcauter, et al. (2014). "Network connectivity abnormality profile supports a categorical-dimensional hybrid model of ADHD." Hum Brain Mapp **35**(9): 4531-43.

Eluvathingal, T. J., K. M. Hasan, et al. (2007). "Quantitative diffusion tensor tractography of association and projection fibers in normally developing children and adolescents." Cereb Cortex **17**(12): 2760-8.

Epstein, J., D. Johnson, et al. (2001). Conners' Adult ADHD Diagnostic Interview for DSM-IV. North Tonawanda, Canada, Multi-Health Systems, Inc.

Epstein, J. N., B. J. Casey, et al. (2007). "ADHD- and medication-related brain activation effects in concordantly affected parent-child dyads with ADHD." J Child Psychol Psychiatry **48**(9): 899-913.

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

Etkin, A., T. Egner, et al. (2006). "Resolving emotional conflict: a role for the rostral anterior cingulate cortex in modulating activity in the amygdala." Neuron **51**(6): 871-82.

Fair, D. A., A. L. Cohen, et al. (2008). "The maturing architecture of the brain's default network." Proc Natl Acad Sci U S A **105**(10): 4028-32.

Fair, D. A., A. L. Cohen, et al. (2009). "Functional brain networks develop from a "local to distributed" organization." PLoS Comput Biol **5**(5): e1000381.

Fair, D. A., N. U. Dosenbach, et al. (2007). "Development of distinct control networks through segregation and integration." Proc Natl Acad Sci U S A **104**(33): 13507-12.

Fair, D. A., J. T. Nigg, et al. (2012). "Distinct neural signatures detected for ADHD subtypes after controlling for micro-movements in resting state functional connectivity MRI data." Front Syst Neurosci **6**: 80.

Fair, D. A., J. Posner, et al. (2010). "Atypical default network connectivity in youth with attention-deficit/hyperactivity disorder." Biol Psychiatry **68**(12): 1084-91.

Fan, L. Y., S. S. Gau, et al. (2014). "Neural correlates of inhibitory control and visual processing in youths with attention deficit hyperactivity disorder: a counting Stroop functional MRI study." Psychol Med **44**(12): 2661-71.

Faraone, S. V. and J. Biederman (1998). "Neurobiology of attention-deficit hyperactivity disorder." Biol Psychiatry **44**(10): 951-8.

Faraone, S. V., J. Biederman, et al. (2006). "The age-dependent decline of attention deficit hyperactivity disorder: a meta-analysis of follow-up studies." Psychol Med **36**(2): 159-65.

Faraone, S. V. and A. E. Doyle (2001). "The nature and heritability of attention-deficit/hyperactivity disorder." Child Adolesc Psychiatr Clin N Am **10**(2): 299-316, viii-ix.

Fassbender, C., J. Schweitzer, et al. (2011). "Working memory in attention deficit/hyperactivity disorder is characterized by a lack of specialization of brain function." PLoS One **6**(11): e27240.

Fassbender, C., H. Zhang, et al. (2009). "A lack of default network suppression is linked to increased distractibility in ADHD." Brain Res **1273**: 114-28.

Fernandez-Corcuera, P., R. Salvador, et al. (2013). "Bipolar depressed patients show both failure to activate and failure to de-activate during performance of a working memory task." J Affect Disord **148**(2-3): 170-8.

Fernandez-Jaen, A., S. Lopez-Martin, et al. (2014). "Cortical thinning of temporal pole and orbitofrontal cortex in medication-naive children and adolescents with ADHD." Psychiatry Res **224**(1): 8-13.

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

Finke, K., W. Schwarzkopf, et al. (2011). "Disentangling the adult attention-deficit hyperactivity disorder endophenotype: parametric measurement of attention." J Abnorm Psychol **120**(4): 890-901.

First, M., M. Gibbon, et al. (1997). Structured Clinical Interview for DSM-IV Axis II Personality Disorders, (SCID-II). Washington, DC, American Psychiatric Press, Inc.

First, M., R. Spitzer, et al. (2002). Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition. (SCID-I/P) New York, Biometrics Research, New York State Psychiatric Institute.

Fischl, B. and A. M. Dale (2000). "Measuring the thickness of the human cerebral cortex from magnetic resonance images." Proc Natl Acad Sci U S A **97**(20): 11050-5.

Fox, M. D., M. Corbetta, et al. (2006). "Spontaneous neuronal activity distinguishes human dorsal and ventral attention systems." Proc Natl Acad Sci U S A **103**(26): 10046-51.

Fox, M. D., A. Z. Snyder, et al. (2005). "The human brain is intrinsically organized into dynamic, anticorrelated functional networks." Proc Natl Acad Sci U S A **102**(27): 9673-8.

Fransson, P., B. Skiold, et al. (2007). "Resting-state networks in the infant brain." Proc Natl Acad Sci U S A **104**(39): 15531-6.

Frith, C. and U. Frith (2008). What Can We Learn from Structural and Functional Brain Imaging? Rutter's Child And Adolescent Psychiatry. M. Rutter, D. Bishop, D. Pineet al. Oxford, Blackwell Publishing Ltd.

Frodl, T. and N. Skokauskas (2011). "Meta-analysis of structural MRI studies in children and adults with attention deficit hyperactivity disorder indicates treatment effects." Acta Psychiatr Scand **125**(2): 114-26.

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

Frodl, T., J. Stauber, et al. (2010). "Amygdala reduction in patients with ADHD compared with major depression and healthy volunteers." Acta Psychiatr Scand **121**(2): 111-8.

Gevins, A. and B. Cutillo (1993). "Spatiotemporal dynamics of component processes in human working memory." Electroencephalogr Clin Neurophysiol **87**(3): 128-43.

Gevins, A., M. E. Smith, et al. (1998). "Monitoring working memory load during computer-based tasks with EEG pattern recognition methods." Hum Factors **40**(1): 79-91.

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

Gomar, J. J., J. Ortiz-Gil, et al. (2011). "Validation of the Word Accentuation Test (TAP) as a means of estimating premorbid IQ in Spanish speakers." Schizophr Res **128**(1-3): 175-6.

Green, D. M. and J. A. Swets (1966/1974). Signal detection theory and psychophysics (A reprint, with corrections of the original 1966 ed.). Huntington, NY, Robert E. Krieger Publishing Co.

Grimm, S., P. Boesiger, et al. (2009). "Altered negative BOLD responses in the default-mode network during emotion processing in depressed subjects." Neuropsychopharmacology **34**(4): 932-43.

Gusnard, D. A., E. Akbudak, et al. (2001). "Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function." Proc Natl Acad Sci U S A **98**(7): 4259-64.

Gusnard, D. A. and M. E. Raichle (2001). "Searching for a baseline: functional imaging and the resting human brain." Nat Rev Neurosci **2**(10): 685-94.

Hale, T. S., S. Bookheimer, et al. (2007). "Atypical brain activation during simple & complex levels of processing in adult ADHD: an fMRI study." J Atten Disord **11**(2): 125-40.

Hart, H., K. Chantiluke, et al. (2014). "Pattern classification of response inhibition in ADHD: Toward the development of neurobiological markers for ADHD." Hum Brain Mapp **35**(7): 3083-94.

Hart, H., A. F. Marquand, et al. (2014). "Predictive neurofunctional markers of attention-deficit/hyperactivity disorder based on pattern classification of temporal processing." J Am Acad Child Adolesc Psychiatry **53**(5): 569-578 e1.

Hart, H., J. Radua, et al. (2013). "Meta-analysis of functional magnetic resonance imaging studies of inhibition and attention in attention-deficit/hyperactivity disorder: exploring task-specific, stimulant medication, and age effects." JAMA Psychiatry **70**(2): 185-98.

Hauser, T. U., R. Iannaccone, et al. (2014). "Role of the medial prefrontal cortex in impaired decision making in juvenile attention-deficit/hyperactivity disorder." JAMA Psychiatry **71**(10): 1165-73.

He, B. J. and M. E. Raichle (2009). "The fMRI signal, slow cortical potential and consciousness." Trends Cogn Sci **13**(7): 302-9.

Hermoye, L., C. Saint-Martin, et al. (2006). "Pediatric diffusion tensor imaging: normal database and observation of the white matter maturation in early childhood." Neuroimage **29**(2): 493-504.

Herpertz, S. C., T. Huebner, et al. (2008). "Emotional processing in male adolescents with childhood-onset conduct disorder." J Child Psychol Psychiatry **49**(7): 781-91.

Herrmann, M. J., S. C. Biehl, et al. (2010). "Neurobiological and psychophysiological correlates of emotional dysregulation in ADHD patients." Atten Defic Hyperact Disord **2**(4): 233-9.

Herrmann, M. J., T. Schreppel, et al. (2009). "Emotional deficits in adult ADHD patients: an ERP study." Soc Cogn Affect Neurosci **4**(4): 340-5.

Hervey, A. S., J. N. Epstein, et al. (2004). "Neuropsychology of adults with attention-deficit/hyperactivity disorder: a meta-analytic review." Neuropsychology **18**(3): 485-503.

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

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

Hoekzema, E., S. Carmona, et al. (2014). "An independent components and functional connectivity analysis of resting state fMRI data points to neural network dysregulation in adult ADHD." Hum Brain Mapp **35**(4): 1261-72.

Hoekzema, E., S. Carmona, et al. (2012). "Laminar thickness alterations in the fronto-parietal cortical mantle of patients with attention-deficit/hyperactivity disorder." PLoS One **7**(12): e48286.

Hulvershorn, L. A., M. Mennes, et al. (2014). "Abnormal amygdala functional connectivity associated with emotional lability in children with attention-deficit/hyperactivity disorder." J Am Acad Child Adolesc Psychiatry **53**(3): 351-61 e1.

Hutton, C., E. De Vita, et al. (2008). "Voxel-based cortical thickness measurements in MRI." Neuroimage **40**(4): 1701-10.

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

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

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

Ivanov, I., J. W. Murrough, et al. (2014). "Cerebellar morphology and the effects of stimulant medications in youths with attention deficit-hyperactivity disorder." Neuropsychopharmacology **39**(3): 718-26.

Jacob, C. and K. P. Lesch (2006). "The Wuerzburg Research Initiative on Adult Attention-Deficit/Hyperactivity Disorder (WURIN-AADHD): multi-layered evaluation of long-term course." Eur Arch Psychiatry Clin Neurosci **256 Suppl 1**: i12-20.

Jenkinson, M., P. Bannister, et al. (2002). "Improved Optimisation for the Robust and Accurate Linear Registration and Motion Correction of Brain Images." Neuroimage **17**(2): 825-841.

Jenkinson, M. and S. Smith (2001). "A global optimisation method for robust affine registration of brain images." Medical Image Analysis **5**(2): 143-156.

Johnston, B. A., B. Mwangi, et al. (2014). "Brainstem abnormalities in attention deficit hyperactivity disorder support high accuracy individual diagnostic classification." Hum Brain Mapp **35**(10): 5179-89.

Jurgens, U. (1984). "The efferent and afferent connections of the supplementary motor area." Brain Res **300**(1): 63-81.

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

Kelly, A. M., A. Di Martino, et al. (2009). "Development of anterior cingulate functional connectivity from late childhood to early adulthood." Cereb Cortex **19**(3): 640-57.

Kelly, A. M., L. Q. Uddin, et al. (2008). "Competition between functional brain networks mediates behavioral variability." Neuroimage **39**(1): 527-37.

Kennedy, D. P., E. Redcay, et al. (2006). "Failing to deactivate: resting functional abnormalities in autism." Proc Natl Acad Sci U S A **103**(21): 8275-80.

Kessler, D., M. Angstadt, et al. (2014). "Modality-spanning deficits in attention-deficit/hyperactivity disorder in functional networks, gray matter, and white matter." J Neurosci **34**(50): 16555-66.

Kessler, R. C., L. Adler, et al. (2006). "The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication." Am J Psychiatry **163**(4): 716-23.

Kitzbichler, M. G., R. N. Henson, et al. (2011). "Cognitive effort drives workspace configuration of human brain functional networks." J Neurosci **31**(22): 8259-70.

Klein, A., J. Andersson, et al. (2009). "Evaluation of 14 nonlinear deformation algorithms applied to human brain MRI registration." Neuroimage **46**(3): 786-802.

Ko, C., J. Yen, et al. (2013). "Brain activation deficit in increased-load working memory tasks among adults with ADHD using fMRI." Eur Arch Psychiatry Clin Neurosci **263**(7): 561-573.

Kobel, M., N. Bechtel, et al. (2010). "Structural and functional imaging approaches in attention deficit/hyperactivity disorder: does the temporal lobe play a key role?" Psychiatry Res **183**(3): 230-6.

Kobel, M., N. Bechtel, et al. (2009). "Effects of methylphenidate on working memory functioning in children with attention deficit/hyperactivity disorder." Eur J Paediatr Neurol **13**(6): 516-23.

Konrad, K., S. Neufang, et al. (2006). "Dysfunctional attentional networks in children with attention deficit/hyperactivity disorder: evidence from an event-related functional magnetic resonance imaging study." Biol Psychiatry **59**(7): 643-51.

Kooij, S. J., S. Bejerot, et al. (2010). "European consensus statement on diagnosis and treatment of adult ADHD: The European Network Adult ADHD." BMC Psychiatry **10**: 67.

Li, F., N. He, et al. (2014). "Intrinsic Brain Abnormalities in Attention Deficit Hyperactivity Disorder: A Resting-State Functional MR Imaging Study." Radiology **272**(2): 514-23.

Li, Y., F. Li, et al. (2014). "Neural hyperactivity related to working memory in drug-naive boys with attention deficit hyperactivity disorder." Prog Neuropsychopharmacol Biol Psychiatry **53**: 116-22.

Liddle, E. B., C. Hollis, et al. (2011). "Task-related default mode network modulation and inhibitory control in ADHD: effects of motivation and methylphenidate." J Child Psychol Psychiatry **52**(7): 761-71.

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

Luman, M., G. Tripp, et al. (2010). "Identifying the neurobiology of altered reinforcement sensitivity in ADHD: a review and research agenda." Neurosci Biobehav Rev **34**(5): 744-54.

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

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

Madre, M., E. Pomarol-Clotet, et al. (2013). "Brain functional abnormality in schizo-affective disorder: an fMRI study." Psychol Med **43**(1): 143-53.

Mahone, E. M., M. E. Ranta, et al. (2011). "Comprehensive examination of frontal regions in boys and girls with attention-deficit/hyperactivity disorder." J Int Neuropsychol Soc **17**(6): 1047-57.

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

Makris, N., L. Liang, et al. (2013). "Toward Defining the Neural Substrates of ADHD: A Controlled Structural MRI Study in Medication-Naive Adults." J Atten Disord.

Makris, N., L. J. Seidman, et al. (2010). "Anterior cingulate volumetric alterations in treatment-naive adults with ADHD: a pilot study." J Atten Disord **13**(4): 407-13.

Marsh, A. A., E. C. Finger, et al. (2008). "Reduced amygdala response to fearful expressions in children and adolescents with callous-unemotional traits and disruptive behavior disorders." Am J Psychiatry **165**(6): 712-20.

Marx, I., G. Domes, et al. (2011). "Enhanced emotional interference on working memory performance in adults with ADHD." World J Biol Psychiatry **12 Suppl 1**: 70-5.

Massat, I., H. Slama, et al. (2012). "Working memory-related functional brain patterns in never medicated children with ADHD." PLoS One **7**(11): e49392.

Mataro, M., C. Garcia-Sanchez, et al. (1997). "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 **54**(8): 963-8.

Mattfeld, A. T., J. D. Gabrieli, et al. (2014). "Brain differences between persistent and remitted attention deficit hyperactivity disorder." Brain **137**(Pt 9): 2423-8.

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

McCarthy, H., N. Skokauskas, et al. (2014). "Identifying a consistent pattern of neural function in attention deficit hyperactivity disorder: a meta-analysis." Psychol Med **44**(4): 869-80.

McCarthy, H., N. Skokauskas, et al. (2013). "Attention network hypoconnectivity with default and affective network hyperconnectivity in adults diagnosed with attention-deficit/hyperactivity disorder in childhood." JAMA Psychiatry **70**(12): 1329-37.

McIntosh, D., S. Kutcher, et al. (2009). "Adult ADHD and comorbid depression: A consensus-derived diagnostic algorithm for ADHD." Neuropsychiatr Dis Treat **5**: 137-50.

Menon, V. (2011). "Large-scale brain networks and psychopathology: a unifying triple network model." Trends Cogn Sci **15**(10): 483-506.

Miller, M., J. Ho, et al. (2012). "Executive functions in girls with ADHD followed prospectively into young adulthood." Neuropsychology **26**(3): 278-287.

Modesto-Lowe, V., M. Chaplin, et al. (2013). "Are motivation deficits underestimated in patients with ADHD? A review of the literature." Postgrad Med **125**(4): 47-52.

Morein-Zamir, S., C. Dodds, et al. (2014). "Hypoactivation in right inferior frontal cortex is specifically associated with motor response inhibition in adult ADHD." Hum Brain Mapp **35**(10): 5141-5152.

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

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

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

Mulligan, R. C., V. S. Knopik, et al. (2011). "Neural correlates of inhibitory control in adult attention deficit/hyperactivity disorder: evidence from the Milwaukee longitudinal sample." Psychiatry Res **194**(2): 119-29.

Nakao, T., J. Radua, et al. (2011). "Gray matter volume abnormalities in ADHD: voxel-based meta-analysis exploring the effects of age and stimulant medication." Am J Psychiatry **168**(11): 1154-63.

Narr, K. L., R. P. Woods, et al. (2009). "Widespread cortical thinning is a robust anatomical marker for attention-deficit/hyperactivity disorder." J Am Acad Child Adolesc Psychiatry **48**(10): 1014-22.

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

O'Gorman, R., M. Mehta, et al. (2008). "Increased cerebral perfusion in adult attention deficit hyperactivity disorder is normalised by stimulant treatment: a non-invasive MRI pilot study." Neuroimage **42**(1): 36-41.

Onnink, A. M., M. P. Zwiers, et al. (2014). "Brain alterations in adult ADHD: effects of gender, treatment and comorbid depression." Eur Neuropsychopharmacol **24**(3): 397-409.

Orinstein, A. J. and M. C. Stevens (2014). "Brain activity in predominantly-inattentive subtype attention-deficit/hyperactivity disorder during an auditory oddball attention task." Psychiatry Res **223**(2): 121-8.

Ou, J., Z. Lian, et al. (2014). "Atomic dynamic functional interaction patterns for characterization of ADHD." Hum Brain Mapp **35**(10): 5262-78.

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

Owen, A. M., K. M. McMillan, et al. (2005). "N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies." Hum Brain Mapp **25**(1): 46-59.

Paloyelis, Y., M. A. Mehta, et al. (2007). "Functional MRI in ADHD: a systematic literature review." Expert Rev Neurother **7**(10): 1337-56.

Passarotti, A., J. Sweeney, et al. (2010). "Emotion processing influences working memory circuits in pediatric bipolar disorder and attention-deficit/hyperactivity disorder." J Am Acad Child Adolesc Psychiatry **49**(10): 1064-1080.

Perlov, E., A. Philipsen, et al. (2008). "Hippocampus and amygdala morphology in adults with attention-deficit hyperactivity disorder." J Psychiatry Neurosci **33**(6): 509-15.

Peterson, B. S., M. N. Potenza, et al. (2009). "An FMRI study of the effects of psychostimulants on default-mode processing during Stroop task performance in youths with ADHD." Am J Psychiatry **166**(11): 1286-94.

Pineda, D. A., M. A. Restrepo, et al. (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.

Pironti, V. A., M. C. Lai, et al. (2014). "Neuroanatomical Abnormalities and Cognitive Impairments Are Shared by Adults with Attention-Deficit/Hyperactivity Disorder and Their Unaffected First-Degree Relatives." Biol Psychiatry **76**(8): 639-647.

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

Plichta, M. M. and A. Scheres (2014). "Ventral-striatal responsiveness during reward anticipation in ADHD and its relation to trait impulsivity in the healthy population: a meta-analytic review of the fMRI literature." Neurosci Biobehav Rev **38**: 125-34.

Plichta, M. M., N. Vasic, et al. (2009). "Neural hyporesponsiveness and hyperresponsiveness during immediate and delayed reward processing in adult attention-deficit/hyperactivity disorder." Biol Psychiatry **65**(1): 7-14.

Pliszka, S., D. Glahn, et al. (2006). "Neuroimaging of inhibitory control areas in children with attention deficit hyperactivity disorder who were treatment naive or in long-term treatment." Am J Psycvhiatry **163**(6): 1052-1060.

Polanczyk, G., M. S. de Lima, et al. (2007). "The worldwide prevalence of ADHD: a systematic review and metaregression analysis." Am J Psychiatry **164**(6): 942-8.

Pomarol-Clotet, E., N. Moro, et al. (2012). "Failure of de-activation in the medial frontal cortex in mania: evidence for default mode network dysfunction in the disorder." World J Biol Psychiatry **13**(8): 616-26.

Pomarol-Clotet, E., R. Salvador, et al. (2008). "Failure to deactivate in the prefrontal cortex in schizophrenia: dysfunction of the default mode network?" Psychol Med **38**(8): 1185-93.

Posner, J., T. V. Maia, et al. (2011). "The attenuation of dysfunctional emotional processing with stimulant medication: an fMRI study of adolescents with ADHD." Psychiatry Res **193**(3): 151-60.

Posner, J., B. J. Nagel, et al. (2011). "Abnormal amygdalar activation and connectivity in adolescents with attention-deficit/hyperactivity disorder." J Am Acad Child Adolesc Psychiatry **50**(8): 828-37 e3.

Posner, J., C. Park, et al. (2014). "Connecting the dots: a review of resting connectivity MRI studies in attention-deficit/hyperactivity disorder." Neuropsychol Rev **24**(1): 3-15.

Posner, J., J. A. Russell, et al. (2009). "The neurophysiological bases of emotion: An fMRI study of the affective circumplex using emotion-denoting words." Hum Brain Mapp **30**(3): 883-95.

Posner, J., F. Siciliano, et al. (2014). "A multimodal MRI study of the hippocampus in medication-naive children with ADHD: what connects ADHD and depression?" Psychiatry Res **224**(2): 112-8.

Potenza, M. N., H. C. Leung, et al. (2003). "An FMRI Stroop task study of ventromedial prefrontal cortical function in pathological gamblers." Am J Psychiatry **160**(11): 1990-4.

Prehn-Kristensen, A., K. Krauel, et al. (2011). "Methylphenidate does not improve interference control during a working memory task in young patients with attention-deficit hyperactivity disorder." Brain Res **1388**: 56-68.

Proal, E., P. Reiss, et al. (2011). "Brain gray matter deficits at 33-year follow-up in adults with attention-deficit/hyperactivity disorder established in childhood." Arch Gen Psychiatry **68**(11): 1122-1134.

Qiu, M. G., Z. Ye, et al. (2011). "Changes of brain structure and function in ADHD children." Brain Topogr **24**(3-4): 243-52.

R_Development_Core_Team (2011). R: A language and environment for statistical computing. Vienna, Austria, R Foundation for Statistical Computing.

Radua, J., E. J. Canales-Rodriguez, et al. (2014). "Validity of modulation and optimal settings for advanced voxel-based morphometry." Neuroimage **86**: 81-90.

Raichle, M. E. (2009). "A paradigm shift in functional brain imaging." J Neurosci **29**(41): 12729-34.

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

Ramos-Quiroga, J. A., R. Bosch, et al. (2012). "Criterion and concurrent validity of Conners Adult ADHD Diagnostic Interview for DSM-IV (CAADID) Spanish version." Rev Psiquiatr Salud Ment **5**(4): 229-35.

Ray, S., M. Miller, et al. (2014). "Structural and functional connectivity of the human brain in autism spectrum disorders and attention-deficit/hyperactivity disorder: A rich club-organization study." Hum Brain Mapp **35**(12): 6032-48.

Reimherr, F. W., B. K. Marchant, et al. (2005). "Emotional dysregulation in adult ADHD and response to atomoxetine." Biol Psychiatry **58**(2): 125-31.

Rosler, M., M. Casas, et al. (2010). "Attention deficit hyperactivity disorder in adults." World J Biol Psychiatry **11**(5): 684-98.

Rubia, K. (2011). ""Cool" inferior frontostriatal dysfunction in attention-deficit/hyperactivity disorder versus "hot" ventromedial orbitofrontal-limbic dysfunction in conduct disorder: a review." Biol Psychiatry **69**(12): e69-87.

Rubia, K., A. A. Alegria, et al. (2014). "Effects of stimulants on brain function in attention-deficit/hyperactivity disorder: a systematic review and meta-analysis." Biol Psychiatry **76**(8): 616-28.

Rubia, K., R. Halari, et al. (2009). "Impulsiveness as a timing disturbance: neurocognitive abnormalities in attention-deficit hyperactivity disorder during temporal processes and normalization with methylphenidate." Philos Trans R Soc Lond B Biol Sci **364**(1525): 1919-1931.

Rubia, K., R. Halari, et al. (2009). "Methylphenidate normalises activation and functional connectivity deficits in attention and motivation networks in medication-naive children with ADHD during a rewarded continuous performance task." Neuropharmacology **57**(7-8): 640-52.

Rubia, K., R. Halari, et al. (2011). "Methylphenidate normalizes fronto-striatal underactivation during interference inhibition in medication-naïve boys with attention-deficit hyperactivity disorder." Neuropsychopharmacology **36**(8): 1575-1586.

Rubia, K., R. Halari, et al. (2011). "Methylphenidate normalizes frontocingulate underactivation during error processing in attention-deficit/hyperactivity disorder." Biol Psychiatry **70**(3): 255-62.

Rubia, K., S. Overmeyer, et al. (1999). "Hypofrontality in attention deficit hyperactivity disorder during higher-order motor control: a study with functional MRI." Am J Psychiatry **156**(6): 891-6.

Rubia, K., A. B. Smith, et al. (2005). "Abnormal brain activation during inhibition and error detection in medication-naive adolescents with ADHD." Am J Psychiatry **162**(6): 1067-75.

Salimi-Khorshidi, G., S. M. Smith, et al. (2011). "Adjusting the effect of nonstationarity in cluster-based and TFCE inference." Neuroimage **54**(3): 2006-19.

Sasayama, D., A. Hayashida, et al. (2010). "Neuroanatomical correlates of attention-deficit-hyperactivity disorder accounting for comorbid oppositional defiant disorder and conduct disorder." Psychiatry Clin Neurosci **64**(4): 394-402.

Sato, J. R., M. Q. Hoexter, et al. (2012). "Evaluation of pattern recognition and feature extraction methods in ADHD prediction." Front Syst Neurosci **6**: 68.

Scheres, A., M. P. Milham, et al. (2007). "Ventral striatal hyporesponsiveness during reward anticipation in attention-deficit/hyperactivity disorder." Biol Psychiatry **61**(5): 720-4.

Schnoebelen, S., M. Semrud-Clikeman, et al. (2010). "Corpus callosum anatomy in chronically treated and stimulant naive ADHD." J Atten Disord **14**(3): 256-66.

Schulz, K. P., J. Fan, et al. (2004). "Response inhibition in adolescents diagnosed with attention deficit hyperactivity disorder during childhood: an event-related FMRI study." Am J Psychiatry **161**(9): 1650-7.

Schweitzer, J. B., D. O. Lee, et al. (2004). "Effect of methylphenidate on executive functioning in adults with attention-deficit/hyperactivity disorder: normalization of behavior but not related brain activity." Biol Psychiatry **56**(8): 597-606.

Schweren, L. J., P. de Zeeuw, et al. (2013). "MR imaging of the effects of methylphenidate on brain structure and function in attention-deficit/hyperactivity disorder." Eur Neuropsychopharmacol **23**(10): 1151-64.

Seidman, L. J., J. Biederman, et al. (2011). "Gray matter alterations in adults with attention-deficit/hyperactivity disorder identified by voxel based morphometry." Biol Psychiatry **69**(9): 857-66.

Seidman, L. J., A. Doyle, et al. (2004). "Neuropsychological function in adults with attention-deficit/hyperactivity disorder." Psychiatr Clin North Am **27**(2): 261-82.

Seidman, L. J., E. M. Valera, et al. (2006). "Dorsolateral prefrontal and anterior cingulate cortex volumetric abnormalities in adults with attention-deficit/hyperactivity disorder identified by magnetic resonance imaging." Biol Psychiatry **60**(10): 1071-80.

Semrud-Clikeman, M., P. A. Filipek, et al. (1994). "Attention-deficit hyperactivity disorder: magnetic resonance imaging morphometric analysis of the corpus callosum." J Am Acad Child Adolesc Psychiatry **33**(6): 875-81.

Semrud-Clikeman, M., S. R. Pliszka, et al. (2006). "Volumetric MRI differences in treatment-naive vs chronically treated children with ADHD." Neurology **67**(6): 1023-7.

Sergeant, J. A. (2005). "Modeling attention-deficit/hyperactivity disorder: a critical appraisal of the cognitive-energetic model." Biol Psychiatry **57**(11): 1248-55.

Shafritz, K. M., K. E. Marchione, et al. (2004). "The effects of methylphenidate on neural systems of attention in attention deficit hyperactivity disorder." Am J Psychiatry **161**(11): 1990-7.

Shaw, P., P. De Rossi, et al. (2014). "Mapping the development of the Basal Ganglia in children with attention-deficit/hyperactivity disorder." J Am Acad Child Adolesc Psychiatry **53**(7): 780-789 e11.

Shaw, P., K. Eckstrand, et al. (2007). "Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation." Proc Natl Acad Sci U S A **104**(49): 19649-19654.

Shaw, P., F. Lalonde, et al. (2009). "Development of cortical asymmetry in typically developing children and its disruption in attention-deficit/hyperactivity disorder." Arch Gen Psychiatry **66**(8): 888-96.

Shaw, P., J. Lerch, et al. (2006). "Longitudinal mapping of cortical thickness and clinical outcome in children and adolescents with attention-deficit/hyperactivity disorder." Arch Gen Psychiatry **63**(5): 540-9.

Shaw, P., M. Malek, et al. (2013). "Trajectories of cerebral cortical development in childhood and adolescence and adult attention-deficit/hyperactivity disorder." Biol Psychiatry **74**(8): 599-606.

Shaw, P. and C. Rabin (2009). "New insights into attention-deficit/hyperactivity disorder using structural neuroimaging." Curr Psychiatry Rep **11**(5): 393-398.

Shaw, P., W. S. Sharp, et al. (2009). "Psychostimulant treatment and the developing cortex in attention deficit hyperactivity disorder." Am J Psychiatry **166**(1): 58-63.

Shehzad, Z., A. M. Kelly, et al. (2009). "The resting brain: unconstrained yet reliable." Cereb Cortex **19**(10): 2209-29.

Sheline, Y. I., D. M. Barch, et al. (2009). "The default mode network and self-referential processes in depression." Proc Natl Acad Sci U S A **106**(6): 1942-7.

Silk, T., A. Vance, et al. (2008). "Dysfunction in the Fronto-Parietal Network in Attention Deficit Hyperactivity Disorder (ADHD): An fMRI Study." Brain Imaging and Behavior **2**: 123–131.

Smith, A. B., E. Taylor, et al. (2006). "Task-specific hypoactivation in prefrontal and temporoparietal brain regions during motor inhibition and task switching in medication-naive children and adolescents with attention deficit hyperactivity disorder." Am J Psychiatry **163**(6): 1044-51.

Smith, S., M. Jenkinson, et al. (2004). "Advances in functional and structural MR image analysis and implementation as FSL." Neuroimage **23**(Suppl 1:S208-19).

Smith, S. M. (2002). "Fast robust automated brain extraction." Hum Brain Mapp **17**(3): 143-55.

Smith, S. M. and T. E. Nichols (2009). "Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference." Neuroimage **44**(1): 83-98.

Sobel, L. J., R. Bansal, et al. (2010). "Basal ganglia surface morphology and the effects of stimulant medications in youth with attention deficit hyperactivity disorder." Am J Psychiatry **167**(8): 977-86.

Sokunbi, M. O., W. Fung, et al. (2013). "Resting state fMRI entropy probes complexity of brain activity in adults with ADHD." Psychiatry Res **214**(3): 341-8.

Sonuga-Barke, E., P. Bitsakou, et al. (2010). "Beyond the dual pathway model: evidence for the dissociation of timing, inhibitory, and delay-related impairments in attention-deficit/hyperactivity disorder." J Am Acad Child Adolesc Psychiatry **49**(4): 345-55.

Sonuga-Barke, E. J. (2003). "The dual pathway model of AD/HD: an elaboration of neuro-developmental characteristics." Neurosci Biobehav Rev **27**(7): 593-604.

Sonuga-Barke, E. J. and F. X. Castellanos (2007). "Spontaneous attentional fluctuations in impaired states and pathological conditions: a neurobiological hypothesis." Neurosci Biobehav Rev **31**(7): 977-86.

Sonuga-Barke, E. J., J. A. Sergeant, et al. (2008). "Executive dysfunction and delay aversion in attention deficit hyperactivity disorder: nosologic and diagnostic implications." Child Adolesc Psychiatr Clin N Am **17**(2): 367-84, ix.

Sowell, E. R., P. M. Thompson, et al. (2003). "Cortical abnormalities in children and adolescents with attention-deficit hyperactivity disorder." Lancet **362**(9397): 1699-707.

Spencer, T. J., A. Brown, et al. (2013). "Effect of psychostimulants on brain structure and function in ADHD: a qualitative literature review of magnetic resonance imaging-based neuroimaging studies." J Clin Psychiatry **74**(9): 902-17.

Spinelli, S., S. Joel, et al. (2011). "Different neural patterns are associated with trials preceding inhibitory errors in children with and without attention-deficit/hyperactivity disorder." J Am Acad Child Adolesc Psychiatry **50**(7): 705-715.

Sporns, O. (2011). Networks of the brain. Cambridge, MA: MIT Press.

Sporns, O. (2014). "Network attributes for segregation and integration in the human brain." Curr Opin Neurobiol **23**(2): 162-71.

Sripada, C., D. Kessler, et al. (2014). "Disrupted network architecture of the resting brain in attention-deficit/hyperactivity disorder." Hum Brain Mapp **35**(9): 4693-705.

Stoy, M., F. Schlagenhauf, et al. (2011). "Reward processing in male adults with childhood ADHD--a comparison between drug-naïve and methylphenidate-treated subjects." Psychopharmacology **215**(3): 467-481.

Strohle, A., M. Stoy, et al. (2008). "Reward anticipation and outcomes in adult males with attention-deficit/hyperactivity disorder." Neuroimage **39**(3): 966-72.

Sun, L., Q. Cao, et al. (2012). "Abnormal functional connectivity between the anterior cingulate and the default mode network in drug-naive boys with attention deficit hyperactivity disorder." Psychiatry Res **201**(2): 120-7.

Surman, C. B., J. Biederman, et al. (2011). "Deficient emotional self-regulation and adult attention deficit hyperactivity disorder: a family risk analysis." Am J Psychiatry **168**(6): 617-23.

Suskauer, S., D. Simmonds, et al. (2008). "fMRI of intrasubject variability in ADHD: anomalous premotor activity with prefrontal compensation." J Am Acad Child Adolesc Psychiatry **47**(10): 1141-1050.

Tamm, L., V. Menon, et al. (2004). "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**(11): 1430-40.

Tanji, J., K. Taniguchi, et al. (1980). "Supplementary motor area: neuronal response to motor instructions." J Neurophysiol **43**(1): 60-8.

Teicher, M., C. Anderson, et al. (2000). "Functional deficits in basal ganglia of children with attention-deficit/hyperactivity disorder shown with functional magnetic resonance imaging relaxometry." Nat Med **6**(4): 470-473.

Tian, L., T. Jiang, et al. (2008). "Enhanced resting-state brain activities in ADHD patients: a fMRI study." Brain Dev **30**(5): 342-8.

Tian, L., T. Jiang, et al. (2006). "Altered resting-state functional connectivity patterns of anterior cingulate cortex in adolescents with attention deficit hyperactivity disorder." Neurosci Lett **400**(1-2): 39-43.

Tomasi, D. and N. D. Volkow (2011). "Abnormal functional connectivity in children with attention-deficit/hyperactivity disorder." Biol Psychiatry **71**(5): 443-50.

Tremols, V., A. Bielsa, et al. (2008). "Differential abnormalities of the head and body of the caudate nucleus in attention deficit-hyperactivity disorder." Psychiatry Res **163**(3): 270-8.

Uddin, L. Q., A. M. Kelly, et al. (2009). "Functional connectivity of default mode network components: correlation, anticorrelation, and causality." Hum Brain Mapp **30**(2): 625-37.

Uddin, L. Q., A. M. Kelly, et al. (2008). "Network homogeneity reveals decreased integrity of default-mode network in ADHD." J Neurosci Methods **169**(1): 249-54.

Urry, H. L., C. M. van Reekum, et al. (2006). "Amygdala and ventromedial prefrontal cortex are inversely coupled during regulation of negative affect and predict the diurnal pattern of cortisol secretion among older adults." J Neurosci **26**(16): 4415-25.

Vaidya, C. J., G. Austin, et al. (1998). "Selective effects of methylphenidate in attention deficit hyperactivity disorder: a functional magnetic resonance study." Proc Natl Acad Sci U S A **95**(24): 14494-9.

Vaidya, C. J., S. A. Bunge, et al. (2005). "Altered neural substrates of cognitive control in childhood ADHD: evidence from functional magnetic resonance imaging." Am J Psychiatry **162**(9): 1605-13.

Valera, E. M., A. Brown, et al. (2010). "Sex differences in the functional neuroanatomy of working memory in adults with ADHD." Am J Psychiatry **167**(1): 86-94.

Valera, E. M., S. V. Faraone, et al. (2005). "Functional neuroanatomy of working memory in adults with attention-deficit/hyperactivity disorder." Biol Psychiatry **57**(5): 439-47.

Valera, E. M., S. V. Faraone, et al. (2007). "Meta-analysis of structural imaging findings in attention-deficit/hyperactivity disorder." Biol Psychiatry **61**(12): 1361-9.

Valera, E. M., R. M. Spencer, et al. (2010). "Neural substrates of impaired sensorimotor timing in adult attention-deficit/hyperactivity disorder." Biol Psychiatry **68**(4): 359-67.

van 't Ent, D., H. Lehn, et al. (2007). "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 **35**(3): 1004-20.

Wager, T. D., K. L. Phan, et al. (2003). "Valence, gender, and lateralization of functional brain anatomy in emotion: a meta-analysis of findings from neuroimaging." Neuroimage **19**(3): 513-31.

Wang, J., T. Jiang, et al. (2007). "Characterizing anatomic differences in boys with attention-deficit/hyperactivity disorder with the use of deformation-based morphometry." AJNR Am J Neuroradiol **28**(3): 543-547.

Wang, L., C. Zhu, et al. (2009). "Altered small-world brain functional networks in children with attention-deficit/hyperactivity disorder." Hum Brain Mapp **30**(2): 638-49.

Ward, M. F., P. H. Wender, et al. (1993). "The Wender Utah Rating Scale: an aid in the retrospective diagnosis of childhood attention deficit hyperactivity disorder." Am J Psychiatry **150**(6): 885-90.

Wechsler, D. (1997). Wechsler Adult Intelligence Scale—3rd Edition (WAIS-3®). San Antonio, TX, Harcourt Assessment.

Whalen, P. J., G. Bush, et al. (1998). "The emotional counting Stroop paradigm: a functional magnetic resonance imaging probe of the anterior cingulate affective division." Biol Psychiatry **44**(12): 1219-28.

Whitfield-Gabrieli, S. and J. M. Ford (2012). "Default mode network activity and connectivity in psychopathology." Annu Rev Clin Psychol **8**: 49-76.

Whitfield-Gabrieli, S., H. Thermenos, et al. (2009). "Hyperactivity and hyperconnectivity of the default network in schizophrenia and in first-degree relatives of persons with schizophrenia." Proc Natl Acad Sci U S A **106**(4): 1279-84.

Wilens, T. E., J. Biederman, et al. (2002). "Attention deficit/hyperactivity disorder across the lifespan." Annu Rev Med **53**: 113-31.

Willcutt, E. G. (2012). "The prevalence of DSM-IV attention-deficit/hyperactivity disorder: a meta-analytic review." Neurotherapeutics **9**(3): 490-9.

Willcutt, E. G., A. E. Doyle, et al. (2005). "Validity of the executive function theory of attention-deficit/hyperactivity disorder: a meta-analytic review." Biol Psychiatry **57**(11): 1336-46.

Wolf, R. C., M. M. Plichta, et al. (2009). "Regional brain activation changes and abnormal functional connectivity of the ventrolateral prefrontal cortex during working memory processing in adults with attention-deficit/hyperactivity disorder." Hum Brain Mapp **30**(7): 2252-66.

Wong, C. G. and M. C. Stevens (2012). "The effects of stimulant medication on working memory functional connectivity in attention-deficit/hyperactivity disorder." Biol Psychiatry **71**(5): 458-66.

Woolrich, M., T. Behrens, et al. (2004). "Multi-level linear modelling for FMRI group analysis using Bayesian inference." Neuroimage **21**(4): 1732-1747.

Woolrich, M. W., B. D. Ripley, et al. (2001). "Temporal autocorrelation in univariate linear modeling of FMRI data." Neuroimage **14**(6): 1370-86.

Worsley, K. (2001). Statistical analysis of activation images. Functional MRI: an introduction to Methods. P. Jezzard, P. Matthews and S. Smith. Oxford, Oxford University Press**:** 251-270.

Yang, H., Q. Z. Wu, et al. (2011). "Abnormal spontaneous brain activity in medication-naive ADHD children: a resting state fMRI study." Neurosci Lett **502**(2): 89-93.

Yang, P., P.-N. Wang, et al. (2008). "Absence of gender effect on children with attention-deficit/hyperactivity disorder as assessed by optimized voxel-based morphometry." Psychiatry Res **164**(3): 245-253.

Yuan, R., X. Di, et al. (2013). "Regional homogeneity of resting-state fMRI contributes to both neurovascular and task activation variations." Magn Reson Imaging **31**(9): 1492-500.

Zametkin, A. J., T. E. Nordahl, et al. (1990). "Cerebral glucose metabolism in adults with hyperactivity of childhood onset." N Engl J Med **323**(20): 1361-6.

Zang, Y. F., Y. He, et al. (2007). "Altered baseline brain activity in children with ADHD revealed by resting-state functional MRI." Brain Dev **29**(2): 83-91.

Zang, Y. F., Z. Jin, et al. (2005). "Functional MRI in attention-deficit hyperactivity disorder: evidence for hypofrontality." Brain Dev **27**(8): 544-50.

Zhang, Y., M. Brady, et al. (2001). "Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm." IEEE transactions on medical imaging **20**(1): 45-57.

Zhu, C. Z., Y. F. Zang, et al. (2008). "Fisher discriminative analysis of resting-state brain function for attention-deficit/hyperactivity disorder." Neuroimage **40**(1): 110-20.

Zou, Q. H., C. Z. Zhu, et al. (2008). "An improved approach to detection of amplitude of low-frequency fluctuation (ALFF) for resting-state fMRI: fractional ALFF." J Neurosci Methods **172**(1): 137-41.