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BRAIN ANATOMY OF ATTENTION DEFICIT/HYPERACTIVITY DISORDER IN CHILDREN AND ADULTS WITH CHILDHOOD ONSET

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A MIS PAPAS Y A MI HERMANO

CONTENTS

SUMMARY

Attention-Deficit/Hyperactivity Disorder (ADHD) is one of the most common neurodevelopmental disorders occurring in childhood. The main symptoms are developmentally excessive levels of inattention, impulsivity and hyperactivity. ADHD occurs in 8 to 12% of school age children worldwide; the majority (60%-85%) continues to meet criteria for the disorder during their teenage years.

Volumetric studies in children with Attention-Deficit/Hyperactivity Disorder (ADHD) have consistently found global reductions of total brain volume with frontal-striatal regions, cerebellum and parieto-temporal regions particularly affected relative to typically developing subjects. The adult diagnosis of ADHD requires onset in childhood, but persistence of ADHD into adulthood is now well documented. This longitudinal course together with smaller brain volumes in children with ADHD has raised questions about brain development into adulthood.

The use of different neuroimaging techniques by independent groups is leading to an improved understanding of the neural substrates underlying the pathophysiology of ADHD. Nowadays, researchers have begun to place more emphasis on the potential contributions of dysfunctional brain circuits, rather than isolated regional abnormalities. Therefore, the aim of this thesis is to examine the neural substrates of ADHD by applying three different anatomic neuroimaging approaches. A secondary aim is to analyze whether these brain differences are related with the diagnosis of ADHD in childhood or whether it is associated with the persistence of the diagnosis in adulthood.

The results of the present dissertation are two-fold. First, in a large sample of children and adolescents with ADHD, we found a striking volumetric reduction in the ventral striatum, a region critically involved in reward processes that is a key relay in cortical-striatal-thalamo-cortical circuits (reward circuit). Second, in adults diagnosed with ADHD in childhood, we found reduced cortical thickness and voxel-based morphometry (VBM) gray matter volume in parietal and motor regions (Dorsal attentional network). Most of these differences were independent of current adult diagnoses status. In other words, these differences were largely found in both individuals with persistent ADHD and

in those who were in remission. By contrast, reward-related regions were diminished in probands with persistent ADHD compared to controls but not in those who were in remission. Thus differences in reward-related circuitry (ventral striatum in children, orbitofrontal cortex, parahippocampus, thalamus, and frontal pole in adults) were associated with the current diagnosis of ADHD, whereas frontal-parietal motor cortex differences in adults with ADHD seem to reflect the trait of having had ADHD in childhood.

Our data allow us to suggest an overall integrative hypothesis that dysfunction in the reward circuit, which was particularly prominent in children and adolescents with ADHD and in the adults with persistent ADHD, reflects ongoing symptoms of ADHD. By contrast, abnormalities in the top-down control dorsal attentional network seem to be related to the trait of having had ADHD in childhood, as the abnormalities were comparable in adults who had remitted or who had persistent ADHD. On the basis of our data, we propose a model of ADHD physiopathology in which two main circuits interact. These are the dorsal attentional network, which seems to be anatomically abnormal in individuals with a history of ADHD, whether or not they are currently affected. As such, we hypothesize that dorsal attentional network deficiencies may be related to the genetic factors associated with ADHD. By contrast, anatomic abnormalities in the reward circuit appear to be related to current ADHD symptoms. Based on our data, we cannot differentiate whether anatomic changes in the reward circuits are the basis for symptomatic remission, or whether such changes in brain circuits reflect brain remodeling secondary to behavioral effects, such as learning and selective reinforcement. This question will have to be addressed in the future through longitudinal brain imaging studies that can incorporate genetic factors and treatment tracking methods.

LIST OF ABREVIATIONS

AACAP	American Academy of Child and Adolescent Psychiatry
ACC	Anterior cingulate cortex
ADD	Attention Deficit Disorder
ADDH	Attention Deficit Disorder with Hyperactivity
ADHD	Attention-Deficit/Hyperactivity Disorder
BA	Brodmann area
BOLD	Blood oxygenation level dependent
CPT	Continuous performance task
CRS-R	Conners Rating Scales-Revised
CS	Central striatum
CSF	Cerebrospinal fluid
DA	Dopamine
dAN	Dorsal attentional network
DAv	Delay aversion
DLS	Dorsolateral striatum
EF	Executive function
dACC	Dorsal anterior cingulate cortex
DICA	Diagnostic Interview for Children and Adolescents
DLPFC	Dorsolateral prefrontal cortex
dPFC	Dorsal prefrontal cortex
DSM-III	Diagnostic and Statistical Manual of Mental Disorders, 3rd edition
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, Revised
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision
FDA	U.S. Food and Drug Administration
FEF	Frontal eye fields
fMRI	Functional magnetic resonance imaging
Hipp	Hippocampus
Hypo	Hypothalamus
ICD-10	International Classification of Diseases, 10th edition
INDI	International Neuroimaging Data-sharing Initiative
IPs	Intraparietal sulcus
IQ	Intelligence quotient
LHb	Lateral habenula
MPH	Methylphenidate
NA	Noradrenaline
NAcc	Nucleus accumbens
NE	Norepinephrine
NIMH	National Institute of Mental Health
OFC	Orbitofrontal cortex

OMPFC	Orbital and medial prefrontal cortex
PFC	Prefrontal cortex
PPT	Pedunculopontine nucleus
r-fMRI	Resting state functional MRI
ROI	Region of interest
RSC	Retrosplenial cortex
SD	Standard deviation
SNc	Substantia nigra, pars compacta
SNr	Substantia nigra, pars reticulata
SNS	Striatonigralstriatal
STN	Subthalamic nucleus
Thal	Thalamus
TPJ	Temporal-parietal junction
VBM	Voxel based morphometry
vmPFC	Ventromedial prefrontal cortex
VMS	Ventro-medial striatum
VP	Ventral pallidum
VS	Ventral striatum
VTA	Ventral tegmental area

THEORETICAL BACKGROUND

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1.1 Attention-Deficit/Hyperactivity Disorder (ADHD)

1.1.1 DESCRIPTION

Attention-Deficit/Hyperactivity Disorder (ADHD) is one of the most common neurodevelopmental disorders occurring in childhood. The main symptoms are developmentally excessive levels of inattention, impulsivity and hyperactivity. According to the American Psychiatric Association, at least 3% to 5% of school age children in the United States are affected with this condition (1). However, current estimates are that ADHD occurs in 8 to 12% of school age children worldwide (2).

Although ADHD was formerly thought to be limited to childhood, its continuation into adolescence and adulthood is no longer in doubt (3). However, all authors agree that the rate of ADHD does decrease substantially to about 40 to 50% of formerly diagnosed children with ADHD continuing to present with impairing symptoms as adults.

1.1.2 HISTORY

In 1718 Alexander Crichton described characteristics related to children with inattention in an article entitled “Mental Restlessness.” In 1902, Stills provided the first modern description of ADHD. He proposed that children with overactivity, aggression, inattention and insolent behavior had a "Defect of Moral Control," which he believed was a medical disorder beyond the patient’s control. After World War I, many children suffered post-influenza encephalitis. Afterwards many of those children presented aggressive behavior, attention deficits and extreme hyperactivity. In 1937, Charles Bradley, who was treating those extremely hyperactive children, reported that the newly synthesized stimulant, amphetamine, could be profoundly helpful for more than half of those extremely hyperactive children (4). Despite the dramatic effects of medication that Bradley had reported, most child psychiatrists did not follow his example. In the 1950’s, pediatricians treating hyperactive children formulated the belief that the symptoms resulted from subtle forms of brain injury, so the disorder was commonly named “minimal brain damage.” In

1968, the second revision of the psychiatric nosology, DSM-II, renamed it "Hyperkinetic Reaction of Childhood." Then, in the 1970's Virginia Douglas proposed that attention deficit should be considered the primary symptom instead of hyperactivity as previously (5). This notion influenced the revised diagnosis presented in DSM III as Attention Deficit Disorder (ADD, without hyperactivity) or Attention Deficit Disorder with Hyperactivity (ADDH). This latter diagnostic entity combined inattention, impulsiveness and hyperactivity symptoms. In 1987, DSM-III-R was published, and ADD and ADDH were combined into a single category: Attention Deficit Hyperactivity Disorder. In 1994, DSM-IV once again subdivided ADHD, this time into predominantly inattentive subtype, predominantly hyperactive-impulsive subtype and combined subtypes (1).

1.1.3 ETIOLOGY

The specific causes of ADHD are not yet known, but as for all complex traits, the etiology of ADHD is thought to involve a combination of multiple genetic factors interacting with environmental factors (6, 7). Candidate environmental factors include pre-, peri- and postnatal stressors. Alterations during pregnancy such as maternal tobacco and alcohol consumption have also been implicated in the developmental of ADHD (8, 9). Other aspects like maternal allergies to certain foods or toxicity caused by exposure to lead are also believed to play a possible role in the genesis of ADHD in some children (10). ADHD is also associated with prematurity and delivery complications (e.g., anoxia) (11). The disorder is also thought to be worsened by circumstances such as poverty, poor diet, inadequate parental management of children's behavior or family problems (12). Nevertheless, twin and family studies all confirm that most of the variation in ADHD symptoms or diagnosis is due to genetic factors alone or in combination with environmental factors (12).

Genetic factors undoubtedly affect all brain functions including those associated with cognition and motivation. A prominent hypothesis based on the biochemistry of treatment with stimulants posits a deficiency in the concentration of monoamine neurotransmitters in individuals with ADHD (13). The monoamine neurotransmitters are dopamine (DA), noradrenaline (NA) and serotonin. The first and most studied hypothesis has focused on dopaminergic dysregulation, which is currently based on the belief that the

psychostimulants inhibit the dopamine transporter and increase the amount of dopamine in synapses (14, 15). Solanto and colleagues proposed that reward dysregulation, specifically the process that mediates sustained effort, is partially modulated by DA in the prefrontal cortex (PFC)(16) . Now, it is known that methylphenidate not only inhibits the dopamine transporter but also the norepinephrine transporter, and that amphetamines affect all three monoamines, including serotonin (14). Implication of NA in ADHD has been recently supported by data that a norepinephrine reuptake inhibitor is efficacious for treating ADHD (17).

In conclusion, ADHD is a multi-factorial disorder including genetic, environmental elements and their interactions together. Most neurochemical hypotheses have focused on the monoamine neurotransmitters, although such evidence is largely still circumstantial and far from compelling.

1.1.4. CLASSIFICATION AND CRITERIA

In 1994, ADHD was subdivided into three subtypes. There are currently two diagnostic manuals that classify symptoms of hyperactivity, inattention and impulsivity in different ways.

On the one hand, in 1992, the International Classification of Diseases, 10th Edition (ICD-10) included three distinct conditions (see Table 1 for complete criteria):

- **Hyperkinetic Disorder:** combination of overactive, poorly modulated behavior with inattention and lack of persistent task involvement; characteristics pervasive over situations and persistent over time.
- **Disturbance of Activity and Attention:** attention deficit disorder or syndrome with hyperactivity and attention deficit hyperactivity disorder. Excludes hyperkinetic disorder associated with conduct disorder.
- **Hyperkinetic Conduct Disorder:** Presence of Hyperkinetic Disorder and Conduct Disorder.

On the other hand, in 1994 the American Psychiatric Association established the following subtypes:

- **Attention-Deficit/Hyperactivity Disorder, Combined Type:** six or more inattentive, and six or more hyperactivity or impulsivity symptoms present for at least six months.
- **Attention-Deficit/ Hyperactivity Disorder, Predominantly Inattentive Type:** six or more inattentive symptoms and less than six hyperactivity-impulsivity symptoms are present for at least six months.

  Attention-Deficit/Hyperactivity Disorder, Predominantly Hyperactive-Impulsive Type: six or more hyperactive-impulsive symptoms and fewer than six inattention symptoms present for at least six months (see Table 2 for complete criteria):

Table. 1. ICD-10 criteria for the diagnosis of Hyperkinetic Disorders

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G1 At least six of the following symptoms of attention have persisted for at least six months, to a degree that is maladaptive and inconsistent with the developmental level of the child:

- (1) often fails to give close attention to details, or makes careless errors in school work, work or other activities;
- (2) often fails to sustain attention in tasks or play activities;
- (3) often appears not to listen to what is being said to him or her;
- (4) often fails to follow through on instructions or to finish school work, chores, or duties in the workplace (not because of oppositional behaviour or failure to understand instructions);
- (5) is often impaired in organising tasks and activities;
- (6) often avoids or strongly dislikes tasks, such as homework, that require sustained mental effort;
- (7) often loses things necessary for certain tasks and activities, such as school assignments, pencils, books, toys or tools;
- (8) is often easily distracted by external stimuli;
- (9) is often forgetful in the course of daily activities.

G2 At least three of the following symptoms of hyperactivity have persisted for at least six months, to a degree that is maladaptive and inconsistent with the developmental level of the child:

- (1) often fidgets with hands or feet or squirms on seat;
- (2) leaves seat in classroom or in other situations in which remaining seated is expected;
- (3) often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, only feelings of restlessness may be present);
- (4) is often unduly noisy in playing or has difficulty in engaging quietly in leisure activities;
- (5) exhibits a persistent pattern of excessive motor activity that is not substantially modified by social context or demands.

G3 At least one of the following symptoms of impulsivity has persisted for at least six months, to a degree that is maladaptive and inconsistent with the developmental level of the child:

- (1) often blurts out answers before questions have been completed;
- (2) often fails to wait in lines or await turns in games or group situations;
- (3) often interrupts or intrudes on others (e.g. butts into others' conversations or games);
- (4) often talks excessively without appropriate response to social constraints.

G4 Onset of the disorder is no later than the age of seven years.

G5 Pervasiveness

The criteria should be met for more than a single situation, e.g. the combination of inattention and hyperactivity should be present both at home and at school, or at both school and another setting where children are observed, such as a clinic. (Evidence for cross-situationality will ordinarily require information from more than one source; parental reports about classroom behaviour, for instance, are unlikely to be sufficient.)

G6 The symptoms in G1 and G3 cause clinically significant distress or impairment in social, academic, or occupational functioning.

G7 The disorder does not meet the criteria for pervasive developmental disorders (F84.-), manic episode (F30.-), depressive episode (F32.-), or anxiety disorders (F41.-).

Table. 2. DSM-IV-TR criteria for the diagnosis of Attention-Deficit/Hyperactivity Disorder (ADHD).

A. Either (1) or (2)

(1). 6 (or more) of the following symptoms of inattention have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

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

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

Impulsivity
(g) often blurts out answers before questions have been completed
(h) often has difficulty awaiting turn
(i) often interrupts or intrudes on others (e.g. butts into conversations or games)
B. Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before age 7 years.
C. Some impairment from the symptoms is present in two or more settings (e.g. at school [or work] and at home).
D. There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning.
E. The symptoms do not occur exclusively during the course of a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorder and are not better accounted for by another mental disorder (e.g. Mood Disorder, Anxiety Disorder, Dissociative Disorder, or a Personality Disorder)

314.01 ADHD, Combined Type - if both A1 and A2 for at least 6 months
314.00 ADHD, Predominantly Inattentive Type
314.01 ADHD, Predominantly Hyperactive-Impulsive Type

1.1.5. ASSESSMENT

The American Academy of Child and Adolescent Psychiatry has established that screening for ADHD should be part of every patient's mental health assessment by specifically asking questions regarding the major symptom domains of ADHD (inattention, impulsivity, and hyperactivity) and determining if those symptoms cause impairment (18). A full evaluation of ADHD is required whenever parents report that the patient has any ADHD symptom (19).

In ideal conditions, the clinician should perform a detailed interview with the parent about each of the 18 ADHD symptoms listed in DSM-IV. For each symptom, the clinician should determine whether it is present as well as its duration, severity, and frequency. Age at onset of the symptoms should be assessed as well. For a research diagnosis to be applied, the patient must have the required number of symptoms, a chronic course, and onset of symptoms during childhood. Presence of impairment should be distinguished from presence of symptoms. After reviewing the ADHD symptoms, the clinician should interview the parent regarding other common psychiatric disorders of childhood. Formal structured and semi-structured interviews like the Schedule for Affective Disorders and Schizophrenia for School-Age Children (20), the National Institute of Mental Health (NIMH) Diagnostic Interview Schedule for Children (21), the DSM-based Diagnostic Interview For Children and Adolescents (DICA) (22), and the Child and Adolescent Psychiatric Assessment are available (23) and are widely used in research studies. Questionnaires, such as the Conners Parent(24), and Teacher (25) Rating Scales–Revised (CRS-R) are an important and efficient part of the diagnostic assessment but cannot be used in isolation to make a diagnosis of ADHD.

Teachers, parents, and older children can/should all report on symptoms to assess for agreement/validity of diagnosis, to document that the ADHD symptoms occur in multiple settings, and consider the special information that each can provide. If the teacher cannot provide a rating scale or the parent declines permission to contact the school, then materials from school, such as work samples or report cards, should be reviewed or inquired about. A thorough medical history is part of the initial evaluation.

After interviewing the parents, the clinician should interview the child or adolescent. For the preschool or young school-age child, the interview may be done along with the parent interview. Older children and adolescents should be interviewed separately from parents. The primary purpose of the interview with the child or adolescent is not to confirm or refute the diagnosis of ADHD. It is important to consider that young children are not often aware of their symptoms. Adolescents may be aware of their symptoms, but will generally minimize their significance. The interview with the child or adolescent allows the clinician to identify signs or symptoms inconsistent with ADHD or suggestive of other serious comorbid disorders (such as mood, psychotic, or substance abuse disorders).

Since numerous medical problems can be associated with ADHD, the neurologic examination is part of a complete diagnostic evaluation. In addition to the traditional neurologic examination, a number of standardized office examinations that tap developmental neurologic functions are available (26). Furthermore, the neurologic examination provides an opportunity to evaluate commonly co-morbid neurologic problems of coordination like dyspraxia, and dysgraphia (27).

Neuropsychological testing is not a necessary part of the diagnostic assessment of ADHD. However, testing executive functions is recommended, although executive function deficits are not always present in ADHD nor are they unique to ADHD. Intelligence should be assessed. Higher IQ ADHD children may compensate for their attention difficulties sufficiently to mask executive dysfunction on traditional measures (19), and this may have implications for future academic outcomes when support and recognition of ADHD have been less available (28).

1.1.6. OUTCOME

Follow-up studies have begun to delineate the life course of ADHD. A majority (60%-85%) of children with ADHD continue to meet criteria for the disorder during their teenage years (3) clearly indicating that ADHD does not remit with the onset of puberty alone. Although only 40% of 18- to 20-year-old "grown up" ADHD patients met the full criteria for ADHD, 90% had at least five symptoms of ADHD and significant impairment, as indicated by a Global Assessment of Functioning score below 60 in one of the major longitudinal studies (29). Adults with a childhood history of ADHD have higher than expected rates of antisocial, and criminal behavior injuries and accidents (30-32) , employment and marital difficulties (33-35) and health problems and are more likely to have teen pregnancies (36).

1.1.7. TREATMENT

Treatment plans for ADHD in children may consist of psychopharmacological and/or behavior therapy (18). Such plans should include parental and child psychoeducation about ADHD and its various treatment options, linkage with community supports, and recommendations for obtaining additional school resources as appropriate.

After reviewing all available evidence, the American Academy of Child and Adolescent Psychiatry concluded that it deemed established that pharmacological interventions for ADHD are more effective than behavioral treatments alone (37). Behavior therapy may be recommended as an initial treatment if the patient's ADHD symptoms are mild with minimal impairment, the diagnosis of ADHD is uncertain, the patient or parents reject medication treatment, or there is marked disagreement about the diagnosis between parents or between parents and teachers (38). Several studies have shown short-term effectiveness of behavioral parent training (38). No evidence supports nonpharmacological interventions other than behavior therapy (19), including cognitive-behavioral therapy and dietary modification. The AACAP practice parameters recommend that the initial psychopharmacological treatment of ADHD should be a trial with an agent approved by the Food and Drug Administration for the treatment of ADHD. The following table lists the currently approved FDA drugs for ADHD.

Table 3.

Generic Class/ Brand Name	Dose Form	Typical Starting Dose	FDA Max/Day	Off-Label Max/Day	Comments
Amphetamine preparations					
Short-acting					Short-acting stimulants often used as initial treatment in small children (<16 kg), but have disadvantage of b.i.d.-t.i.d. dosing to control symptoms throughout day
Adderall[a]	5, 7.5, 10, 12.5, 15, 20, 30 mg tab	3–5 y: 2.5 mg q.d.; ≥6 y: 5 mg q.d.–b.i.d.	40 mg	>50 kg: 60 mg	
Dexedrine[a]	5 mg cap	3–5 y: 2.5 mg q.d.			
DextroStat[a]	5, 10 mg cap	≥6 y: 5 mg q.d.–b.i.d.			
Long-acting					
Dexedrine Spansule	5, 10, 15 mg cap	≥6 y: 5–10 mg q.d.–b.i.d.	40 mg	>50 kg: 60 mg	Longer acting stimulants offer greater convenience, confidentiality, and compliance with single daily dosing but may have greater problematic effects on evening appetite and sleep
Adderall XR	5, 10, 15, 20, 25, 30 mg cap	≥6 y: 10 mg q.d.	30 mg	>50 kg: 60 mg	
Lisdexamfetamine	30, 50, 70 mg cap	30 mg q.d.	70 mg	Not yet known	Adderall XR cap may be opened and sprinkled on soft foods
Methylphenidate preparations					
Short-acting					Short-acting stimulants often used as initial treatment in small children (<16 kg) but have disadvantage of b.i.d.-t.i.d. dosing to control symptoms throughout day
Focalin	2.5, 5, 10 mg cap	2.5 mg b.i.d.	20 mg	50 mg	
Methylin[a]	5, 10, 20 mg tab	5 mg b.i.d.	60 mg	>50 kg: 100 mg	
Ritalin[a]	5, 10, 20 mg	5 mg b.i.d.	60 mg	>50 kg: 100 mg	
Intermediate-acting					Longer acting stimulants offer greater convenience, confidentiality, and compliance with single daily dosing but may have greater problematic effects on evening appetite and sleep
Metadate ER	10, 20 mg cap	10 mg q.a.m.	60 mg	>50 kg: 100 mg	
Methylin ER	10, 20 mg cap	10 mg q.a.m.	60 mg	>50 kg: 100 mg	
Ritalin SR[a]	20 mg	10 mg q.a.m.	60 mg	>50 kg: 100 mg	
Metadate CD	10, 20, 30, 40, 50, 60 mg	20 mg q.a.m.	60 mg	>50 kg: 100 mg	
Ritalin LA	10, 20, 30, 40 mg	20 mg q.a.m.	60 mg	>50 kg: 100 mg	Metadate CD and Ritalin LA caps may be opened and sprinkled on soft food
Long-acting					
Concerta	18, 27, 36, 54 mg cap	18 mg q.a.m.	72 mg	108 mg	Swallow whole with liquids Nonabsorbable tablet shell may be seen in stool.
Daytrana patch	10, 15, 20, 30 mg patches	Begin with 10 mg patch q.d., then titrate up by patch strength	30 mg	Not yet known	
Focalin XR	5, 10, 15, 20 mg cap	5 mg q.a.m.	30 mg	50 mg	
Selective norepinephrine reuptake inhibitor					
Atomoxetine					Not a schedule II medication
Strattera	10, 18, 25, 40, 60, 80, 100 mg cap	Children and adolescents <70 kg: 0.5 mg/kg/day for 4 days; then 1 mg/kg/day for 4 days; then 1.2 mg/kg/day	Lesser of 1.4 mg/kg or 100 mg	Lesser of 1.8 mg/kg or 100 mg	Consider if active substance abuse or severe side effects of stimulants (mood lability, tics); give q.a.m. or divided doses b.i.d. (effects on late evening behavior); do not open capsule; monitor closely for suicidal thinking and behavior, clinical worsening, or unusual changes in behavior

Note: FDA = U.S. Food and Drug Administration; ADHD = attention-deficit/hyperactivity disorder.
[a] Generic formulation available.

Medications Approved by the FDA for ADHD (Alphabetical by Class) (*From: Pliszka et al., JAACAP, 2007).*

Stimulants are recommended as the first line medication choice to treat ADHD (39-41). At the present time, the following drugs have been approved by the FDA: dextroamphetamine, D and D,L-methylphenidate (MPH), mixed amphetamine salts, atomoxetine (18) and guanfacine [refs]. Several randomized controlled trials in the past 30

years have consistently reported the effectiveness of stimulants for ADHD symptoms (the effect size of stimulant treatment relative to placebo is large, averaging about 1.0, among the largest for psychotropic medications) (18). Physicians are free to choose between the two stimulant types (MPH or amphetamine) because evidence suggests the two are equally efficacious in the treatment of ADHD. The most common side effects of stimulants are appetite decrease, weight loss, insomnia, or headache. Less common side effects of stimulants include tics and emotional lability/irritability.

Atomoxetine is currently considered as a second line pharmacological treatment. Direct comparisons of the efficacy of atomoxetine with that of MPH (42) and amphetamine (18) have shown a greater treatment effect of the stimulants, and in a meta-analysis of atomoxetine and stimulant studies, the effect size for atomoxetine was 0.62 compared with 0.91 and 0.95 for immediate-release and long-acting stimulants, respectively. However, atomoxetine may be considered as the first medication for ADHD in individuals with an active substance abuse problem, comorbid anxiety, or tics. Atomoxetine is preferred if the patient experiences severe adverse effects to stimulants such as mood lability or tics. Adverse effects of atomoxetine that occurred more often than with placebo include gastrointestinal distress, sedation, and decreased appetite (18).

1.2 Neuropsychology of ADHD

The neuropsychological literature of ADHD is extensive and will not be treated comprehensively. Classical models have been largely rooted in psychological theory and the fundamental concepts of executive function and motivation. The principal theories deriving from these perspectives will be briefly discussed. This section will end with alternative perspectives which are instead based in neuronal findings from basic science.

1.2.1 EXECUTIVE FUNCTIONS (EF)

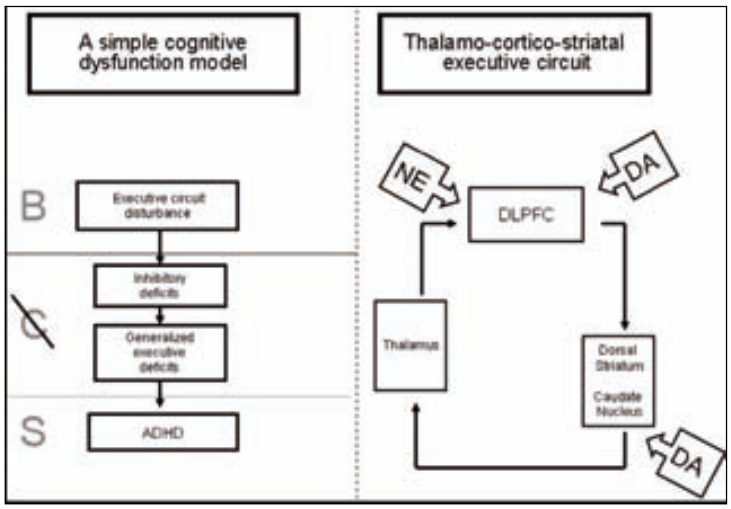


Fig. 1. Representation of simple cognitive deficit model of attention deficit hyperactivity disorder (Barkley 1997) and association with frontal striatal circuitry (Alexander et al. 1990). Slashed C: refers to dysfunction in cognitive processes; DLPFC: Dorsolateral prefrontal cortex; NE: norepinephrine; DA: dopamine. (extracted from Sonuga-Barke 2005)

Children with ADHD tend to have more deficiencies in tasks designed to assess executive function than children without ADHD (43). The executive functions involve attention, planning, response inhibition, problem solving, initiation, cognitive estimation and working memory. The relevance of the frontal lobes is demonstrated by the frontal syndrome that can result from frank damage to certain cerebral frontal areas. This is characterized by apathy, lack of inhibition, lack of motivation and difficulty achieving goals (44).

Pennington and Ozonoff raised the question of which specific domains of executive processes were most involved in ADHD subjects. They pointed out that the evidence was strongest for response inhibition and planning (45). Barkley then proposed that a deficit in response inhibition in ADHD patients should be considered the fundamental deficit

responsible for all other executive functions impairments (13). While this theory has attracted much attention, the data have rarely been supportive, and have mostly falsified the Barkley hypothesis. Berwid et al. (46), noting the overwhelming evidence that children with ADHD have worse performance on the Continuous Performance Task (CPT), which reflects sustained attention deficits (47), suggested that such deficits be considered primary. Also some authors have focused on working memory deficits in ADHD (48).

Despite the extensive literature on executive functions and ADHD, it is clear that executive function deficits are insufficient to be diagnostically relevant for ADHD. Although they are associated with the disorder, the associations are at best moderate, and insufficiently specific (49).

1.2.2 DELAY AVERSION

Motivational processes have also been explored in ADHD (49). The motivational hypothesis related to ADHD with the most support is referred to as the Delay Aversion (DAv) theory. This hypothesis is grounded on the observation that children with ADHD tend to prefer small immediate rewards to larger but delayed rewards. DAv refers to the unwillingness to wait for an objectively preferable but delayed outcome. According to this theory, children with ADHD become frustrated, inattentive or hyperactive if required to accept a delayed alternative instead of an immediate option (50). Sonuga-Barke suggested that the difficulty in waiting for delayed rewards is caused by an alteration in the circuits that process rewards, and that it is independent of executive dysfunctions. He suggested that DAv is associated with thalamo-cortical-striatal circuit linking the anterior cingulate and orbitofrontal cortex to ventral striatum (nucleus accumbens). The amygdala is also implicated in the motivational significance of rewards (50).

1.2.3 DUAL PATHWAY MODELS

Muller and Zelazo noted an important distinction with regard to executive function (51). First, they differentiated pure cognitive processes, such as the ability to suppress automatic processes or prepotent responses and maintain task instructions or representations in working memory. They described these as “Cool EF processes” and related them to the dorsolateral prefrontal cortex (DLPC) and caudate nucleus. Second, they denominated “Hot

EF processes" those related to the orbital (OFC), anterior cingulate cortex and ventral striatum. Within these processes, they identified some of the functions required to resolve emotional conflicts or to appreciate the affective content in a specific situation. Muller and Zelazo proposed that ADHD should be considered a disorder of "cool functions."

In parallel, Sonuga-Barke formulated a dual pathway model of ADHD (52). This model was intended to reconcile the two groups of processes (executive and motivational) previously mentioned in single-pathway models. Sonuga-Barke postulated that executive functions and delay aversion could be complementary rather than competing accounts of ADHD (see Fig. 2).

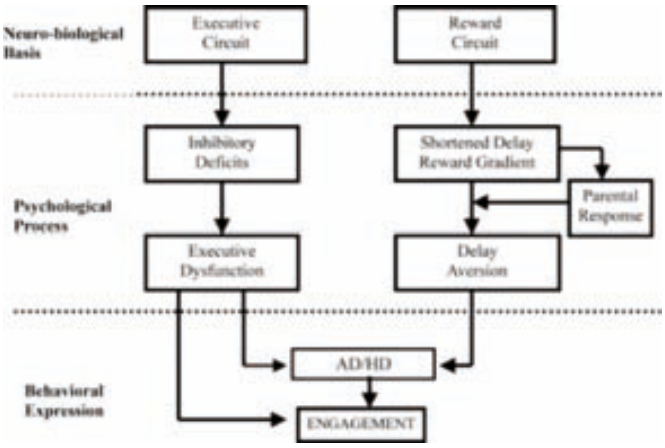


Fig. 2. The dual/pathway model (extracted from Sonuga-Barke 2003).

1.3 New neuropsychological perspectives based on basic neuroscience.

1.3.1 INTEGRATING HOT AND COOL EXECUTIVE FUNCTIONS

Building on previous models, Castellanos et al. suggested that ADHD could represent not only deficiencies in cool EF, but also in the regulation of cool EF by hot EF processes (53). This perspective was based on the seminal observations by Suzanne Haber of the anatomic pathways through which information flows in the non-human primate through the cortico-striatal-thalamo-cortical circuits (54, 55).

1.3.2 CORTICO-STRIATAL CIRCUITS

Haber et al., divided the striatum into three different components: 1) ventro-medial striatum (VMS) divided into shell and core, 2) central striatum (CS) and 3) dorsolateral striatum (DLS), based on each region having its own cortical inputs and its own relationship to limbic, associative and motor cortex. While the efferent projections from the VMS go to the dorsal midbrain, projections from the DLS are limited to the ventrolateral substantia nigra (SN), and the CS is intermediate between VMS and DLS. The relationship of each of these regions with the midbrain varies because of their different nigrostriatal projections. The VMS receives limited projections from the midbrain, but it influences a wide range of dopamine neurons, whereas the DLS receives the largest amount of midbrain projections and it influences a limited midbrain region (55).

One of the major findings of Haber et al. was that each striatal region contained three different components, a dorsal group of cells, a group of cells that lies within each reciprocal terminal field and a ventral component composed of the efferent terminals. These three components for each striatonigrostriatal (SNS) projection system occupy a different position within the midbrain. The VMS projects dorsomedially, the DLS projects ventromedially and the CS system projects between those two (54).

Based on these observations, Haber et al. proposed a circuit in which information from the limbic system feeds into the motor system and affects motor outcomes through the three components mentioned before, suggesting that rather than a direct limbic-motor interface, information flows through several circuits prior to reaching the motor striatum. See Figure below:

Extracted from: Haber et al., J. Neurosci. 2000;20:2369-2382

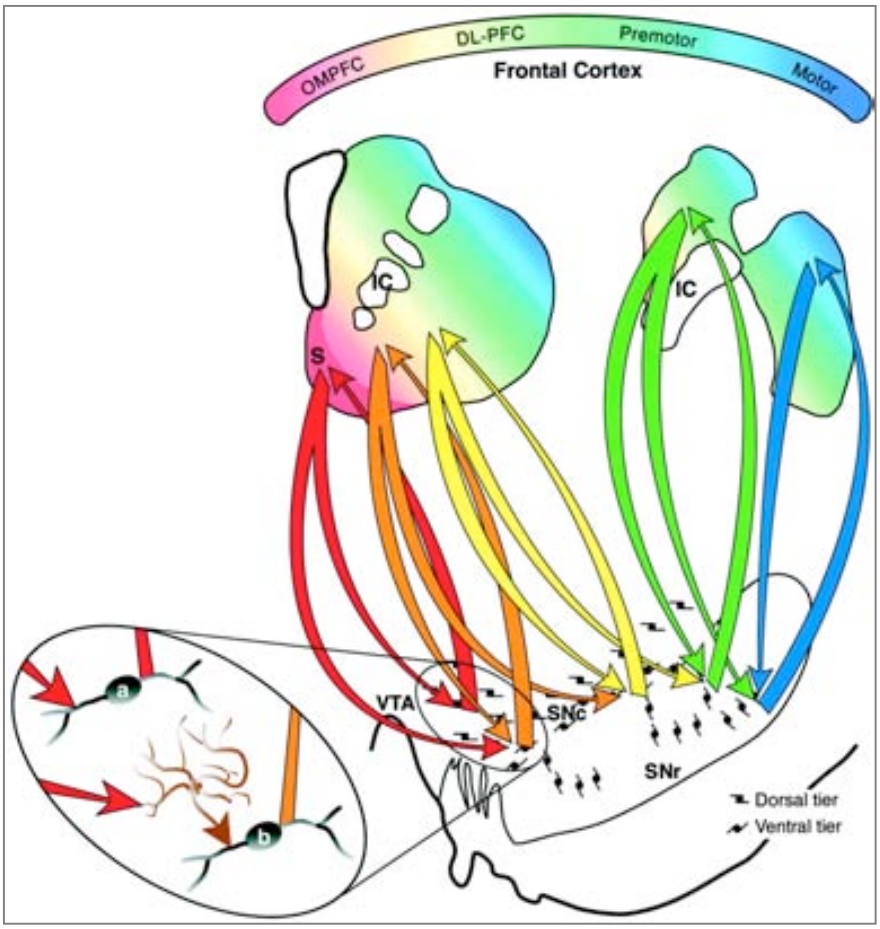


Fig. 3. DL-PFC, Dorsolateral prefrontal cortex; IC, internal capsule; OMPFC, orbital and medial prefrontal cortex; S, shell; SNc, substantia nigra, pars compacta; SNr, substantia nigra, pars reticulata; VTA, ventral tegmental area.

The three different subdivisions of the striatum receive forebrain inputs from specific cortical regions. The amygdala, hippocampus and Brodmann cortical area 25 project to the shell of the nucleus accumbens; the dorsal prefrontal cortex projects to the central striatum and the premotor and motor cortex project to the dorsolateral striatum. The ventral striatal regions influence more dorsal striatal regions via spiraling SNS projections as follows:

1. First loop: the midbrain projects from the shell to the ventral tegmental area (VTA) and ventromedial substantia nigra pars compacta (SNc) and from the VTA to the shell thus forming a closed loop (in red).
2. Second loop: the ventromedial SNc projects to the nucleus accumbens core forming the first spiral projection (in orange).
3. Third, fourth and fifth loops: from the nucleus accumbens core, projections go more

dorsally and continue through other pathways influencing more dorsal striatal regions (in yellow, green and blue).

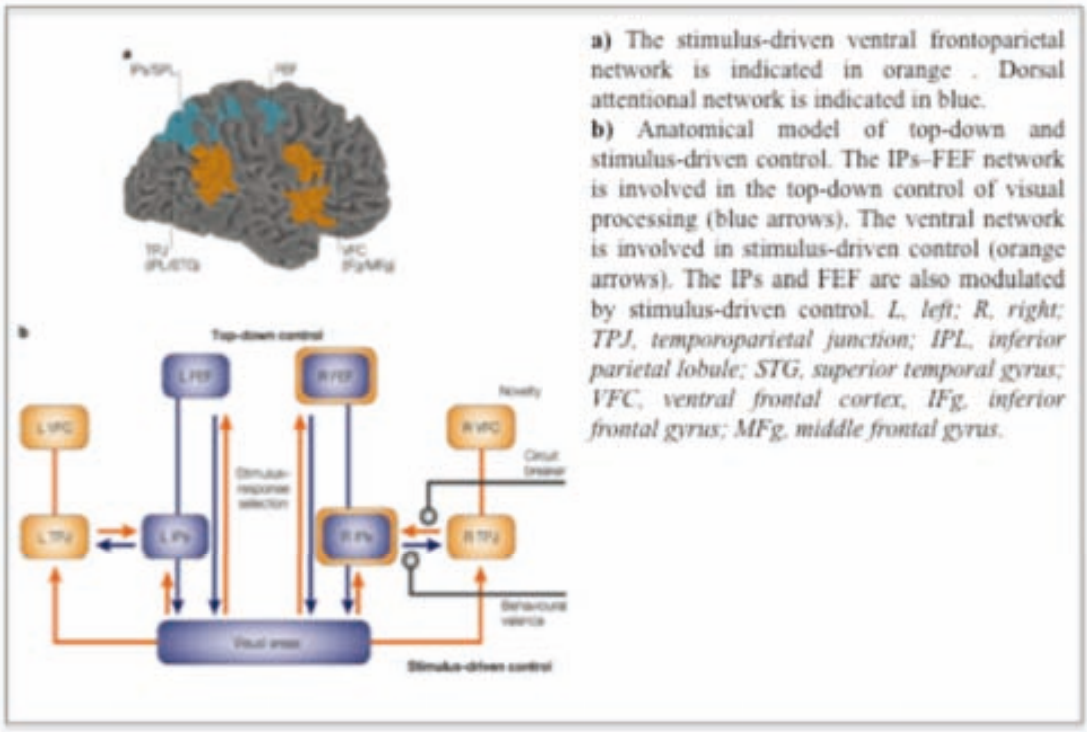
The establishment of a neuroscience-grounded neuropsychology also serves to highlight another circuit/network that has emerged from the work included in this thesis and which has the potential to serve as a unifying concept in models of ADHD pathophysiology. Specifically, authors have increasingly reported anatomic and functional abnormalities in ADHD in frontal and parietal regions that appear to be components of the dorsal attentional network (56, 57). Below the dorsal attentional network is described in more detail:

DORSAL ATTENTIONAL NETWORK

The bilateral dorsal attentional network (dAN) is constituted by two main regions: the intraparietal sulcus (IPs) and the conjunction of the precentral and superior frontal sulcus (frontal eye fields, FEF). This network mediates goal-directed, top-down processes during attentional functioning and interacts with a right-sided ventral system which is stimulus-driven, bottom-up (56) (Fig. 4a).

These two segregated neural systems control visual attention. Specifically, the dorsal network is more involved in the selection of sensory information and responses to stimuli, whereas the ventral network (temporoparietal and ventral frontal cortex) detect relevant sensory events, mostly when they are salient and unattended. In particular, as described by Corbetta and Shulman (2002), the two key regions of the dorsal attentional network are involved in four distinct roles in mediating specific top-down processes (Fig. 4b). First, with regards to top-down control of spatial attention, the dAN regions along with the occipital cortex together perform the sensory analyses of cues. While the occipital cortex responds transiently to cues, the IPs and FEF show a more sustained response involved in the control of the location of attention. Second, during top-down "attention to different features of the object," the FEF and IPs are also recruited. Different regions of the IPs are activated by different cues, suggesting that there is some specialization within the parietal cortex depending on the information that is attended (58). The parietal cortex is also involved in switching attention between two objects at the same location. Third, the dAN is also important for response selection. In particular, the IPs shows preparatory

activity that is selective for different effectors and the FEF are associated with preparatory activity observed prior to eye movement. Fourth, top-down "signals for task sets" refers to the linkage between detection of stimuli and response selection. This linkage is underpinned by the convergence of the regions that constitute the dAN. During responses, neurons in the IPs area respond more to eye movement preparation, whereas neurons in the posterior and medial region of the parietal cortex respond more to arm movement preparation (59).



a) The stimulus-driven ventral frontoparietal network is indicated in orange . Dorsal attentional network is indicated in blue.
b) Anatomical model of top-down and stimulus-driven control. The IPs–FEF network is involved in the top-down control of visual processing (blue arrows). The ventral network is involved in stimulus-driven control (orange arrows). The IPs and FEF are also modulated by stimulus-driven control. *L, left; R, right; TPJ, temporoparietal junction; IPL, inferior parietal lobule; STG, superior temporal gyrus; VFC, ventral frontal cortex, IFg, inferior frontal gyrus; MFg, middle frontal gyrus.*

Fig 4. Interaction between dorsal and ventral attentional networks (extracted **and modified from Corbetta and Shulman 2002)**

In summary, the dorsolateral parietal attentional network is involved in top-down cognitive functions, such as selection of stimuli and of responses. The main role of this network is to link sensory representations that are relevant with motor processes and to dynamically control these links. As will be described below, this dorsal attentional network appears to be importantly implicated in persistent ADHD in adults.

This section has focused on recent perspectives of neuropsychology grounded in neuroscience as opposed to classical psychology which has highlighted the complex loops and spirals of information linking limbic, cognitive, and motor circuits through the basal ganglia, on the one hand, and the dorsal attentional network, on the other. While these circuits and principles are presumed to not be exhaustive in ADHD, they provide the theoretical grounding for the observations reported in the papers to be discussed below.

1.4 Neuroimaging and ADHD

1.4.1 BRAIN IMAGING APPROACHES

1.4.1.1 Anatomic MRI Imaging

1.4.1.1.1 Manual Tracing of Regions-of-Interest (ROI)

In traditional morphometry, the volume of the whole brain or its sub-regions is measured by drawing regions of interest (ROIs) on brain image slices and then calculating the enclosed volume. The manual volumetric method can only be performed on predefined ROIs, therefore it is necessary to first define the anatomical borders of any given ROI. For the intra- and inter-rater variability to be measured for reliability purposes, more than one human tracer has to delineate the borders in a number of individual brains (60, 61). On one hand, this method has the advantage of high face validity (62). On the other hand, it is time-consuming and does not allow segmentation between grey and white matter (62).

1.4.1.1.2 Voxel Based Morphometry

An alternative procedure for measuring the size of brain structures is the automated method of segmentation known as voxel based morphometry (VBM). The use of this technique has increased recently. With this approach differences in regional volumes are investigated throughout the whole brain. It involves a voxel-wise comparison of the local concentration of gray matter between two groups of subjects. The procedure is relatively simple and includes high resolution spatially normalization for the images of every subject into stereotactic space. Then a segmentation process of the gray matter, white matter and cerebrospinal fluid (CSF) from the spatially normalized images is needed. Finally the segments of grey matter are smoothed so that each voxel represents the average of itself and its neighbors (61). Afterwards, voxel-wise parametric statistical tests, which compare the smoothed gray-matter images from the two groups, are performed. For statistical purposes corrections for multiple comparisons are made using different statistical methods, such as using Gaussian random fields theory or the False Discovery Rate (62).

1.4.1.1.3 Measurement of Cortical Thickness

The cortex of the brain is a convoluted mantle with a two-dimensional structure. That is the main reason why many investigators desire to characterize cortical anatomy with its surface geometry in mind. For that purpose, measuring the thickness of the gray matter is one of the main ways of estimating the volume or density of neuronal cell bodies in a given region (63). Analysis of the cortex is a complex topic, and although there is some variation in techniques applied, this approach has advanced rapidly in the last few years (64).

Cortical thickness is commonly assessed on the basis of the grey matter in segmented neuroimaging data, usually from the local or average distance between the white matter surface and the pial surface. In other cases, cortical thickness is calculated by averaging the distances between the white matter surface and its grey matter counterpart. Cortical thickness is relatively stable across a range of brain sizes, across or within species (64). The typical thickness of the cortical mantle in humans is between 2 and 5mm (64). With age,

the cortex thins at an approximate rate of 10um per year (65). In some brain disorders, deviation from this pattern of normative thinning appears to be diagnostically relevant, such as in Alzheimer´s disease (66) or in Williams syndrome (67).

1.4.1.2 Functional MRI Imaging

1.4.1.2.1 Task Based Functional Imaging

Since 1990, functional MRI (fMRI) has been used to detect brain regions involved in a specific task, process or emotion. Functional MRI has dominated the neuroimaging field for the past two decades, due to its high sensitivity, low invasiveness and relatively easy application and availability (68). The approach of fMRI involves measuring changes in the regional blood flow (hemodynamic response) and its relation with a neural activity in the brain (69).

The standard fMRI method only detects differences of brain activation between several conditions. In other words, the subject has to be asked to alternatively perform a task or be stimulated to trigger a process or emotion. These conditions are repeated and can be followed by periods of rest; this set of conditions is usually called fMRI, but can also be described as task-based functional imaging (69). The detection of brain regions related with the paradigm or task is based on the Blood Oxygenation Level Dependent (BOLD) effect. More specifically, local signals are detected when blood flow increases in specific regions after the performance of the experimental condition. This increase in blood flow occurs approximately 1 to 5 seconds after the onset of neural activity. This blood flow increase reaches a peak over 5-6 seconds and then falls back to baseline. These changes in the hemodynamic response allow investigators to analyze this regional activity and localize it (69).

1.4.1.2.2 Functional Imaging – Resting State

Resting state functional MRI (r-fMRI) is a novel and powerful method for measuring regional interactions that occur regardless of task performance. It is based on the complementary study of low frequency fluctuations (<0.1 Hz) in the BOLD signal recorded during resting state which reveals patterns of synchronization that delineate the intrinsic functional architecture of the brain (70-72).

These fluctuations have shown strong correlations at rest even in distant gray matter regions. The spatial patterns of R-fMRI correlations are stable, in that they are similar across multiple 'resting' states, such as eyes-open, eyes-closed, and fixation, and across individuals and sessions (73). The advantages of this technique include that it does not require performance of a specific task, which avoids the difficulty of designing or selecting experimental designs, it does not require that patients undergo training in a task, and is therefore particularly useful for developmental and clinical populations (74-81).

1.4.2 NEUROIMAGING FINDINGS AND ADHD

Neuroimaging methods applied to subjects with ADHD have increased rapidly in sophistication during the last decade. Although most of the neuroimaging studies in ADHD have reported differences in frontal regions, nowadays there is an increasing interest in exploring the brain more broadly. The ADHD field has shifted from solely focusing on potential differences in prefrontal regions toward the identification of neural substrates/circuits underpinning ADHD- relevant behaviours, wherever they may be located (82).

1.4.2.1 Structural MRI Findings in ADHD

Volumetric studies in ADHD have demonstrated that this disorder is associated with slightly but significantly smaller total brain volume (83), particularly in the prefrontal cortex, anterior and posterior cingulate cortex, cerebellum (84), caudate nucleus (85) and parietal regions (86-88). More recently, the limbic system (e.g., hippocampus, amygdala) (84) has also been implicated in the pathophysiology of ADHD.

Specifically, in children, McAlonan et al., analyzing 28 children with ADHD and 31 typically development matched subjects, reported significantly smaller grey matter volumes in frontal cortex, globus pallidus, parietal cortex (Brodmann area (BA) 7, including precuneus), superior occipital cortex and cerebellum, independent of comorbidity (89).

Seidman et al. in a volumetric study of 24 adults with ADHD contrasted with 18 comparisons, found smaller grey matter volumes in the prefrontal cortex and the anterior cingulate cortex. Adults with ADHD also showed a larger nucleus accumbens (NAcc), which is consistent with reward mechanism alterations in ADHD (90).

Complementary analyses of cortical thickness reveal overall decreased cortical thickness in children (91-94) and adults with ADHD with reductions in ACC, medial frontal regions and parieto-temporo-occipital cortex. Recently, Almeida et al. found cortical thinning in right frontal lobe of children, adolescents and adults with ADHD (95).

In summary, volumetric studies in ADHD have extended not only to prefrontal regions but to limbic regions (amygdala and hippocampus) and basal ganglia (ventral striatum), as well as parietal cortex (specifically BA7) and superior occipital area. Nevertheless, although the number of studies of the anatomy of ADHD has increased, the tendency to publish underpowered studies with small sample sizes has continued because of the substantial costs of brain imaging. The preponderance of underpowered studies effectively increases the prevalence of Type I errors, which means that most results must be still be interpreted with caution.

1.4.2.2 Functional – Task-based MRI Findings in ADHD

The number and quality of fMRI studies in ADHD have been increasing as recently reviewed qualitative by Bush et al., (96), and quantitative by Dickstein et al. (97). The former was an overview of the main imaging techniques being used to study ADHD. The conclusions of that qualitative review were that there is a dysfunction of fronto-striatal circuitry in ADHD including the prefrontal cortex and the dorsal ACC and striatum.

In light of these results, Dickstein applied a voxel-wise quantitative meta-analytic method, Activation Likelihood Estimation (98) to 17 functional MRI studies of ADHD. They reported statistically reduced activation for individuals with ADHD in ACC, inferior, medial and dlPFC, basal ganglia, thalamus, and portions of parietal cortex ($p<0.05$, whole brain corrected). Although this meta-analysis supported previous conclusions regarding dysfunction in prefrontal regions, it also implicated other circuits, such as thalamus, ventral striatum and parietal cortex (97).

In summary, although functional imaging is not yet able to provide diagnostically useful information in ADHD, recent progress suggests that clinical utility of imaging may eventually occur. In the meantime, imaging data is being used to test focused hypotheses regarding the neurobiological substrates of ADHD. Specifically in fMRI the main locus of dysfunctions that have been detected in ADHD are prefrontal and parietal regions and the cerebellar-striato-thalamo-cortical circuit.

1.4.2.3 Functional – Resting State MRI Findings in ADHD

Although resting state-fMRI is a very novel technique, several studies suggest that ADHD is characterized by abnormal patterns of functional connectivity (81, 99-103). For example, Castellanos et al., 2008, demonstrated significant decreases ($p<.0004$) in the functional connectivity between the dorsal anterior cingulate cortex (dACC) and precuneus/retrosplenial cortex (RSC) in subjects with ADHD. This initial application of resting state approaches to the examination of ADHD-related decreases in default network functional connectivity identified the dACC/RSC circuit as a potential novel locus of dysfunction in ADHD. Castellanos et al. also reported decreases in functional connectivity between the precuneus and other default network regions (e.g., ventromedial PFC and posterior cingulate) (81). Results from applying the resting state approach, although still preliminary, are suggesting that the physiopathology of ADHD may be underpinned by a dysfunction of connections between key regions rather than abnormalities in discrete brain areas.

AIMS OF THE PROJECT

AIMS

Despite the use of different neuroimaging approaches by independent groups, there is increasing convergence of results in specific regions, which suggests that we are close to understanding the pathophysiological substrates of ADHD. Nowadays, researchers have begun to place more emphasis on the potential contributions of dysfunctions in brain circuits, rather than regional abnormalities alone. Therefore, the main goal of the present thesis is to examine the neural substrates of the pathophysiology of ADHD and their relation with relevant behaviors by applying different neuroimaging techniques.

This thesis consists of three different studies (published papers) each with its own objective:

Paper 1.*"Ventro-striatal Reductions Underpin Symptoms of Hyperactivity and Impulsivity in Attention-Deficit/Hyperactivity Disorder."*

Aim: To examine the ventral striatum of ADHD children compared with matched controls and to test whether the differences were associated with ratings of hyperactivity/impulsivity.

Paper 2. *"Brain Gray Matter Deficits at 33-Year Follow-Up in Adults with Attention-Deficit/Hyperactivity Disorder Established in Childhood."*

Aims:

To test whether adults with a childhood diagnosis of ADHD, relative to comparisons, exhibit cortical thinning and decreased gray matter in specific regions; to assess whether anatomic differences are associated with current adult ADHD diagnosis by contrasting those with persistent ADHD versus ADHD in remission.

Paper 3. *"Actividad funcional cerebral en estado de reposo: redes en conexión."*

Aim: To review the current literature on resting state fMRI and the main collaborative projects that are being assembled to take advantage of this approach. Specifically, this paper provides the first introduction to this relatively new field in Spanish, to inform investigators in Spain and Latin America about the promise and potential to start formulating hypotheses based on this approach as a way of investigating psychiatric disorders including ADHD.

METHODS AND RESULTS

STUDY 1

Biological Psychiatry, 2009: "Ventro-striatal Reductions Underpin Symptoms of Hyperactivity and Impulsivity in Attention-Deficit/Hyperactivity Disorder"

(Published)

Ventro-Striatal Reductions Underpin Symptoms of Hyperactivity and Impulsivity in Attention-Deficit/Hyperactivity Disorder

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Background: Models of attention-deficit/hyperactivity disorder (ADHD) classically emphasize the relevance of executive processes and, recently, reward circuits. The neural bases of reward processes have barely been explored in relation to this disorder, in contrast to extensive neuroimaging studies that examine executive functions in patients with ADHD. To our knowledge, no previous studies have analyzed the volume of the ventral striatum, a key region for reward processes in ADHD children.

Methods: We used a manual region-of-interest approach to examine whether there were volumetric differences in the ventral striatum of ADHD children. Forty-two children/adolescents with ADHD (ages 6–18), and 42 healthy control subjects matched on age, gender, and handedness were selected for the study.

Results: The ADHD children presented significant reductions in both right and left ventro-striatal volumes ($t = 3.290$, $p = .001$; and $t = 3.486$, $p = .001$, respectively). In addition, we found that the volume of the right ventral striatum negatively correlated with maternal ratings of hyperactivity/impulsivity ($r = -.503$, $p = .003$).

Conclusions: Our study provides neuroanatomical evidence of alterations in the ventral striatum of ADHD children. These findings coincide with previous explicative models as well as with recent reports in behavioral and functional neuroimaging studies. Furthermore, the negative correlations we observed strongly uphold the relation between the ventral striatum and symptoms of hyperactivity/impulsivity.

Key Words: Accumbens, ADHD, attention-deficit/hyperactivity disorder, delay aversion, reward, ventral striatum

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disease characterized by symptoms of inattention, hyperactivity, and impulsivity. Clinicians specify, according to DSM-IV-TR criteria (1), three ADHD subtypes: inattentive, hyperactive/impulsive, and combined. The most commonly prescribed pharmacological treatment for ADHD is methylphenidate (MPH). This psychostimulant ameliorates ADHD symptoms, presumably by blocking dopaminergic (DA) and noradrenergic transporters, thereby enhancing the levels of these catecholamines in the mesocortical and mesolimbic circuits (2).

Classical neuropsychological models point to abnormalities in executive functions (EF), especially poor inhibitory control, as the core ADHD deficit (3). Therefore, neuroimaging studies have focused on exploring brain regions known to be involved in these processes (e.g., the prefrontal cortex and the dorsal striatum). This body of research has provided grounds for theories postulating that ADHD arises from DA abnormalities in frontostriatal–cerebellar circuits, especially in the dorsolateral-prefrontal cortex, caudate nucleus, and cerebellar vermis (4,5).

Recently, however, several authors have questioned whether dysregulations in frontostriatal executive circuits fully account for ADHD pathophysiology (6–9). Consequently, there has been a growing interest in elucidating other processes that might be involved in the disorder.

Multiple studies have underlined the importance of motivational aspects, particularly those related to reward management. Results derived from these studies identified the existence of an atypical response to reinforcements in children with ADHD (10). In particular, one of the observations is a greater tendency of children with ADHD to choose smaller but immediate rewards over larger but delayed ones (11–17). These findings, alongside evidence from animal models (18–21), led some authors to suggest the presence of a shorter and steeper delay-of-reinforcement gradient in ADHD (7). Furthermore, it has been proposed that abnormalities in the reward mechanism lead patients to experience delay aversion and, when delays become unavoidable, to present symptoms of hyperactivity as a compensatory mechanism (8,22–24). Interestingly, findings across different species have pinpointed the role of the ventral striatum in reinforcement mechanisms. Specifically, it has been suggested that accumbens nucleus (the key ventro-striatal nucleus) is involved in codifying and computing the value of future rewards and therefore acts as a driving force to perform goal-directed actions (25,26).

Consequently, current accounts of ADHD postulate the existence of at least two different but not mutually exclusive ADHD endophenotypes: those characterized by EF abnormalities, presumably produced by dysfunctions in DA-mesocortical branches; and those characterized by abnormalities in reward management processes, which are thought to result from alterations in DA-mesolimbic circuits (7,9). Although the specific relation between

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Table 1. Clinical and Demographic Data

	Control Subjects $n = 42$ (7♀)	ADHD $n = 42$ (7♀)	ADHD-C $n = 25$ (5♀)	ADHD-H/I $n = 6$ (1♀)	ADHD-I $n = 11$ (1♀)
Age (Years), Mean (SD), [Range]	11.43 (2.73) [6–18]	11.26 (2.9) [6–18]	10.84 (2.6) [7–17]	10.33 (4) [7–16]	12.72 (2.5)[a] [9–16]
Handedness, *n* (%)	R = 32, CD = 8, L = 2	R = 32, CD = 8, L = 2	R = 18, CD = 5, L = 2	R = 4, CD = 2, L = 0	R = 10, CD = 1, L = 0
CAP Father Inat, Mean (SD)		90.97 (6.7)	93.05 (7.2)	91.8 (7.4)	93.4 (5.7)
CAP Father H/I, Mean (SD)		91.38 (8.9)	92.5 (8.9)	92.8 (3.2)	88.1 (10.8)
CAP Mother Inat, Mean (SD)		93.39 (6.9)	92.65 (8.2)	95.5 (2.8)	94.1 (5)
CAP Mother H/I, Mean (SD)		92 (8.3)	93.1 (6.9)	96.25 (4.2)	87.6 (11.1)
CAP Teacher Inat, Mean (SD)		90.85 (9.4)	88.3 (10.9)	93.8 (4)	92.5 (5.5)
CAP Teacher H/I, Mean (SD)		87.79 (11.2)	87.9 (10.3)	97 (2.2)[b]	82.4 (13.4)[b]
Medicated Subjects, *n* (%)		33 (79%)	20 (48%)	5 (12%)	8 (19%)
Dose of MPH (mg/kg), Mean (SD)		.67 (.14)	.69 (.15)	.64 (.09)	.66 (.20)
Drug Treatment Duration (Weeks), Mean (SD)		51.95 (74.2)	66.5 (82.1)	78.4 (64.5)	73.12 (59.2)
Age of First Medication (Yrs), Mean (SD)		9.76 (3.3)	9.4 (3.8)	9.4 (3.57)	11 (2.3)

This table shows demographic and clinical data of attention-deficit/hyperactivity disorder (ADHD) and control subjects as well as for each of the ADHD subtypes. Quantitative variables are expressed by their mean and their SD. Categorical variables are shown as the number of subjects belonging to each category (*n*) and percentage of subjects in each category with regard to the total (%). Clinical values derived from *Child Attention Problems Rating Scales* are expressed as percentiles. Variables concerning medication status were only computed for those subjects that were under medication at the time of the scanning session.

ADHD-C, attention-deficit/hyperactivity disorder—combined subtype; ADHD-H/I, attention-deficit/hyperactivity disorder—hyperactive/impulsive subtype; ADHD-I, attention-deficit/hyperactivity disorder—inattentive subtype; ♀, number of female subjects; R, right-handed; CD, cross dominance; L, left-handed; CAP, Child Attention Problems Rating Scales; Inat, subscale of inattention; H/I, subscale of hyperactivity/impulsivity; MPH, methylphenidate; (mg/kg), milligrams of methylphenidate divided by children's weight in kilograms.

[a]Statistical trend ($p = .054$).

[b]Significant difference between both values according to *t* test comparison ($p < .05$).

these two circuits and the different ADHD subtypes still remains unanswered, animal and neuroimaging studies suggest that alterations in mesolimbic circuits (especially in the ventral striatum) are related to hyperactive/impulsive symptoms but not to symptoms of inattention (25,27,28). Furthermore, a recent behavioral study performed on a healthy population reported that delay-discounting gradient was related to hyperactive/impulsive traits (the higher the levels of hyperactivity/impulsivity, the steeper the discount) but unrelated to traits of inattention (29).

The neural circuitry underlying reward-related processing has barely been explored, in contrast to numerous studies aimed at investigating EF in ADHD children as well as their neurobiological substrates. The few existing functional studies investigating reward processing in ADHD have consistently found hypoactivation of the ventral striatum during reward anticipation (28,30,31). However, to date, not a single structural study has analyzed ventro-striatal volume in ADHD children or its relation to hyperactive/impulsive symptoms.

The present study applies a manual region-of-interest (ROI) analysis to structural magnetic resonance imaging scans to examine whether there are volumetric differences in the ventral striatum of ADHD children. We also aim to assess whether the volume of this structure is related to parent and teacher ratings of hyperactivity/impulsivity and inattention. Our hypothesis is that the ventro-striatal volume of ADHD children would be less than that of their matched control cases. In addition, we predict this volume to be negatively related to hyperactive/impulsive symptoms.

As a secondary goal, we also explore whether ventro-striatal volume is modulated by MPH exposure (dosage/duration), because evidence indicates that psychostimulants can alter the functionality (32,33) and morphology of the ventral striatum (34,35).

Methods and Materials

Eighty-four children/adolescents between the ages of 6 and 18 were recruited for the study. The experimental group included 42 ADHD children diagnosed according to DSM-IV-TR criteria. The control group consisted of 42 unrelated healthy children, who were matched for gender, age, and handedness on a participant-by-participant basis. The study was approved by the Hospital Universitari Vall d'Hebron ethics committee, and parental informed consent was obtained from all the participants. See Table 1 for a description of the sample.

Two different raters (EP and IM), blind to group information, manually drew ventro-striatal regions in coronal slices. The ROI was delineated in MRIcro (http://www.sph.sc.edu/comd/rorden/mricro.html) by applying previously established criteria (36). In addition, total brain volume (TBV) was estimated with the segmentation algorithms of SPM2 (http://www.fil.ion.ucl.ac.uk/spm/).

Before ROI delimitation, tracers participated in a training period provided by an expert neuroradiologist (JCS). After training, raters individually constructed 20 ventro-striatal ROIs. The inter-rater reliability, as calculated by means of the intraclass correlation coefficient, showed a high agreement between raters (*ICC* = absolute agreement = .93). Additionally, we performed an analysis of spatial reliability (intersection/union), obtaining an average ROI overlap of .81 (37).

The original measurement of the ROI was divided by the TBV, aiming to consider not only absolute values of the ventral striatum (VStr) but also relative values with respect to total intracranial volume (VStr/TBV).

We performed independent sample *t* tests and computed Cohen's *d* effect size to assess ventro-striatal volume differences between the control and the ADHD group.

In addition, Spearman's correlations were calculated to evaluate the association between VStr/TBV volume and the clinical scores for the subscales of hyperactivity/impulsivity and inattention, as extracted from reports by mothers, fathers, and teachers.

Finally, to assess whether there were significant volumetric differences resulting from pharmacological status, we computed independent sample *t* tests comparing: 1) medicated with unmedicated patients; 2) medicated patients with their respective matched control subjects; and 3) unmedicated patients with their corresponding matched control subjects. Additional correlations

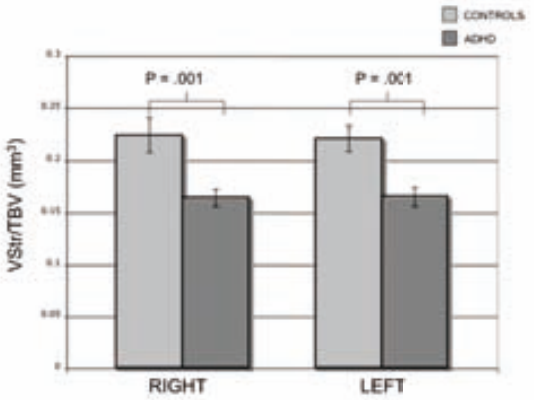

Figure 1. Volumetric differences in the right and left ventral striatum between attention-deficit/hyperactivity disorder (ADHD) and control subjects. Error bars represent the SEM. VStr/TBV, volume of ventral striatum corrected for total brain volume.

between VStr/TBV volume and pharmacological indexes (dose and duration) were examined for the same reason.

See also Supplement 1 for further details about this section as well as additional tests evaluating volumetric differences across ADHD subtypes.

Results

The *t* test comparisons revealed that ADHD children had lower VStr volumes than healthy matched control subjects (all $p < .001$). These differences remained significant after TBV correction—VStr/TBV (all $p \leq .001$). Our study indicated that ADHD subjects showed a reduction of 26.65% (from 10.54% to 42.80%) and 25.28% (from 10.86% to 39.73%) in the right and left VStr/TBV, respectively, thereby producing a bilateral decrease of 25.99% (from 12.14% to 39.83%). All the effect size coefficients were large, ranging from .72 to 1.01 (Figure 1, Table 2).

Correlational analysis showed a significant negative association between children's right VStr/TBV volume and their mothers' ratings of hyperactivity/impulsivity ($r = -.503$; $p = .003$) (Figure 2). We also observed a negative association, albeit not statistically significant, between right VStr/TBV volume and the ratings of hyperactivity/impulsivity provided by the children's fathers ($r = -.327$; $p = .059$).

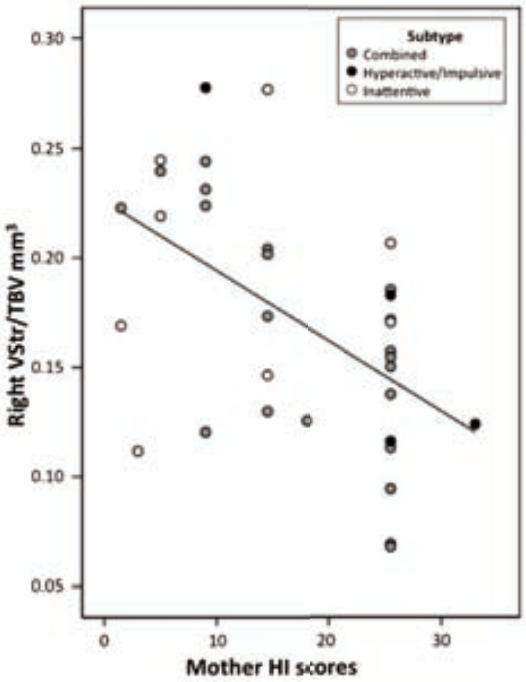

Figure 2. Correlations between the relative volume of the right ventral striatum (VStr/TBV) and clinical ratings of hyperactivity/impulsivity (HI) according to the mother. For illustrative purposes we displayed separate symbol for each subtype group.

The *t* tests revealed no significant differences between medicated and unmedicated patients in any of the volumetric measures. However, these tests indicated a trend toward reduced left ventro-striatal volume in the medicated group as compared with the unmedicated group ($p = .066$). To further assess the effect of medication, we separately compared ventro-striatal volume between the 33 medicated patients and their matched control

Table 2. Group Comparison of Ventro-Striatal Volumes

	Control Subjects $n = 42$, (± SD)	ADHD $n = 42$, (± SD)	*t*	*p*	CI 95%	Effect Size
R. VStr	245.41 (80.22)	180.64 (58.33)	4.231	<.001	34.317–95.212	.92
L. VStr	244.92 (80.46)	183.01 (71.92)	3.718	<.001	28.782–95.039	.81
BIL. VStr	490.33 (131.02)	363.66 (119.16)	4.635	<.001	72.312–181.039	1.01
R. VStr/TBV	.225 (.104)	.165 (.056)	3.290	.001	.024–.096	.72
L. VStr/TBV	.221 (.084)	.165 (.061)	3.486	.001	.024–.088	.76
BIL. VStr/TBV	.445 (.171)	.330 (.105)	3.735	<.001	.054–.177	.81

This table lists the results of *t* test comparisons between attention-deficit/hyperactivity disorder (ADHD) children and their matched control subjects. Both absolute and relative volumes are displayed. Quantitative variables are expressed by their mean value in cubic millimeters and their SD. Effect sizes are calculated by Cohen's *d* index.

CI, confidence interval; R. VStr, absolute volume of right ventral striatum; L. VStr, absolute volume of left ventral striatum; BIL. VStr, absolute volume of bilateral ventral striatum; TBV, total brain volume; R. VStr/TBV, relative volume of right ventral striatum; L. VStr/TBV, relative volume of left ventral striatum; BIL. VStr/TBV, relative volume of bilateral ventral striatum.

subjects as well as between the nine unmedicated patients and their matched control subjects. All previous findings were maintained in the case of medicated subjects (all $p \leq .009$). Group comparisons for the unmedicated subjects pointed in the same direction. Both, right and left VStr/TBV were numerically reduced; however, these reductions only reached statistical significance when comparing the bilateral VStr/TBV index ($p = .049$). This bilateral decrease seems to be mainly produced by smaller right ventro-striatal volume (RVStr/TBV $p = .058$) (see Tables 2, 3 and 4 in Supplement 2).

Finally, we did not find any significant correlation between the duration or the dose of pharmacological treatment and ventro-striatal volume (all $p > .20$).

See Supplement 2 for subtype comparisons as well as other details about this section.

Discussion

In accordance with our hypotheses, results indicate that ADHD children have a volumetric reduction in the ventral part of the striatum, which is associated with hyperactive/impulsive symptoms. These findings match those of animal models of ADHD as well as lesion studies (38). For instance, it has been reported that, after damage to the accumbens nuclei, rats behave in a more impulsive manner—as inferred by the animal's preference to choose small/immediate over large/delayed rewards—and develop motor hyperactivity (25). In addition, a recent neuroanatomical study based on surface deformation maps reported that boys with ADHD show volumetric compressions in different striatal regions, among them a region likely to correspond to our measure of the right ventral striatum (39).

We did not find any significant difference between medicated and unmedicated children or find a significant association between the volume of the ventral striatum and the dose or the duration of pharmacological treatment. However, we noticed that the left ventro-striatal volume of the medicated patients was slightly, yet not significantly, decreased as compared with the unmedicated patients. This was an unexpected observation, given that animal studies suggest the opposite pattern. In particular, these studies have reported increased density of synaptic spines (34) and increased number of synaptic contacts (35) in the nucleus accumbens after chronic MPH exposure. In the current sample, only nine subjects with heterogeneous subtypes diagnosis were MPH-naive at the time of the scan. Therefore, further studies with larger and more homogeneous samples of MPH-naive patients are needed to draw solid conclusions about the effect of MPH medication on the volume of this region. Nevertheless, when we compared unmedicated ADHD subjects with their matched control subjects, we observed a significant reduction of bilateral ventro-striatal volume, which seems to be produced mostly by decreases in the right volume. This finding suggests that the reduced ventro-striatal volume is more likely to be a feature of the illness rather than merely the results of MPH exposure.

To our knowledge, this is the first study that specifically examines the volume of the ventral striatum in ADHD children. Only one structural study performed by Seidman *et al.* volumetrically analyzed this structure in adult patients (40). The authors observed, in contrast to our results, an increase of the ventro-striatal volume. However, in Seidman's study, volumetric measures were not corrected for TBV, and group differences did not reach the level of significance established by the authors for exploratory analyses.

It is difficult to compare directly our results with those of Seidman, because of sample and methodological discrepancies. Concerning sample discrepancies, the main difference is in the age of the subjects; whereas Seidman studied adult patients, we focused on ADHD children/adolescents. This introduces an important confounding factor, especially because it has been observed that many brain abnormalities thought to characterize ADHD result from delays in brain maturation rather than complete deviations from normal brain morphology (41). In addition, it has been reported that chronic MPH administration can produce structural changes in the ventral striatum (34,35). It is therefore conceivable that the increased ventro-striatal volume reported by Seidman was caused by brain plasticity mechanisms, likely related to long-term psychostimulant exposure. Although analyses in our sample did not show any significant correlation between the duration of pharmacological treatment and ventro-striatal volume, longitudinal studies might be useful to further investigate this possibility. Concerning methodological differences, the most relevant discrepancy is the ROI segmentation method. We used a manual approach, whereas Seidman used a semiautomatic one. Manual ROI segmentations have their advantages and disadvantages as compared with the semiautomatic ROI segmentations. On the one hand, manual methods have the weakness of being very time-consuming and potentially presenting high variability of the measurement (this latter problem was partially solved in our study by obtaining high indexes of reliability). On the other hand, the main advantage of manual ROI analyses is that they have enhanced anatomical validity, because they allow examination of the images without the normalization processes that are inherent in all automatic and semiautomatic measures.

The literature provides several reasons to expect that the ventral striatum is related to ADHD pathophysiology. For instance, animal models of ADHD highlight the importance of DA-mesolimbic circuits—particularly, the afferents to the ventral striatum (18,20). The ventral striatum is a major target of mesolimbic-DA projections from the ventral tegmental area and plays a key role in effective responses to delayed rewards. It is known that ventral tegmental area dopamine-releasing neurons fire after the delivery of unexpected rewards and that, in the process of learning, the response of these neurons transfers to the cues that signal the rewards (42–44). Consequently, current accounts of ADHD suggest that the atypical response to reinforcements observed in ADHD patients stems from abnormalities in the firing pattern of DA-mesolimbic cells (7,9,45–47). In particular, these models proposed that either a generalized hypodopaminergic function (7,9) or a specific failure in the transfer of DA signaling (47) might underlie the preference of these patients for immediate rewards.

In addition, lesion studies have reported that damage in the accumbens nuclei decreases the ability of rats to wait for large rewards. Interestingly, these lesions not only lead rats toward impulsive behaviors but also toward increased locomotor activity (25).

Actually, functional magnetic resonance imaging studies have already observed reduced ventro-striatal activation during reward processing, in both adults (30,31) and children (28) with ADHD. Indeed, two of these studies also found a negative correlation between ventro-striatal activation and hyperactive/impulsive symptoms (28,30).

Taken together, these findings also led us to hypothesize that the volume of the ventral striatum would negatively correlate with the ratings of hyperactivity/impulsivity. We found, in accor-

dance with previous predictions, a negative association between right ventro-striatal volume and mothers' rating of hyperactivity/impulsivity. Interestingly, the volume of this region was exclusively correlated with the subscale of hyperactivity/impulsivity but not with the subscale of inattention. However, we must stress that the conclusions derived from the correlational analysis cannot be extended to the control sample, because we lack ratings of hyperactivity/impulsivity or inattention for this group.

To analyze our findings in greater depth, we performed exploratory analysis comparing the volume of the ventral striatum across the different ADHD subtypes. Although the small number of subjects in the hyperactive/impulsive and the inattentive subtypes calls into question the validity of the analysis, our data suggest that ventro-striatal reductions are particularly relevant in the pathophysiology of hyperactive/impulsive and combined subtypes (see Results section in Supplement 2). Further studies with larger samples are encouraged to assess the relevance of ventro-striatal reductions across the different subtypes.

In summary, our study reports ventro-striatal volumetric reductions in ADHD children that seem to be especially linked to the symptoms of hyperactivity/impulsivity. These findings support recent explicative models of ADHD, which stress the relevance of reward brain circuits in the pathogenesis of the disorder.

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Supplementary material cited in this article is available online.

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Supplement 1 - Methods and Materials

Participants

Participants with ADHD were referred by the *"Servei de Paidopsiquiatria"* at the *Vall d'Hebron Hospital* and controls were recruited from the community. Subsamples of the subject groups used in the present research have been included in two previous studies (1, 2).

Through clinical interviews (3), a psychiatrist and a psychologist diagnosed and classified ADHD participants into the three ADHD subtypes (hyperactive/impulsive, inattentive, and combined), according to DSM-IV TR criteria (4). Only those receiving a consensus diagnosis were eligible for the study. The *Child Attention Problem* (CAP) rating scale (5) was also administered to the parents and teachers of the ADHD children, in order to obtain an index of clinical severity. Clinical scores were not available for all the ADHD children, since not all returned the questionnaires. Correlation analyses with clinical ratings were, therefore, performed only for those subjects with forms filled out by their parents and teachers, that is the 34 subjects (20 combined, 5 hyperactive/impulsive and 9 inattentive) with forms from the father and a teacher, and the 33 subjects (20 combined, 4 hyperactive/impulsive and 9 inattentive) with the form from the mother. Exclusion criteria for the sample consisted of: comorbidity with other psychiatric disorders (including dyslexia, anxiety, depression and ADHD in the case of control subjects) as measured by DICA-IV TR (3); and birth complications (such as perinatal anoxia or less than 34 weeks of gestation). Five of the ADHD patients (4 of the combined subtype and 1 of the hyperactive/impulsive subtype) also met criteria for oppositional defiant disorder (ODD) diagnosis, 5 for conduct disorder (CD) (4 of the combined subtype and 1 of the

hyperactive/impulsive subtype) and one of the hyperactive/impulsive children met criteria for both ODD and CD. All of them were receiving medication at the time of the scanning. The intelligence coefficient (IQ) was measured using the Wechsler Intelligence Scale for Children (WISC-III) (6). The ADHD children took the full test, while the IQs of the control cases were estimated on the basis of vocabulary and block design subscales. Those participants with an estimated IQ below 80 were excluded from the study.

MRI acquisition

Structural MRI data were acquired using a 1.5-T scanner (Signa, General Electric, Milwaukee, USA). T1-weighted, 3D axial images were obtained using a fast spoiled gradient echo pulse sequence. Imaging parameters were as follows: repetition time, 13.2ms; echo time, 4.2 ms; flip angle, 15º; number of excitations, 1; matrix size, 256x256x60; voxel size, 0.94x0.94x2mm.

Image processing

First, images underwent visual inspection to ensure quality. The scanned sample of 42 children with ADHD and 42 control children was derived from a total of 105 subjects who were considered eligible for our study. However, we discarded the images of 25 subjects (17 ADHD and 8 controls) because of image artifacts (basically produced by movement) or matched imbalance between the ADHD and controls subjects (differences in age, gender or handedness). Before ROI delineation, we oriented the images into standardized head positions on the basis of AC-PC landmarks. Two different raters, blind to group information, manually delineated ventro-striatal volume in coronal slices. The ROI was delineated by applying previously established criteria (7). Landmarks were as follows:

1) the posterior limit of the ventral striatum (VStr) was established as the most caudal slice anterior to the anterior commisure; 2) a line perpendicular to the internal capsule demarked VStr regions, starting at the most inferior and external point of the lateral ventricle; 3) the anterior limit was set as the most rostral slice before external capsule separated the caudate from the putamen; 4) paraolfactory gyrus delimitated the inferior and medial landmarks of VStr. On average the VStr was measured on 4 slices (*sd*=0.90). The volume of the ROI was obtained by multiplying the number of voxels pertaining to the ROI by the size of the voxel in each of the three dimensions. Visualization and delimitation of the images were performed with MRIcro software (http://www.sph.sc.edu/comd/rorden/mricro.html). In addition, total brain volume (TBV) was estimated using the segmentation algorithms of SPM2 (Wellcome Department of Cognitive Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm/), according to the steps described below. First, we created a sample specific template, as well as the gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF) *a priori,* based on images of both ADHD children and control children. Second, the 3D images were segmented into three compartments (GM, WM and CSF). Third, the volume of GM, WM and CSF in cubic millimeters (mm^3) was calculated by multiplying the number of voxels of each of the compartments by the size of the voxel. Finally, TBV was obtained by summing GM and WM. We did not include the CSF in the TBV computation given the poor estimation obtained using the standard SPM segmentation routines.

Statistical analysis

Statistical analyses were performed with the SPSS 16.0 package. ROI measures in voxels were transformed into mm^3 by multiplying the number of voxels considered to

pertain to the ROI by the size of the voxel in each of the three coordinates (X, Y and Z). The ROI (VStr) was then divided by the total brain volume (VStr/TBV), aiming to take into consideration not only absolute values but also relative values with respect to total intracranial volume.

Spearman's correlations were calculated to assess the association between VStr/TBV volume and the clinical scores for the subscales of hyperactivity/impulsivity and inattention as computed from reports by mothers, fathers and teachers. Correlational analyses were performed for the whole ADHD sample as well as for the combined subtype. Since clinical ratings are extracted from qualitative measurements, their scores were rank ordered within the whole ADHD sample.

Besides the statistical analysis reported in the main article, we also performed supplementary tests aimed at outlining the volume of the ventral striatum across the three ADHD subtypes. In particular, we applied an analysis of covariance (ANCOVA) to the ADHD sample, in which the diagnostic subtype was introduced as a between subjects fixed factor, and age and gender as covariates. Moreover, we performed independent sample t-test comparisons between the three subtypes and their matched controls. That is, children in the ADHD groups (combined, hyperactive/impulsive and inattentive) were exclusively compared with those healthy children that, during the sampling, were individually selected to match gender, age and laterality criteria. This analysis offered us an alternative approach to examine subtype differences and provided us with an estimation of how each of the subtypes differs from healthy matched controls. Furthermore, subtype analyses were also recalculated for the medicated subsample. We did not repeat the analyses for the un-medicated subjects given the small number of patients pertaining to each of the subtypes (5 combined, 1 hyperactive/impulsive and 3 inattentive). We should emphasize that all the

results derived from subtype comparisons should be interpreted with caution, given the small number of subjects belonging to the hyperactive/impulsive and the inattentive groups.

Finally, in order to test whether volumetric reductions were generalized throughout the entire striatum or specific to the ventral portion, we performed mean comparisons of caudate nucleus volume and repeated correlational analyses in a subsample of subjects. The caudate nucleus is, to date, the striatal region that has been the most extensively connected with ADHD (8). This nucleus, together with the putamen, forms the dorsal striatum. The volumes of the caudate nucleus (which included the head and the body) were obtained from a previous study using a subset of the present sample (1). In particular, 53 subjects (22 ADHD and 31 controls) of the current sample were also used in the Trèmols *et al.* study. However, the final sample in which we performed these comparisons was reduced to 42 subjects (21 control subjects and 21 ADHD children (10 combined, 4 hyperactive/impulsive and 7 inattentive)) in order to match the control and ADHD children for gender, age and handedness. For comparative reasons, t-test comparisons of VStr/TBV were also repeated for the same subsample of subjects.

A *p-value* below 0.05 was considered statistically significant for all tests.

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Supplement 2 - Results

Total Brain Volume

The TBV measure, which includes gray matter and white matter, was slightly lower in ADHD subjects in comparison to controls. However, this decrease did not significantly differ between groups (controls: mean=1133.3 mm^3; SD=131.8 mm^3; ADHD: mean=1106.3 mm^3; SD=97.1 mm^3; mean diff=26.97; IC 95% from -23.27 to 77.22 mm^3; *p* value=0.289).

Subtype Analyses

According to the ANCOVA analysis, there were no significant differences between the ADHD subtypes, neither for absolute volumes, nor for relative volumes (all $p>0.385$). However, t-test comparisons between each subtype and their matched controls indicated that absolute volumes were bilaterally reduced in the combined ($p<0.001$) and hyperactive/impulsive children ($p=0.016$) but not in inattentive children ($p=0.176$). With regard to relative volumes, bilateral reductions only reach significance for the combined subtype ($p=0.001$), but not in the hyperactive/impulsive ($p=0.066$) or the inattentive ($p=0.205$) subtypes. Interestingly, the effect-size coefficients show that mean differences, in both absolute and relative volumes, are especially prominent in children of the hyperactive/impulsive subtype (Cohen's $d=1.68$ for bilateral VStr, and 1.19 for bilateral VStr/TBV), are less accentuated in the combined subtype (Cohen's $d=1.06$ for bilateral VStr, and 0.98 for bilateral VStr/TBV), and are nearly absent in children of the inattentive subtype (Cohen's $d=0.60$ for bilateral VStr, and 0.56 for bilateral VStr/TBV). Detailed data about the

ventro-striatal volume t-test comparisons between each subtype and their matched control are presented below (see also supplemental table 1).

Supplemental Table 1. Subtype comparisons of ventro-striatum volumes

	Subtype comparisons					
Statistical measures	**M-ctrls (25)**	**ADHD-C (25)**	**M-ctrls (6)**	**ADHD-H/I (6)**	**M-ctrls (11)**	**ADHD-I (11)**
R. VStr						
Mean (mm3)	246	170.78	274.51	179.49	228.2	203.69
S.D	85.03	61.02	85.47	52.9	67.44	52.82
T value	3.594		2.315		0.949	
P value	**0.001**		**0.043**		0.354	
CI 95%	33.134 to 117.301		3.579 to 186.443		−29.371 to 78.389	
Effect size	1.02		1.34		0.40	
L. VStr						
Mean (mm3)	249.74	177.65	244.17	188.73	234.38	192.08
S.D	96.06	76.04	50.23	30.91	54.37	81.68
T value	2.942		2.303		1.430	
P value	**0.005**		**0.044**		0.168	
CI 95%	22.825 to 121.361		1.791 to 109.079		−19.414 to 104.018	
Effect size	0.83		1.33		0.61	
BIL. VStr						
Mean (mm3)	495.74	348.43	518.67	368.23	462.57	395.76
S.D	151.34	125.08	100.31	77.56	94.75	126.22
T value	3.751		2.906		1.404	
P value	**<0.001**		**0.016**		0.176	
CI 95%	68.355 to 226.266		35.106 to 265.786		−32.451 to 166.073	
Effect size	1.06		1.68		0.60	
R. VStr/ TBV						
Mean (mm3)	0.212	0.154	0.243	0.166	0.242	0.189
S.D	0.073	0.055	0.082	0.062	0.165	0.049
T value	3.206		1.819		1.026	
P value	**0.002**		0.099		0.317	
CI 95%	0.022 to 0.095		−0.017 to 0.171		−0.055 to 0.162	
Effect size	0.90		1.05		0.66	
L. VStr/ TBV						
Mean (mm3)	0.215	0.157	0.213	0.173	0.238	0.177
S.D	0.079	0.063	0.041	0.039	0.112	0.067
T value	2.820		1.706		1.558	
P value	**0.007**		0.119		0.135	
CI 95%	0.016 to 0.098		−0.012 to 0.091		−0.021 to 0.143	
Effect size	0.80		1.06		0.66	
BIL. VStr/ TBV						
Mean (mm3)	0.427	0.311	0.456	0.339	0.481	0.366
S.D	0.129	0.106	0.097	0.097	0.27	0.106
T value	3.472		2.066		1.309	
P value	**0.001**		0.066		0.205	
CI 95%	0.048 to 0.183		−0.009 to 0.242		−0.067 to 0.297	
Effect size	0.98		1.19		0.56	

ADHD, attention-deficit/hyperactivity disorder; M-ctrls, matched controls; ADHD-C, attention-deficit/hyperactivity disorder - combined subtype; ADHD-H/I, attention-deficit /hyperactivity disorder – hyperactive/impulsive subtype; ADHD-I, attention-deficit/hyperactivity disorder - inattentive subtype; R. VStr, absolute volume of right ventral striatum; L. VStr, absolute volume of left ventral striatum; BIL. VStr, absolute volume of bilateral ventral striatum; TBV, total brain volume; R. VStr/TBV, relative volume of right ventral striatum; L.VStr/TBV, relative volume of left ventral striatum; BIL.VStr/TBV, relative volume of bilateral ventral striatum.

This table shows the results of t-test comparisons between groups as well as between subtypes and their matched controls. Both absolute and relative volumes are displayed. Values in boldface refer to significant differences between samples. Quantitative variables are expressed by their mean value in cubic millimeters and their standard deviation (SD). Effect sizes are calculated by Cohen´s *d* index.

Combined subtype and matched control comparisons

Ventro-striatal volume was found to be lower in the combined subtype as compared to its matched control group (all $p \leq 0.007$). Reductions were observed in both relative and absolute volumes. With regard to relative values, we found a bilateral VStr/TBV reduction of 27.15% (from 11.41 to 42.9). This reduction was due to a decrease of 27.62% (from 10.30 to 44.98) and 26.66% (from 7.66 to 45.72) in the right VStr/TBV and left VStr/TBV respectively. It is worth mentioning that all the differences were large in size (Cohen's *d* ranging from 0.8 to 1.06).

Hyperactive/impulsive subtype and matched control comparisons

In the case of the hyperactivity/impulsive subtype, significant reductions were restricted to absolute values. Although decreases in relative volumes did not reach significance ($p = 0.066$ for bilateral VStr/TBV), the size of the differences are larger than those obtained for the rest of the comparisons (all Cohens' *d* coefficients >1.05).

Inattentive subtype and matched control comparison

There were no significant differences in ventro-striatal measures between inattentive children and matched controls either for absolute volumes or for relative measures. Furthermore, effect sizes of the volumetric differences were relatively small (Cohen's *d* ranging from 0.4 to 0.66)

The Effect of Medication on Ventro-Striatal Volume

Group analyses comparing medicated to un-medicated ADHD children as well as the medicated and the un-medicated ADHD groups to their respective matched

control groups, are reported in the main manuscript. For detailed information about these analyses see supplemental tables 2, 3 and 4.

The ANCOVA analysis revealed no significant difference between subtypes in the medicated sample (all $p>0.34$). Independent sample t-tests show that only the difference between the combined subtype and its matched controls reached significance (combined vs. matched controls all $p\leq0.011$; hyperactive/impulsive vs. matched controls all $p\geq0.058$; and inattentive vs. matched controls all $p\geq0.197$; see supplemental table 2).

Supplemental Table 2. Ventro-striatal comparisons between medicated and un-medicated ADHD children

	Medicated (33) Mean (SD)	Un-medicated (9) Mean (SD)	T value	P value	CI 95%	Effect size
R. VStr	196.65 (63.68)	176.28 (57.05)	0.927	0.359	-24.035 to 64.789	0.34
L. VStr	218.52 (69.82)	173.33 (70.41)	1.710	0.095	-8.232 to 98.619	0.64
BIL. VStr	415.18 (107.19)	349.60 (119.88)	1.485	0.145	-23.693 to 154.834	0.58
R. VStr/TBV	0.161 (0.054)	0.18 (0.063)	0.938	0.354	-0.022 to 0.062	0.33
L. VStr/TBV	0.156 (0.059)	0.198 (0.057)	1.887	0.066	-0.029 to 0.086	0.71
BIL. VStr/TBV	0.316 (0.105)	0.378 (0.096)	1.579	0.122	-0.017 to 0.142	0.62

Abbreviations as above.

This table shows the results of t-test comparisons between medicated and un-medicated ADHD children. Both absolute and relative volumes are displayed. Quantitative variables are expressed by their mean value in cubic millimeters and their standard deviation (SD). Effect sizes are calculated by Cohen´s *d* index.

Supplemental Table 3. Group and subtype comparisons of ventro-striatal volumes for the medicated subsample

	Group comparisons		Subtype comparisons					
Statistical measures	**Ctrls (33)**	**ADHD (33)**	**M-ctrls (20)**	**ADHD-C (20)**	**M-ctrls (5)**	**ADHD-H/I (5)**	**M-ctrls (8)**	**ADHD-I (8)**
R. VStr								
mean(mm3)	235.11	176.28	236.13	166.86	245.99	184.33	225.73	194.8
S.D	79.6	57.05	89.03	58.41	55.09	57.64	74.39	55.01
T value	3.451		2.91		1.729		0.945	
P value	**0.001**		**0.006**		0.122		0.36	
CI 95%	24.769 to 92.886		21.081 to 117.478		-20.562 to 143.891		-39.233 to 101.088	
Effect size	0.85		0.92		0.93		0.47	
L. VStr								
mean (mm3)	237.37	173.33	243.72	162.6	241.39	196.45	218.97	185.68
S.D	83.49	70.41	100.87	66.95	55.64	27.33	45.59	95.84
T value	3.368		3.001		1.621		0.887	
P value	**0.001**		**0.005**		0.144		0.39	
CI 95%	26.058 to 102.023		26.389 to 135.843		-18.982 to 108.878		-47.198 to 113.767	
Effect size	0.83		0.84		1.02		0.44	
BIL. VStr								
mean (mm3)	472.47	349.6	479.85	329.46	487.39	380.78	444.69	380.49
S.D	132.57	119.88	154.36	117.95	72.38	79.61	107.09	146.16
T value	3.949		3.462		2.216		1.002	
P value	**<0.001**		**0.001**		0.058		0.333	
CI 95%	60.714 to 185.023		62.455 to 238.336		-4.349 to 217.574		-73.191 to 201.613	
Effect size	0.97		1.09		1.40		0.50	
R. VStr/ TBV								
mean (mm3)	0. 218	0.160	0.203	0.150	0.215	0.174	0.259	0.178
S.D	0.111	0.054	0.075	0.053	0.051	0.066	0.192	0.046
T value	2.709		2.586		1.083		1.167	
P value	**0.009**		**0.014**		0.311		0.263	
CI 95%	0.015 to 0.101		0.011 to 0.094		−0.032 to 0.08		−0.068 to 0.231	
Effect size	0.66		0.81		0.69		0.58	
L. VStr/ TBV								
mean (mm3)	0.216	0.156	0.208	0.143	0.208	0.184	0.241	0.168
S.D	0.089	0.059	0.080	0.055	0.043	0.033	0.131	0.077
T value	3.238		2.967		0.984		1.355	
P value	**0.002**		**0.005**		0.354		0.197	
CI 95%	0.023 to 0.098		0.020 to 0.108		−0.045 to 0.126		−0.042 to 0.187	
Effect size	0.79		0.93		0.62		0.68	
BIL. VStr/ TBV								
mean (mm3)	0.435	0.317	0.411	0.293	0.423	0.359	0.501	0.346
S.D	0.183	0.105	0.126	0.100	0.061	0.096	0.319	0.118
T value	3.219		3.259		1.264		1.281	
P value	**0.002**		**0.002**		0.242		0.221	
CI 95%	0.045 to 0.192		0.044 to 0.191		−0.053 to 0.182		−0.104 to 0.413	
Effect size	0.79		1.03		0.79		0.64	

Abbreviations as above.

This table shows the results of t-test comparisons between groups as well as between subtypes and their matched controls only for the medicated subsample. Both absolute and relative volumes are displayed. Values in boldface refer to significant differences between samples. Quantitative variables are expressed by their mean value in cubic millimeters and their standard deviation (SD). Effect sizes are calculated by Cohen´s *d* index.

Supplemental Table 4. Group comparison of ventro-striatal volume for the un-medicated subsample

	Controls (9) Mean (SD)	Un-medicated (9) Mean (SD)	T value	P value	CI 95%	Effect size
R. VStr	283.186 (74.779)	196.655 (63.682)	2.643	**0.018**	17.124 to 155.937	1.25
L. VStr	272.623 (64.802)	218.52 (69.822)	1.704	0.108	-13.214 to 121.42	0.80
Bil. VStr	555.809 (107.446)	415.175 (107.185)	2.780	**0.013**	33.389 to 247.879	1.31
R. VStr/ TBV	0.246 (0.074)	0.180 (0.063)	2.044	0.058	-0.002 to 0.135	0.96
L. VStr/ TBV	0.236 (0.062)	0.197 (0.957)	1.364	0.191	-0.021 to 0.098	0.64
Bil. VStr/ TBV	0.482 (0.112)	0.378 (0.095)	2.130	**0.049**	0.000 to 0.209	1.00

Abbreviations as above.

This table shows the results of t-test comparisons between un-medicated ADHD patients and their matched controls. Both absolute and relative volumes are displayed. Values in boldface refer to significant differences between samples. Quantitative variables are expressed by their mean value in cubic millimeters and their standard deviation (SD). Effect sizes are calculated by Cohen's *d* index.

Group Comparisons of Ventral Striatum and Caudate Volumes

We found no significant differences in the volumes of the caudate nuclei between ADHD patients and their matched healthy subjects (all p>0.282 for Cdt/TBV comparisons) but we did find significant differences in all the ventro-striatal measures for these subject groups (all p<0.036 for VStr/TBV comparisons). Regarding correlational analyses, no significant associations were found between the caudate volumes and the ratings of hyperactivity/impulsivity or inattention (smaller *p* value =0.08 for the correlation between mothers' scores of hyperactivity/impulsivity and right Cdt/TBV (r=-0.426)). However, the negative association among the symptoms of hyperactivity/impulsivity and right VStr/TBV remains significant (r=-0.577, p=0.01 for mothers' scores and r=-0.481, p=0.032 for fathers' scores). In sum, these findings suggest that the ventro-striatal reductions reported in the paper are not solely the result of a generalized decrease of the striatal region.

Supplemental Table 5. Group comparisons of ventro-striatal and caudate volumes

	Controls (21) Mean (SD)	ADHD (21) Mean (SD)	T value	P value	CI 95%	Effect size
R. VStr/TBV	0.2355	0.1723	2.170	**0.036**	0.0043 to 0.12208	0.67
L.VStr/TBV	0.2457	0.1788	2.941	**0.007**	0.02017 to 0.11367	0.90
BIL. Vstr/TBV	0.4812	0.3511	2.726	**0.009**	0.03364 to 0.22661	0.84
R. Cdt/TBV	2.3657	2.0733	1.091	0.282	-0.2493 to 0.8341	0.33
L. Cdt/TBV	1.9596	2.0200	-0.270	0.789	-0.5130 to 0.3921	-0.08
BIL. Cdt/TBV	2.1627	2.0467	0.503	0.618	-0.3498 to 0.5818	0.15

Abbreviations as above.

This table shows the results of t-test comparisons between ADHD patients and their matched controls for the ventral striatum and the dorsal striatum. Both absolute and relative volumes are displayed. Values in boldface refer to significant differences between samples. Quantitative variables are expressed by their mean value in cubic millimeters and their standard deviation (SD). Effect sizes are calculated by Cohen's *d* index.

STUDY 2

Archives of General Psychiatry, 2011: "Brain Gray Matter Deficits at 33-Year Follow-Up in Adults with Attention-Deficit Hyperactivity Disorder Established in Childhood"

(In press)

Decision letter

Date: 2011-04-15 10:09:43

Last Sent: 2011-04-15 10:09:43

Triggered By: Joseph Coyle

CC: Redacted

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Subject: PSY11-0174 Decision Letter

Message: April 15, 2011

Dr. F Xavier Castellanos
Institute for Pediatric Neuroscience
NYU Child Study Center
215 Lexington Avenue, Room 1417
New York, NY 10016

RE: Brain Gray Matter Deficits at 33-Year Follow-Up in Adults with Attention-Deficit/Hyperactivity Disorder Established in Childhood

Dear Dr. Castellanos:

We have completed our review of your manuscript and are pleased to accept it for publication in Archives of General Psychiatry. Your manuscript is accepted with the understanding that its contents, all or in part, have not been published elsewhere and will not be published elsewhere except in abstract form or with the permission of the editor.

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Sincerely yours,

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Editor, Archives of General Psychiatry
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Brain Gray Matter Deficits at 33-Year Follow-Up in Adults with Attention-Deficit/Hyperactivity Disorder Established in Childhood

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Abstract

Context: Volumetric studies have reported relatively decreased cortical thickness and gray matter volumes in adults with Attention-Deficit/Hyperactivity Disorder (ADHD) whose childhood status was retrospectively recalled. We present the first prospective study combining cortical thickness and voxel-based morphometry (VBM) in adults diagnosed with ADHD in childhood.

Objective: In adults who had Combined Type ADHD in childhood, to 1) test whether they exhibit cortical thinning and decreased gray matter in regions hypothesized related to ADHD, and 2) test whether anatomic differences are associated with current ADHD diagnosis, including persistence versus remission.

Design: Cross-sectional analysis embedded in a 33-year prospective follow-up at mean age 41.

Setting: Research outpatient center.

Participants: ADHD probands were from a cohort of 207 6-12 year old Caucasian boys; male comparison subjects (n=178) had been free of ADHD in childhood. We obtained MRI scans in 59 probands and 80 comparisons (28% and 45% of original samples, respectively).

Main Outcome Measure: Whole-brain VBM and vertex-wise cortical thickness analyses.

Results: Cortex was significantly thinner in ADHD probands than comparisons in the dorsal attentional network and limbic areas (FDR<0.05, corrected). Additionally, gray matter was significantly decreased in probands in right caudate, right thalamus and bilateral cerebellar hemispheres. Probands with persistent ADHD (n=17) did not differ significantly from remitters (n=26) at FDR<0.05. At uncorrected p<0.05, remitters had thicker cortex relative to those with persistent ADHD in medial occipital cortex, insula, parahippocampus, and prefrontal regions.

Conclusions: We observed anatomic gray matter reductions in adults with childhood ADHD, regardless of current diagnosis. The most affected regions underpin top-down control of attention and regulation of emotion and motivation. Exploratory analyses suggest that diagnostic remission may result from compensatory maturation of prefrontal, cerebellar, and thalamic circuitry.

CONTEXT

Volumetric studies in children with Attention-Deficit/Hyperactivity Disorder (ADHD) have consistently found global reductions of total brain volume with prefrontal cortex, anterior and posterior cingulate cortex, basal ganglia, cerebellum and parieto-temporal regions particularly affected relative to typically developing subjects.[1-4] These findings are consistent with a model of ADHD as a disorder of frontal-striatal-cerebellar circuitry. The diagnosis of ADHD requires onset in childhood, but persistence of ADHD into adulthood is now well documented.[4, 5] This longitudinal course together with smaller brain volumes in children with ADHD has raised questions about brain development into adulthood.

A sparse literature on brain anatomy in adults with ADHD also reports decreased volumes in orbitofrontal cortex,[6] anterior cingulate cortex (ACC),[7, 8] dorsolateral prefrontal cortex (DLPFC),[9] superior frontal cortex and cerebellum.[10] Complementary analyses of cortical thickness[11] reveal overall decreased cortical thickness in children[11-14] and adults with ADHD with reductions in ACC, medial frontal regions and parieto-temporo-occipital cortex.[12-14] Recently, Almeida et al.[15] found cortical thinning in right frontal lobe of children, adolescents and adults with ADHD.

Faute de mieux, investigations of structural brain abnormalities in adults have relied on adults' retrospective recall of their childhood status.[8, 9, 16-22] The documented inaccuracies of such reports[23] highlight the advantage of assessing brain anatomy in individuals with established childhood-onset ADHD prospectively followed into adulthood. Additionally, clinical ADHD remits in a substantial proportion of individuals followed into adulthood,[24, 25] but the neurobiology of remission has not been previously examined in middle adulthood.

We report cortical thickness and voxel-based morphometry (VBM) analyses on the largest sample to date of adults with childhood ADHD diagnoses (mean age 8) consistent with DSM-IV. Follow-up assessments occurred at mean ages 18, 25 and 41 (18FU, 25FU, and 41FU, respectively). At 18FU, a comparison group free of childhood ADHD, matched for age, sex, ethnicity, and childhood social class was recruited.[26-30] Systematic diagnostic assessments at each follow-up were conducted by interviewers "blind" to past history and group membership. At 41FU, we conducted anatomic brain magnetic resonance imaging in probands with childhood ADHD and comparisons. We performed analyses based on childhood diagnosis as well as on current diagnostic status in adulthood. Primary aims were to: (1) test whether adults with a childhood diagnosis of Combined Type ADHD (probands), relative to comparisons, exhibit cortical thinning and decreased gray matter in regions hypothesized to be related to ADHD,[12-14, 31] and (2) assess whether anatomic differences are associated with current ADHD diagnosis.

METHODS

PARTICIPANTS

The ADHD group originally comprised 207 6 to 12 year-old Caucasian boys referred to a research clinic from 1970 to 1977 (mean age 8.3 years). Briefly, they were referred by schools because of behavioral problems, had elevated parent and teacher ratings of hyperactivity, IQ$\geq$85, and a diagnosis of Hyperkinetic Reaction of Childhood.[32, 33] Children with a pattern of aggressive or antisocial behavior were excluded to rule out comorbid conduct disorder. Further details of proband characteristics appear in previous publications.[30, 34] These subjects were assessed at mean ages 18.4±1.3, 25.0±1.3, and 41.2±2.7. Comparison male subjects (n=178) were recruited at 18FU. Medical center

pediatric charts were reviewed for children seen for routine physical exams from 1970-1977 when they were 6 through 12 years-old, group-matched for probands' race, childhood socioeconomic status and geographical residence. Parents of suitable children (by then adolescents) were called, informed of the study and, if interested, recruited, provided parents reported that no teacher had complained about their child's behavior in elementary school. Refusal was low (circa 5%).

ADULT-FOLLOW UP ASSESSMENT (41FU)

On average 33 years after initial childhood diagnosis, clinical data were obtained on 135 male probands (65% of original sample, 69% of those living) and 136 male comparisons (76% of 178 recruited in adolescence, 77% of those living). Major DSM-IV disorders, as well as multiple aspects of function, were assessed for the interval between 25FU and 41FU by trained clinicians "blind" to all antecedent data. A special interview, Assessment of Adult Attention Deficit Hyperactivity Disorder,_ was developed for diagnosing DSM-IV ADHD in adults (see eMethods and eInstrument). Current ADHD was defined as meeting DSM-IV criteria during the preceding six months. Participants were invited to take part in an anatomical MRI study. Due to refusals and MRI exclusions (see Table 1), we obtained MRI scans in 59 ADHD probands and 80 comparisons. Nearly all probands (n=57; 97% of those scanned) were treated with methylphenidate in childhood between ages 6 and 12, for an average of 2.2 years.[35] (See Author e-Table 1 for further details of childhood medication treatment, including thioridazine.[30]) All participants provided written informed consent as approved by the NYU School of Medicine Institutional Review Board.

To test whether cortical thickness differed as a function of current ADHD, we subdivided probands into three subgroups: 1) those who met diagnostic criteria for DSM-

IV ADHD at 41FU ("persistents" n=17, including seven Predominantly Inattentive, six Predominantly Hyperactive/Impulsive, and four Combined Type); 2) those who did not ("remitters" n=26); and 3) those diagnosed with ADHD Not Otherwise Specified ("ADHD-NOS" n= 16; see eMethods). Comparisons were dichotomized into subjects who did not meet criteria for any type of ADHD ("non-ADHD comparisons" n=57) and those who were diagnosed with ADHD-NOS ("comparisons with ADHD" n=23). Although all probands and all comparisons were included in initial vertex-wise and VBM analyses, subgroup analyses focused on current diagnostic status. Accordingly, probands and comparisons with current ADHD-NOS, which is not well-defined and did not differ between groups (27% and 29%, respectively), were excluded from subgroup analyses.

IMAGING

Anatomic T1-weighted images were obtained on a 3T Siemens Trio with an 8-channel Siemens head coil (41 scans; 20 ADHD probands, 21 comparisons) and a 3T Siemens Allegra with a Siemens single channel head coil (98 scans; 39 ADHD probands, 59 comparisons; proportions did not differ significantly across scanners, $(\chi_{(1)})^2$=0.96, p=0.33) with the following parameters: TR=2100ms; flip angle=12; slice thickness=1.5mm; inversion time=1100ms; matrix=192x256; FOV=172.5mm. The only parameter that differed was TE, which was 3.87ms on the Trio and 3.90ms on the Allegra.

Structural MRI scans were preprocessed through the fully automated CIVET-MNI pipeline.[36-39] The initial preprocessing step was to mask MRI native images using an automated brain extraction method.[40] Data were corrected for non-uniformity artifacts and registered to stereotaxic space (MNI152) using a 9-parameter linear transformation. Voxel-

wise tissue type classification was performed using a neural network classifier followed by a partial volume estimation step.[38, 41]

For VBM, the classified tissue maps were blurred with a Gaussian kernel of 10mm full width at half-maximum. Cortical thickness measures were assessed using a fully automated algorithm which defines the distances between a set of vertices at the white matter (WM) surface and then expands outward to find the intersection with GM in order to generate surface meshes that represent WM and GM interfaces.[42] A total of 40,962 linked vertices were calculated per hemisphere. Each individual cortical thickness map was blurred using a 30mm surface-based diffusion-smoothing kernel to reduce noise while preserving anatomical location, as this method produces less volumetric blurring than the equivalent Gaussian kernel.[43]

STATISTICAL ANALYSES

Global cortical thickness

We obtained a single global cortical thickness value for each subject by averaging across all 81,924 vertices. Linear regression models controlled for age at time of scan and scanner model (Trio vs. Allegra).

Vertex-wise and voxel-based morphometry analyses

Following the study aims, group analyses tested for regional differences in cortical thickness and GM density between (1) all adults with a childhood diagnosis of Combined Type ADHD and all comparisons; (2a) persistents versus non-ADHD comparisons; (2b) remitters versus non-ADHD comparisons; and (2c) persistents versus remitters. For each comparison, we regressed cortical thickness at each of 81,924 vertices or whole-brain GM

density on group, controlling for age at time of scan and scanner model. The software package 'mni.cortical.statistics' (Brain Imaging Centre of the Montreal Neurological Institute) for the R environment[44] was used for cortical thickness analyses and the FMRIB Software Library (FSL, www.fmrib.ox.ac.uk) tool Feat, for VBM. Results were thresholded using a false discovery rate (FDR) of 0.05.[45, 46] Maps of t-statistics for group effects on cortical thickness at each vertex or GM density at each voxel were projected onto an average brain template revealing clusters that differed significantly between groups. We retained clusters comprising at least 50 contiguous vertices for cortical thickness[47] and five voxels for VBM.

Region-based analyses of cortical thickness and voxel-based morphometry

To test whether childhood or current ADHD was associated with significant differences in specific regions, we performed *post-hoc* region-of-interest (ROI)-based analyses. For each participant, we computed mean cortical thickness or GM density within each cluster exhibiting significant (FDR<0.05) group differences in primary analyses by averaging across all vertices or voxels within each cluster. We then compared the diagnostic subgroups of probands (persistents, remitters) and the comparisons without current ADHD, Bonferroni corrected for the number of clusters. For completeness, Author e-Table 2 contains means and SD for the subgroups with current ADHD-NOS.

Exploratory analyses of cortical thickness

To further investigate primary hypotheses for which no FDR<0.05 vertices were found, we reexamined subgroup differences heuristically using an uncorrected p<0.05

threshold with a cluster threshold of 50 vertices.[47] Because of significant between-group differences in IQ, we confirmed cortical thickness results by also adjusting for IQ.

RESULTS

Table 1 summarizes the derivation of the sample. A larger proportion of comparisons (45% of originally enrolled participants) than probands (29%) had analyzable MRI scans. This discrepancy reflects a significantly higher rate of unavoidable factors in probands (27%) (i.e., deaths, incarcerations and MRI exclusions) than in comparisons (12%) ($\chi^2_{(1)}$=12.08, p<0.001). By contrast, rates of refusal, failure to schedule or to locate subjects did not differ significantly (45% of probands versus 43% of comparisons). Accordingly, results are based on anatomic images from 59 ADHD probands and 80 comparisons.

We compared diagnoses and demographic information at 18FU of subjects who were scanned and those who were not (data available for 57/59 probands and all comparisons; see Author e-Table 3). Within both proband and comparison groups, individuals scanned and those not scanned did not differ significantly on prevalence of ADHD, Antisocial Personality Disorder, mood or anxiety disorders, any DSM-III disorders, age at referral, IQ, socioeconomic status, or Teacher Conners Hyperactivity Factor score. However, scanned probands had significantly higher rates of alcohol substance use disorder (SUD), non-alcohol SUD, and any SUD than probands who were not scanned (Author e-Table 3)

DEMOGRAPHICS

Probands and comparisons did not differ significantly in age at scan, or in lifetime prevalence of substance abuse or dependence (see Table 1). As expected, probands and

comparisons differed significantly in IQ in childhood and 41FU assessments. See Author e-Table 5 for demographics of subgroups based on current diagnosis. Current substance use and comorbid diagnoses are presented in Author e-Table 5.

GLOBAL CORTICAL THICKNESS

Surface-wide, mean cortical thickness was significantly lower in probands (n=59) than comparisons (n=80) (mean ± SD 3.18±0.11mm and 3.24±0.11mm, respectively; $p<0.001$ in regression controlling for age and scanner; Cohen's d=0.54). At 41FU, probands with persistent ADHD differed significantly from non-ADHD comparisons (3.14±0.13mm and 3.25±0.10mm, respectively; p=0.0005; d=1.02). The remitters (3.20±0.11mm) also differed from non-ADHD comparisons in overall cortical thickness (p=0.04, d=0.48). However, persistents and remitters did not differ significantly (p=0.10, d=0.51).

VERTEX-WISE ANALYSES OF CORTICAL THICKNESS

Figure 1A displays the multiple clusters of vertices (detailed in Table 2) for which the cortex was significantly thinner (surface-wide FDR<0.05) in ADHD probands; the largest cluster extended from right precuneus to precentral gyrus. Other right hemisphere clusters were located in inferior parietal lobe, temporal pole, and insula. Left hemisphere clusters were located in superior frontal gyrus/frontal pole, precentral gyrus, insula, temporal pole, and cuneus. There was no instance in which cortical thickness was significantly increased in probands. As shown in eFigure1 and Author e-Table 6, after covarying for IQ (in addition to scanner and age), significant cluster centers remained largely unchanged in location, but the clusters were less extensive.

In order to assess associations with current ADHD diagnosis, we performed vertex-wise comparisons among the different diagnostic subgroups. The 17 individuals with

persistent ADHD differed significantly from the 57 non-ADHD comparisons in most but not all the regions identified in the initial inclusive analyses (see Table 2 and Figure 1B). Additionally, this analysis revealed thinner cortex related to persistent ADHD in the left medial occipital cortex and right subgenual ACC. Using FDR<0.05, remitters (n=26) did not differ significantly from non-ADHD comparisons; persistents and remitters also did not differ in any region at this threshold. There were no vertices at which cortical thickness was significantly associated with lifetime or current substance abuse diagnoses, dimensional measures of substance abuse, lifetime smoking history, or thioridazine treatment, nor were there any significant interactions between group and scanner for any cortical or VBM measures.

REGION-BASED ANALYSES OF CORTICAL THICKNESS

To examine potential differences associated with remission from childhood ADHD, we focused on the clusters in which ADHD probands exhibited significantly thinner cortex than comparisons (FDR<0.05). Both remitters and persistents had thinner cortex than non-ADHD comparisons, with medium to large effect sizes. Average effect sizes between persistents and non-ADHD comparisons (d=0.73) were larger than for remitters (d=0.52), although all confidence intervals overlapped (not shown); persistents and remitters did not differ significantly from each other in any cluster at FDR<0.05 (see Table 2).

EXPLORATORY VERTEX-WISE ANALYSES

When vertex-wise results were thresholded at p<0.05 (uncorrected), we observed thinner cortex for persistents versus remitters in insula, bilateral temporal cortex including right temporal pole and in left occipital Brodmann area (BA) 19, orbitofrontal cortex and

medial ACC (see Figure 2, Author e-Table 7). There were no regions exceeding our cluster size threshold of 50 vertices in which remitters exhibited thinner cortex than those with persistent ADHD.

EXPLORATORY REGION-BASED ANALYSES

In the clusters that differentiated persistents from remitters in exploratory vertex-wise analyses, persistents differed markedly from non-ADHD comparisons (average d=0.75), whereas remitters did not (average d=0.03; $t_{(9)}$=8.26, p<0.0001). Relative to comparisons, remitters had (non-significantly) greater cortical thickness in left superior temporal gyrus extending to insula and orbitofrontal cortex, left parahippocampus, left ACC, and left medial occipital cortex (see Author e-Table 7).

VOXEL-BASED MORPHOMETRY

As shown in Table 3 and Figure 3, GM density was significantly greater (FDR<0.05) for comparisons than for probands in many of the same regions identified through cortical thickness analyses as well as in subcortical regions inaccessible to cortex-based measures. Figure 4 displays decreased GM in probands in right caudate, right thalamus and bilateral cerebellar hemispheres. VBM analyses of diagnostic subgroups or of medication treatment in childhood with methylphenidate or thioridazine did not yield significant results even with more lenient thresholds (FDR≤0.2).

COMMENT

In a prospective 33-year longitudinal follow-up of 59 probands (mean age 41 years) with established ADHD in childhood and 80 prospectively enrolled non-ADHD comparisons, we found an overall significant reduction in mean cortical thickness in

probands. Beyond this global difference, the greatest cortical thinning associated with childhood ADHD was located in bilateral parietal lobes, temporal poles, insula, precentral gyri, frontal poles, and right precuneus. No cortical region was significantly thicker in probands than comparisons. Although less sensitive,[48] VBM also revealed significantly decreased GM in probands versus comparisons in right precentral, bilateral parietal, left temporal, and right cuneus. Additionally, VBM detected decreased GM in probands in caudate, thalamus and cerebellar hemispheres.

With respect to current adult diagnosis, probands with persistent ADHD differed most from non-ADHD comparisons in the same cortical regions identified in our primary analyses, as well as in additional clusters in left medial occipital cortex and subgenual ACC. Probands with remitted ADHD did not differ significantly from persistents when analyses were corrected for full-brain comparisons. In exploratory uncorrected analyses, probands with persistent ADHD exhibited reduced cortical thickness relative to remitters in bilateral medial occipital lobes, temporal lobes extending to insula, and left parahippocampus.

Our results extend prior volumetric and cortical thickness findings in ADHD. First, consistent with decreased total cerebral volume in ADHD,[2-4] our observation of reduced global cortical thickness in probands with ADHD confirms prior reports.[13, 14, 20] Furthermore, although we found less frontal and prefrontal cortical thinning in ADHD than others,[12-15, 20, 49] we confirmed thinner cortical mantle in occipito-parietal,[12, 13, 20] temporal cortex and precentral regions[13, 14] in ADHD. In subcortical analyses, we also confirmed anatomic abnormalities in caudate,[3, 50, 51] thalamus[52, 53] and cerebellum[3] in ADHD.

Studies of cortical thickness in adults with ADHD have focused on specific regions associated with executive function and attentional control.[54, 55] Makris et al.[9] selected nine

parcellation units (from 48) per hemisphere and found thinner cortex related to ADHD in prefrontal and cingulate cortex and inferior parietal lobe, albeit without correcting for multiple comparisons.[9] A cross-sectional study of children, adolescents and adults found that individuals with ADHD, regardless of age, had significantly thinner right superior frontal cortex than controls.[15] In the adults with ADHD, the specific reduction, with correction for multiple comparisons limited to the frontal lobe, was localized to BA9. In contrast, we did not find group differences in much of prefrontal cortex but found widespread cortical thinning in bilateral parietal-temporal cortex. We found similar results in analyses that included all participants as well as in those limited to probands with persistent ADHD versus non-ADHD comparisons. The latter contrasts are comparable to studies in adults that define group membership by current diagnostic status.[15, 20]

Studies of cortical thickness in children with ADHD are more numerous than those in adults,[12-14, 33, 47, 56, 57] and typically have examined the entire cerebrum, although nearly all (except[14]) report results uncorrected for multiple comparisons. Thinner cortex has been reported in children with ADHD in prefrontal and precentral regions[12, 14] parietal and temporal lobes[12, 13] and inferior frontal gyrus bilaterally.[58] In our main analyses, we applied FDR full-brain correction for multiple comparisons, and observed significant differences whether groups were defined by initial childhood history or by current adult diagnoses. We speculate that the robustness of our results reflects having established the diagnosis of ADHD in childhood as well as our medium to large sample sizes.

Broadly, our results implicate disruptions in large-scale neural systems involved in the regulation of both attention and emotion in adults with childhood ADHD. We found convincing converging anatomic evidence implicating the dorsal attentional network[55] and distributed regions within limbic circuits that were thinner in ADHD probands than in

comparisons. Similar findings were obtained when we contrasted probands with persistent ADHD versus comparisons without ADHD. However, we failed to observe hypothesized group differences in prefrontal regions.[1, 3] Below we discuss our main findings and non-findings in turn.

First, we found widespread thinner cortex and decreased GM density in bilateral parietal and precentral regions, overlapping areas of the dorsal attentional network. The bilateral dorsal network, which mediates goal-directed, top-down executive control processes, interacts with a right-sided ventral system (stimulus-driven, bottom-up) during attentional functioning,[1, 55] particularly in redirecting attention. The core areas constituting the dorsal attentional network include the intraparietal sulcus and the conjunction of the precentral and superior frontal sulcus (frontal eye fields)[55] which were particularly affected in the ADHD probands. Strikingly, we also observed significantly thinner cortex in precuneus and superior parietal lobe, which along with the dorsal network core regions are implicated in top-down processing of shifting of attention.[59] These findings are consistent with studies of ADHD that report abnormal patterns of activation in parietal regions[52] during working memory,[60-62] attentional[63-65] or response inhibition tasks.[66, 67]

We also found occipital cortical thinning in probands with persistent ADHD versus non-ADHD comparisons. Occipital cortex has been recently found to interact with the dorsal network in maintaining attention[59] and in suppressing responses to irrelevant stimuli.[68, 69] Individuals with ADHD are easily distracted when required to ignore extraneous signals.[70, 71] Top-down control deficits when responding to irrelevant stimuli are associated with impaired working memory.[72, 73] Abnormal activation of occipital cortex has been found in youth[74] and adults[75-77] with ADHD during working memory tasks. Similarly, in a meta-analysis of functional imaging studies, children and adolescents with ADHD

showed activation decreases in left middle occipital gyrus (BA19) compared to controls.[52] Additionally, a recent VBM study in adults with ADHD found significant bilateral reduction of GM volume only in early visual cortex.[78]

Our VBM analysis revealed cerebellar, thalamic and striatal GM deficits in ADHD. Cerebellar involvement in ADHD is well-established, with findings in children reported mostly in the vermis,[1-4, 79] and in the hemispheres in adults, as in this sample.[60, 80, 81] Early anatomical studies of ADHD did not specifically examine thalamic nuclei, although thalamic hypoactivation emerged in an unbiased meta-analysis.[52] Recently, several studies have identified thalamic abnormalities in children/adolescents[53, 82] and adults with ADHD.[83, 84]

Second, our analyses revealed thinner cortex in probands, and particularly those with persistent ADHD, across multiple limbic regions such as temporal poles (BA38), insula (BA13) and subgenual ACC (BA25). The insula and ACC play important roles in sensorimotor, emotional and cognitive function.[85, 86] Specifically, subgenual ACC is implicated in emotional processing and pain perception.[87] In humans, subgenual ACC is functionally connected with multiple limbic regions including temporal poles[88] and insula.[89] In turn, the insula, along with participating in performance of demanding tasks,[90] is clearly also related to affective processing.[91] Abnormal activations in insula and subgenual ACC were reported in a meta-analysis of ADHD functional imaging.[52]

Cortical thickness studies in ADHD have downplayed findings in the temporal pole, which have been reported but not discussed.[12-14] The temporal pole (BA38) is classified as a paralimbic region, based on its interconnections with both amygdala and orbitofrontal cortex, and is implicated in social and emotional processes.[92] Altered activation in temporal pole is associated with deficits in face recognition[93-100] and mentalizing, i.e., theory of

mind.[101-104] The temporal poles have been proposed as a channel for the integration of emotion and perception, playing an important role in both emotional and social functions.[92]

Our findings are consistent with pathophysiological models of ADHD highlighting not only cognitive executive functions ("cool" processes) but also emotion/motivational deficits ("hot" processes).[105] Anatomic "spiraling" circuits begin with emotion/motivation pathways which influence "cool" cognitive processes, which in turn control motor responses.[106] We observed thinner cortex in regions subserving both emotional regulation (temporal pole, insula, parahippocampus and subgenual ACC) and top-down attentional regulation (dorsal attentional network and medial occipital cortex). Further, our exploratory analyses suggest that thinner cortex and diminished gray matter in the dorsal attentional network and limbic relay regions is related to the trait of having had ADHD in childhood, regardless of current diagnostic status.

Third, the lack of proband-comparison differences in prefrontal cortex or ACC was unexpected.[8, 9, 17, 20, 21] To better understand possible differences between persistents and remitters, we performed uncorrected exploratory analyses. In regions in which we found suggestive differences, we observed remarkable congruence between remitters and controls in left superior temporal gyrus, ACC, parahippocampus, and occipital cortical thickness as well as in thalamus and cerebellum gray matter density. We cannot rule out that remitters may have differed from persistents in these regions since childhood, but the most parsimonious explanation is offered by the hypothesis that remission entails compensatory processes[12, 107] underpinned by prefrontal cortical maturation. While we found supporting evidence for ACC and orbitofrontal involvement in diagnostic remission of ADHD, our data also suggest superior temporal, medial occipital and thalamo-cerebellar involvement in remission.

Our findings must be interpreted in light of several limitations. First, despite our prospective longitudinal design, we examined brain imaging data only cross-sectionally in middle adulthood. Nevertheless, this is the largest sample of children with ADHD followed into adulthood, obviating the unreliability of retrospective recall of childhood symptoms. Additionally, we report on the largest sample to date of adults with confirmed childhood ADHD who had remitted. We were able to analyze imaging data from only 28% of initially diagnosed probands with ADHD and 45% of comparison subjects. However, these probands and comparisons did not differ from the original sample, and the probands studied did not differ significantly from those excluded on nearly all clinical and demographic variables, except for significantly higher rates of substance use disorders at 18FU in scanned probands. Nevertheless, we did not observe significant relationships between brain anatomic measures and substance use disorders. Finally, as is generally the case, our probands had significantly lower IQ than comparisons both in childhood/adolescence and adulthood. The issue of whether to covary for IQ in disorders such as ADHD is not settled.[108] As shown in eFigure1 and Author e-Table 7, our principal findings of persistent differences in brain anatomy survived covarying for IQ even with conservative full-brain correction.

We were surprised by the rate of ADHD-NOS diagnosed in comparisons, which was comparable to the rate in probands. We speculate that secular changes in the general public's awareness of ADHD may have contributed. While we cannot rule out instrument-related error (see eInstrument), using similar approaches did not yield high rates of ADHD symptoms in comparisons in two previous "blind" assessments.[24, 26] Nevertheless, analyses excluding ADHD-NOS did not alter results appreciably.

Subjects were limited to Caucasian males, since the number of originally diagnosed females with ADHD was too small for meaningful statistical comparisons. Thus our results may not generalize to ADHD in women or to other racial or ethnic groups. However, this constraint avoided potential confounds from possible sex, ethnic, or socioeconomic differences. Exclusion of conduct disorder comorbidity (see eText) in childhood also averted confusion as to the origin of the deficits found in cortical thickness or GM density.

We cannot comment on cortical thickness or GM density in ADHD in the absence of medication treatment, as all but four of the scanned probands were treated with methylphenidate as children. We also did not detect significant effects of childhood treatment with stimulants or thioridazine in cortical thickness or VBM analyses. Medication treatment has been reported to affect cortical thickness[47] although the durability of such effects is unknown, and treatment had been discontinued for all subjects for several decades.

For logistical reasons, we used two scanners. Fortunately, scans were approximately counterbalanced across probands and comparisons, and there were no significant main effects or interactions related to scanner type. Secondary analyses (see eFigure2) also showed that we obtained comparable results when we examined only the 98 scans obtained on the Allegra scanner. Finally, the analyses presented here were limited to cortical thickness and VBM; ongoing analyses will examine white matter structure using diffusion tensor imaging.

In conclusion, in this first study of childhood ADHD prospectively examined in adulthood, we found thinner overall cortex in probands with childhood ADHD that was even more pronounced in those with persistent ADHD. Beyond this global effect, we also

detected significant reductions in cortex thickness in parietal, temporal and posterior frontal regions corresponding to the dorsal attentional network and limbic areas. These findings were largely echoed by VBM, which additionally highlighted decreased GM in caudate. These regions underpin top-down control of attention and the regulation of emotion and motivation and were comparably diminished in probands with remitted ADHD or persistent ADHD. Thus these differences seem to primarily reflect the childhood diagnosis of ADHD. By contrast, remitters tended to differ from persistents in medial occipital cortex, temporal pole, insula, orbitofrontal cortex, parahippocampus, frontal pole, and subcortically in cerebellum and thalamus. This supports the suggestion that symptom amelioration and diagnostic remission may result in part from compensatory maturation of frontal–thalamic–cerebellar circuits.[107, 109]

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Table and Figure Legends

Table 1. Derivation of MRI Sample and Demographics

* All ADHD probands and comparisons: Caucasian

**Hollingshead and Redlich (1958) scale, based on the participant's education and occupation.

†Highest Grade Completed

WAIS: Wechsler Adult Intelligence Scale. Obtained for 39 (66%) of the 59 Probands and all Comparisons.

WASI: Wechsler Abbreviated Scale of Intelligence. Obtained on 54 (92%) of the 59 Probands and 73 (91%) of the 80 Comparisons.

***Completed by the "blind" clinician that conducted the mental status and diagnostic assessments.

Table 2. Cortical Thickness Values for Significant Clusters for Subgroups Defined by Current ADHD Diagnostic Status in Mid-Adulthood.

Results for regions which survived FDR<0.05 and extent > 50 vertices in analyses of the entire sample (Figure 1a).

Non-ADHD Controls: comparisons who did not meet criteria for any type of ADHD at 41FU longitudinal assessment; ES: Effect Size; BA: Brodmann area; L.: Left; Sup.: Superior; Temp.: Temporal; G.: Gyrus; R.: Right; Inf.: Inferior. P-values surviving Bonferroni correction for multiple comparisons or ES>.50 are indicated in bold.

Table 3. Grey Matter Density within Clusters for Subgroups Defined by Current ADHD Diagnostic Status in Mid-Adulthood.

Results for regions which survived FDR<0.05 and extent > 5 voxels in analyses of the entire sample (Figures 3 and 4). Non-ADHD Controls: comparisons who did not meet criteria for any type of ADHD at 41FU longitudinal assessment; ES: Effect Size; BA: Brodmann area; L: Left; Sup: Superior; Temp: Temporal; G: Gyrus; R: Right; Inf: Inferior. OFC: Orbitofrontal cortex; P-values surviving Bonferroni correction for multiple comparisons or ES>.50 are indicated in bold.

Figure 1.

(A) t-map of the significant cortical thinning in probands with ADHD (n=59) compared to comparisons (n=80). **(B)** t-map of the significant cortical thinning in probands with persistent ADHD (n=17) compared to non-ADHD comparisons (n=57). False Discovery Rate (FDR) threshold depends on the data and is different for the right and left hemispheres. Here the t-statistics at the lowest FDR threshold are projected across each hemisphere for each comparison.

Figure 2.

Exploratory uncorrected analyses ($p<0.05$) reveal regions in which remitted probands (n=27) exhibit thicker cortex than probands with persistent ADHD (n=17). See Author e-Table 7 for peaks and coordinates of clusters.

Figure 3.

Comparisons (N=80) exhibit greater gray matter density (left) and cortical thickness (right) in the bilateral dorsal attentional network than probands (n=59) with childhood combined type ADHD. Images are in radiological convention, right is left and left is right.

Figure 4.

Voxel-based morphometry reveals that comparisons (N=80) exhibit significantly greater gray matter density (FDR <0.05) in right ventral caudate, right thalamus, bilateral cerebellum than probands (n=59) with childhood combined type ADHD. Images are in radiological convention, right is left and left is right.

			ADHD Male Probands N (%)	Male Comparisons N (%)
	207 (100)	178 (100)		
INITIAL SAMPLE				
Unable to locate	21 (10)	20 (11)		
Deceased	15 (7)	5 (3)		
Incarcerated	6 (3)	1 (1)		
Refused MRI	43 (21)	34 (19)		
Not evaluated prior to termination of funding	29 (14)	22 (12)		
SUBTOTAL-AVAILABLE FOR SCAN	93 (45)	96 (54)		
MRI Exclusions:				
Size (too large for scanner)	17 (8)	6 (3)		
Claustrophobic	7 (3)	3 (2)		
Metal contraindications	3 (2)	1 (1)		
Failed scan quality criteria	7 (3)	6 (3)		
TOTAL NUMBER WITH USABLE DATA	**59 (29)**	**80 (45)**		
DEMOGRAPHICS*	**Mean (SD)**	**Mean (SD)**	*t*	P (2-tailed)
Age at Follow-Up (Years)	41.1 (2.7)	41.3 (3.1)	0.51	0.61
Socioeconomic Status** at Follow-Up	3.37 (1.1)	2.48 (1.0)	5.01	0.001
Educational Attainment†	13.5 (2.4)	15.6 (2.3)	5.31	0.001
WAIS Full Scale IQ at 18FU	104(13)	113(13)	3.58	0.001
WASI Full Scale IQ at 41FU	101 (13)	110 (15)	3.42	0.001
Global Assessment Scale Rating***	63.4 (12.5)	71.4 (10.5)	4.05	0-001

Table 1. Derivation of MRI Sample and Demographics

* All ADHD probands and comparisons: Caucasian

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†Highest Grade Completed
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***Completed by the "blind" clinician that conducted the mental status and diagnostic assessments

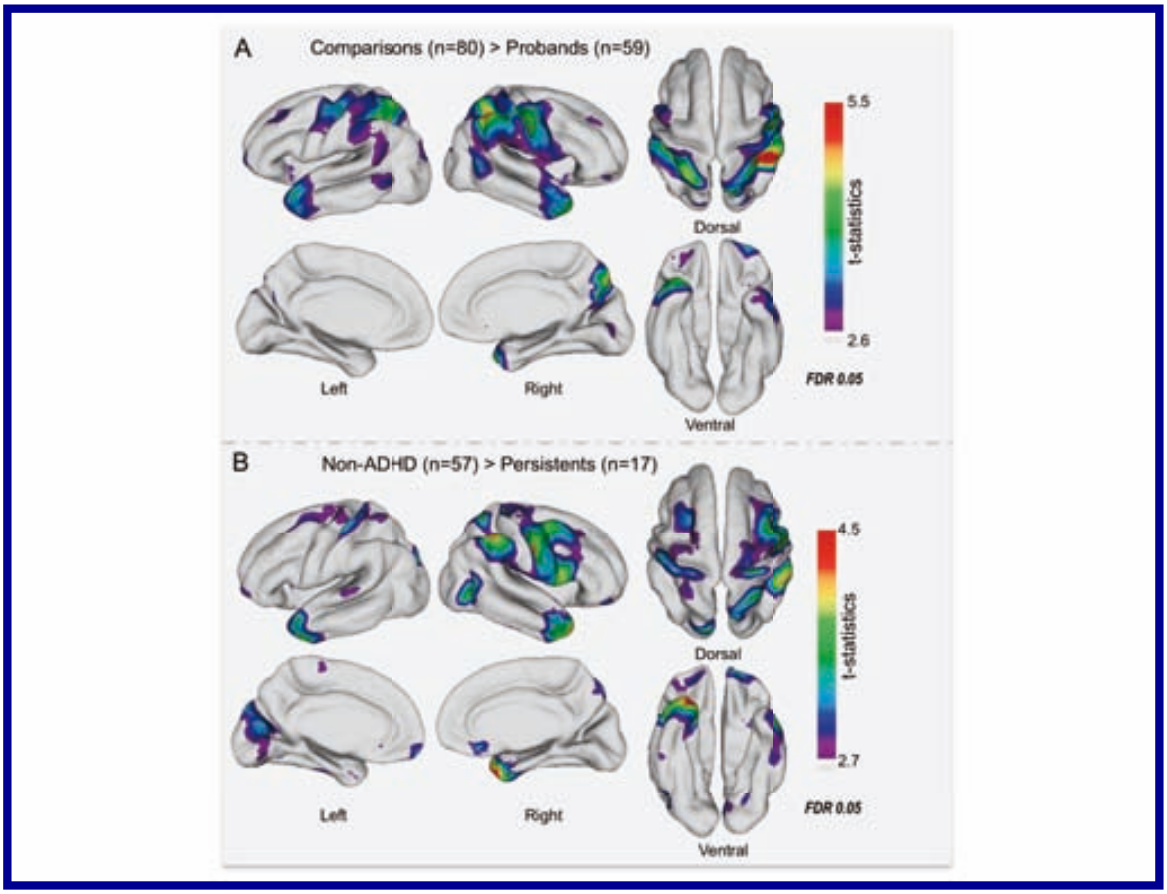
Regions	MNI X, Y, Z (No. of vertices)	Non-ADHD Controls (n=57)		Probands w/ Persistent ADHD (n=17)		Remitted Probands (n=26)		Non-ADHD Controls vs. Persistents		Non-ADHD Controls vs. Remitters		Remitters vs. Persistents	
		mean	SD	mean	SD	mean	SD	p	ES	p	ES	p	ES
L Sup Parietal (BA7)	-26, -55, 68 (4,290)	2.97	0.13	2.85	0.17	2.86	0.13	0.004	**0.83**	**0.000**	**0.88**	0.978	0.01
L Precentral G (BA6)	-35, 37, 36 (784)	3.35	0.13	3.26	0.15	3.26	0.16	0.022	**0.65**	0.006	**0.67**	0.917	-0.03
L Sup Temp G (BA38)	-54, 10, -22 (915)	3.80	0.19	3.60	0.23	3.66	0.19	**0.001**	**0.98**	**0.002**	**0.75**	0.401	0.26
L Frontal Pole (BA10)	-31, 62, -6 (638)	3.23	0.18	3.06	0.18	3.11	0.23	**0.001**	**0.96**	0.010	**0.62**	0.453	0.24
L Cuneus (BA19)	-13, -91, 35 (618)	2.78	0.20	2.65	0.17	2.73	0.16	0.025	**0.63**	0.325	0.23	0.134	0.48
L Precuneus (BA31)	-6, -65, 30 (62)	3.35	0.20	3.23	0.19	3.26	0.15	0.028	**0.62**	0.029	**0.53**	0.630	0.15
R. Precuneus (BA7)	10, -73, 51 (1148)	3.23	0.16	3.12	0.13	3.15	0.15	0.010	**0.73**	0.040	0.49	0.430	0.25
R Inf Parietal (BA40)	49, -40, 50 (4836)	3.03	0.14	2.91	0.18	2.93	0.14	0.007	**0.77**	**0.002**	**0.74**	0.828	0.07
R Sup Temp G (BA38)	30, 15, -40 (1141)	3.87	0.27	3.62	0.25	3.75	0.22	**0.001**	**0.96**	0.044	0.48	0.080	**0.56**
R Temporal G extending to Insula (BA13)	48, -1, -3 (315)	3.81	0.21	3.69	0.24	3.72	0.21	0.049	**0.55**	0.053	0.46	0.747	0.10
R Precentral G (BA6)	58, 0, 36 (315)	3.41	0.15	3.27	0.19	3.35	0.18	**0.003**	**0.86**	0.109	0.38	0.207	0.40
R Frontal Pole (BA10)	27, 47, 32 (98)	3.37	0.16	3.28	0.17	3.27	0.18	0.057	**0.53**	0.021	**0.56**	0.907	-0.04
R Middle Frontal G (BA9)	25, 47, -14 (130)	3.36	0.20	3.19	0.18	3.33	0.17	**0.002**	**0.90**	0.497	0.16	0.011	**0.83**
R Occipital (BA19)	27, -87, 26 (210)	2.96	0.20	2.86	0.19	2.87	0.19	0.095	0.47	0.079	0.42	0.862	0.05
R Occipital (BA18)	10, -80, 10 (94)	2.79	0.20	2.69	0.21	2.71	0.19	0.079	0.49	0.080	0.42	0.776	0.09

Table 2. Cortical Thickness Values for Significant Clusters for Subgroups Defined by Current ADHD Diagnostic Status in Mid-Adulthood. Results for regions which survived FDR<0.05 and extent > 50 vertices in analyses of the entire sample (Figure 1a). Non-ADHD Controls: comparisons who did not meet criteria for any type of ADHD at 41FU longitudinal assessment; ES: Effect Size; BA: Brodmann area; L.: Left; Sup.: Superior; Temp.: Temporal; G.: Gyrus; R.: Right; Inf.: Inferior. P-values surviving Bonferroni correction for multiple comparisons or ES>.50 are indicated in bold

Regions	Maximum Z-scores	MNI Peak (No. of voxels)	Non - ADHD Controls (n=57)		Probands Persistent ADHD (n=17)		Probands Remitters ADHD (n=26)		Non-ADHD Controls vs. P-ADHD		Non-ADHD Controls vs. Remitters		Remitters vs. P-ADHD	
			mean	SD	mean	SD	mean	SD	p	ES	p	ES	P	ES
L Sup Parietal (BA7)	5.3	-28, -58, 66 (1747)	0.42	0.04	0.39	0.03	0.39	0.05	0.003	0.86	0.001	**0.78**	0.993	0
L Cerebellum	4.01	-14, -70, -34 (430)	0.57	0.15	0.51	0.14	0.56	0.16	0.146	0.41	0.821	0.05	0.279	0.34
L Inf Cerebellum	3.44	-32, -42, -58 (41)	0.41	0.17	0.28	0.15	0.34	0.18	0.009	0.74	0.116	0.38	0.27	0.35
L Middle Temp G (BA21)	3.32	-48, 10, -42 (32)	0.39	0.1	0.33	0.1	0.34	0.11	0.048	0.56	0.088	0.41	0.682	0.13
L Temp-occipital (BA37)	3.5	-50, -42, -22 (17)	0.6	0.08	0.55	0.09	0.54	0.07	0.024	0.64	0.002	**0.78**	0.724	-0.1
Brainstem extending to Cerebellum	3.37	0, -44, -48 (16)	0.36	0.14	0.3	0.12	0.32	0.11	0.1	0.46	0.148	0.35	0.653	0.14
L Temp-parahippocampal (BA35)	3.33	-34, -10, -22 (13)	0.75	0.06	0.73	0.06	0.72	0.07	0.117	0.44	0.027	**0.53**	0.727	-0.1
L Frontal pole (BA10)	3.31	-16, 52, 32 (9)	0.45	0.05	0.43	0.06	0.43	0.06	0.062	0.52	0.035	**0.51**	0.972	0.01
R Parietal Postcentral (BA3) extending to BA6	4.7	48,-18, 56 (1196)	0.41	0.04	0.37	0.04	0.38	0.05	0	1.04	0.003	**0.72**	0.444	0.24
R Cerebellum	3.84	32, -60, -38 (235)	0.51	0.17	0.44	0.14	0.53	0.17	0.146	0.41	0.581	-0.1	0.078	**0.56**
R Thalamus	3.94	4, -8, 12 (170)	0.73	0.1	0.7	0.09	0.74	0.07	0.202	0.36	0.541	-0.2	0.065	**0.59**
R Occipital, Cuneus (BA18/19)	3.88	2, -76, 36 (122)	0.67	0.05	0.63	0.06	0.65	0.05	0.005	0.79	0.082	0.42	0.2	0.41
R Sup Frontal G (BA10)	4.25	12, 64, 12 (68)	0.47	0.06	0.45	0.04	0.46	0.05	0.261	0.31	0.398	0.2	0.696	0.12
R Frontal lobe (BA6)	3.66	12, -12, 78 (32)	0.46	0.11	0.41	0.11	0.45	0.14	0.107	0.45	0.75	0.08	0.319	0.31
R Middle Frontal G (BA10) extending to OFC (BA11)	3.41	24, 38, -18 (23)	0.51	0.06	0.45	0.05	0.47	0.06	0.001	0.96	0.005	**0.69**	0.434	0.25
R Temp Fusiform (BA36)	3.23	34, -34, -26 (13)	0.63	0.08	0.58	0.05	0.6	0.07	0.014	0.69	0.062	0.45	0.423	0.25
R Caudate	3.3	8, 20, -2 (5)	0.51	0.09	0.49	0.07	0.48	0.1	0.41	0.23	0.18	0.32	0.715	-0.1
R Middle Temp (BA21) extending to (BA38)	3.16	52, 6, -32 (5)	0.55	0.06	0.52	0.05	0.51	0.08	0.063	0.52	0.009	**0.63**	0.614	-0.2
R Middle Temp (BA21) extending to (BA38)	5.3	46, 8, -42 (5)	0.52	0.06	0.51	0.08	0.51	0.05	0.557	0.16	0.561	0.14	0.894	0.04
Anterior Cingulate/limbic (BA24)	3.53	0, 44, -10 (20)	0.82	0.04	0.79	0.04	0.81	0.04	0.016	0.68	0.248	0.28	0.246	0.37

Table 3. Grey Matter Density within Clusters for Subgroups Defined by Current ADHD Diagnostic Status in Mid-Adulthood.
Results for regions which survived FDR<0.05 and extent > 5 voxels in analyses of the entire sample (Figures 3 and 4). Non-ADHD Controls: comparisons who did not meet criteria for any type of ADHD at 41FU longitudinal assessment; ES: Effect Size; BA: Brodmann area; L: Left; Sup: Superior; Temp: Temporal; G: Gyrus; R: Right; Inf: Inferior. OFC: Orbitofrontal cortex; P-values surviving Bonferroni correction for multiple comparisons or ES>.50 are indicated in bold.

Figures1 and Figure 2



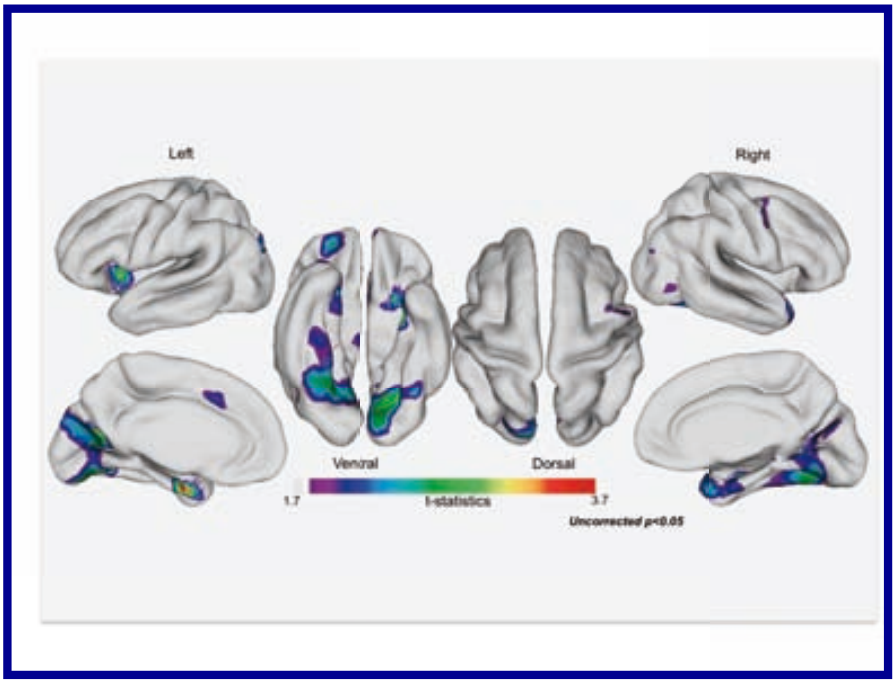


Figure 3.

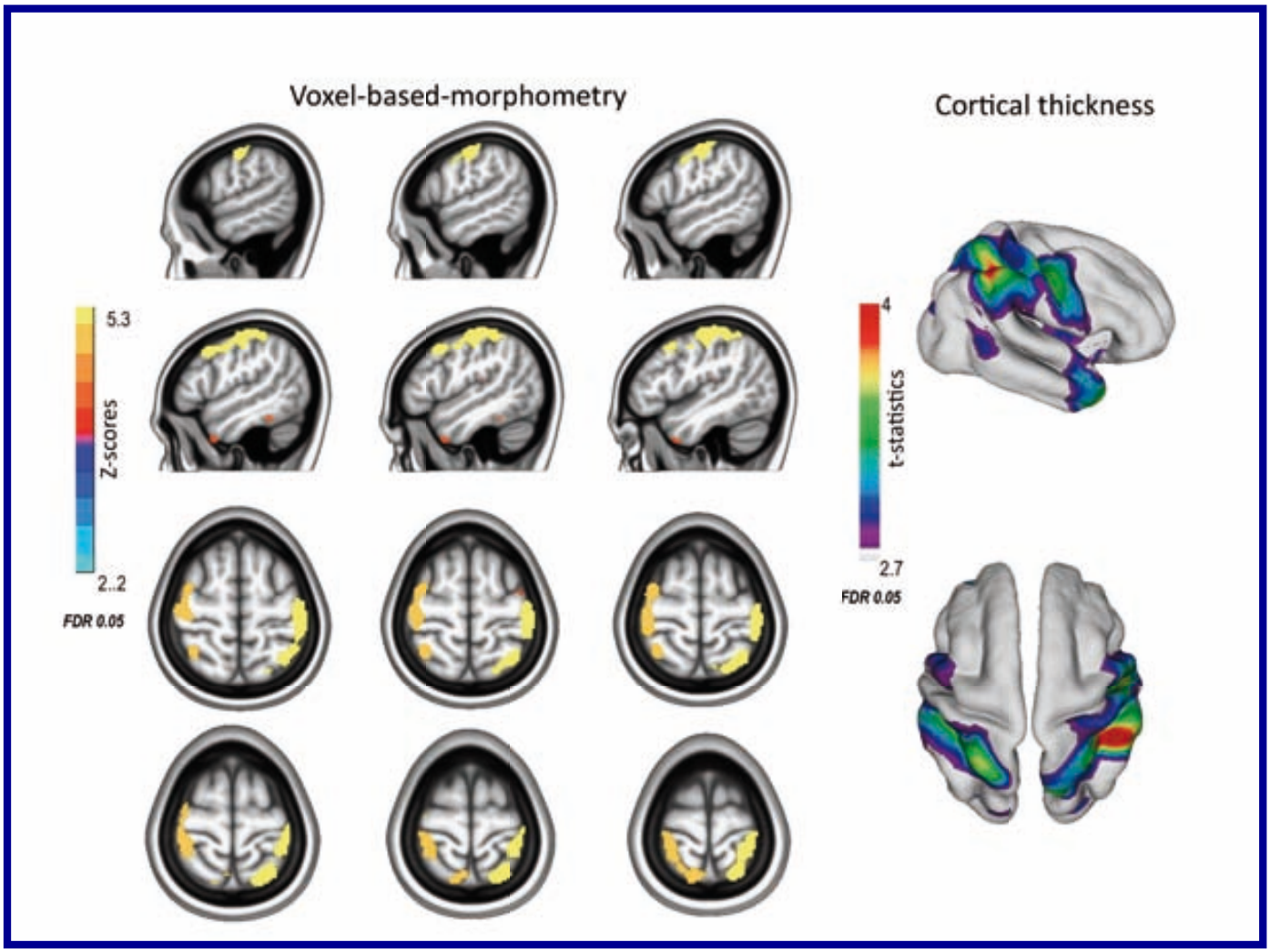
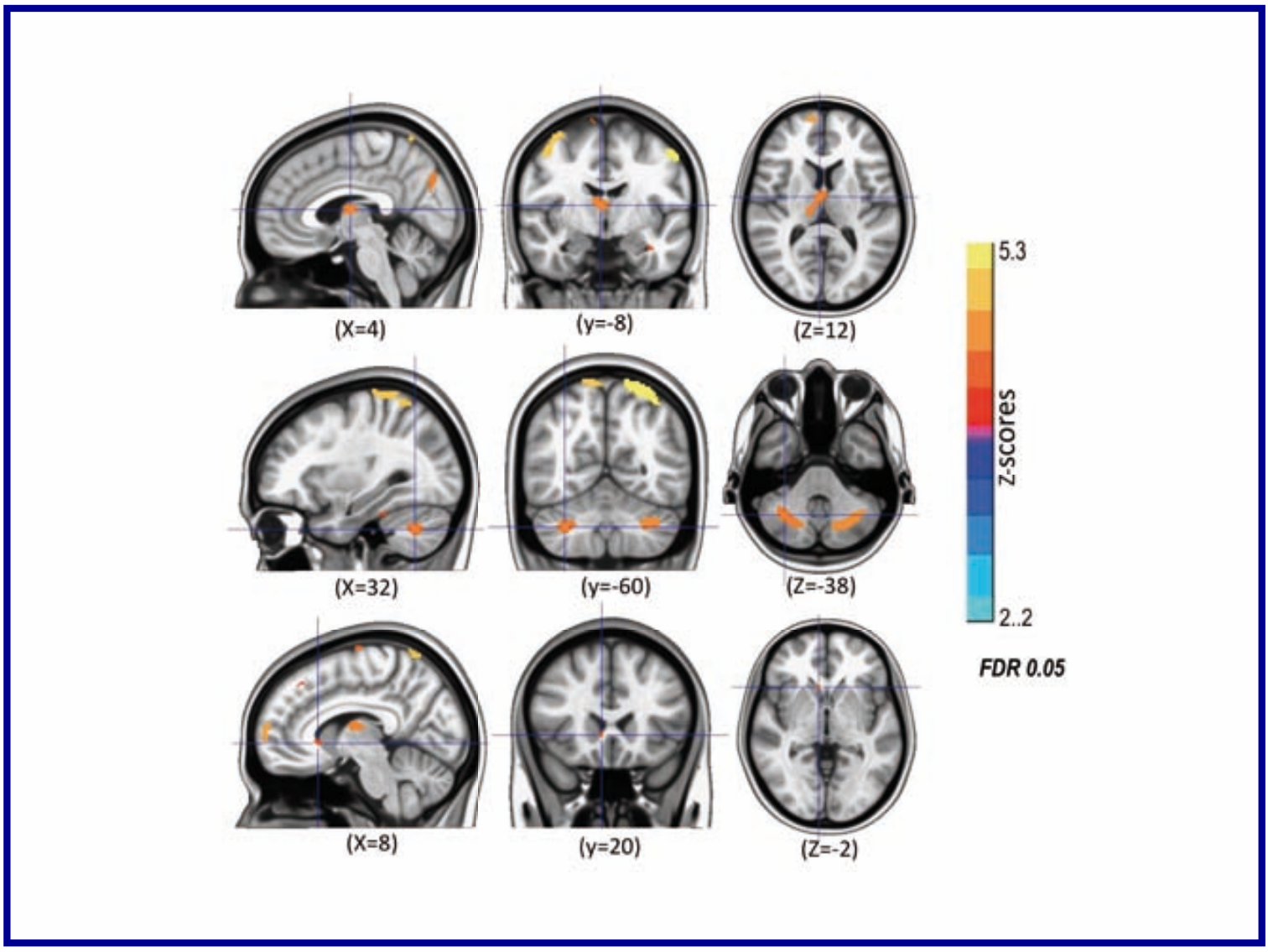

Voxel-based-morphometry
Cortical thickness
5.3
Z-scores
2..2
FDR 0.05
4
t-statistics
2.7
FDR 0.05

Figure 4.



Supplementary material

eMethods

Diagnostic Assessments

Subjects were administered semi-structured interviews by clinicians (Ph.D. clinical psychologists or advanced-level clinical psychology doctoral students) who completed a rigorous training program supervised by Salvatore Mannuzza, Ph.D., and who demonstrated high reliability on all major disorders of interest on the following instruments. Our diagnostic assessments combined standard instruments and a detailed examination of ADHD symptoms. Axis I DSM-IV disorders such as Mood, Anxiety, and Psychotic Disorders were assessed with the Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Non-Patient Edition (SCID-I/NP).[1] Because of the importance of characterizing substance use and abuse in detail, we incorporated relevant sections from the Psychiatric Research Interview for Substance and Mental Disorders Version 6.0 (PRISM).[2] We designed a novel component for this study which specifically assesses ADHD symptoms, the Assessment of Adult Attention-Deficit/Hyperactivity Disorder (AAA; Mannuzza, Klein, Castellanos, unpublished; see eInstrument, below).

All interviewers were blind to subject group (probands, controls), past history (i.e., data from previous follow-ups, and from childhood), and study hypotheses. Interviewers wrote comprehensive clinical narratives that were reviewed for diagnostic accuracy and completeness. Based on 75 interviews diagnosed independently by Dr. Mannuzza from audio recorded interviews and narratives, chance-corrected reliability kappas were as follows: ADHD: 0.95 (ranging from 0.88 to 1.00, depending on the DSM-IV subtype); Antisocial Personality Disorder: 0.84; Alcohol Substance Use Disorder: 0.96; non-alcohol Substance Use Disorder: 0.97; Mood Disorders: 0.79; Anxiety Disorders: 0.96; and any DSM-IV disorder: 0.92.

Neurological Disorders

At follow-up all participants were queried about intervening medical or neurological disorders, and none reported traumatic or other brain injury. At study enrollment, probands were evaluated neurologically and neurological disorders were explicit exclusions. Further, at FU41 (the most recent wave of data collection), Probands and Comparisons did not differ significantly in rates of neurological conditions in adulthood (convulsive disorders, repeated headaches, etc. – data not shown).

ADHD Not Otherwise Specified (ADHD-NOS)

Subjects diagnosed as having ADHD-NOS did not meet full DSM-IV criteria but they had to meet the impairment criterion and the exclusion criteria. For example, if a subject reported experiencing 4 of 9 clinically impairing, inattentive behaviors that were creating problems at home and at work, and that were not explained by another disorder, the diagnosis of ADHD-NOS was applied.

ADHD in Remission

To receive a diagnosis of ADHD-NOS, subjects had to fulfill the DSM-IV ADHD Impairment Criterion. If they did not (i.e., if their ADHD behaviors did not impair their functioning), then they were considered remitted. So, for example, a person reporting difficulty sustaining attention at work "occasionally," and that his wife "sometimes" remarked that he wasn't paying attention, but that these behaviors did not have negative functional impact (e.g., they did not represent a major problem at work, never substantially affected the subject's occupational performance, didn't result in repeated arguments with his wife), would be considered remitted if he also denied impairment related to all other ADHD behaviors (distractibility, disorganization, forgetting, etc.). In summary, remitters were defined by the absence of clinically significant impairment while ADHD-NOS was defined by the presence of clinically significant impairment without meeting full DSM-IV-TR criteria.

59 probands was r=-0.02, p=0.85. By contrast, the CTRS includes 4 items that correspond to DSM-IV CD behaviors: destructive, steals, lies, and truancy. The mean (SD) of these items for the 59 probands with MRI data was 0.60 (.56), i.e., between Not at all and Just a little. This supports that CD symptoms were extremely low in the probands recruited into the study. The Pearson correlation between CD ratings and mean cortical thickness in the 59 probands was r=0.10 p=0.42. Thus, we did not find evidence in support of either surrogate measures of ODD or CD as likely origins of our principal results.

References

1. First MB, Spitzer RL, Gibbon M, Williams JB. *Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Non-patient Edition (SCID-I/NP)*. New York: Biometrics Research, New York State Psychiatric Institute; 2002.

2. Hasin DS, Samet S, Meydan J, Miele GM, Endicott J. *Psychiatric Research Interview for Substance and Mental Disorders (PRISM), Version 6.0*; 2001.

eTable 1. Childhood treatment of the 59 ADHD male probands with anatomic MRI data at adult follow-up at mean age 41 (41FU)

Medication	Number of Subjects Treated with Medication N(%)	Cumulative Number of Days Treated with Indicated Medication [not necessarily consecutive days]				
		Mean	Median	SD	Mini-Mum	Maxi-mum
Methylphenidate	55 (93)	789.9	613	640.2	9	2486
Dextroamphetamine	10 (17)	300.7	176	353.6	22	1202
Pemoline	3 (5)	205.0	222	44.0	155	238
Any of Above*	55 (93)	855.7	735	660.1	9	2486
Imipramine	10 (17)	186.4	109.5	182.4	71	664
Thioridazine	34 (58)	242.1	149	203.5	3	682

*All the individuals who were treated with dextroamphetamine or pemoline were also treated with methylphenidate

eTable 2. Grey matter density and cortical thickness within clusters for subgroups of controls with ADHD-NOS and probands with ADHD-NOS at 41FU

Regions	Controls with ADHD-NOS (n=23)		Probands with ADHD-NOS (n=16)	
	mean	SD	mean	SD
Grey matter density clusters				
L Sup Parietal (BA7)	0.42	0.04	0.41	0.05
L Cerebellum	0.55	0.15	0.51	0.08
L Inf Cerebellum	0.41	0.17	0.34	0.13
L Middle Temporal gyrus (BA21)	0.37	0.09	0.38	0.08
L Temporo-occipital (BA37)	0.57	0.09	0.57	0.08
Brainstem extending to Cerebellum	0.32	0.14	0.27	0.08
L Temporal-parahippocampal (BA35)	0.74	0.07	0.72	0.06
L Frontal pole (BA10)	0.45	0.06	0.43	0.07
R Parietal Postcentral (BA3) extending to BA6	0.40	0.05	0.40	0.05
R Cerebellum	0.49	0.19	0.46	0.1
R Thalamus	0.72	0.11	0.71	0.1
R Occipital, Cuneus (BA18/19)	0.65	0.07	0.65	0.06
R Sup Frontal gyrus (BA10)	0.47	0.06	0.45	0.05
R Frontal lobe (BA6)	0.47	0.09	0.44	0.09
R Middle Frontal gyrus (BA10) extending to Orbitofrontal cortex (BA11)	0.49	0.07	0.47	0.06
R Temporal Fusiform (BA36)	0.64	0.07	0.64	0.07
R Caudate	0.52	0.11	0.48	0.11
R Middle Temporal (BA21) extending to (BA38)	0.55	0.07	0.54	0.08
R Middle Temporal (BA21) extending to (BA38)	0.51	0.07	0.49	0.08
Anterior Cingulate/limbic(BA24)	0.80	0.05	0.78	0.04
Cortical thickness clusters (mm)				
L Sup Parietal (BA7)	2.95	0.18	2.85	0.17
L Precentral G (BA6)	3.34	0.16	3.26	0.15
L Sup Temp G (BA38)	3.73	0.23	3.60	0.23
L Frontal Pole (BA10)	3.19	0.22	3.06	0.18
L Cuneus (BA19)	2.79	0.15	2.65	0.17
L Precuneus (BA31)	3.28	0.20	3.23	0.19
R Precuneus (BA7)	3.18	0.20	3.12	0.13
R Inf Parietal (BA40)	3.01	0.17	2.91	0.18
R Sup Temp G (BA38)	3.87	0.29	3.62	0.25
R Temporal G extending to Insula (BA13)	3.79	0.22	3.69	0.24
R Precentral G (BA6)	3.38	0.21	3.27	0.19
R Frontal Pole (BA10)	3.38	0.15	3.28	0.17
R Middle Frontal G (BA9)	3.41	0.25	3.19	0.18
R Occipital (BA19)	2.98	0.19	2.86	0.19
R Occipital (BA18)	2.75	0.15	2.69	0.21

BA: Brodmann area; L: Left; R: Right; Sup: Superior; Inf: Inferior

eTable3
Participants with vs. without Anatomic MRIs

STAGE 1 CONTRASTS-
ALL SUBJECTS WITH DATA AT Late Adolescent ASSESSMENT AT Mean Age 18 [18FU]

Classification of All Male Subjects		
Assessments	**Probands (n = 207) N**	**Controls (n = 178) N**
MRI Completed, 18FU Diagnostic Data Obtained	59	81
MRI Not Completed, 18FU Diagnostic Data Obtained	136	97
SUBTOTAL	**195**	**178****
MRI Completed, No 18FU Data Obtained	2	0
MRI Not Completed, No 18FU Data Obtained	10*	0

*7 of these Probands did not have any follow-up data (18FU, 25FU, or 41FU)

**All 178 Controls were recruited at 18FU

The following Stage 1 Contrasts were based on the 195 Male Probands and 178 Male Controls with 18FU data. Analyses in eTable3 include 2 Probands and 1 Control who were scanned at 41FU but whose data did not pass quality control criteria.

eTable3a
Ongoing (at 18FU) Diagnostic Status of Probands

Ongoing (at 18FU) DSM-III Late Adolescent Diagnoses	Definite Only			Probable or Definite		
	Probands w/MRIs (n=59) N (%)	Probands w/o MRIs (n=136) N (%)	p (2-tailed)	Probands w/MRIs (n=59) N (%)	Probands w/o MRIs (n=136) N (%)	p (2-tailed)
Antisocial Personality/ Conduct Disorder	15 (25)	36 (27)	.88	20 (34)	39 (29)	.47
Alcohol SUD*	7 (12)	3 (2)	.005	8 (14)	6 (4)	.02
Non-Alcohol SUD**	11 (19)	10 (7)	.02	13 (22)	12 (9)	.01
Any SUD**	15 (25)	11 (8)	.001	16 (27)	16 (12)	.01
Any Mood Disorder	0	0	- - -	1 (2)	2 (2)	.91
Any Anxiety Disorder	0	1 (1)	.51	0	1 (1)	.51
Any DSM-III Dis.***	22 (37)	40 (29)	.28	26 (44)	45 (33)	.14

*SUD = Substance Use Disorder
**Excluding Nicotine Dependence
***Excluding Attention Deficit Disorder (rates shown in eTable3c and eTable3d)

eTable3b
Ongoing (at 18FU) Diagnostic Status of Controls

Ongoing (at 18FU) DSM-III Late Adolescent Diagnoses	Definite Only			Probable or Definite		
	Controls w/MRIs (n=81) N (%)	Controls w/o MRIs (n=97) N (%)	p (2-tailed)	Controls w/MRIs (n=81) N (%)	Controls w/o MRIs (n=97) N (%)	p (2-tailed)
Antisocial Personality/ Conduct Disorder	5 (6)	7 (7)	.78	6 (7)	8 (8)	.84
Alcohol SUD*	3 (4)	5 (5)	.64	5 (6)	7 (7)	.78
Non-Alcohol SUD**	2 (3)	1 (1)	.46	3 (4)	1 (1)	.23
Any SUD**	4 (5)	6 (6)	.72	6 (7)	8 (8)	.84
Any Mood Disorder	0	2 (2)	.19	1 (1)	3 (3)	.41
Any Anxiety Disorder	3 (4)	0	.06	3 (4)	0	.06
Any DSM-III Dis.***	10 (12)	12 (12)	.99	16 (20)	15 (16)	.45

*SUD = Substance Use Disorder
**Excluding Nicotine Dependence
***Excluding Attention Deficit Disorder (rates shown in eTable3c and eTable3d)

eTable3c Ongoing (at 18FU) Attention Deficit Disorder in Probands			
Ongoing (at 18FU) DSM-III Late Adolescent ADD Symptoms and Diagnosis	**Probands with MRIs (n=59) N (%)**	**Probands without MRIs (n=136) N (%)**	**p (2-tailed)**
Definite Attention Deficit Disorder with/without Hyperactivity	21 (36)	50 (37)	.88
Clinically Significant			
Inattention	30 (51)	64 (47)	.63
Impulsivity	30 (51)	67 (49)	.84
Hyperactivity	24 (41)	47 (35)	.42

eTable3d Ongoing (at 18FU) Attention Deficit Disorder in Controls			
Ongoing (at 18FU) DSM-III Late Adolescent ADD Symptoms and Diagnosis	**Controls with MRIs (n=81) N (%)**	**Controls without MRIs (n=97) N (%)**	**p (2-tailed)**
Definite Attention Deficit Disorder with/without Hyperactivity	3 (4)	2 (2)	.51
Clinically Significant			
Inattention	7 (9)	10 (10)	.71
Impulsivity	7 (9)	11 (11)	.55
Hyperactivity	7 (9)	5 (5)	.36

eTable3e
Childhood Characteristics of Probands

Variable	Probands with MRIs (n=59) Mean (SD)	Probands without MRIs (n=136) Mean (SD)	p (2-tailed)
Age at Referral (months)	99.4 (20.4)	100.8 (19.4)	.63
SES at Referral*	3.3 (0.9)	3.2 (1.1)	.49
WISC Full Scale IQ	105.6 (12.4)	103.5 (11.8)	.26
Conners Hyperactivity Factor**	2.2 (0.5)	2.1 (0.4)	.39

*Hollingshead & Redlich, (1958) based on parent education and occupation (1-Upper class to 5-Lower class)
**Based on the Conners Teacher Rating Scale (0-Not at all to 3-Very much)

STAGE 2 CONTRASTS-
SUBJECTS KNOWN TO BE DECEASED
AT 41FU REMOVED

At follow-up at mean age 41 (41FU), 15 Probands and 5 Controls were known to be deceased. However, 1 of these Probands had not participated in any of the follow-ups (18FU, 25FU, or 41FU). Therefore, the following Stage 2 Contrasts were based on 181 Male Probands (i.e., 195 minus 14) and 173 Male Controls (i.e., 178 minus 5) who were not known to be deceased at 41FU, and who had 18FU data. Analyses include 2 Probands and 1 Control who were scanned at 41FU but whose data did not pass quality control criteria.

eTable3f
Ongoing (at 18FU) Diagnostic Status of Probands
Not Known to be Deceased at 41FU

Ongoing (at 18FU) DSM-III Late Adolescent Diagnoses	Definite Only			Probable or Definite		
	Probands w/MRIs (n=59) N (%)	Probands w/o MRIs (n=122) N (%)	p (2-tailed)	Probands w/MRIs (n=59) N (%)	Probands w/o MRIs (n=122) N (%)	p (2-tailed)
Antisocial Personality/ Conduct Disorder	15 (25)	32 (26)	.91	20 (34)	35 (29)	.48
Alcohol SUD*	7 (12)	2 (2)	.003	8 (14)	5 (4)	.02
Non-Alcohol SUD**	11 (19)	9 (7)	.02	13 (22)	11 (9)	.02
Any SUD**	15 (25)	10 (8)	.002	16 (27)	15 (12)	.01
Any Mood Disorder	0	0	- - -	1 (2)	2 (2)	.98
Any Anxiety Disorder	0	1 (1)	.49	0	1 (1)	.49
Any DSM-III Dis.***	22 (37)	36 (30)	.29	26 (44)	40 (33)	.14

*SUD = Substance Use Disorder
**Excluding Nicotine Dependence
***Excluding Attention Deficit Disorder (rates shown in eTable3h and eTable3i)

eTable3g
Ongoing (at 18FU) Diagnostic Status of Controls
Not Known to be Deceased at 41FU

Ongoing (at 18FU) DSM-III Late Adolescent Diagnoses	Definite Only			Probable or Definite		
	Controls w/MRIs (n=81) N (%)	Controls w/o MRIs (n=92) N (%)	p (2-tailed)	Controls w/MRIs (n=81) N (%)	Controls w/o MRIs (n=92) N (%)	p (2-tailed)
Antisocial Personality/ Conduct Disorder	5 (6)	5 (5)	.84	6 (7)	6 (7)	.82
Alcohol SUD*	3 (4)	4 (4)	.83	5 (6)	5 (5)	.84
Non-Alcohol SUD**	2 (3)	1 (1)	.49	3 (4)	1 (1)	.25
Any SUD**	4 (5)	5 (5)	.88	6 (7)	6 (7)	.82
Any Mood Disorder	0	1 (1)	.35	1 (1)	2 (2)	.64
Any Anxiety Disorder	3 (4)	0	.06	3 (4)	0	.06
Any DSM-III Dis.***	10 (12)	9 (10)	.59	16 (20)	12 (13)	.23

*SUD = Substance Use Disorder
**Excluding Nicotine Dependence
***Excluding Attention Deficit Disorder (rates shown in eTable3h and eTable3i)

eTable3h
Ongoing (at 18FU) Attention Deficit Disorder in Probands Not Known to be Deceased at 41FU

Ongoing (at 18FU) DSM-III Late Adolescent ADD Symptoms and Diagnosis	Probands with MRIs (n=59) N (%)	Probands without MRIs (n=122) N (%)	p (2-tailed)
Definite Attention Deficit Disorder with/without Hyperactivity	21 (36)	43 (35)	.96
Clinically Significant			
Inattention	30 (51)	57 (47)	.60
Impulsivity	30 (51)	60 (49)	.83
Hyperactivity	24 (41)	41 (34)	.35

eTable3i
Ongoing (at 18FU) Attention Deficit Disorder in Controls
Not Known to be Deceased at 41FU

Ongoing (at 18FU) DSM-III Late Adolescent ADD Symptoms and Diagnosis	**Controls with MRIs (n=81)** **N (%)**	**Controls without MRIs (n=92)** **N (%)**	**p (2-tailed)**
Definite Attention Deficit Disorder with/without Hyperactivity	3 (4)	2 (2)	.55
Clinically Significant			
Inattention	7 (9)	9 (10)	.80
Impulsivity	7 (9)	10 (11)	.62
Hyperactivity	7 (9)	5 (5)	.41

eTable3j
Childhood (Time 1) Characteristics of Probands
Not Known to be Deceased at 41FU

Variable	Probands with MRIs (n=59) Mean (SD)	Probands without MRIs (n=122) Mean (SD)	p (2-tailed)
Age at Referral (months)	99.4 (20.4)	101.1 (19.7)	.58
SES at Referral*	3.3 (0.9)	3.2 (1.1)	.41
WISC Full Scale IQ	105.6 (12.4)	103.0 (11.6)	.17
Conners Hyperactivity Factor**	2.2 (0.5)	2.1 (0.4)	.41

*Hollingshead & Redlich, (1958) based on parent education and occupation (1-Upper class to 5-Lower class)
**Based on the Conners Teacher Rating Scale (0-Not at all to 3-Very much)

eTable 4. Demographic characteristics of the 139 ADHD probands and non-ADHD male controls with analyzable anatomic MRI data at 41FU

Adult Variable	Probands without ADHD (remitters) (n = 26)	Probands with Persistent ADHD (n = 17)	Probands with ADHD NOS (n = 16)	Non-ADHD Controls (n = 57)	Controls with ADHD NOS (n = 23)	*F*	p (two-tailed)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)		
Age at Follow-Up (Years)	41.0 (2.5)	41.2 (2.7)	41.0 (3.0)	41.3 (3.0)	41.5 (3.5)	0.12	0.98
Socioeconomic Status* at 41FU	3.2 (1.1) [A]	3.7 (1.2) [B,C]	3.4 (1.0) [D]	2.4 (1.1) [A,B,D]	2.7 (.9) [C]	7.1	0
Educational Attainment**	13.9 (2.8) [E]	13.7 (2.1) [F]	12.7 (2.1) [G,H]	15.7 (2.2) [E,F,G]	15.4 (2.4) [H]	7.78	0
WASI* Full Scale IQ**	104.2 (11.8)	100.7 (13.4)	97.1 (14.7) [I]	111.9 (12.7) [I]	104.8 (18.6)	4.56	0.002
Global Assessment Scale Rating****	67.5 (14.9)	61.5 (8.9) [J]	58.8 (9.7) [K]	73.5 (10.5) [J,K,L]	65.9 (8.3) [L]	8.23	0

Hollingshead and Redlich (1958) scale, based on the participant's education and occupation. This 5-point scale ranges from 1-upper social class to 5-lower social class.

**Highest Grade Completed (12- high school, 16- 4 years of college, etc.)

***Wechsler Abbreviated Scale of Intelligence. WASIs were only obtained on 74 (92%) of the 80 Controls.

****The Global Assessment Scale was completed by the "blind" clinician that conducted the diagnostic assessment.

Pairwise comparisons using Tukey's HSD

[A] pairwise comparison significant ($p = .024$)
[B] pairwise comparison significant ($p < .001$)
[C] pairwise comparison significant ($p = .028$)
[D] pairwise comparison significant ($p = .006$)
[E] pairwise comparison significant ($p = .008$)
[F] pairwise comparison significant ($p = .014$)
[G] pairwise comparison significant ($p < .001$)
[H] pairwise comparison significant ($p = .006$)
[I] pairwise comparison significant ($p = .003$)
[J] pairwise comparison significant ($p = .001$)
[K] pairwise comparison significant ($p < .001$)
[L] pairwise comparison significant ($p = .042$)

eTable 5. Comorbidity of adult mental disorders among the 59 ADHD male probands and the 80 non-ADHD male comparisons with analyzable anatomic MRI data at 41FU

Ongoing DSM-IV Disorder (Past 6 Months)	Probands (n = 59) N (%)	Comparisons (n = 80) N (%)	χ2	p (2 tailed)
Attention Deficit Hyperactivity Disorder				
Full DSM-IV-TR Criteria*	17 (29)	0	26.26	.001
Not Otherwise Specified (NOS)	16 (27)	23 (29)	0.04	.83
Either of Above	33 (56)	23 (29)	10.43	.001
Antisocial Personality Disorder	9 (15)	0	13.05	.001
Substance Use Disorder				
Alcohol	2 (3)	14 (18)	6.64	.01
Non-Alcohol**	9 (15)	6 (8)	2.12	.15
Either of Above**	11 (19)	16 (20)	.04	.84
Mood Disorder	5 (8)	7 (9)	0.00	--
Anxiety Disorder	8 (14)	4 (5)	3.15	.12
ANY DSM-IV DISORDER***	26 (44)	27 (34)	1.53	.22

*Inattentive, Hyperactive-Impulsive, or Combined
**excluding Nicotine Dependence
***excluding ADHD and Nicotine Dependence

eTable 6. Significant (FDR 0.05) cortical thickness clusters without or with adjustment for IQ in inclusive analyses. See Figure 1 and eFigure1.

Without IQ as covariate			With IQ as covariate		
Region	MNI coordinates	vertices #	Region	MNI coordinates	vertices #
L Sup Parietal (BA7)	-26, -55, 68	4,290	L Sup Parietal (BA7)	-25, -55, 68	827
L Precentral G (BA6)	-35, 37, 36	784	L Precentral G (BA6)	-45, -13, 53	115
L Sup Temp G (BA38)	-54, 10, -22	915	L Sup Temp G (BA38)	-54, 10, 22	108
L Frontal Pole (BA10)	-31, 62, -6	638	L Frontal Pole (BA10)	-31, 62, -6	179
L Cuneus (BA19)	-13, -91, 35	618			
L Precuneus (BA31)	-6, -65, 30	62			
R Precuneus (BA7)	10, -73, 51	1148			
R Inf Parietal (BA40)	49, -40, 50	4836	R Inf Parietal (BA40) extending to BA6	49, -40, 50	2,693
R Sup Temp G (BA38)	30, 15, -40	1141	R Sup Temp G (BA38)	30, 15, -40	374
R Temporal G extending to Insula (BA13)	48, -1, -3	315			
R Precentral G (BA6)	58, 0, 36	315			
R Frontal Pole (BA10)	27, 47, 32	98			
R Middle Frontal G (BA9)	25, 47, -14	130			
R Occipital (BA19)	27, -87, 26	210			
R Occipital (BA18)	10, -80, 10	94			

L: Left; BA: Brodmann area; G: Gyrus; Sup: Superior; R: Right; Inf: Inferior

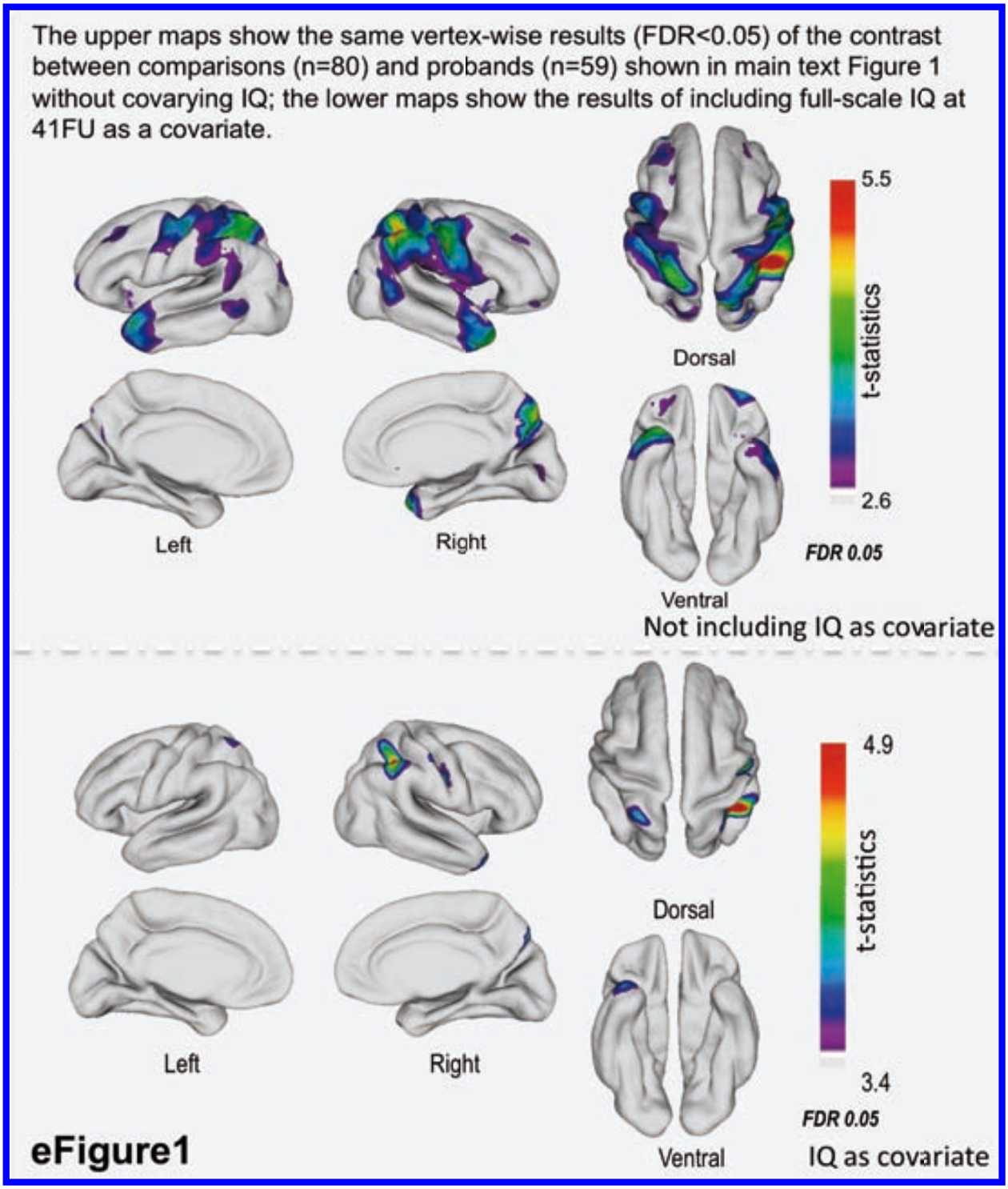
eTable7. Cortical thickness within clusters differentiating remitters vs. persistents in uncorrected vertex-wise analyses

Regions	MNI X, Y, Z (No. of vertices)	Non-ADHD Controls (n=57)		Probands w/ Persistent ADHD (n=17)		Remitted Probands (n=26)		Non-ADHD Controls vs. Persistents		Non-ADHD Controls vs. Remitters		Remitters vs. Persistents	
		mean	SD	mean	SD	mean	SD	p	ES	p	ES	p	ES
L Sup Temporal (BA38) extending to Insula (BA13) and Orbitofrontal (BA11)	-43,10, -19 (635)	3.94	0.37	3.64	0.30	3.96	0.33	**0.004**	**0.83**	0.787	-0.06	**0.003**	**1.00**
L Parahippocampus	-27, -5, -28 (246)	3.94	0.28	3.76	0.25	4.01	0.25	0.025	**0.63**	0.229	-0.29	**0.003**	**0.98**
L Anterior Cingulate	-6, 18, 40 (142)	3.70	0.19	3.67	0.18	3.75	0.23	0.588	0.15	0.240	-0.28	0.213	0.40
L Occipital (BA17/18)	-15, -69, 23 (1881)	3.04	0.14	2.89	0.11	3.04	0.12	**0.0001**	**1.12**	0.996	0.00	**0.0003**	**1.23**
R Temporo-insular (BA13)	37, 10, 9 (319)	4.03	0.22	3.81	0.27	3.98	0.28	**0.001**	**0.96**	0.360	0.22	0.055	**0.62**
R Frontal Pole (BA10)	22, 51, -15 (315)	3.35	0.20	3.18	0.18	3.32	0.17	**0.002**	**0.89**	0.497	0.16	0.013	**0.81**
R Temporal Pole (BA38), extending to Insula	47, 9, -12 (978)	3.91	0.23	3.64	0.29	3.86	0.20	**0.0002**	**1.10**	0.406	0.20	**0.004**	**0.94**
R Occipital (BA17/18/19)	25, -68, -11 (2111)	3.30	0.13	3.21	0.14	3.31	0.11	0.015	**0.69**	0.851	-0.04	0.015	**0.79**
R Precentral (BA6)	53, 2, 41 (130)	3.26	0.16	3.08	0.26	3.21	0.18	**0.001**	**0.97**	0.141	0.35	0.072	**0.58**
R Occipital/parietal (BA19)	32, -78, 30 (78)	2.98	0.20	2.94	0.28	2.97	0.22	0.448	0.21	0.782	0.07	0.672	0.13

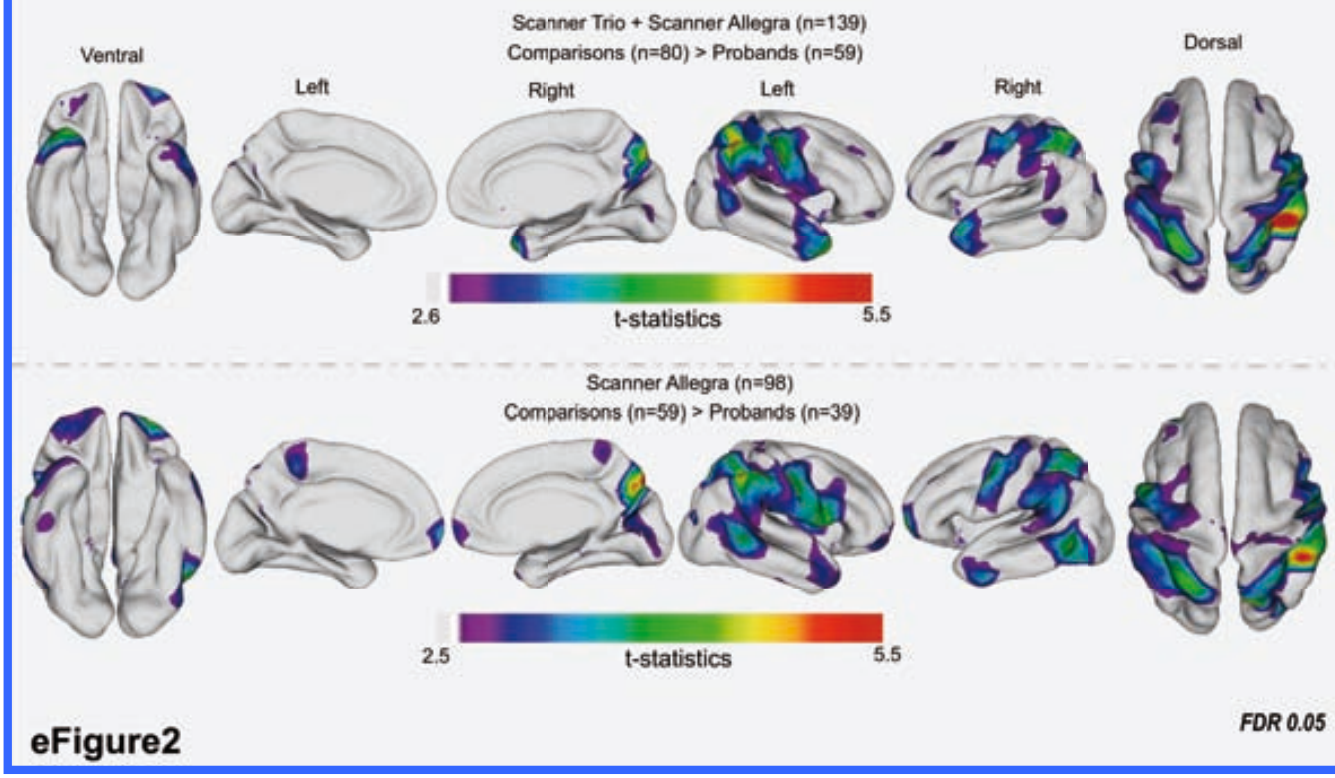
L: Left; BA: Brodmann area; Sup: Superior; R: Right

P-values surviving Bonferroni correction for multiple comparisons or ES>.50 are indicated in bold.

Supplementary figures



Upper row maps show results from combining data across two scanners. The lower maps show results obtained from the Allegra only. In both cases, FDR 0.05 has been applied.



eFigure2

FDR 0.05

STUDY 3

Revista de Neurología, 2011: Actividad funcional en estado de reposo: redes en conexión

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Actividad funcional cerebral en estado de reposo: redes en conexión

Erika Proal, Mar Álvarez-Segura, María de la Iglesia-Vayá, Luis Martí-Bonmatí, F. Xavier Castellanos, y el Spanish Resting State Network (SRSN)

Resumen. El análisis de la conectividad funcional mediante resonancia magnética funcional (RMf) puede llevarse a cabo durante la realización de una tarea, la percepción de un estímulo o en estado de reposo. En tales casos, el estudio de la señal de baja frecuencia en la actividad cerebral a través del contraste BOLD en estado de reposo ha revelado patrones de actividad cortical sincronizados, lo que ha permitido describir la arquitectura funcional intrínseca del cerebro humano. La comunidad científica internacional dispone de recursos compartidos que contribuirán mediante este análisis de RMf en estado de reposo a la obtención de diagnósticos y tratamientos más precisos y avanzados en el campo de las neurociencias. Recientemente, el Spanish Resting State Network (SRSN) se ha aunado a este proyecto colaborativo creando una estructura de habla española para la cooperación entre los distintos grupos de investigación en neurociencias (http://www.nitrc.org/projects/srsn).

Palabras clave. Actividad intrínseca cerebral. Conectividad funcional. Estado de reposo. Fluctuaciones de baja frecuencia. Fluctuaciones espontáneas. ICA. Redes en conexión. RM funcional.

Introducción

La posibilidad de medir la actividad funcional en el cerebro mediante la señal producida por los cambios dependientes del nivel de oxigenación sanguínea (contraste BOLD) ha convertido a la resonancia magnética funcional (RMf) en una herramienta útil en neurociencia cognitiva. Gracias a la RMf se han podido identificar asociaciones entre la activación y/o desactivación de áreas cerebrales frente a diferentes estímulos o respuestas durante la realización de tareas cognitivas específicas [1]. En los últimos años esta investigación sobre la actividad evocada ha sido muy productiva para destacar los elementos neuronales asociados con el funcionamiento cerebral (especificidad funcional).

Se sabe que la energía consumida por la actividad neuronal generada durante la realización de tareas es menor del 5% de toda la energía empleada por el cerebro [2]. Por ello, la mayor parte de nuestro conocimiento acerca del funcionamiento cerebral proviene del estudio de actividades que consumen poca cantidad de energía. Durante mucho tiempo, en el campo de la neuroimagen se consideró la actividad de fondo no relacionada con la ejecución de tareas cognitivas (actividad intrínseca o espontánea) como ruido aleatorio de muy baja frecuencia, por lo cual se excluía y se desaprovechaba. Se ha comprobado que estas activaciones no son aleatorias, sino que están bien estructuradas y organizadas [3,4]. Varios estudios han demostrado que estas fluctuaciones intrínsecas y espontáneas son importantes para conocer la conectividad funcional cerebral.

La actividad intrínseca cerebral está presente en todo cerebro y puede estudiarse en cualquiera condición. Resulta interesante evaluarla durante el estado de reposo, o sea, sin imponer ninguna tarea específica más allá del reposo y la quietud durante los minutos que tarda la adquisición. Como se discutirá posteriormente, la idea de estudiar la actividad espontánea a través de la señal BOLD en estado de reposo brinda importantes implicaciones clínicas, debido tanto a la facilidad de su implementación como a sus resultados fiables y reproducibles [5].

Curiosamente, el hecho de estudiar la conectividad funcional mediante señales de baja frecuencia y en estado de reposo no es exclusivo de la RMf, ya que ha sido también una de las principales vías de estudio de datos electroencefalográficos.

En este trabajo se ofrece una revisión general de la conectividad funcional mediante la RMf en estado de reposo –RMf-reposo; *resting state functional connectivity* (RSFC)–. Específicamente, como objetivo se comentarán los principales conceptos subyacentes a esta aproximación así como las técnicas de análisis más utilizadas. Además, se informará so-

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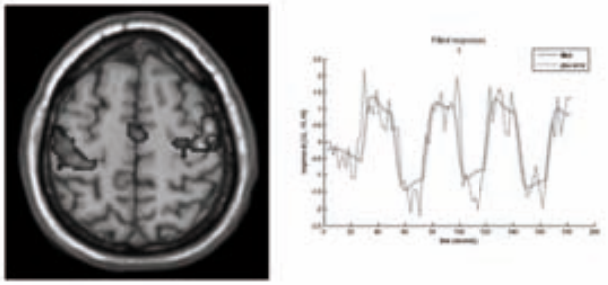
Figura. Circuito motor tal como se puede obtener en cualquier laboratorio por medio de la resonancia magnética funcional (RMf)-tarea motora inducida (ejemplo obtenido en el Servicio de Radiología del Hospital Quirón de Valencia, España, y gracias a la participación de G. García). Esta imagen muestra la similitud con el hallazgo original de [3], en donde se observan las correlaciones de un ROI (región de interés) en la corteza motora al realizar la RMf en estado de reposo.



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bre la consistencia de los resultados obtenidos y su interpretación. Por último, se destacará la importancia que tienen los novedosos proyectos colaborativos cuyo principal objetivo es compartir datos en repositorios comunes, de manera que contribuyen a acelerar el proceso de desarrollo de normas estadísticas y patrones de normalidad universales. Nos centraremos principalmente en el Spanish Resting State Network (SRSN), red creada en el último año y conformada por diferentes instituciones españolas para facilitar nuestra participación en esta iniciativa global en el ámbito de la neurociencia.

Conectividad funcional

La conectividad funcional se define como la dependencia temporal de la actividad neuronal entre regiones cerebrales anatómicamente separadas [6,7]. Esa dependencia temporal se relaciona con la conectividad estructural, o sea, con las conexiones fasciculares directas que pueden estudiarse mediante métodos de RM basados en difusión (tractografía por RM) [8,9]. Sin embargo, la conectividad funcional también puede existir entre regiones que no estén directamente enlazadas por haces axonales [9].

La comunicación funcional entre regiones es de suma importancia para llevar a cabo procesos cognitivos que integran información a través de diferentes regiones cerebrales (integración funcional) [10]. Estudiando la actividad intrínseca espontánea por el método de RMf-reposo, es posible delimitar redes o circuitos de conectividad funcional completos que, a su vez, resultan útiles para conocer más a fondo la organización del cerebro y así delinear los posibles correlatos neuronales relacionados con diferentes patologías.

Fluctuaciones espontáneas en la señal BOLD (RSFC)

La conectividad funcional puede analizarse bien mediante estudios de RMf inducidos por una tarea (RMf-tarea) o por estudios con RMf-reposo [11]. El mayor conocimiento del funcionamiento cerebral proviene de estudios realizados con RMf-tarea. Sin embargo, una de las preocupaciones más comunes dentro de los estudios de la RMf-tarea ha sido la eliminación del ruido inherente que existe en la señal BOLD. Los investigadores han reducido su contribución promediando los datos para incrementar la señal y disminuir el ruido. La actividad de base, considerada inicialmente como ruido, se atribuyó durante mucho tiempo a las señales fisiológicas, tanto cardíacas como respiratorias.

Fue en 1995 cuando Biswal et al observaron por primera vez que una fracción considerable de este ruido mostraba patrones organizados y coherentes entre sistemas cerebrales conocidos [3]. El trabajo de Biswal tenía como objetivo examinar los patrones de actividad neuronal del sistema motor, y para ello a los sujetos experimentales se les aplicó una tarea estándar de oposición de dedos para, a continuación, adquirir una RMf-reposo sin pedirles que hicieran algo o reaccionaran ante ningún estímulo motor. El análisis de los resultados mostró que durante la tarea de pulsación de dedos se activaron varias regiones implicadas en la respuesta motora: el área motora primaria y la suplementaria. Asimismo, al hacer el segundo análisis en estado de reposo se seleccionó un único vóxel o región de interés localizado en el área motora, y se analizó su patrón de correlación temporal con el resto de los vóxeles en el cerebro. Interesantemente, se observaron correlaciones entre las fluctuaciones del vóxel seleccionado y las fluctuaciones de las mismas regiones que se activaron durante la tarea de pulsación; es decir, tanto durante la realización de tarea como en estado de reposo se destacaron áreas y circuitos casi idénticos (Figura).

El hallazgo de esta observación ha atraído la curiosidad de muchos investigadores. A partir del reconocimiento de este fenómeno, y a través de innumerables estudios después de 15 años, se ha podido

validar la existencia de circuitos cerebrales bien definidos. Dada su potencial aplicación a poblaciones clínicas, la RMf-reposo está siendo cada vez más aceptada como herramienta válida para la investigación neurocientífica [12].

Adquisición de datos: RMf-reposo y principales técnicas de análisis

Adquisición

Durante la adquisición de 5 a 10 min (véanse los parámetros en la tabla) de RMf-reposo [13] se le pide al sujeto que permanezca sin moverse y con los ojos abiertos mirando un punto fijo en la pantalla o el equipo de RM. Con esta aproximación se pueden extraer las fluctuaciones espontáneas de la señal BOLD. Estas oscilaciones espontáneas estudiadas en la RMf-reposo se encuentran específicamente en el rango de 0,01-0,1 Hz [14]. Es importante mencionar que el momento de adquisición de RMf-reposo, bien antes o después de una RMf-tarea, influye en las señales registradas [15], por lo que es recomendable que la adquisición se realice al principio del estudio. También vale reconocer que la actividad intrínseca cerebral no es exclusiva de la RMf-reposo. De hecho, obteniendo datos de RMf-tarea inducida también se pueden extraer este tipo de oscilaciones de frecuencia baja, aplicando un método de regresión que detecte y descarte toda aquella señal que se encuentre relacionada con la ejecución de tarea (contrario a un análisis ordinario de datos de RMf-tarea).

Tabla. Propuesta de parámetros para la secuencia de RS-RMf. En este caso se trata de un escaner de 3 T de Siemens Tim Trio. La secuencia se debe ajustar a criterio de los técnicos que la programen y dependiendo de las especificaciones técnicas de la máquina.

Tamaño del vóxel	3 mm isotrópicos, con separación de 0,3 mm entre cortes
Tiempo de repetición	Entre 2 y 2,5 s
Duración	Al menos 6 min, 10 min óptimo; intentar obtener por lo menos 150 volúmenes incluyendo todo el cerebro y cerebelo
Número de canales de la antena (*head coil*)	32
Duración de secuencia para localización (*scout sequence*)	1 min
Duración de secuencia para corregir pérdidas de señal (*field map*)	2-3 min
Secuencia anatómica	MPRAGE (*magnetization prepared rapid acquisition gradient echo sequence*) con vóxeles isotrópicos de 1 mm
DTI (*diffusion tensor imaging*) opcional	30 direcciones y vóxeles isotrópicos de 2,5 mm

Principales técnicas de análisis

Las técnicas para analizar la actividad cerebral espontánea en estado de reposo han aumentado considerablemente en los últimos años [13,16]. A continuación revisaremos con amplitud las dos técnicas más utilizadas en la actualidad.

Hypothesis-driven o modelos dependientes de hipótesis

Este tipo de análisis (de vóxel semilla), que se conoce como análisis ROI por sus siglas en inglés (*region of interest*), es uno de los dos enfoques que más se utilizan para analizar datos de conectividad funcional en estado de reposo. El análisis por vóxel semilla es un método basado en hipótesis (*hypothesis-driven*), en el cual se selecciona una región de interés o semilla y se analiza cómo se conecta funcionalmente con otra ROI o con todos los vóxeles del resto del cerebro. Este análisis se lleva a cabo correlacionando las series temporales extraídas de la señal BOLD de la secuencia en estado de reposo a partir de una semilla seleccionada y comparándola con las series temporales de las demás áreas cerebrales, y de esta manera se obtiene un mapa de conectividad funcional que delinea todas aquellas áreas que tienen una alta correlación con la ROI seleccionada [17,18]. La semilla puede seleccionarse bien *a priori*, dependiendo del objetivo del investigador, o bien tomando como base resultados de estudios tradicionales de RMf por tarea inducida o estudios por metaanálisis [19].

Pongamos como ejemplo que un investigador esté interesado en medir y cuantificar el grado de correlación entre distintas áreas del circuito motor. La circunvolución precentral podría ser una buena candidata como semilla, ya que esta región ha mostrado activaciones en diversos estudios cuando se ejecutan tareas motoras sencillas en las que se le pide al voluntario mover su mano. Una vez que se selecciona esta semilla y después de realizar el análisis de RSFC, los resultados mostrarán aquellas regiones cerebrales que están correlacionando con esta semilla, por lo que estas áreas se deberán considerar funcionalmente conectadas. La sencillez de este método hace que el análisis por vóxel semilla tenga una gran ventaja, aunque debe reconocerse que se limita a proporcionar resultados vinculados a conexiones cerebrales ligadas a regiones especifi-

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cas y predeterminadas. La mayor limitación de esta técnica es que los resultados dependen de la selección inicial de las semillas y, por lo tanto, hay que escogerlas con mucho cuidado para evitar sesgos de selección.

Data-driven o modelos dirigidos por los datos, también denominados independientes del modelo

Para evitar definir *a priori* una región específica y así poder examinar los patrones de conectividad funcional a través de todas las regiones cerebrales, se han diseñado los métodos de análisis independientes del modelo, es decir, sin hipótesis previa. Recientemente, el análisis de componentes independientes (ICA) ha demostrado ser una técnica idónea para identificar elementos que describen la actividad en una red ampliamente dispersa [10]. Los métodos basados en el ICA son especialmente útiles cuando no se conocen las regiones que están implicadas en una tarea determinada o no se conoce la conectividad funcional [20-22].

La técnica de ICA se basa en la descomposición de los datos de la RMf en componentes independientes, y se trata de una extensión de los métodos clásicos de separación ciega de fuentes (*blind source separation*). Esta técnica separa o descompone las series temporales de las fluctuaciones detectadas para así identificar el máximo número de componentes independientes que definen redes funcionales (o circuitos funcionales). Además, esta técnica permite detectar otro tipo de señales, como, por ejemplo, señales fisiológicas o ruidos relacionados con movimientos de acomodación de la cabeza. Específicamente, el ICA toma en consideración todos los vóxeles cerebrales utilizando un algoritmo matemático que los separa entre diferentes sistemas (circuitos o componentes) que correlacionan entre sí y que a su vez son independientes [23,24]. Aunque este análisis tiene muchas ventajas y su aplicabilidad ha abierto las puertas a nuevas posibilidades en el diseño de estudios y análisis, los mapas generados con este método son normalmente más complejos de interpretar en comparación con los generados con el análisis por vóxel semilla [2] y, por consiguiente, su aplicabilidad presenta algunas restricciones y limitaciones [25]. La metodología de esta técnica ha sido analizada por diferentes autores y existen diferentes variaciones del método [26]. Específicamente, el ICA ha servido para poder explicar de una manera mejor la estructura funcional cerebral a gran escala, se han detectado y replicado muchos circuitos consistentemente gracias a esta técnica [20,27,28] y también se está utilizando en el análisis de los estudios de poblaciones clínicas con demencia de tipo Alzheimer o estados preclínicos de la enfermedad [26,27], depresión [29], esquizofrenia [30,31] enfermedad de Huntington [32], esclerosis múltiple [33] o epilepsia del lóbulo temporal [34].

Circuitos funcionales identificados en estado de reposo

Aunque un individuo se encuentre en estado de reposo, no se puede descartar que esté realizando algún tipo de actividad mental que no es posible controlar ni conocer, como, por ejemplo, imaginar o evocar algún recuerdo. Este tipo de actividad se plasma en cambios de la actividad neuronal [2]. Sin embargo, a pesar de las particularidades propias de la actividad mental en cada individuo, la actividad intrínseca cerebral persiste con rasgos inter e intraindividuales a lo largo del tiempo notoriamente estables. Esto se ha demostrado con hallazgos consistentes de RMf-reposo durante el sueño [34], anestesia [35,36] y el estado de coma [37].

A través de estudios comparativos de actividad durante RMf-tarea y con RMf-reposo, se han observado un conjunto de regiones cerebrales que se activaba consistentemente en reposo dentro del escáner y que se desactivaba ante la demanda de tareas o la presencia de un estímulo [27,35-37]. A este primer conjunto de regiones o circuito observado en estado de reposo se le dio el nombre de circuito de activación por defecto o CAD –en inglés, *default mode network* (DMN)– [38]. La distinción entre el fenómeno de actividad espontánea intrínseca observada mediante RSFC y CAD es clara. La actividad intrínseca cerebral que forma la base de la RSFC existe en todo el cerebro, mientras que el CAD es uno más de los circuitos funcionales que pueden identificarse mediante el examen de la actividad intrínseca cerebral [2].

El CAD está compuesto por una serie de regiones cerebrales interconectadas, que muestran un patrón de desactivación durante la ejecución de tareas cognitivas de cualquier tipo, pero que están muy activas en estado de reposo. Este circuito se ha relacionado con la propia monitorización de estados internos y de la memoria autobiográfica [39]. Las regiones que conforman esta red son la corteza frontal ventromedial y dorsomedial, el cíngulo anterior (incluyendo partes sub, pre y supragenuales), el cíngulo posterior, el precúneo, la corteza parietal lateral y el hipocampo [35]. Después de conocerse el CAD [38] se encontró otro circuito anticorrelacionado con éste, que suele estar activado durante la realización

de tareas cognitivas. Este circuito frontoparietal se denomina *task-positive network*. Este circuito asociado a tareas está fuertemente relacionado con el CAD, pero de forma inversa: cuando la señal BOLD está incrementada en un circuito, ésta se encuentra disminuida en el otro. Este circuito está principalmente conformado por regiones cerebrales dorsales encargadas del procesamiento de la atención (circunvolución intraparietal, campo de visión frontal) [40] junto con regiones ventrales y dorsales, la ínsula y la corteza motora suplementaria observadas comúnmente durante la demanda de tareas cognitivas [36]. Debido a que el CAD fue la primera red intrínseca en describirse, se ha estudiado en profundidad y se ha relacionado con ciertas patologías clínicas. No obstante, es importante destacar que no es el único sistema funcional que exhibe fluctuaciones espontáneas coherentes en estado de reposo. Hoy en día se ha observado que muchos de los sistemas corticales documentados están activos en reposo. Estudios iniciales han descrito alrededor de ocho circuitos consistentes, entre ellos el sistema somatomotor [3], el circuito dorsal y ventral de la atención [41], el circuito visual y el circuito auditivo [27,42]. Incluso se ha podido demostrar que este patrón de actividad entre circuitos es consistente a través de diferentes sujetos [27]; sin embargo, no existe un acuerdo en cuanto al número apropiado de circuitos o componentes obtenidos mediante el ICA. En algunas publicaciones se han encontrado hasta 42 [28] y otros incluso indican muchos más [13,43].

Ventajas de la RMf-reposo

Aunque los estudios de RMf-reposo se complementan con los de RMf-tarea inducida, estudiar la conectividad funcional en estado de reposo tiene ventajas propias. Algunas de ellas se enumeran a continuación:

- Se puede obtener rápidamente un estudio funcional adecuado sin requerir la aplicación de paradigmas de estimulación. Esta ventaja hace que la RMf sea aplicable a muchas poblaciones clínicas que antes habían quedado excluidas, como niños, pacientes con deterioros cognitivos, parálisis, problemas auditivos y afasias [44]. Incluso se ha corroborado que las fluctuaciones espontáneas persisten bajo condiciones de sueño o diferentes tipos de anestesia, lo cual facilita el estudio de pacientes con agitaciones o bajo sedación.
- Se pueden delinear circuitos cerebrales completos *in vivo* [2], de manera que una misma adquisición puede utilizarse para estudiar distintos sistemas cerebrales, al contrario de la RMf-tarea, la cual requiere de adquisiciones específicas para poder estudiar cada una de las funciones que se pretende analizar. Recientemente se ha demostrado que la identificación de estos circuitos puede ser beneficiosa para fines prequirúrgicos, ya que pueden identificarse los circuitos asociados con el daño que presenta el paciente y esto a su vez puede servir como guía para la cirugía y favorecer los resultados de ésta [44].
- Se pueden trazar diferencias en cuanto a cada individuo, ya que se ha demostrado que no sólo se pueden analizar diferencias grupales en grandes poblaciones de sujetos, sino también adquirir valores individuales [19,45].
- Estudios recientes han demostrado que esta técnica es compatible con la evaluación de estudios longitudinales (a corto y a largo plazo), además de que permite la reproductibilidad entre sujetos [46,47] y a través de diversos laboratorios [48].
- Puede servir como biomarcador de cambios funcionales en todas las etapas del desarrollo de la vida de un sujeto [49]. La RMf-reposo ha permitido apreciar que los patrones de conectividad locales que se observan comúnmente en niños se distribuyen con el tiempo y van siendo reemplazados por conexiones más focales cercanas y por la emergencia de conexiones distantes [50]. También se ha descubierto que la conectividad funcional entre regiones corticales y subcorticales disminuye progresivamente con la edad [39].
- Esta técnica se puede utilizar para identificar diferencias en los circuitos funcionales entre grupos de pacientes con trastornos neuropsiquiátricos comparados con sujetos control. Esta última ventaja ha resultado muy relevante y ha despertado un gran interés. Muchas de las enfermedades del sistema nervioso central se conceptualizan en la actualidad como trastornos complejos de la conectividad neural [21], y uno de los objetivos principales de la RMf-reposo es estudiar la conectividad funcional cerebral *in vivo* de una manera más completa y comprensiva de la que se puede alcanzar mediante la RMf-tarea.

En el siguiente punto abordaremos una de las aplicaciones más relevantes en poblaciones clínicas que se ha conseguido con la RMf-reposo.

Demencia y RMf-reposo

El síndrome de desconexión más paradigmático es la enfermedad de Alzheimer, ya que los estudios

neuroanatómicos han demostrado una disrupción de las asas aferentes y eferentes entre el hipocampo y otras áreas cerebrales [51]. El área más estudiada ha sido el hipocampo, ya que es una de las primeras zonas afectadas por la enfermedad y empeora sustancialmente con la progresión de la enfermedad. Además, a través de estudios previos con RM de alta resolución espacial se ha demostrado atrofia de éste, lo que podría ofrecer un importante valor diagnóstico [52]. Por esta razón los estudios de conectividad funcional se han centrado fundamentalmente en el CAD, en el que se ha encontrado una reducción de la conectividad [53]. Las áreas anormales del CAD en las que aparece más disrupción han sido el córtex cingular posterior y el hipocampo [35,54].

No obstante, lo más llamativo es que no sólo en pacientes con enfermedad de Alzheimer, sino incluso en pacientes con déficit cognitivo leve, se ha hallado una reducción de la conectividad al compararlos con controles [53]. Estos hallazgos abren la posibilidad del uso de los coeficientes de oscilaciones espontáneas en estado de reposo de frecuencias bajas en el hipocampo como biomarcador precoz de la enfermedad [53].

Proyectos colaborativos: redes en conexión

El estudio de un fenómeno tan importante como la conectividad funcional cerebral por medio de la RMf-reposo está revolucionando la neurociencia clínica y la neuropsiquiatría. Los nuevos pasos tratan de conocer con mayor detalle la compleja dinámica del cerebro humano. Durante los últimos años se han empezado a lanzar iniciativas globales a través de espacios públicos comunes de datos, conformados por diversos centros de investigación e instituciones de salud a nivel mundial. Compartir datos y facilitar su accesibilidad por medio de estos repositorios ha permitido empezar a marcar propiedades estadísticas específicas en un amplio rango de medidas del funcionamiento cerebral.

El primer proyecto de compartición de datos de RMf-reposo, 1000 Functional Connectomes Project (http://www.nitrc.org/projects/fcon_1000/), se lanzó con el objetivo principal de poner a disposición pública un conjunto de datos procedentes de 35 laboratorios diferentes repartidos por todo el mundo [48]. Estudios realizados con esta base de datos han revelado hallazgos muy interesantes en el índice de conectividad funcional cerebral (ICFC), al marcar diferencias en los patrones de conectividad cerebral intrínseca entre hombres y mujeres que no son fácilmente perceptibles en otros estudios con muestras más pequeñas [48]. También se han podido observar cambios en el ICFC a través de las diferentes etapas del desarrollo [39,49].

A pesar de que los hallazgos de este primer proyecto colaborativo han sido de gran importancia, los datos del 1000 Functional Connectomes Project cuentan con información fenotípica restringida (solamente edad y sexo), por lo que se planteó la necesidad de integrar un nuevo proyecto llamado INDI: International Neuroimaging Data-sharing Initiative (http://fcon_1000.projects.nitrc.org/), que se distingue del proyecto anterior en tres aspectos principales:

- Los miembros integrantes comparten datos regularmente (semanal, mensualmente).
- Los datos cuentan con variables fenotípicas más completas (cociente intelectual, datos demográficos específicos, baterías neuropsicológicas).
- Se cuenta no sólo con sujetos control, sino también con muestras de poblaciones clínicas (como el trastorno por déficit de atención/hiperactividad).

Aunándose a estas iniciativas, y a colación del congreso internacional de la Organization for Human Brain Mapping (HBM 2010, Barcelona), se convocó a todos los grupos de investigación de los cuales se tenía conocimiento que trabajaban con datos obtenidos con RMf-reposo, para configurar lo que hoy es el núcleo del SRSN, una estructura de habla española de cooperación entre distintos grupos de investigación en neurociencias (http://www.nitrc.org/projects/srsn).

Es importante destacar que estas iniciativas no están separadas, sino más bien unidas por un mismo objetivo, trabajan en un proceso de colaboración y conexión constante, haciendo que la red internacional de apoyo crezca cada vez más y, por consiguiente, se puedan ir formulando propuestas de nuevas iniciativas.

Unir esfuerzos para promover una cultura científica colaborativa servirá para entender mejor el funcionamiento cerebral mediante la obtención de patrones de normalidad en la conectividad funcional. Recientemente el National Institute of Mental Health de Estados Unidos ha destacado los esfuerzos para describir el 'Connectome humano' en el segundo lugar dentro de los 10 avances más importantes durante el 2010 que están contribuyendo a un cambio en la forma de abordar los trastornos mentales (http://www.nimh.nih.gov/about/director/index-nimh.shtml). De esta manera también nos podremos acercar a un mejor entendimiento de las enfermedades neurológicas y psiquiátricas, con lo

que contribuiremos de una forma más rápida a elaborar diagnósticos más completos y precisos al estratificar la gravedad de la enfermedad y sus fenotipos y a mejorar la eficacia de los tratamientos. Sin embargo, lo más destacable de los proyectos colaborativos, en los que se pretende compartir tanto información como conocimiento, es que los resultados de las investigaciones repercutan de alguna forma (biomarcadores específicos de conectividad funcional) en el usuario final: los pacientes.

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Functional cerebral activity in a state of rest: connectivity networks

Summary. Functional connectivity can be measured during task-based functional magnetic resonance imaging (fMRI), or in the absence of specific stimuli or tasks. In either case, the study of low frequency fluctuations in the BOLD signal reveals patterns of synchronization which delineate the intrinsic functional architecture of the brain. The scientific community now has available shared resources to accelerate the exploitation of resting state fMRI with the objectives of improving diagnostic methods and leading to better treatments grounded in neuroscience. Fomenting a collaborative scientific culture will accelerate our understanding of the underlying phenonmemna. Recently, the Spanish Resting State Network (SRSN) has joined this collaborative effort by creating a setting to facilitate collaboration among the various neuroscience research groups working in Spanish (http://www.nitrc.org/projects/srsn).

Key words. Connectivity networks. Functional connectivity. Functional MRI. ICA. Intrinsic cerebral activity. Low frequency fluctuations. Spontaneous fluctuations. State of rest.

DISCUSSION

DISCUSSION

The main goal of the present thesis was to examine the neural substrates of the pathophysiology of ADHD and their relation with relevant behaviors by applying a range of different neuroimaging techniques. The new perspective of researchers in the ADHD field is that the physiopathology of the disorder may be underpinned by abnormal connections among several regions (circuits) rather than discrete regional abnormalities. This is the perspective that forms the basis for the two different empirical studies I conducted in individuals with ADHD applying three different anatomical MRI techniques. Also included is a synthetic published review that highlights the importance of a novel neuroimaging approach that is expected to further advance this field.

The two different empirical studies (Paper 1 and Paper 2) were performed to analyze brain anatomy of individuals with ADHD. The first compared children/adolescents with ADHD to controls. The second was focused on adults with a childhood diagnosis of ADHD versus controls. Additionally, this study of adults also distinguished subgroups based on adult diagnostic status: those who no longer met criteria for ADHD (remitters) and those who continued to meet DSM-IV criteria as adults (persistents). Below I explain the main contributions of each of the four papers presented in this dissertation.

The first experimental project (Paper 1) was the first study to analyze the volume of the ventral striatum using the fully manual traditional approach of hand-tracing. Although the technique of hand-tracing ROI is time consuming and requires great care to maintain reliability, it is considered the gold-standard method, as it is more precise than semi-automated or fully automated methods. We found that ventral striatum volumes were diminished by approximately 26% in children with ADHD compared to controls (an effect size exceeding 0.8SD). This is the largest effect reported in the ADHD literature for an anatomic volumetric difference. Further, obtaining volumes of the ventral striatum allowed us to relate those ventral striatum volumes to hyperactivity/impulsivity symptoms; we found a significant negative correlation between symptoms and ventral striatal volume.

The second empirical project (Paper 2, in press) has many unique features. First, it is the only study that combines two different anatomic approaches (VBM and cortical thickness) (104) in adults with ADHD. Second, this sample has been clinically followed up for 33 years, on average. One of the advantages of such a prospective design is that we did not have to rely on retrospective diagnostic recall regarding childhood ADHD symptoms and diagnoses. Finally, by studying individuals at an average age of 41, we were able to examine brain abnormalities related with diagnoses in adulthood, particularly in contrasting ADHD remission and persistence. Finally, this is the largest study in the literature on adults with ADHD and controls.

The third component of this dissertation (Paper 3) is a review of the most novel approach to functional imaging - resting state fMRI. The purpose of the review was to inform clinical investigators about the extraordinary value of this research tool as a way of investigating the pathophysiology of neuropsychiatric conditions broadly, including diagnoses such as ADHD. The paper announces the formation of open communities of scientists, including the Spanish Resting State Network and the International Neuroimaging Data-sharing Initiative (INDI), that have been formed to facilitate dissemination of information about resting state fMRI and the phenomenon of open data sharing that is becoming the norm in the resting-state fMRI community. In particular, INDI released sets of anatomic and resting state fMRI data from 285 children (ages 7-21) with ADHD and 491 healthy controls. See http://fcon_1000.projects.nitrc.org/indi/adhd200/ .This data release is the basis of an international competition to diagnose ADHD on the basis of brain imaging data that is expected to reveal new information regarding the pathophysiology of this disorder.

The general findings of the present dissertation are two-fold. First, in a large sample of children and adolescents with ADHD, we found a striking volumetric reduction in the ventral striatum, a region critically involved in reward processes that is a key relay in cortical-striatal-thalamo-cortical circuits. Second, in adults diagnosed with ADHD in childhood, we found reduced cortical thickness and VBM gray matter volume in parietal and motor regions. Most of these differences were independent of current adult diagnoses status. In other words, these differences were largely found in both individuals with persistent ADHD and in those who were in remission. By contrast, reward-related regions were diminished in probands with persistent ADHD compared to controls. Thus differences in reward-related circuitry (ventral striatum in children, orbitofrontal cortex, parahippocampus, thalamus, and frontal pole in adults) were

associated with current diagnosis of ADHD, whereas frontal-parietal motor cortex differences in adults with ADHD seem to reflect the trait of having had ADHD in childhood.

It is worth noting that although the two empirical studies were designed and executed in completely different manners, the results are internally consistent in highlighting two particular networks/circuits in ADHD. We focus on these two circuits in turn below. They are the dorsal attentional network, on one hand, and the limbic reward-related circuit described by Haber, on the other.

In the following paragraphs I discuss these main empirical findings in relation to the basic neuroscience models that have been described along with their possible implications for understanding the physiopathology underpinning the different ADHD relevant-behaviors.

The Dorsal Attentional Network

In Paper 2, our results highlighted abnormalities in regions related to the **dorsal attentional network** (Fig. 5A & 5B) (56). This network mediates goal-directed, top-down executive control processes and interacts during visual attentional functioning, particularly in reorienting attention, with a right-sided ventral system which is stimulus-driven (see Fig. 4A in red). The intraparietal sulcus (BA40) and the frontal eye fields (BA6) are the main regions involved in attention shifting and controlling spatial attention (56).

We found volumetric reductions in parietal and precentral regions, i.e., in the dorsal attentional network, in the adult sample diagnosed with ADHD in childhood relative to the comparison group. Similarly, in cortical thickness analyses we detected widespread cortical thinning in parieto-occipital and motor regions (Fig. 5B). These differences remained comparable when we subdivided our ADHD sample into persistent and remitter subgroups. This suggests that abnormalities in these parieto-occipital and motor regions are ascribable to the trait of having ADHD in childhood rather than current adult diagnosis status. Other cortical thickness studies have also revealed reductions in parieto-temporo-occipital cortex (93, 94, 105).

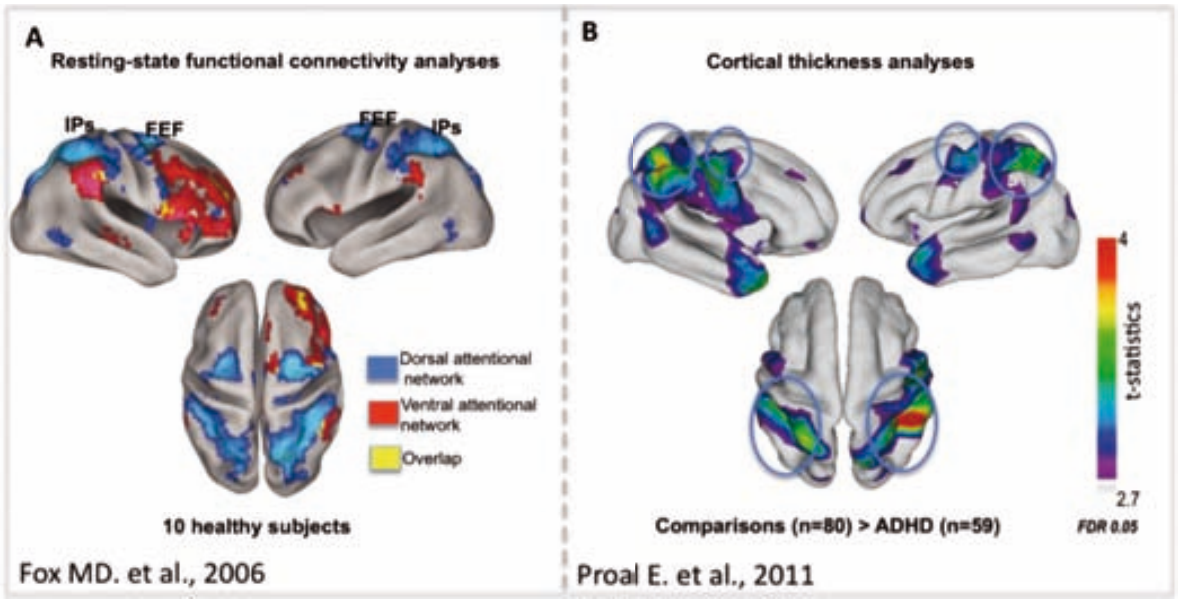

Fig. 5

ADHD imaging studies have also found abnormalities in parietal, occipital and precentral regions associated with ADHD using traditional functional imaging. For example, Dickstein et al., applying a meta-analytic method, gathered results from 16 different functional imaging studies that compared ADHD subjects with controls during the performance of executive and response inhibition tasks. Bilateral parietal regions (BA7, BA40), medial occipital cortex (BA19) and motor regions (BA 6) were some of the main areas in which controls demonstrated significantly greater probability of activation relative to ADHD subjects. More recent studies have shown greater activation of the parietal cortex of ADHD patients during a response inhibition task (106, 107). In addition, abnormal patterns of parietal activity have been reported during working memory (108-110) and attentional tasks (111-113).

Another affected region in our sample was the precuneus (BA7), which also has been observed as interacting with the intraparietal sulcus and the frontal eye fields in shifting attention in response to instructions from symbolic cues (114). The precuneus and the intraparietal sulcus are functionally and anatomically segregated, which suggests that they have complementary roles in shifting and maintaining attention (115). The process of shifting attention to unattended stimuli (stimuli-driven orientation) is often measured by response to unexpected stimuli tasks which was thought to be exclusively related to the ventral attentional system. Previous work has tended to confuse two different processes: expectation and reorientation (58). The stimuli-driven reorienting function is usually studied by applying the

"oddball task" (116) in which subjects have to perceive an unusual stimulus (the "oddball") in a series of familiar stimuli. This task is associated with activation of the right temporal-parietal junction (TPJ) and the ventral frontal cortex, key regions of the ventral attentional network (56). Oddball tasks have been used to analyze attentional processing in ADHD, as individuals with ADHD commit more commission errors and have slower or more variable reaction times compared with controls (117, 118). Such difficulties during performance of oddball tasks in ADHD are associated with aberrations in attention system areas beyond the ventral attentional regions. Other involved areas include superior and inferior parietal (119, 120), precuneus, thalamus (119), superior temporal cortex (121), cingulate and basal ganglia (120, 121). In our sample of adults, which did not include task-based approaches, voxel based morphometry analyses corroborated differences in subcortical regions such as thalamus and caudate in adults with childhood ADHD compared to controls. Specifically, abnormalities in the thalamus were more extensive in individuals with persistent ADHD in adulthood.

The differentiation between the dorsal and ventral attentional networks is a relatively recent development (57). One of the most perceptive studies examined whether the ventral network is the only one underpinning the two subprocesses of "attention shifting" (i.e., expectation and reorientation) or whether each of those is underpinned by different neural circuits. This ingenious study was performed in healthy subjects using fMRI during both a specific task and rest (122). Shulman et al. manipulated the probability of salient visual cues and examined fMRI during two different epochs: 1) while visual cues shifted attention away from the stimulus, and 2) while subjects maintained their attention on a stream of visual stimuli. They also analyzed resting state functional connectivity to determine whether regions that showed specific task modulations formed consistent networks. Results revealed three different networks: the ventral attentional (TPJ and ventral prefrontal cortex), the basal ganglia/fronto-insular network and the dorsal attentional network. The first two networks were related to shifting attention, the first when the cue was expected, and the second when it was unexpected. Moreover, resting state results showed that these two circuits are not connected, i.e., that they act separately. The dorsal attentional network was activated for unexpected and expected shifts and also in the presence of spatially selective modulations, indicating its role in shifting spatial attention. "Shift regions" may enable spatially selective sustained regions (i.e., the intraparietal sulcus) to suppress visual areas (i.e., occipital cortex) that would otherwise respond to irrelevant

signals during task performance (123). Occipital cortex has been recently found to interact with the dorsal network in maintaining attention (122) and in suppressing responses to irrelevant stimuli (124, 125).

This inclusion of the occipital cortex in models of regions modulation attention is interesting because we found occipital cortical thinning in probands with persistent ADHD versus non-ADHD comparisons. Previously, the occipital cortex was not considered to be relevant to ADHD, even though many neuroimaging studies in ADHD have found differences in this area (specifically middle occipital BA18, BA19). However, such results have typically been reported in tables or figures but not discussed (97, 126-128). A recent exception is a VBM study in adults with ADHD which found reductions only in bilateral early visual cortex volume (129).

In summary our results suggest that the dorsal attentional network is implicated in the physiopathology of ADHD, regardless of adult diagnosis status. Although investigators refer to the core regions of the dorsal attentional network as if they were homogeneous elements (e.g., intraparietal sulcus or frontal eye fields), each contains multiple functional subcomponents (130-132) and we found that ADHD individuals had decreases in both such functional subcomponents. These findings suggest that dysfunction in dorsal attentional regions underpin the trait of childhood ADHD, representing the substrate for dysfunction in voluntary top-down orienting and in directing attention (132).

Limbic Reward-related Circuitry

Reward is a key component of learning, shaping appropriate responses to stimuli and developing goal-directed behaviors (133). Because of associated difficulties in individuals with ADHD ascribable to such processes, ADHD investigators have focused attention on brain areas related to reward-related processes (134-137).

The cortico-basal ganglia system is known as the reward network. The nucleus accumbens (NAcc) has long been considered the center of this system, based on pharmacological, behavioral and physiological studies (138-143). Particularly in ADHD, the NAcc has been reported as a key region implicated in the reward/motivation deficits hypothesized to be involved in the disorder (135, 137, 144, 145). Although few structural neuroimaging studies have reported abnormalities in this region (90), several functional imaging

studies have found dysfunction in NAcc activation during reward processing tasks in ADHD (136, 137, 146, 147).

The first experimental study of the present thesis (paper 1), showed that children with ADHD have a robust bilateral volumetric reduction in the ventral striatum (NAcc) compared to healthy matched controls. These differences remained statistically significant after correcting for total brain volume (Fig. 6B).

The NAcc is key component of the "cortico-striato-nigro-striatal" circuit proposed by Haber in 2000. In the cortico-striato-nigro-striatal circuit (Fig. 6A), the NAcc receives projections from limbic regions, projects to the ventral tegmental area (VTA) and to the substantia nigra pars compacta (SNc) and receives back projections from these two regions. While projections from the VTA return to the NAcc shell, the SNc projects to the NAcc core (55).

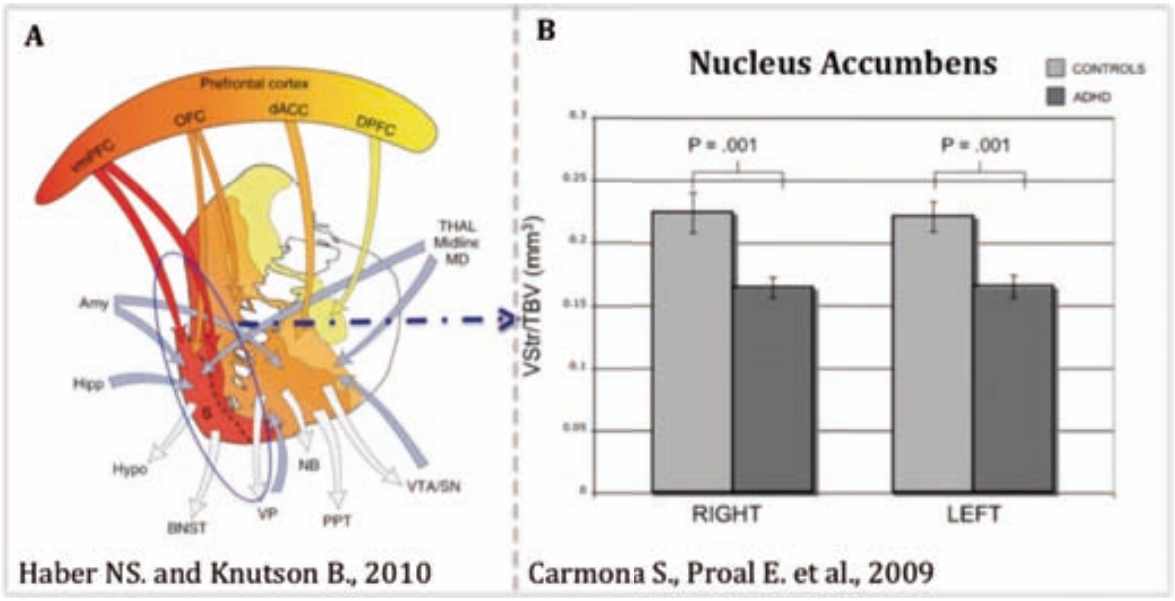

Fig. 6.

Although formerly it was thought that only the dopamine system originating in the VTA was involved in motivation and addiction (148), it is now clear that both VTA and SNc play important roles (148). In order to test this pathway in individuals with ADHD, Volkow et al., applying positron emission tomography, measured synaptic dopamine markers in the accumbens regions (149). They found a disruption of this pathway in subjects with ADHD compared with healthy adults. They also found a negative correlation between the reduction of

dopamine synaptic markers and inattention symptoms. This relationship suggests that dopaminergic disruption may mediate clinical symptoms, because this specific pathway plays an important role in learning stimuli reward associations (149).

We also found a significant negative association between right ventral striatum volume and mothers' ratings of hyperactivity/impulsivity. We also observed a negative association, albeit not significant, between right ventral striatum volume and fathers' ratings. In rats, damage to the nucleus accumbens causes impulsive behaviors consisting of choosing small/immediate rewards rather than larger/delayed rewards as well as an increase in motor hyperactivity (150, 151).

In summary, NAcc abnormalities likely underpin ADHD. These results are particularly relevant in light of recent mechanistic models of ADHD, which highlight the importance of reward circuitry in the pathophysiology of ADHD, particularly in those individuals with hyperactivity/impulsivity symptoms (134).

However, even though the NAcc has been considered the central region for reward processing, recent animal and human studies have demonstrated that regions that are implicated in reward are more extensive (133, 152, 153). The key additional regions of the reward pathway include the anterior cingulate cortex, orbitofrontal cortex, ventral pallidum and midbrain dopamine neurons. Other modulatory regions include the dorsal prefrontal cortex, amygdala, hippocampus, thalamus and lateral habenular nucleus (133) (Fig. 7A).

In the second empirical project (Paper 2) we did not find differences in the ventral striatum of adults with ADHD, although we found abnormalities in regions that act together with the ventral striatum and regulate the reward circuitry (133) (Fig. 7B).

For example we observed grey matter decreases in caudate volume of adults who were diagnosed with ADHD in childhood. The caudate nucleus is also involved in reward-based learning and receives input from the dorsal prefrontal cortex (154, 155). Also the caudate nucleus, specifically the part that is adjacent to the ventricle, receives projections from the ventromedial PFC (vmPFC), which in turn sends focal projections to the NAcc, including the shell (152).

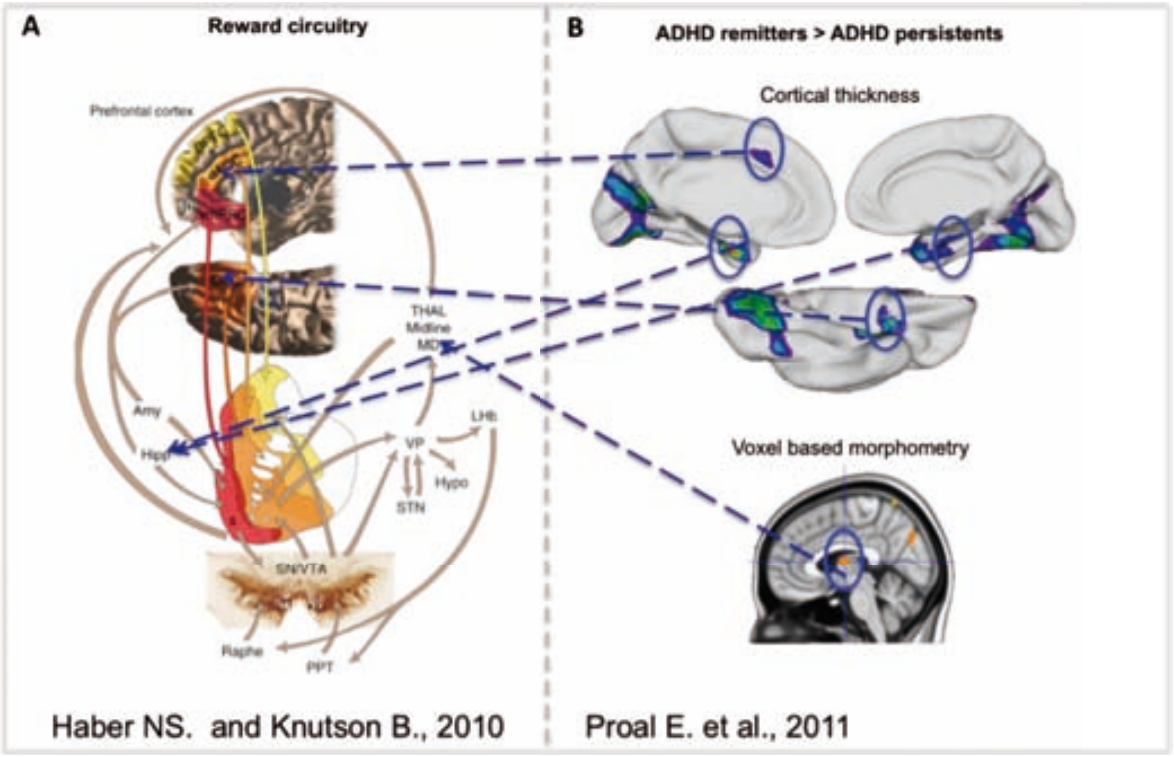

Fig. 7 A.Ventral striatum send projections to ventral pallidum and to the ventral tegmental area. The VP projects back to prefrontal regions through the thalamus (medial dorsal nucleus). Other regions regulate the reward circuit; including hippocampus, amygdala, lateral habenular nucleus and brainstem structures.
Amy=amygdala; dACC=dorsal anterior cingulate cortex; dPFC=dorsal prefrontal cortex; Hipp=hippocampus; LHb=lateral habenula; hypo=hypothalamus; OFC=orbital frontal cortex; PPT=pedunculopontine nucleus; S=shell, SNc=substantia nigra, pars compacta; STN=subthalamic nucleus.; Thal=thalamus; VP=ventral pallidum; VTA=ventral tegmental area; vmPFC=ventral medial prefrontal cortex. B. On the top, cortical thickness exploratory differences ($p<.05$, uncorrected) between ADHD remitters and ADHD persistents. On the bottom voxel based morphometry analyses are shown; the effect size of the difference in the thalamus between remitters and persistents was 0.60.

In exploratory analyses, uncorrected results suggested differences between ADHD remitters and ADHD persistents, and remarkable congruence between ADHD remitters and controls in regions implicated in the reward circuitry such as orbitofrontal cortex, ACC, parahippocampus, thalamus and frontal pole (Fig. 7B).

Specifically, there are projections from the medial area of the frontal pole (BA10) to the ventral striatum. Studies using tracer injections have shown that this frontal area (BA10) overlaps with inputs from vmPFC (156) suggesting that both vmPFC and frontal area BA10 terminate in the NAcc (133). Furthermore, the hippocampal formation projects to a limited area of the VS. The main terminal is located in the most medial and ventral parts of the VS and essentially confined to the NAcc shell. These inputs overlap with those received from amygdala

and vmPFC. The existence of these convergent fibers makes the VS, mainly the NAcc, a key region for processing emotional and motivational information (133).

The thalamus is another important component of the reward circuit. This region is the last link for information returning to the cortex and does not pass information passively, but rather regulates several connections with the cortex. The thalamus receives input from the deep layers and projects the inputs received from the basal ganglia, to the superficial, middle and deep layers of the cortex. Basal ganglia projections to the thalamus go to different thalamic subnuclei, and each thalamic subnucleus receives inputs from different cortical areas. Specifically the medial dorsal thalamus, implicated in the reward circuit, has reciprocal connections with the lateral and orbitofrontal cortex and nonreciprocal connections from medial prefrontal areas (157). The thalamus not only relays information back to the cortex, but is an important center of integration of pathways that underpin the ability to modulate behaviors (157).

Regarding our results, we cannot rule out that remitters may have differed from persistents in the regions implicated in reward process since childhood, but the most parsimonious explanation is offered by the hypothesis that remission entails compensatory processes (93, 158) underpinned by prefrontal cortical maturation. Therefore, our data suggest that regions that are underpinning the reward circuit are involved in the remission of the disorder.

CONCLUSION

CONCLUSION

For achieving goals, an individual must combine an appropriate behavioral response to external stimuli, motivation and appropriate response to reward cues. In other words, that process requires a mixture of three actions: appreciation of the possibility of reward, planning and motor control (133). Those functions do not work in isolation. Rather, pathways such as reward and dorsal attentional network must interact with each other. Through these interactive circuits, reward information can be channeled through cognitive and motor pathways (133). The modification of goal-directed behaviors requires continual processing of complex chains of events and requires the feed forward organization of striato-nigra-striatal and thalamo-cortical connections (133). In this way, information can be channeled from limbic regions to cognitive areas (dorsal attentional network), allowing the individual to respond appropriately to cues (122).

Our data allows us to suggest an overall integrative hypothesis that dysfunction in the reward circuit, which was particularly prominent in children and adolescents with ADHD and in the adults with persistent ADHD, reflects ongoing symptoms of ADHD (Fig. 8). By contrast, abnormalities in the top-down control dorsal attentional network seem to be related to the trait of having had ADHD in childhood, as the abnormalities were comparable in adults who had remitted or who had persistent ADHD (Fig. 8). Confirmation of these hypotheses will likely involve functional imaging approaches as well as the anatomic studies described in this thesis. Although such studies are not included, Paper 3 provides an explanation and rationale for one type of functional imaging study, obtained without a specific task, i.e., during rest.

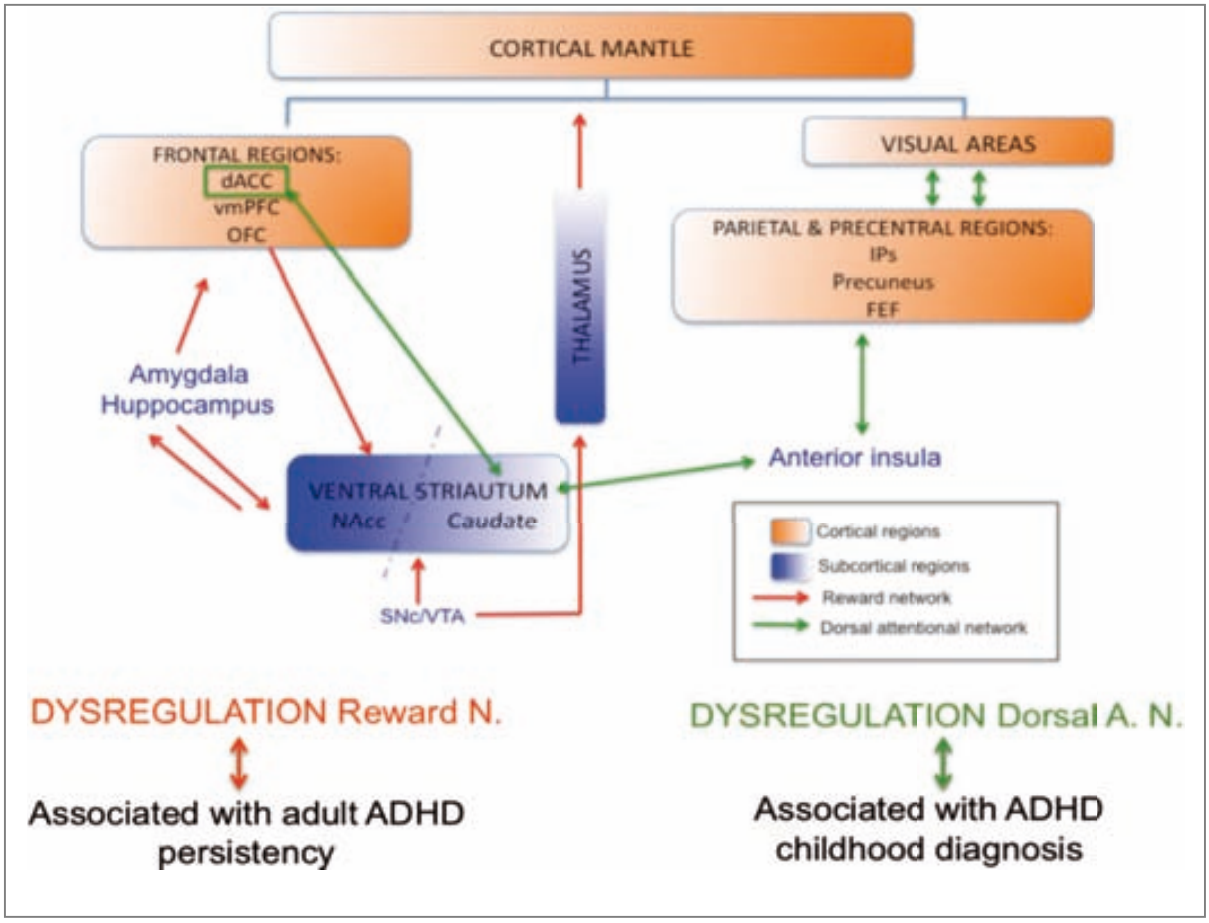

Fig. 8 Neural model underpinning ADHD physiopathology (proposed by Erika Proal on the basis of the data contained in the present thesis and based on the neuroanatomical models formulated by Corbetta and Shulman 2000 and Haber and Schultz 2010).
dACC=dorsal anterior cingulate cortex; dPFC=dorsal prefrontal cortex; vmPFC=ventromedial prefrontal cortex; OFC=orbitofrontal cortex; NAcc=nucleus accumbens, SNc=substantia nigra, pars compacta; VTA=ventral tegmental area; IPs=Intraparietal sulcus; FEF=frontal eye fields.

Future Directions - Functional Imaging in ADHD

Traditional functional imaging studies are being conducted in ADHD at an ever increasing rate. However, task-based fMRI studies have numerous inherent challenges which go far beyond the selection of a given task that will be robust to differential age and ability levels and to practice or strategy effects. The diversity and inconsistency of findings has been difficult to condense in other than broad terms (97). As a result, investigators have begun to place greater emphasis on the potential contributions of abnormalities in connectivity between regions, rather than regional abnormalities alone. In ADHD, studies of white matter volume and integrity have suggested decreases in structural connectivity (83). Awareness of ADHD as a dysconnection syndrome has been accelerated by the recent emergence of "resting state" fMRI. While this growing literature will not be reviewed here, the technique of resting state imaging, which can be

performed across multiple imaging centers and aggregated, has the potential to lead to the collection of large-scale collaborative samples needed to examine the complexity of the brain with sufficient statistical power. Paper 3 describes the rationale and potential of this imaging approach and the formation of the Spanish Resting State Network as a means of facilitating the diffusion of this novel and powerful new method.

ACKNOWLEDGEMENTS

ACKNOWLEDGEMENTS *(en castellano)*

AGRADECIMIENTOS! Es un apartado que envuelve tantas cosas… por un lado saber que es la parte final de una etapa y por otro saber que es complicado poder escribir en unos párrafos todo lo que implicó conocer, visitar y aprender en cada lugar y en cada instante de este proyecto. Es un recuento, un cierre, pero a la vez para mi es un comienzo….

En el verano del 2007, poco después de terminar mi carrera pasaban muchas dudas por mi cabeza, pero de algo si estaba muy segura, quería enfocarme en saber e investigar más a fondo el cerebro humano. ¿Como una psicóloga en México podía meterse al área de neurociencias? Una sola plática con el Dr. Jesús Ramírez en el Instituto Nacional de Neurología y Neurocirugía de México me dio la clave, y él tal vez sin ni siquiera darse cuenta de lo que había despertado en mí. Tenía que irme al extranjero, tenía que adquirir conocimientos que me dieran la oportunidad de aportar algo diferente y necesario a mi regreso a México. Tome la decisión y tres meses después con la beca que me habían otorgado y mis maletas en mano me fui a España.

Llegar ahí fue toda una aventura, conocer personas nuevas, un mundo totalmente distinto para mí. Pero se convirtió en un lugar mágico en donde descubrí la pasión por lo que aprendía y me encontré con personas muy valiosas que hasta la fecha forman parte de mi vida.

Tengo que empezar agradeciendo al Dr. Adolf Tobeña, al primero que conocí al llegar al departamento de psiquiatría y jefe del mismo, siempre me brindó confianza y se convirtió en una persona clave acompañándome como profesor de algunos cursos y como consejero en momentos de decisiones importantes. Pero también quiero agradecerle porque me llevo con el mejor equipo con el que pude trabajar: LA UNITAT DE RECERCA DE NEUROCIENCIA COGNITIVA, afirmándome que había llegado en el momento justo y que además era un grupo muy joven y dinámico. Y tenia razón!!, entrar a ese grupo fue de las mejores cosas que me ha pasado, en donde conocí a excelentes compañeros de trabajo pero sobre todo muy buenos amigos, empezando por Oscar Vilarroya, mi asesora de tesis favorita Susana Carmona, mi mejor amiga Ana Moreno, Elseline, Ramón, Daniel, Pepus, Joe, Joan Carles, Jordi Fouquet.

Mi segunda casa eran las oficinas del Forum, justo hasta el fondo del centro, un cuarto grande que compartíamos todos, donde hubo risas y también momentos de frustración y ahí Oscar Vilarroya jefe y amigo nos daba la libertad de jugar y poner en marcha nuestras ideas. Creer en mi, darme la confianza para desarrollar lo que pensaba y alentarme siempre que lo necesitaba, fue lo más valioso que Oscar como jefe me dejo. Me dio la tarea de encargarme de un proyecto del cuál siempre me sentí privilegiada y agradecida de poder ser parte de el y además el cuál me serviría como proyecto de tesina. Debo confesar que nunca pasó por mi mente que ese estudio traería tantas buenas consecuencias futuras, pero eso sí, al tener los primeros resultados comenzamos a soñar! Y digo comenzamos, porque fue un momento en donde Susana Carmona mi asesora de tesis y amiga enfocó su atención y entre las dos trabajamos duro para poder sacar lo mejor del proyecto. Días enteros, noches sin dormir, comiendo galletas de todo tipo y quedándonos madrugadas mirando por la ventana como las personas se iban de fiesta de San Juan y pidiendo comida a la chinita del "FOLUM" mientras seguíamos pensando en como redactar mejor en inglés y en el núcleo accumbens de los sujetos

con TDAH! Susana me enseño la pasión por trabajar en esto, la implicación que puede tener hacer ciencia. Siempre me lo dijo… hacer investigación se convierte en una adicción! Y así ha sido. Desde el comienzo, admiré que a pesar de ser tan joven, era tan buena, dedicada, apasionada e inteligente y eso me motivo a seguir su ejemplo.

Durante esa época viví momentos de mucho cansancio, a veces frustración, pero saber que contaba con personas con las cuales compartir esa etapa, como Ana Moreno, quien se convirtió en mi mejor amiga, hacían que con un cortadito, un croissant y una buena platica por la mañana el día se volviera totalmente diferente. Soñábamos tantas cosas juntas…. pero esos sueños gracias a poderlos compartir con ella fueron tomando sentido. Hasta hoy, Ana es una compañera y colega magnífica y una persona que estoy segura que permanecerá como amiga a lo largo de mi vida.

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Y así fue, después de largas horas de platica con ellas y pedir consejos a Oscar, Susana, Ana, Elseline, decidí que me encontraba entre dos opciones, una era irme por 6 meses a aprender más a algún grupo en Estados Unidos antes de comenzar la tesis y la segunda era regresar a mi país y realizar el proyecto de tesis ahí. No me convencía mucho la primera, pues me daba miedo e implicaba varias cosas (el idioma, no me gustaba tanto EEUU, otra vez saltar a algo nuevo y dejar lo que ya había construido en España). Así que decidí dejarlo a la suerte y puse como condición personal que solo iba a intentar aplicar en el mejor grupo de neuroimagen y TDAH, y que si en ese me aceptaban entonces tendría que ir, sino, regresaría a mi país. Le escribí directamente al jefe del laboratorio de la Universidad de Nueva York (NYU), el Dr. F. Xavier Castellanos y para mi suerte, contesto inmediatamente!!! Yo no sabía que hacer, ni que sentir pues era momento de tomar una decisión para dar el siguiente paso. Entre emoción y mucho miedo tome de nuevo mis maletas y me fui Nueva York.

Bien dicen que cuando uno toma una decisión no puede ver las repercusiones que traerá en el futuro con facilidad. Pero bastan momentos como hoy que estoy escribiendo, para poder juntar los puntos clave y sin miedo a equivocarme saber que irme a NY fue la mejor decisión que pude haber tomado en ese momento. No podía creer que estaba ahí! Que conocería al Dr. Castellanos! Que vería a personas como Mike Milham, Clare Kelly, Adriana Di Martino de las cuáles había leído tanto. Tampoco imagine que de quererme quedar 6 meses o 1 año me quedaría casi 2 años!

Todavía recuerdo la primera platica con Mike Milham diciéndome que no quería asustarme pero que ahí trabajaban muy intensamente. Y así fue, 2 años de mucha intensidad profesional, trabajando hasta tarde y en fines de semana, completamente a ritmo New Yorkino! Aprendí muchas cosas, pero sobre todo aprendí que cuando te encuentras en un equipo con personas de primer nivel y trabajando todos con mucha pasión se obtienen cosas impresionantes. Agradezco a cada uno de los postdocs porque siempre me hicieron sentir parte del equipo, Clare, Xinian, Maki, Maarten y después la llegada de Chrissie, Manu, Juan, Camille, todos de diferentes culturas y con tanto que aportar, personas brillantes, con entusiasmo y con un corazón increíble. También tengo que agradecer a Adriana Di Martino por mostrarme con su ejemplo que con determinación se pueden lograr los objetivos y a Mike Milham un líder muy

joven del cuál aprendí de cada aportación que el daba y con su forma tan sutil de decir siempre "no me convence lo que hiciste" me hizo aprender a defender con mejores bases mis ideas.

Estar en la universidad de NY y vivir en esa ciudad fue como estar en un sueño, dentro de mi proyecto, tuve el gran privilegio de encontrar a una persona que después de admirarlo a la distancia y a través de sus escritos, se convirtió en mi guía profesional, mi mentor y maestro del alma: F. Xavier Castellanos. Creyó en mí desde el primer día que nos conocimos, tuve la suerte de trabajar con él juntos en un mismo proyecto. Xavier es un apasionado de su trabajo, me enseño con un ejemplo diario que la ciencia hay que saberla disfrutar, jugar con ella y sobre todo detectar las habilidades de uno mismo para poderlas potencializar, aprender a ver la capacidad de los demás y juntar esos esfuerzos para llegar a grandes resultados. Quiero agradecerle y dedicar gran parte de esta tesis a él, por haber ido de la mano conmigo, por enseñarme que los momentos más frustrantes son parte del proceso e incluso los que lo vuelven más fuerte y especial, por confiar cada instante en mi y por seguir hasta hoy siendo mas que un mentor, el mejor de los colegas y el mejor de los amigos.

No puedo dejar de mencionar a dos personas, maestros, colegas con los cuales por su gran trayectoria profesional y experiencia fue un PRIVILEGIO poder trabajar: Salvatore Manuzza y Rachel Klein. Sal, siempre confiando en mí y dándome consejos profesionales y personales, se convirtió en un consejero y especial amigo. Rachel, una mujer de admirar! determinada, siempre pendiente en los detalles, tratando de mejorar el trabajo de los demás con su experiencia, con su dinamismo e inteligencia me mostraba que siempre había algo que se podía mejorar, es un gran ejemplo para mí, como mujer y profesionalmente.

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Y como dejar de mencionar a los integrantes del "latin room", Nicoletta Adamo, Mar Álvarez, Samuele Cortese, quienes juntos convertimos nuestra oficina en un lugar en donde podíamos desahogar las frustraciones, los únicos integrantes del lab que como buenos latinos tomábamos hora para salir a convivir y comer lunch! Ellos hicieron que mis días fueran más divertidos y se volvieron mis confidentes.

Solo me queda decir que cada paso de esta etapa fue única, poder vivir en Barcelona y en NY, juntar experiencias con personas tan enriquecedoras… y ahora escribiendo desde mi país, México, unos meses después de decidir que lo mejor era volver. Con la tesis por terminar, con varios proyectos por concluir en NY, con tristeza de dejar lo que construí en mis mundos en el extranjero, pero con entusiasmo de poder aportar lo que esta etapa de vida me ha dejado como lo había pensado desde el comienzo de mi doctorado. Y estoy aquí, escribiendo este recuento, terminando la tesis junto a personas que me han apoyado a no desanimarme como Zazhil mi compañera de departamento y mejor amiga, cerca de mis amigas Natalia, Tatiana, Daniela, Paulina, Adriana, que son mis hermanas y estando cerca de mi familia sobre todo mis padres y mi hermano a los que les dedico completamente esta tesis por ser mis mejores ejemplos de vida. Me han apoyado en cada paso que he decidido dar, siempre recordándome que la vida esta llena de cambios y que hay que recibirlos con los brazos abiertos porque los cambios bien pensados son símbolo de crecimiento. Se cierra este capítulo, pero se suma a los nuevos que vendrán…Gracias de nuevo a todos los que fueron parte de esta gran etapa, por compartir cada instante conmigo y por creer en mí….

ACKNOWLEDGEMENTS *(in english)*

ACKNOWLEDGEMENTS! There is so much to say… on one hand, this represents the end of one phase, and on the other, it is not easy to write in few words how meaningful every place and moment of this project has been. This narrative represents closure, but at the same time it is also another start….

In the Summer of 2007, shortly after graduating, I had many doubts, but one thing I knew. I wanted to focus on learning about the human brain in depth. But how could a Psychologist in Mexico enter into neuroscience? I met once with Dr. Jesús Ramírez at the Instituto Nacional de Neurología y Neurocirugía de México, and he gave me the key I was searching for, perhaps without even knowing it. He told me I would need to study abroad, to obtain the type of training that I could then bring back to Mexico. I decided to follow his advice, and three months later, I took my newly granted fellowship and my suitcases in hand and went to Spain.

Arriving there was an entire adventure of meeting new people, of learning a completely new world. But it soon became a magical place in which I discovered my passion for what I was learning and I came to know amazing people who are now a part of my life.

I have to start by thanking Dr. Adolf Tobeña, the first person I met on arriving at the Department of Psychiatry which he directs. He always filled me with confidence and he became one of my mainstays, in his role as professor of several courses, and my advisor with regard to all important decisions. But I also want to thank him for leading me to the best group with which I would work, THE COGNITIVE NEUROSCIENCE RESEARCH UNIT (URNC), telling me that I had arrived at just the right moment, and that it was a young dynamic group. And he was right!! Becoming part of this team was one of the best things to happen to me. It was here that I met excellent colleagues and good friends, beginning with Oscar Vilarroya, the lab chief, Susanna Carmona, my thesis advisor, Ana Moreno, Elseline, Ramón, Daniel, Pepus, Joe, Joan Carles, and Jordi Fouquet.

My second home was the offices of the Forum, in the farthest reaches of the Center – a large shared space, in which we laughed together and experienced moments of frustration. There, Oscar Vilarroya, lab chief but also friend, gave us the freedom to play with ideas and put them to the test. Oscar's gifts to me as lab chief were his belief in me and his encouragement whenever I needed it, which gave me the confidence to develop my thoughts. He gave me my own project, which always felt like a privilege for which I will always be grateful, and which served as the basis for my Master's thesis. I have to confess that I never dreamed that this original project would bring so many positive future consequences, but that's how it developed, and from that moment we began to dream! And I mean we, because I didn't do it by myself there were moments when Susanna Carmona, my thesis advisor, and I put all out attention on this project and worked together with all our strength to make it a success. Entire days would turn into working throughout the night, eating cookies of all types while we watched from the window while the entire city celebrated the feast of St. John with fireworks, with us ordering Chinese food from the "FOLUM" while we continued working on how best to write about the nucleus accumbens and ADHD in English! Susanna taught me her passion for this work, and for

the importance that science can have. She always warned me, research becomes an addiction! And that's what has happened. From the beginning, I admired that despite her youth, she is such a dedicated, passionate, intelligent good person who became my model.

During those periods I experienced fatigue, sometimes frustration, but I knew that I could rely on people like Ana Moreno, who has become one of my best friends, who with a coffee, a crossiant, and a pep talk could make sure that the day would turn out totally differently. We shared so many dreams… and as we shared them, those dreams started to take shape. As I write this, Ana has become a magnificent colleague who I know will be a friend for life.

I also want to thank Julia Balcazar and Daniela Dominguez, my Mexican roommates. What a group we were!!! I always loved going home because they always reminded me that living in Barcelona is an amazing privilege! We went out together, had wonderful times, got to know each other, and they also helped me to think through my next steps as I completed my first step towards my doctoral degree, my master's thesis!

And that is how it played out, after many hours of discussions with them and obtaining advice from Oscar, Susanna, Ana, Elseline, I decided I had to choose between two options, of either spending 6 months with a group in the U.S. before beginning my dissertation, or returning to my country, and working on my dissertation there. I was not all that enthusiastic about the first option, which worried me for several reasons (the language, I was not all that enamored of the U.S., once again starting anew and leaving behind all I had created in Spain). So I decided to leave it to the fates and that I would only apply to the best neuroimaging group working on ADHD. If they accepted me, I would have to go. Otherwise, I would return to Mexico. I wrote directly to the chief of the lab at NYU, Dr. F. Xavier Castellanos, and it was my good luck that he wrote back immediately!! I didn't know what to do, nor what to feel, but it was now the time to decide on the next step. With my heart in my throat, I made up my mind, took my suitcases in hand again and went to New York.

It's said that when we make important decisions we can't always see what the future will bring. But it is one of the values of reflecting as I write these words that I can now see clearly that going to NY was the best possible decision I could have made at that moment. I could not believe that I was really there! That I would get to know Dr. Castellanos! That I would see people like Mike Milham, Clare Kelly, Adriana Di Martino, whose work I had been reading. Nor did I imagine that my plan to stay 6 months would turn into 1 year and then into almost 2!

I still recall my first meeting with Mike Milham, who said that he did not want to frighten me but that all in the lab worked very intensely. And that is how it was, 2 years of the most intense work, late hours during the week and during weekends, completely following the rhythms of New York! I learned so much, but most of all, that when one works with such an excellent team, and everyone is passionate and fully engaged, then amazing things are accomplished. I want to thank every one of the post-docs because they always made me feel that I was one of them, Clare, Xi-Nian, Maki, Maarten, and later, Chrissie, Manu, Juan, Camille – all from different cultures and all with something to contribute, all brilliant, enthusiastic, and with huge hearts. I also want to specifically thank Adriana Di Martino for showing me by example that with determination, we can reach our goals, and Mike Milham, the leader of the group despite his youth, from whom I learned much from each encounter, and who by subtly telling me, "you haven't yet convinced me" taught me how to defend my ideas with stronger evidence.

To be at NYU and to live in New York was like living a dream. And after having read and admired his work from a great distance, I was now working with and getting to know the person who has become my teacher, my mentor, and even my spiritual guide, F. Xavier

Castellanos. He believed in me from the first day we met, and it has been my great good fortune to work closely with him on this project. Xavier is passionate about his work, but he brings a playful attitude to this that surprised me, and he taught me by his daily example to experience the joy of science. He also taught me that we have to find our own strengths, those of our colleagues, and how to join them to achieve great things. I want to thank him and dedicate a major part of this thesis to him, for having taken me by the hand, for having taught me that the moments of greatest frustration are all part of the process, which make us stronger, and specially for trusting in me every moment and for being even now more than a mentor, the best of colleagues and the best of friends.

I cannot fail to mention two superb colleagues with whom it was a PRIVILEGE to work: Salvatore Manuzza and Rachel Klein. Sal always trusted me and provided me with his best professional and personal advice, becoming a friend and counselor. Rachel, a woman I admire, is determined, always thoughtful about all issues, striving to use her great experience to advance the quality of the work of all around her. Rachel's dynamism and intelligence proved to me that there is always room for improvement, and she has become one of my touchstones as a model for me, as a woman and professional.

I also thank Phil Reiss for the countless hours we spent together struggling on the analyses and also for their important contributions thanks to Alex Zijdenbos, Jason Lerch, Yong He and María Ramos.

And how could I not mention my colleagues of the "Latin Room"? Nicoletta Adamo, Mar Álvarez, and Samuele Cortese, together, we made our shared office into a place in which we could discharge our frustrations. And as the only "Latin" lab members, we would go out regularly and eat lunch! They enlivened my days and became my confidants.

All that is left to say is that each step of this process was unique and wonderful. To have lived in Barcelona and NY, to work with such amazing people… and as I write these words, to be back in my Mexico, a few months after having decided that the next best step was to return. While this dissertation is now completed, and I still am working on several projects with NYU colleagues, I am aware of my sadness at having left behind the lives I build in those worlds, but at the same time I am filled with excitement at being able to bring back what I have learned, as I planned from the beginning. And as I write this narrative, I am finishing my dissertation surrounded by those who have supported me, such as my roommate and best friend Zazhil, my friends Natalia, Tatiana, Daniela, Laura, Paulina, Adriana that I consider as my sisters and my family, above all my parents and my brother, to whom I dedicate this entire dissertation for being my best models of how to live life. They have supported me through every step of the way, always reminding me that life is full of change and that embracing change helps us to grow and take on new challenges. So this chapter is now done, but it will be followed by others to come… I thank once more all those who were part of this great adventure, for sharing every moment with me, and for believing in me….

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