ADHD

A Need For Change

KCU Homecoming CME 2019

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The Enigmatic Nature of ADHD

So what is it really?

The need for diagnostic clarity and certainty

Our Outline For Discussion

Prevalence

Comorbidities and Risks

Executive Functioning

Functional MRI Results

Assessment

Treatment

PEDIATRIC PREVALENCE

In 2016:

The estimated number of children and adolescents ever diagnosed with ADHD, according to ***parent report***, was consistent with previous estimates from the National Survey of Children's Health.

Approximately 9.4% of children 2-17 years of age (6.1 million) had ever been diagnosed with ADHD, according to ***parent report*** in 2016.
Ages 2-5: Approximately 388,000 children
Ages 6-11: Approximately 2.4 million children
Ages 12-17: Approximately 3.3 million children

M. Danielson, et al. Prevalence of Parent-Reported ADHD Diagnosis and Associated Treatment Among U.S. Children and Adolescents, 2016. Journal of Clinical Child & Adolescent Psychology, Volume 47, 2018

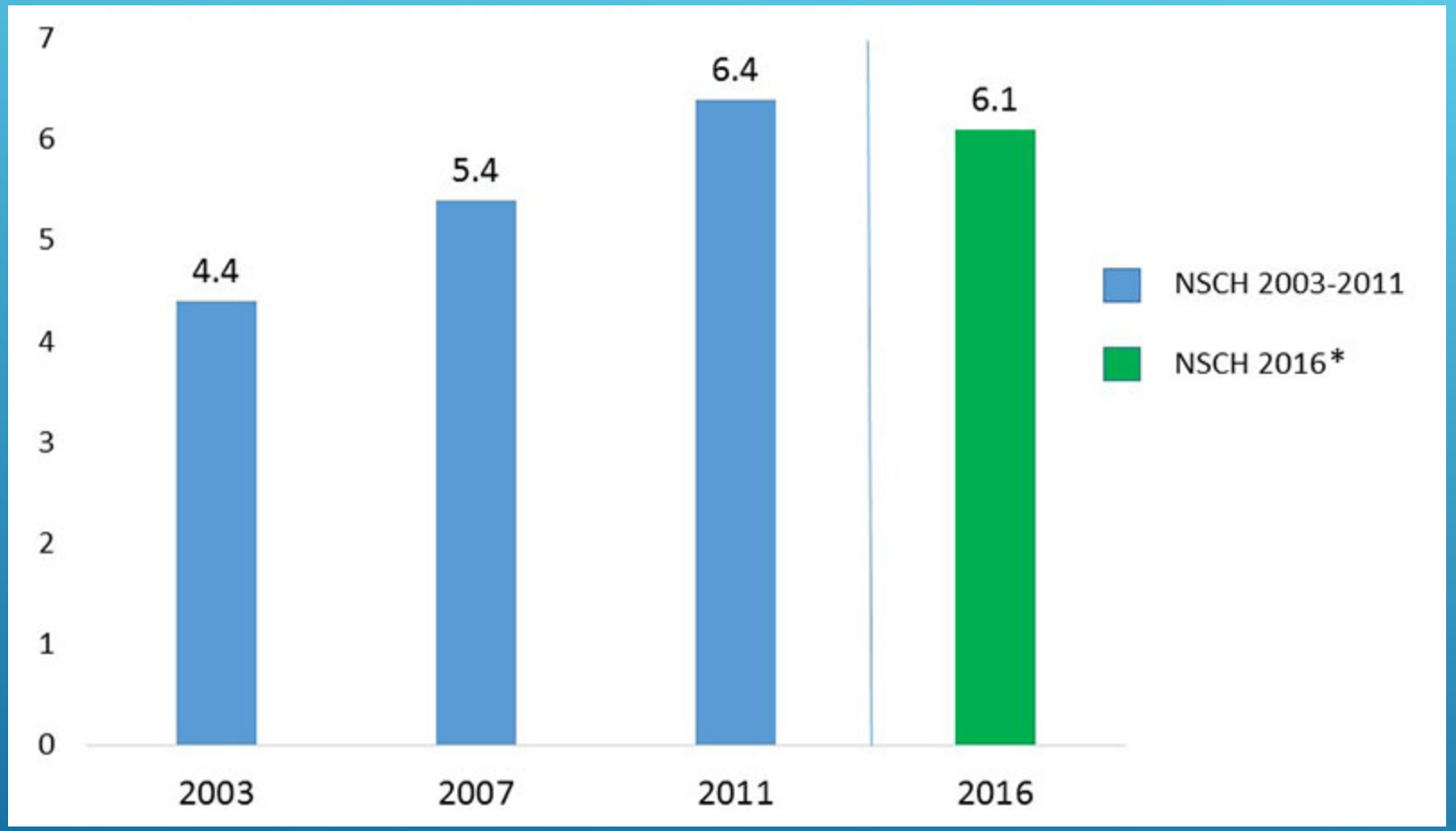
PEDIATRIC PREVALENCE

Parent report on ADHD diagnosis in previous years:

The percent of children 4-17 years of age ever diagnosed with ADHD had previously increased, from 7.8% in 2003 to 9.5% in 2007 and to 11.0% in 2011-12.

The number of young children (ages 2-5) who had ADHD at the time of the survey increased by more than 50% from the 2007-2008 survey to the 2011-12 survey.

M. Danielson, et al. Prevalence of Parent-Reported ADHD Diagnosis and Associated Treatment Among U.S. Children and Adolescents, 2016. Journal of Clinical Child & Adolescent Psychology, Volume 47, 2018


7
6
5
4
3
2
1
0
4.4
5.4
6.4
6.1
2003
2007
2011
2016
NSCH 2003-2011
NSCH 2016*

PEDIATRIC PREVALENCE

The National Institute of Mental Health Diagnostic Interview Schedule for Children–IV (DISC-IV), a structured diagnostic interview instrument designed for use in epidemiologic studies, was used to assess the presence of ADHD based on DSM-IV criteria.

A total of 3907 children aged 8 to 15 years participated in NHANES from 2001 to 2004, with data regarding DSM-IV ADHD diagnostic status available for 3082 children (78.9% of total).

Froehlich et al. Arch Pediatr Adolesc Med. 2007;161(9):857-864

PEDIATRIC PREVALENCE

In a nationally representative sample of children aged 8 to 15 years, 8.7% met DSM-IV criteria for any type of ADHD in the year prior to the survey, equivalent to approximately 2.4 million children.

Only 39% had some medication treatment

Only 32% had consistent medication treatment during the past year

Girls were less likely to have their disorder recognized

The poorest children were least likely to receive consistent ADHD medication treatment.

Froehlich et al. Arch Pediatr Adolesc Med. 2007;161(9):857-864

ADULT PREVALENCE

National Comorbidity Survey Replication

Estimated the prevalence, comorbidity, and impairment of adult ADHD in the US.

The estimated prevalence of clinician-assessed adult ADHD is 4.4%

Only 10.9% of respondents with adult ADHD received treatment for ADHD in the 12 months before interview (12.1% of females vs. 10.1% of males, $z = 0.4$, $p = .657$)

National Comorbidity Survey Replication
Kessler et al. Am J Psychiatry. 2006 April; 163(4): 716–723.

HAS PREVELANCE INCREASED?

- updated the two most comprehensive systematic reviews of studies addressing the prevalence of ADHD
- included 135 studies published from 1985 to 2012
- conducted a meta-regression analysis to test the effect of time on variability of estimates and updated previous analyses to explore the effect of methods and geographical location of studies

Polanczyk, G., et al. International Journal of Epidemiology, 2014, Vol. 43, No. 2

HAS PREVELANCE INCREASED?

- results showed when controlling for study methods, prevalence estimates did not vary as a function of year of study during the past three decades

- the true prevalence of the disorder did not increase from 1985 to 2012

- Indicates that increasing rates of diagnosis of ADHD are related to increasing awareness and access to services

Polanczyk, G., et al. International Journal of Epidemiology, 2014, Vol. 43, No. 2

COMORBIDITY

Adult ADHD is significantly comorbid with a wide range of other psychiatric disorders, with odds ratios of 2.7–7.5 for mood disorders, 1.5–5.5 for anxiety disorders, ***1.5–7.9 for substance disorders***, and 3.7 for intermittent explosive disorder

A significantly higher proportion of females than males with adult ADHD received treatment for mental or ***substance problems*** in the 12 months before interview (53.1% vs. 36.5%, z = 2.6, p = .014)

However, only 25.2% of treated cases received treatment for ADHD (22.8% of females vs. 27.7% of males, z = 0.5, p = .598)

National Comorbidity Survey Replication
Kessler et al. Am J Psychiatry. 2006 April; 163(4): 716–723.

COMORBIDITY

ADHD and CHILDHOOD SUICIDE

- Analyzed National Violent Death Reporting System (NVDRS) surveillance data capturing suicide deaths from 2003 to 2012 for 17 US states

- Participants included all suicide decedents aged 5 to 14 years

- Among suicide decedents with known mental health problems childhood decedents more often experienced ADHD and less often experienced depression/dysthymia compared with early adolescent decedents

Sheftall et al. PEDIATRICS Volume 1 38, number 4, October 2016

EXECUTIVE FUNCTIONING

To understand ADHD we must first understand what is meant by 'executive functioning'

Major features of executive function include:

- inhibitory control
- attention shifting
- working memory
- goal-directed behavior
- strategic planning

S. Goldstein and J.A. Naglieri (eds.), Handbook of Executive Functioning.
DOI 10.1007/978-1-4614-8106-5_2,

EXECUTIVE FUNCTIONING

Executive functioning gives us the ability

- to assess a situation
- to distinguish relevant vs. irrelevant
- to filter out extraneous information
- to adapt plans to current environment and situation
- to initiate focused actions based on the plan
- to assess effect of action in an ongoing fluid manner

EXECUTIVE FUNCTIONING

- executive functioning relies on various distributed networks, which include frontal and posterior regions of the cerebral cortex, as well as subcortical regions

S. Goldstein and J.A. Naglieri (eds.), *Handbook of Executive Functioning*. DOI 10.1007/978-1-4614-8106-5_2, © Springer Science+Business Media New York 2014

EXECUTIVE DYSFUNCTION IN ADHD

- An information processing dysfunction within the Prefrontal Cortex

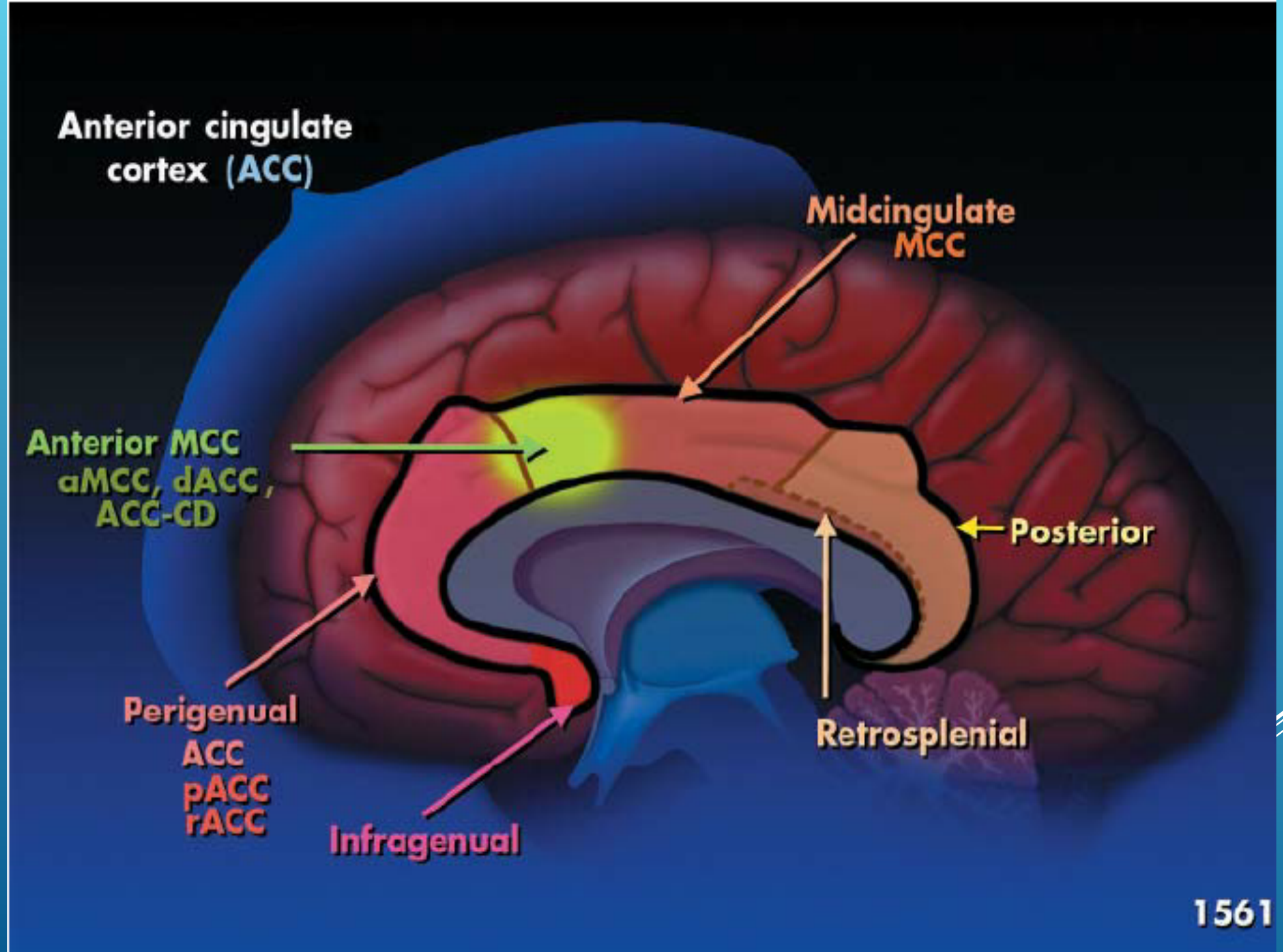
- Primarily due to a deficiency of dopamine and norepinephrine activity

IMAGING STUDIES

DORSAL ANTERIOR MIDCINGULATE CORTEX

The most consistent cross-study and cross-modality data identifying a region as dysfunctional in ADHD has been provided for the dorsal anterior midcingulate cortex (daMCC)

G Bush. Cingulate, Frontal and Parietal Cortical Dysfunction in Attention-Deficit/Hyperactivity Disorder Biol Psychiatry. 2011 June 15; 69(12): 1160–1167. doi:10.1016/j.biopsych.2011.01.022


Anterior cingulate cortex (ACC)
Midcingulate MCC
Anterior MCC aMCC, dACC, ACC-CD
Posterior
Perigenual ACC pACC rACC
Infragenual
Retrosplenial
1561

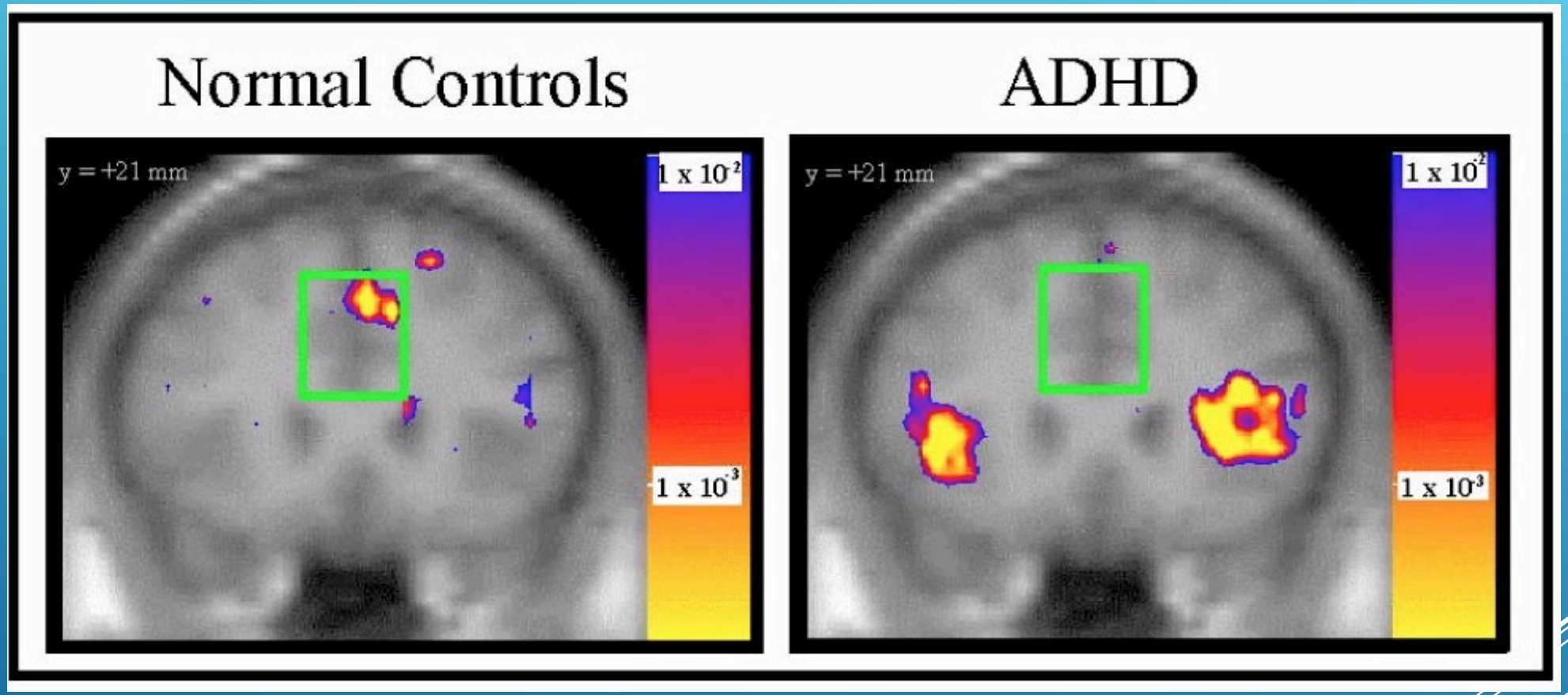
DORSAL ANTERIOR MIDCINGULATE CORTEX

Numerous fMRI, PET and event-related potential (ERP) studies have reported daMCC hypofunction in ADHD using a variety of tasks and techniques.

The daMCC integrates goal and feedback related information from various sources and uses this information to modulate activity in executive brain regions that direct attention and produce motor responses.

G Bush. Cingulate, Frontal and Parietal Cortical Dysfunction in Attention-Deficit/Hyperactivity Disorder Biol Psychiatry. 2011 June 15; 69(12): 1160–1167. doi:10.1016/j.biopsych.2011.01.022

DORSAL ANTERIOR MIDCINGULATE CORTEX



The daMCC Shows Hypofunction in ADHD during Counting Stroop
Dorsal anterior midcingulate cortex (daMCC) activated in healthy controls, but not in subjects with ADHD, during the Counting Stroop

Meta-analysis of Functional Magnetic Resonance Imaging Studies of Inhibition and Attention in ADHD

A comprehensive literature search of FMRI studies in ADHD using inhibition and attention tasks.

Two main meta-analyses were performed:

(1) inhibition tasks, further divided into motor response and interference inhibition

(2) attention tasks, including cued target detection, selective and divided attention, continuous performance task and mental rotation tasks

Hart et al. JAMA Psychiatry. 2013;70(2):185-198. Published online December 17, 2012. doi:10.1001/jamapsychiatry.2013.277

INHIBITION TASKS

Regions of ***decreased activation*** (red and orange) in patients with ADHD compared with healthy controls is shown

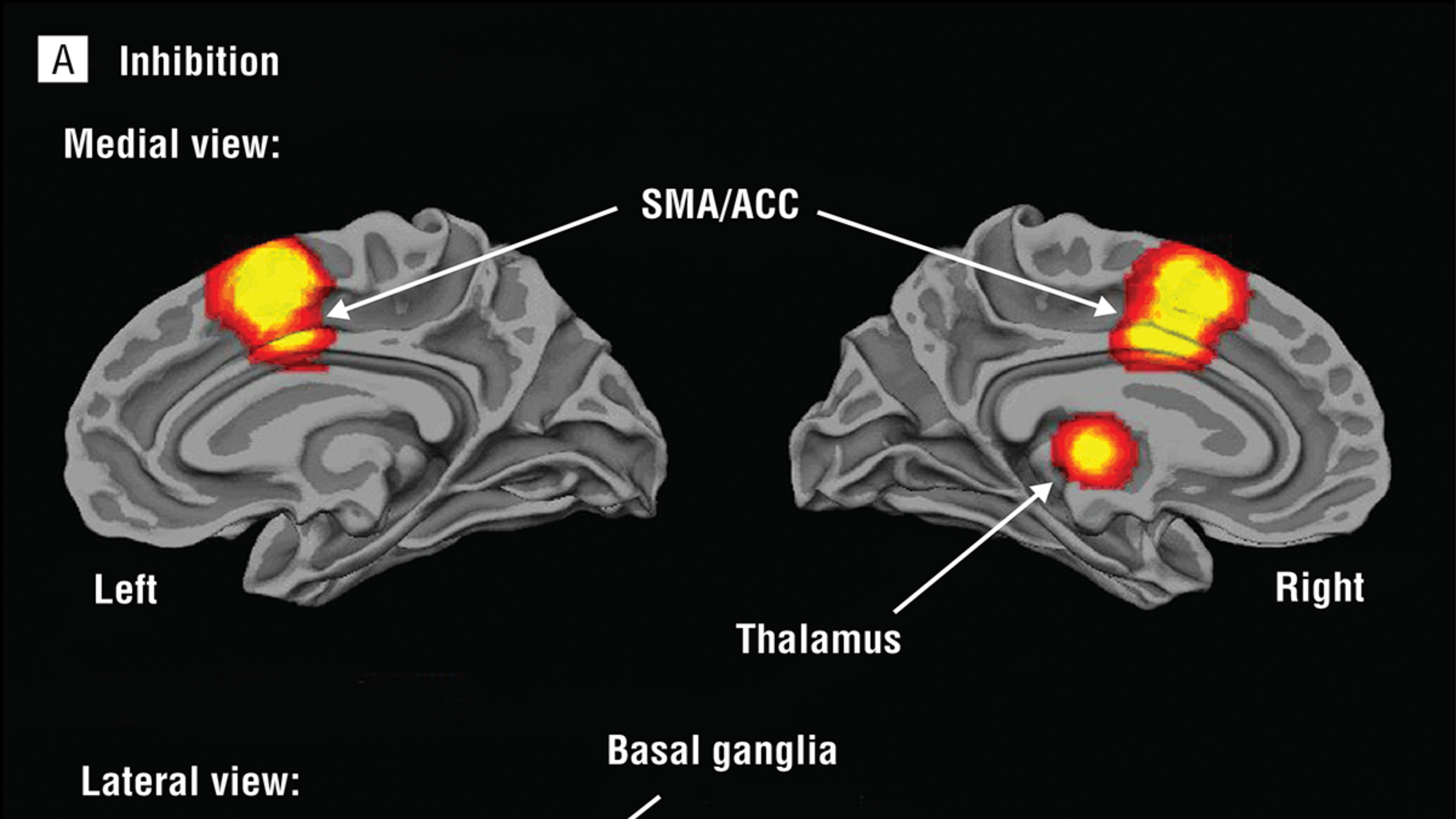
- in the right inferior prefrontal cortex (IFC) extending into the insula

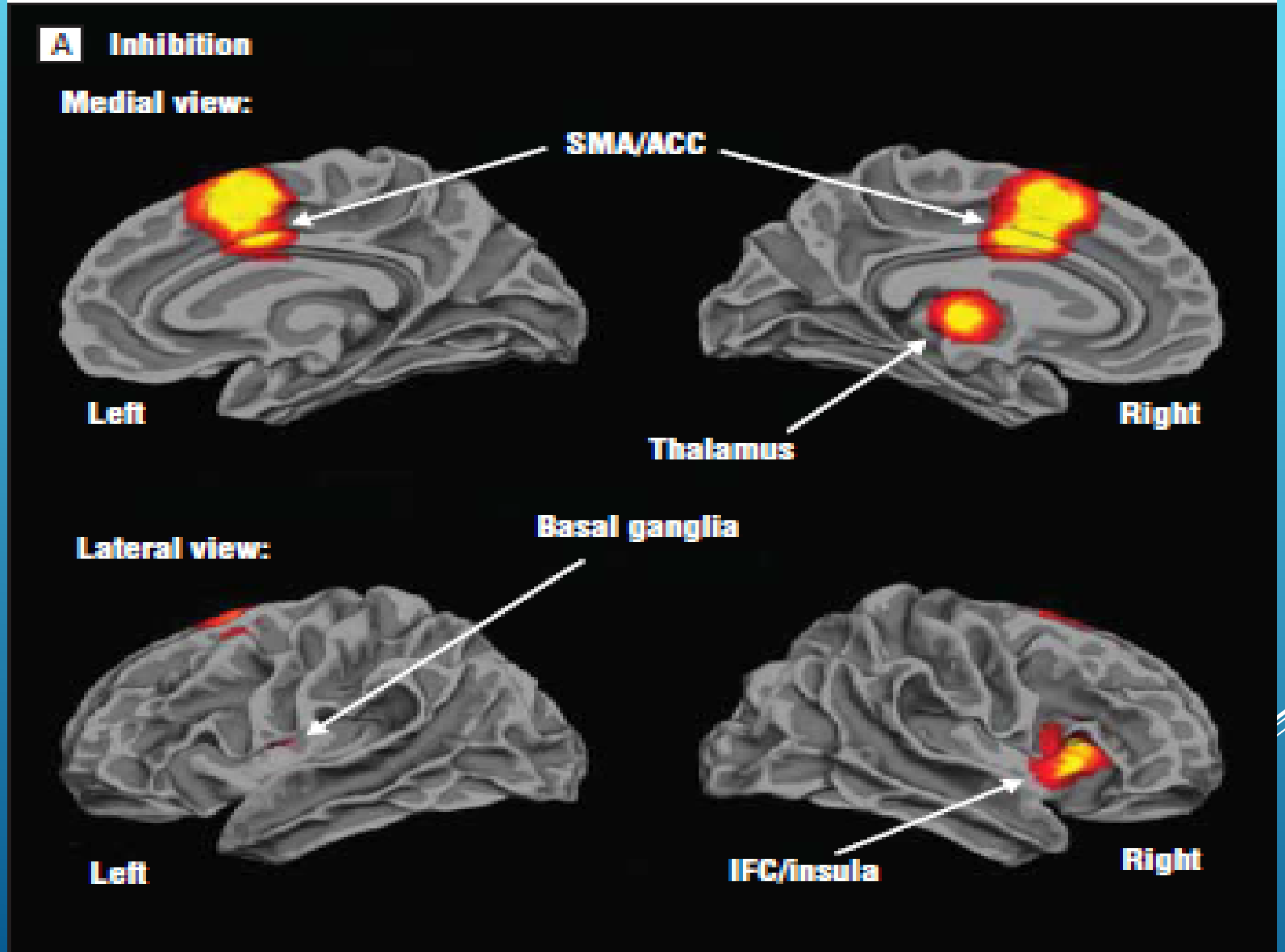
- in a cluster comprising the supplementary motor area (SMA)

- and the cognitive division of anterior cingulate cortex (ACC)

- in the left caudate extending into the putamen and insula, and in the right mid-thalamus

Hart et al. JAMA Psychiatry. 2013;70(2):185-198. Published online December 17, 2012. doi:10.1001/jamapsychiatry.2013.277


A Inhibition
Medial view:
SMA/ACC
Left
Right
Thalamus
Basal ganglia
Lateral view:


A
Inhibition
Medial view:
SMA/ACC
Left
Right
Thalamus
Lateral view:
Basal ganglia
Left
IFC/insula
Right

ATTENTION TASKS

Decreased activation (red and orange) is shown

- in the right dorsolateral prefrontal cortex (DLPFC)

- in the left putamen and globus pallidus

- in the right posterior thalamus (pulvinar) and caudate tail extending into the posterior insula
- in the right inferior parietal lobe

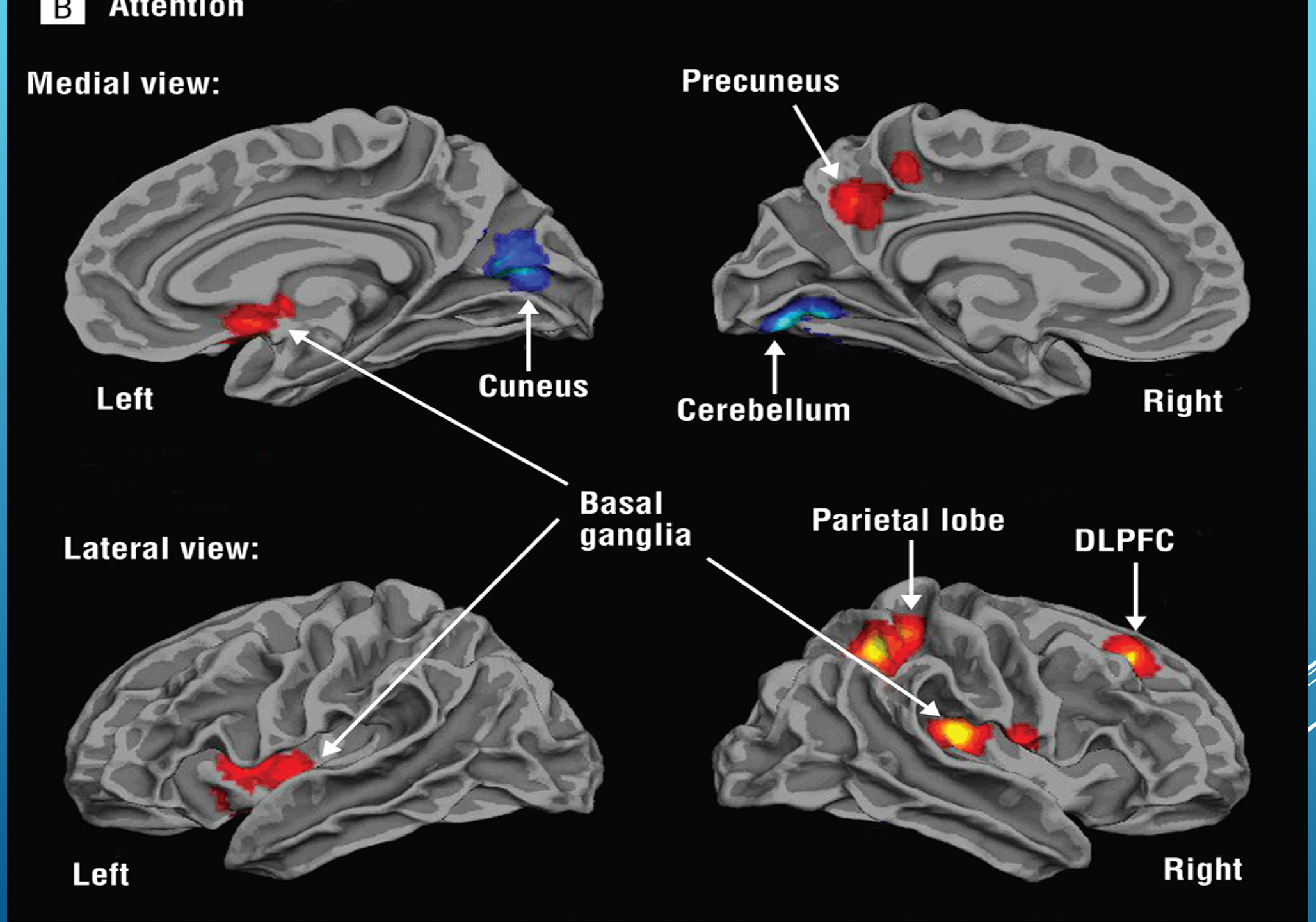
- and in the precuneus and superior temporal lobe

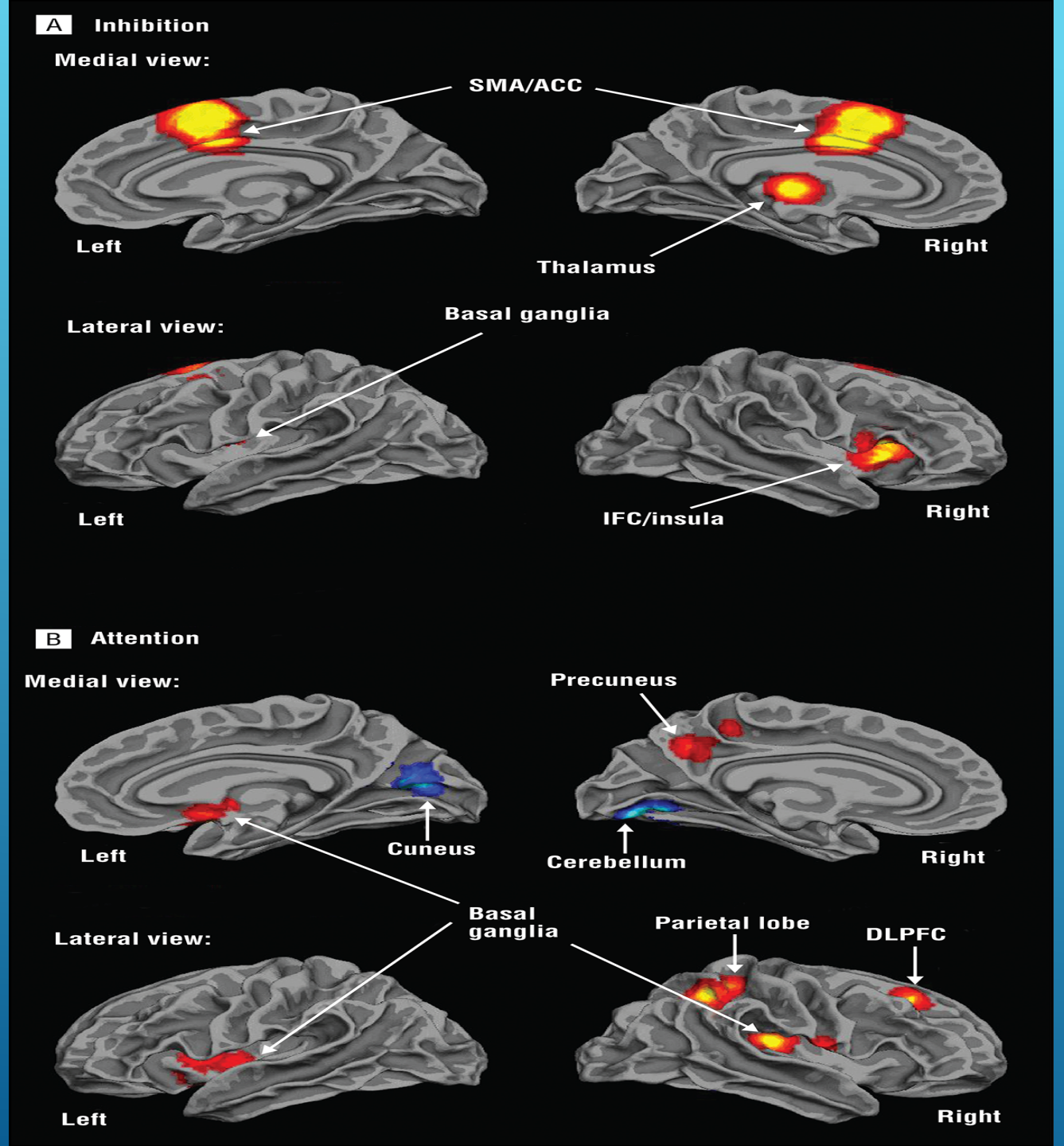
Increased activation(blue) in patients was seen

- in the left cuneus

- and in the right cerebellum

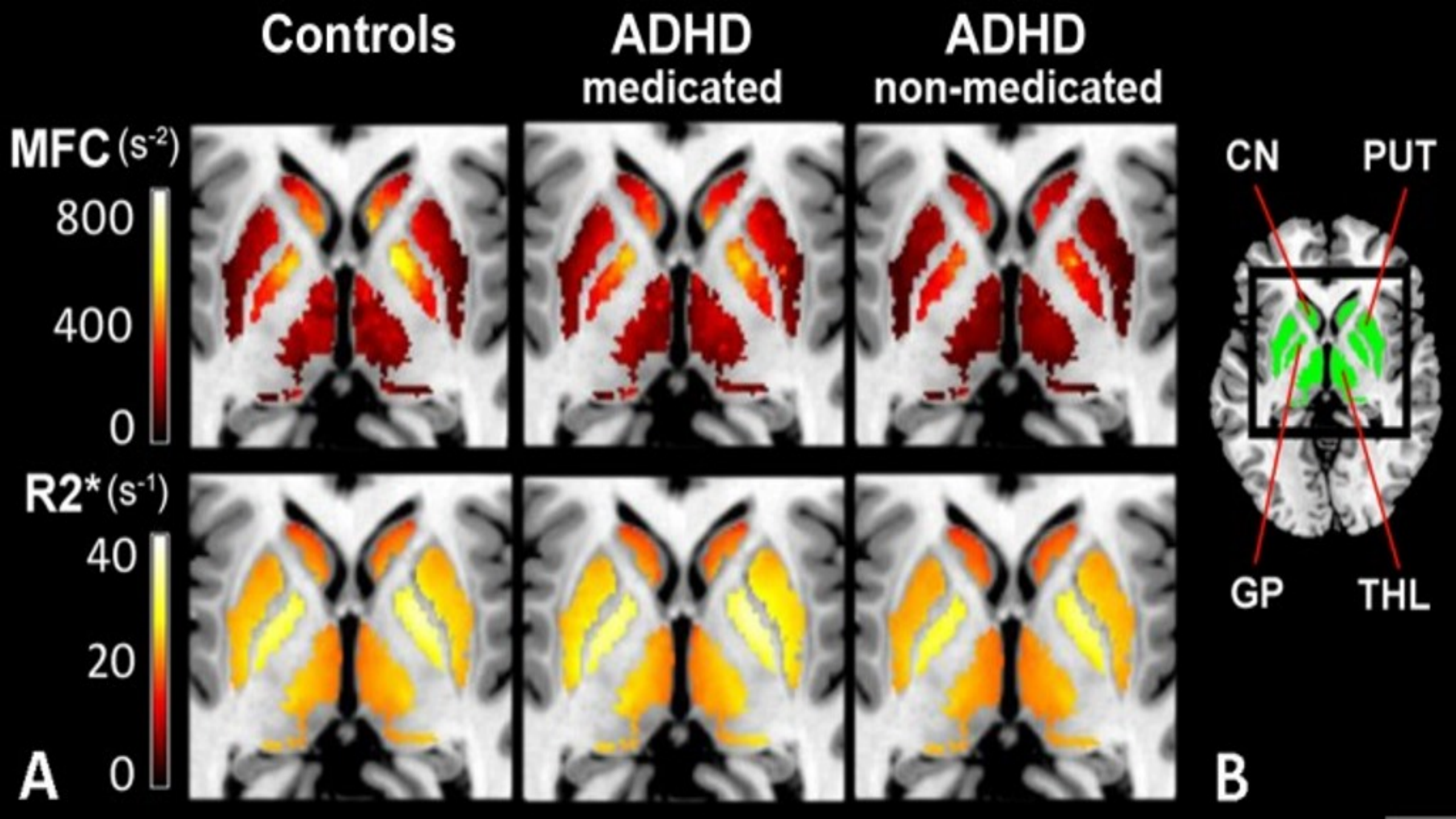
Hart et al. JAMA Psychiatry. 2013;70(2):185-198. Published online December 17, 2012. doi:10.1001/jamapsychiatry.2013.277


B Attention
Medial view:
Precuneus
Cuneus
Left
Cerebellum
Right
Basal ganglia
Lateral view:
Parietal lobe
DLPFC
Left
Right


A Inhibition
Medial view:
SMA/ACC
Left
Thalamus
Right
Lateral view:
Basal ganglia
Left
IFC/insula
Right
B Attention
Medial view:
Precuneus
Left
Cuneus
Cerebellum
Right
Basal ganglia
Lateral view:
Parietal lobe
DLPFC
Left
Right

Multimodal MR imaging indexes of brain iron consisting of conventional water proton relaxation rates and the recently developed magnetic field correlation (MFC) metric were used to examine brain iron levels in medication-naive and psychostimulant-medicated children and adolescents with ADHD and in typically developing control subjects.

Adisetiyo, V. et al. Radiology. August 2014; 272(2): 524–532.
Published online 2014 May 30. doi: 10.1148/radiol.14140047


Controls
ADHD
medicated
ADHD
non-medicated
MFC (s-2)
800
400
0
R2* (s-1)
40
20
0
A
CN
PUT
GP
THL
B

Subgroup averages of MFC and R2*. A, MFC and R2* parametric maps for 27 control subjects, 10 ADHD patients with a history of psychostimulant treatment (ADHD-medicated subgroup), and 12 medication-naïve ADHD patients (ADHD-nonmedicated subgroup). Qualitative differences between control subjects and ADHD subgroups are visible only on MFC maps. B, ROIs (green) used to mask parametric maps. CN = caudate nucleus, GP = globus pallidus, PUT = putamen, THL = thalamus.

Adisetiyo, V. et al. Radiology. August 2014; 272(2): 524–532.
Published online 2014 May 30. doi: 10.1148/radiol.14140047

ASSESSMENT

The need for diagnostic clarity

THE DSM-V DIAGNOSTIC CRITERIA

What symptoms must a person have for a diagnosis of ADHD?

In making the diagnosis, children still should have six or more symptoms of the disorder.

In people 17 and older the DSM-5 states they should have at least five symptoms.

INATTENTIVE TYPE

Fails to give close attention to details or makes careless mistakes

Has difficulty sustaining attention

Does not appear to listen

Struggles to follow through on instructions

Has difficulty with organization

Avoids or dislikes tasks requiring a lot of thinking

Loses things

Is easily distracted

Is forgetful in daily activities

HYPERACTIVE TYPE

Fidgets with hands or feet or squirms in chair

Has difficulty remaining seated

Runs about or climbs excessively in children; extreme restlessness in adults

Difficulty engaging in activities quietly

Acts as if driven by a motor; adults will often feel inside like they were driven by a motor

Talks excessively

Blurts out answers before questions have been completed

Difficulty waiting or taking turns

MEDICAL HISTORY

Any complications during your mother's pregnancy or during your birth that caused any injury?

Developmental delays, such as problems learning to walk, poor coordination, late starting to speak, language acquisition problems, speech articulation problems, or other delays?

Any history of specific learning problems or disorders, such as dyslexia or other reading problems?

MEDICAL HISTORY

Have you ever experienced trauma of any kind:
- such as emotional abuse
- witnessed violence or abuse in the home
- suffered physical battering or abuse
- suffered sexual molestation, harassment, or assault

Have you ever been knocked unconscious, suffered a concussion, or had brain trauma of any kind?

Have you ever experienced an episode of unexplained loss of consciousness?

MEDICAL HISTORY

Have you ever had a seizure, even as child with a high fever (pediatric febrile seizure)?

Have you ever had a prolonged high fever of 103 degrees or higher that did not respond to medication or other treatments to bring it down?

Have you ever had an infectious illness that may have affected your nervous system? (spinal meningitis or herpetic encephalopathy)?

Do you have any form of chronic, ongoing illness mild to severe, medically treated or not?

Do you take non-prescription medications or supplements?

MEDICAL HISTORY

Is there any family genetic history for:
- major psychiatric illness
- addictive behaviors or compulsive behaviors with an addictive component, such as alcoholism, pathological gambling, anorexia nervosa, or pathological substance abuse

Is there any genetic family history of cardiac abnormalities:
- cardiac valve problems
- death at a young age due to heart attack
- cardiac arrhythmias?

THINGS THAT LOOK LIKE ADHD !

Anxiety

Depression

Bipolar

Borderline Personality Disorder

Autistic disorders

Sleep Disturbance

Nighttime variant Asthma

Substance Abuse

TOURETTE'S SYNDROME TRIAD

Tourette's syndrome is now viewed as a neuropsychiatric spectrum disorder in which tics are commonly associated with obsessive–compulsive symptoms that do not always meet the full diagnostic criteria for obsessive–compulsive disorder (OCD) and with disturbances of attention that do not always meet the full criteria for attention deficit–hyperactivity disorder (ADHD).

The combination of tics, OCD, and ADHD is often called "the Tourette's syndrome triad."

Children tend to suppress tics(sometimes subconsciously), and this can be missed during an evaluation.

This is important to remember because stimulant medications can exacerbate tics.

If you diagnose substance abuse, screen for ADHD

Prevalence of attention-deficit hyperactivity disorder in substance use disorder patients: A meta-analysis and meta-regression analysis

After assessing the quality of the retrieved studies, 29 studies were selected.

ADHD is present in almost one out of every four patients with SUD.

K Oortmerssen et al, Prevalence of attention-deficit hyperactivity disorder in substance use disorder patients: A meta-analysis and meta-regression analysis. Drug and Alcohol Dependence Volume 122, Issues 1–2, 1 April 2012, Pages 11-19

ADHD & SUBSTANCE ABUSE DISORDERS

THE BIG CONTROVERSY

Is it enabling or is it good treatment?

The present naturalistic study consisted of a long-term follow-up of 60 male patients with ADHD and comorbid severe SUD.
All participants had received compulsory inpatient treatment due to severe substance abuse.
Thirty patients had received pharmacological treatment for ADHD, and 30 patients were pharmacologically untreated.
The group that received pharmacological treatment for ADHD exhibited fewer substance abuse relapses, received more frequently voluntary treatments in accordance with a rehabilitation plan, required less frequent compulsory care, were more frequently accommodated in supportive housing or a rehabilitation center, and displayed a higher employment rate than the non-treated group.

Muld et al. Long-Term Outcomes of Pharmacologically Treated Versus Non-TreatedAdults with ADHD and Substance Use Disorder: A Naturalistic Study. Journal of Substance Abuse Treatment 51 (2015) 82-90

TEST INSTRUMENTS

ADHD Comprehensive Teacher's Rating Scale (ACTeRS): Boys' and girls' form
- Attention problems, hyperactivity, lack of social skills, oppositional

ADHD Rating Scale
- Symptoms of ADHD according to DSM-IV criteria

Childhood Attention Problems Scale
- Combined measure of attention problems, impulsivity, hyperactivity

Conners 3rd Edition: Short version
- Selected items from the long version to measure inattention, hyperactivity/impulsivity, learning problems, executive function, aggression, and peer relations

BASC Monitor Rating Scale
- Attention/adaptive problems, hyperactivity, problems with internalizing

Vanderbilt Assessment Scales
- Symptoms of ADHD according to DSM-IV criteria; screen for comorbid conditions (ODD, CD, anxiety, depression)

TOVA

Test of Variables of Attention

Custom-designed hardware precisely measures reaction times (±1 ms)

Language and culture-free testing (with 8 different test instruction languages)

Extensively normed by gender for ages 4 to 80+

Embedded Performance Validity to flag unusual performance

Immediately available, easy-to-read report

Home and School Success Strategies available for treatment options

Any personnel can be trained to administer the test

Sufficiently long to measure vigilance

Shorter test for young children

CONNERS CONTINUOUS PERFORMANCE TEST

- A task-oriented computerized assessment of attention-related problems in individuals aged 8 years and older.

- By indexing the respondent's performance in areas of inattentiveness, impulsivity, sustained attention, and vigilance, the Conners CPT 3 can be useful to the process of diagnosing Attention-Deficit/Hyperactive Disorder (ADHD) and other neurological conditions related to attention.

CONNERS CONTINUOUS PERFORMANCE TEST

- Administration time 15 minutes

  1 minute practice test, 14 minute test time

- Device: a lap top computer

  Subjects use space bar or mouse to respond

Conners' Adult ADHD Rating Scales – Self-Report: Long Version (66 Questions)

C. Keith Conners, Ph.D., Drew Erhardt, Ph.D., Elizabeth Sparrow, Ph.D.

NORMATIVE DATA

Consists of 1,026 nonclinical adults, while the normative data for the observer forms consist of ratings by spouses, family members, or friends of 943 nonclinical adults.

RELIABILITY

High coefficients across the various normative groups

VALIDITY

The scale structure of the CAARS is appropriate and makes sense both empirically and theoretically.

The CAARS discriminates between relevant groups.

The CAARS correlates with the measures believed to measure related constructs.

TREATMENT

The American Academy of Pediatrics (AAP) clinical practice guidelines

For preschool-aged children (4–5 years of age)

Prescribe evidence-based parent- and/or teacher-administered behavior therapy as the first line of treatment

Prescribe methylphenidate if the behavior therapy does not provide significant improvement and the child continues to have moderate to severe symptoms.

The American Academy of Pediatrics (AAP) clinical practice guidelines

Elementary school–aged children (6–11 years of age)

Prescribe FDA approved medications for ADHD and/or evidence-based parent and/or teacher-administered behavior therapy as treatment for ADHD, although preferably both medication and behavior therapy should be used together

The evidence is particularly strong for stimulant medications

The American Academy of Pediatrics (AAP) clinical practice guidelines

Adolescents (12–18 years of age)

Prescribe FDA approved medications for ADHD with the assent of the adolescent

And may prescribe behavior therapy as treatment for ADHD, although preferably both medication and behavior therapy should be used together.

MEDICATIONS

Why Do We Need Treatment Alternatives to Stimulants?

- Stimulants do not exhibit substantial efficacy across all aspects of the disorder
- 25% to 35% of patients do not receive a therapeutic benefit from stimulants because of inadequate symptom relief, intolerable side effects, or nonadherence
- Stimulants are more prone to abuse and diversion

Wilens TE, Spencer TJ. The stimulants revisited. Child Adolesc Psychiatr Clin N Am. 2000;9:573603

ALPHA 2 ADRENERGIC AGONISTS

GUANFACINE AND CLONIDINE

- alternatives to stimulants based on their ability to modulate noradrenergic tone in the PFC
- This modulation is a consequence of both enhanced noradrenergic input from the locus coeruleus and direct postsynaptic stimulation of alpha 2A receptors

Arnsten AF, Scahill L, Findling RL. Alpha2 adrenergic receptor agonists for the treatment of attention deficit/hyperactivity disorder: emerging concepts from new data. J Child Adolesc Psychopharmacol. 2007;17:393406.

BUPROPION

- an antidepressant with mixed catecholaminergic effects

- A meta-analysis of five randomized trials found bupropion led to a higher response rate and a greater reduction in inattentive and overall ADHD symptoms

- advantages of bupropion include the lack of abuse liability, single daily dosing, and efficacy for co-occurring anxiety and depression

- **Bupropion may increase the risk of seizure**

Maneeton N, Maneeton B, Srisurapanont M, Martin SD. Bupropion for adults with attention-deficit hyperactivity disorder: meta-analysis of randomized, placebo-controlled trials. Psychiatry Clin Neurosci 2011; 65:611.

ATOMOXETINE

- inhibits presynaptic norepinephrine reuptake, resulting in increased synaptic norepinephrine and dopamine
- A meta-analysis of 12 clinical trials comparing atomoxetine with placebo found atomoxetine to be modestly more effective in reducing the core symptoms
- The most common side effects are dry mouth, insomnia, nausea, decreased appetite, constipation, decreased libido, erectile dysfunction, urinary hesitancy, dizziness, and sweating
- can produce QTc prolongation
- should be used with caution in patients with cardiovascular risk factors

Michelson D, Adler L, Spencer T, et al. Atomoxetine in adults with ADHD: two randomized, placebo-controlled studies. Biol Psychiatry 2003; 53:112.

MODAFINIL

ADULTS ONLY

Binds to dopamine transporter, inhibiting dopamine reuptake

In controlled trials, modafinil appeared to improve the core symptoms of ADHD compared with placebo

However, it was associated with serious dermatologic and psychiatric reactions (Stevens Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms, anxiety, mania, hallucinations, and suicidal ideation)

Kevin Krull, Ph.D.; Pharmacology of drugs used to treat attention deficit hyperactivity disorder in children and adolescents; UpToDate

STIMULANTS

METHYLPHENIDATE

- is a pure re-uptake inhibitor of catecholamines, especially dopamine

AMPHETAMINE

- is a re-uptake inhibitor of catecholamines AND also releases catecholamines

Journal of Attention Disorders Vol. 3(4):200-211 (2000)

STIMULANTS

ADVANTAGES OF METHYLPHENIDATE

- Better CPT response
- Better with comorbid Tourette's
- Better with visuo-motor disorder
- Possibly better with comorbid Learning Disorder
- Less anorexia, less weight loss
- Less sleep delay

Journal of Attention Disorders Vol. 3(4):200-211 (2000)

STIMULANTS

ADVANTAGES OF AMPHETAMINE

- More consistent response day-to-day
- Higher proportion of patients with good/excellent response
- Better with comorbid Conduct Disorder/Oppositional Defiant Disorder
- Less depression/apathy
- Fewer stomachaches
- May be better with high IQ

Journal of Attention Disorders Vol. 3(4):200-211 (2000)

METHYLPHENIDATE

- Effectively reduces symptoms of inattention, hyperactivity, and impulsivity in up to 80% of children with ADHD
- Increases extracellular dopamine (DA) levels in the brain by blocking the DA transporters in the synapse
- Safety investigations on the effects of methylphenidate on DA function in the developing brain are scarce in children
- Regardless of this alarming paucity of findings, increasingly greater numbers of children and young adolescents are exposed to methylphenidate, many of whom likely do not meet the criteria for ADHD

Schrantee, A. et al. JAMA Psychiatry September 2016 Volume 73, Number 9

METHYLPHENIDATE

- In children it may cause neurochemical imprinting
- Methylphenidate treatment induces persistent increases in the CBF response to an acute challenge with methylphenidate in children
- Methylphenidate treatment during a specific period of maturation alters the CBF response, likely reflecting increased DA neurotransmission due to neurochemical imprinting by methylphenidate
- 6 years after enrollment, medication management was associated with a transient increase in the prevalence of anxiety and depression

Schrantee, A. et al. JAMA Psychiatry September 2016 Volume 73, Number 9