ADHD: Attention-Deficit/Hyperactivity Disorder

Core symptoms:

- Attention Deficit
- Hyperactivity
- Impulsivity

Der Struvwelpeter 1845

Heinrich Hoffman

History

- Early descriptions by Melchior Weikard and Alexander Crichton in the 18’th century.
- George F. Still: ”defects of moral control” 1902.
- MBD: Minimal Brain Damage, Minimal Brain Dysfunction. Perception, conceptualisation, language, memory, attention, impulse control, motor function. Diffuse criteria, overinclusive.
- Knobloch & Pasamanick: ”the continuum of reproductive casualty” 1956. Regarded as consequences of birth injuries, especially asphyxia.

Hyperactivity

- Chess and others 1960.
- Hyperkinesis

Attention Deficit

- Virginia Douglas 1972. Attention deficit as the core symptom.
- DSM-III: ADD with hyperactivity and ADD without hyperactivity.

DAMP: Deficit in Attention Motor control and Perception, according to C. Gillberg and I.C. Gillberg

- Problems with attention, impulses control and motor activity
- Motor dysfunction
- Perceptual problems

ADHD

- ADHD first defined in DSM-III-R 1987. Different definition from DSM-IV and DSM-5. ADHD without hyperactivity possible.
- ADHD according to DSM-IV 1994, resembles the current definition in DSM-5.
- Hyperkinetic Disorder (HKD): ICD-10. More severe combined form according to the definition. Six symptoms of inattention in combination with 3 of 5 symptoms of hyperactivity and 1 of 4 symptoms of impulsivity (often talks excessively counted as impulsivity).

ADHD according to DSM-5.

A. Persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development, as characterized by 1 and/or 2:

1. Inattention: Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:

Note: The symptoms are not solely a manifestation of oppositional behavior, defiance, hostility, or failure to understand tasks or instructions. For older adolescents and adults (age 17 and older), at least five symptoms are required.

- a. Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or during other activities (e.g., overlooks or missesdetails, work is inaccurate).
- b. Often has difficulties sustaining attention in tasks or play activities (e.g., has difficulties remaining focused during lectures, conversations or lengthy reading).
- c. Often does not seem to listen when spoken to directly (e.g., mind seems elsewhere, even in the abscence of any obvious distraction).
- d. Often doesn not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (e.g., starts tasks but quickly loses focus and is easily sidetracked).
- e. Often has difficulty organizing tasks and activities (e.g., difficulty managing sequential tasks; difficulty keeping materials and belongings in order; messy, disorganized work; has poor time management; fails to meet dedlines).
- f. Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (e.g., schoolwork or homework; for older adolescents and adults, preparing reports, completing forms, reviewing lengthy papers).
- g. Often loses things necessary for tasks or activities (e.g., school materials, pencils, books, tolls, wallets, keys, paperwork, eyeglasses, mobile telephones).
- h. Is often easily distracted by extraneous stimuli (e.g., for older adolescents and adults, may include unrelated thoughts).
- i. Is often forgetful in daily activities (e.g., doing chores, running errands,; for older adolescents and adults, returning calls, paying bills, keeping appointments).

ADHD continued

2. Hyperactivity and impulsivity: Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:

Note: The symptoms are not solely a manifestation of oppositional behavior, defiance, hostility, or a failure to understand tasks or instructions. For older adolescents and adults (age 17 and older), at least five symptoms are required.

- a. Often fidgets with or taps hands or feet or squirms in seat.
- b. Often leaves seat in situations when remaining seated is expected (e.g., leaves his or her place in the classroom, in the office or other workplace, or in other situations that require remaining in place).
- c. Often runs about or climbs in situations where it is inappropriate. (Note: In adolescents or adults, may be limited to feeling resless).
- d. Often unable to play or engage in leisure activities quietly.
- e. Is often ”on the go”, acting as if ”driven by a motor” (e.g., is unable to be or unconfortable being still for extended time, as in restaurants, meetings; may be experienced by others as being restless or difficult to keep up with).
- f. Often talks excessively.
- g. Often blurts out an answer before a question has been completed (e.g., completes people’s sentences; cannot wait for turn in conversation).
- h. Often has difficulty waiting his or her turn (e.g., while waiting in line).
- i. Often interrupts or intrudes on others (e.g., butts into conversations, games or activities; may start using other people’s things without asking or receiving permission; for adolescents and adults, may intrude into or take over what others are doing).

ADHD continued

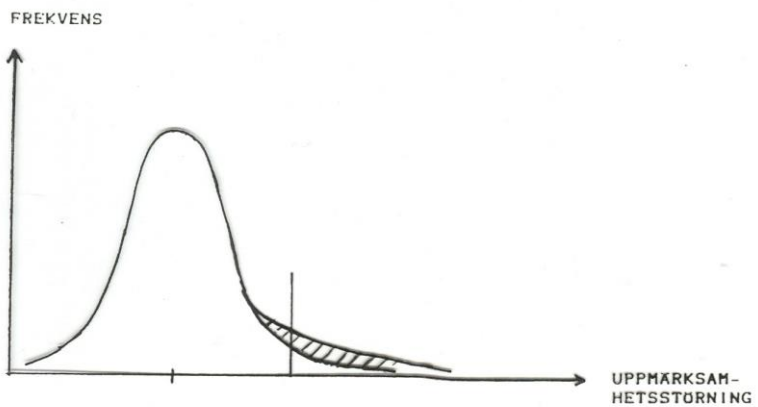
- B. Several inattentive or hyperactive-impulsive symptoms were present prior to age 12 years.
- C. Several inattentive or hyperactive-impulsive symptoms are present in two or more settings (e.g., at home, school, or work; with friends or relatives; in other activities).
- D. There is clear evidence that the symptoms interfere with, or reduce the quality of social, academic, or occupational functioning.
- E. The symptoms do not occur exclusively during the course of schizophrenia or another psychotic disorder and are not better explained by another mental disorder (e.g., mood disorder, anxiety disorder, dissociative disorder, personality disorder, substance intoxication or withdrawal).

ADHD, continued

Specify whether:

- Combined presentation
- Predominantly inattentive presentation
- Predominantly hyperactive/impulsive presentation
- In partial remission
- Severity: mild, moderate, severe


FREKVENS
UPPMÄRKSAM-
HETSSTÖRNING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Criticism

- Unclear limits against normality and other diagnoses. Diffuse phenotype creating difficulties for the genetic research.
- The diagnosis is defined by subjective criteria. Objective methods have poor sensitivity and specificity.
- Heavy increase in number of indiviuals who are diagnosed. Risk of overdiagnosing.
- Differences between countries: many in the United States, few in France and Italy.
- ADHD is a heterogenous condition with multiple causation.

Support for the meaningfulness of the ADHD-diagnosis

- Many individuals have symptoms according to the definition of ADHD. These individuals often have impairments in every-day life and poor prognosis in comparison with individuals without these symptoms and need treatment and support.
- Neuroimage studies show significant differences between individuals with a diagnosis compared with controls without a diagnosis. Gives support for important neurobiological factors underlying the diagnosis.
- Heritability studies show a high heritability for ADHD.

Prevalence

- A broad range of prevalence estimates exist but global metaanalyses show prevalence of 5.29%, 95% CI: 5.01-5.56 (Polanczyk et al. 2007, 2014).
- Differences in estimates due to differences in assessment methods used. Differences if functional impairment is required or not.
- Huge differences in number of individuals clinically diagnosed. Over- and underdiagnosing.

Gender

- Girls are underdiagnosed.
- Earlier estimates: boys/girls: 6/1. Now: boys/girls: 2/1 (higher in clinical samples than in research).
- Adults: men/women: 1/1.
- Girls and women have same problems (same criteria) as boys and men but in a subtler way. Girls shall be compared with girls and not with boys. Girls have better social function and less hyperactivity and physical aggression.

Diagnosis in adulthood

- At least half of children with ADHD continue to fulfill the criteria in adulthood.
- Many adults who no longer fulfill criteria have remaining problems, in partial remission.
- Few good longitudinal studies but estimates of about 20% no longer having any symptoms or problems.
- Existence of an adult variant resembling ADHD but with adult onset? (Moffit et al. 2015)

ADHD is a heterogenous condition

Multiple ethiological factors:

- High heritability: 75-80%. Probably several hundreds of relevant genes. Power problems in research. Candidate genes: genes involved in synaptic formation, lignins and receptors for neurotransmittors: e.g. DRD-4-7 repeat. FOSp2?
- Chromosomal abnormalities: 22 q 11, Fragile-X
- Pre- and perinatal factors, prematurity, IUGR.
- Brain damage: asphyxia, encephalitis.
- Alcohol consumption in pregnancy. Smoking?
- Attachment disorder, extreme deprivation.

Positive sides of ADHD

- Fantasy and creativity.
- Spontaneity
- High level of activity. Can do much work if it is interesting and stimulating
- Seeking adventure. Dares to do things others would not.

The nature of ADHD symptoms

- A syndrome of boredom.
- Dimensional and not categorical, cf. hypertension or short stature contra diabetes or tuberculosis.
- Is not always obvious, like when the person does something very interesting and rewarding.
- Sometimes it looks like a lack of willpower, but this not true.

The theory of executive functions

- Difficulties with working memory.
- Difficulties with affect regulation.
- Difficulties with planning and organising.
- Difficulties with alertness, arousal and energy.
- Difficulties keeping focus.
- Executive functions in every-day situations, ecological validity (Barkley, Brown)

Control functions

- The frontal lobes and its connections are important for self control.
- Cerebral control functions are late to develop. Diagnosis is usually not recommended before 5 years of age.
- Children with ADHD resembles younger children. Maturational lag.
- Control functions fuctions less well when a person is tired, stressed, anxious or has taken alcohol or drugs.

Different kinds of ADHD

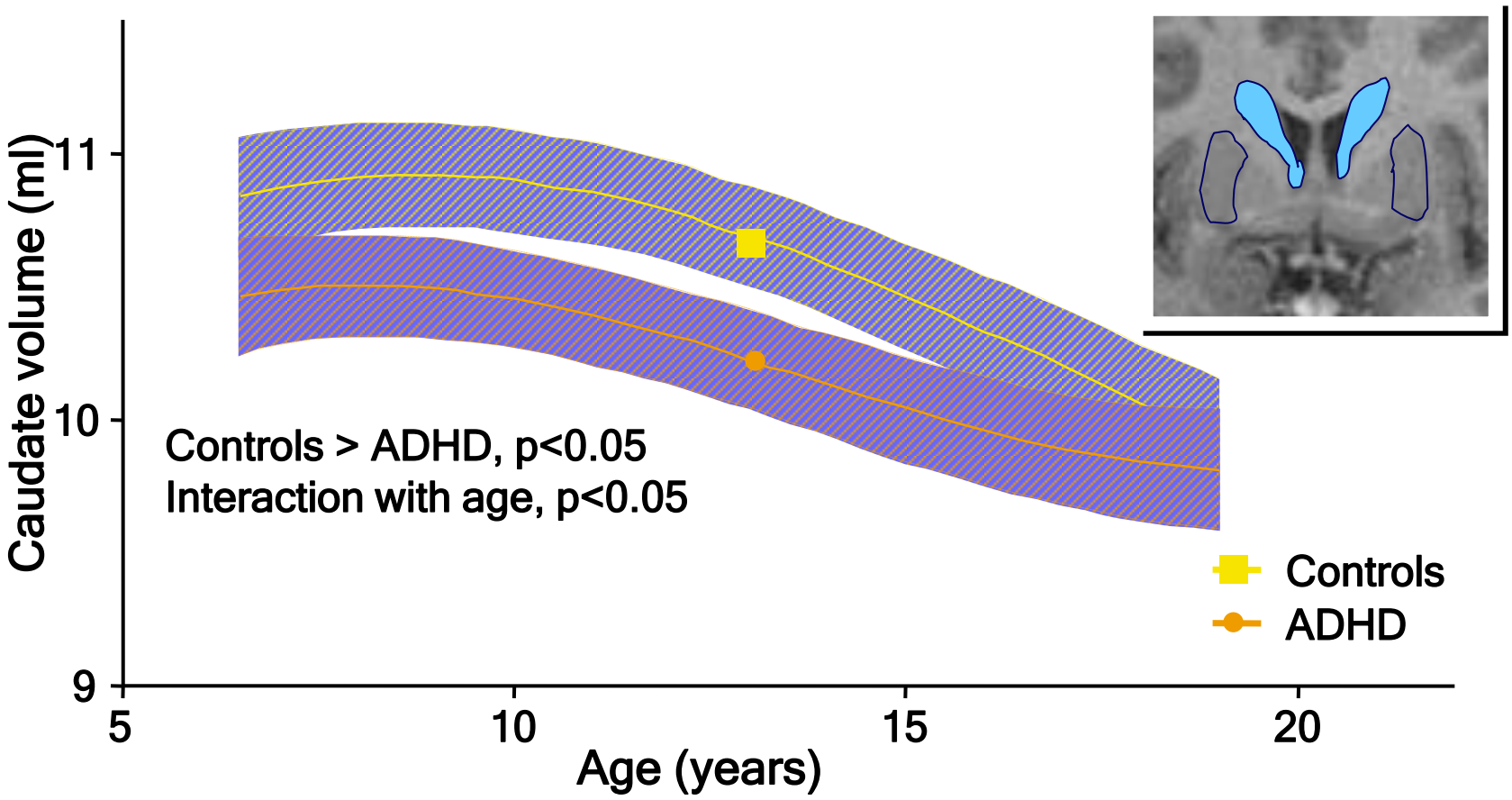
- Sluggish cognitive tempo according to Barkely: Individual who are slow in cognitive tempo, daydreaming often anxious. Control for somatic conditions: hypothyreosis, iron-deficiency, neurodegenerative disorders, et cetera.
- ADD: Often some degree of hyperactivity/impulsivity at som age. Hyperactivity often diminish with age.
- Problems with motor function (Developmental Coordination Disorder: DCD) and/or perception among almost half of individuals with ADHD (Deficits in Attention Motor control and Perception: DAMP). More cognitive problems and autistic symptoms in this group.

Theories concerning the brain function in ADHD

- *Delay aversion*: Difficulties waiting for reward. The brain stem, connections between the limbic system and the frontal lobes. Reward areas (nc accumbens).
- *Executive funktions*: Working memory regultion and activation. Gyrus cinguli, frontal lobes, basal ganglia.
- *Timing*. Time sequences in behaviour and motor functions. Cerebellum, basal ganglia, motor cortex, coordination left-right: corpus callosum
- Difficulties for the brain to change from resting state to activation, difficulties to abandon the ”default mode”
- Immature brain, longer time for cortical maturation.

AETIOLOGY

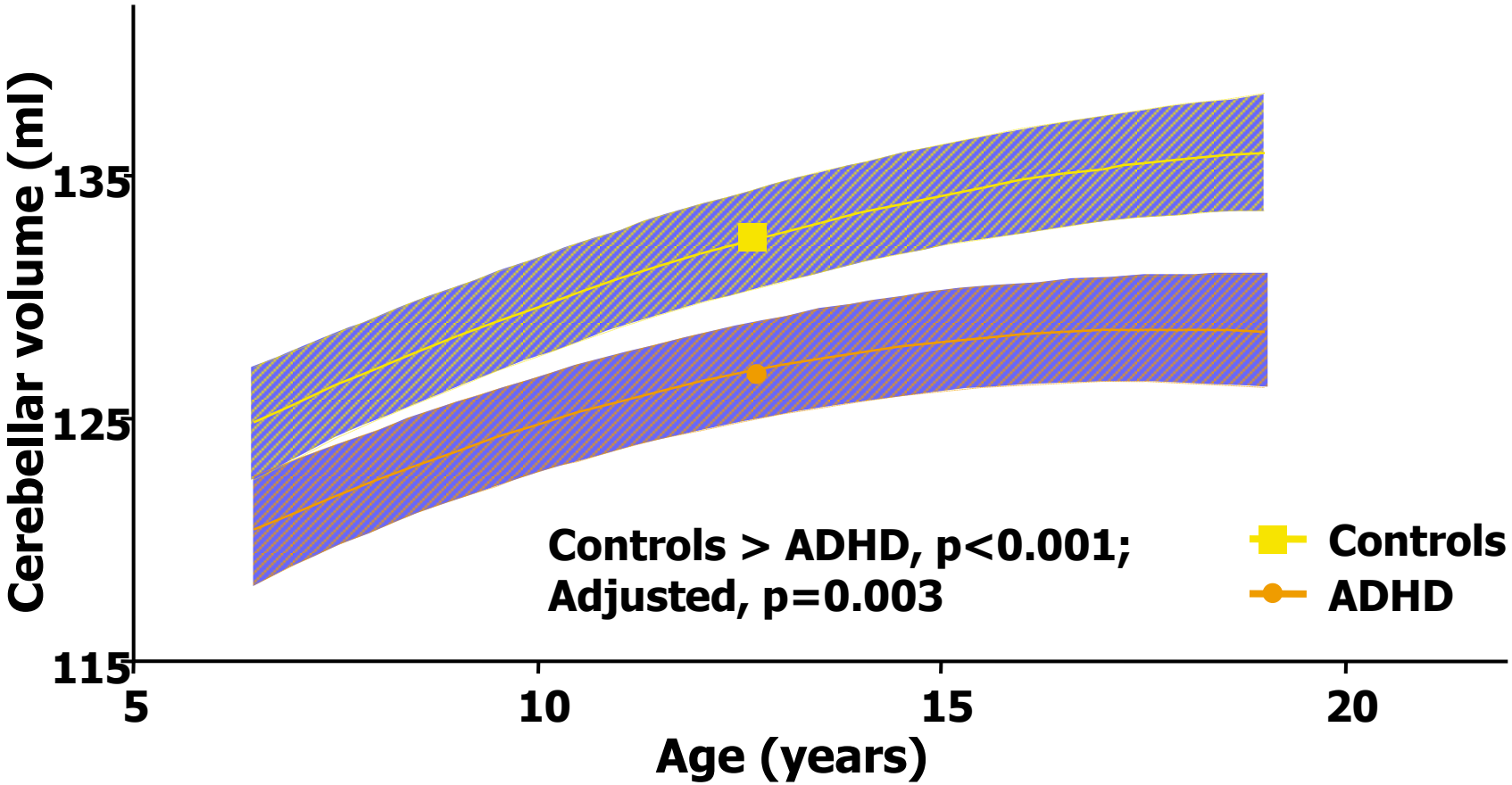
Neuroanatomy – caudate volume



Castellanos *et al* 2002

AETIOLOGY

Neuroanatomy – cerebellar volume



Castellanos *et al* 2002

Cross-sectional studies indicate in the meta-analysis that treatment results in the recovery of structural deficits; however, longitudinal studies are necessary to prove this finding.

Frodl T, Skokauskas N. *Acta Psychiatr Scand 2012: 125: 114–126*

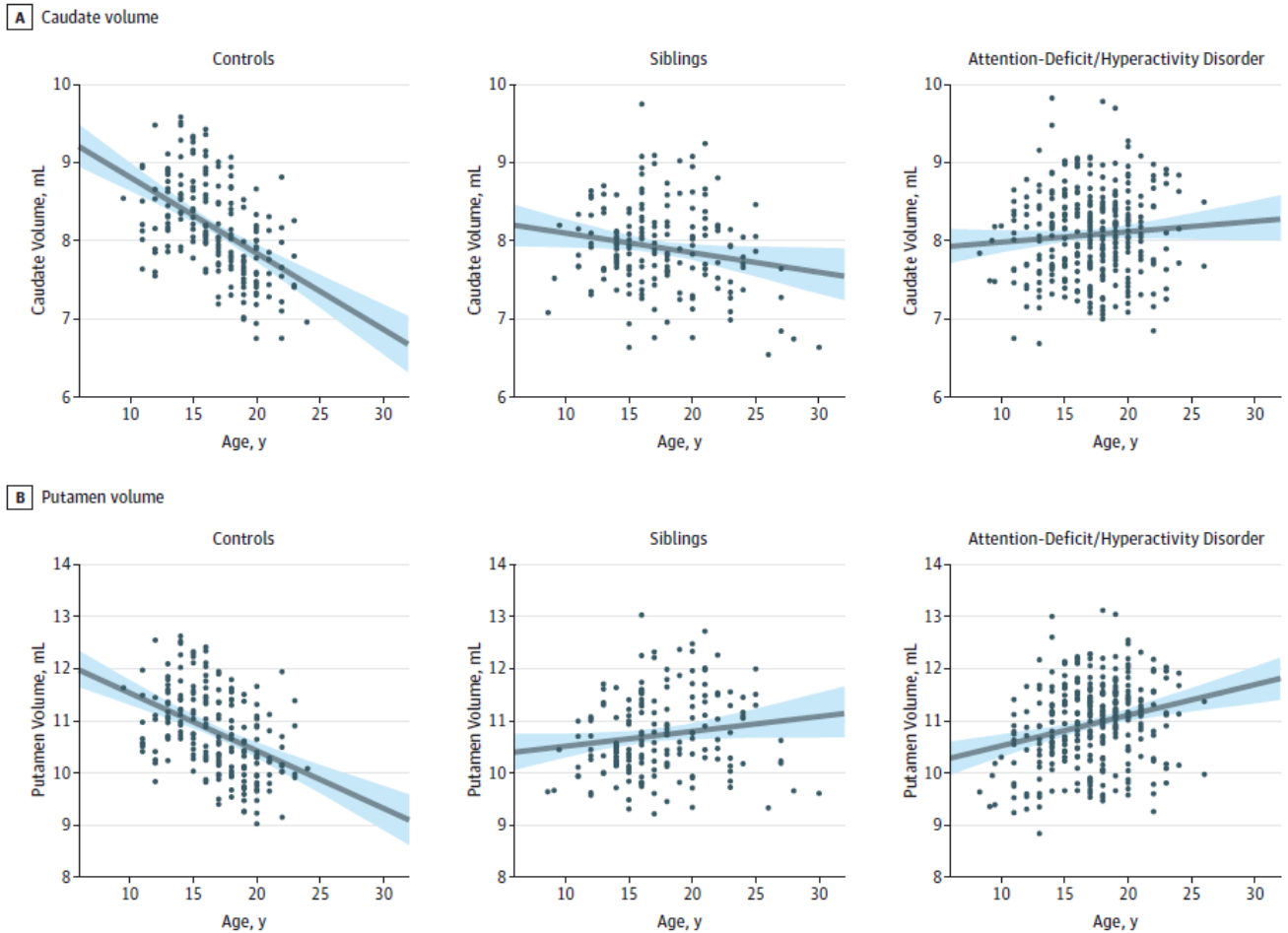
CLINICAL POINTS

1. Stimulant treatment for ADHD is known to be efficacious but concerns about effects on the developing brain remain.

2. Our review of structural and functional neuroimaging studies finds no evidence that stimulant treatment negatively impacts brain development or function. In contrast, these studies suggest that stimulant treatment attenuates the brain abnormalities that have been associated with ADHD.

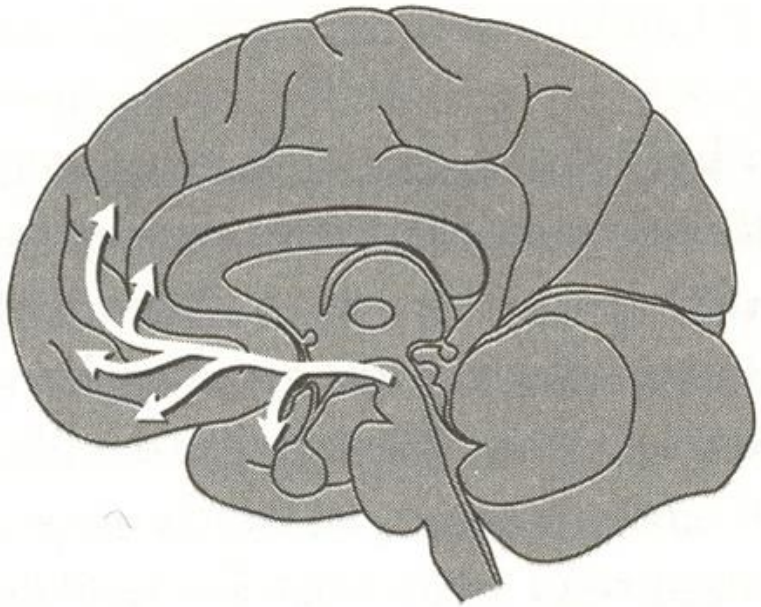
Spencer et al. J Clin Psychiatry. 2013 September ; 74(9): 902–917.

Figure 2. Group-by-Age Interaction on Caudate Nucleus Volume (A) and Putamen Volume (B)



JAMA Psychiatry May 2015 Volume 72, Number 5

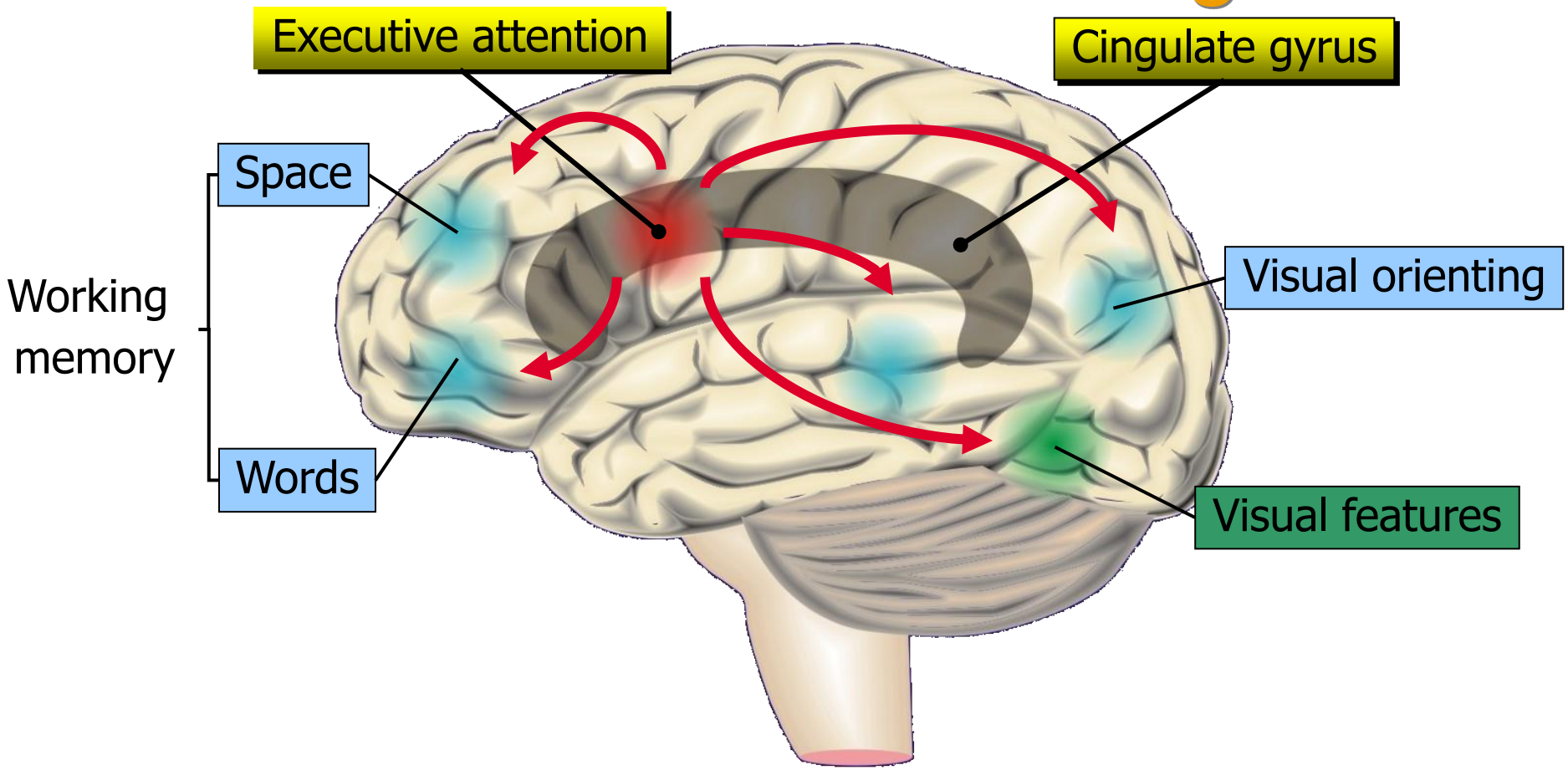
Corina U. Greven, PhD; Janita Bralten, Msc; Maarten Mennes, PhD; Laurence O'Dwyer, PhD; Kimm J. E. van Hulzen, PhD; Nanda Rommelse, PhD; Lizanne J. S. Schweren, MSc; Pieter J. Hoekstra, MD, PhD; Catharina A. Hartman, PhD; Dirk Heslenfeld, PhD; Jaap Oosterlaan, PhD; Stephen V. Faraone, PhD; Barbara Franke, PhD; Marcel P. Zwiers, PhD; Alejandro Arias-Vasquez, PhD; Jan K. Buitelaar, MD, PhD



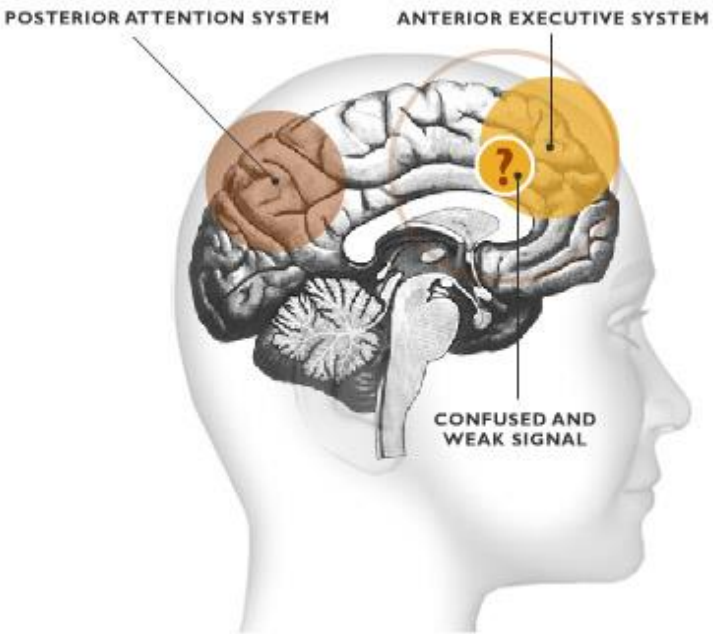
The seeking for pleasure system

AETIOLOGY

Neuropsychology – disturbance of executive functioning



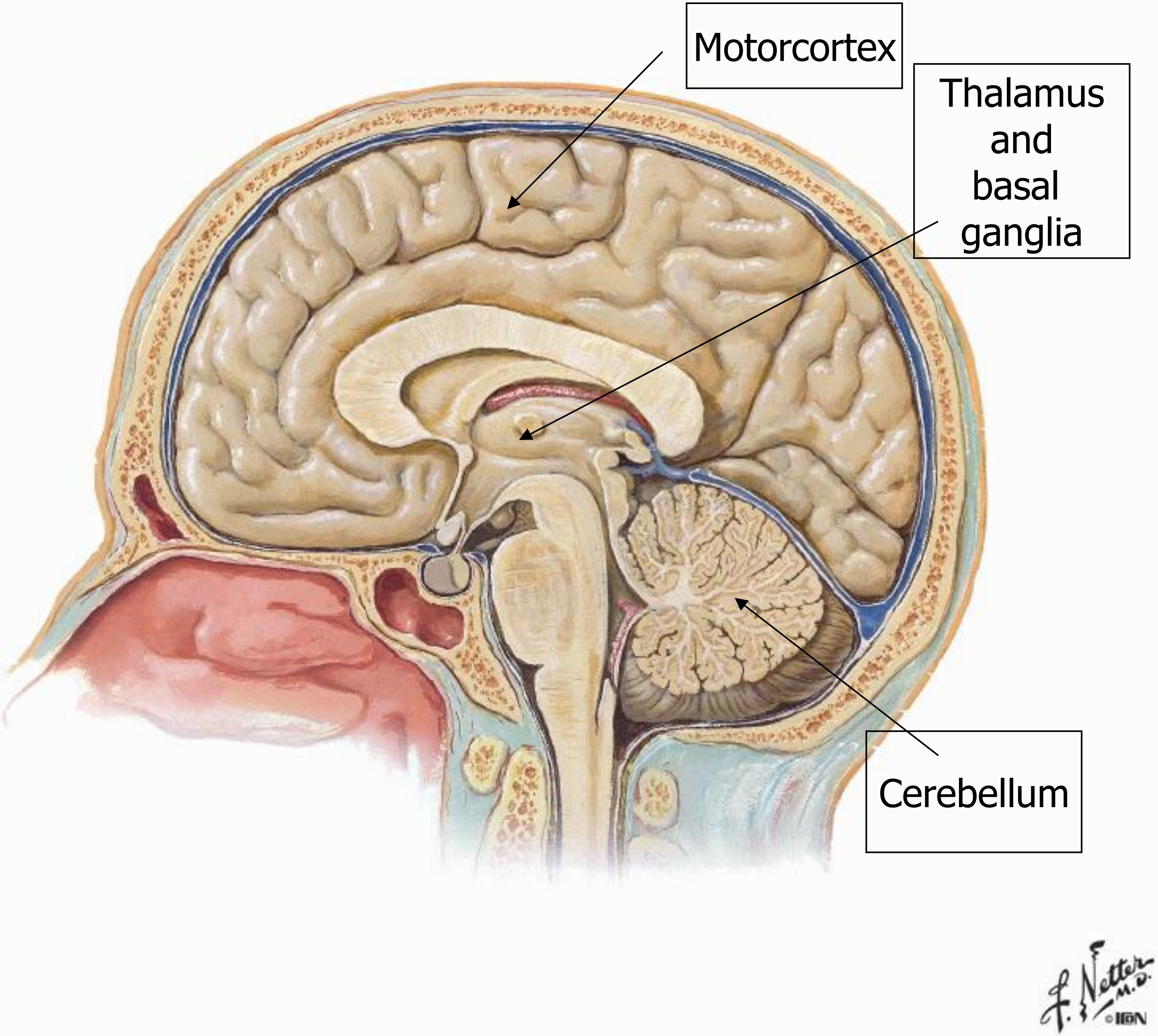
Adapted from Posner & Raichle 1999



CONCEPT ONE

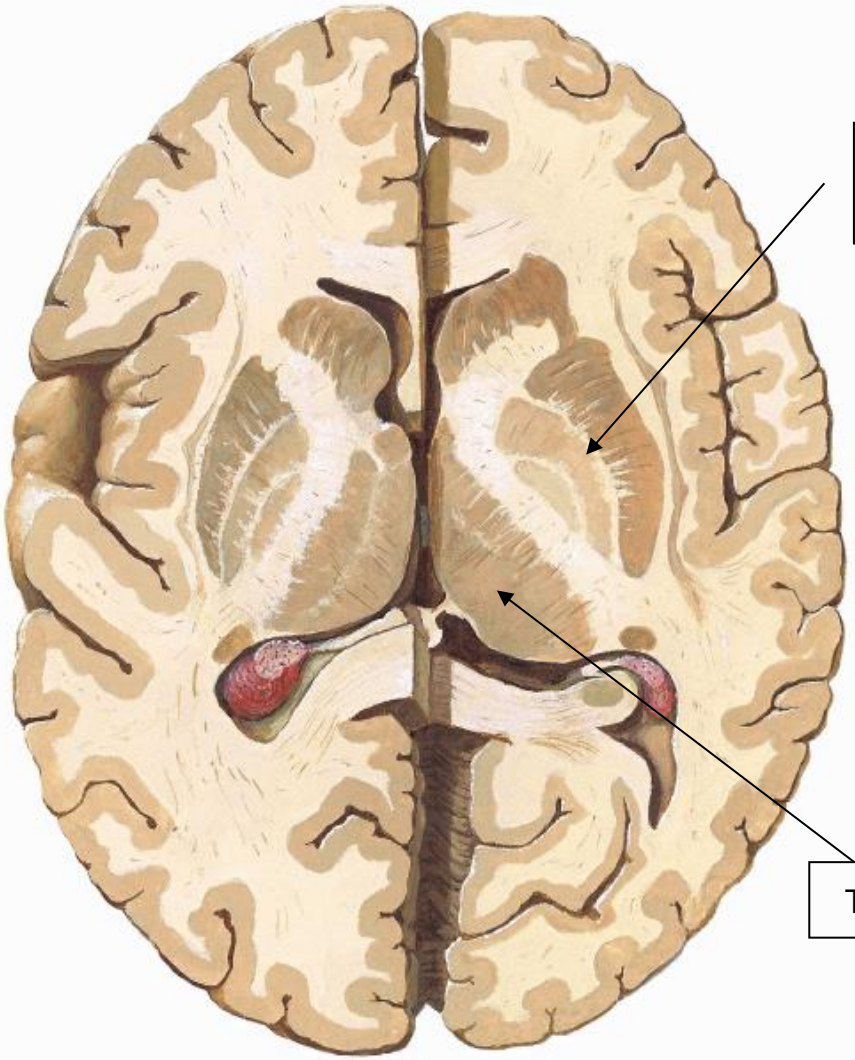
ABNORMALITY IN POSTERIOR AND ANTERIOR CONNECTIONS

Cerebrum - Brain In Situ
Sagittal Section - Medial View



Basal Nuclei (Ganglia)

Horizontal Sections through Cerebrum

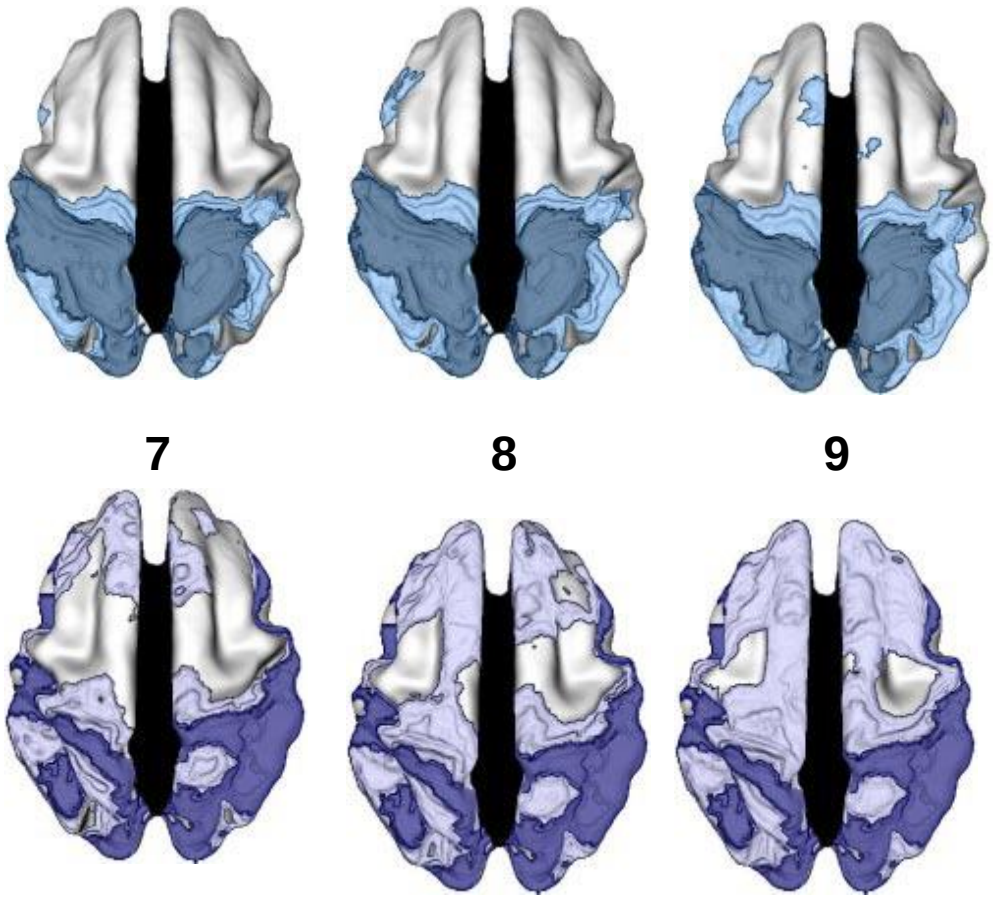


Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation

P. Shaw†‡, K. Eckstrand†, W. Sharp†, J. Blumenthal†, J. P. Lerch § , D. Greenstein†, L. Clasen†, A. Evans § , J. Giedd†, and J. L. Rapoport†

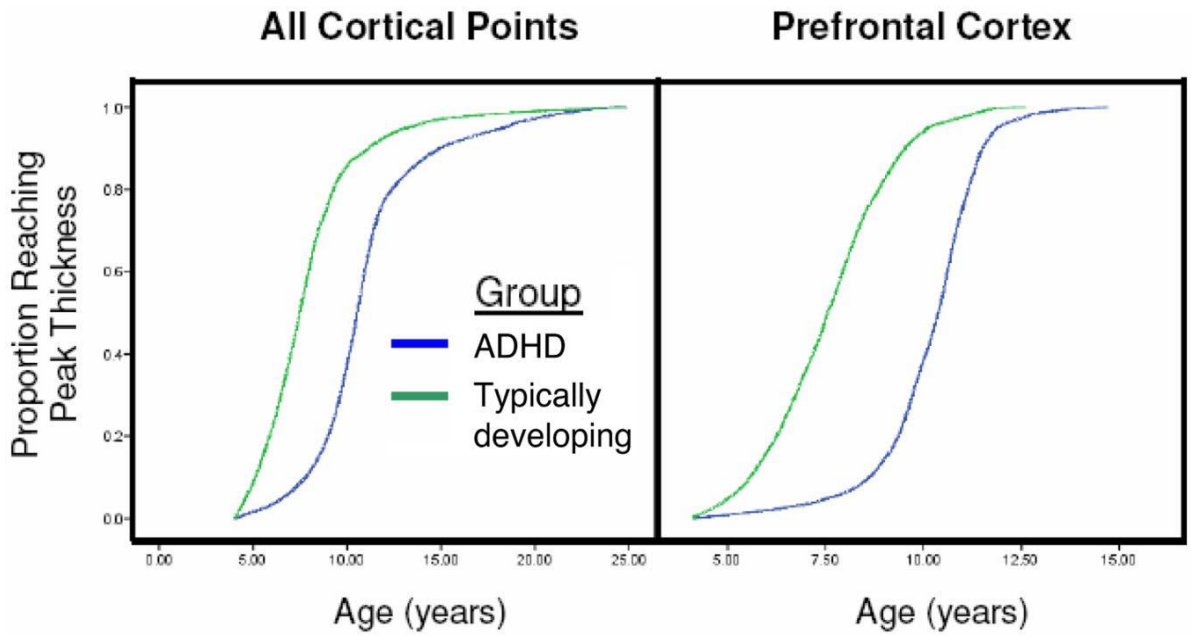
PNAS _ **December 4, 2007** _ vol. 104 _ no. 49 _ **19651**

ADHD

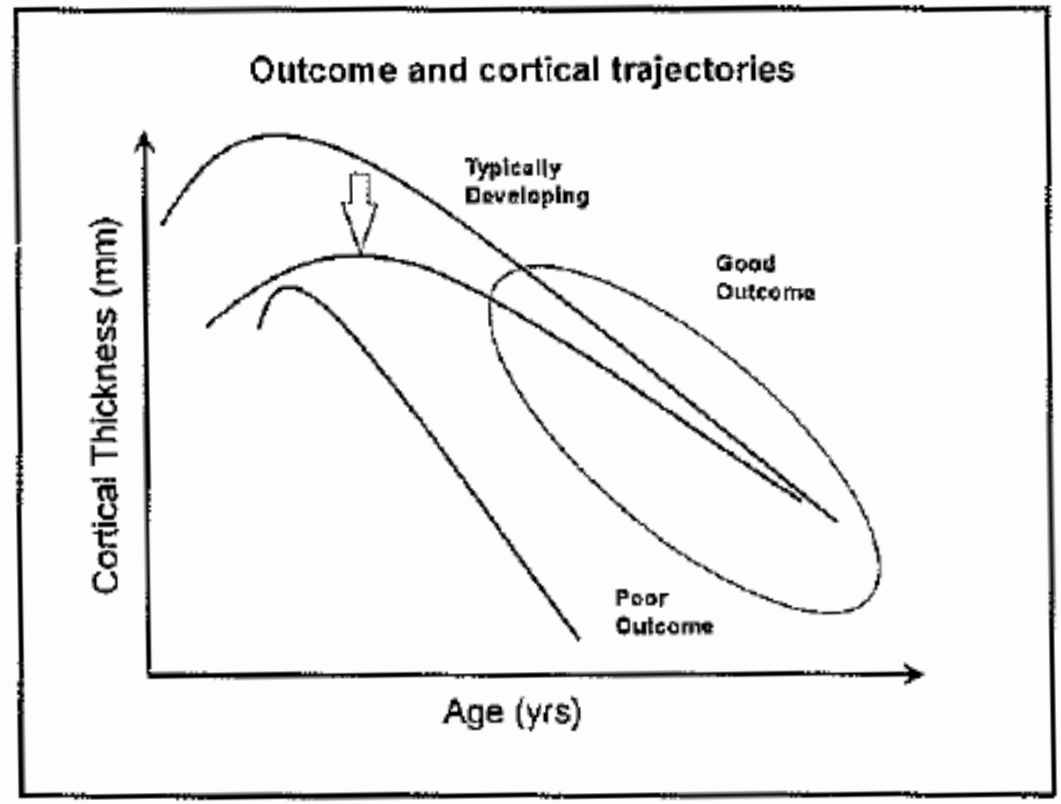


7 **8** **9**

Typically developing controls

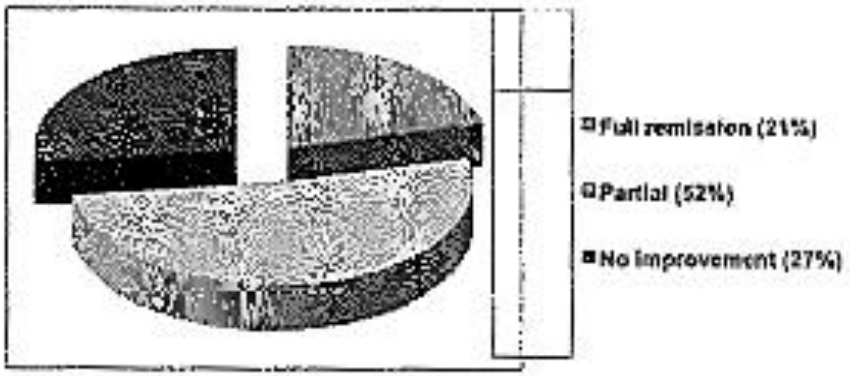


3. Kaplan–Meier curves illustrating the proportion of cortical points that had attained peak thickness at each age for all cerebral cortical points (*Left*) an frontal cortex (*Right*). The median age by which 50% of cortical points had attained their peak differed significantly between the groups (all $P < 1.0 \times 10$


Outcome and cortical trajectories
Typically Developing
Good Outcome
Poor Outcome
Cortical Thickness (mm)
Age (yrs)

Outcome of ADHD

Adolescent outcome in NIH cohort (N=132)



Comorbidity

- The same conditions can constitute differential diagnoses as well as comorbidites.
- Up to 85% of older adolescents and adults with ADHD have at least one comorbid diagnosis.
- Oppositional Defiant Disorder and Conduct Disorder: 30-50% i childhood.
- Intellectual disability
- Learning disablilities: language impairment, dyslexia, dyscalculia.
- Motor and/or perceptual impairment
- Brain damage
- Epilepsy
- Anxiety
- Depression
- Bipolar disease
- Personality disorder: especially antisocial personality disorder and borderline personality disorder.
- Substance abuse
- Eating disorders: Obesity, anorexia

Prognosis

The functional deficits created by ADHD leads to a poorer prognosis compared to individuals without a diagnosis (Spencer, Mick Biederman 2007):

- Lower socio-economic status
- Work difficulties
- Unemployment
- Criminality
- Substance abuse
- Traffic accidents
- Separations and divorces
- Higher mortality
- Comorbid psychiatric disorders
- Somatic disease.

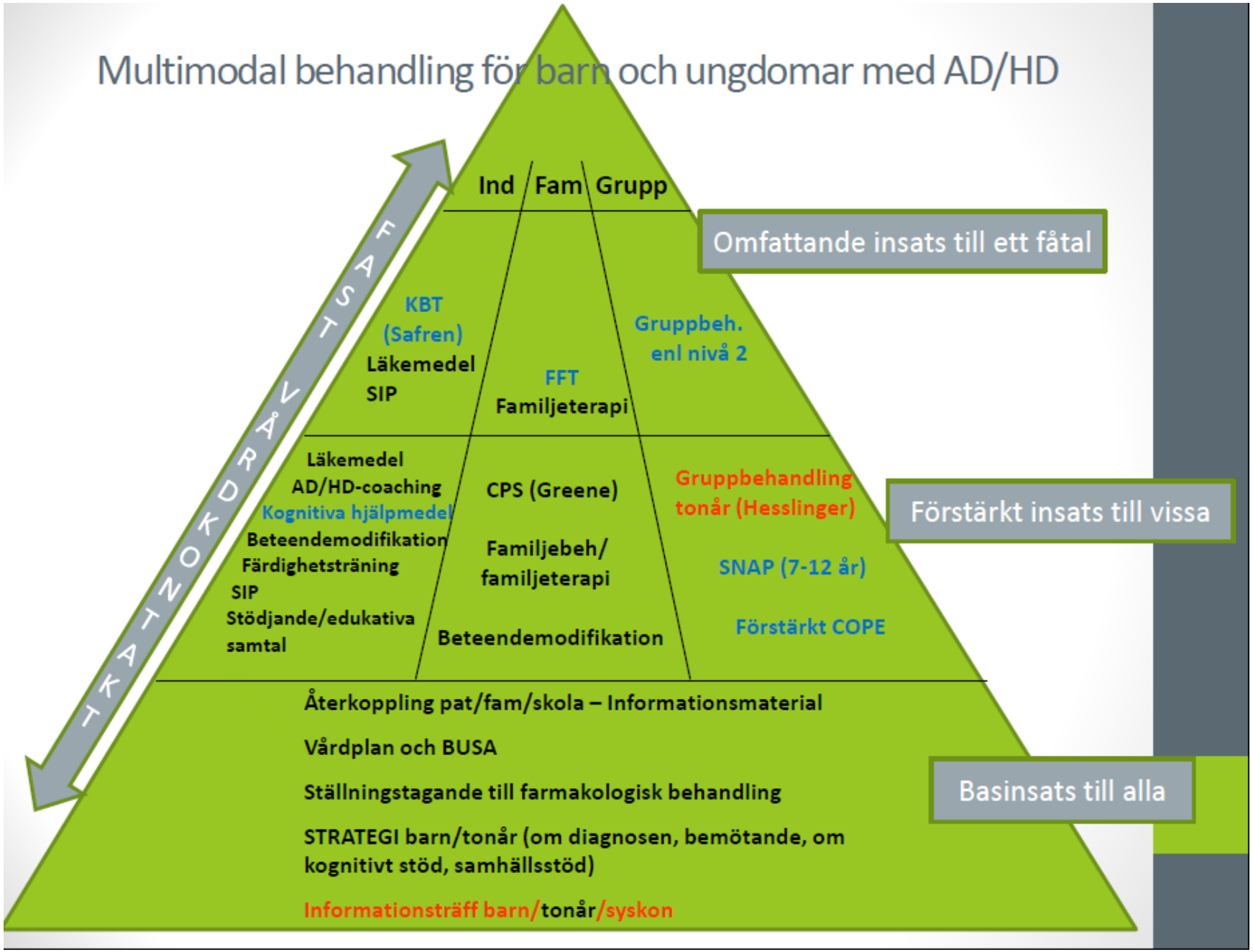
Assessment

- Difficulties diagnosing ADHD in early age. Differential diagnosis with language impairment, intellectual impairment, autism spectrum disorder. ESSENCE: Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations. Several common symptoms and comorbidity.
- Cognitive testing: WPPSI, WISC, WAIS.
- Developmental history by parents, somatic disease, language development, motor development, social development. Behaviour.
- Description from preschool, school, observation at clinic and at school.
- Neurological and somatic examination: soft signs, minor physical anomalies. Lab.tests, EEG.
- Interview with the child (apropriate for age).
- Rating scales: SNAP-IV, ADHD-RS. To parents and teachers.
- Think of differential diagnoses and comorbidity. ADHD-symptoms should be chronic, from an early age, not just in connection with trauma or stress and global and not situational and not better described by another diagnosis.
- Sleep-pattern: Many patients with ADHD have sleep difficulties.
- Warning: cognitive regression may point to a neurological condition. CT, MRI and EEG.
- BRIEF: Behavior Rating Inventory of Executive Function.
- TEA-Ch: Test for Everyday Attention for Children.
- CPT: Continuous Perfomance Test. Different objective computer tests: Conners, IVA, Qb, TOVA et cetera.

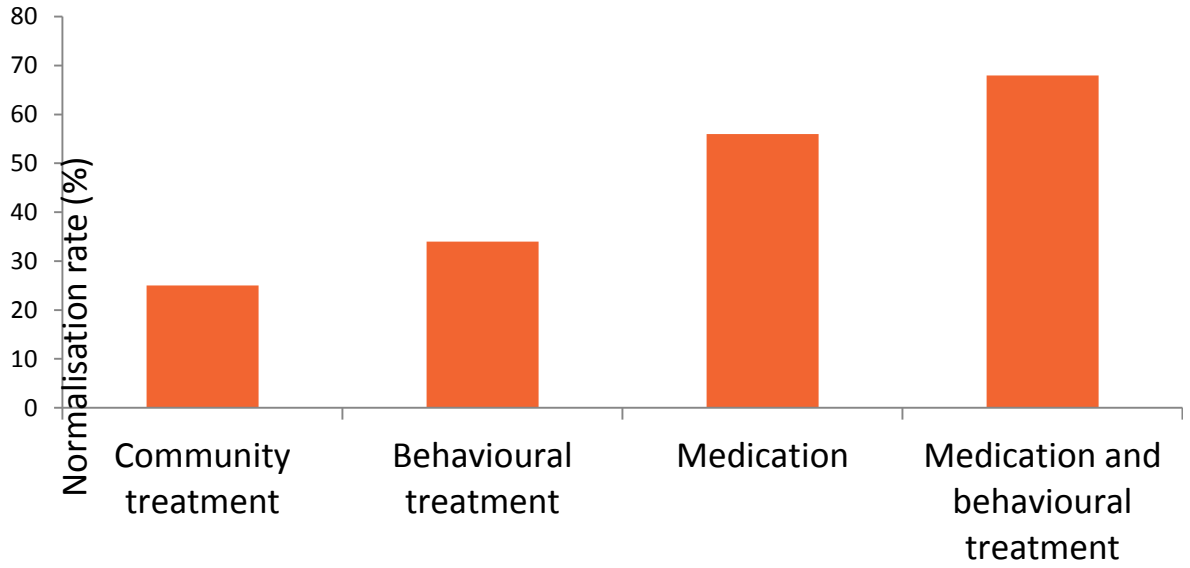
Multimodal Treatment

- Information and education for parents and teachers.
- Treatment for parents with ADHD or other psychiatric problems (like depression).
- Parent training programs (like ”The incredible years” or ”COPE”).
- Educational methods: ”token economy”, rewards, special education, many breaks, help to structure and organise school work, teacher assistant, special schools.
- Behaviour modification.
- Heavy bed cover at night. Time aids, Apps on mobilephone or IPAD. Occupational therapists.
- Treatment of comorbid conditions.
- Training of working memory. Needs more evidence base.
- White noise and vestibular stimulation. Needs more evidence base.
- Neurofeedback. Needs more evidence base.
- Help to organise activities.
- Coaching.
- Family therapy
- Individual supportive therapeutic contact
- Cognitive Behavioral Treatment/ Dialectic Behavioral Treatment (Solanto, Saffren, Hesslinger) : individually or in group.
- Pharmacological treatment

Multimodal behandling för barn och ungdomar med AD/HD



Multimodal treatment improves efficacy[1,2]



Double blind trial of 579 children

1. Reproduced with permission from the European Interdisciplinary Network for ADHD Quality Assurance, EINAQ. 2. Swanson JM et al. J Am Acad Child Adolesc Psychiatry. 2001; 40(2):168–179

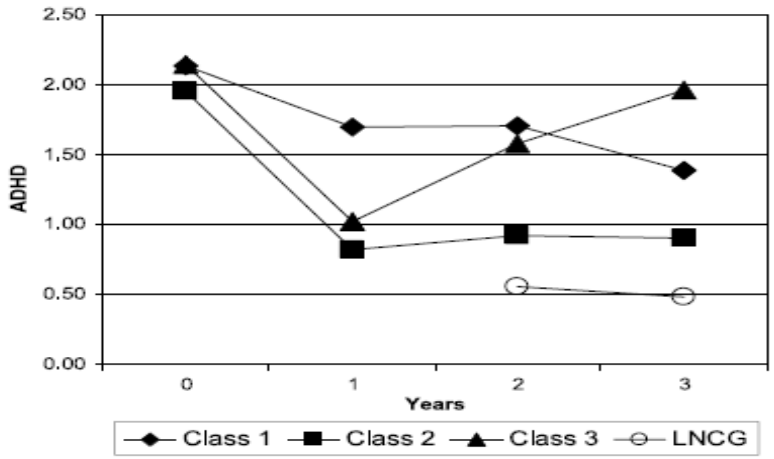


Fig. 1 Average ADHD symptom score over time by latent class. LNCG = local Normative Comparison Group. Reproduced with permission from Wolters Kluwer Health. Originally published in Swanson JM, Hinshaw SP, Arnold LE et al. Secondary evaluations of MTA 36-month outcomes: propensity score and growth mixture model analyses. *J Am Acad Child Adolesc Psychiatry*. 2007;46(8):1003–1014.

Pharmacological treatment

- Several studies show good short-term effects of central stimulant medication and atomoxetine from six years of age.
- Pharmacological treatment only is insufficent for patients with comorbidity.
- Many patients stop taking medicine, better adherence to medication in multimodal treatment programs (Young 2011)
- The MTA-study showed better effect with a combination of medicine and behavioural treatment than medication alone.
- Some individuals (14%) have less effect after one year or more of pharmacological treatment.
- Multimodal treatment is recommended in guidelines (NICE, European guidelines).
- Melatonine can be of use for treating sleep disorder.

Substances

Centralstimulants:

- *Metylfenidate*: Concerta, Ritalin, Medikinet, Equasym
- *Amfetamine*: Metamina, Elvanse/Vyvanse (prodrug)

Selektive noradrenaline uptake inhibitor:

- *Atomoxetine*: Strattera

Alpha-2A agonist:

- *Guanfacine*: Intuniv

Other:

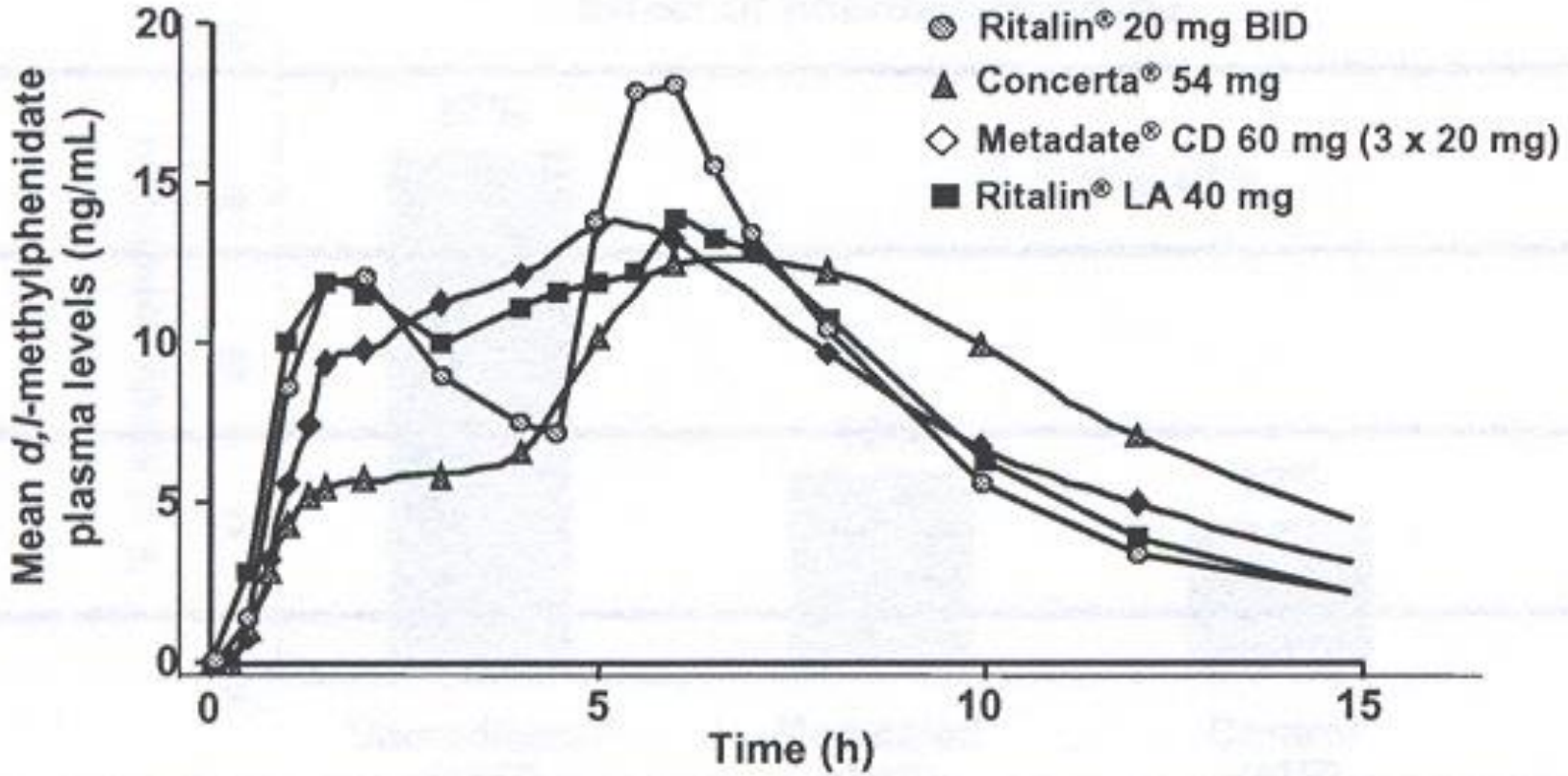
- Imipramine, bupropione, nicotine, clonidine, modafinil, venlafaxine

Nora Volkow et al. JAMA 2009

Conclusion—A reduction in dopamine synaptic markers associated with symptoms of inattention was shown in the dopamine reward pathway of participants with ADHD.

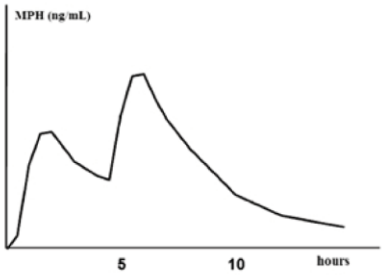
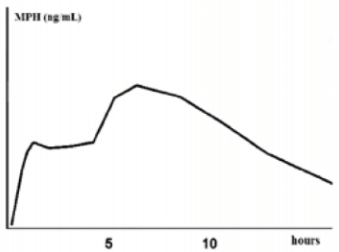
Others have described overactive DAT as an explanation of altered dopamine signaling in ADHD.

Comparison of Extended-release Methylphenidate Dosage Forms*



* For comparative purposes only, not the results of a single head-to head trial. Data on file, Novartis Pharmaceuticals.

Gonzalez MA et al. Int J Clin Pharmacol Ther 2002; 40:175-184.

MPH IR BID 	% IR	% ER	CONCERTA XL 	% IR	% ER
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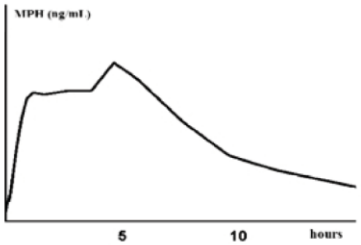
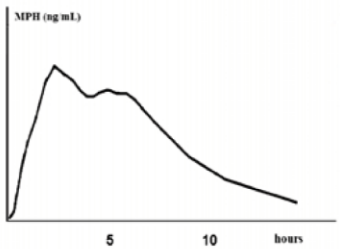
EQUASYM XL 			MEDIKINET RETARD 		
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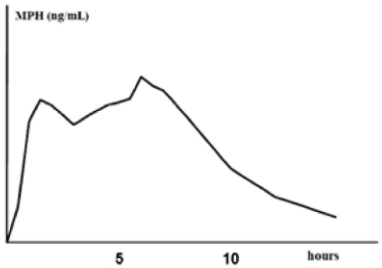
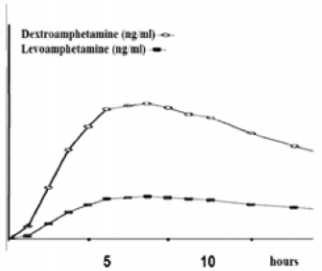
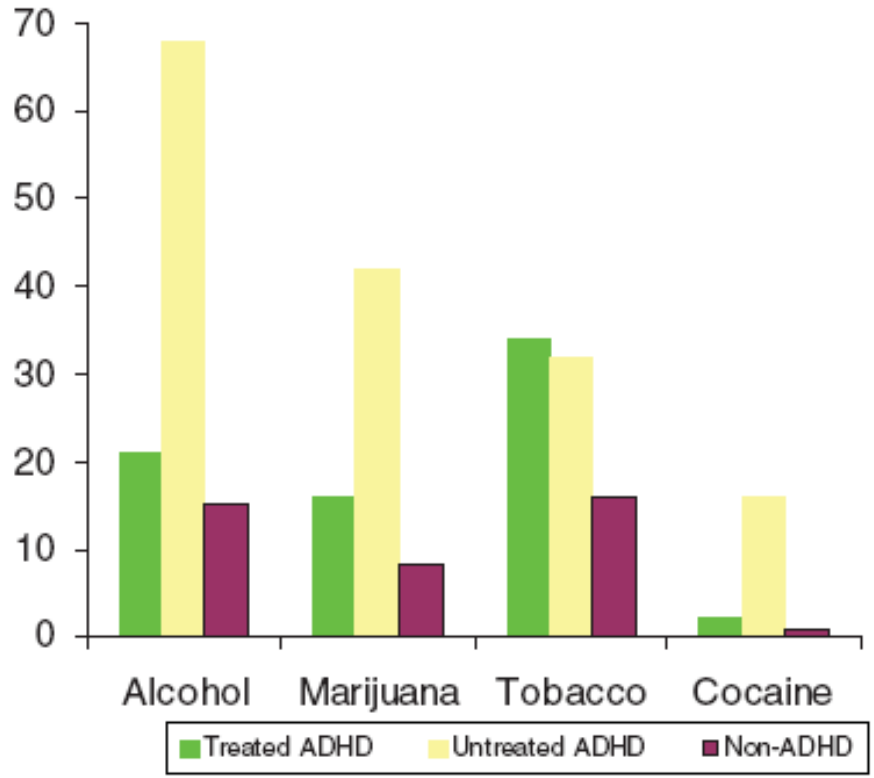
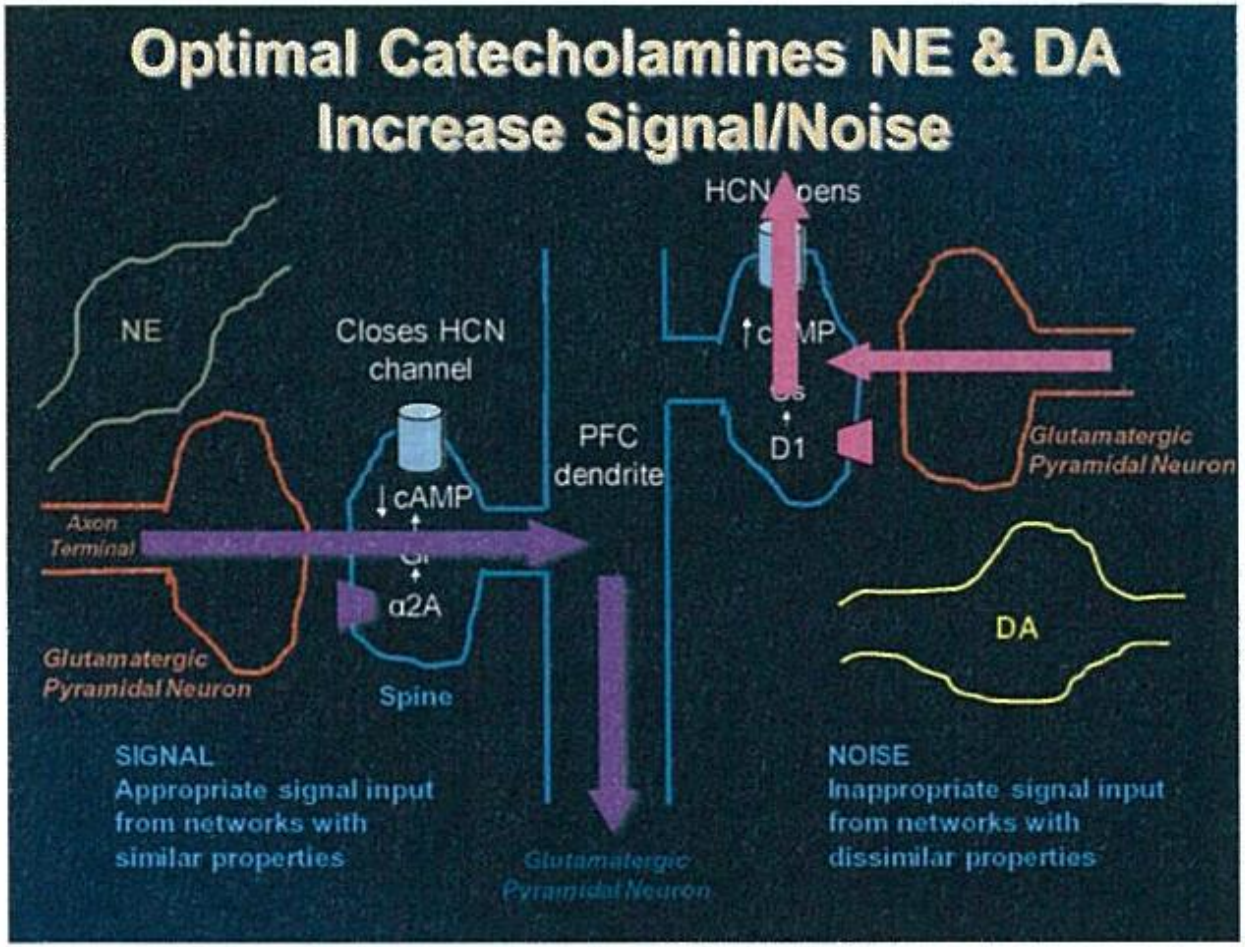
RITALIN LA 			ADDERALL XR 		
	50%	50%		50%	50%

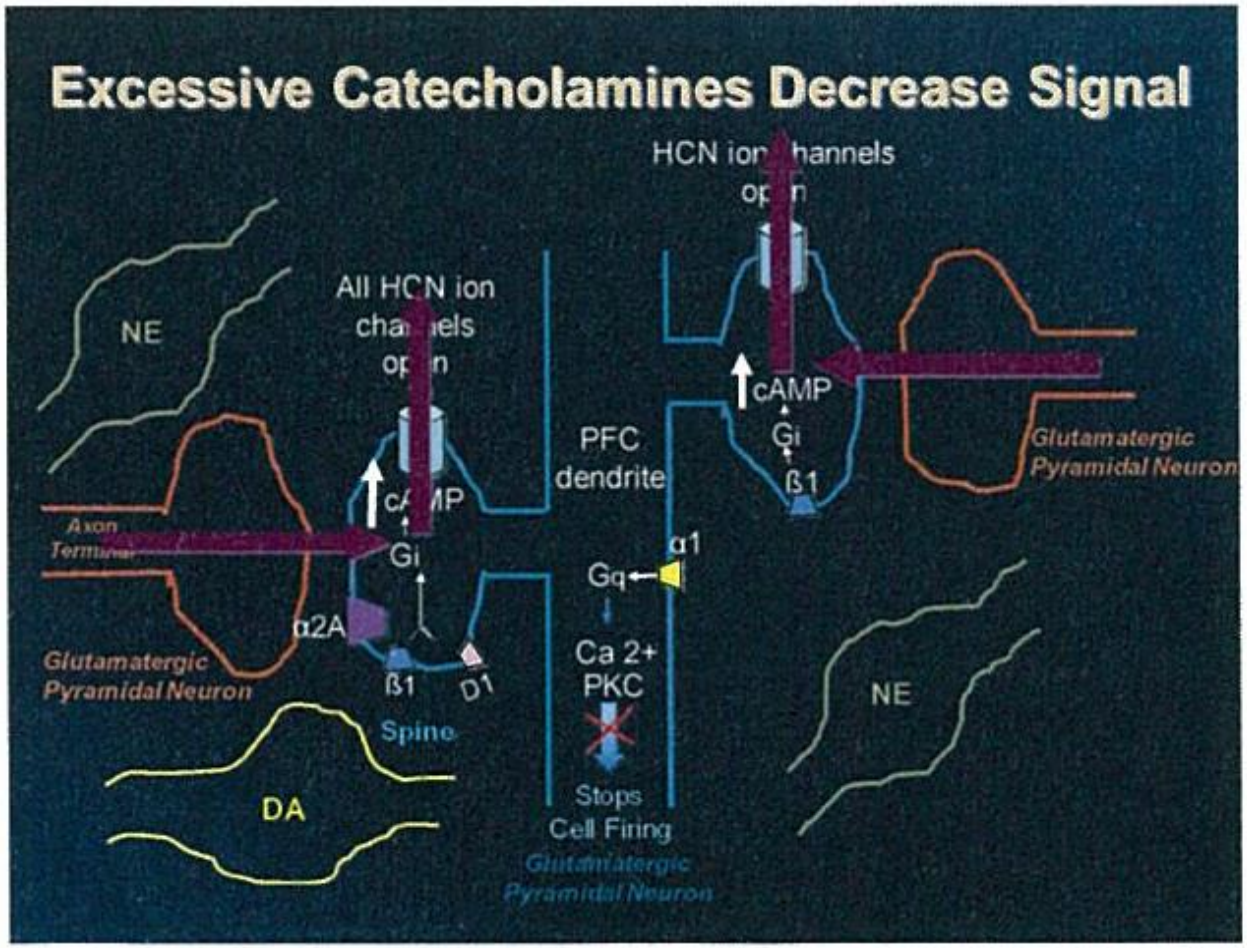
Fig. 1 MPH and amphetamine plasma levels over time with different preparations and their IR/ER proportions Note: curves for MPH IR BID, *Medikinet retard* provided by Medice, for *Adderall XR* provided by Shire; for *Ritalin LA* see: Markowitz et al. [39]; for *Concerta XL* and *Equasym XL* see: Gonzalez et al. [21]; all curves are adapted to a common time-scale. Doses of different products are not equivalent so there is no common Y-axis and direct comparisons should not be made for the absolute levels

Figure 3
Prevalence of Substance Use Disorder (SUD) Subtypes at 4-Year Follow-up, by ADHD Medication Status

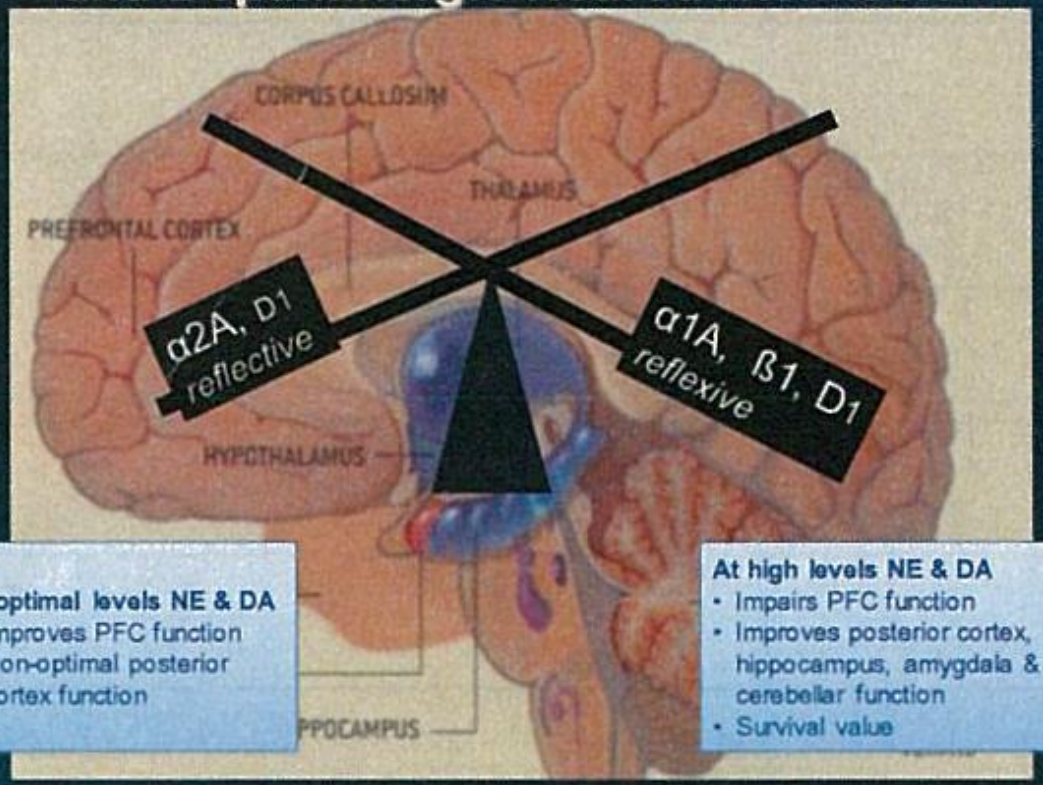


Source: Biederman, Wilens, Mick, Spencer, and Faraone (1999).


Optimal Catecholamines NE & DA Increase Signal/Noise
HCN opens
NE
Closes HCN channel
↑cAMP
D1
PFC dendrite
Glutamatergic Pyramidal Neuron
↓cAMP
Axon Terminal
α2A
DA
Glutamatergic Pyramidal Neuron
Spine
SIGNAL
Appropriate signal input from networks with similar properties
NOISE
Inappropriate signal input from networks with dissimilar properties
Glutamatergic Pyramidal Neuron

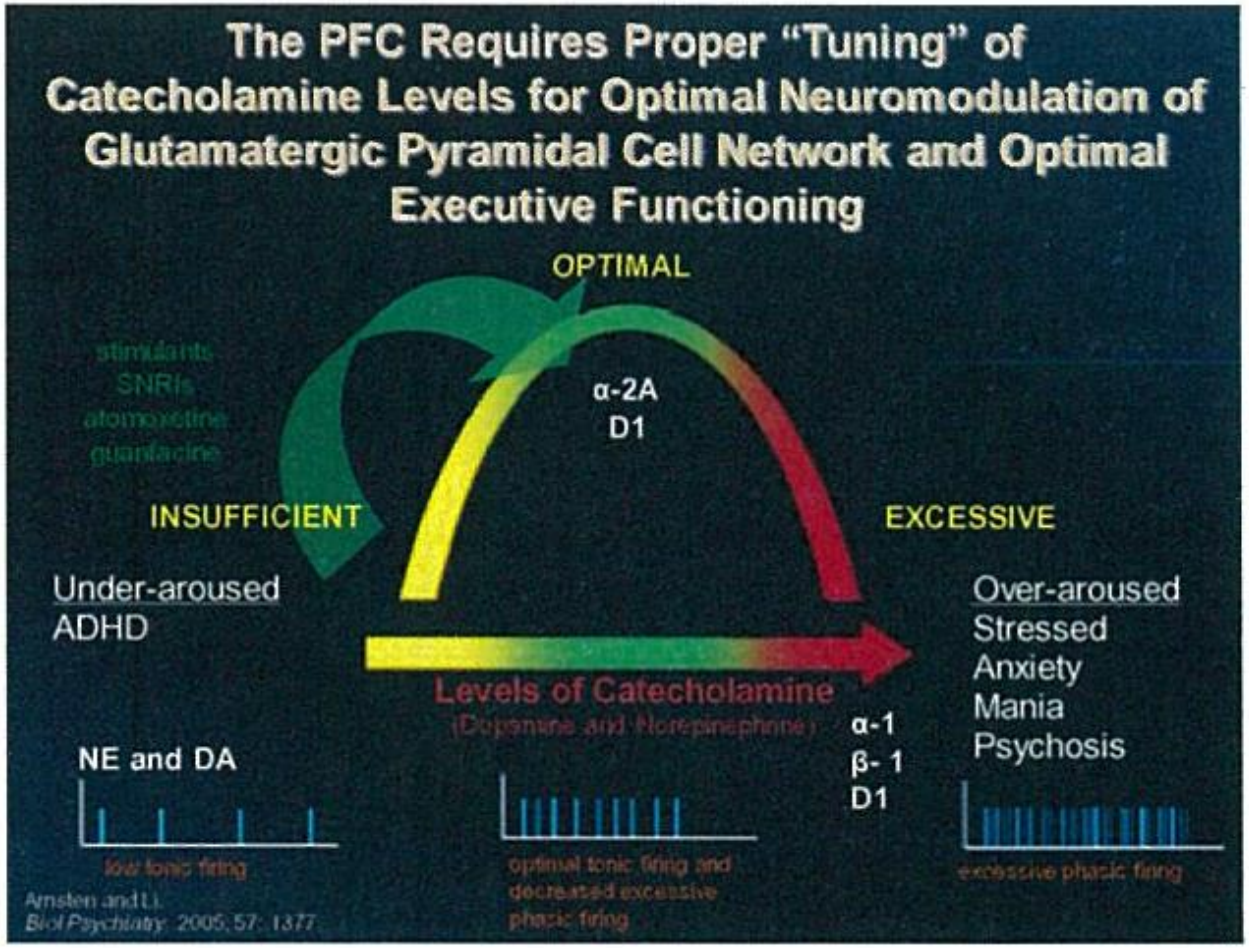

Excessive Catecholamines Decrease Signal
HCN ion channels open
All HCN ion channels open
NE
cAMP
Gi
ß1
PFC dendrite
Glutamatergic Pyramidal Neuron
Axon Terminal
α1
Gq
Gi
α2A
Ca 2+
PKC
Glutamatergic Pyramidal Neuron
ß1
D1
Spine
NE
DA
Stops Cell Firing
Glutamatergic Pyramidal Neuron

Stress & Anxiety Increases Noradrenergic and Dopaminergic Neurotransmission



At optimal levels NE & DA
- Improves PFC function
- Non-optimal posterior cortex function

At high levels NE & DA
- Impairs PFC function
- Improves posterior cortex, hippocampus, amygdala & cerebellar function
- Survival value


The PFC Requires Proper "Tuning" of Catecholamine Levels for Optimal Neuromodulation of Glutamatergic Pyramidal Cell Network and Optimal Executive Functioning
OPTIMAL
stimulants
SNRIs
atomoxetine
guanfacine
α-2A
D1
INSUFFICIENT
EXCESSIVE
Under-aroused
ADHD
Over-aroused
Stressed
Anxiety
Mania
Psychosis
Levels of Catecholamine
(Dopamine and Norepinephrine)
α-1
β- 1
D1
NE and DA
low tonic firing
optimal tonic firing and decreased excessive phasic firing
excessive phasic firing
Arnsten and Li
Biol Psychiatry 2005; 57: 1377

Treatment of ODD: Oppositional Defiant Disorder and CD: Conduct Disorder

- If ADHD or ASD: treatment and support for these conditions.
- Depression can be present.
- Adjustment of home and school situation.
- CPS: Collaborative Proactive Solutions (Ross Green)
- FFT: Functional Family Therapy
- MST: Multi Systemic Treatment, MTFC: Multidimensional Treatment Foster Care.
- Combination of central stimulants and guanfacine, neuroleptics.

Other treatments

- Omega-3: some evidence but for a minority and not as effective as central stimulants.
- Diet: anecdotal case-descriptions.
  Buitelaar et al: effect of extreme diet.
  Feingold-diet: not evidence based.

When is there an effect of the medication?

- Central stimulants give immediate effect (testing of pharmacological effect may be done quickly with CPT-tests).
- Effect of Strattera after 4-6 weeks.

On-off effect

- A negative experience when the effect of Central stimulants disappears.
- Agitation when no longer an effect of CS.
- The patient can feel when the medicin starts having an effect – sometimes may be positive.
- Easy with CS cocerning drug-hollidays ro medication only when needed.
- No on-off effect of Strattera or Intunive.

When is the effect needed?

- Early morning.
- AM.
- During schoolday.
- Afternoon, home-work.
- Evening (car driving, sport activities)
- Bedtime.

Common side effects

Side effect	**CS**	**Atomoxetine**
Apetite	++	+
Nausea	+	+
Stomach pain, headache	+	+
Nervousness, depressive mode	+	(+)
Tired	-	++
Personality change	(+)	-
Change of length/weight	+ (?)	-
Tics	+	-
Sleep diffculties	++	-

Blood pressure, cardiovascular effects

- Increased puls rate.
- In a few cases hypertonia. Lower dose? Treatment of hypertonia?
- Take care if known heart disease. Heredity. ECG.
- Intunive: lowers blood-pressure.

Length/Weight

- Sometimes significant loss of apetite.
- Usually better after longer time of treatment.
- CS eat more at evening.

Tourette's syndrome

Described 1885 by Georges Gilles de la Tourette

Famous historical persons with Tourette's syndrome:
Peter the great, Samuel Johnsson

Tics: 0,5 – 1%, boys/girls: 3/1

Often comorbid Obsessive Compuslive diorder (OCD): 30 – 60%,
ADHD: 60%, ASD: 4,5%

Criteria

Note: A tic is a sudden, rapid, recurrent, nonrhytmic motor movement or vocalization.

- A. Both multiple motor an one or more vocal tics have been present at some time during the illness, although not necessarily concurrently.
- B. The tics may wax and wane in frequency but have persisted for more than 1 year since first tic onset.
- C. Onset is before age 18 years.
- D. The disturbance is not attributable to the physiological effects of a substance (e.g., cocaine) or another medical condition (e.g., Huntington’s disease, postviral encephalitis).

Other problems

- Disturbed sleep: 23%
- Affective diorder (depression, mania): 20%
- Anxiety: 20%
- Self-injury: 14%
- Coprolalia: 14%

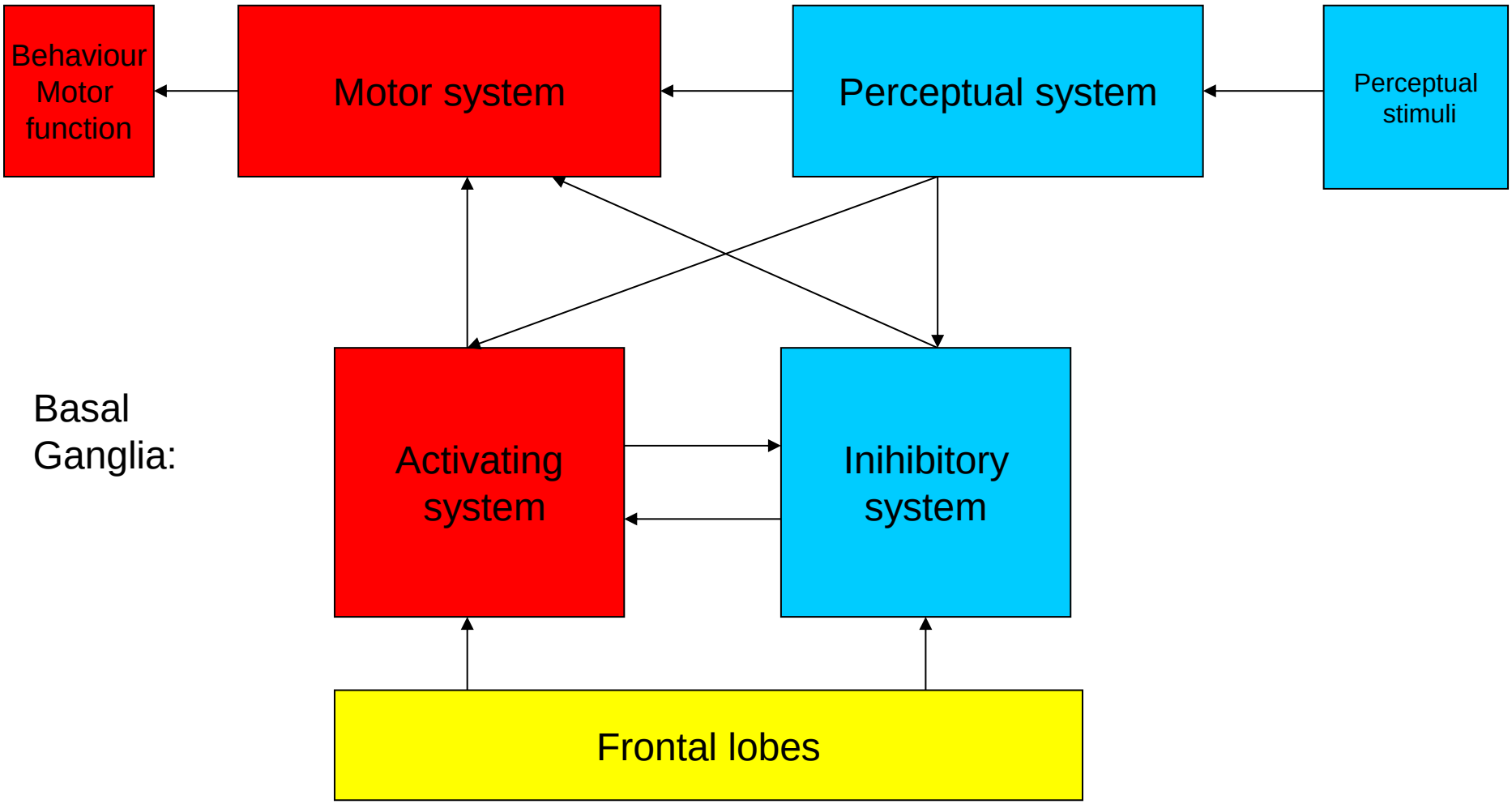
Prognosis:

1/3 no tics in adulthood

1/3 mild tics in adulthood

1/3 severe tics in adulthood

Basal ganglia



Function of the basal ganglia

- Initiate movement and behaviour according to inherited and conditioned programmes.
- Sustain movement and behaviour, regulate muscle tonus and speed.
- Stops movement and behaviour.
- In cooperation with cerebellum, motor cortex and the frontal lobes. Input from sensory cortical areas.

Causes

Genetics – high heritability

Dopaminergic systems in the frontal lobes and basal ganglia.

Some evidence of involvement of noradrenergic and serotonergic systems.

Female relatives of boys with TS have more often OCD than TS (about 3 times more often).

PANDAS (Paediatric Autoimmune Neurological Disorders Associated with group-A Streptococcal infection):

Tics, OCD symptoms, affective symptoms.

Antibiotics, immunoglobulines, tics-treatment.

PANS: Pediatric Acute-onset Neuropsychiatric Syndrome – other infectious agents. (Orefici et al. 2016).

Treatment

- Tiredness, boredom and stress increases tics. Endogenous factors. Tics varies over hours, days months. Important with understanding from other people.
- Cognitive Behavioural Therapy has effect but can be difficult for younger patients or those with ASD.

Pharmacological treatment

- *Against tics:*
  Neuroleptics, often aripriprazole or risperidone. Alfa-2 agonists: guanfacine or clonidine.
- *Against ADHD:*
  Centralstimulants, atomoxetine, guanfacine, Clonidine.
- *Against OCD:*
  SSRI, clomipramine