The Neurobiology of ADHD and Related Disorders

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Disclosure: AFTA and Yale University receive royalties from Shire Pharmaceuticals from the sale of Intuniv™ (extended release guanfacine) for the treatment of ADHD and related disorders.
Attention Deficit Hyperactivity Disorder-

- Impaired regulation of attention, hyperactivity, impulsivity; often continues into adulthood
- ~7.2% of school-aged children in the U.S. (4.1 million children) had a current ADHD diagnosis in 2007 (http://www.cdc.gov)
Better awareness and diagnosis, but also:

- Increasing demands for “top-down” self-control and organization needed to succeed in the Information Age.
- Many schools are unable to give children extra help or resources without an official diagnosis.

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Oppositional Defiant Disorder or Conduct Disorder (inappropriate aggression)
Tourette’s Syndrome (tics)
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Disorders with symptoms that can look like ADHD:
- Stress or Post-traumatic stress disorder- e.g. from a family going through a divorce, or more gravely, from child abuse or witnessing traumatic events
- Bipolar disorder (mania)
- Lead poisoning
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ADHD is a biological disorder:
It is highly heritable, similar to eye color- (e.g. alterations in genes related to brain development and neuromodulation)
The brains of patients with ADHD show replicable differences

What is the neurobiological basis of ADHD?

Impaired maturation and/or function of the prefrontal cortex
The Prefrontal Cortex Regulates Attention, Behavior and Emotion

Prefrontal Cortex

Most highly evolved brain region

Mental Representation (“Mental Sketch Pad”)

Foundation of abstract thought

Working Memory

The Prefrontal Cortex Regulates Attention, Behavior and Emotion

- Prefrontal Cortex
- Top-down control of attention, action and emotion
- Ability to plan ahead and to have the patience to wait for a larger reward (impulse control)

The Prefrontal Cortex Regulates
Attention, Behavior and Emotion

Prefrontal Cortex
Executive Functions:
Planning and organizing
High-order decision-making
Insight and judgment
Inhibition of inappropriate actions

The Prefrontal Cortex Regulates Attention, Behavior and Emotion

Thought
sensory association cortices
caudate

Cerebellum via pons

Prefrontal Cortex

Top-down regulation of:

Sensory association cortices, hippocampus

NE, DA, 5HT cell bodies

Top-down attention: Stimulus relevance e.g. studying for a test

Bottom-up attention: Stimulus salience (moving, bold, loud) e.g. video games

Widespread Connections

- Motor, premotor cortices
- Caudate, putamen, subthalamic nuc.

Prefrontal Cortex

- Top-down regulation of:

Action

- Inhibition of inappropriate, impulsive actions
  (especially right hemisphere)

- Cerebellum via pons

Widespread Connections

- Prefrontal Cortex
- Top-down regulation of:
  - Inhibition of inappropriate emotions, e.g. aggression
- hypothalamus
- nuč. accumbens
- amygdala
- Brainstem eg PAG
- NE, DA, 5HT cell bodies

In humans, the right hemisphere is specialized for inhibition, while the left hemisphere is the "generative" hemisphere.

Lesions:
- **Left Generative**: Reduced initiative, depression
- **Right Inhibitory**: Impulsive, mania, sociopathy

The right, inferior PFC is especially important for inhibiting inappropriate actions.

Normal Development:
The Right inferior PFC grows larger between ages 4-20

Shaw et al. (2009) Arch Gen Psych
Altered Maturation of PFC in ADHD

ADHD:
Laterality unchanged
(Right hemisphere does not enlarge)

Shaw et al. (2009) Arch Gen Psych
Reduced Structure and Function of PFC in ADHD

Reduced Right inferior dIPFC functional activity

Motor inhibition
(similar results with impaired attention)

Reduced PFC connectivity

Reduced PFC volume
Makris et al, (2007)
Disorder Specific Changes

Reduced Right inferior dIPFC functional activity

Motor inhibition
(similar results with impaired attention)


Reduced Right Orbital PFC functional activity in Conduct Disorder

Impaired regulation of emotion
Lead poisoning is associated with reduced PFC gray matter, perhaps due to mimicking calcium and increasing intracellular stress signaling pathways in PFC neurons.
Mania Mimics ADHD

The right PFC is underactive during mania

Understanding the neurobiology of the prefrontal cortex provides clues to what may cause these disorders, as well as how to rationally treat symptoms of prefrontal cortical dysfunction.
Prefrontal Neuronal Network Connections

Top-down goals are represented by recurrent excitation in pyramidal cell networks in prefrontal cortex: The pioneering work of Patricia Goldman-Rakic

Prefrontal Neuronal Network Connections

Prefrontal cortical pyramidal cell networks connect via glutamate NMDA receptor synapses on spines

Top-down control requires strong connections with neurons bringing in relevant information ("signals"), and weaker connections to those with irrelevant information ("noise")

Prefrontal Neuronal Network Connections Are Altered by the Arousal Systems

Like Goldilocks, PFC has to have everything “just right”

Prefrontal Neuronal Network Connections Are Altered by the Arousal Systems

Ca\(^{2+}\)-cAMP signaling weakens connectivity by opening K\(^+\) channels

(saves energy, as recurrent excitation is energy intensive)

Moderate levels of norepinephrine (NE) release engage high affinity α2A-ARs. NE α2A-ARs inhibit Ca^{2+}-cAMP-K^{+} signaling and strengthens signals.
Prefrontal Neuronal Network Connections Are Altered by the Arousal Systems

Moderate levels of norepinephrine (NE) release engage high affinity $\alpha_2A$-AR. NE $\alpha_2A$-ARs inhibit $Ca^{2+}$-cAMP-$K^+$ signaling and strengthens signals. DA D1R increases $Ca^{2+}$-cAMP-$K^+$ signaling and decreases noise.

Optimal Prefrontal Cortical Regulation of Attention, Behavior and Emotion

Moderate levels of norepinephrine (NE) release engage high affinity α2A-AR.
NE α2A-ARs inhibit Ca2+-cAMP-K+ signaling and strengthens signals.
DA D1R increases Ca2+-cAMP-K+ signaling and decreases noise.

Uncontrollable Stress Takes PFC “Off-Line” and Switches Control to More Primitive Systems

High levels of NE release engage lower affinity $\alpha_1$-AR and $\beta_1$-AR which increase Ca$^{2+}$-cAMP-K$^+$ signaling and reduce firing.

High levels of DA D1R also increase Ca$^{2+}$-cAMP-K$^+$ signaling and decrease all network firing.

Uncontrollable Stress Takes PFC “Off-Line” and Switches Control to More Primitive Systems

High levels of catecholamines strengthen the activity of more primitive circuits

Uncontrollable Stress Takes PFC “Off-Line” and Switches Control to More Primitive Systems

Why stress can mimic ADHD

Chronic Stress: Architectural Changes

- Prefrontal Cortical Synapses Disconnect
  - K⁺
  - AC cAMP

- Amygdala
- Prefrontal Cortex

- Sensory Cortex
- Striatum
- Amygdala

- Chronic Stress
  - Dopamine
  - Norepinephrine

- Signal
  - Ca²⁺ → AC → cAMP
  - α₂A-AR
  - β₁-AR
  - D₁R

- Noise

Chronic Stress
Chronic stress leads to loss of PFC spines and function (reversible)

Activated by lead poisoning
Prefrontal Cortical Synapses Disconnect

Lead Exacerbates Stress Signaling Pathways in PFC

Activated by lead poisoning
Prefrontal Cortical Synapses Disconnect

Prefrontal Cortex

Activated by lead poisoning

May help to explain loss of PFC gray matter seen with lead poisoning

Bipolar Disorder Linked to Genetic Alterations that Exacerbate Stress Signaling Pathways in PFC

Prefrontal Cortical Synapses Disconnect Prefrontal Cortex

Right PFC underactive during mania

Regulation of emotion

Meta-cognition
Insight

Regulation of action

Why bipolar disorder can mimic ADHD

Prefrontal Cortex

Relevance to ADHD Genetics and Medications
Relevance to ADHD Genetics

Genes related to:
- norepinephrine: DBH, ADRA2A, NET
- Dopamine: DAT1, DRD5
- Both catecholamines: DRD4, COMT, MAOA
- cholinergic: CHRNA4
- serotonergic: 5-HTT, HTR1B, HTR2A
- Synaptic transmission (vesicle release): SNAP25
- CNS development and plasticity: BDNF

A variety of genetic alterations can disrupt the precise modulation of PFC circuits needed for PFC function

Prefrontal Cortex

Prefrontal Cortical Glutamate Synapses

α2A-AR

norepinephrine

K⁺

AC → cAMP

D1R

dopamine

NET

DAT

Relevance to ADHD Medications

Transporters take up norepinephrine and dopamine
Stimulants (methylphenidate, amphetamines)

Stimulants block NE and DA transporters and increase catecholamines in PFC
Clinically-relevant (i.e. low) doses of methylphenidate preferentially increase catecholamines in PFC

Stimulants (methylphenidate, amphetamines)

Why excessive doses of stimulant can impede cognitive flexibility

- Excessive levels of catecholamines in PFC weakens PFC function
- Increased catecholamines in primitive circuits, e.g. striatum, strengthens habitual responding

Berridge and Devilbiss (2011) Biological Psychiatry 69:e101-11;
Atomoxetine selectively blocks norepinephrine transporters (NETs). The NET takes up both NE and DA in PFC. 

An optimal dose of atomoxetine is needed to enhance PFC physiology.

Guanfacine and Clonidine

Guanfacine enhances PFC physiology

Guanfacine Strengthens PFC Function

PFC functions improved by guanfacine in monkeys:

- Improved working memory
- Reduced distractibility
- Improved Impulse control (ability to wait for a larger reward)
- Improved regulation of emotional response (reversal of emotional habit)

Guanfacine: Clinical Use

PFC disorders improved by guanfacine in patients:

- ADHD
- Tourette’s (tics)
- ODD (inappropriate aggression)
- PTSD/emotional trauma in children
- Behavioral disinhibition in autism
- Mild traumatic brain injury
- Stroke/encephalitis in association cortex
- Substance abuse
- Emergence delirium

Understanding the neurobiology of the prefrontal cortex has helped guide new treatments for cognitive disorders.
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If you are interested, recent reviews:

**Overall review on prefrontal cortex:**

**Stress effects on prefrontal cortex:**
Arnsten et al, Scientific American, April 2012

**ADHD and its treatment:**