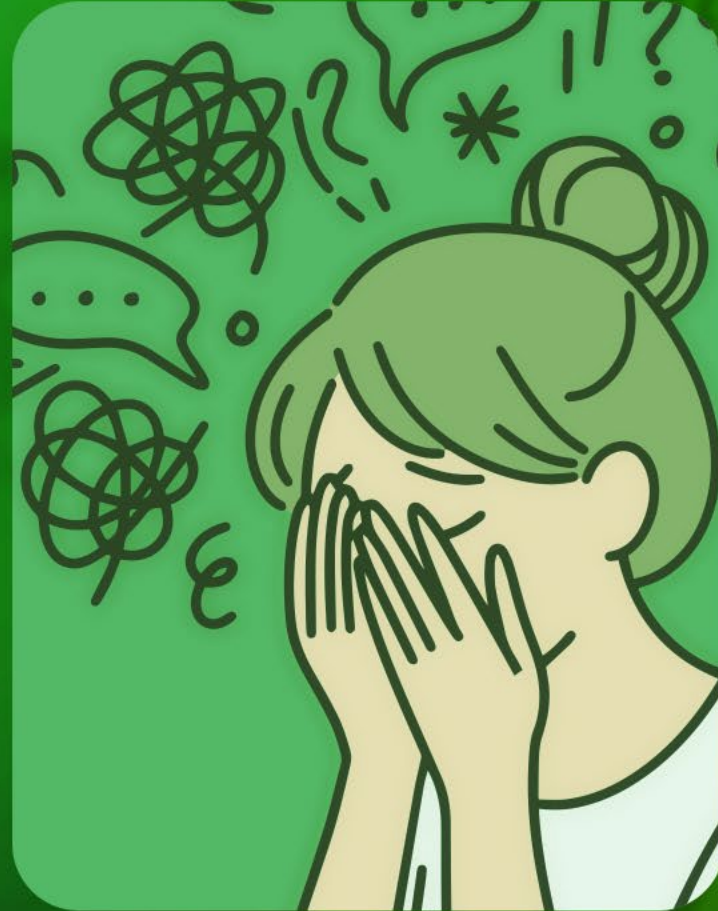


Features Out of Focus:
***Recognition and
Treatment of Emotional
Dysregulation and
Executive Dysfunction
in ADHD***

Module 2



Faculty

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Faculty Disclosures

- **Rakesh Jain, MD, MPH:** Advisory Board — Adamas, Alkermes, Corium, Eisai, Indivior, Intra-Cellular Therapies, Ironshore, Janssen, Lilly, Lundbeck, Merck, Neos Therapeutics, Neurocrine Biosciences, Otsuka, Pamlab, Pfizer, Inc., Shire, Sunovion, Supernus, Takeda, Teva Pharmaceuticals, Tris Pharmaceuticals; Consultant — AbbVie (Allergan), Acadia, Adamas, Alfasigma, Axsome Therapeutics, Inc., Cingulate Therapeutics, Corium, Eisai, Evidera, Impel, Janssen, Lilly, Lundbeck, Merck, Neos Therapeutics, Neurocrine Biosciences, Osmotica, Otsuka, Pamlab, Pfizer, Inc., Sage Therapeutics, Shire, Sunovion, Supernus, Takeda, Teva Pharmaceuticals; Grant/Research Support — AbbVie (Allergan), Lilly, Lundbeck, Otsuka, Pfizer, Inc., Shire, Takeda; Speakers Bureau — AbbVie (Allergan), Alkermes, Axsome Therapeutics, Inc., Corium, Eisai, Indivior, Intra-Cellular Therapies, Ironshore, Janssen, Lilly, Lundbeck, Merck, Neos Therapeutics, Neurocrine Biosciences, Otsuka, Pamlab, Pfizer, Inc., Shire, Sunovion, Takeda, Teva Pharmaceuticals, Tris Pharmaceuticals

Disclosures

- The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration)
- Applicable CME staff have no relationships to disclose relating to the subject matter of this activity
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Learning Objectives

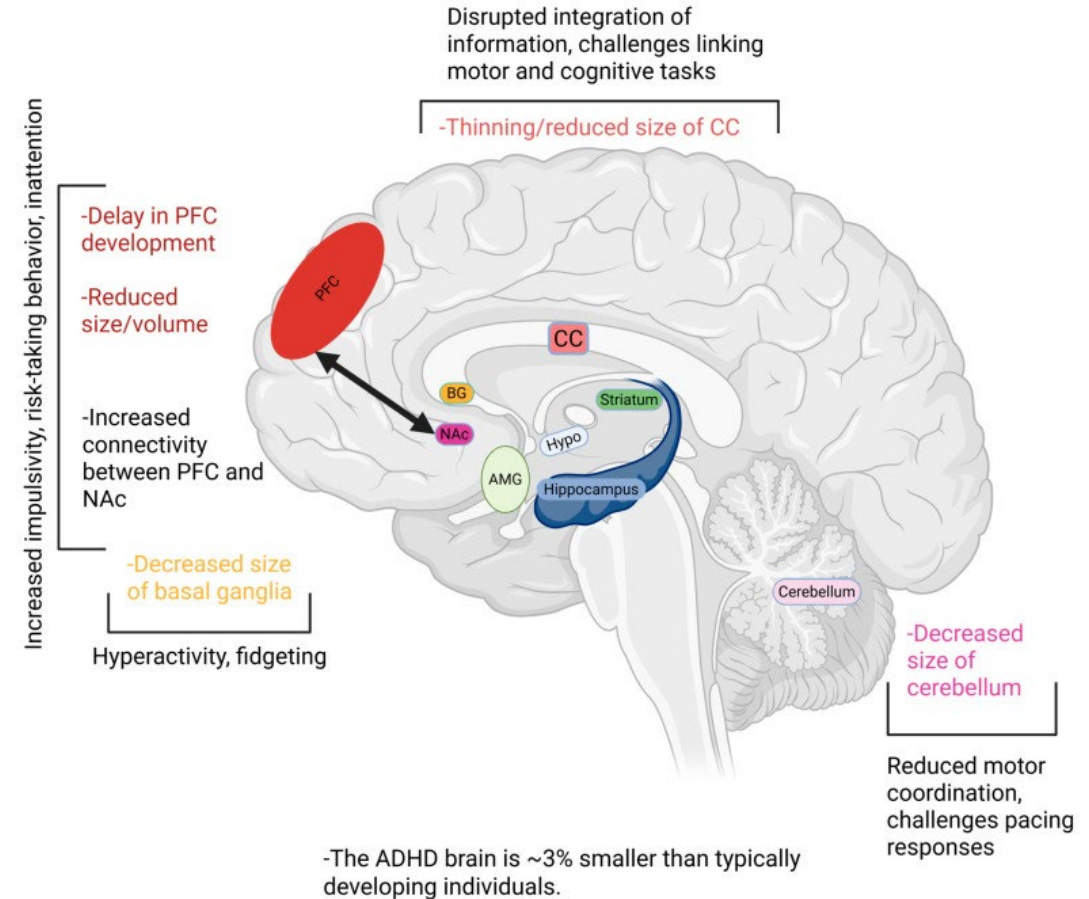
- Explain how the serotonin system interacts with dopamine and norepinephrine in the regulation of emotion and cognition in ADHD

Integration of Neurobiological Evidence into a More Comprehensive Model of ADHD

Brain Regions Altered in ADHD

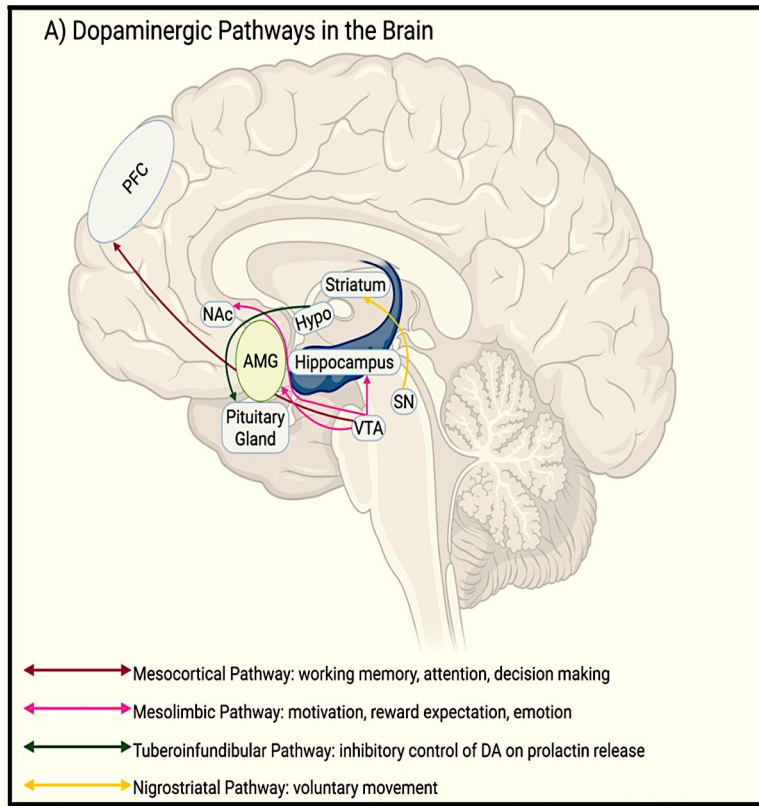
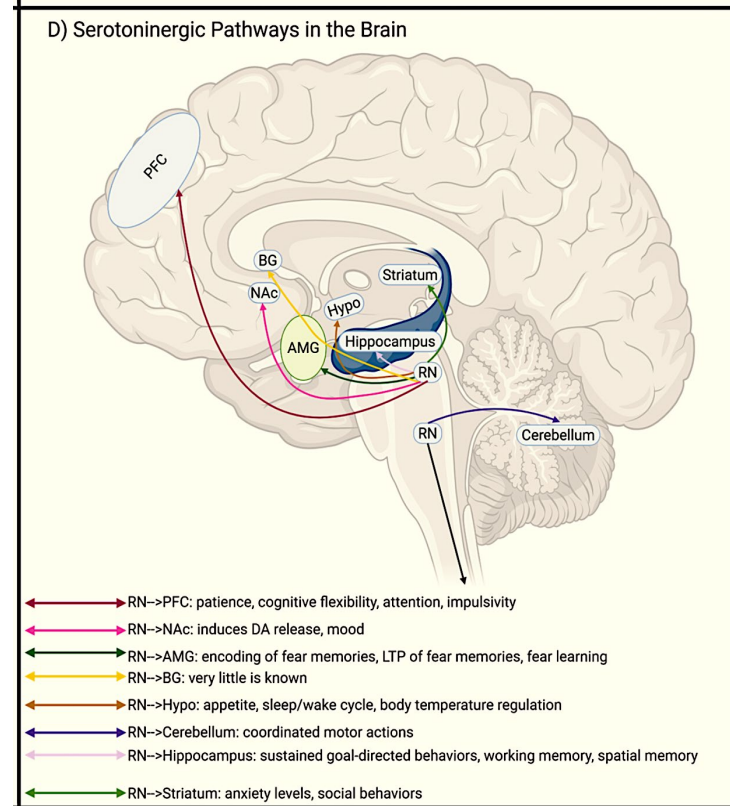
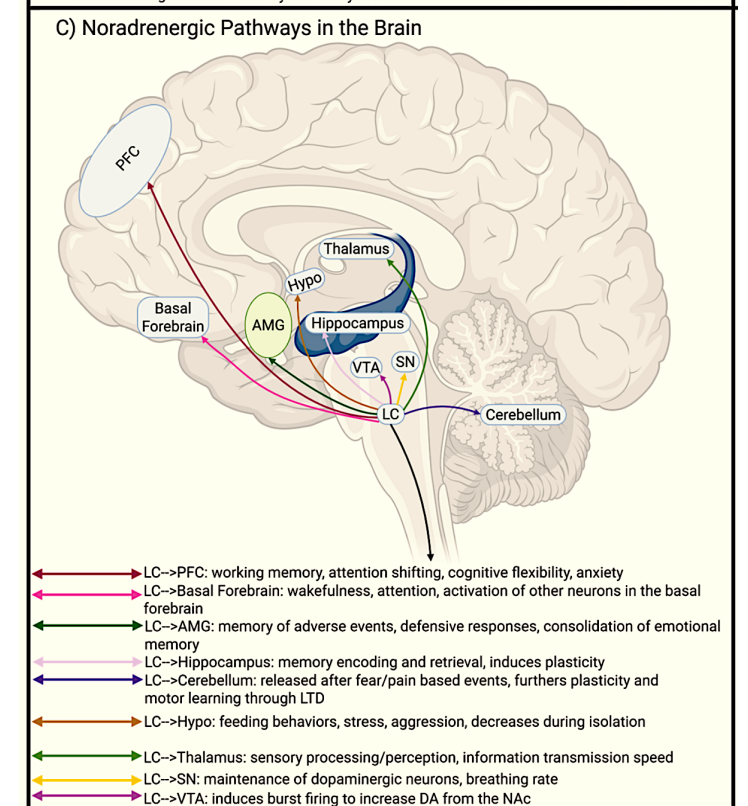
In ADHD, there are many 'macro' pathologies

1. Brain size abnormalities
2. Brain connectivity abnormalities
3. These map onto the 'classic' symptoms of ADHD (inattention, hyperactivity, impulsivity)
4. Importantly, **they also map onto areas involved in emotional dysregulation and executive dysfunction in ADHD**



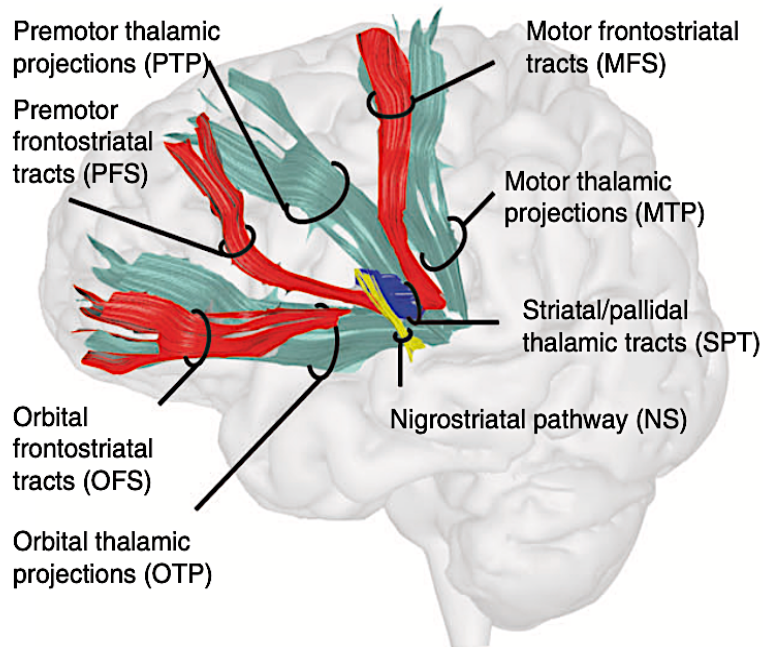
There is an overall decrease in total brain volume in ADHD: a loss of white matter volume (10.7%) and grey matter volume (3.9%), which is approximately **3% total decrease in brain volume**.

These Regions Are Innervated by Dopamine, Serotonin, and Norepinephrine



DA, 5-HT, and NE are the three neurotransmitters binding attention, impulsivity, and emotional regulation centers of the brain

Frontostriatal and thalamic projections



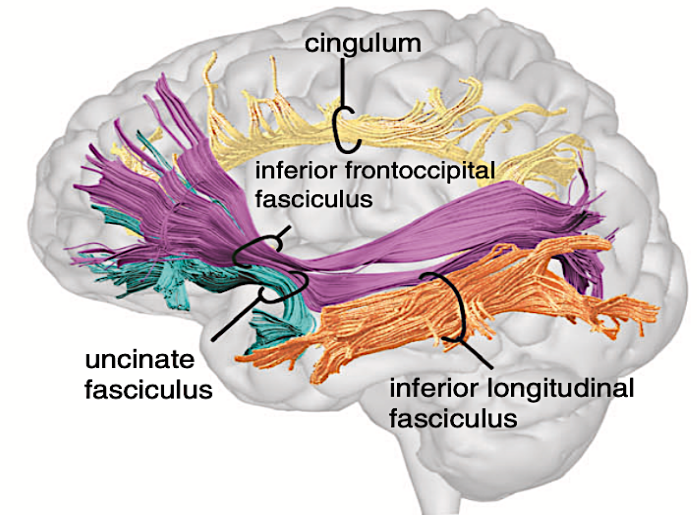
Associated impairment

FS pathways: inattention, impulsivity, executive dysfunction, poor schooling, ADHD symptom severity.

Thalamus and ATR: inattention, impulsivity, ADHD symptom severity.

White Matter Alterations in ADHD

Other association tracts



Associated impairment

CING: inattention, executive dysfunction, poor working memory, ADHD symptom severity and age-related remission of hyperactive-impulsive symptoms, emotional problems.

UNC: inattention, impulsivity, poor working memory and verbal intelligence, inattentive symptoms, emotional problems, and callous-unemotional behaviors.

ILF: inattention and executive dysfunction, ADHD symptom severity, poor adaptive functioning, emotion dysregulation.

ILOF: inattention, ADHD symptom severity, poor adaptive functioning, emotion dysregulation, callous-unemotional behaviors.

Functional Differences in ADHD

DMN abnormalities are shared between ADHD and 'classic' mood disorders, such as MDD and BD, and are associated with **increased impulsivity, greater emotional dysregulation, and even suicidality.**

Resting State Functional Connectivity:

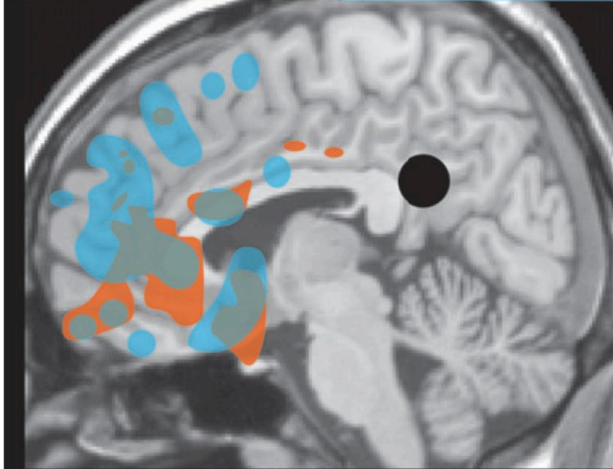
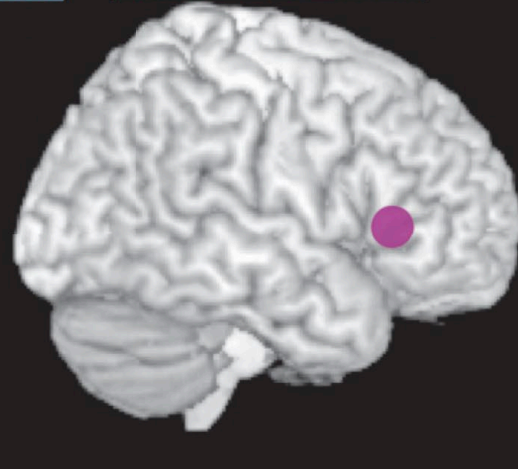
Within Default Mode Network (DMN)

persistent ADHD < control

persistent ADHD < remitted ADHD

DMN to Prefrontal Cortex

persistent ADHD > control



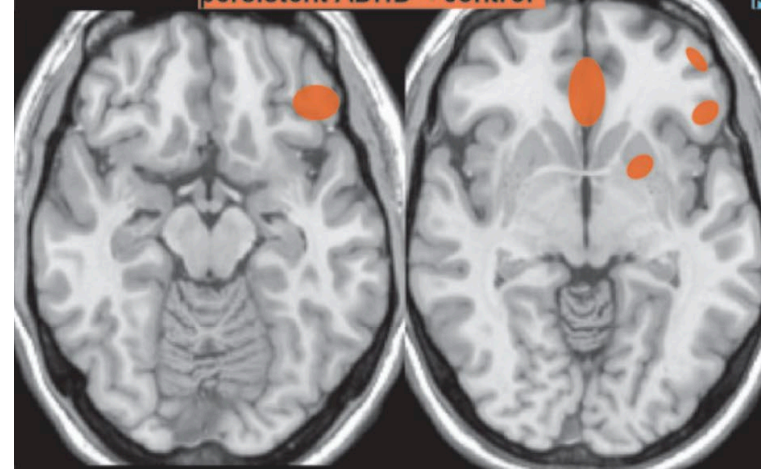
Task Associated Functional Connectivity:

Cognitive Control

persistent ADHD < control

Response Preparation

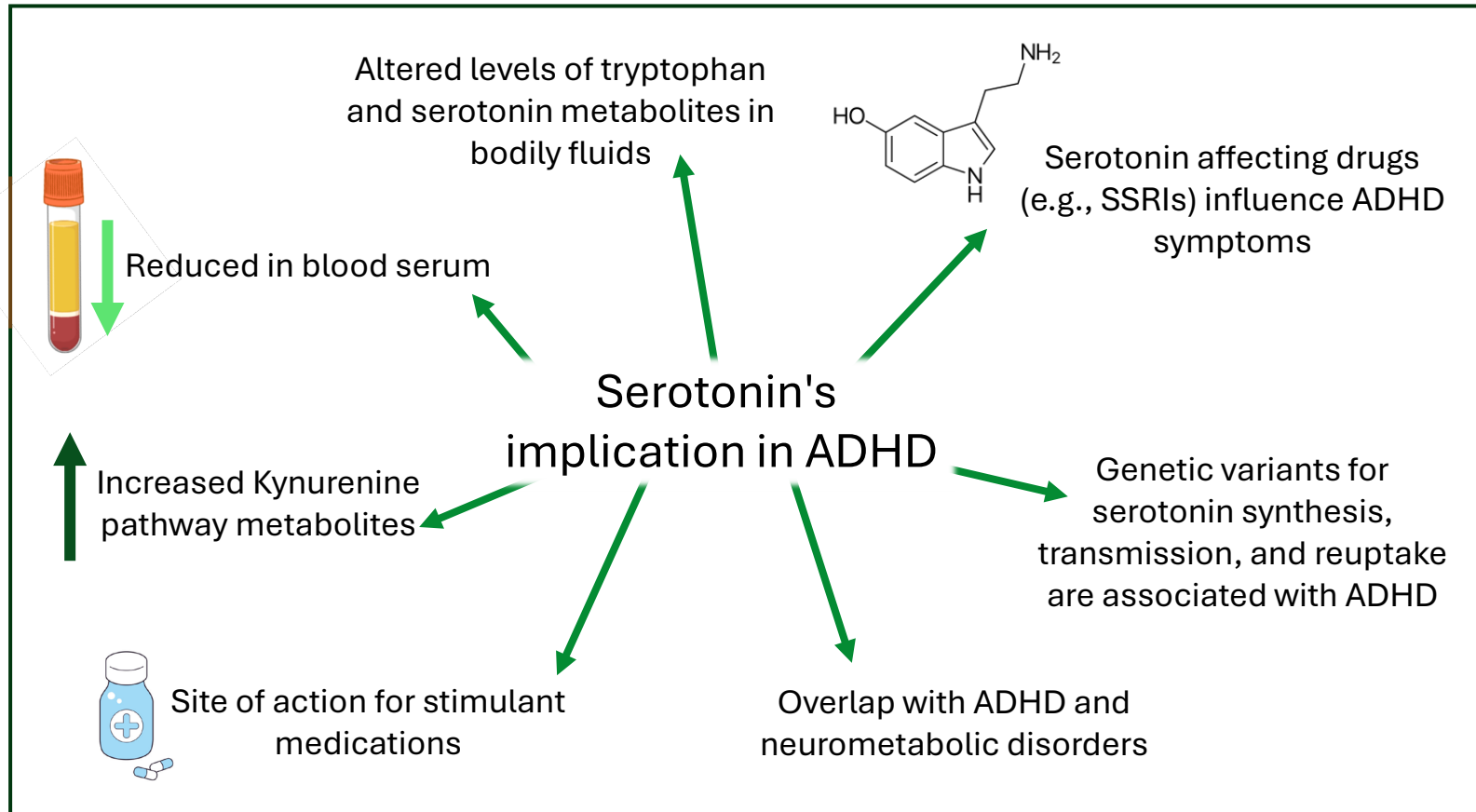
persistent ADHD < remitted ADHD



MDD = major depressive disorder; BD = bipolar disorder.

Jadidian A et al. J Neuropsychiatry Clin Neurosci 27:3, Summer 2015; We Y et al. J Psych Research 2024. Sept 177; 2111-218; Huang W-S, et al. J Clin Psychiatry 2025 Nov 19;87(1):25m15906

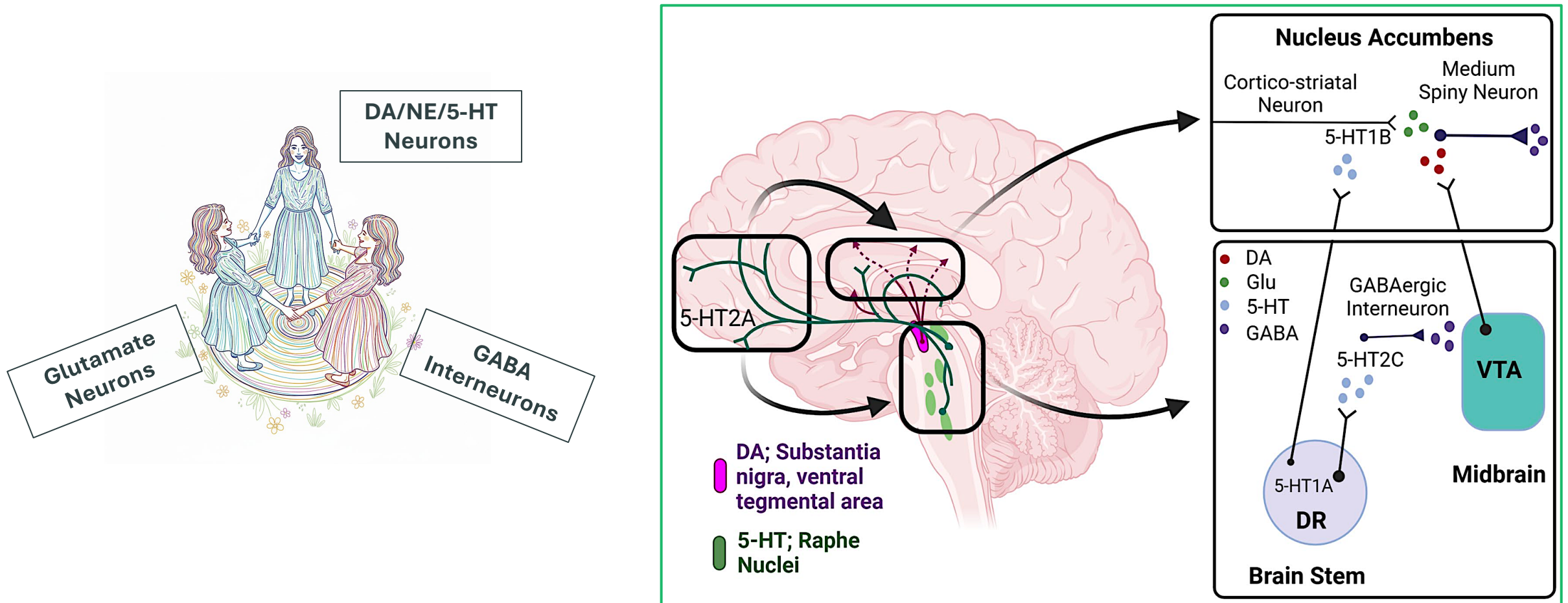
Evidence for Serotonin Dysfunction in ADHD Is Rapidly Gathering Steam



The role of serotonin in the following is well established:

- Major depression
- Impulsivity
- Emotional dysregulation
- Sleep

ADHD Is a Story of Autoreceptors, Heteroreceptors, And Interactions of Multiple Neurotransmitters



Key Learning Points

- The serotonergic system may represent an important, yet neglected therapeutic target in ADHD, particularly for symptoms of emotional dysregulation
- Neurobiology reveals structural and functional abnormalities in the brain that tie the 'classic' symptoms of ADHD to emotional dysregulation and executive dysfunction
 - At the receptor level, DA, NE, and 5-HT, along with glutamate and GABA (and their auto- and hetero-receptors) are implicated in ADHD and emotional and executive function dysregulation

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Thank You!

