

ADHD Neurobiology

The Interplay Between Dopamine, Norepinephrine, And Serotonin

ADHD NEUROBIOLOGY: NE, DA, AND 5-HT INTERPLAY

The interplay between NE, DA, 5-HT plays a critical role in ADHD neurobiology and is complex; changes in one can affect others¹

ADHD symptoms reflect contributions from all three neurotransmitter systems.

Core symptoms²

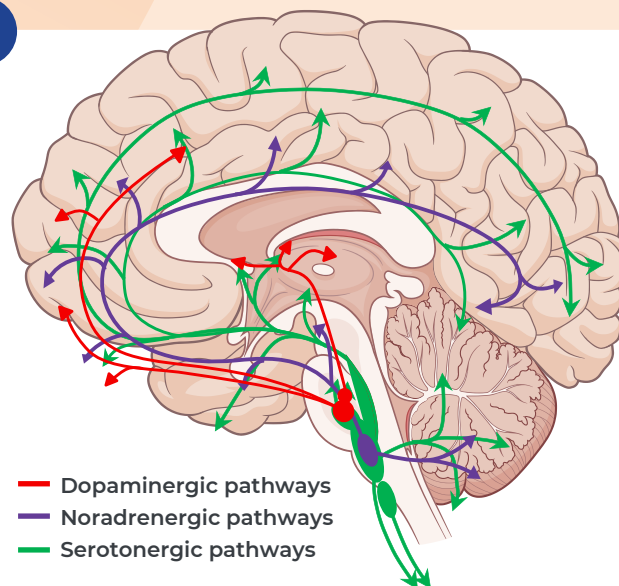
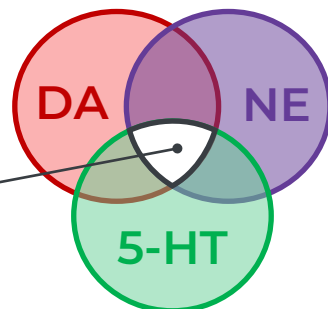
Inattention, hyperactivity, impulsivity

Associated features²

Emotional dysregulation, executive dysfunction

Comorbidities^{2*}

Anxiety, depression



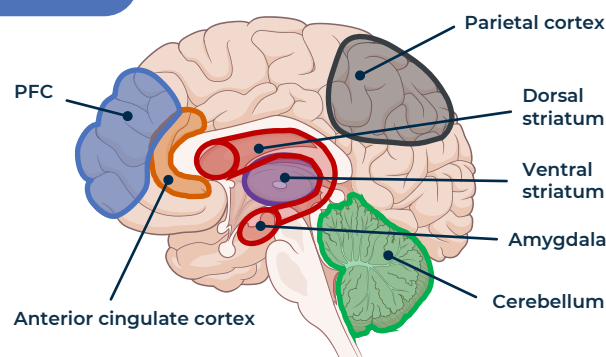
— Dopaminergic pathways
— Noradrenergic pathways
— Serotonergic pathways

BRAIN STRUCTURES AND NETWORKS IMPLICATED IN ADHD

NE, DA, and 5-HT neurotransmission influences cortical and subcortical function, suggesting key roles in the neurobiology of ADHD^{1,3}

Physiological Functions^{4,5}

- DA** Movement, mood, attention, learning and memory, and reward processing
- NE** Attention, arousal, signal-to-noise processing, mood regulation, and stress response
- 5-HT** Mood, perception, appetite, aggression, anxiety, and reward processing



Brain Networks Implicated In ADHD⁶

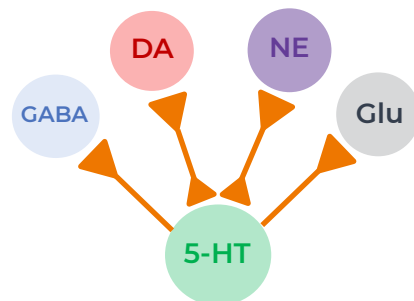
- Executive control network
- Reward network
- Alerting network and default mode network

EMERGING EVIDENCE SUPPORTS 5-HT IN INTEGRATED MODEL OF ADHD

Recent findings support the inclusion of 5-HT as part of an "integrative model" of ADHD neurobiology that involves 3 monoamines: DA, NE, and 5-HT.⁶⁻¹⁰

- Interactions with dopaminergic and noradrenergic systems, where neurotransmitters modulate one another's activity⁵
- Disruption of 5-HT signaling pathways, potentially contributing to ADHD neurobiology^{3,5}
- Altered 5-HT bioavailability, resulting from systemic changes in transport, synthesis, and metabolism⁸⁻¹⁷
- Genetic risk factors and changes, leading to altered neurotransmitter interactions and/or aberrant 5-HT signaling¹⁸⁻²⁰

5-HT interacts with other neurotransmitters (DA and NE, as well as GABA and Glu)⁵



*Additional major comorbidities include sleep disorders and SUDs.

5-HT, serotonin; ADHD, attention-deficit/hyperactivity disorder; DA, dopamine; GABA, γ-aminobutyric acid; Glu, glutamate; NE, norepinephrine; PFC, prefrontal cortex.

References:

1. Faraone SV, Radonjić NV. *Tas Psych*. 2023;1:28.
2. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 5th ed, text revision. Arlington, VA: American Psychiatric Association; 2022.
3. Faraone SV, et al. *Nat Rev Dis Primers*. 2024;10(1):11.
4. da Silva BS, et al. *Discov Ment Health*. 2023;3(1):2.
5. Pourhamzeh M, et al. *Cell Mol Neurobiol*. 2022;42(6):1671-1692.
6. Faraone SV, et al. *Neurosci Biobehav Rev*. 2025;176:106275.
7. Koirala S, et al. *Nat Rev Neurosci*. 2024;25(12):759-775.
8. Spivak B, et al. *Acta Psychiatr Scand*. 1999;99(4):300-304.
9. Hercigonja Novkovic V, et al. *Neuropsychobiology*. 2009;59(1):17-22.
10. Lee SK, et al. *J Phys Ther Sci*. 2015;27(9):2915-2919.
11. Kautzky A, et al. *Transl Psychiatry*. 2020;10(1):104.
12. Oades RD, et al. *World J Biol Psychiatry*. 2002;3(2):96-100.
13. Trujillo V, et al. *Behav Brain Res*. 2024;462:114867.
14. Biskup CS, et al. *Acta Psychiatr Scand*. 2016;134(2):161-171.
15. Johansson J, et al. *Behav Brain Funct*. 2011;7:40.
16. Castellanos FX, et al. *Psychiatry Res*. 1994;52(3):305-316.
17. Moriarty M, et al. *Anal Bioanal Chem*. 2011;401(8):2481-2493.
18. Faraone SV, et al. *Springer, Cham*; 2023:1-28.
19. Wang Y, et al. *Neurosci Lett*. 2021;760:136086.
20. Sudre G, et al. *Mol Psychiatry*. 2023;28(2):792-800.

PsychU is supported by Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC) and Otsuka America Pharmaceutical, Inc. (OAPI) — committed supporters of the mental health treatment community. The information provided through PsychU is intended for the educational benefit of mental health care professionals and others who support mental health care. It is not intended as, nor is it a substitute for, medical care, advice, or professional diagnosis. Health care professionals should use their independent medical judgement when reviewing PsychU's educational resources. Users seeking medical advice should consult with a health care professional. No CME or CEU credits are available through any of the resources provided by PsychU. Some of the contributors may be paid consultants for OPDC and OAPI.