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Pathophysiology of Agitation Associated With Alzheimer's Dementia (AD)

The Potential Role of the Norepinephrine, Serotonin, and Dopamine (NSD) Neurotransmitter Systems

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Poll Question for Audience

- How familiar are you with the pathophysiology of agitation in AD?
  - Not at all familiar
  - Slightly familiar
  - Somewhat familiar
  - Moderately familiar
  - Extremely familiar

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Outline

- Loss of Behavior Regulation in Agitation associated with AD
- Monoamine Systems in Agitation associated with AD Pathophysiology
  - Norepinephrine
  - Serotonin
  - Dopamine
- Summary

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Loss of Behavior Regulation in Agitation Associated with AD

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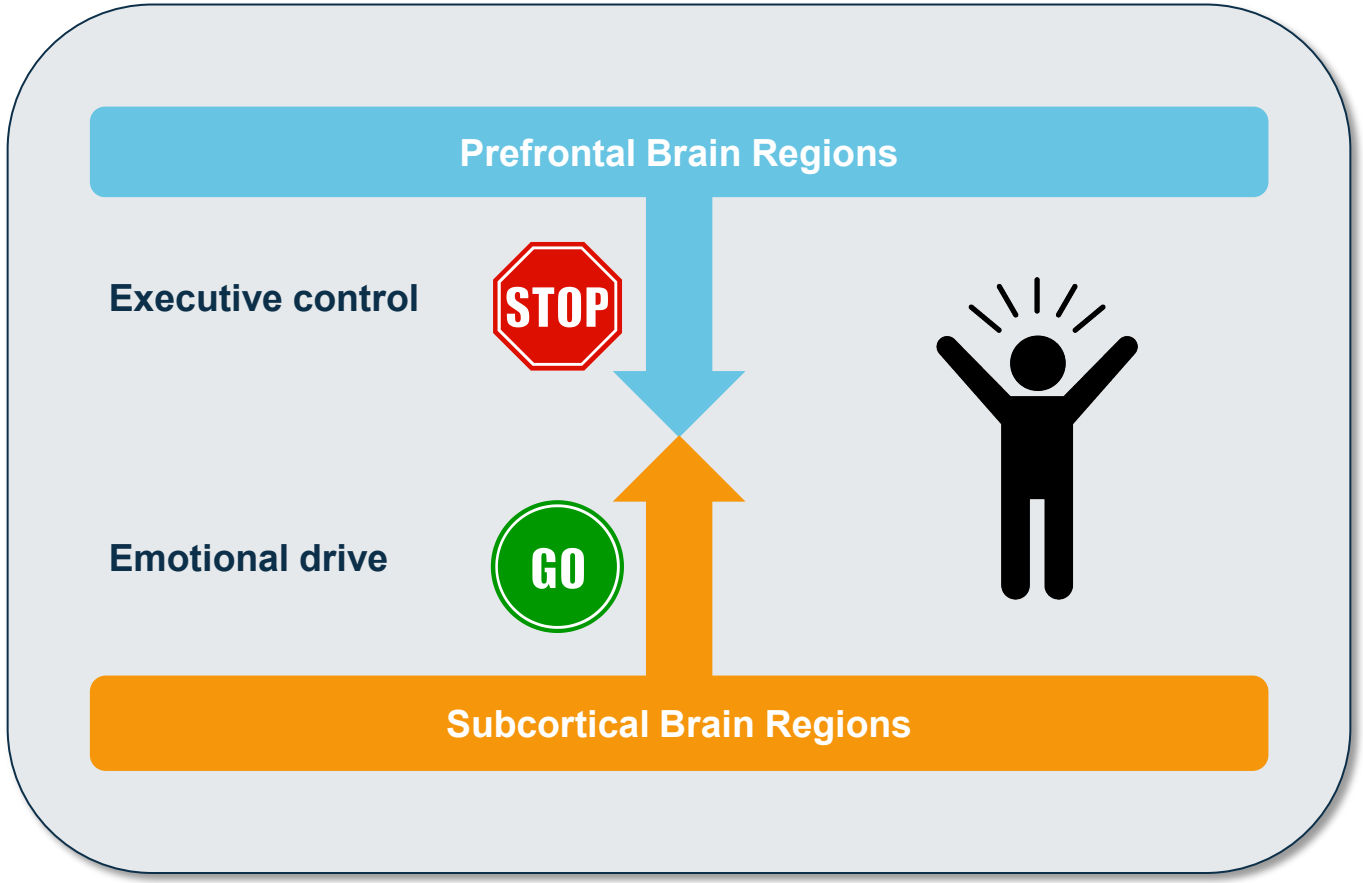
Behavior is regulated by balance between executive control and emotional drive[1,2]



1. Ray RD, et al. *Neurosci Biobehav Rev*. 2012;36(1):479-501. 2. Arnsten AF, et al. *Neurobiol Stress*. 2015;1:89-99.

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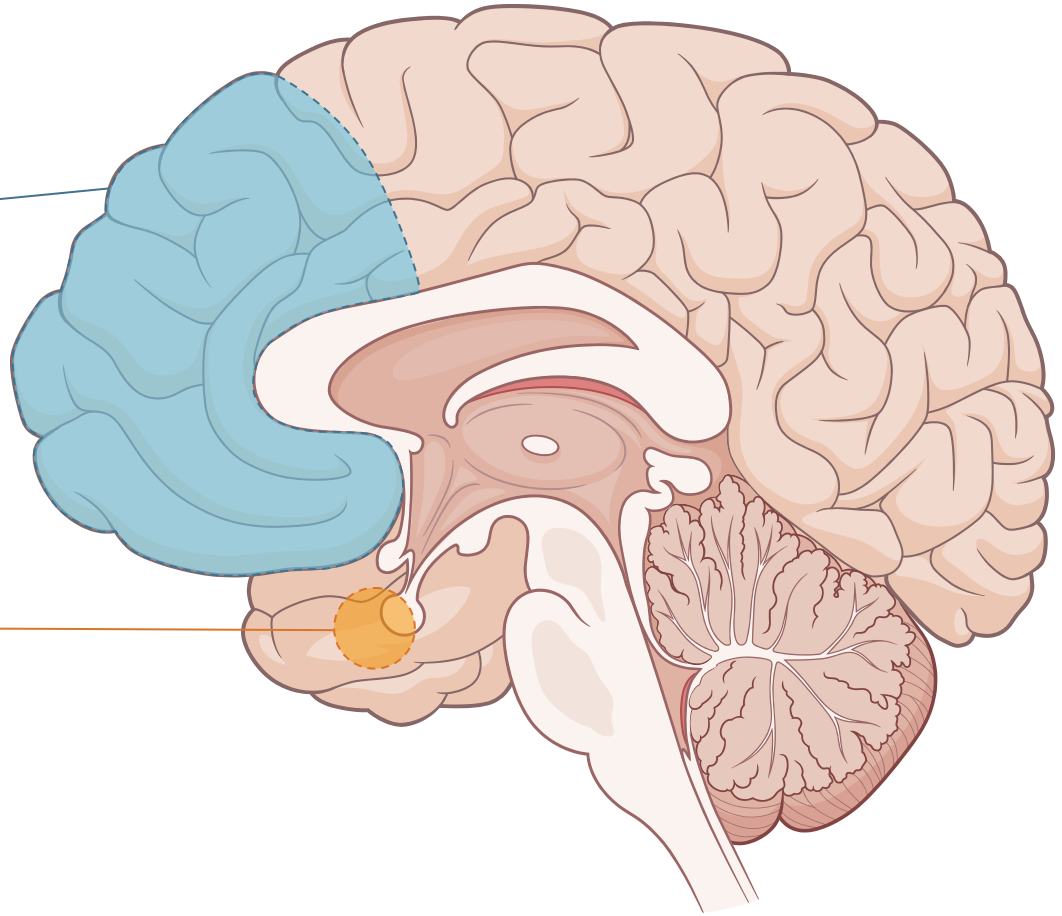
Key Prefrontal and Subcortical Brain Regions Mediate Executive Control and Emotional Drive

Executive Control

Prefrontal Cortex (PFC)
Top-down regulation of behavior, thought, and emotion[1,2]

Emotional Drive

Subcortical Regions Including Amygdala
Emotional hub of the brain[1,2]



1. Salzman CD, et al. *Annu Rev Neurosci*. 2010;33:173-202. 2. Arnsten AF, et al. *Neurobiol Stress*. 2015;1:89-99.

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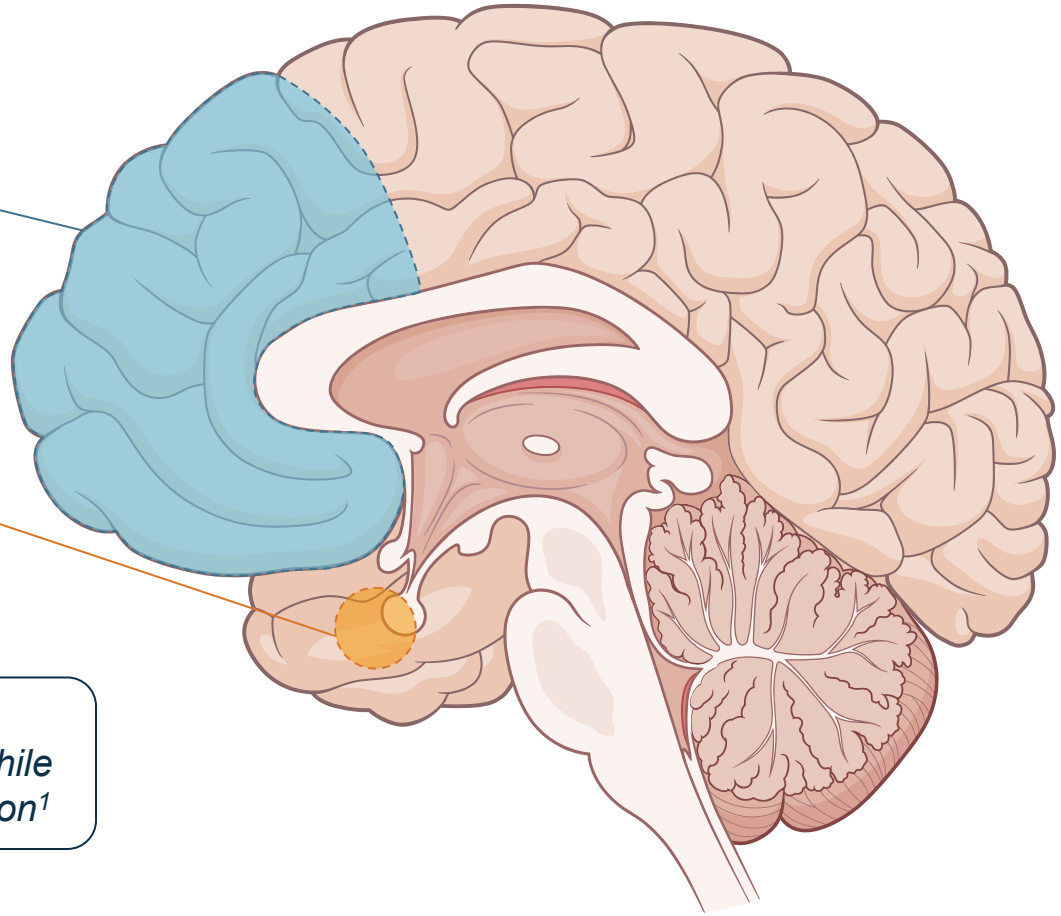
Tau Pathology and Neurodegeneration in Key Prefrontal and Subcortical Brain Regions May Increase the Risk of Developing Agitation Associated with AD

Prefrontal Cortex (PFC)

- Agitation is associated with PFC tau pathology* and neurodegeneration in patients with AD[2-5]

Amygdala

- The amygdala is severely impacted in AD, with tau pathology observed at relatively early stages of the disease[6,7]



**In patients with AD, increased CSF levels of total tau and phosphorylated tau were associated with greater agitation, while there was no relationship between levels of $A\beta_{1-42}$ and agitation[1]*

$A\beta_{1-42}$, β-amyloid peptide (1-42); AD, Alzheimer's dementia; CSF, cerebrospinal fluid

1. Bloniecki V, et al. *Dement Geriatr Cog Disord Extra*. 2014;4(2):335-343. 2. Tekin S, et al. *Ann Neurol*. 2001;49(3):355-361. 3. Guadagna S, et al. *Neurobiol Aging*. 2012;33(12):2798-2806. 4. Hu X, et al. *Curr Alzheimer Res*. 2015;12(3):266-277. 5. Trzepacz PT, et al. *Alzheimers Dement*. 2013;9(5 Suppl):S95-S104.e1. 6. Esiri MM, et al. *J Neurol Neurosurg Psychiatry*. 1990;53(2):161-165. 7. Braak H, et al. *Acta Neuropathol*. 1991;82(4):239-259.

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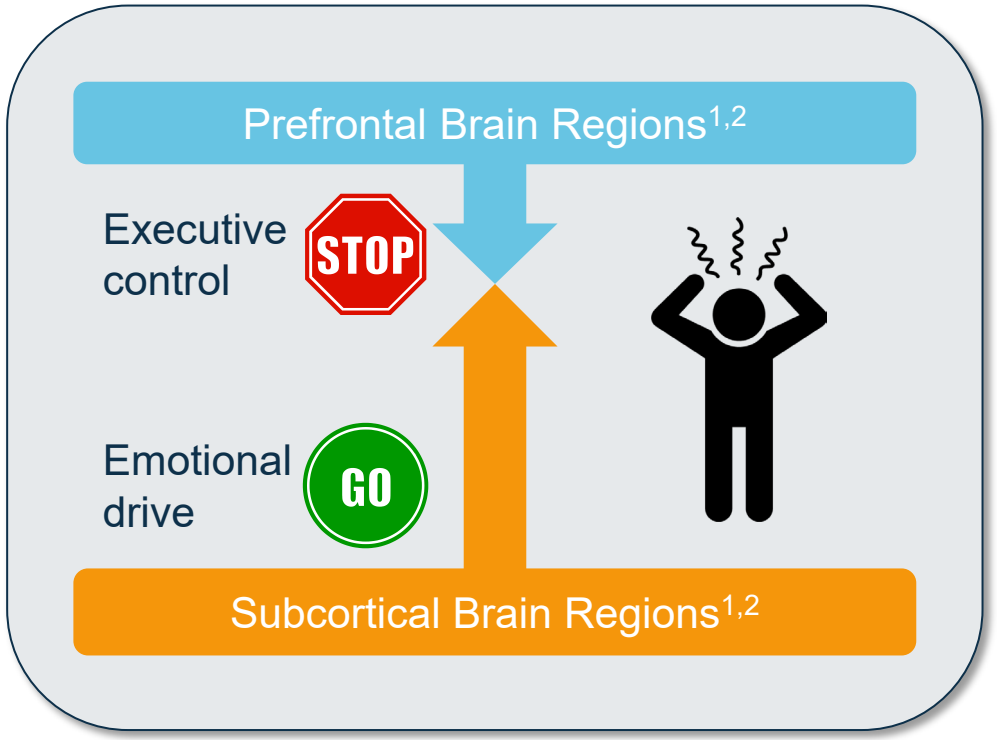
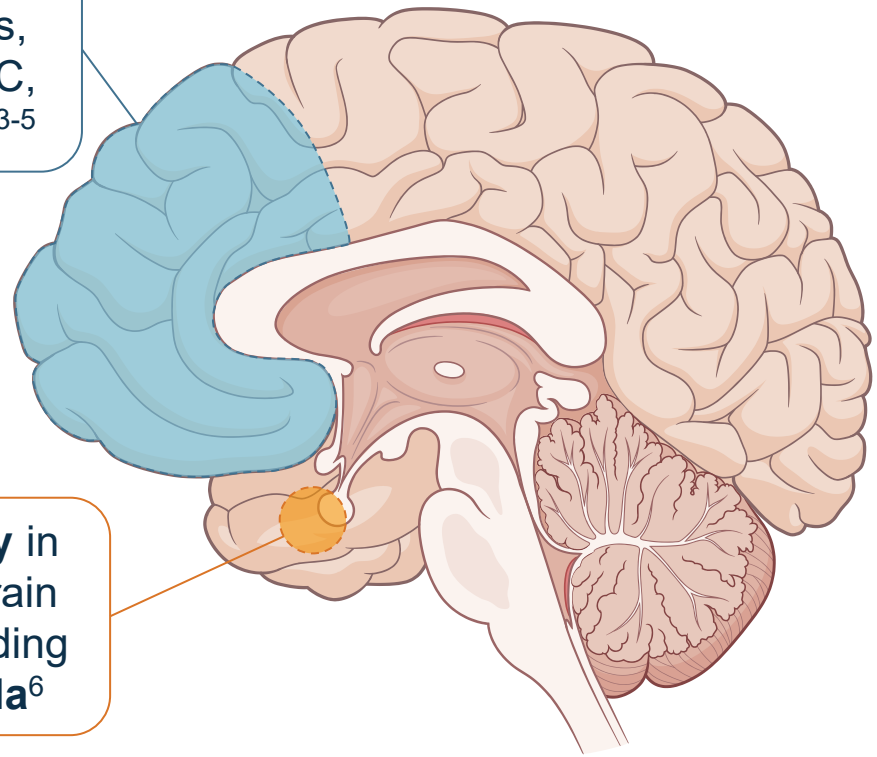
Agitation in AD Is Associated With an Imbalance Between Executive Control and Emotional Drive



Hypoactivity in **prefrontal** regions, including the dlPFC, vmPFC, and OFC[3-5]



Hyperactivity in subcortical brain regions, including the **amygdala**[6]

dlPFC, dorsolateral PFC; OFC, orbitofrontal cortex; PFC, prefrontal cortex; vmPFC, ventromedial PFC

1. Rosenberg PB, et al. *Mol Aspects Med*. 2015;43-44:25-37. 2. Carrarini C, et al. *Front Neurol*. 2021;12:644317. 3. Hirono N, et al. *Arch Neurol*. 2000;57(6):861-866. 4. Banno K, et al. *Neuropsychiatr Dis Treat*. 2014;10:339-348. 5. Ng KP, et al. *Transl Neurodegener*. 2021;10(1):1. 6. Wright CI, et al. *Biol Psychiatry*. 2007;62(12):1388-1395.

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Poll Question for Audience

- How aware were you that agitation might be a result of an imbalance between executive control and emotional drive?
    - Not at all aware
    - Slightly aware
    - Somewhat aware
    - Moderately aware
    - Extremely aware

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Monoamine Systems in Agitation associated with AD Pathophysiology

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Poll Question for Audience

- How familiar are you with the role of noradrenaline, serotonin, and dopamine (NSD) in the pathophysiology of agitation?
  - Not at all familiar
  - Slightly familiar
  - Somewhat familiar
  - Moderately familiar
  - Extremely familiar

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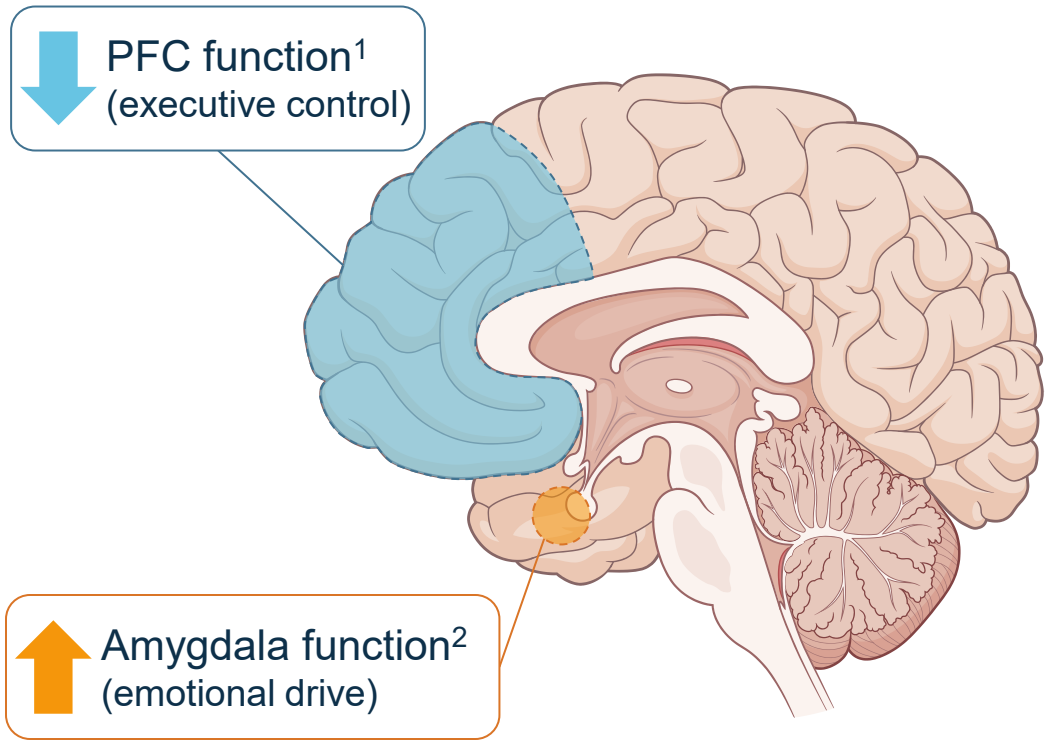
Dysfunction of Monoamine/NSD Neurotransmitter Systems May Disrupt the Balance Between Executive Control and Emotional Drive



Monoamine system status in AAD	Potential relationship with agitation behavior
Norepinephrine system hyperactivity[3]	• Impaired executive control[4] • Increased emotional drive[4]
Serotonin system deficits[5]	• Altered PFC regulation of the amygdala[6] • Increased aggression and impulsivity[7]
Dopamine system relatively preserved[5]; however, serotonin deficits can increase striatal dopamine[8]	• Increased striatal dopamine activity may lead to agitation[9]

AAD, agitation in Alzheimer's dementia; NSD, norephinephrine, serotonin, and dopamine; PFC, prefrontal cortex

1. Banno K, et al. *Neuropsychiatr Dis Treat*. 2014;10:339-348. 2. Wright CI, et al. *Biol Psychiatry*. 2007;62(12):1388-1395. 3. Jacobs HI, et al. *Mol Psychiatry*. 2021;26(3):897-906. 4. Arnsten AF, et al. *Neurobiol Stress*. 2015;1:89-99. 5. Lanctôt KL, et al. *J Neuropsychiatry Clin Neurosci*. 2001;13(1):5-21. 6. Evers EA, et al. *Curr Pharm Des*. 2010;16(18):1998-2011. 7. Duke AA, et al. *Psychol Bull*. 2013;139(5):1148. 8. Cox SM, et al. *Br J Psychiatry*. 2011;199(5):391-397. 9. Lindenmayer JP. *J Clin Psychiatry*. 2000;61 Suppl 14:5-10.

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Noradrenergic System Hyperactivity May Impact the Balance Between Executive Control and Emotional Drive

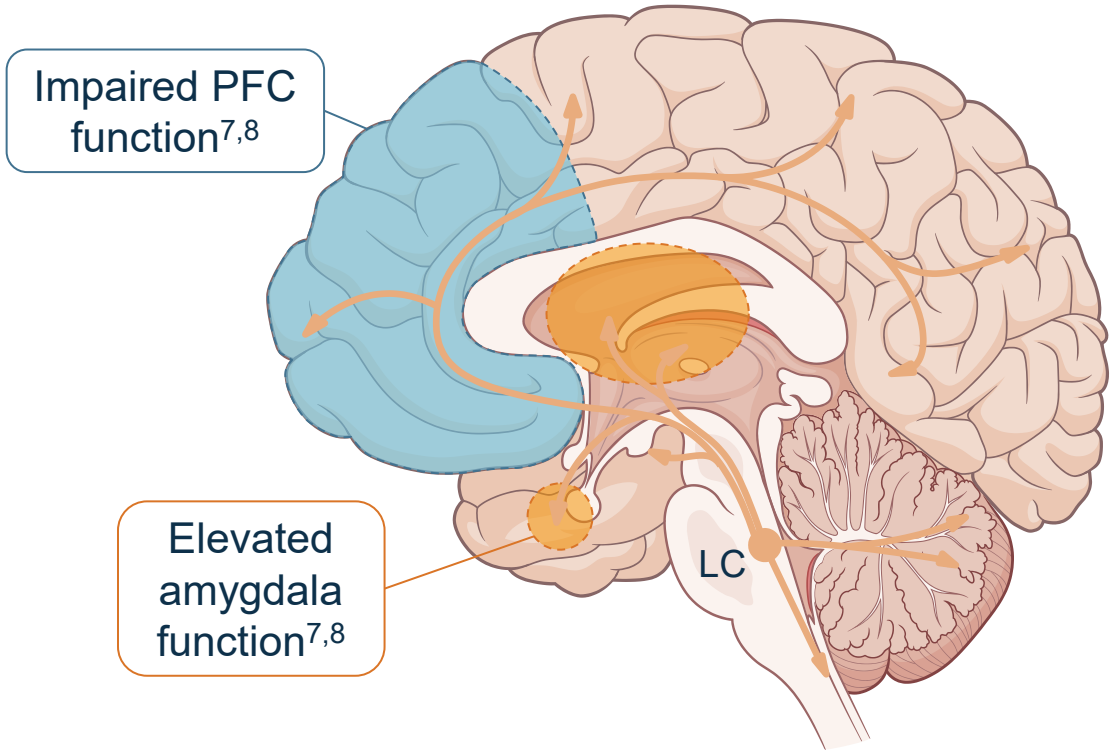
System Pathology

AD is associated with tau pathology and neuronal loss in the locus coeruleus (LC), resulting in compensatory noradrenergic hyperactivity[1-6]

Receptor Activity

Impaired PFC function and elevated amygdala function may be driven, in part, through the activation of α_1-adrenoceptors[7,8]

Effects of Noradrenergic System Hyperactivity on Executive Control and Emotional Drive



AD, Alzheimer's dementia; PFC, prefrontal cortex

1. Theofilas P, et al. *Alzheimers Dement*. 2017;13(3):236-246. 2. Gannon M, et al. *Brain Res*. 2019;1702:12-16. 3. Szot P, et al. *Neuroscience*. 2007;146(1):471-480. 4. Gulyás B, et al. *Neurochem Int*. 2010;56(6-7):789-798. 5. Jacobs HI, et al. *Mol Psychiatry*. 2021;26(3):897-906. 6. Sharp SI, et al. *Am J Geriatr Psychiatry*. 2007;15(5):435-437. 7. Miller CWT, et al. *West J Emerg Med*. 2020;21(4):841-848. 8. Arnsten AF, et al. *Neurobiol Stress*. 2015;1:89-99.

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Noradrenergic System Hyperactivity via α_1-Adrenoceptors May Impair PFC Function and Drive Amygdala Function

Optimal levels of NE are important for appropriate PFC activity[1-3]

Important Note: *prolonged exposure to excessive NE desensitizes α_{2C}-adrenoceptors[4,5]*

Rodent studies indicate that:

- Hyperactivation of α_1-adrenoceptor drives amygdala function[6,7]
- Blockade of α_1-adrenoceptors decreases fear and anxiety-like behaviors[7,8]

NE, norepinephrine; PFC, prefrontal cortex

1. Miller CWT, et al. *West J Emerg Med*. 2020;21(4):841-848. 2. Arnsten AF. *Nat Rev Neurosci*. 2009;10(6):410-422. 3. Arnsten AF, et al. *Neurobiol Stress*. 2015;1:89-99. 4. Uys MM, et al. *Front Psychiatry*. 2017;8:144. 5. Bücheler MM, et al. *Neuroscience*. 2002;109(4):819-826. 6. Gu Y, et al. *Mol Psychiatry*. 2020;25(3):640-654. 7. Ferry B, et al. *Eur J Pharmacol*. 1999;372(1):9-16. 8. Cecchi M, et al. *Neuropharmacology*. 2002;43(7):1139-1147.

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AD Is Associated With Noradrenergic System Hyperactivity, Which May Contribute to Agitation Behaviors

AD is associated with noradrenergic system pathology and compensatory hyperactivity[1-4]

Pathology in AD

In patients with AD, tau accumulation in LC neurons begins early in the course of the disease, with LC degeneration occurring as the disease progresses[1,2]

Compensatory effects that enhance overall NE sensitivity

Patients with AD show increased noradrenergic innervation of the PFC, increased NE synthesis capacity, and reduced NE reuptake[2-4]

In patients with AD, agitation is associated with greater noradrenergic system activity[5,6]

- Increased noradrenergic receptor expression within the PFC[5]
- Elevated levels of the NE metabolite MHPG[6]

Noradrenergic system hyperactivity may contribute to agitation in patients with AD by impairing their ability to focus attention and cope with stressful stimuli[7]

AD, Alzheimer's dementia; LC, locus coeruleus; MHPG, 3-methoxy-4-hydroxyphenylglycol; NE, norepinephrine; PFC, prefrontal cortex

1. Theofilas P, et al. *Alzheimers Dement*. 2017;13(3):236-246. 2. Gannon M, et al. *Brain Res*. 2019;1702:12-16. 3. Szot P, et al. *Neuroscience*. 2007;146(1):471-480. 4. Gulyás B, et al. *Neurochem Int*. 2010;56(6-7):789-798. 5. Sharp SI, et al. *Am J Geriatr Psychiatry*. 2007;15(5):435-437. 6. Jacobs HI, et al. *Mol Psychiatry*. 2021;26(3):897-906. 7. Herrmann N, et al. *J Neuropsychiatry Clin Neurosci*. 2004;16(3):261-276.

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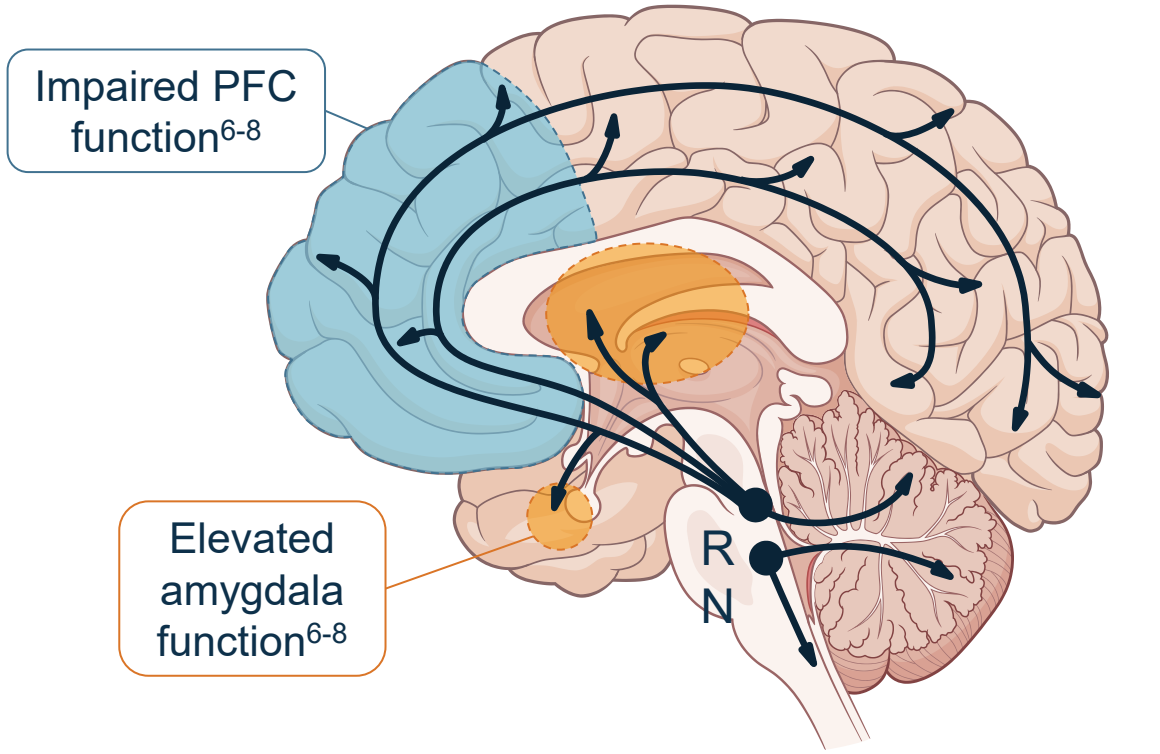
Serotonergic System Deficits May Impact the Balance Between Executive Control and Emotional Drive

System Pathology
AD is associated with decreased levels of serotonin in the frontal cortex and amygdala and loss of serotonergic neurons in the RN[1-4]

Receptor Activity
Serotonin 5-HT_{1A} receptor binding in the PFC and amygdala is associated with reduced aggression and impulsivity[5]

Effects of Serotonergic System Deficits on Executive Control and Emotional Drive



AD, Alzheimer's dementia; PFC, prefrontal cortex; RN, raphe nuclei

1. Lanctôt KL, et al. *J Neuropsychiatry Clin Neurosci*. 2001;13(1):5-21. 2. Garcia-Alloza M, et al. *Neuropsychologia*. 2005;43(3):442-449. 3. Vermeiren Y, et al. *Neurobiol Aging*. 2014;35(12):2691-2700. 4. Lanctôt KL, et al. *Neuropsychopharmacology*. 2002;27(4):646-654. 5. Nelson RJ, et al. *Nat Rev Neurosci*. 2007;8(7):536-546. 6. Duke AA, et al. *Psychol Bull*. 2013;139(5):1148. 7. Evers EA, et al. *Curr Pharm Des*. 2010;16(18):1998-2011. 8. Passamonti L, et al. *Biol Psychiatry*. 2012;71(1):36-43.

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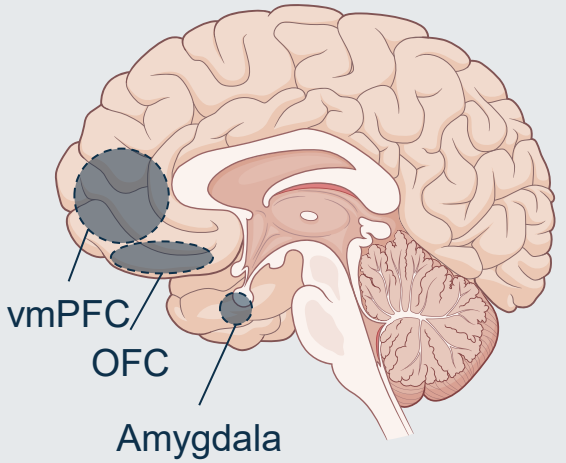
Serotonergic System Deficits Are Associated With PFC and Amygdala Dysfunction

Aggression was associated with decreased 5-HT_{1A} binding in the PFC and amygdala in healthy adults[1]

5-HT_{1A} receptor binding in the PFC and amygdala is associated with reduced aggression and impulsivity in rodents[2-4]

5-HT depletion can decrease OFC activity, increase amygdala activity, and alter vmPFC-amygdala connectivity[5-7]



5-HT, serotonin; OFC, orbitofrontal cortex; PFC, prefrontal cortex; vmPFC, ventromedial PFC

1. Nelson RJ, et al. *Nat Rev Neurosci*. 2007;8(7):536-546. 2. Puig MV, et al. *Mol Neurobiol*. 2011;44(3):449-464. 3. Centenaro LA, et al. *Psychopharmacology (Berl)*. 2008;201(2):237-248. 4. Stein C, et al. *Synapse*. 2000;38(3):328-337. 5. Duke AA, et al. *Psychol Bull*. 2013;139(5):1148. 6. Evers EA, et al. *Curr Pharm Des*. 2010;16(18):1998-2011. 7. Passamonti L, et al. *Biol Psychiatry*. 2012;71(1):36-43.

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AD Is Associated With Serotonergic System Deficits, Which May Contribute to Agitation Behaviors

Patients with AD show pronounced serotonergic system deficits, including in the PFC and amygdala[1,2]

- Loss of serotonergic neurons in the RN[1]
- Decreased concentrations of 5-HT and its metabolite 5-HIAA in multiple brain regions, including the PFC[1,2]
- Decreased levels of serotonin 5-HT_{1A} and 5-HT_{2A} receptors in the frontal cortex and amygdala[1]

Agitation in patients with AD is associated with greater serotonergic system deficits[1-3]

- Decreased levels of 5-HT and 5-HIAA in the PFC[1-3]
- Decreased binding to the platelet serotonin transporter system[1]

5-HIAA, 5-hydroxyindoleacetic acid; 5-HT, serotonin; AD, Alzheimer's dementia; PFC, prefrontal cortex; RN, raphe nuclei

1. Lanctôt KL, et al. *J Neuropsychiatry Clin Neurosci*. 2001;13(1):5-21. 2. Garcia-Alloza M, et al. *Neuropsychologia*. 2005;43(3):442-449. 3. Vermeiren Y, et al. *Neurobiol Aging*. 2014;35(12):2691-2700.

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Dopaminergic System Dysfunction May Contribute to Agitated and Aggressive Behaviors

System Pathology

The dopaminergic system is relatively spared in AD[1]

5-HT is an important regulator of DA activity, suggesting that 5-HT deficits in patients with AD may lead to DA dysregulation[1-4]

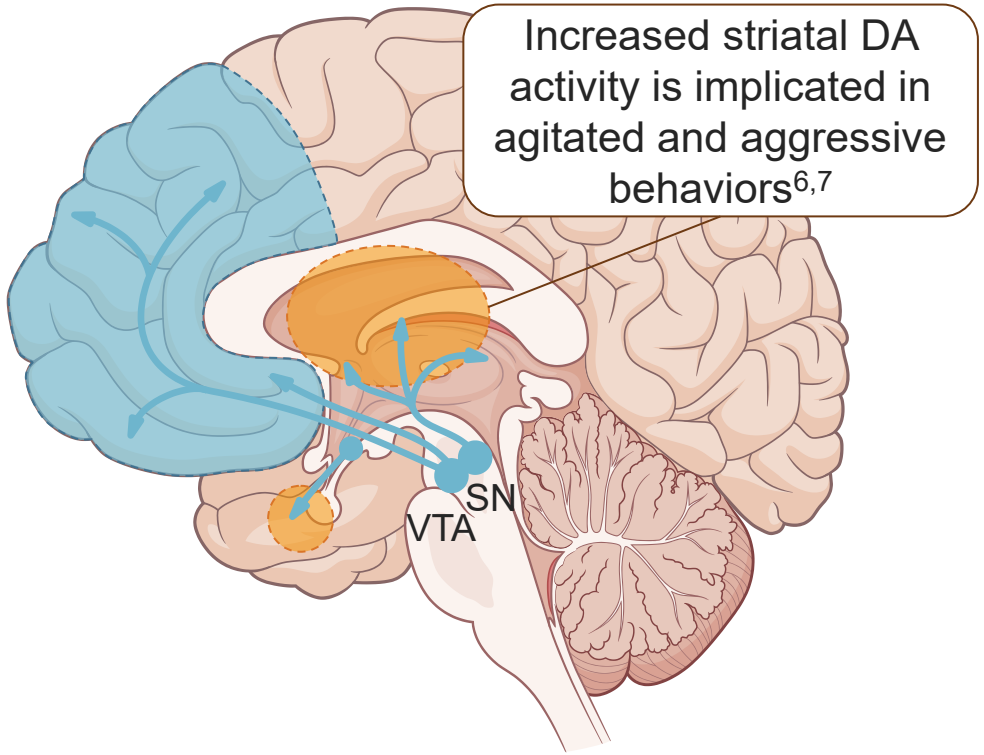
DA in the midbrain integrates top-down and bottom-up information processing, so DA system dysfunction might alter this control[5]

Receptor Activity

Dopamine D_2 receptor antagonism is associated with reduced aggressive behaviors[6,7]

While some antipsychotics act as D_2 receptor antagonists, others act as partial D_2 receptor agonists to modulate dopaminergic signaling downward from a hyperactive state without fully silencing D_2 receptor activity[8]

Effects of Dopaminergic System Dysfunction



5-HT, serotonin; AD, Alzheimer's dementia; DA, dopamine; PFC, prefrontal cortex; SN, substantia nigra; VTA, ventral tegmental area

1. Lanctôt KL, et al. *J Neuropsychiatry Clin Neurosci*. 2001;13(1):5-21. 2. Aral H, et al. *J Neurochem*. 1984;43(2):388-393. 3. Kelland MD, et al. *J Pharmacol Exp Ther*. 1990;253(2):803-811. 4. Cox SM, et al. *Br J Psychiatry*. 2011;199(5):391-397. 5. Beeler JA, et al. *eNeuro*. 2019;6(2):ENEURO.0345-18.2019. 6. De Deyn PP, et al. *Clin Neurol Neurosurg*. 2005;107(6):497-508. 7. Beiderbeck DI, et al. *Psychoneuroendocrinology*. 2012;37(12):1969-1980. 8. Stahl SM. 4th ed. Cambridge University Press; 2013.

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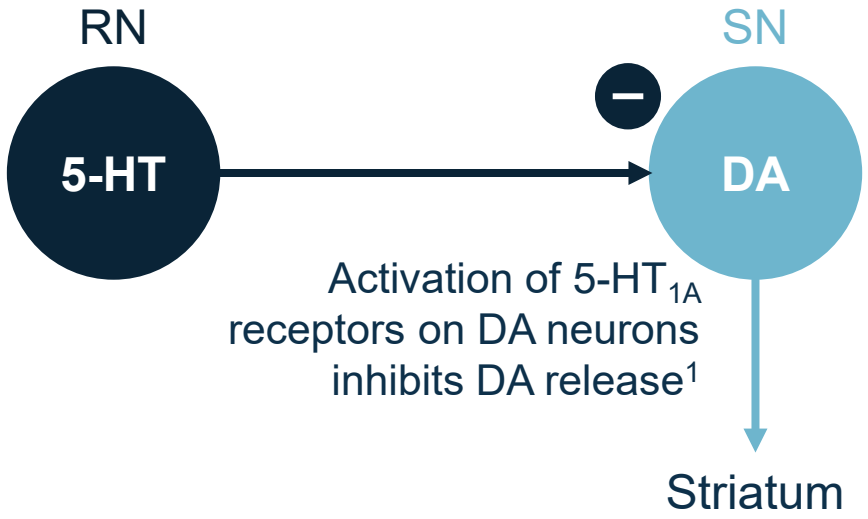
The Dopaminergic System May Be Dysregulated in Patients With AD

5-HT deficits in the striatum and substantia nigra (SN) of patients with AD could cause DA dysregulation[1-4]

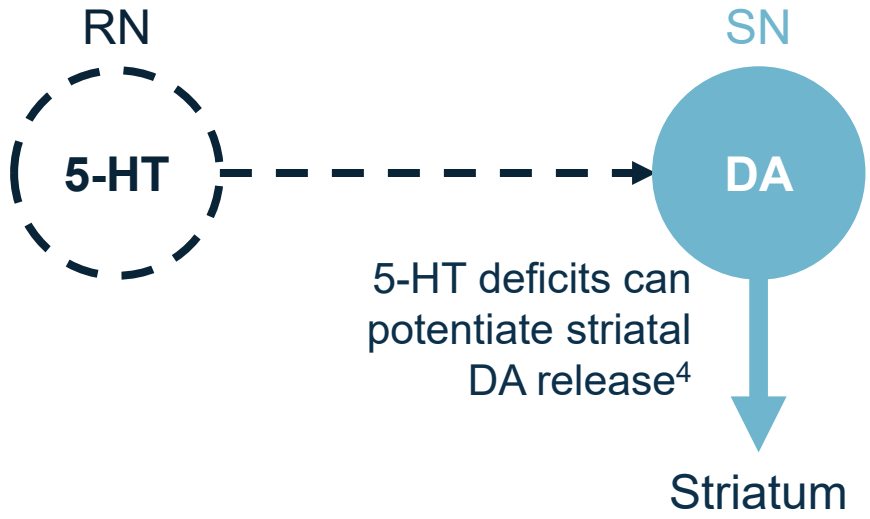
Serotonin is an important regulator of dopaminergic activity[1,2]

5-HT neurons from the raphe nuclei synapse with DA neurons[1,2]



Reduction of serotonin can increase striatal dopaminergic activity[1-4]

AD is associated with 5-HT deficits in the striatum and SN[3]



5-HT, serotonin; AD, Alzheimer's dementia; DA, dopamine; RN, raphe nuclei

1. Lanctôt KL, et al. *J Neuropsychiatry Clin Neurosci*. 2001;13(1):5-21. 2. Kelland MD, et al. *J Pharmacol Exp Ther*. 1990;253(2):803-811. 3. Aral H, et al. *J Neurochem*. 1984;43(2):388-393. 4. Cox SM, et al. *Br J Psychiatry*. 2011;199(5):391-397.

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Increased Striatal Dopamine Activity May Be Implicated in Agitated and Aggressive Behaviors

In both human and rodent studies, dopamine D_2 receptor antagonism is associated with reduced aggressive behaviors[1-4]

- In rodents, increased aggressive behavior was associated with higher DA release in and greater activation of the ventral striatum[1]
- In rodents, stimulation of D_2 receptors increased aggression, while antagonism of striatal dopamine D_2 receptors decreased aggression[1-3]
- Treatment with a D_2 receptor antagonist was associated with improved agitation and aggression in patients with dementia[4]

DA, dopamine

1. Beiderbeck DI, et al. *Psychoneuroendocrinology*. 2012;37(12):1969-1980. 2. Nikulina EM, et al. *Neurosci Behav Physiol*. 1992;22(5):364-369. 3. Couppis MH, et al. *Psychopharmacology (Berl)*. 2008;197(3):449-456. 4. De Deyn PP, et al. *Clin Neurol Neurosurg*. 2005;107(6):497-508.

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Summary

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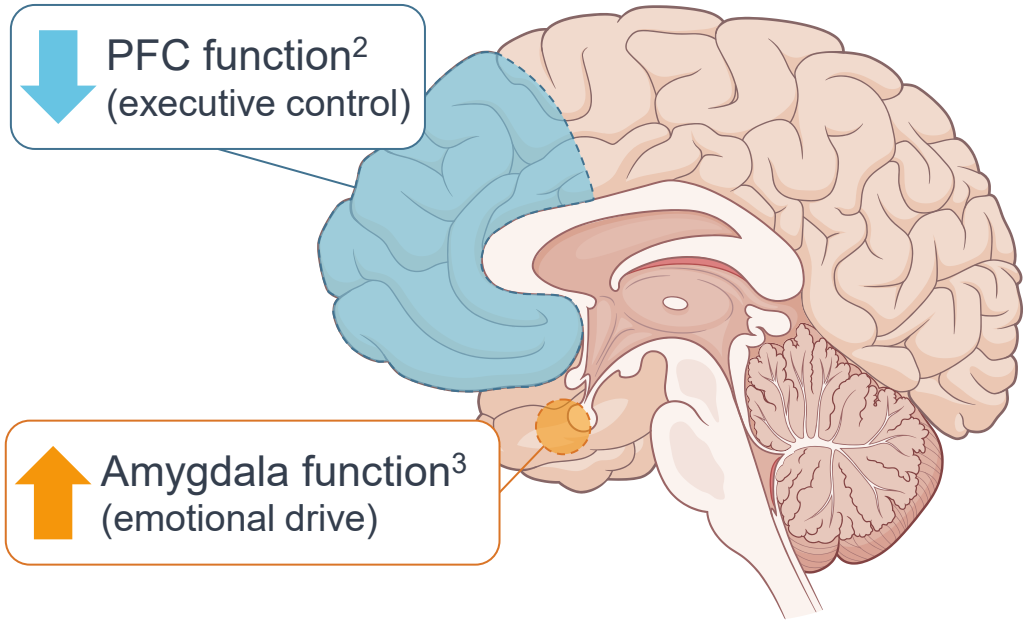
Monoamine/NSD Neurotransmitter Systems in Agitation associated with AD Pathophysiology

Tau pathology and neurodegeneration in key prefrontal and subcortical brain regions may increase the risk of developing agitation associated with AD[1]

AAD may reflect an imbalance between top-down executive control and bottom-up emotional drive[1]



Monoamine system status in AAD	Potential relationship with agitation behavior
Norepinephrine system hyperactivity[4]	• Impaired executive control[5] • Increased emotional drive[5]
Serotonin system deficits[6]	• Altered PFC regulation of the amygdala[7] • Increased aggression and impulsivity[8]
Dopamine system relatively preserved[6]; however, serotonin deficits can increase striatal dopamine[9]	• Increased striatal dopamine activity may lead to agitation[10]

AAD, agitation in Alzheimer's dementia; NSD, norepinephrine, serotonin, and dopamine system; PFC, prefrontal cortex

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Poll Question for Audience

- After participating in this educational activity, how might the role of the NSD system impact the way you think about managing agitation associated with AD?
  - No impact at all
  - Slightly impacts
  - Somewhat impacts
  - Moderately impacts
  - Very much impacts

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Pathophysiology of Agitation Associated With Alzheimer's Dementia (AD)

The Potential Role of the Norepinephrine, Serotonin, and Dopamine (NSD) Neurotransmitter Systems

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