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Pathophysiology Of Agitation Associated With Dementia Due To Alzheimer's Disease

The Potential Role Of The Norepinephrine, Serotonin, And Dopamine (NSD) Neurotransmitter Systems

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Objectives

Review the broad range of agitation symptoms associated with dementia due to Alzheimer's disease

Understand brain pathology and behavior dysregulation in agitation associated with dementia due to Alzheimer's disease

Learn about the monoaminergic dysfunction of agitation associated with dementia due to Alzheimer's disease

Agitation Presents A Broad Spectrum Of Symptoms

- Agitation associated with dementia due to Alzheimer's disease is **a common and treatable condition** with a broad range of symptoms. It requires distinct treatment options from those used for cognitive impairment[1-3]
- Despite its prevalence, **agitation is often under-recognized** by caregivers and underdiagnosed by HCPs[4-6]

Symptoms of **agitation manifest as both non-aggressive and aggressive** behaviors, such as[7,8]

EXCESSIVE MOTOR ACTIVITY:
Pacing, restlessness, repetitiveness, and gesturing

VERBAL AGGRESSION:
Screaming, using profanity, and asking repetitive questions

PHYSICAL AGGRESSION:
Hitting, kicking, punching, biting, and throwing things

HCP, health care provider.

References:

1. Cummings J, et al. *Int Psychogeriatr*. 2015;27(1):7-17.
2. Cohen-Mansfield J. Instruction manual for the Cohen-Mansfield Agitation Inventory (CMAI). Research Institute of the Hebrew Home of Greater Washington; 1991.
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4. Halpern R, et al. *Int J Geriatr Psychiatry*. 2019;34(3):420-431.
5. Lanctôt KJ, et al. *Alzheimers Dement (N Y)*. 2017;3(3):440-449.
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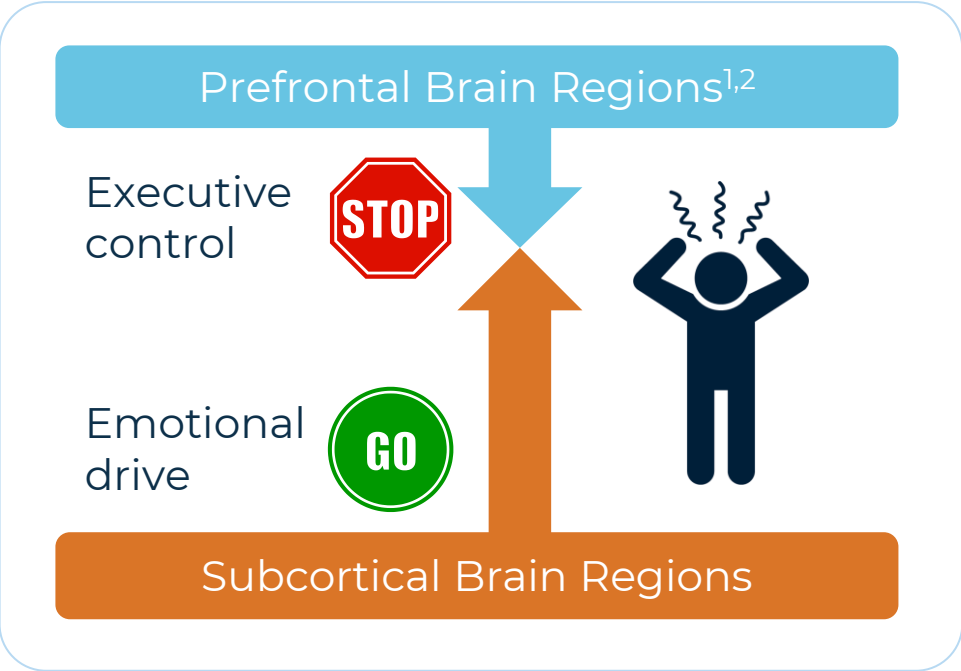
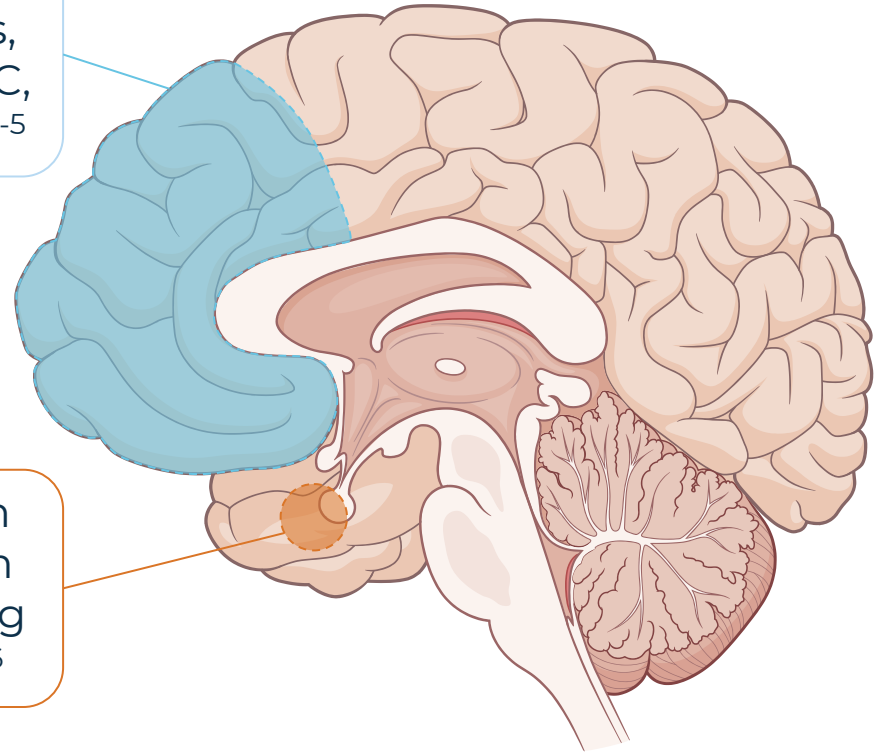
Agitation Is Associated With An Imbalance Between Executive Control And Emotional Drive



Hypoactivity in **prefrontal** regions, including the dlPFC, vmPFC, and OFC[1,3-5]



Hyperactivity in subcortical brain regions, including the **amygdala**[1,6]

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

References:

1. Cummings JL, et al. *CNS Spectr*. 2024:1-10.
2. Rosenberg PB, et al. *Mol Aspects Med*. 2015;43-44:25-37.
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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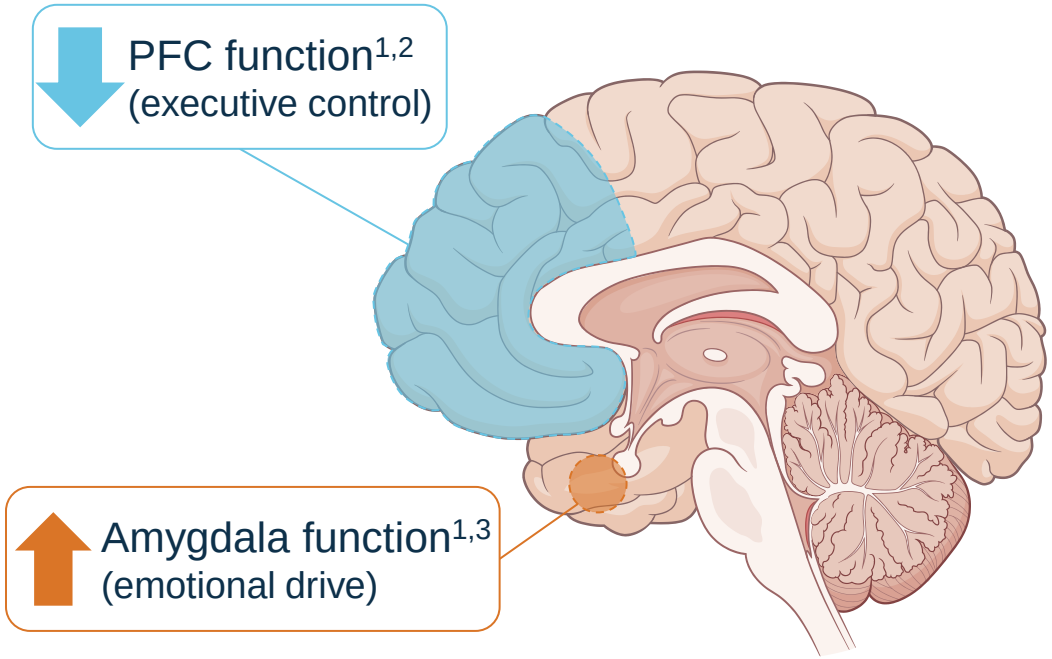
Dysfunction Of Monoamine/NSD Neurotransmitter Systems May Disrupt The Balance Between Executive Control And Emotional Drive



Monoamine System Status	Potential Relationship With Agitation Behavior
NE system hyperactivity[1,4]	• Impaired executive control[1,5] • Increased emotional drive[1,5]
5-HT system deficits[1,6]	• Altered PFC regulation of the amygdala[1,7] • Increased aggression and impulsivity[1,8]
DA system relatively preserved; however, 5-HT deficits can increase striatal DA[1,6,9]	• Increased striatal dopamine activity may lead to agitation[1,10]

5-HT, serotonin; DA, dopamine; NE, norepinephrine; NSD, norepinephrine, serotonin, dopamine; PFC, prefrontal cortex.

References:

1. Cummings JL, et al. *CNS Spectr*. 2024:1-10.
2. Banno K, et al. *Neuropsychiatr Dis Treat*. 2014;10:339-348.
3. Wright CI, et al. *Biol Psychiatry*. 2007;62(12):1388-1395.
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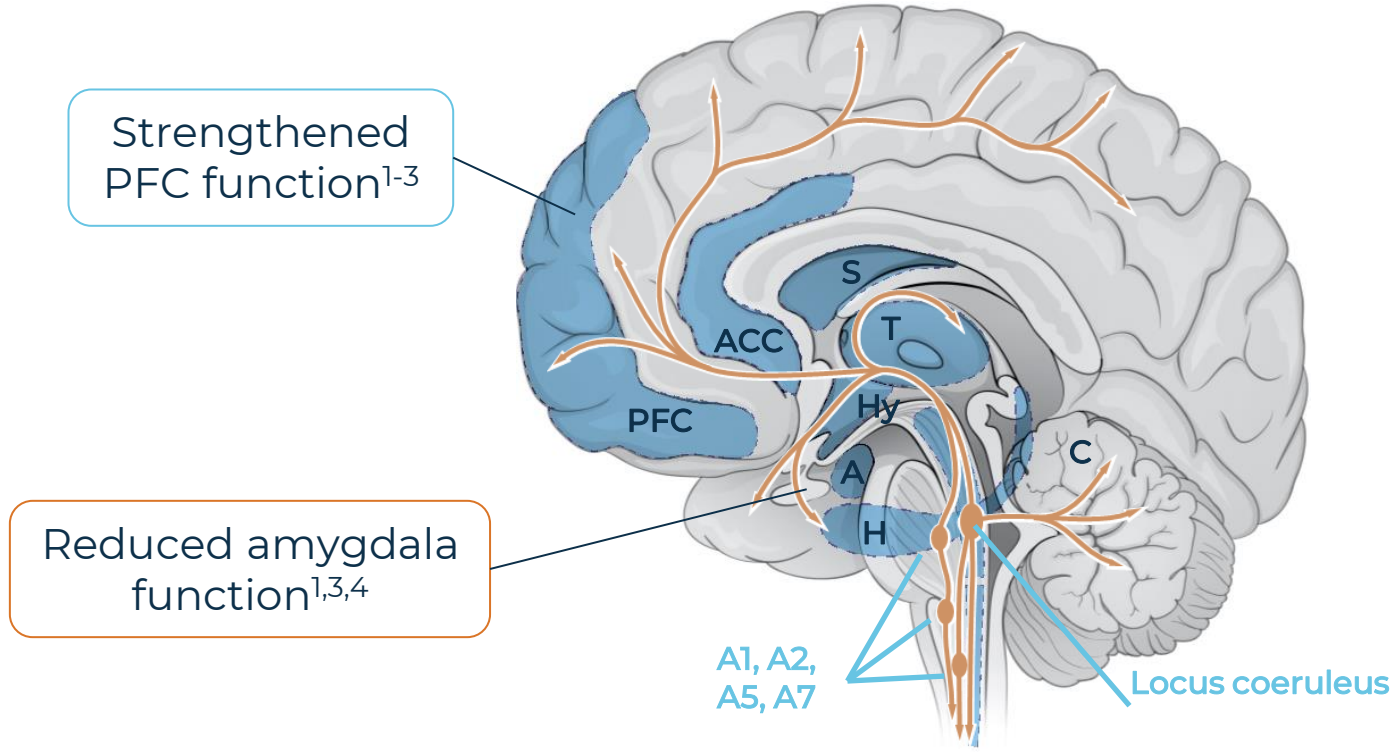
Hypothetical Role Of α_{1B}-Adrenoreceptor Antagonism In Possibly Improving Balance Between Executive Control And Emotional Drive

In an overactive noradrenergic state, animal model studies indicate that α_1-adrenergic receptor antagonism may strengthen PFC function and reduce amygdala function[1-4]

Hypothetical Effects Of α_1-Adrenoreceptor Antagonism



α1B, alpha-1B; A, amygdala; ACC, anterior cingulate cortex; C, cerebellum; H, hippocampus; Hy, hypothalamus; PFC, prefrontal cortex; S, striatum; T, thalamus.

References:

1. Cummings JL, et al. *CNS Spectr*. 2024:1-10.
2. Arnsten AF. *Nat Rev Neurosci*. 2009;10(6):410-422.
3. Gannon M, et al. *Brain Res*. 2019;1702:12-16.
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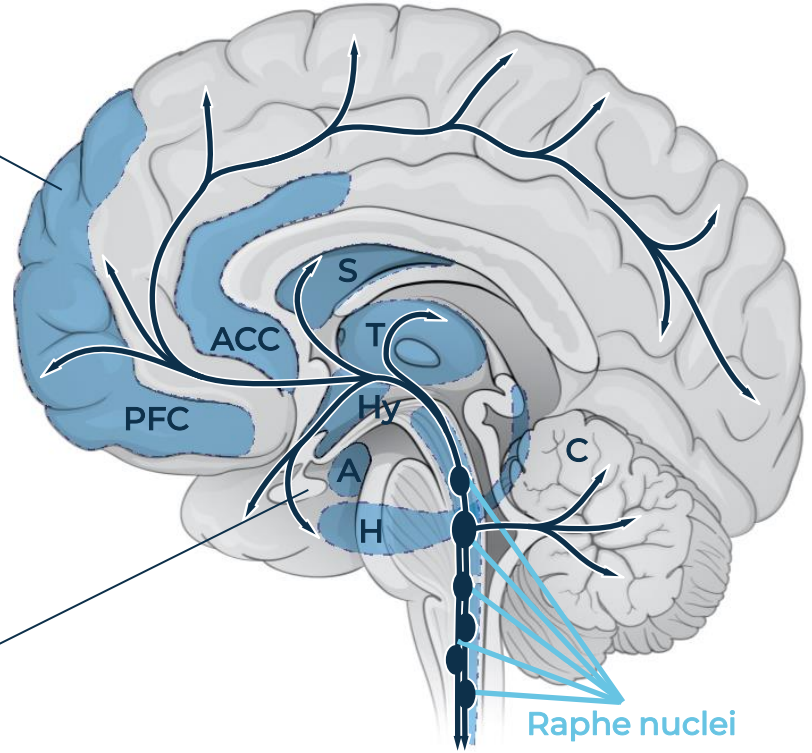
Hypothetical Role Of 5-HT_{1A} Partial Agonism In Possibly Improving Balance Between Executive Control And Emotional Drive

Animal model studies indicate that 5-HT_{1A} receptor partial agonism in the PFC and amygdala may reduce agitation behaviors[1-4]

Hypothetical Effects Of 5-HT_{1A} Receptor Partial Agonism

PFC Function
Reduced aggression and impulsivity[1-3]



Decreased amygdala activity[1,4]

5-HT_{1A}, 5-hydroxytryptamine receptor 1A; amygdala; ACC, anterior cingulate cortex; C, cerebellum; H, hippocampus; Hy, hypothalamus; PFC, prefrontal cortex; S, striatum; T, thalamus.

References:
1. Cummings JL, et al. *CNS Spectr*. 2024:1-10.
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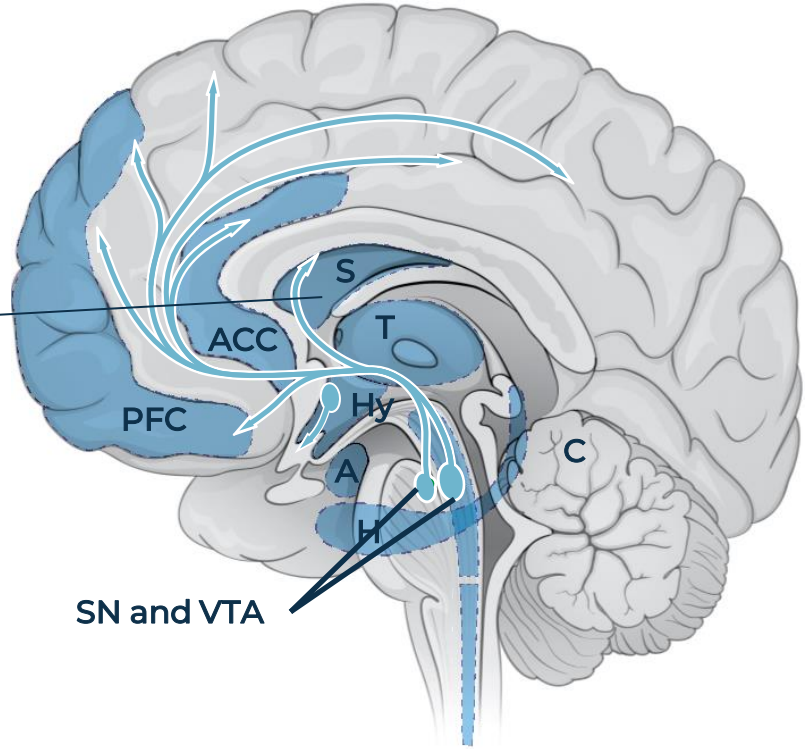
Hypothetical Role Of D_2 Partial Agonism In Possibly Regulating Striatal Dopamine Activity To Address Agitation Symptoms

Partial agonism of D_2 receptors may help normalize dopamine transmission within the striatum[1,2]

Animal model studies indicate that blockade of striatal D_2 receptors may decrease aggressive behavior[1,3,4]

Hypothetical Effects Of D_2 Receptor Partial Agonism

Striatal Function
Decreased aggressive behavior[1,3,4]



A, amygdala; ACC, anterior cingulate cortex; C, cerebellum; D2, dopamine D2 receptor; H, hippocampus; Hy, hypothalamus; PFC, prefrontal cortex; S, striatum; SN, substantia nigra; T, thalamus; VTA, ventral tegmental area.

References:
1. Cummings JL, et al. *CNS Spectr*. 2024:1-10.
2. Inoue A, Nakata Y. *Jpn J Pharmacol*. 2001;86(4):376-380.
3. Couppis MH, et al. *Psychopharmacology (Berl)*. 2008;197(3):449-456.
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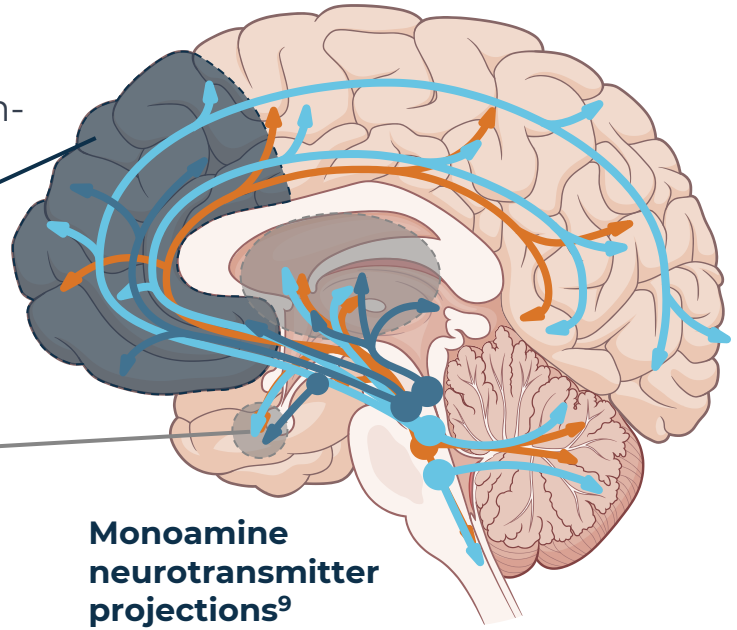
Brain Pathology and Monoaminergic Dysfunction

Imbalance between executive control and emotional drive may arise from the accumulation of tau pathology and neurodegeneration within key brain regions. A consequence of this pathology is the dysfunction of the monoamine/NSD neurotransmitter systems[1]

Agitation associated with dementia due to Alzheimer's disease may reflect an imbalance between top-down **executive control** and bottom-up **emotional drive**[1,2]

Prefrontal cortex
(executive control)
Impaired function[1,3]

Amygdala
(emotional drive)
Increased function[1,4]



Monoamine neurotransmitter projections[9]

Norepinephrine Serotonin Dopamine

Dysfunction of NSD neurotransmitter system may contribute to imbalance between **executive control** and **emotional overdrive**[1,5-8]

Norepinephrine system[1,5]
Increased activity

Serotonin system[1,7]
Decreased activity

Dopamine system[1,8]
Dysregulation

NSD, norepinephrine, serotonin, and dopamine.

References:

1. Cummings JL, et al. *CNS Spectr*. 2024:1-10.
2. Rosenberg PB, et al. *Mol Aspects Med*. 2015;43-44:25-37.
3. Banno K, et al. *Neuropsychiatr Dis Treat*. 2014;10:339-348.
4. Wright CI, et al. *Biol Psychiatry*. 2007;62(12):1388-1395.
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8. Lindenmayer JP. *J Clin Psychiatry*. 2000;61(Suppl 14):5-10.
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Summary

- Agitation associated with dementia due to Alzheimer's disease presents with a wide range of symptoms. It is associated with an imbalance between executive control and emotional drive, potentially stemming from dysfunction in monoamine/NSD neurotransmitter systems

- Potential therapeutic strategies for agitation associated with dementia due to Alzheimer's disease involve targeting specific receptors (ie, α_{1B}-adrenoreceptors, 5-HT_{1A} receptors, and D_2 receptors) which may improve the balance between executive control and emotional drive or address agitation symptoms

α1B, alpha-1B; 5-HT_{1A}, 5-hydroxytryptamine receptor 1A; D2, dopamine D2 receptor; NSD, norepinephrine, serotonin, and dopamine.

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