Proposed Roles Of Modulating Norepinephrine In Psychiatric Illnesses

May 2025 US.PSY.D.25.00017

This program is paid for by
Otsuka Pharmaceutical Development
& Commercialization, Inc. (OPDC).

Speakers are employees and/or paid
consultants of Otsuka Pharmaceutical
Development & Commercialization, Inc.

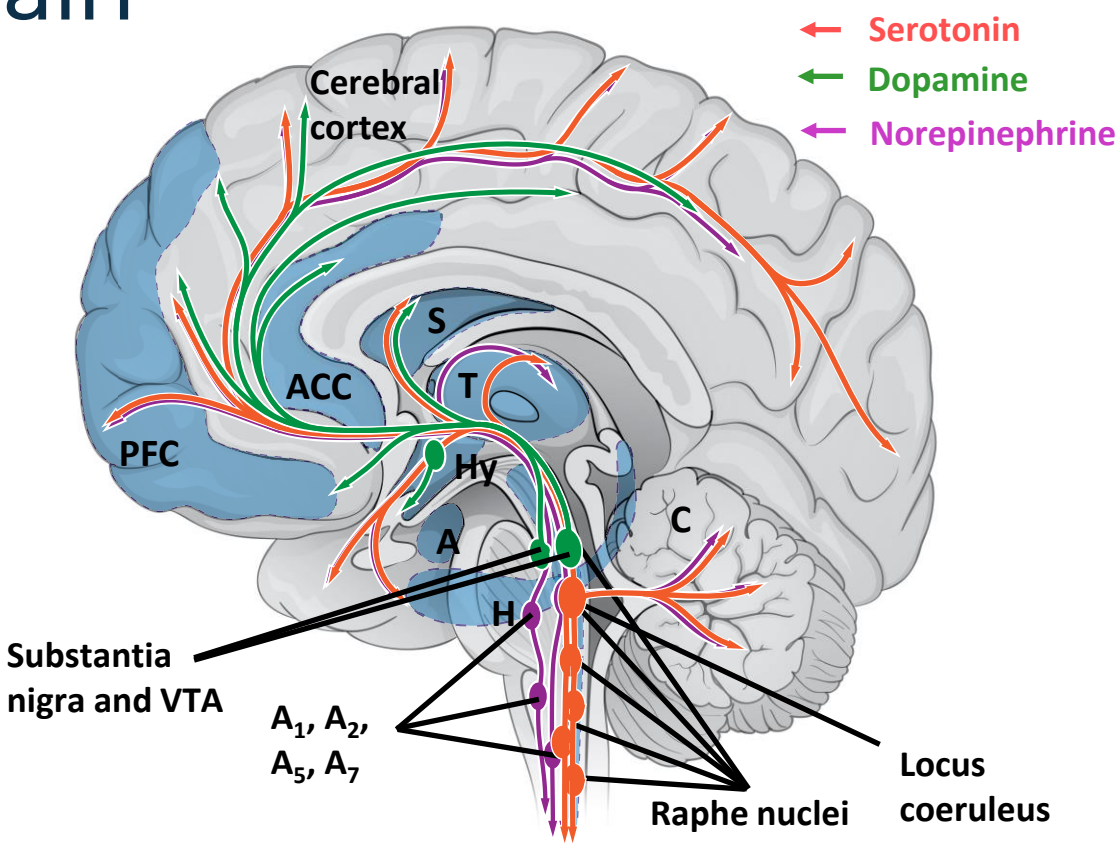
Objectives

- Explore the overlapping monoaminergic pathways and circuitry
- Describe the brain norepinephrine system including the distribution of adrenergic receptors in the brain
- Describe how norepinephrine signaling may directly and indirectly modulate dopamine and serotonin activity
- Explore how dysregulation of the norepinephrine system plays a role in MDD, agitation in Alzheimer's dementia, PTSD, and schizophrenia
- Explore the proposed therapeutic areas where modulation of norepinephrine signaling may be clinically relevant

MDD, major depressive disorder; PTSD, post-traumatic stress disorder.

Monoamine Pathways Overlap In Several Areas Of The Brain[1-8]

- NE pathways project from several nuclei in the brainstem, rostrally to limbic areas and the neocortex, and caudally to the spinal cord[1]
- DA neurons of the substantia nigra and ventral tegmentum project to the striatum and the frontal and cingulate cortex
    - DA neurons in the hypothalamus also regulate neuroendocrine processes[1]
- In the raphe nuclei, 5-HT neurons extend to most parts of the brain, including the cerebellum, spinal cord, thalamus and hypothalamus, and myriad neocortical areas[1]



5-HT, serotonin; A, amygdala; ACC, anterior cingulate cortex; C, cerebellum; DA, dopamine; H, hippocampus; Hy, hypothalamus; NE, norepinephrine; PFC, prefrontal cortex; S, striatum; T, thalamus; VTA, ventral tegmental area.

References:

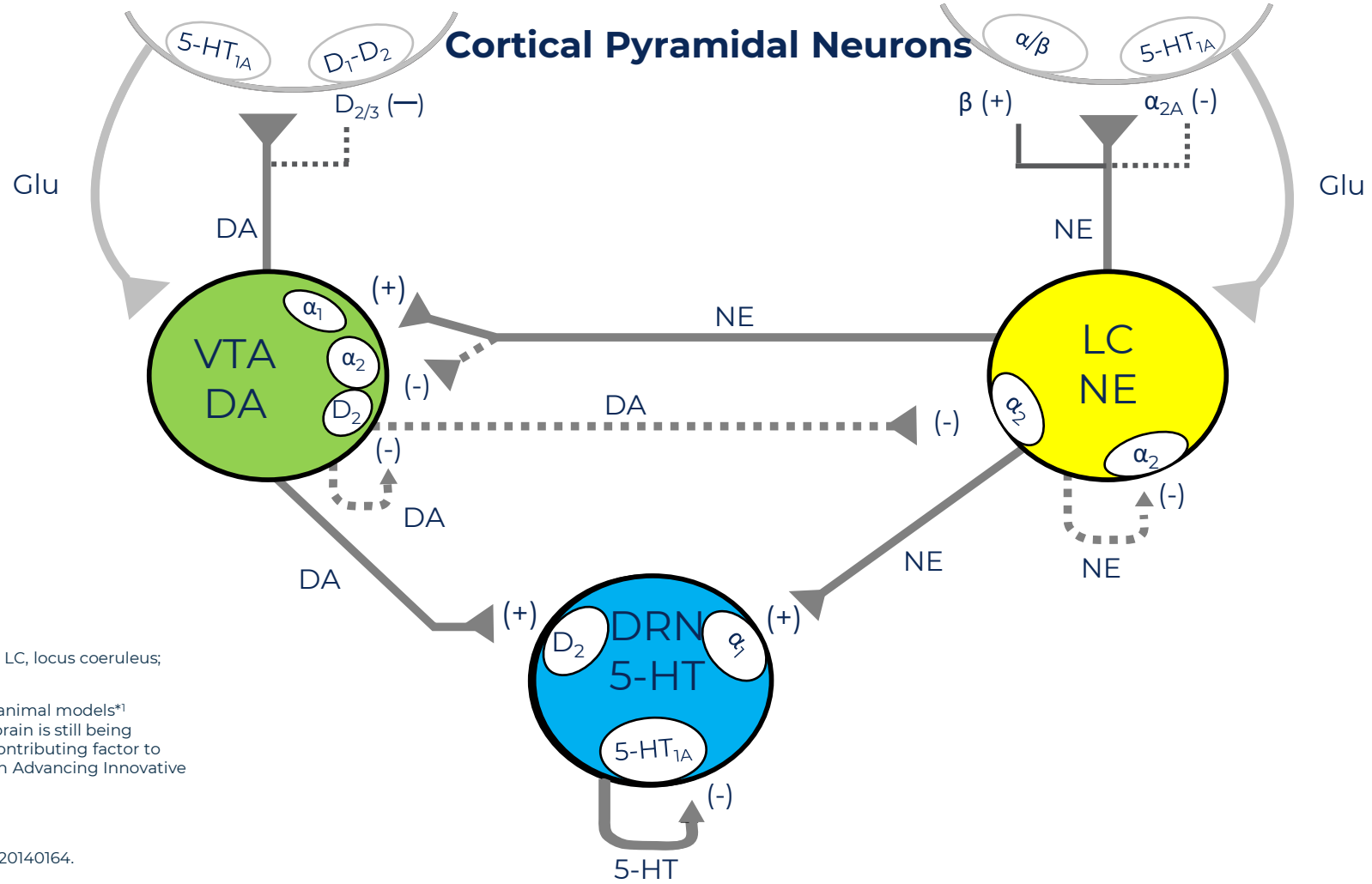
1. Fuchs E, Flügge G. *Dialogues Clin Neurosci.* 2004;6(2):171-183.
2. Stahl SM. Chapter 6: Mood Disorders. In: *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Application*. 4th ed. Cambridge University Press; 2013:284-369
3. Jacobs BL, Azmitia EC. *Physiol Rev.* 1992;72(1):165-229.
4. Abercrombie ED, et al. *J Neurochem.* 1989;52(5):1655-1658.
5. Stanford SC. *Pharmacol Ther.* 1995;68(2):297-242.
6. Meana JJ, et al. *Biol Psychiatry.* 1992;31(5):471-490.
7. Garcia-Sevilla JA, et al. *J Neurochem.* 1999;72(1):282-291.
8. Roiser JP, Sahakian BJ. *CNS Spectr.* 2013;18(3):139-149.

PsychU® Improving mental health care... together®

Neural Circuitry Of Monoamines Overlap

+ indicates stimulatory effect
— indicates inhibitory effect

Note: This is a synthesis of data from multiple studies across species



5-HT, serotonin; DA, dopamine; DRN, dorsal raphe nucleus; Glu, glutamate; LC, locus coeruleus; NE, norepinephrine; VTA, ventral tegmental area;

Hypothetical model of brain neural circuitry, primarily supported through animal models*[1]
*Although the exact cellular taxonomy and neural circuitry of the human brain is still being determined, animal models have been and continue to be an important contributing factor to this effort, as discussed by members of the human Brain Research Through Advancing Innovative Neurotechnologies (BRAIN) Initiative[2]

References:
1. El Mansari M, et al. *CNS Neurosci Ther.* 2010;16(3):e1-17.
2. Jorgenson LA, et al. *Philos Trans R Soc Lond B Biol Sci.* 2015;370(1668):20140164.

Symptoms Across Psychiatric Illnesses May Implicate Malfunctioning Cortical Circuits

Dorsolateral Prefrontal Cortex (dlPFC)[1]
- Cognitive deficits

Ventromedial Prefrontal Cortex (vmPFC)[2]
- Decreased arousal such as blunted affect
- Negative emotions

Corticolimbic Circuitry[3,4,5]
- Cognitive and social processing deficits

Cerebellar Projections To Frontal Cortex[6]
- Cognitive deficits

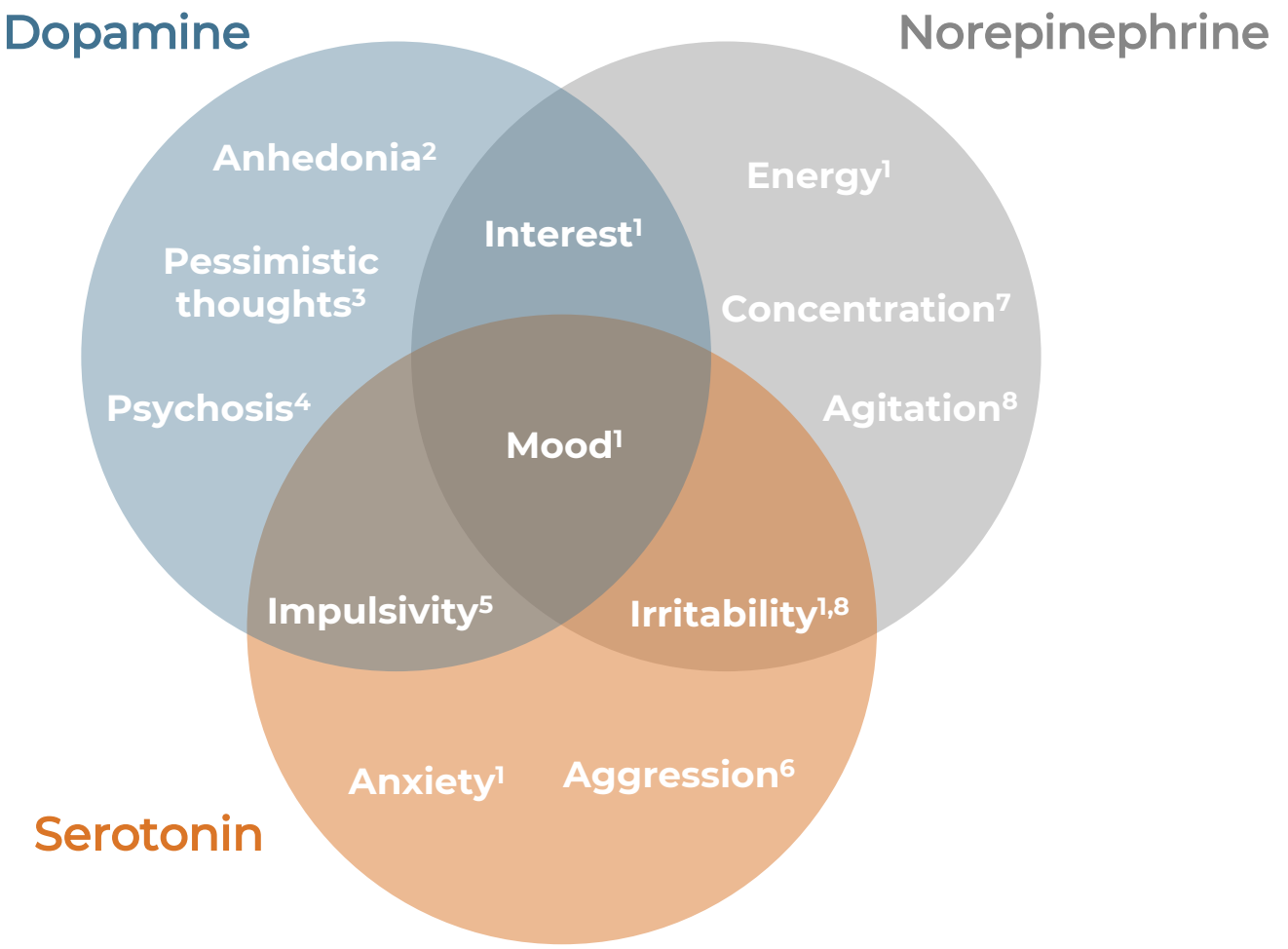
References:

1. Huang ML, et al. *Medicine (Baltimore).* 2017;96(25):e7228.
2. Schneider B, et al. *Neuropsychologia*. 2017;107:84-93.
3. Modinos G, et al. *Transl Psychiatry*. 2017;7(4):e1083.
4. Moench KM, et al. *Neurobiol Stress. 2016;3:23-33.*
5. Bickart KC, et al. *Neuropsychologia.* 2014;63:235-248.
6. Phillips JR, et al. *Front Public Health*. 2015;3:66.

PsychU® Improving mental health care... together®

Monoamine Neurotransmitter System Dysfunction Associated With Psychiatric Symptoms[1-8]

Noradrenergic, serotonergic, and dopaminergic systems have established roles in psychiatric conditions[1,2,7,8]



References:

1. Nutt DJ. *J Clin Psychiatry*. 2008;69(suppl E1):4-7.
2. Belujon P, Grace AA. *Int J Neuropsychopharmacol*. 2017;20(12):1036-1046.
3. Sharot T, et al. *Curr Biol*. 2012;22(16):1477-1481.
4. Kesby JP, et al. *Transl Psychiatry*. 2018;8(1):30.
5. Dalley JW, Roiser JP. *Neuroscience*. 2012;215:42-58.
6. Seo D, et al. *Aggress Violent Behav*. 2008;13(5):383-395.
7. Moret C, et al. *Neuropsychiatr Dis Treat*. 2011;7(suppl 1):9-13.
8. Yamamoto K, et al. *Psychiatry Clin Neurosci*. 2014;68(1):1-20.

Norepinephrine's Influence On Psychiatric Symptoms

DA and 5-HT have long been hypothesized to play a role in psychiatric illnesses. More recently, NE has emerged as a potential therapeutic target.[1]

Arousal

Insomnia, hypersomnia, or disrupted sleep pattern[1]

Affect

Depressed mood or suicidal ideations; diminished expressions of emotions and pleasure[1]

Cognition

Diminished ability to think or concentrate[1]

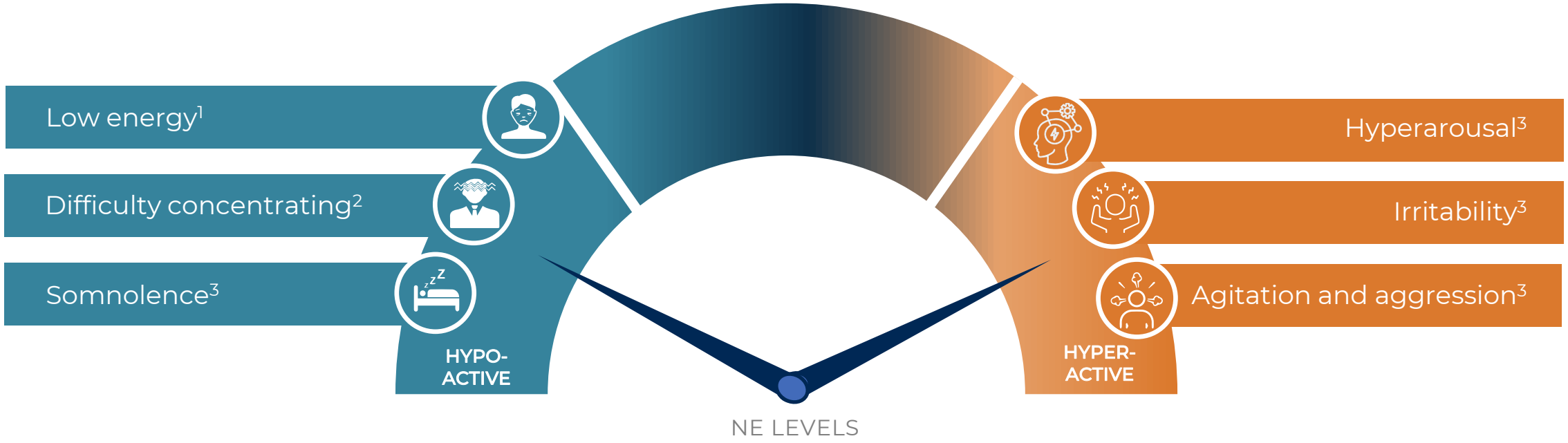
NE has been hypothesized to play a role in a variety of behaviors, and notably: aberrant regulation of cognition, arousal, and valence systems[1,2]

5-HT, serotonin; DA, dopamine; NE, norepinephrine.

References:

1. Maletic V, et al. *Front Psych*. 2017;8:42.
2. Goddard AW, et al. *Depression and Anxiety*. 2010;27(4):339-350

Dysregulation Of The Noradrenergic System Is Associated With A Wide Array Of Psychiatric Symptoms



Adrenoceptors (ARs) can modulate symptoms caused by noradrenergic system dysregulation

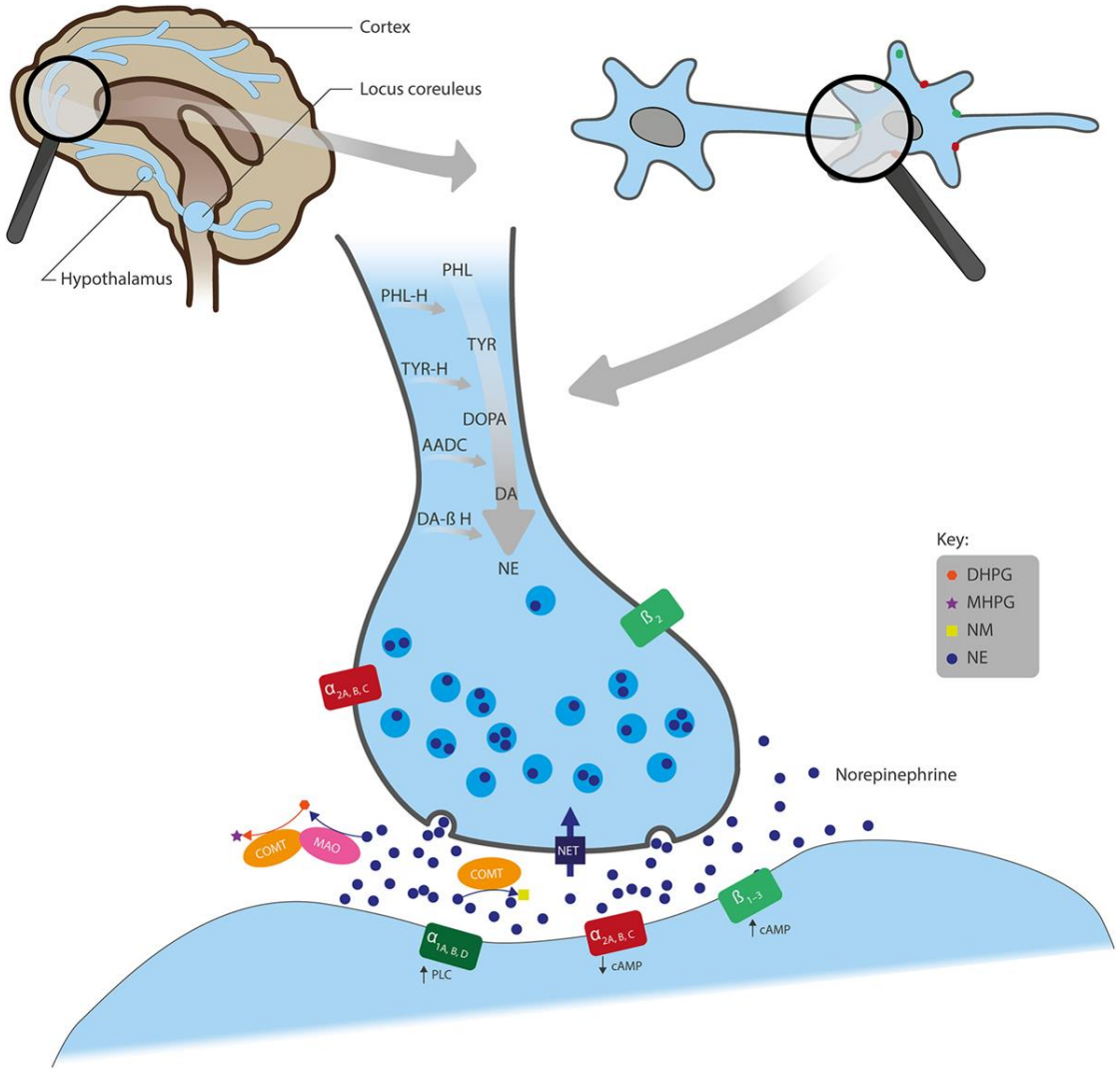
NE, norepinephrine.

References:

1. Nutt DJ. *J Clin Psychiatry*. 2008;69(suppl E1):4-7.
2. Moret C, et al. *Neuropsychiatr Dis Treat*. 2011;7(suppl 1):9-13.
3. Yamamoto K, et al. *Psychiatry Clin Neurosci*. 2014;68(1):1-20.

Norepinephrine In The Synapse[1]

- Noradrenergic neurons originate from the locus coeruleus and project to regions of the forebrain, including the cortex and hypothalamus
- NE is synthesized from the amino acids TYR and PHL and is converted to DOPA, DA, and further to NE by the enzymes TYR-H, AADC, and DA β-H, respectively, after which NE is stored in presynaptic vesicles
- Following its release into the synaptic cleft, NE exerts its effects through binding to the adrenergic receptors (ARs): α_{1A}, α_{1B}, and α_{1D}; α_{2A}, α_{2B}, and α_{2C}; or β_1, β_2, and β_3.
    - α1- and β-ARs have a stimulatory effect on cell signaling, whereas α2-ARs inhibit signaling
- ARs are mainly located post-synaptically, while α_2- and β_2-AR subtypes can also be localized pre-synaptically
- NE is removed from the synaptic cleft by either reuptake via NET (expressed on the presynaptic terminals of NE neurons and glial cells), inactivation through the catabolic enzyme COMT to NM, or metabolism by MAO into several transitional metabolites, including its principal brain metabolite, MHPG



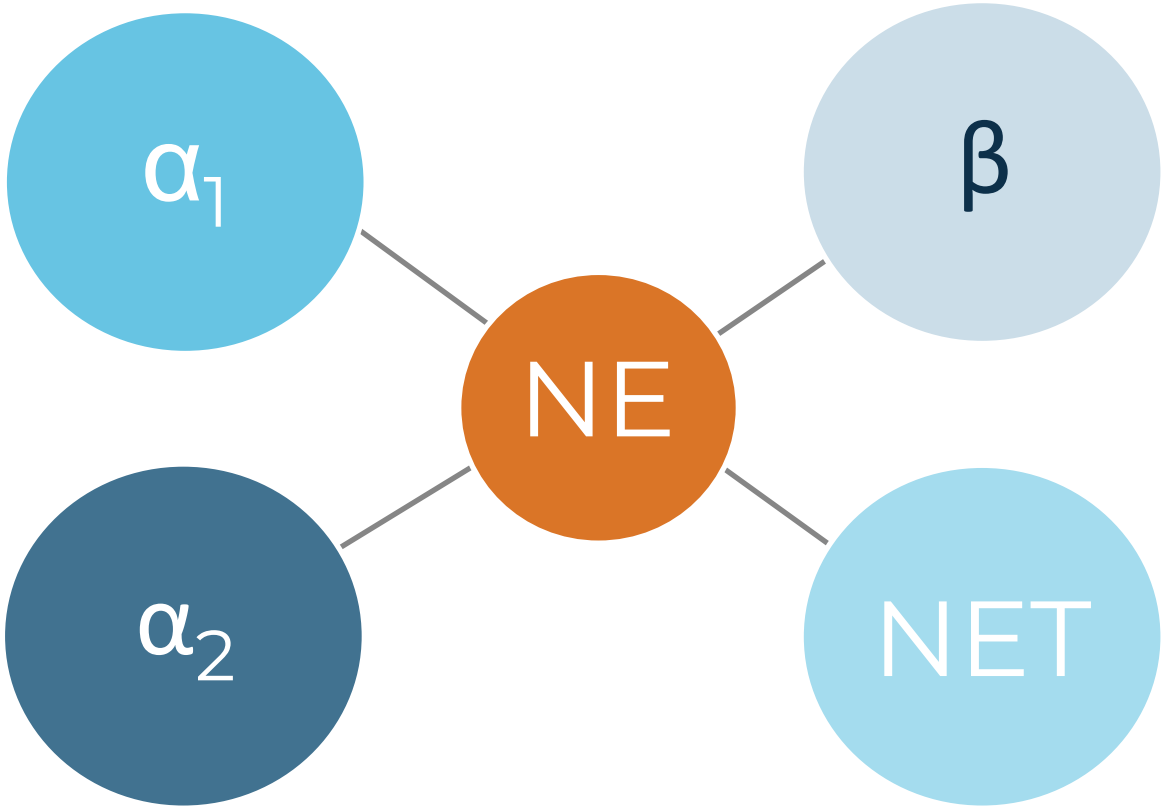
AADC, l-aromatic amino acid decarboxylase; cAMP, cyclic adenosine monophosphate; COMT, catechol O-methyltransferase; DA, dopamine; DA β-H, dopamine β-hydroxylase; DHPG, dihydroxyphenyl glycol; DOPA, 3,4-dihydroxyphenylalanine; MAO, monoamine oxidase; MHPG, 3-methoxy-4-hydroxyphenylglycol; NE, norepinephrine; NET, NE transporter; NM, normetanephrine; PHL, phenylalanine; PHL-H, phenylalanine hydroxylase; PLC, phospholipase C; TYR, tyrosine; TYR-H, tyrosine hydroxylase.

References:

1. Maletic V, et al. *Front Psych.* 2017;8:42.

Localization Of Norepinephrine Receptors In The Brain

$\alpha_{1A/D}$- Cortex[1]
α_{1B}- Ubiquitous[1]
α_{1C}- Cortex and cerebellum[1]



β_1- Ubiquitous[2]
β_2- Hippocampus, thalamus, and cerebellum[2]

α_{2A}- Ubiquitous and high in LC[3]
α_{2B}- Thalamus[3]
α_{2C}- Cortex, basal ganglia, olfactory tubercle, and hippocampus[3]

LC, cortex, cerebellum, thalamus, caudate and putamen[4]

LC, locus coeruleus; NE, norepinephrine; NET, norepinephrine transporter.

References:

1. Price DT, et al. *Mol Pharmacol.* 1994;45(2):171-175.
2. Nicholas AP, et al. *Neuroscience.* 1993;56(4):1023-1039.
3. Saunders C, et al. *Pharmacol Ther.* 1999;84(2):193-205.
4. Schou M, et al. *Eur Neuropsychopharmacol.* 2005;15(5):517-520.

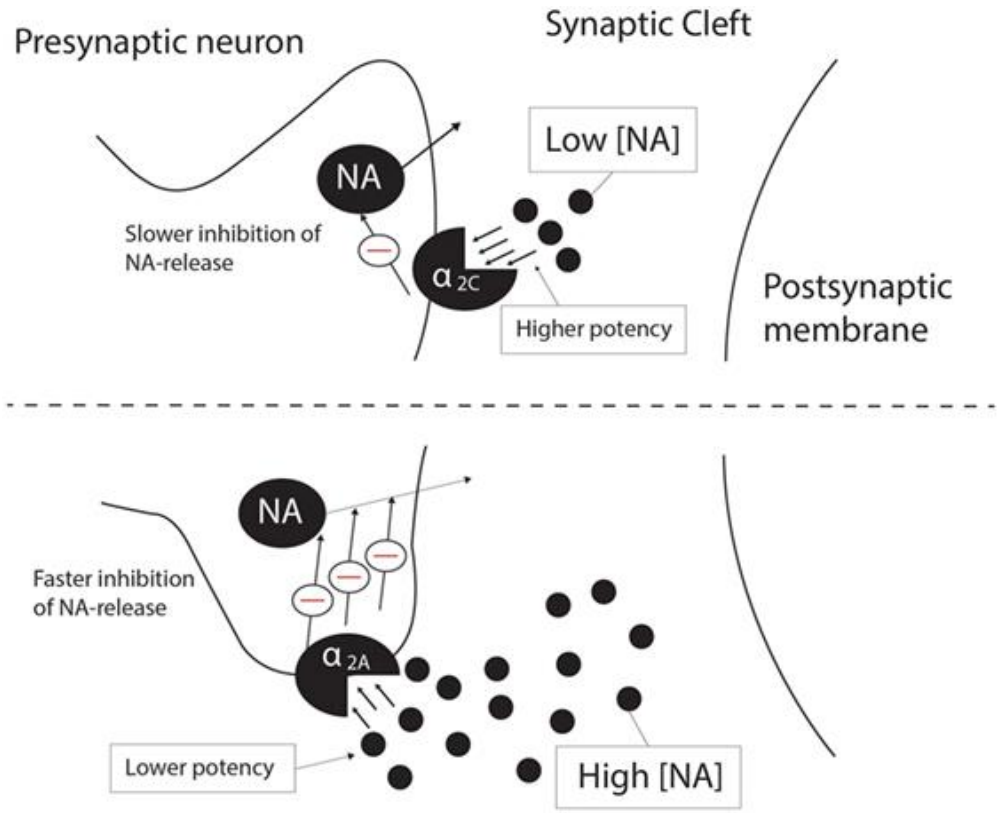
Variations In Norepinephrine Concentration May Be Linked To Receptor Activation

Differential presynaptic inhibition of NA released by the α_{2c}-AR and the α_{2a}-AR[2]

Low NE[2]: NE preferentially engages α_{2c}

At low endogenous NA concentrations (10–100 nM), the α_{2c}-AR is responsible for inhibition of NA release, while the α_{2a}-AR inhibits NA release at high endogenous NA concentrations (0.1–10µM)[2]

High NE[1,2]: NE preferentially binds α_1 and has a lower affinity for α_{2a}



Adrenergic receptors in the brain bind exclusively to norepinephrine as epinephrine is not synthesized de novo in the brain and does not cross the blood brain barrier

https://www.frontiersin.org/journals/psychiatry/articles/10.3389/fpsyt.2017.00144/full

AR, adrenergic receptors; NA, noradrenaline*; NE, norepinephrine*; nM, nanometer; µM, micrometer.
*These are identical terms.

References:

1. Ramos BP, et al. *Pharmacol Ther.* 2007;113(3):523-536.
2. Uys MM, et al. *Front Psychiatr.* 2017;8(144):1-23.

Variations In Norepinephrine Concentration May Be Linked To Receptor Activation

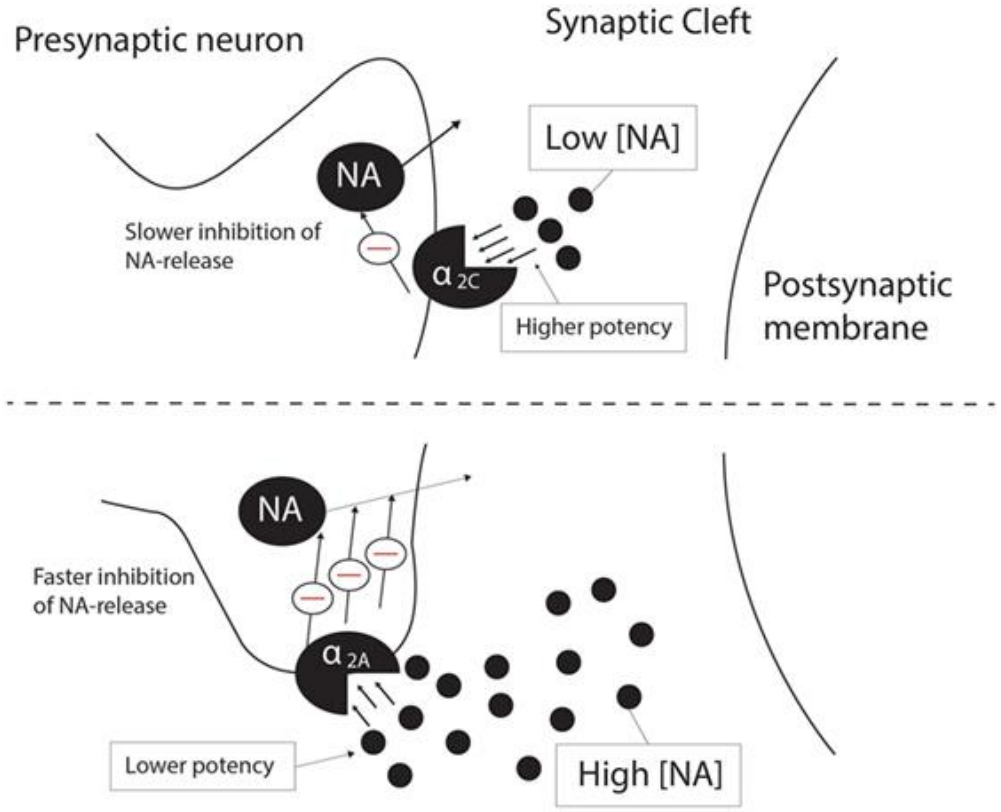
Differential presynaptic inhibition of NA release by the α_{2c}-AR and the α_{2a}-AR[2]

Low NE[2]: NE preferentially engages α_{2c}

At low endogenous NA concentrations (10–100 nM), the α_{2c}-AR is responsible for inhibition of NA release, while the α_{2a}-AR inhibits NA release at high endogenous NA concentrations (0.1–10µM)[2]

High NE[1,2]: NE preferentially binds α_1 and has a lower affinity for α_{2a}

Theoretically, modulation of NE activity can be done via α_1 and α_2 blockade



Adrenergic receptors in the brain bind exclusively to norepinephrine as epinephrine is not synthesized de novo in the brain and does not cross the blood brain barrier

https://www.frontiersin.org/journals/psychiatry/articles/10.3389/fpsyt.2017.00144/full

AR, adrenergic receptors; NA, noradrenaline*; NE, norepinephrine*; nM, nanometer; µM, micrometer.
*These are identical terms.

References:

1. Ramos BP, et al. *Pharmacol Ther.* 2007;113(3):523-536.
2. Uys MM, et al. *Front Psychiatr.* 2017;8(144):1-23.

PsychU® Improving mental health care... together®

Norepinephrine α Receptors May Directly And Indirectly Modulate Dopamine And Serotonin[1]

Direct Modulation	Dopamine	5HT
α_{2c} antagonism	↑ circulating DA	↑ circulating 5-HT
α_{2a} agonism		↓ 5-HT synthesis
α_{2a} antagonism		↑ 5-HT synthesis
$\alpha_{2b/c}$ antagonism		↑ 5-HT synthesis

Indirect Via GABA, Glutamate, and Acetylcholine

α_{2c} antagonism:

- Increases GABA release in areas of high dopaminergic neurons
- Regulates glutamate cortical transmission (which may be exponentially beneficial with a D2 antagonist)
- Increases striatal acetylcholine, decreasing dopamine release (and potentially serotonin)

5-HT, serotonin; D2, dopamine 2; DA, dopamine; GABA, gamma-aminobutyric acid.

Reference:

1. Uys MM, et al. *Front Psychiatr.* 2017;8(144):1-23.

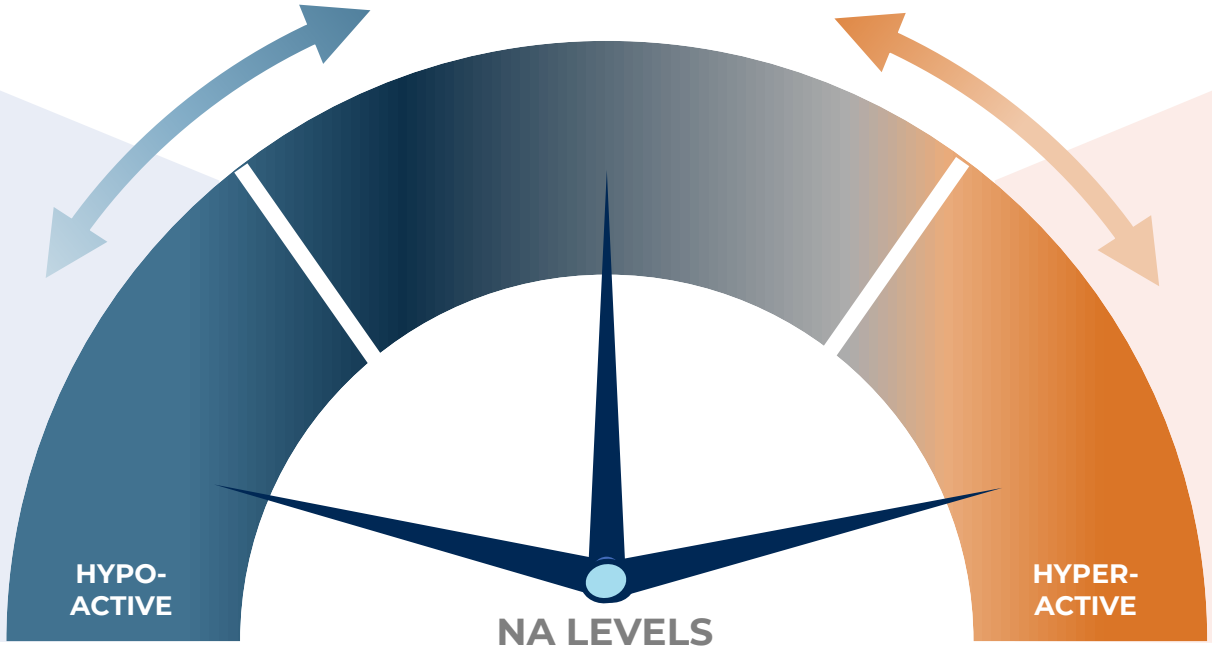
α-Adrenoreceptors Can Modulate Noradrenergic Tone

Evidence suggests that α_2-ARs are preferentially activated at low NA levels, while α_1-ARs are preferentially activated at high NA levels[2]. Among the α_2-AR subtypes, α_{2c}-ARs have a higher affinity for NA compared to α_{2a}-ARs, which allows α_{2c}-ARs to be activated at lower NA concentrations compared to α_{2a}-ARs[2].

The impacts of α-AR antagonism can depend on levels of NA activity, which can be high and low across different brain regions[1-5,*]

Conditions including MDD are associated with **low NA levels[4,6]**

Selective α_2-AR antagonism can **increase NA levels[1,2]**



Conditions including agitation in Alzheimer's dementia, PTSD, and MDD are associated with **high NA levels[3,4,7]**

Selective α_1-AR antagonism can **block the action of excessive NA levels[3]**

*Low levels of NA engage high-affinity α_2-ARs but not low-affinity α_1-ARs.[3] In contrast, high levels of NA engage low-affinity α_1-ARs, while α_2-ARs, particularly α_{2c}-ARs, are subject to desensitization upon prolonged exposure.[1,3]
AR, adrenergic receptor; MDD, major depressive disorder; NA, noradrenaline; PTSD, post-traumatic stress disorder.

References:
1. Bücheler MM, et al. *Neuroscience*. 2002;109(4):819-826.
2. Uys MM, et al. *Front Psychiatr*. 2017;8(144):1-23.
3. Arnsten AFT, et al. *Neurobiol Stress*. 2015;1:89-99.
4. Yamamoto K, et al. *Psychiatry Clin Neurosci*. 2014;68(1):1-20.
5. Maletic V, et al. *Front Psychiatry*. 2017;8:42.
6. Moret C, et al. *Neuropsychiatr Dis Treat*. 2011;7(suppl 1):9-13.
7. Gannon M, et al. *Brain Res*. 2019;1702:12-16.

PsychU® Improving mental health care... together®

Norepinephrine α Receptor Antagonism Hypothesized Clinical Utility

NE Receptor (Antagonist)	Proposed Psychiatric Therapeutic Effects	Concern Of Side Effects
α_1	PTSD[1] Nightmares[1] Anxiety[2] Anxious depression[2]	Transient dizziness[1] Orthostatic hypotension[1]
α_{2A}	Memory[3] Cognition[3] ADHD[3]	Cardiovascular side effects[3]
α_{2c}	Memory[3] Cognition[3] Cognitive deficits in MDD[3] Cognitive deficits in Schizophrenia[3] Mood disorders[3] Schizophrenia[3] Alzheimer's disease[3]	Unknown[3*]

MDD, Major Depressive Disorder; NE, norepinephrine; PTSD, Post Traumatic Stress Disorder; ADHD, Attention Deficit Hyperactivity Disorder.

References:

*unknown beyond non-specific α receptor blockade; hypothesis that α_2 antagonists may decrease peripheral adrenergic side effects

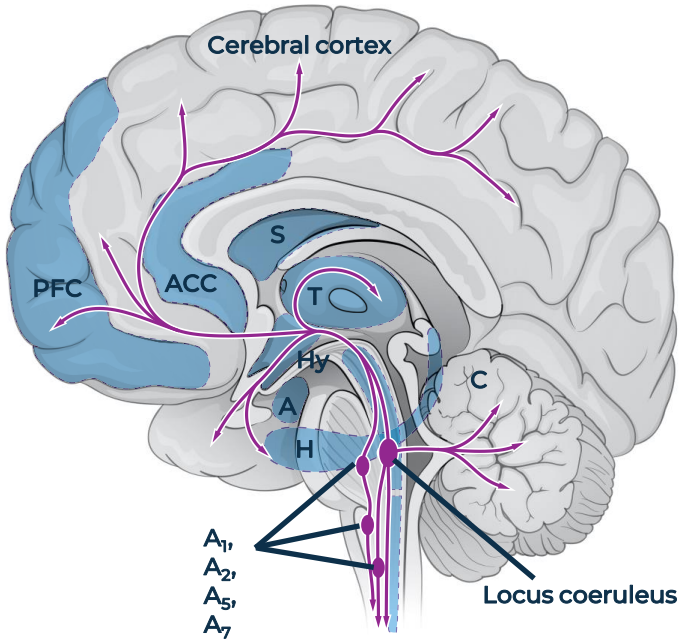
References:

1. Kung et al *Mayo Clin Proc* 2012. 87;9:890-900.
2. Goddard AW, et al *Depression and Anxiety*. 2010;27(4):339-350
3. Uys MM, et al. *Front Psychiatr.* 2017;8(144):1-23.

Noradrenergic System Dysfunction In Major Depressive Disorder[1-6]

- NE neurons of the locus coeruleus project to numerous brain regions, including the limbic and cortical regions, as well as the thalamus, cerebellum, and spinal cord, while NE neurons of cell groups A_1, A_2, A_5, and A_7 project to a more restricted array of regions[1]
- Many of the targeted regions play key roles in wakefulness, energy levels, attention, and behaviors related to agitation, irritability, aggression, and fear[1,7,8]
- Noradrenergic system dysfunction is associated with an array of symptoms, including low energy, concentration difficulties, somnolence, agitation, and irritability[2-4]
- The effects of NE are mediated by three classes of adrenoceptors (ARs), which are widely distributed throughout the brain and involved in important symptoms of MDD[5]

Circuitry[1,6]



Adrenergic Receptors[5]

α_1			α_2			β		
α_{1A}	**α_{1B}**	α_{1D}	α_{2A}	α_{2B}	**α_{2C}**	β_1	β_2	β_3

- Low energy[2]
- Difficulty Concentrating[3]
- Somnolence[4]
- Agitation[4]
- Irritability[4]

MDD, major depressive disorder.

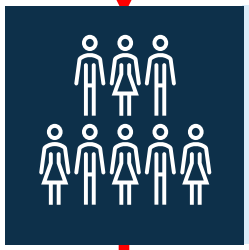
References:

1. Fuchs E, Flügge G. *Dialogues Clin Neurosci*. 2004;6(2):171-183.
2. Nutt DJ. *J Clin Psychiatry*. 2008;69(suppl E1):4-7.
3. Moret C, Briley M. *Neuropsychiatr Dis Treat*. 2011;7(suppl 1):9-13.
4. Yamamoto K, et al. *Psychiatry Clin Neurosci*. 2014;68(1):1-20.
5. Maletic V, et al. *Front Psychiatry*. 2017;8:42.
6. Levinson S, et al. *Front Neuroimaging*. 2023;1:1009399.
7. Stahl SM. Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications. 4th ed. Cambridge University Press; 2013.
8. Roiser JP, Sahakian BJ. *CNS Spectr*. 2013;18(3):139-149.

Norepinephrine And MDD[1]

Recent hypotheses suggest **MDD is predominantly linked to more intricate neuroregulatory systems and neuronal circuits that result in disrupted neurotransmitter systems**

Data from STAR*D showed only a minority of patients with MDD reach symptom remission with first-line therapies



An expert panel suggests that there is **evidence of high and low adrenergic signaling contributing to depressive symptoms***

There may be subgroups of patients with NE dysregulation that need to be considered when selecting pharmacologic treatment

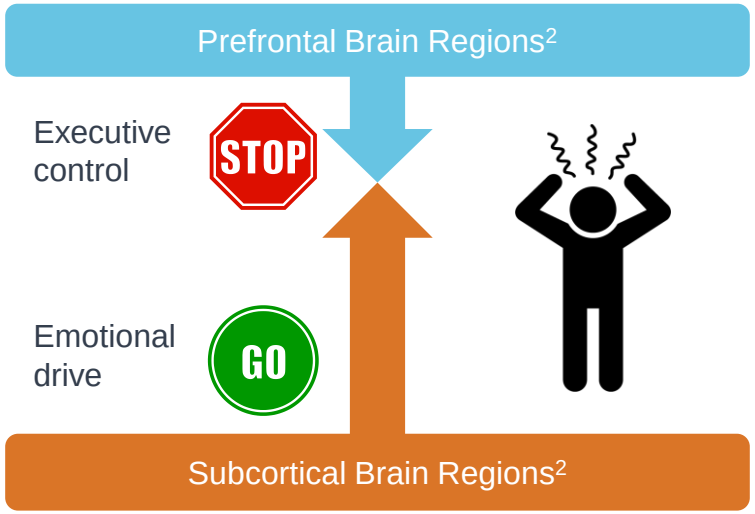
- **It may be vital to target NE activity in patients with TRD**
- **Results of a meta-analysis evaluating NE dysregulation in MDD identified NE as a possible treatment pathway for patients that require more personalized, targeted therapy, like those with TRD**

*The expert panel consisted of 5 experts who participated in a consensus panel meeting and reviewed available evidence of altered noradrenergic activity and its potential role in common psychiatric disorders.
MDD, major depressive disorder; NE, norepinephrine; STAR*D, Sequenced Treatment Alternatives to Relieve Depression; TRD, treatment-resistant depression.

Reference:

1. Jain R, et al. *J Clin Psychiatry*. 2024;85(4):plunaro2417ah.

Agitation In Alzheimer's Dementia Is Associated With An Imbalance Between Executive Control And Emotional Drive

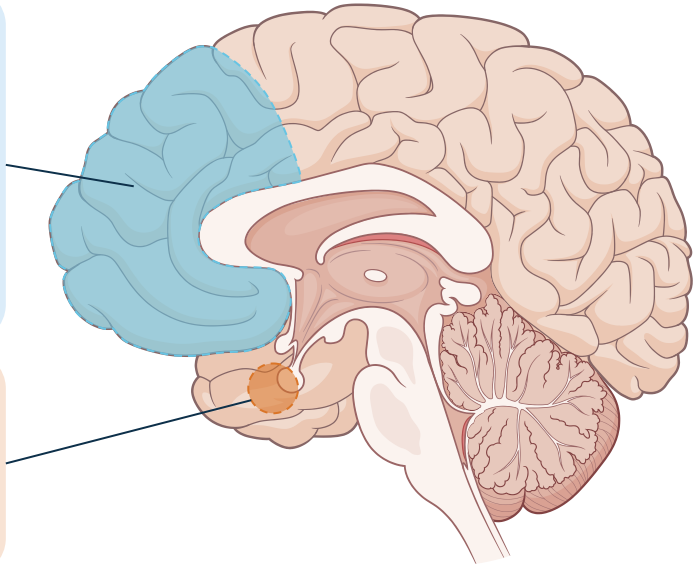


Hypoactivity in **prefrontal** regions, including the dlPFC, vmPFC, and OFC[3-5]

- A study of 20 dementia patients, including 16 patients with AD, aggressive patients showed hypoperfusion in the right and left superior frontal cortices compared to nonaggressive patients[3]

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

- Amygdala activity correlated with the severity of irritability and agitation symptoms in AD



Agitation in Alzheimer's dementia was proposed to arise out of deficits in regulating emotional responses and/or attentional resources and may involve deficits in problem-solving[1,2]

- Agitated patients with Alzheimer's disease (AD) appear to have dysfunction in the frontal cortex, anterior cingulate cortex, orbitofrontal cortex, amygdala, and insula, which overlap with circuits that underlie inflated estimations of threat cost or probability, as well as maladaptive control of responses[1]
- Agitation was proposed to be an emotionally hyperreactive state largely based on misinterpretation of threats ultimately rooted in cognitive deficits[1]
- Frontal lobe dysfunction is thought to contribute to the production of abnormal emotional responses to external stimuli, thereby causing aggressive or agitated states[2]

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

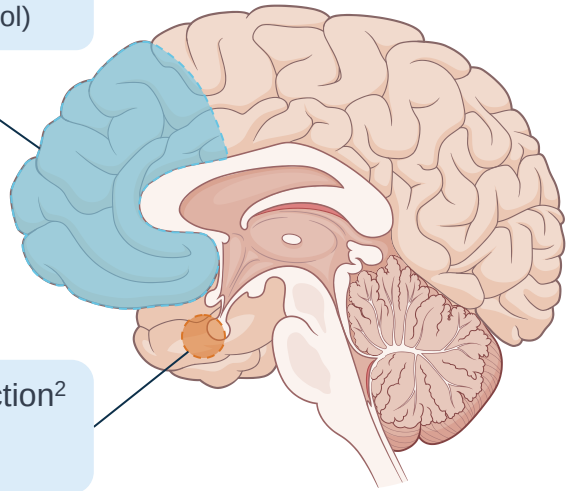
References:

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.

PsychU® Improving mental health care... together®

Dysfunction Of Monoamine/NSD Neurotransmitter Systems May Disrupt The Balance Between Executive Control And Emotional Drive

PFC function[1]
(executive control)



Amygdala function[2]
(emotional drive)

Monoamine System Status In Agitation In Alzheimer's Dementia	Potential Relationship With Agitation Behavior
NA system hyperactivity[3]	• Impaired executive control[4] • Increased emotional drive[4]
5-HT system deficits[5]	• Altered PFC regulation of the amygdala[6] • Increased aggression and impulsivity[7]
DA system relatively preserved[5]; however, 5-HT deficits can increase striatal DA[8]	• Increased striatal dopamine activity may lead to agitation[9]

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

References:

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.

PsychU® Improving mental health care... together®

Norepinephrine And Agitation In Alzheimer's Dementia[1]

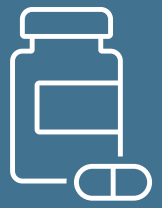
The Paradox

Although agitation in Alzheimer's dementia suggests excessive CNS noradrenergic signaling, the loss of locus coeruleus noradrenergic neurons in AD seems inconsistent with this hypothesis

The Resolution

Compensatory upregulation of the CNS noradrenergic system

- Concentrations of NE (and its metabolite) in CSF are elevated in advanced AD
- Increased CNS noradrenergic signaling contributing to agitation have been demonstrated in studies



Demonstrated increases in NE contributing to agitation in Alzheimer's dementia provided rationale for trials of postsynaptic AR antagonists and atypical antipsychotics:

- Beta adrenergic receptor antagonists can reduce agitation in Alzheimer's dementia but also cause bradycardia
- Alpha-1 adrenergic receptor antagonists may reduce agitation in Alzheimer's dementia and were found to be well tolerated with careful dose titration
- Atypical antipsychotics with alpha-1 antagonist activity are widely prescribed off-label
- There is an FDA-approved atypical antipsychotic for the treatment of agitation in Alzheimer's dementia that acts as an alpha-1b and alpha-2c antagonist

AD, Alzheimer's disease; AR, adrenergic receptor; CNS, central nervous system; CSF, cerebrospinal fluid; FDA, Food and Drug Administration; NE, norepinephrine.

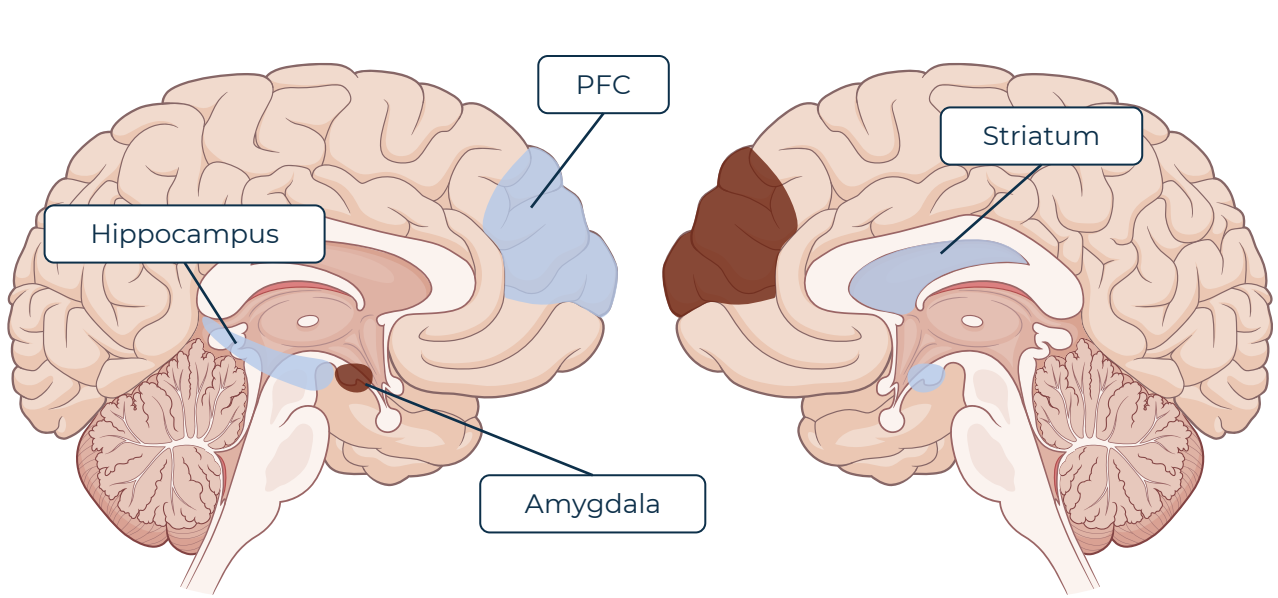
References:

1. Jain R, et al. *J Clin Psychiatry*. 2024;85(4):plunaro2417ah.

PTSD Is A Dynamic Disorder Involving Fluctuations Between Contrasting Forms Of Emotional Dysregulation[1]

Monoamine neurotransmitter systems regulate key brain regions involved in emotional regulation[2-7]

- Elevated NE levels are thought to contribute to arousal and intrusion symptoms[10]
- 5-HT deficits have been linked to mood and arousal symptoms[10]
- Stress can alter serotonin 5-HT1A receptors in the hippocampus, which can alter mood and influence the development of trauma-related disorders[11,12]
- DA dysregulation may contribute to mood symptoms, such as anhedonia and emotional numbing, as well as avoidance symptom[6,7]



Heightened emotional and autonomic experience (eg, re-experiencing, fear)

Emotional undermodulation ← → **Emotional overmodulation**

Diminished emotional experience and autonomic blunting (eg, numbing)

5-HT, serotonin; DA, dopamine; NE, norepinephrine; PFC, pre-frontal cortex; PTSD, post-traumatic stress disorder.

References:

1. Yehuda R, et al. *Nat Rev Dis Primers*. 2015;1:15057.
2. Arnsten AF. *Nat Rev Neurosci*. 2009;10(6):410-422.
3. Arnsten AF. *Nat Neurosci*. 2015;18(10):1376-1385.
4. Bocchio M, et al. *Front Neural Circuits*. 2016;10:24.
5. Krystal JH, et al. *Brain Res*. 2009;1293:13-23.
6. Torrisi SA, et al. *Front Pharmacol*. 2019;10:404.
7. Vander Weele CM, et al. *Brain Res*. 2019;1713:16-31.
8. Strawn JR, et al. *Depress Anxiety*. 2008;25(3):260-271.
9. Young EA, et al. *Arch Gen Psychiatry*. 2004;61(4):394-401.
10. Sherin JE, et al. *Dialogues Clin Neurosci*. 2011;13(3):263-278.
11. Lewis MW, et al. *Transl Psychiatry*. 2020;10(1):237.
12. Mahar I, et al. *Neurosci Biobehav Rev*. 2014;38:173-92.

PsychU® Improving mental health care... together®

Norepinephrine And PTSD[1]

Studies show elevated sympathetic and central nervous system (SNS and CNS) noradrenergic signaling in PTSD

- Increased NE concentrations at rest and in response to trauma cues
- A study using neuromelanin MRI in the locus coeruleus showed elevated signals in patients with PTSD

Demonstrated increases in noradrenergic signaling in PTSD provided rationale for anti-adrenergic pharmacotherapies

- Studies have supported adrenergic antagonists for the use of PTSD-related nightmares and reduction of PTSD symptoms

CNS, central nervous system; MRI, magnetic resonance imaging; NE, norepinephrine; PTSD, post-traumatic stress disorder; RCT, randomized controlled trials; SNS, sympathetic nervous system.

Reference:

1. Jain R, et al. *J Clin Psychiatry*. 2024;85(4):plunaro2417ah.

Norepinephrine And Schizophrenia[1]

Causes of schizophrenia symptoms were thought to be due to impairments in the neuromodulation of dopamine, serotonin, and glutamate; however, NE activity may also play a significant role

- NE activity may precipitate cognitive deficits that precede schizophrenia onset and predict worse outcomes

Altered NE activity may be related to the majority of positive and negative symptoms scored by the PANSS (positive correlation)

- Anxiety, agitation, tension due to excessive anxiety or agitation, poor attention or awareness, and alterations in cognitive functioning may be attributed to altered NE signaling

It is important for clinicians to be cognizant of the symptoms patients may experience that could be related to NE activity

Results of a meta-analysis evaluating NE dysregulation in schizophrenia identified NE as a possible treatment pathway for patients who require more personalized, targeted therapy

NE, norepinephrine; PANSS, positive and negative syndrome scale.

Reference:

1. Jain R, et al. *J Clin Psychiatry*. 2024;85(4):plunaro2417ah.

Regulating Monoaminergic Activity May Hold Therapeutic Potential

One way to regulate monoaminergic activity could involve the use of second-generation antipsychotics (SGAs)[1]

SGAs have multiple targets, including DA, 5-HT, and NE systems, and they are also a common therapy across MDD, agitation in Alzheimer's dementia, PTSD, and schizophrenia[1-3]

Therefore, modulating NE, in addition to DA and 5-HT, may help manage symptoms related to arousal, affect, and cognition

5-HT, serotonin; DA, dopamine; MDD, major depressive disorder; NE, norepinephrine; PTSD, post-traumatic stress disorder.

References:

1. Miyamoto et al. *Mol Psychiatry*. 2005;10(1):79-104.
2. Jain R, et al. J Clin Psychiatry. 2024;85(4):plunaro2417ah.
3. Chen et al. *Curr Opin Psych* 2011. 24: 10-17.

PsychU® Improving mental health care... together®

Summary

Monoamine systems (dopamine, serotonin, and norepinephrine) overlap and regulate mood and cognition, through interconnected circuits

The norepinephrine system, originating in the locus coeruleus, has widespread projections and adrenergic receptors throughout the brain, influencing cognition and emotional regulation

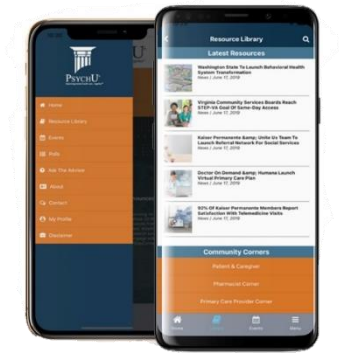
Imbalance in norepinephrine signaling contributes to disorders such as MDD, agitation in Alzheimer's dementia, PTSD, and schizophrenia

Modulation of norepinephrine signaling holds therapeutic potential through targeted adrenergic receptor treatments

MDD, major depressive disorder; PTSD, post-traumatic stress disorder.

Get Your Resources On The Go

Download the PsychU App from Google Play or from the Apple App Store!



Subscribe to The PsychU Community Podcast on the Spotify app or on the Apple Podcasts app.

Connect with us on social media:

PsychU® Improving mental health care... together®

PsychU®
Improving mental health care... together®

Thank you for attending today's live program!

Tell us what you thought by scanning the QR code and taking a quick survey. We look forward to seeing you again!

Proposed Roles Of Modulating Norepinephrine In Psychiatric Illnesses

May 2025 US.PSY.D.25.00017