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Proposed Roles of Modulating Norepinephrine in Psychiatric Illnesses

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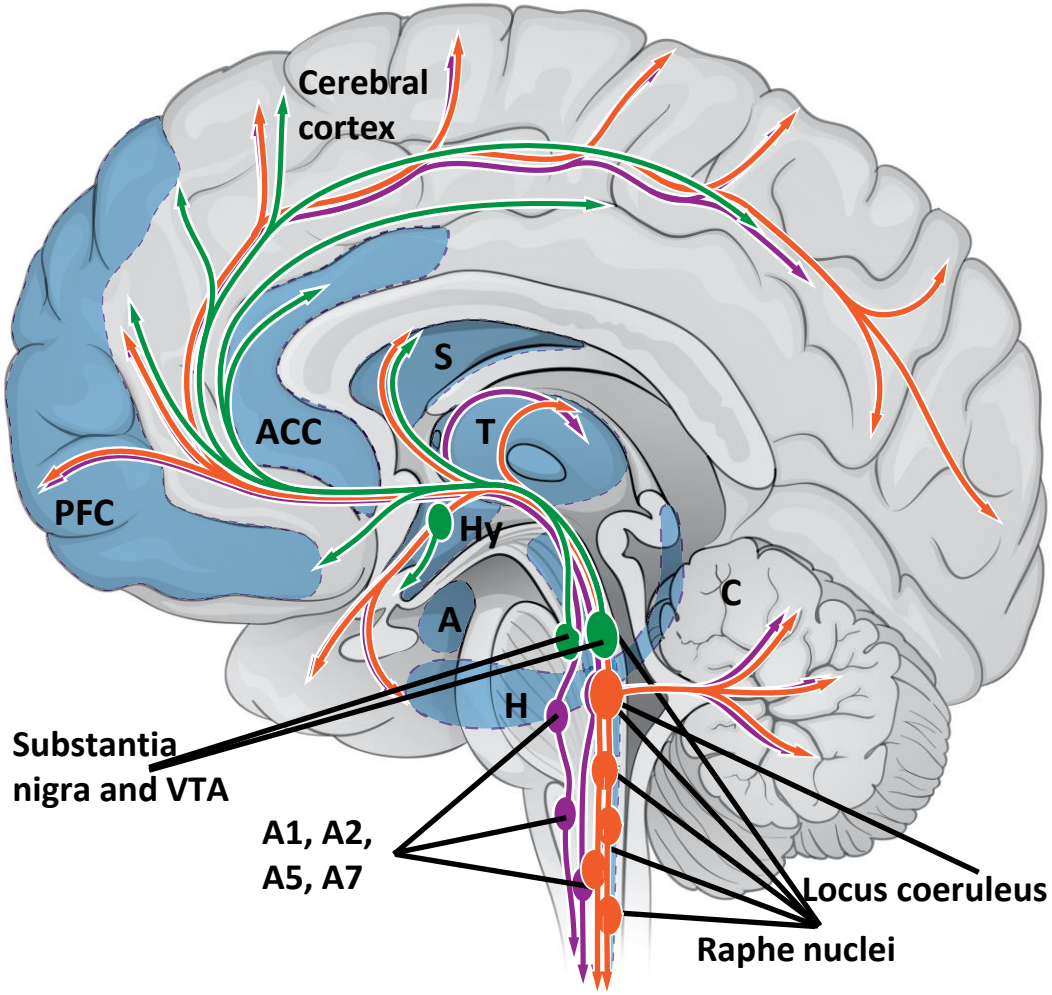
Objectives

- Explore the overlapping monoaminergic pathways
- Examine the overlapping monoaminergic 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 the proposed therapeutic areas where modulation of norepinephrine signaling may be clinically relevant

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



Serotonin

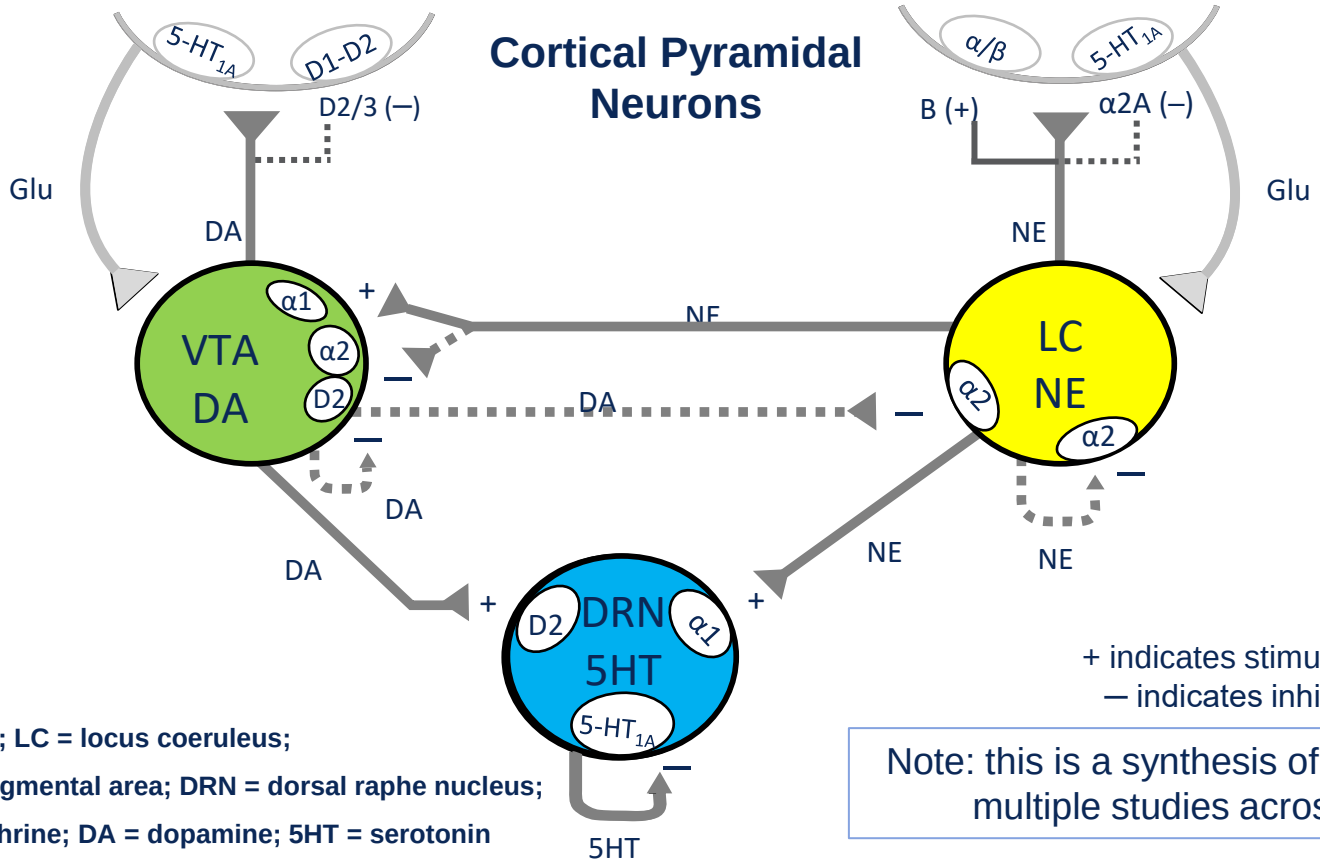
Dopamine

Norepinephrine

A = Amygdala; ACC = Anterior Cingulate Cortex; C = Cerebellum; H = Hippocampus; Hy = Hypothalamus; NA = Nucleus Accumbens; PFC = Prefrontal Cortex; S = Striatum; T = Thalamus; VTA = Ventral Tegmental Area

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

Neural Circuitry Of Monoamines Overlap



+ indicates stimulatory effect
– indicates inhibitory effect

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

Glu = glutamate; LC = locus coeruleus;

VTA = ventral tegmental area; DRN = dorsal raphe nucleus;

NE = Norepinephrine; DA = dopamine; 5HT = serotonin

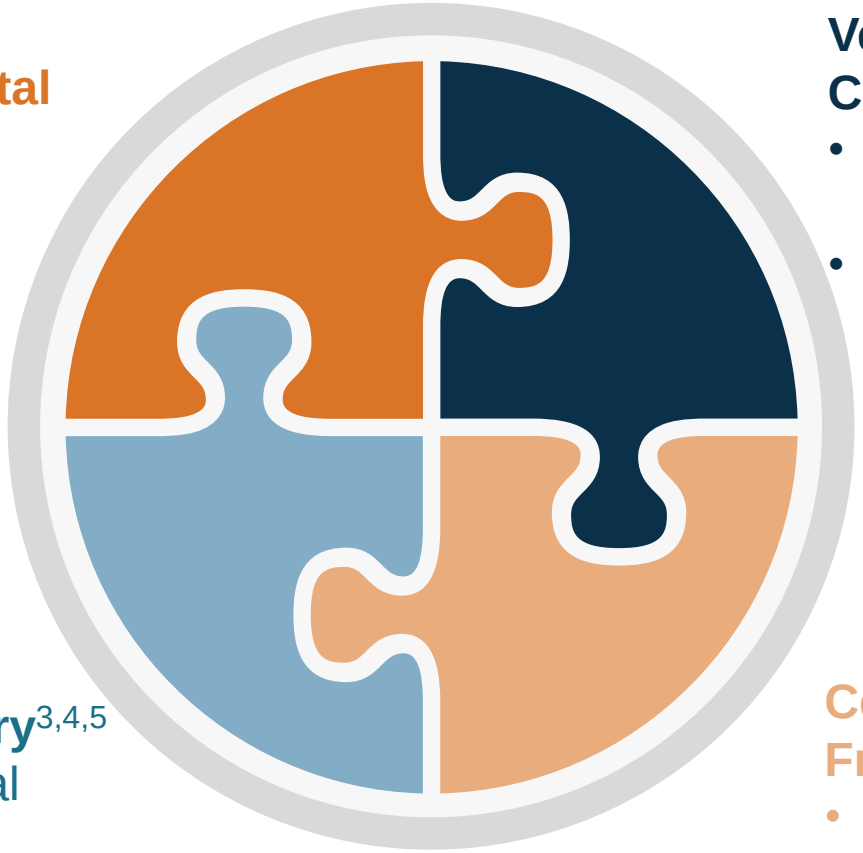
Hypothetical model of brain neural circuitry, primarily supported through animal models*[1]
*Although the exact cellular taxonomy and neural circuitry of the human brain is still being determined, animal models have been and continue to be an important contributing factor to this effort, as discussed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

1. El Mansari et al. *CNS Neurosci Ther.* 2010;16(3):e1-17.
2. Jorgenson et al. *Philos Trans R Soc Lond B Biol Sci.* 2015;370(1668):1-12.

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

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

Psychiatric Illnesses Share Common Symptoms

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

Arousal[1]

Affect[1]

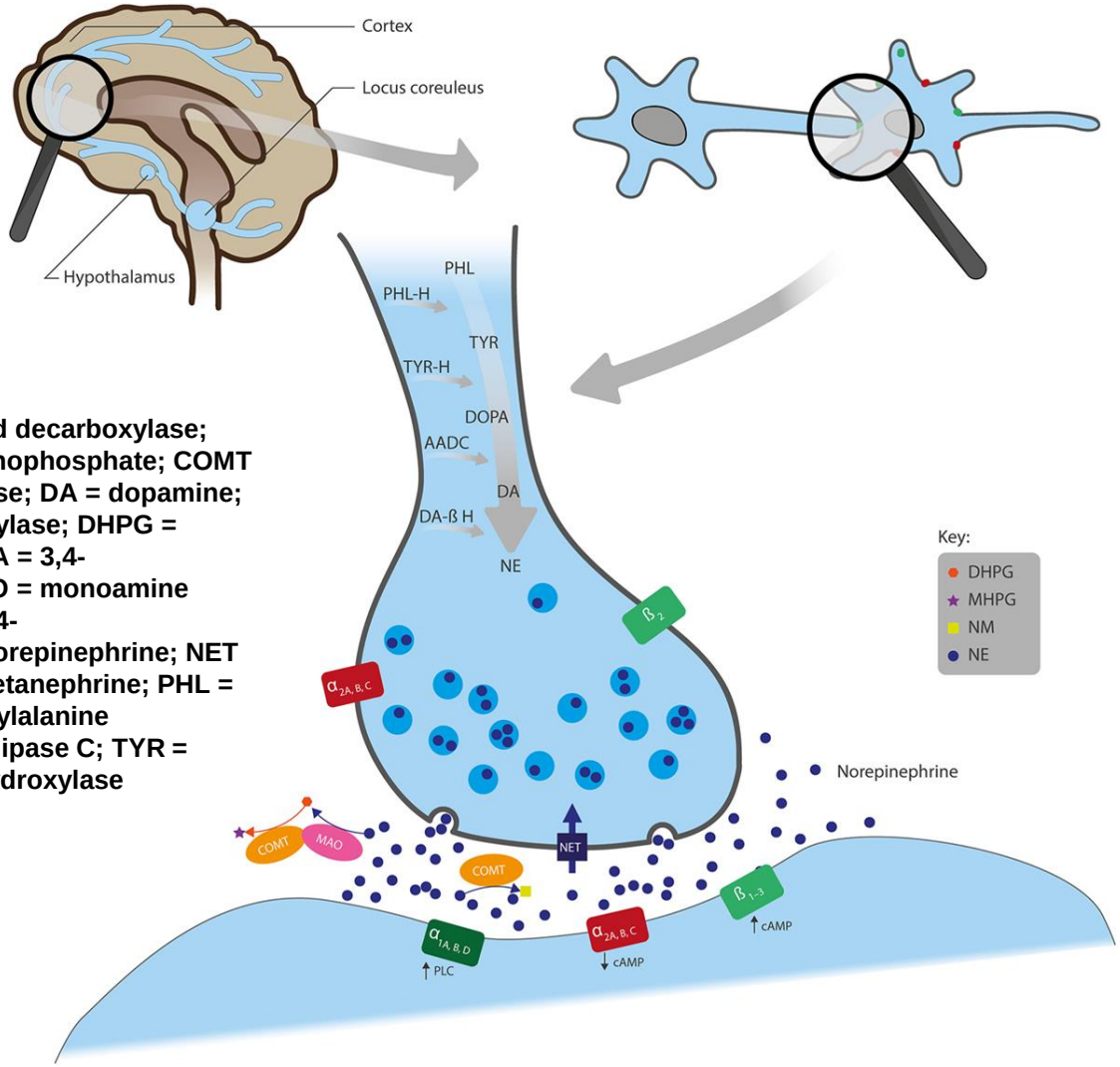
Cognition[1]

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

1. Maletic et al *Front Psych* 2017..8 (42): 1-12.
2. Goddard et al *Depression and Anxiety*. 2010 . 27: 339-350

DA = Dopamine; 5HT = Serotonin; NE = Norepinephrine

Norepinephrine in the Synapse[1]

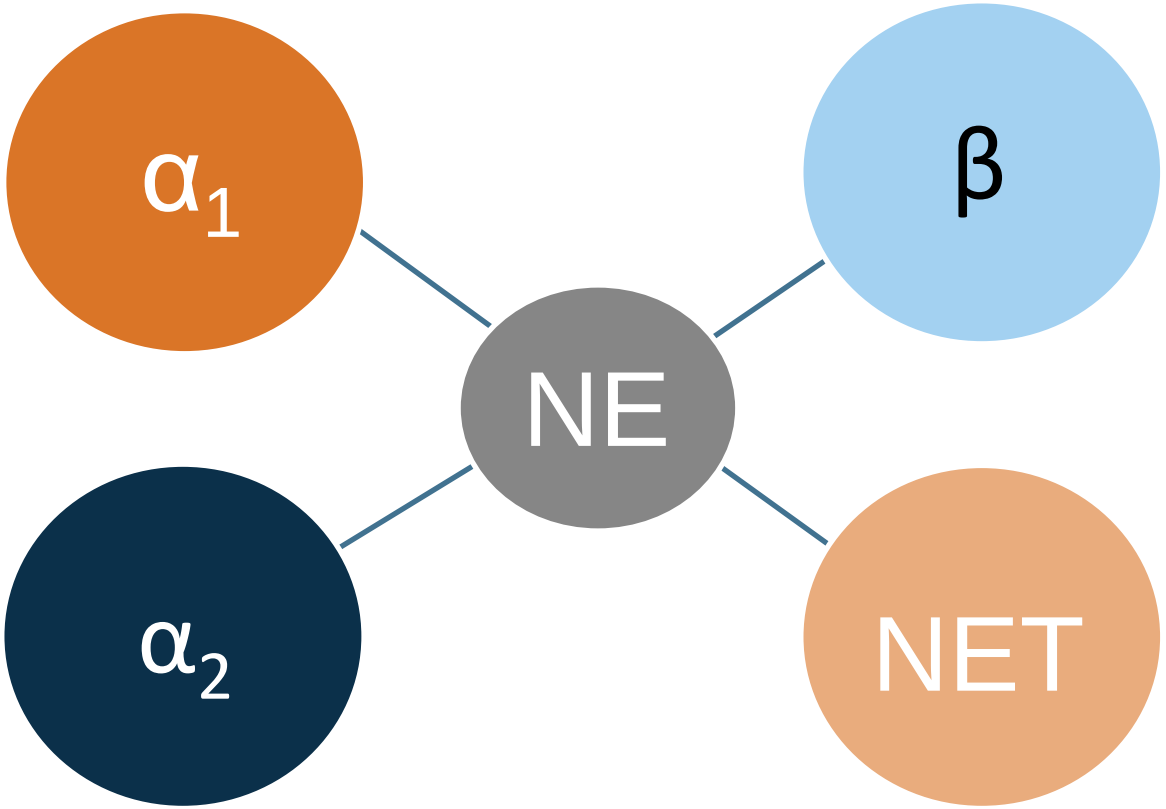


AADC = l-aromatic amino acid decarboxylase; cAMP = cyclic adenosine monophosphate; COMT = catechol O-methyltransferase; DA = dopamine; DA β-H = dopamine β-hydroxylase; DHPG = dihydroxyphenylglycol; DOPA = 3,4-dihydroxyphenylalanine; MAO = monoamine oxidase; MHPG = 3-methoxy-4-hydroxyphenylglycol; NE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

1. Maletic et al *Front Pscyh* 2017. 8 (42): 1-12

Localization of Norepinephrine Receptors in the Brain

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



β_1- Ubiquitous[2]
β_2- hippocampus, thalamus, & cerebellum[2]

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

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

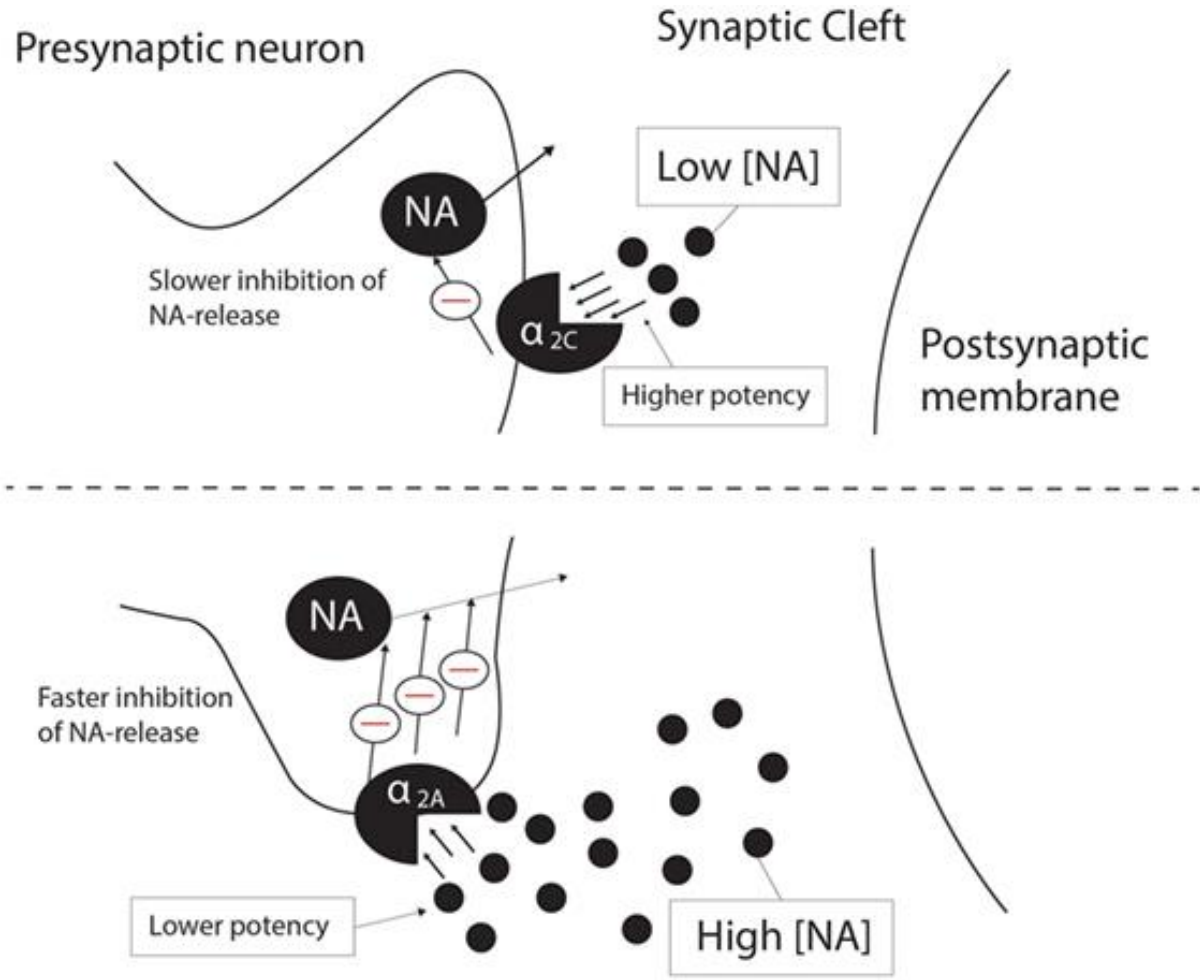
1. Price et al. *Mol Pharmacol.* 1994;45(2):171-175.
2. Nicholas et al. *Neuroscience.* 1993;56(4):1023-1039.
3. Saunders et al. *Pharmacol Ther.* 1999;84(2):193-205.
4. Schou et al. *Eur Neuropsychopharmacol.* 2005;15(5):517-520.

NE = norepinephrine; NET = norepinephrine transporter

Variations in Norepinephrine Concentration May Be Linked to Receptor Activation

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

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



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

NE = norepinephrine*; NA = noradrenaline*
***these are identical terms**

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

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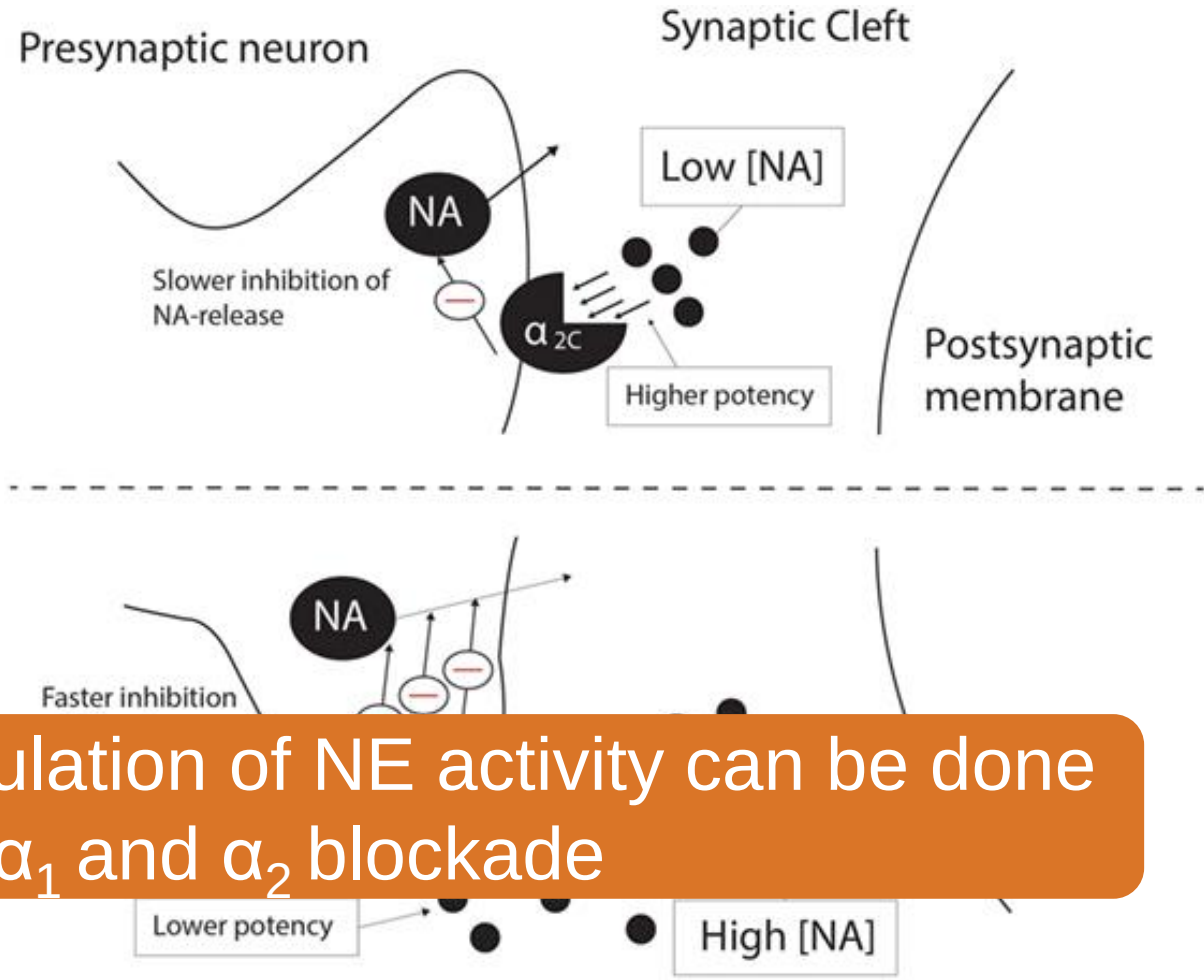

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Theoretically, modulation of NE activity can be done via α_1 and α_2 blockade

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

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

Direct Modulation	Dopamine	5HT
α_{2c} antagonism	↑ circulating DA	↑ circulating 5HT
α_{2a} agonism		↓ 5HT synthesis
α_{2a} antagonism		↑ 5HT synthesis
$\alpha_{2b/c}$ antagonism		↑ 5HT 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)
  - Increase striatal acetylcholine decreasing dopamine release (and potentially serotonin)

1. Uys et al *Front Psych* 2017. 8(144): 1-23

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]

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

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

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

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, SZ, and BP[1-3]

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

1. Miyamoto et al. *Mol Psychiatry*. 2005;10(1):79-104.
2. Lindström et al. *J Affect Disord.* 2017;213:138-150.
3. Chen et al. *Curr Opin Psych* 2011. 24: 10-17.

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