Neuroscience Education Institute

CAN YOU SAY HEY? THE MANY FACES OF SEROTONIN 5HT2A

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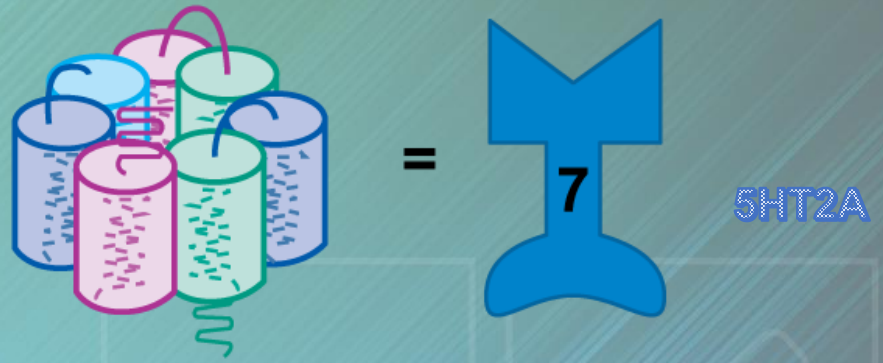
Learning Objectives

- Recognize the neuroscience behind the serotonin 5HT2A receptor in order to better understand psychiatric illnesses

- Utilize knowledge of the serotonin 5HT2A receptor to help reduce specific psychiatric symptoms or side effects via on- and off-label prescribing

The 5HT2A Receptor: A Good Target

Twelve-transmembrane
region transporter
~ 30% of psychotropic drugs



Seven-transmembrane region
G-protein linked
~ 30% of psychotropic drugs

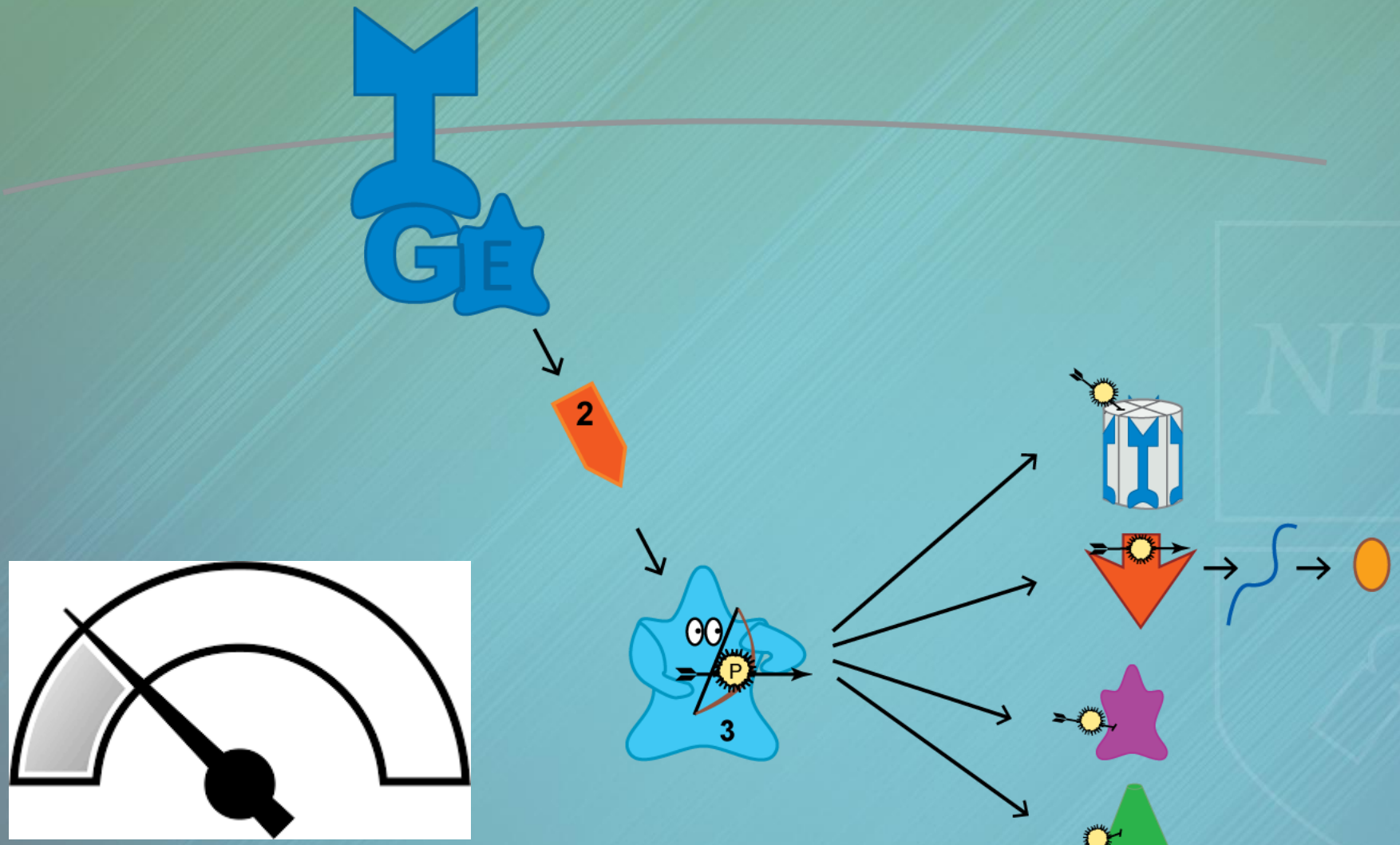
Enzyme
~ 10% of psychotropic drugs

Four-transmembrane region
ligand-gated ion channel
~ 20% of psychotropic drugs

Six-transmembrane region
voltage-gated ion channel
~ 10% of psychotropic drugs

Stahl SM. Stahl's essential psychopharmacology, 5th ed; 2021.

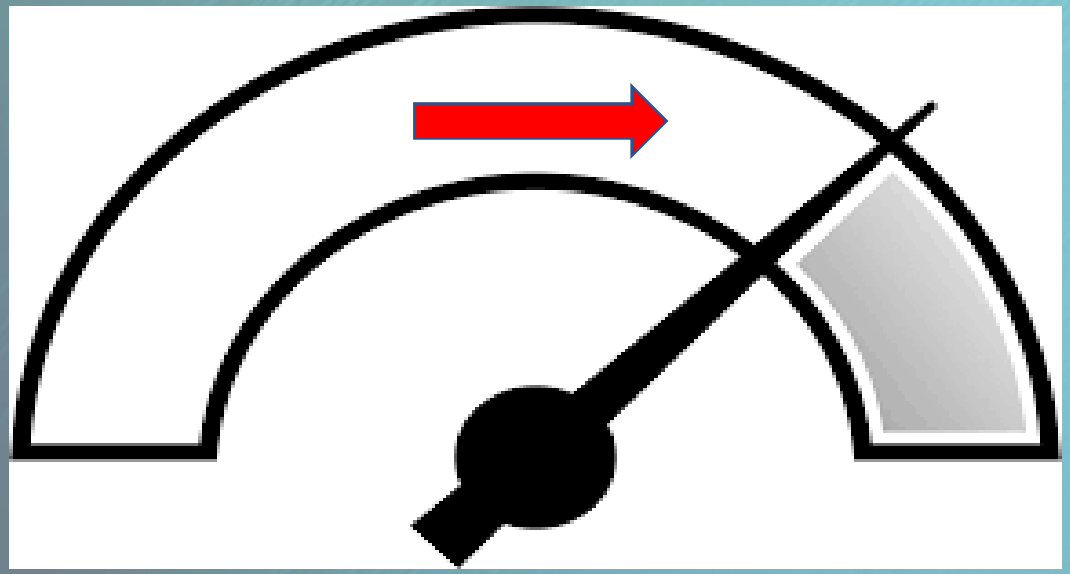
5HT2A Receptors Are G-Protein Linked

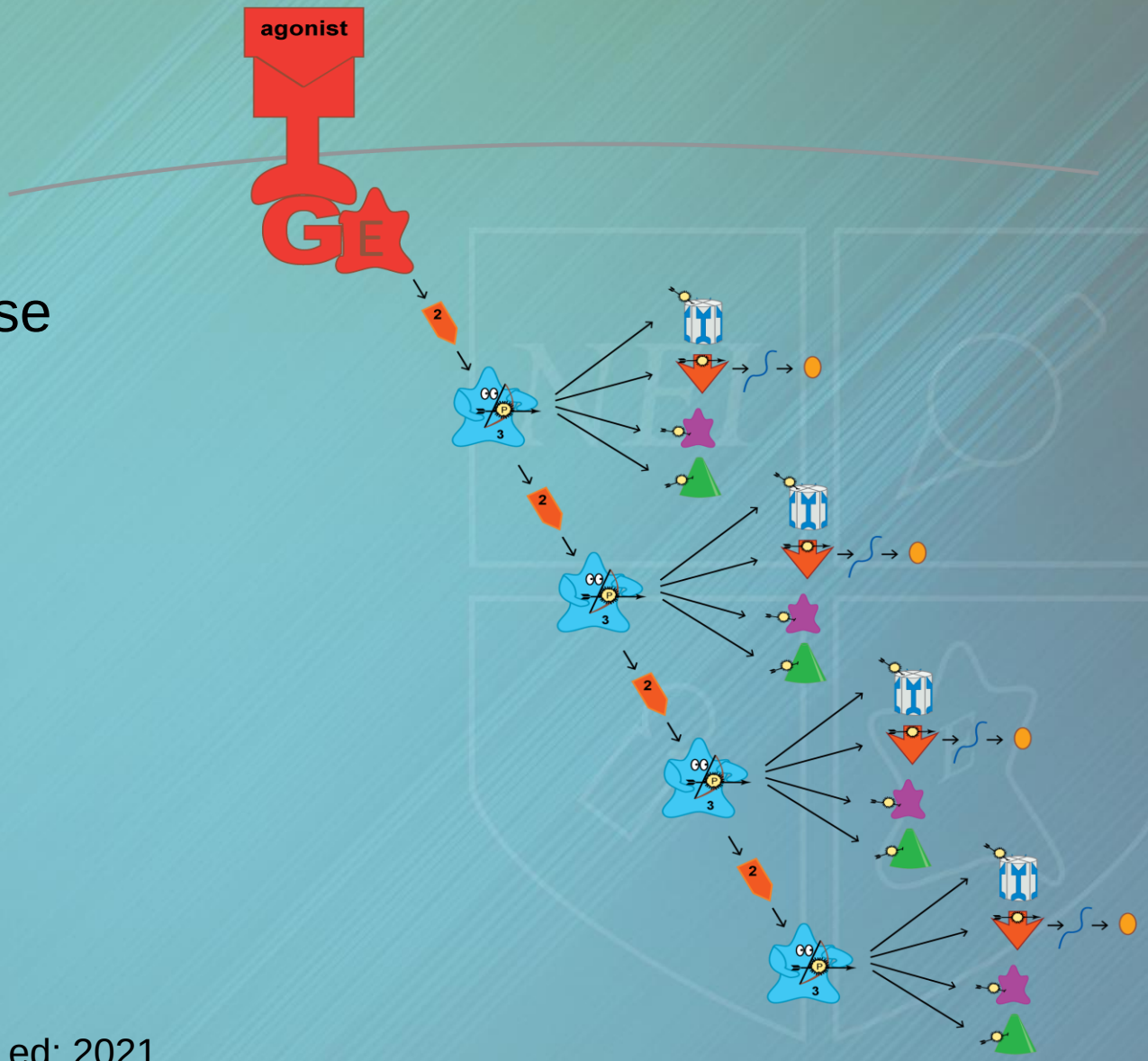


Stahl SM. Stahl's essential psychopharmacology, 5th ed; 2021.

5HT2A Agonism

- Baseline constitutive activity is increased
- 5HT when bound to its 2A receptor tends to be stimulating in nature
- Neurocircuitry firing tends to increase
- Consider using LSD to trip





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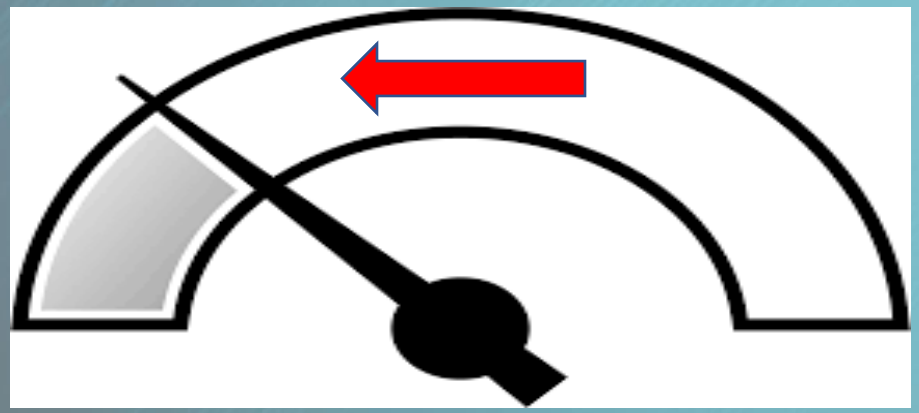
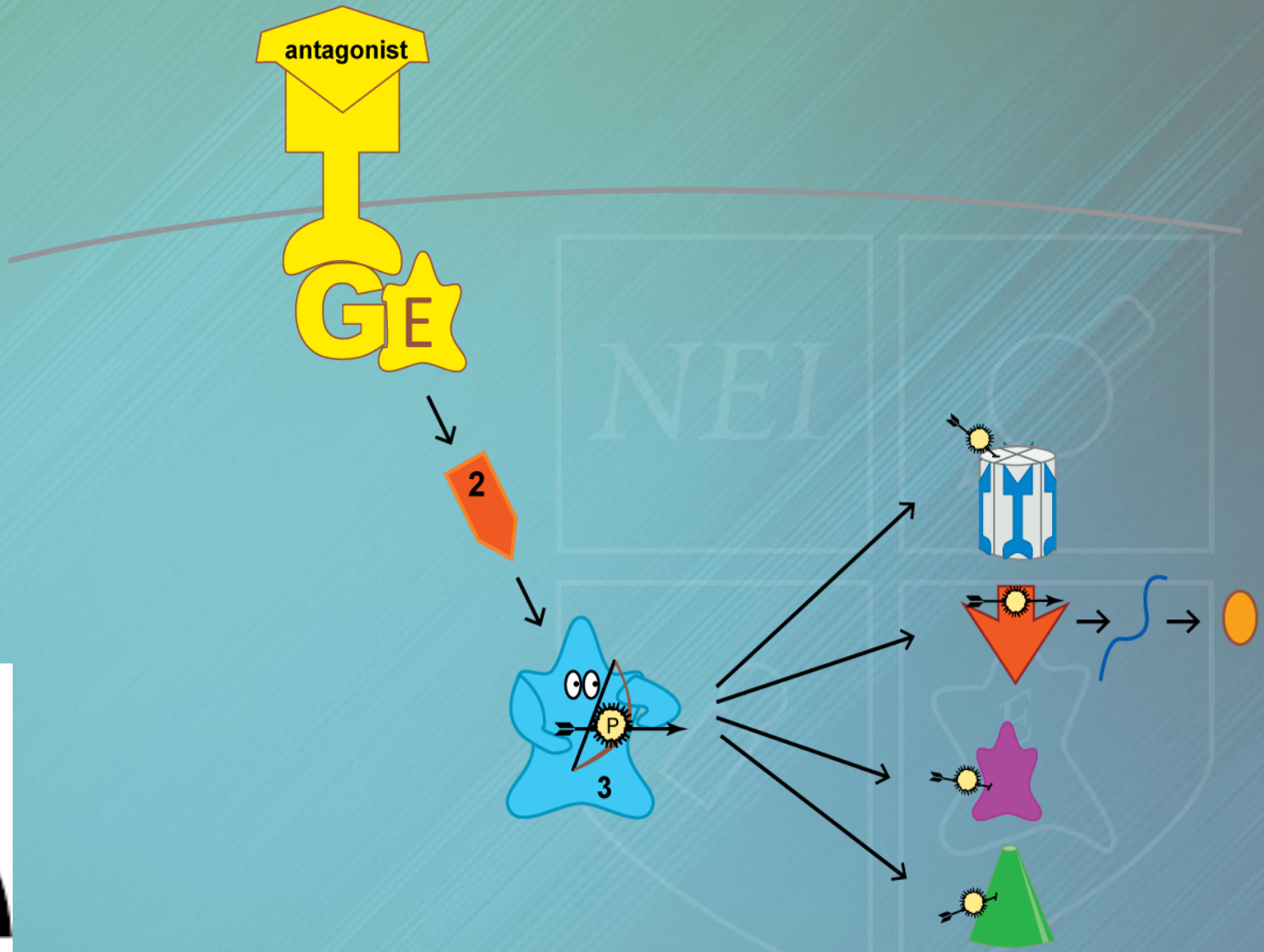
5HT2A Antagonism

- Antagonizing lowers activity at least back to constitute baseline
- Consider how SSRIs may lead to activating side effects if too much serotonin binds to 5HT2A receptors
- By blocking 5HT2A with another drug such as a sedating antidepressant, may return serotonin circuitry activity to normal and alleviate the side effect

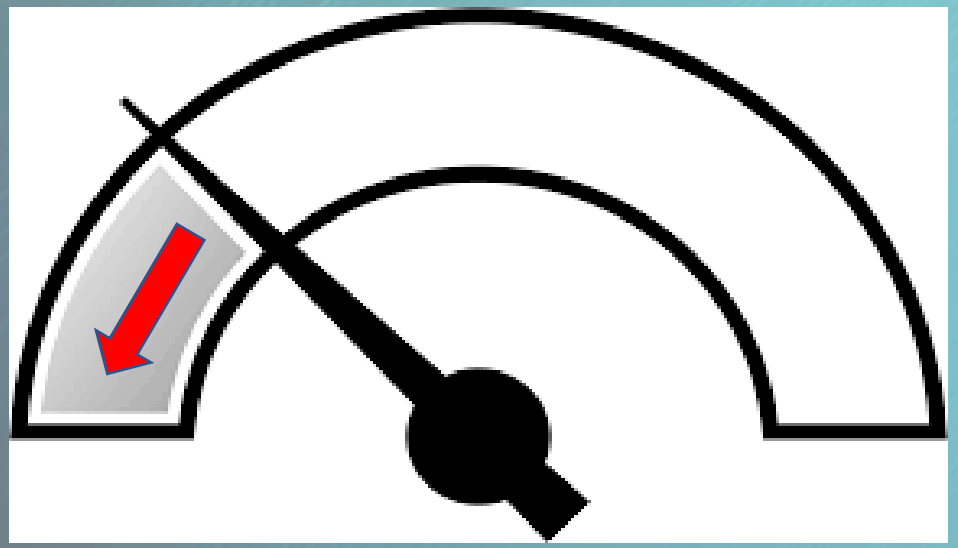




Stahl SM. Stahl's essential psychopharmacology, 5th ed; 2021.

Some 5HT2A Antagonists Are Inverse

Inverse Agonist: Beyond Antagonism; Even the Constitutive Activity Is Blocked



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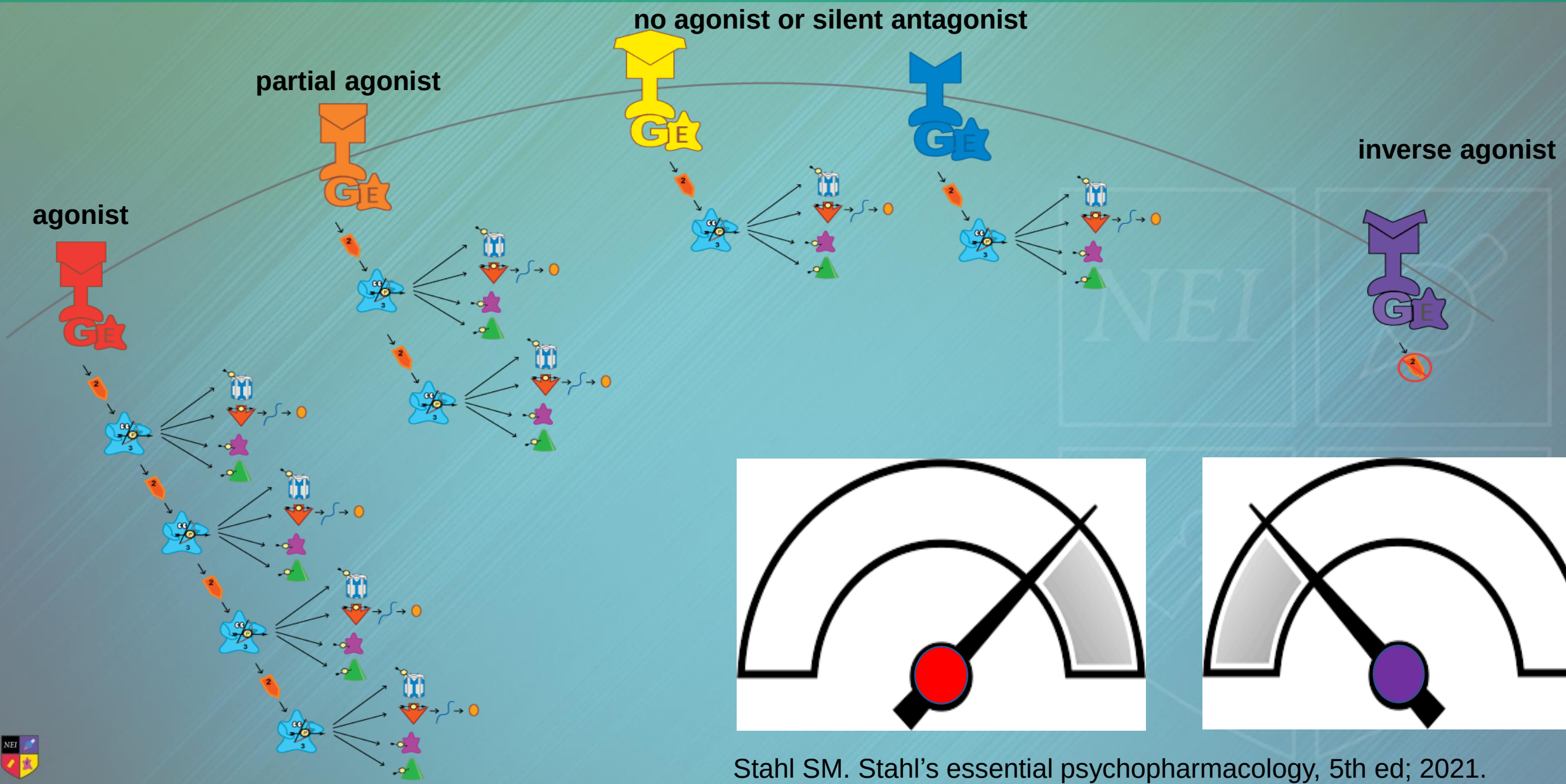
Putting the Agonism-Antagonism Spectrum Together



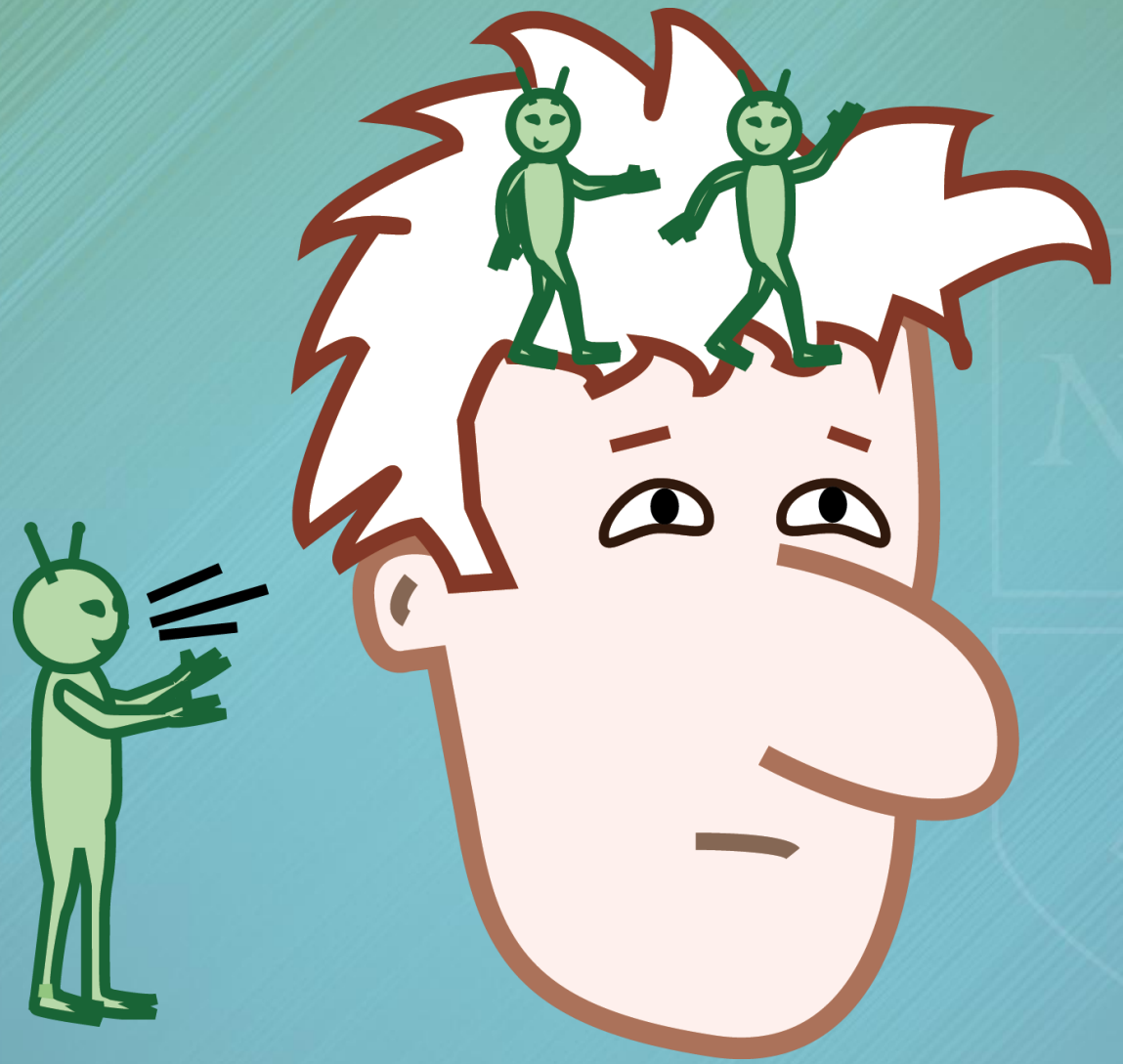
Stahl SM. Stahl's essential psychopharmacology, 5th ed; 2021.

Possible Clinical Benefits From 5HT2A Manipulation

Serotonin and Psychosis	5HT2A	Antagonist or Inverse Agonist Use	• Decrease Parkinson's psychosis • Decrease dementia-related psychosis • Lower drug-induced EPS • ? Reduction of negative symptoms in schizophrenia • ? Mood stabilizing in bipolar disorder • ? Antidepressant in bipolar disorder • ? Improve insomnia • ? Improve anxiety and agitation
		Agonist	• Psychotomimetic actions • Experimental for TRD • Psychotherapy augmentation

Stahl SM. Stahl's essential psychopharmacology, 5th ed; 2021.

Psychosis and 5HT2A

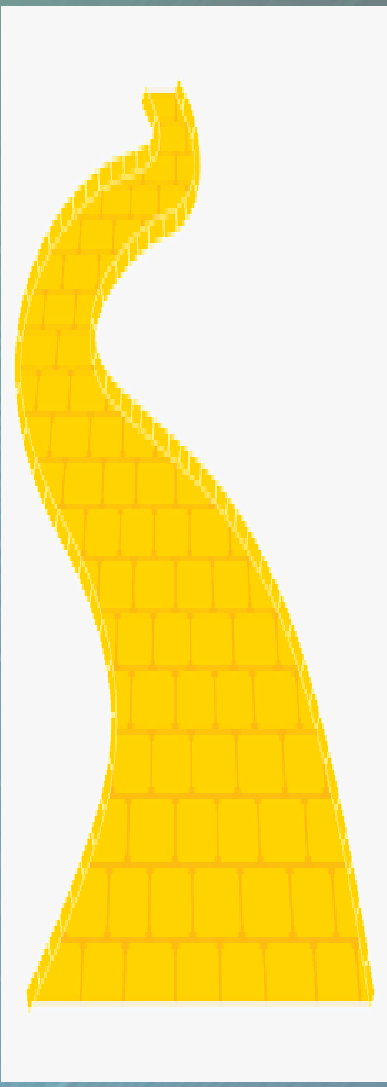


Let's Take a Walk on the Serotonin Pathway

Dopamine Theory
Hyperactive dopamine at D2 receptors in the mesolimbic pathway

Glutamate Theory
NMDA receptor hypofunction

Serotonin Theory
5HT2A receptor hyperfunction in the cortex



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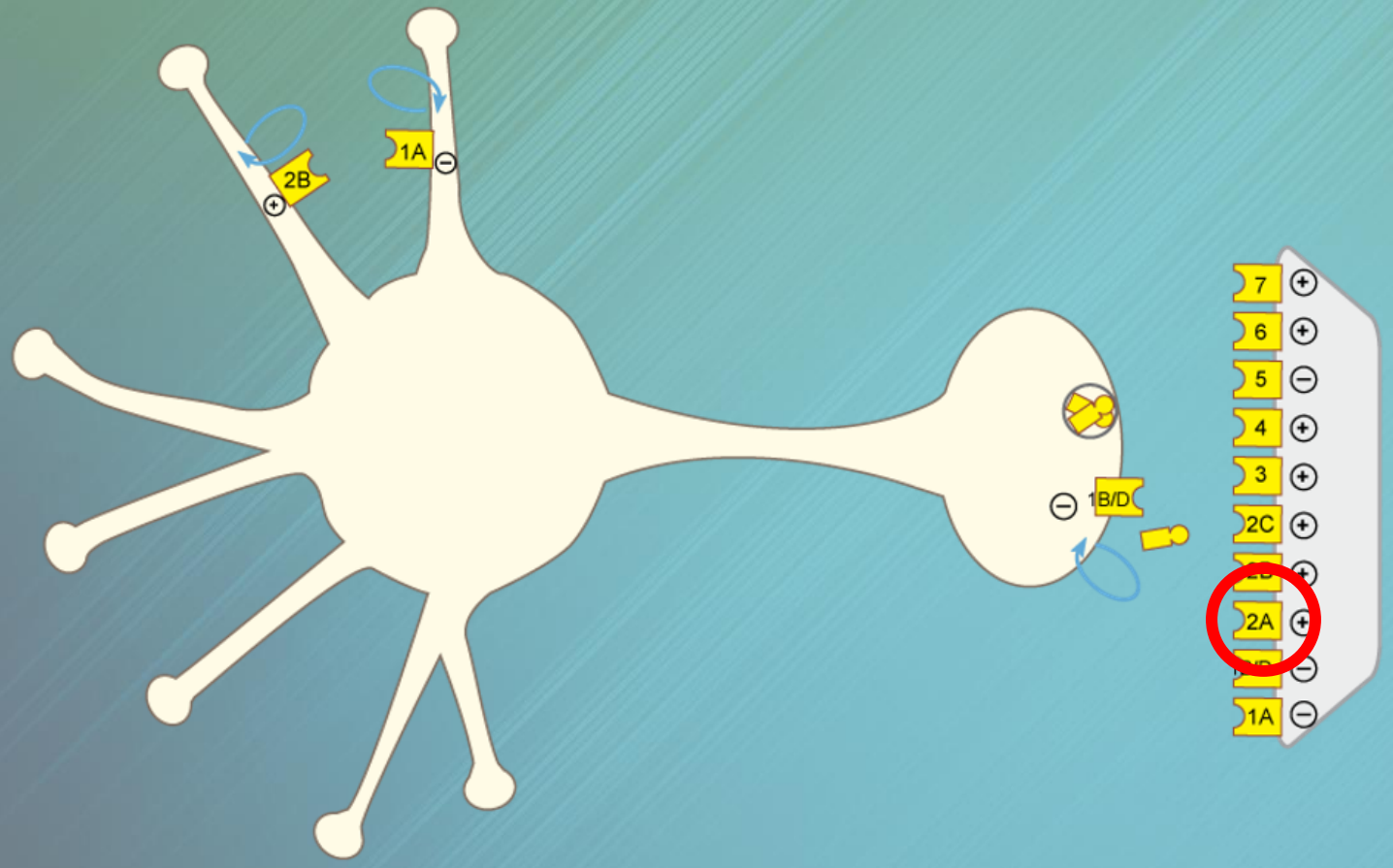
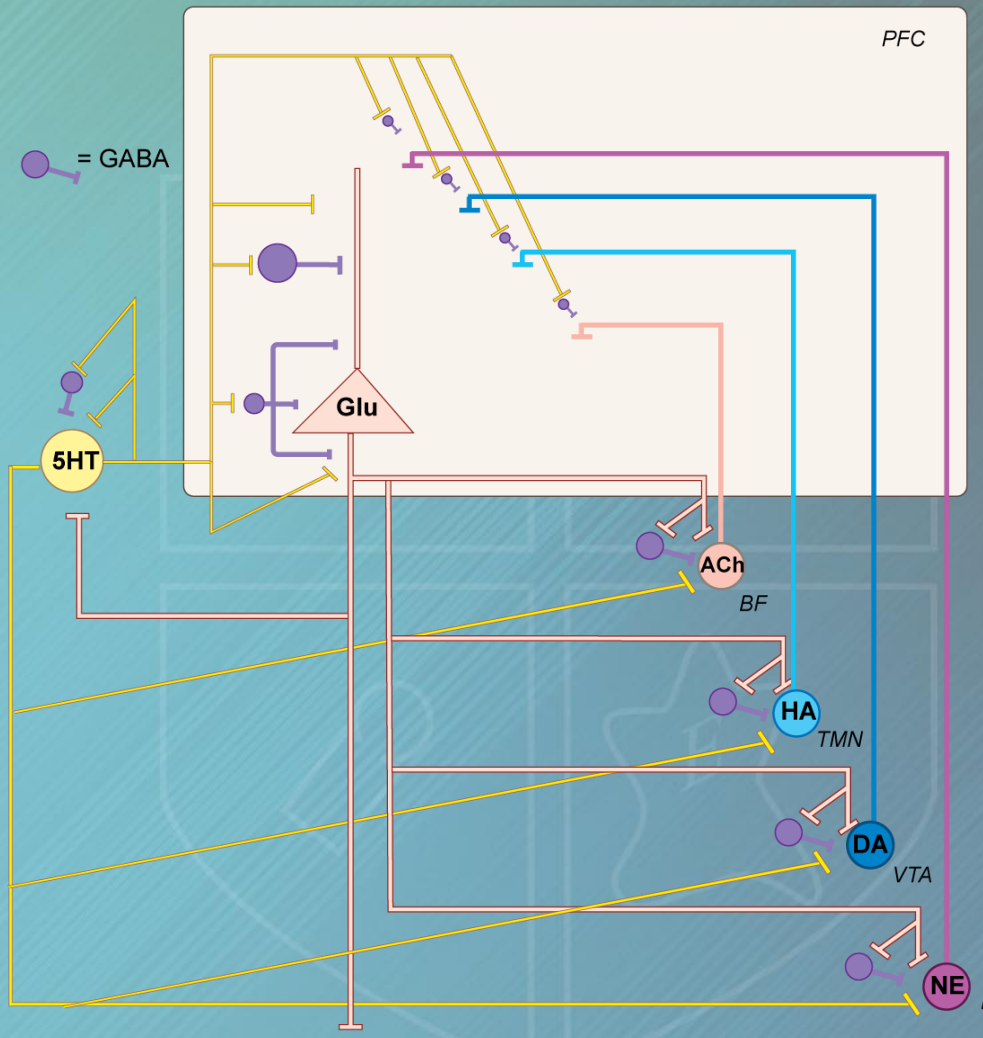
There Are Several Types of 5HT Receptors That Regulate Many Brain Circuits





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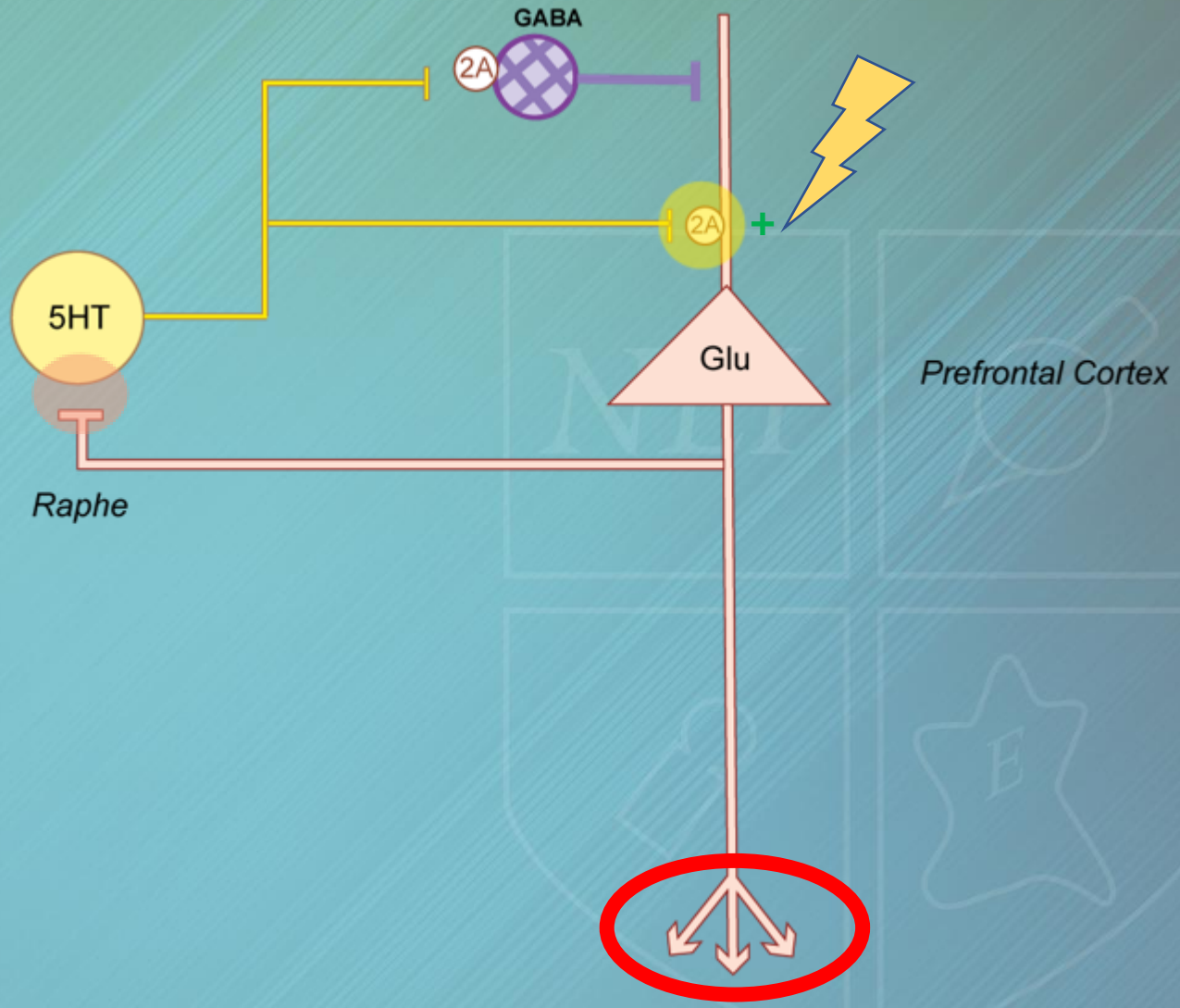
Serotonin and Glutamate

- Glutamatergic activity can change based on the location of 5HT2A
- 5HT2A are always excitatory if situated on glutamate neurons and *increase* glutamate release



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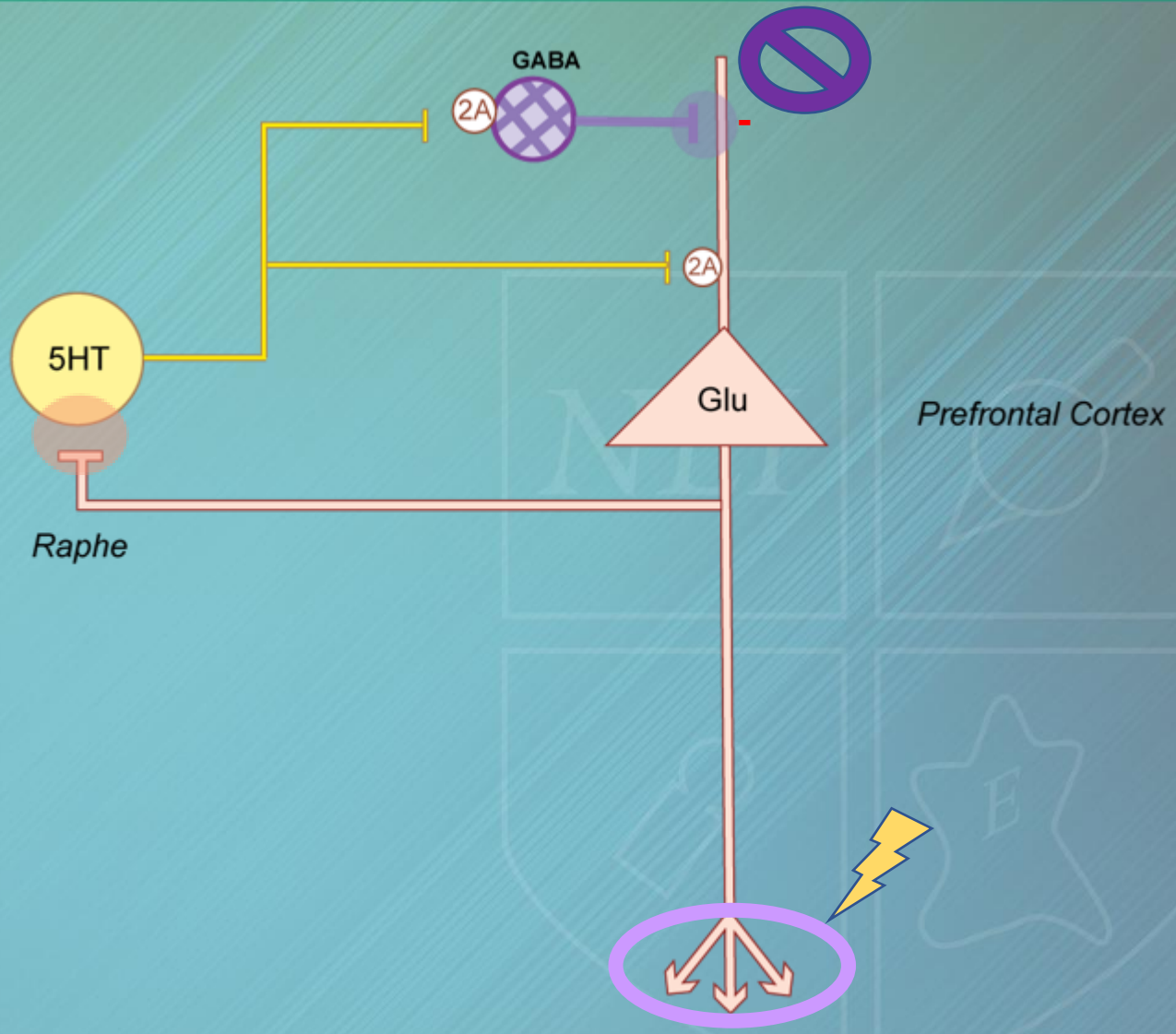

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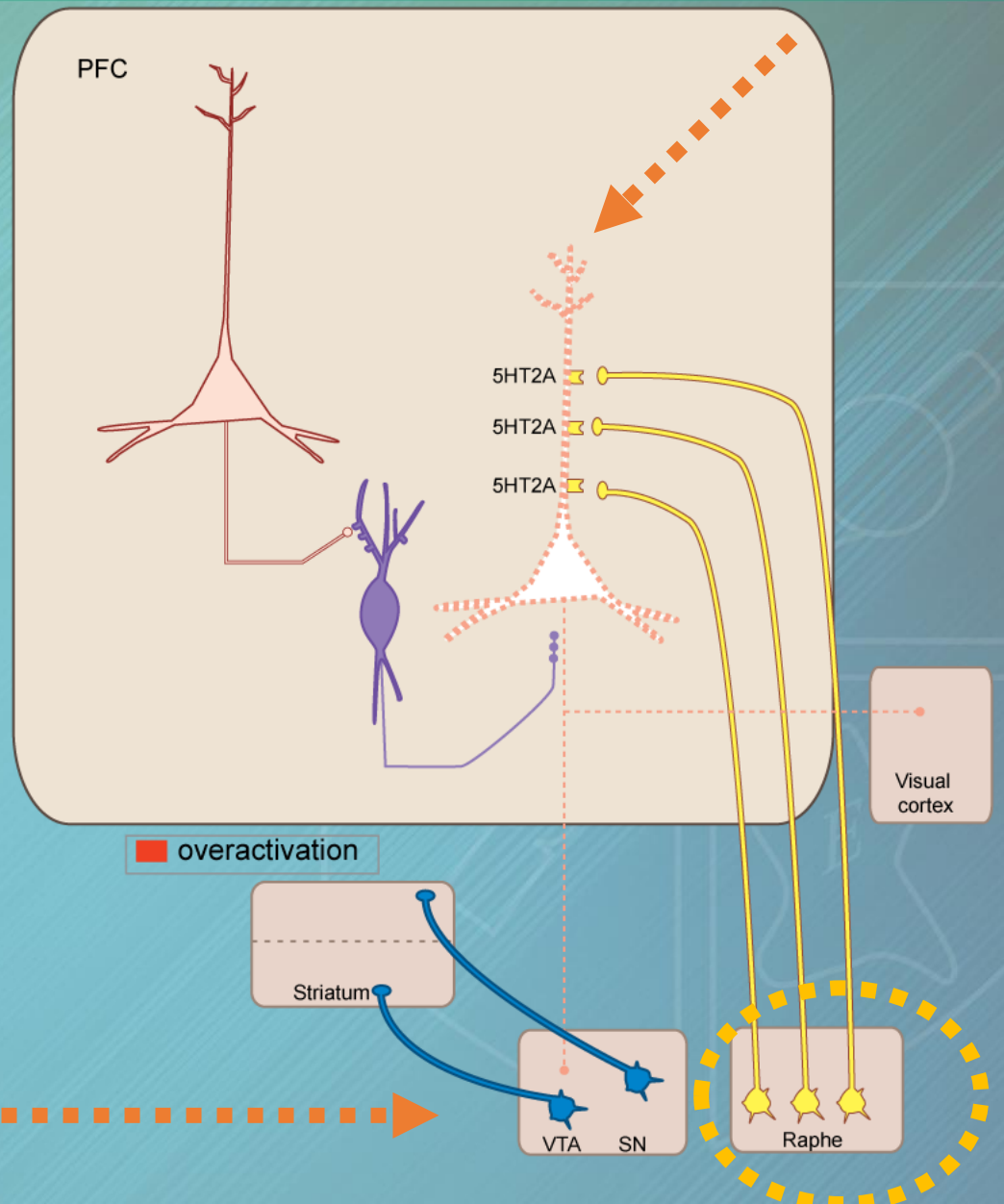
Serotonin Psychosis Hypothesis

- At baseline, 5HT2A are not activated
- GABA transmission is tonic baseline
- Glutamatergic neurons are not very active
- DA output from the VTA is tonic baseline
- No psychosis occurs



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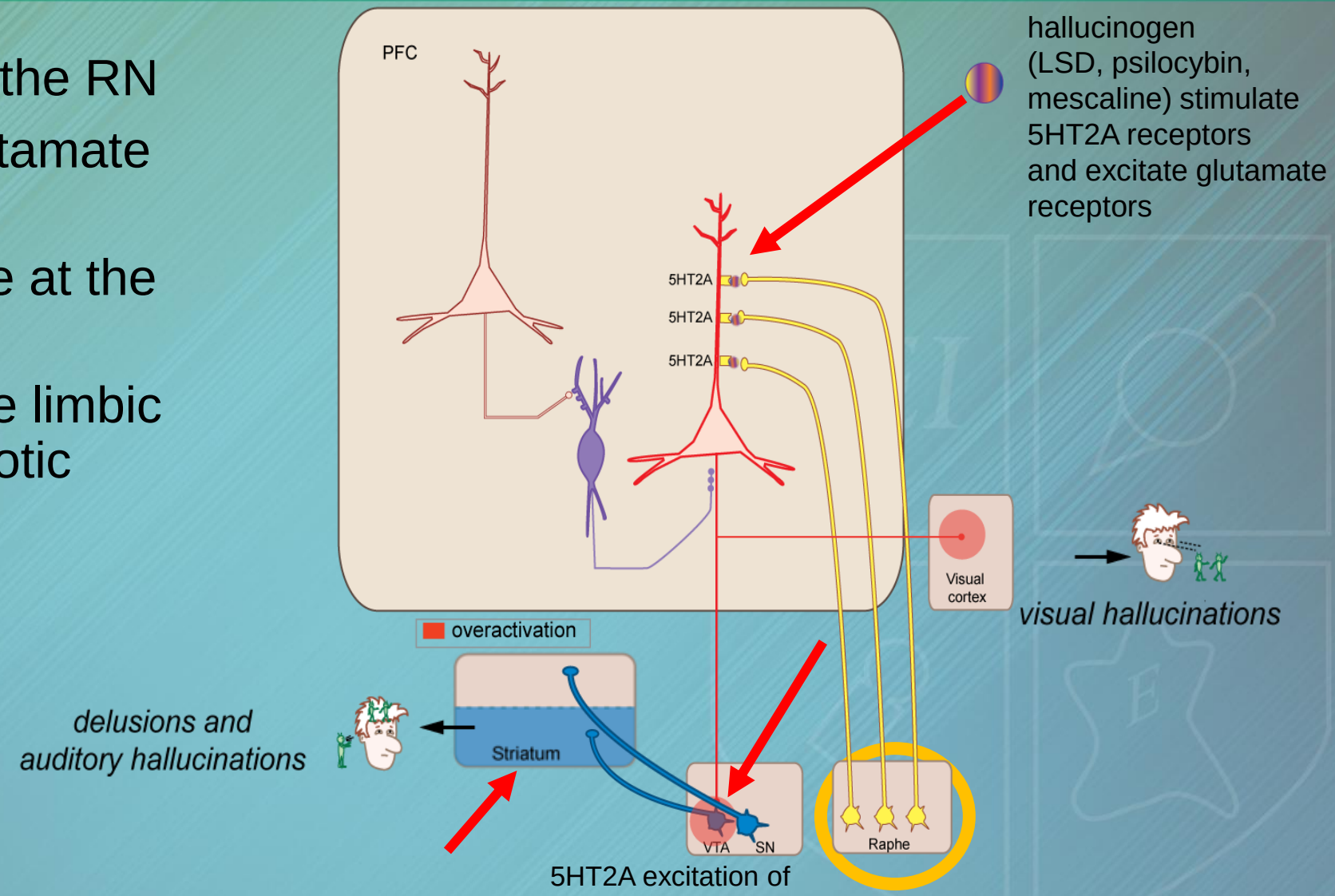
Serotonin, Glutamate, and Dopamine

- 5HT activity increases in the RN
- Stimulates 5HT2A on glutamate neurons next
- Releases more glutamate at the VTA
- Excites DA neurons in the limbic pathways creating psychotic symptoms



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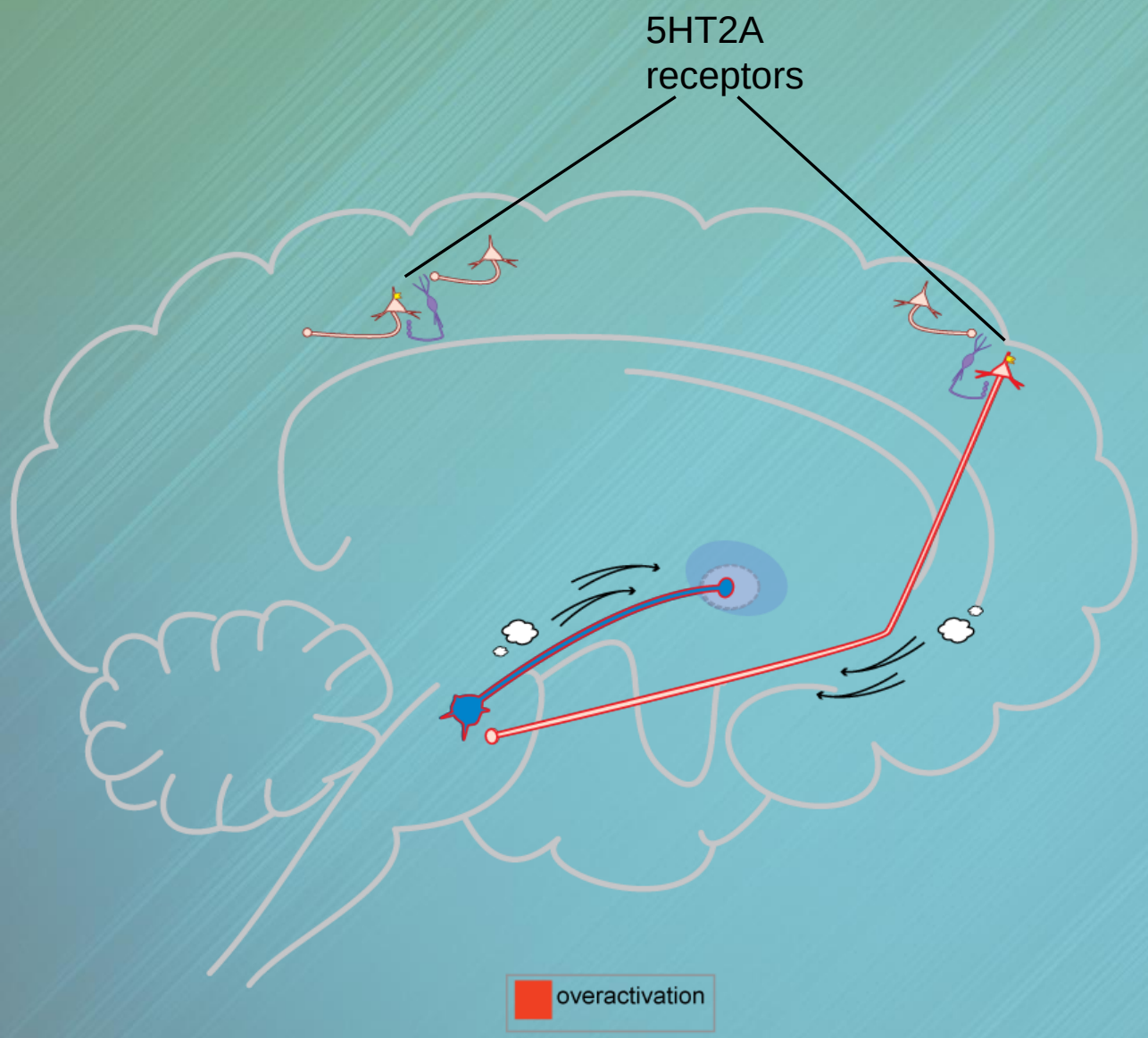
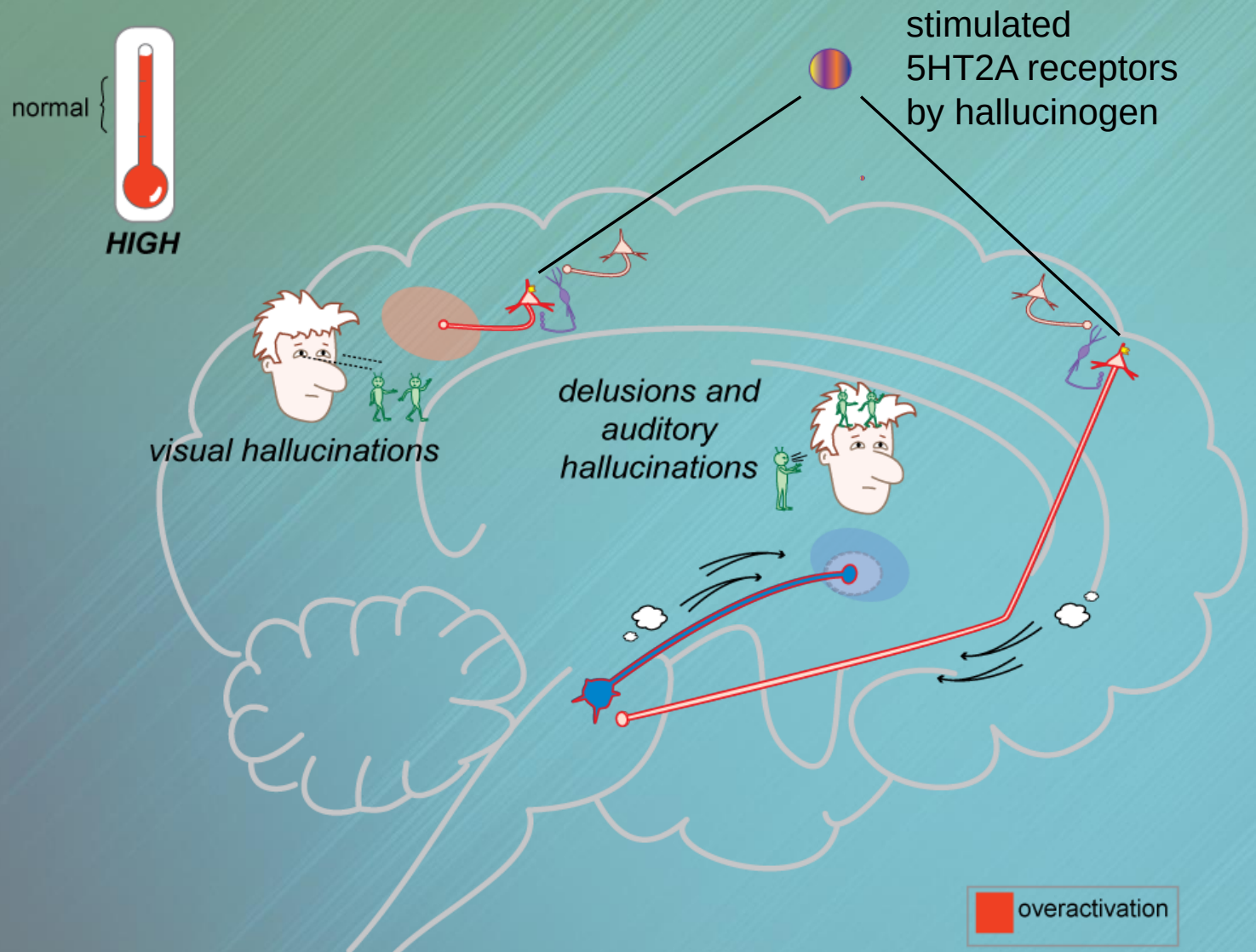
Balanced Serotonin and GABA

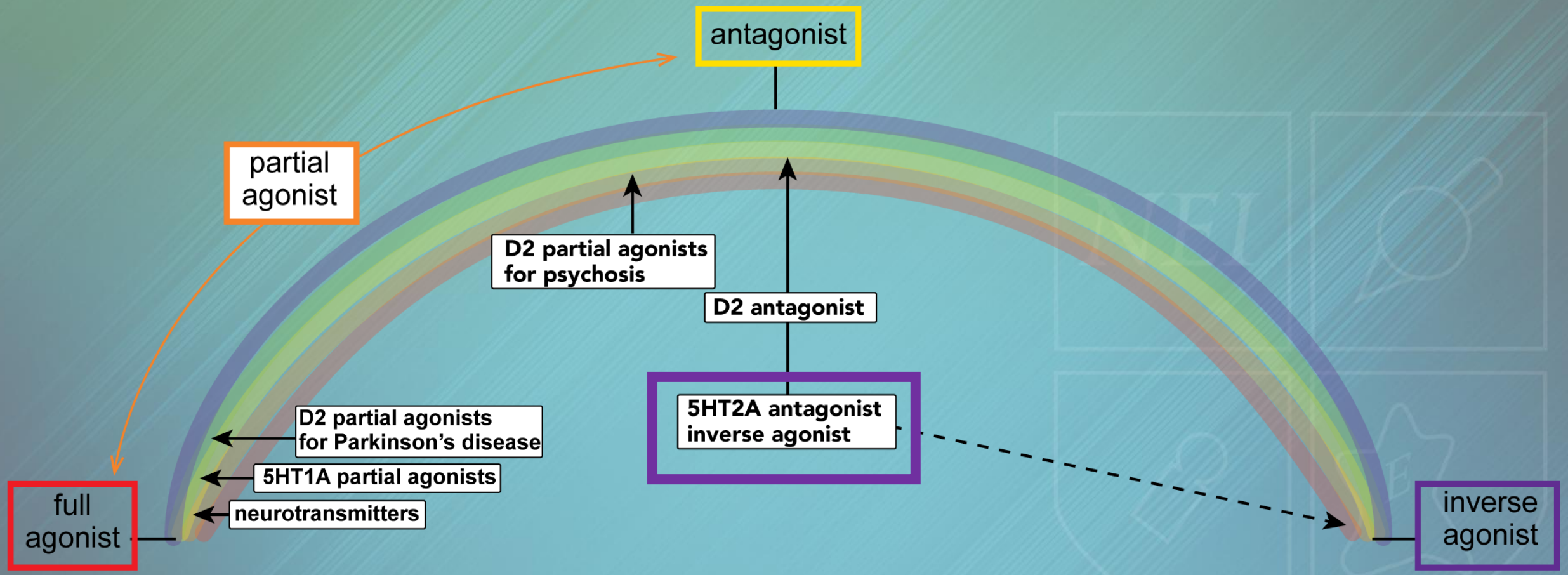


Excess Serotonin Leads to Glutamate/Dopamine Excess



5HT2A Antagonism in Psychotic Disorder Treatment

- Lowers Psychosis
- Lowers EPS



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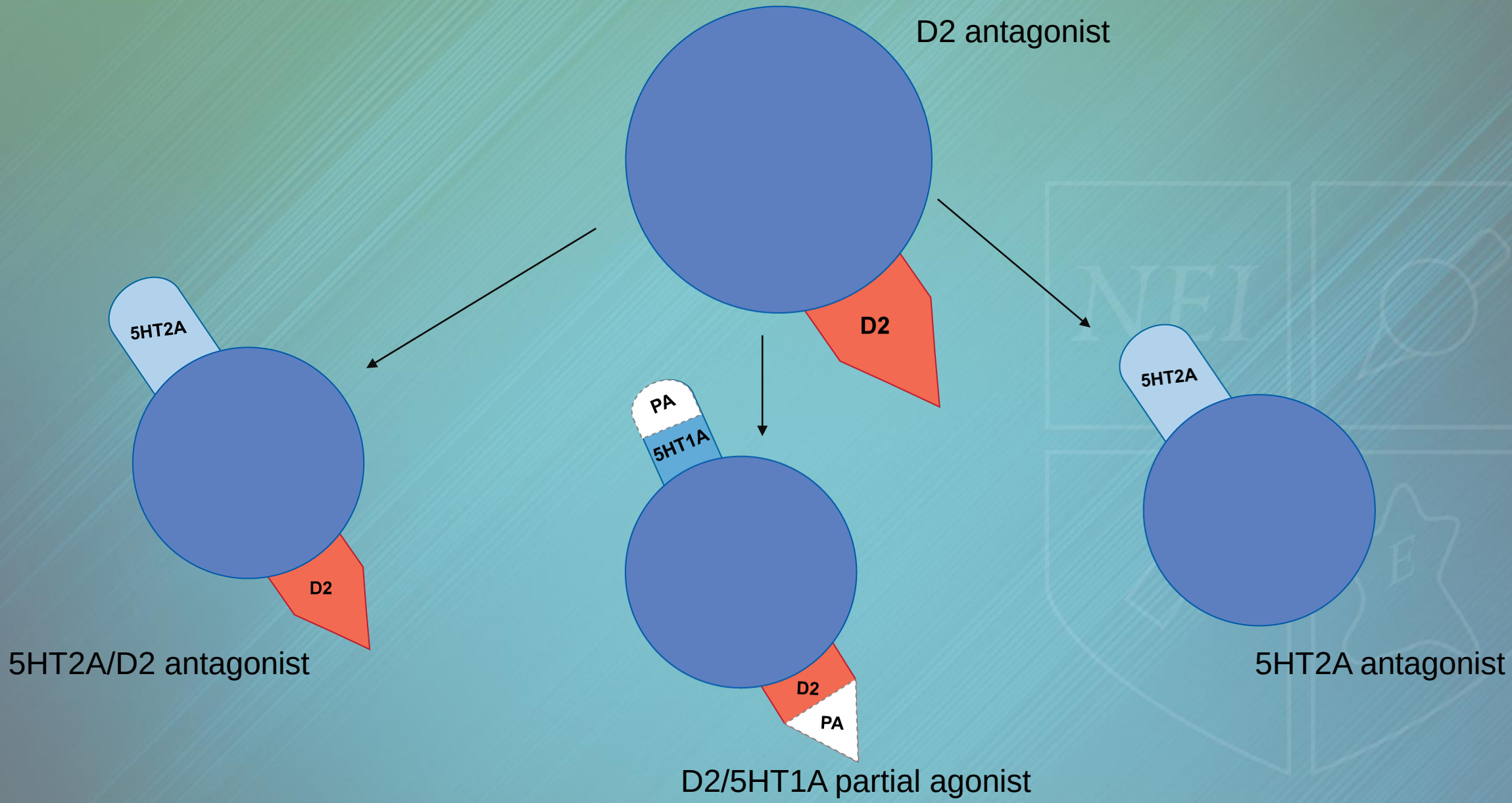
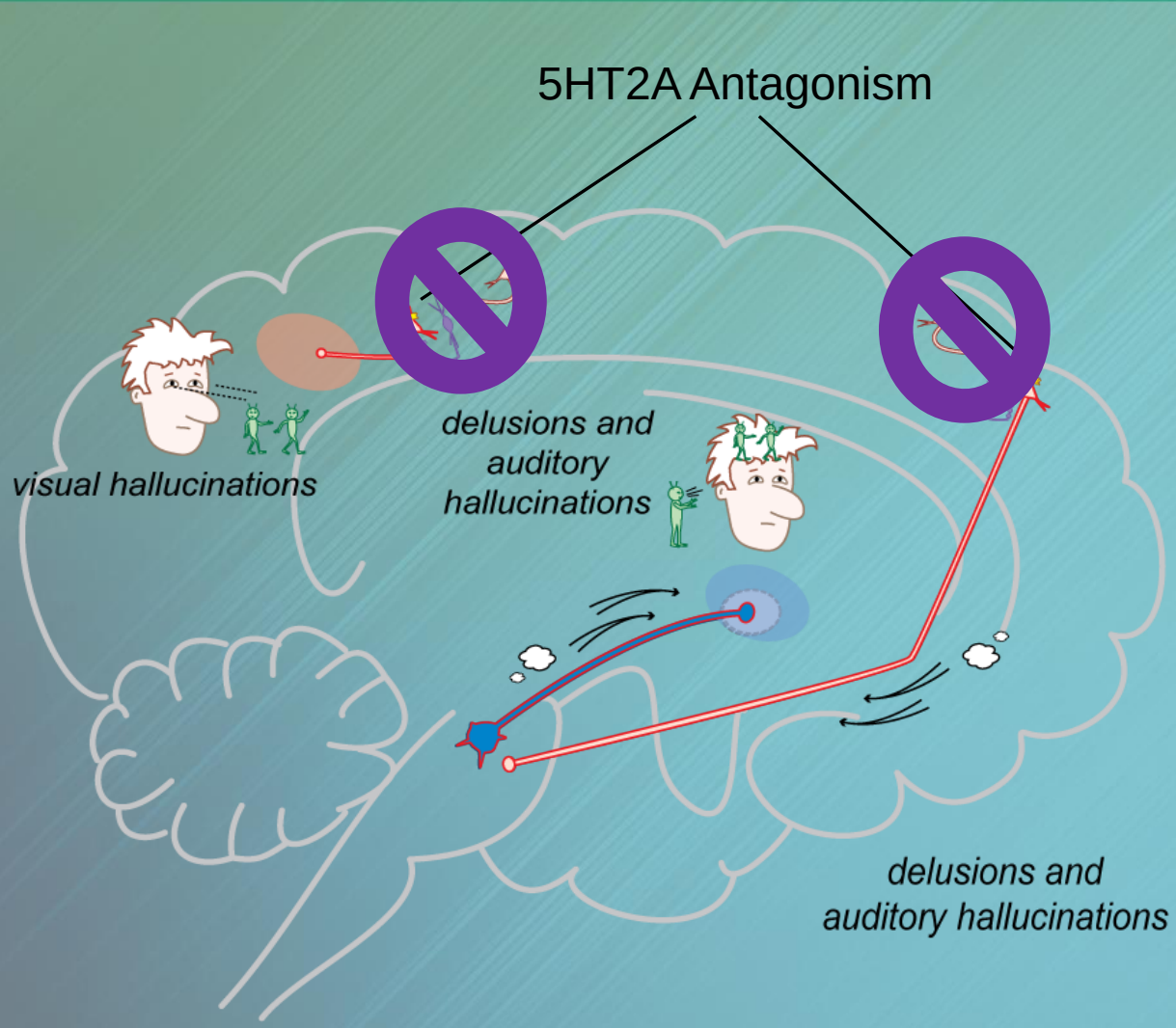
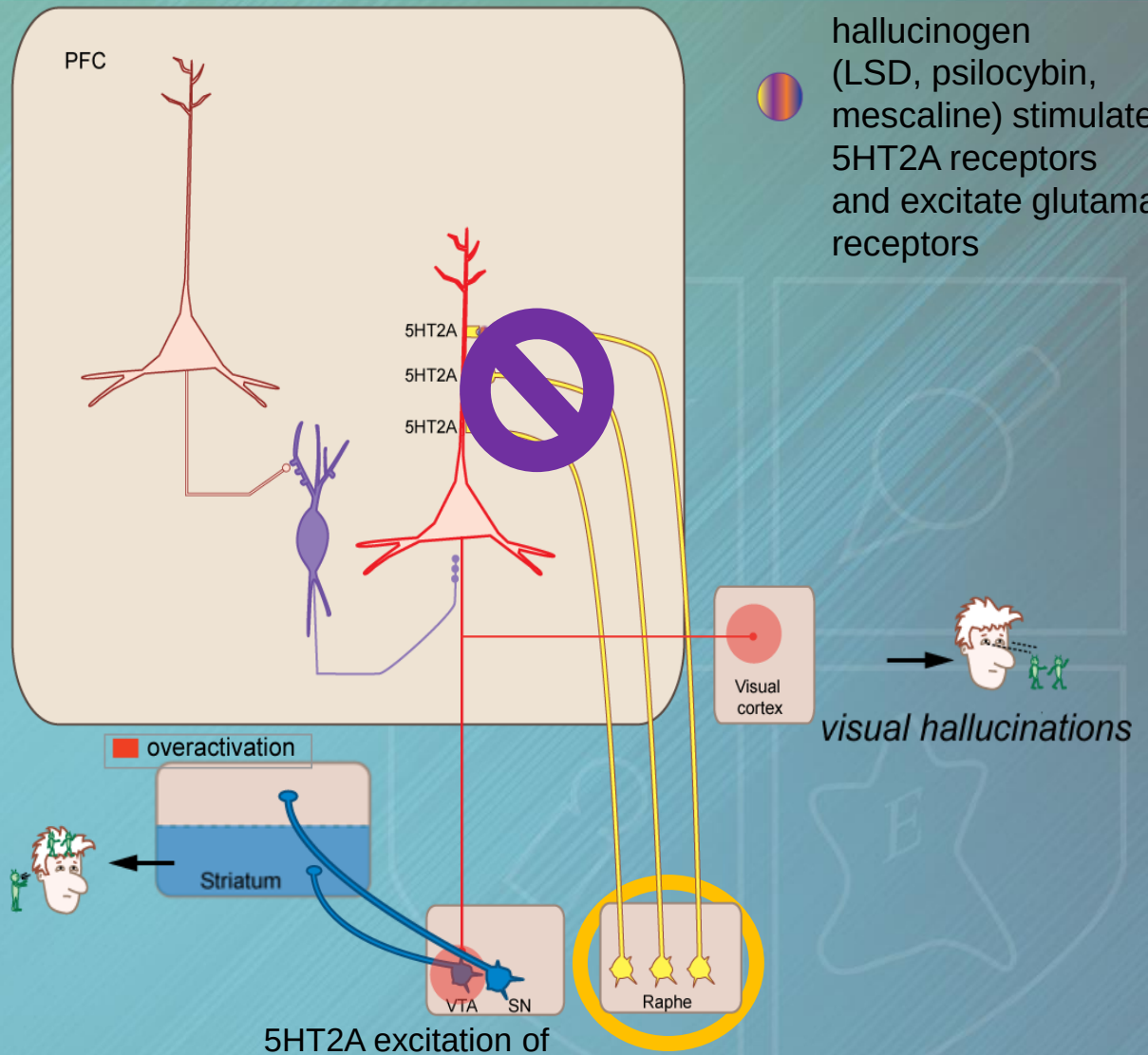
All Atypical Antipsychotics Block 5HT2A



Serotonin, Glutamate, and Dopamine





hallucinogen (LSD, psilocybin, mescaline) stimulate 5HT2A receptors and excite glutamate receptors

5HT2A excitation of glutamate by hallucinogens causes mesolimbic DA hyperactivity and psychosis

Stahl SM. Stahl's essential psychopharmacology, 5th ed; 2021.

Types of Psychosis

- **Schizophrenia**
- Combining 5HT2A antagonists with D2 antagonists
  - May improve positive symptoms
  - To a lesser degree negative ones
- Likely 5HT2A affinity increases, D2 antagonism may need to be less for treating positive symptoms

- **Parkinson's disease psychosis and dementia-related psychosis**
- 5HT2A antagonism alone can be useful as monotherapy
- Possibly allowing D2 antagonism and its side effects to be lessened or avoided

Stahl SM. Stahl's essential psychopharmacology, 5th ed; 2021.

EPS and 5HT2A

5HT2A Antagonism Helps Lower EPS?

- All atypicals have 5HT2A antagonism
- Dual receptor antagonism lowers EPS compared to typical antipsychotics
  - Akathisia
  - Parkinsonism
  - Dystonia
- Off-label addition of sedating antidepressants might help as they antagonize 5HT2A
  - Especially for akathisia

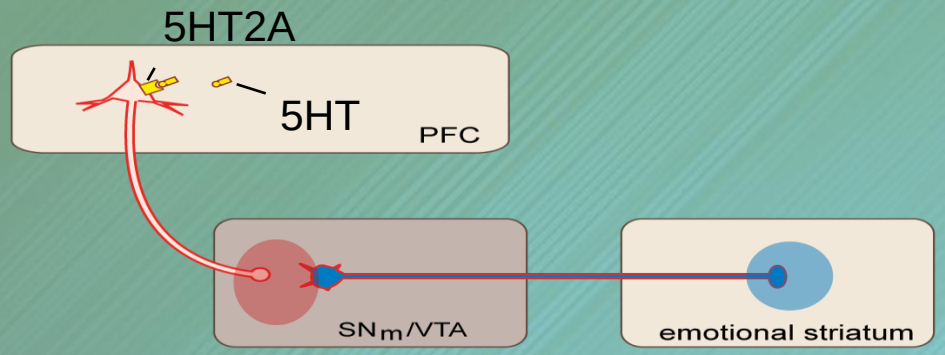
Praharaj SK et al. Ther Adv Psychopharmacol 2015;5(5):307-13.
Laoutidis ZG, Luckhaus C. Int J Neuropsychopharmacol 2014;17(5):823-32.
Stahl SM. Stahl's essential psychopharmacology, 5th ed; 2021.

EPS Lowering Mechanism

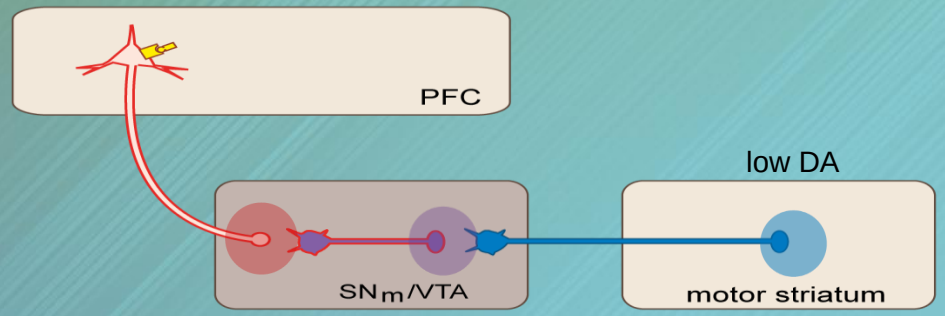
Case 1

- A 30-year-old male is treated to remission with haloperidol, a typical antipsychotic, for his psychosis but develops akathisia. He does not want to relapse and go back to the hospital so refuses to change medications.

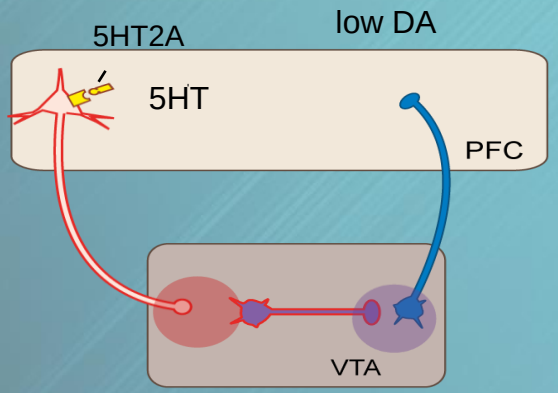
  What agents are typically used to treat this *and,* theoretically, which might be able to lower EPS by lending 5HT2A blockade?



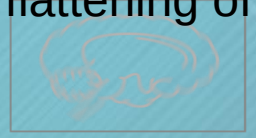
hallucinations



drug-induced parkinsonism (DIP)

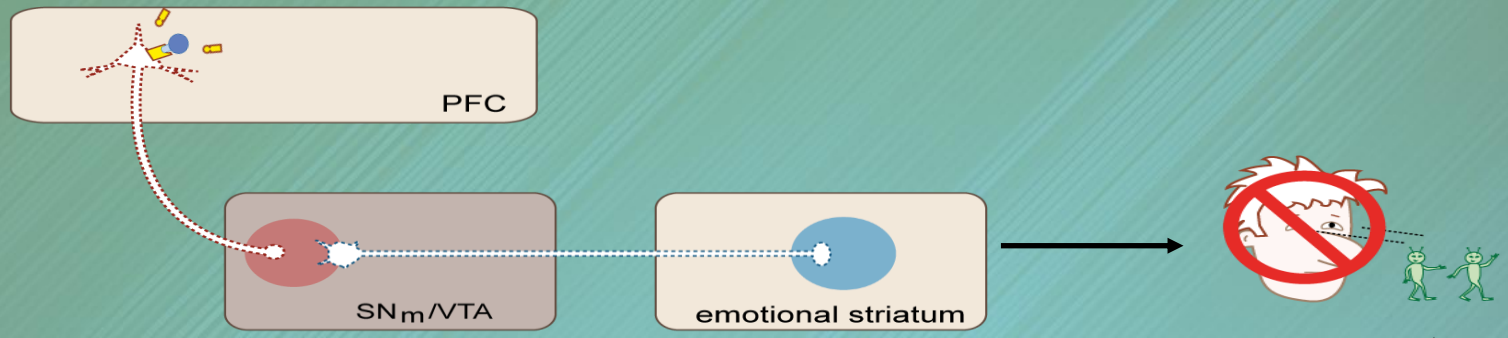


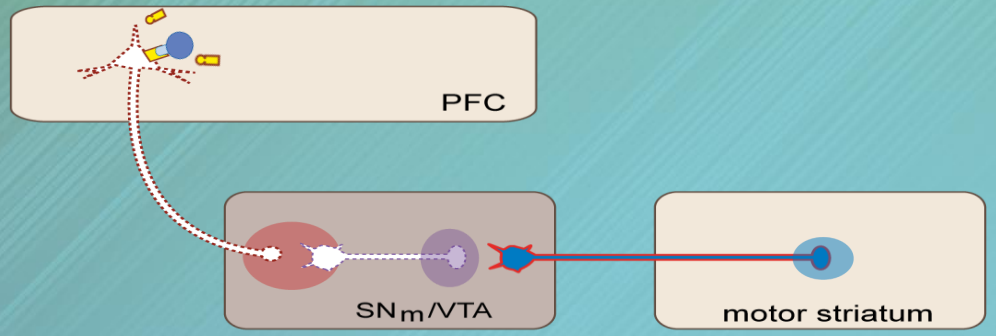
emotional blunting,
flattening of affect



lack of mental sharpness

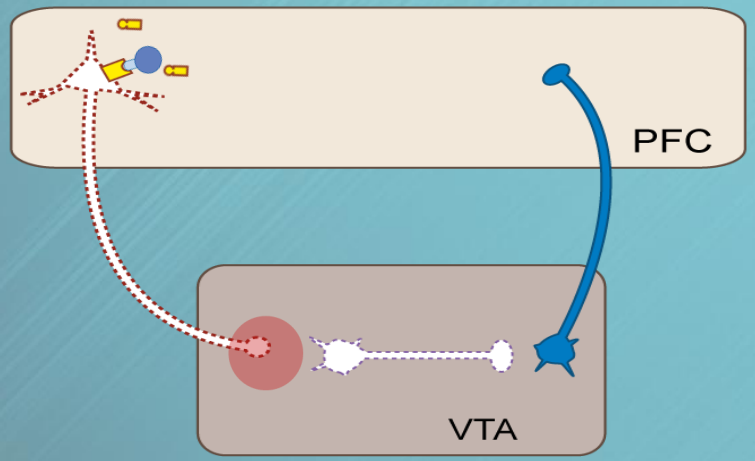
5HT2A antagonist





decreased positive symptoms

reduction in DIP



Do 5HT2A Antagonist Antidepressants Help EPS?

- Yes, for mirtazapine and trazodone for akathisia
- Not sure for parkinsonism or dystonia

Study or subgroup	Mirtazapine Events	Total	Control Events	Total	Weight	Risk ratio M-H, Fixed, 95% CI
Poyurovsky *et al.* [2003]	7	13	1	13	33.3%	7.00 [1.00–49.16]
Poyurovsky *et al.* [2006]	13	30	2	30	66.7%	6.50 [1.60–26.36]
Total (95% CI)		**43**		**43**	**100.0%**	**6.67 [2.14–20.78]**
Total events	20		3			

Heterogeneity: $\chi^2 = 0.00$, df = 1 ($p = 0.95$); $I^2 = 0\%$
Test for overall effect: $Z = 3.27$ ($p = 0.001$)

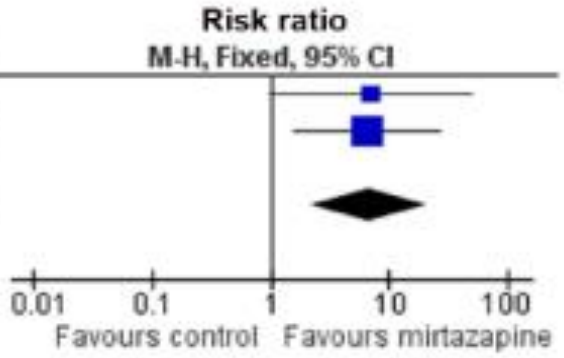


Figure 2. Forest plot showing response rate (at least two-point reduction in BAS Global Scale) in randomized controlled trials comparing mirtazapine with placebo for antipsychotic-induced acute akathisia ($N = 86$). CI, confidence interval; M-H, Mantel–Haenszel.

Study or subgroup	Mirtazapine Events	Total	Control Events	Total	Weight	Risk ratio M-H, Fixed, 95% CI
Poyurovsky *et al.* [2003]	5	13	0	13	20.0%	11.00 [0.67–180.65]
Poyurovsky *et al.* [2006]	10	30	2	30	80.0%	5.00 [1.19–20.92]
Total (95% CI)		**43**		**43**	**100.0%**	**6.20 [1.74–22.08]**
Total events	15		2			

Heterogeneity: $\chi^2 = 0.25$, df = 1 ($p = 0.62$); $I^2 = 0\%$
Test for overall effect: $Z = 2.82$ ($p = 0.005$)

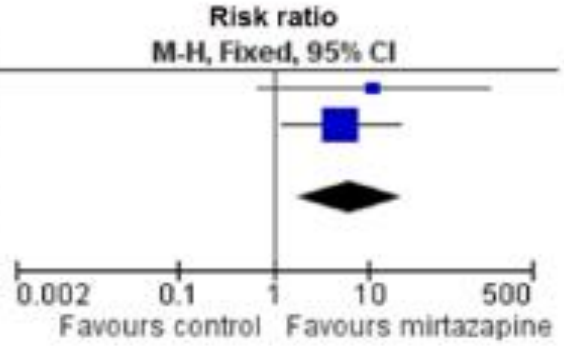
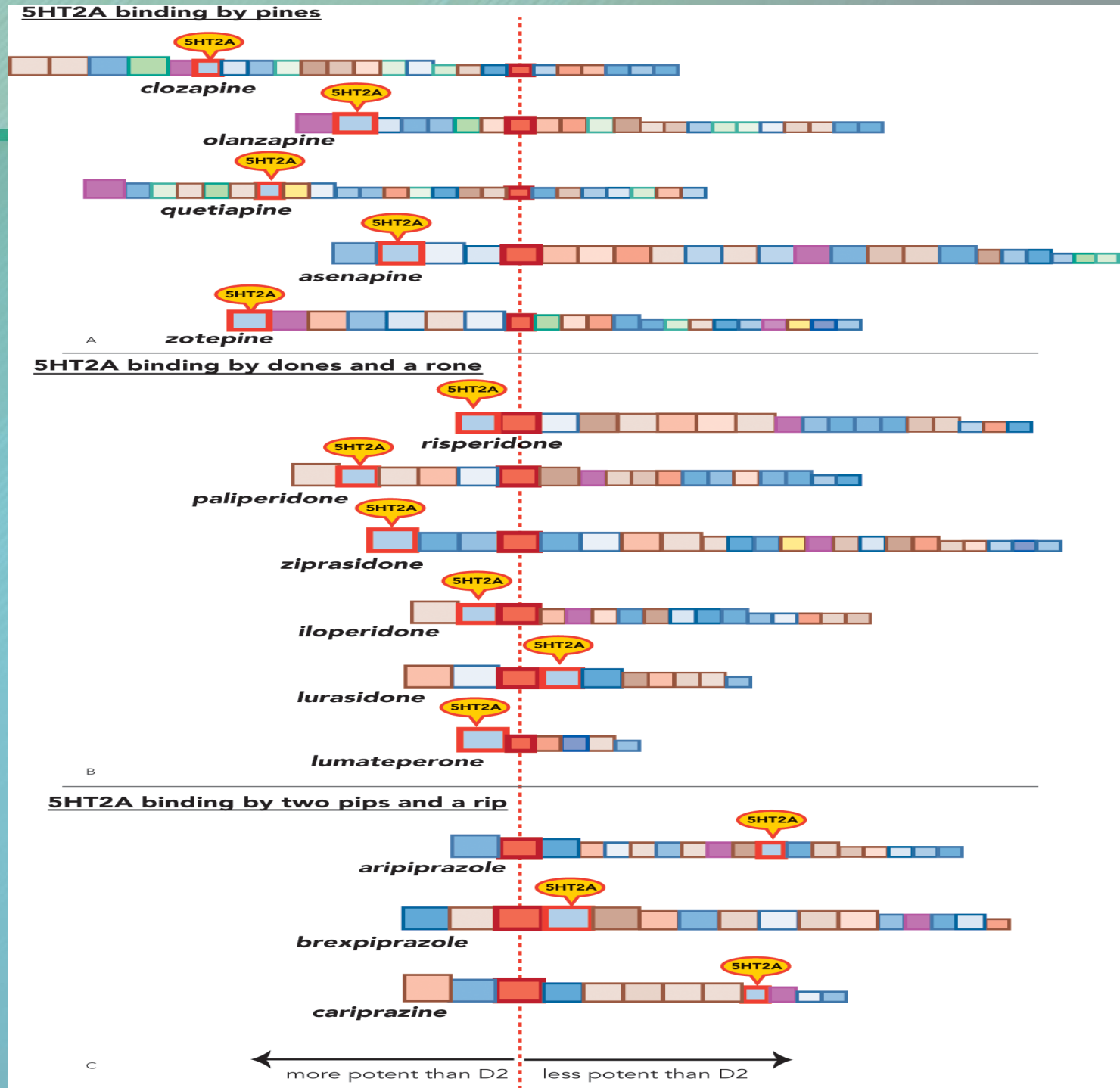


Figure 3. Forest plot showing complete remission (0 or 1 on BAS Global Scale) in randomized controlled trials comparing mirtazapine and placebo for antipsychotic-induced acute akathisia ($N = 86$). CI, confidence interval; M-H, Mantel–Haenszel.

Praharaj SK et al. Ther Adv Psychopharmacol 2015;5(5):307-13; Shams-Alizadeh N et al. J Clin Psychopharmacol 2020;40(6):611-4.

What is 5HT2A-ness?

- 5HT2A antagonistic affinity relative to D2 affinity
- Theoretically, as 5HT2A affinity increases, then EPS risk should lessen



Stahl SM. Stahl's essential psychopharmacology, 5th ed; 2021.

	Receptors										
	D2 Antag	D2/3 Partial Ag	5HT2A Antag	5HT1A Partial Agonism	5HT2C Antag	5HT7 Antag	NRI	SRI	H1 Antag	A1 Antag	AChm Antag
SGA											
Risperidone	x		x								
Paliperidone	x		x			x				x	
Ziprasidone	x		x				x	x			
Iloperidone	X		x							x	
Lurasidone	x		x			x					
Clozapine	x		x	x	x	x			x	x	
Olanzapine	x		x		x				x		x
Quetiapine	x		x	x	x	x	x		x	x	x
Asenapine	x		x		x	x					x
Aripiprazole	x	x	x	x		x					
Brexpiprazole	x	x	x	x							
Cariprazine	x	x	x	x							
Lumateperone	x	x	x	x							
								x			
	Lowers Psychosis	Lowers MDD	Lowers EPS	Lowers MDD	Lowers MDD	Lowers MDD	Lowers MDD	Lowers MDD	Lowers Agitation	Increases Sedation	Increases Antichol
	Lowers Mania	Lowers EPS	Lowers MDD	Lowers Anxiety	Increases Weight			Lowers Anxiety	Increases Weight	Increases Dizziness	
			Improves sleep						Increase Sedation	Improves sleep	
	DONES +++	PIPS, RIPS, RONES +++	PINES +++	PINES +++	PINES+++				Improves Sleep		
				PIPS, RIPS, RONES +++					PINES+++		PINES+++

Schwartz T. Practical psychopharmacology: basic to advanced principles; 2017.

Are Loxapine and Perphenazine Atypical?

Loxapine

Dopamine Receptors	Loxapine Affinity (Kb)
D_1	29 nM
D_2	2.4 nM
D_3	NS
D_4	12 nM
D_5	28 nM

Serotonin Receptors	Loxapine Affinity (Kb)
5-HT_{1A}	NS
5-HT_{2A}	2.1 nM
5-HT_{2C}	22 nM
5-HT_4	NS
5-HT_6	NS
5-HT_7	NS

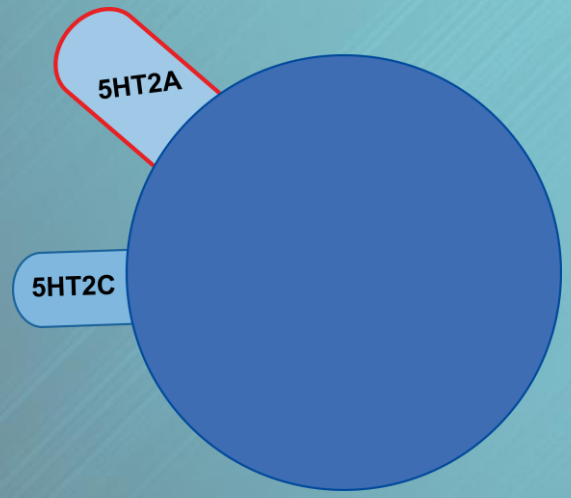
Perphenazine

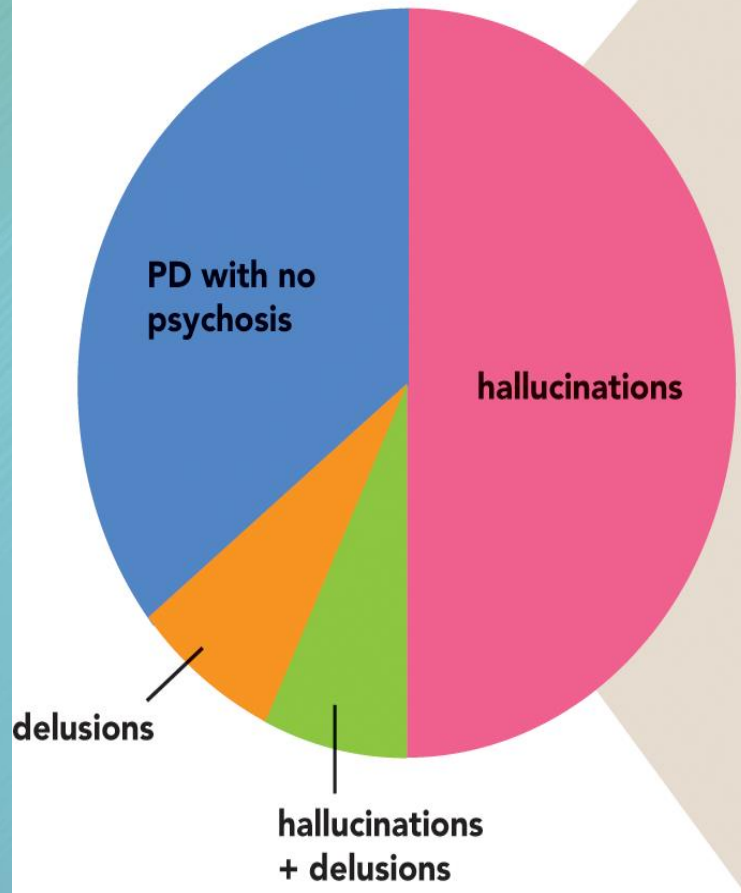
Drug	D_{2Long}	5-HT_{2A}	$D_{4.4}$	M_1
Perphenazine	3.4 ± 0.9	5.8 ± 1	140 ± 14	2,000 ± 130
DAPZ	85 ± 3	54 ± 9	690 ± 54	130 ± 8
OHPZ	4.1 ± 0.3	38 ± 3	620 ± 11	3,400 ± 310
Haloperidol	6.4 ± 2	70 ± 13	4.8 ± 0.3	5,300 ± 940
Clozapine	470 ± 160	4.3 ± 0.2	64 ± 7	8.1 ± 1

Ferreri F et al. Int J Neuropsychopharmacol 2018;21(4):355-60; Glazer WM. J Clin Psychiatry 1999;60(Suppl 10):42-6.

Is Pimavanserin Atypical or an Atypical Atypical?

- Approved for psychosis associated with Parkinson's disease
- High affinity for 5HT2A antagonism
- None for D2
  - 34mg/d
- Side effects
  - Nausea
  - QTc increases up to 17msec
- 3A4 inhibitors increase levels





Type of Hallucinations Observed in Patients with PD Psychosis

Visual 62.5%

Auditory 45%

Tactile 22.5%

Olfactory 2.5%

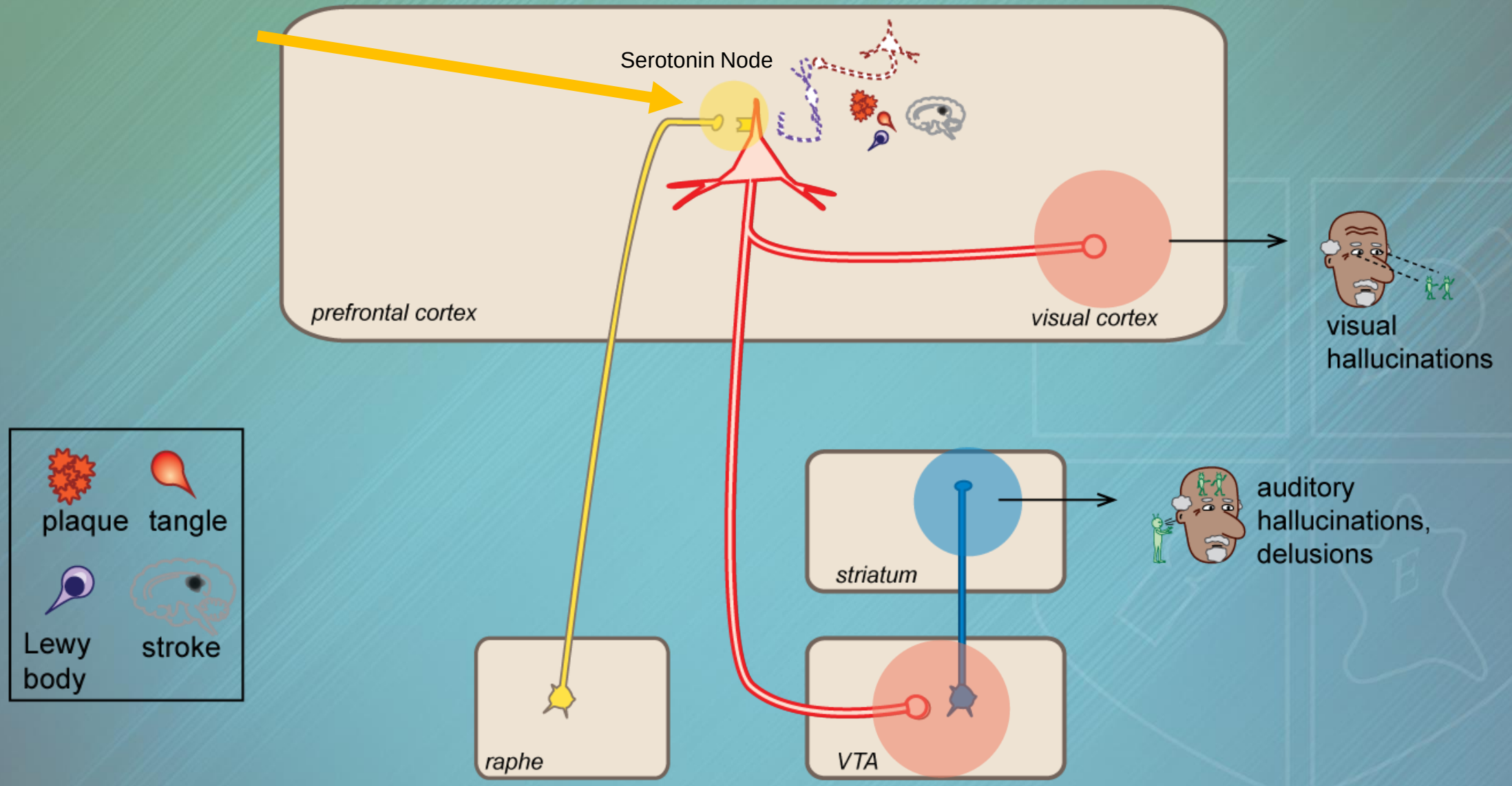
Minor* 45%

Visual + Auditory + Tactile + Olfactory 2.5%

** Minor hallucinations include passage hallucinations and sense of presence*

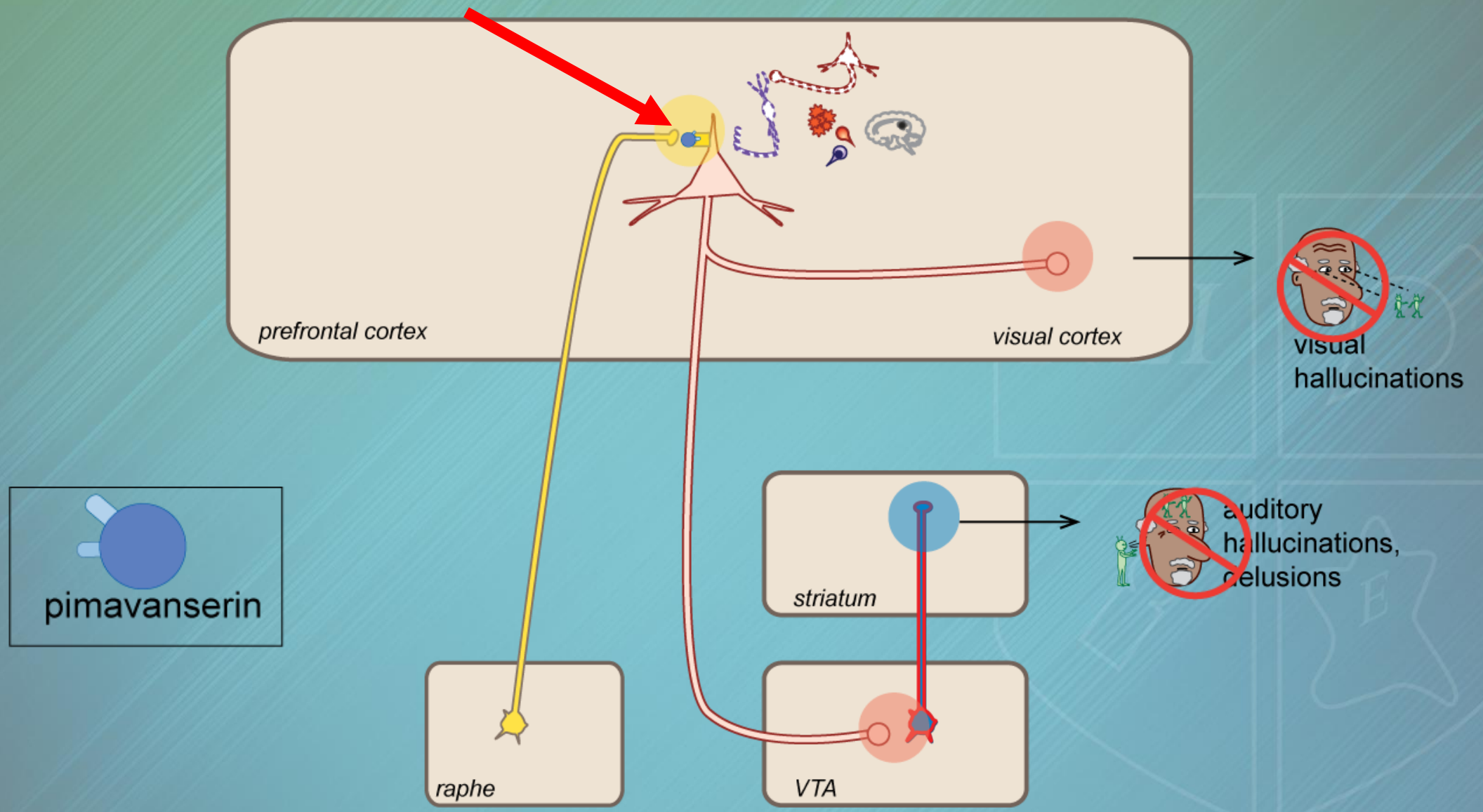
Stahl SM. Stahl's essential psychopharmacology, 5th ed; 2021.

Dementia-Related Psychosis

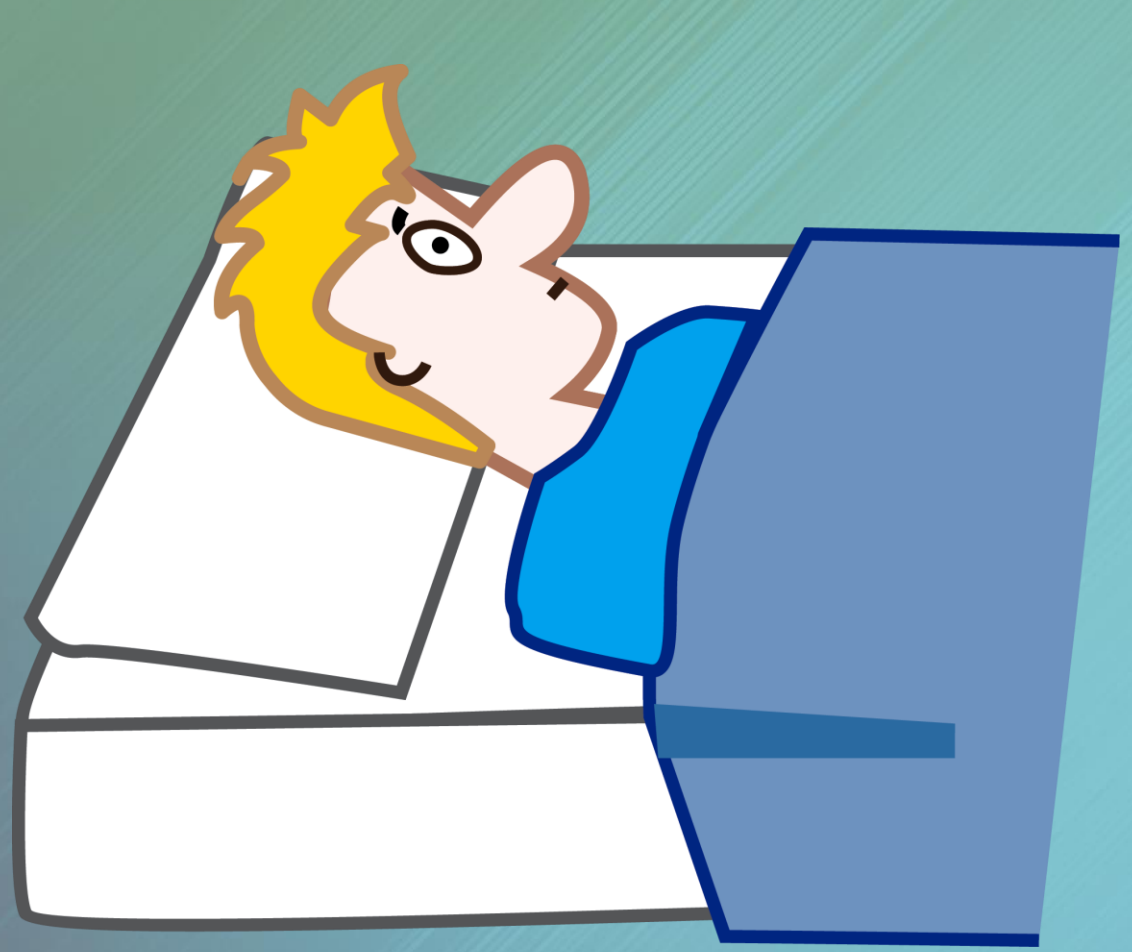


Stahl SM. Stahl's essential psychopharmacology, 5th ed; 2021.

Treatment of Dementia-Related Psychosis



5HT2A for Insomnia and Mood



Case 2

- A 30-year-old female is treated to near depressive remission with fluoxetine, an SSRI, but her insomnia continues and has even worsened with this treatment. She does not want to change the SSRI due to fear of relapse.

  What agents are typically used to treat insomnia *and,* theoretically, which might be able to improve sleep by lending 5HT2A blockade?

5HT2A Antagonism

•Improves Sleep

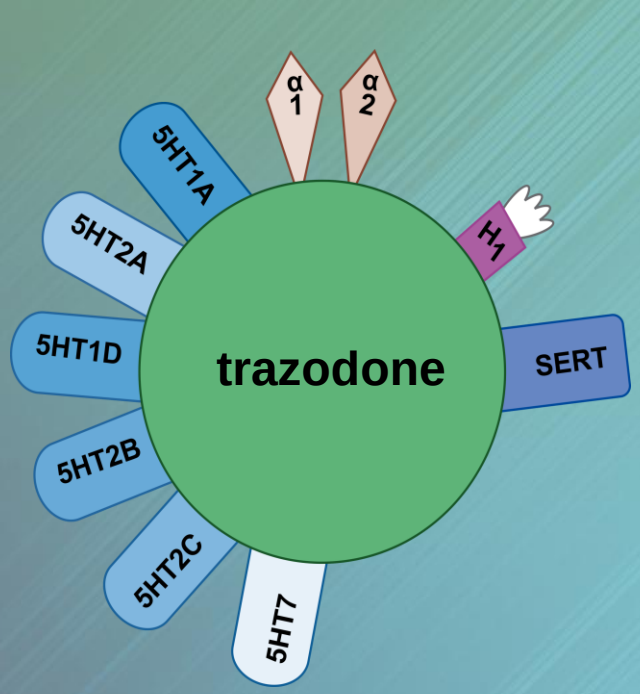
- 5HT2A agonists promote wakefulness
- Antagonists
  - Increases slow-wave sleep (SWS)
  - Lower REM
  - Increase maintenance + efficiency
- Applicable to MDD + GAD

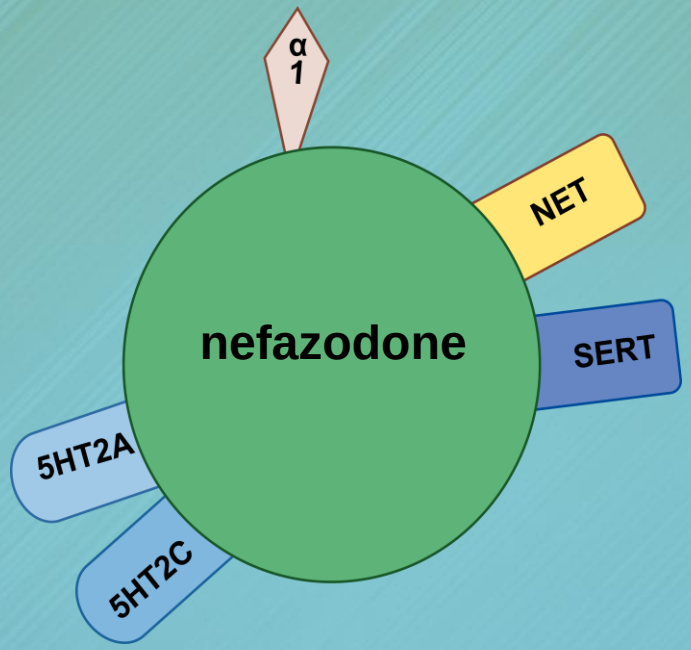
•Improves Mood

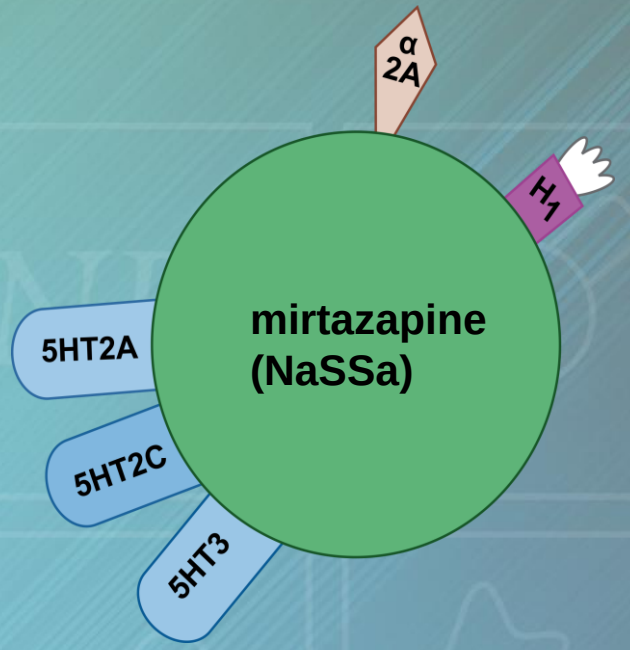
- Increasing 5HT levels/activity associated with improved affect
- 5HT2A receptors populate the PFC and VMPFC
- Interact with GLU, GABA neurons/ receptors
  - Agonism creates downstream *lowering* of DR, LC, VTA activity
  - Antagonism increases serotonin, norepinephrine, and dopamine activity

Celada P et al. J Psychiatry Neurosci 2004;29(4):252-65; Vanover KE, Davis RE. Nat Sci Sleep 2010;2:139-50; Griebel G et al. Neuropharmacology 2013;70:19-26; Argyropoulos SV, Wilson SJ. Int Rev Psychiatry 2006;17(4):237-45.

Which Antidepressants Block 5HT2A?





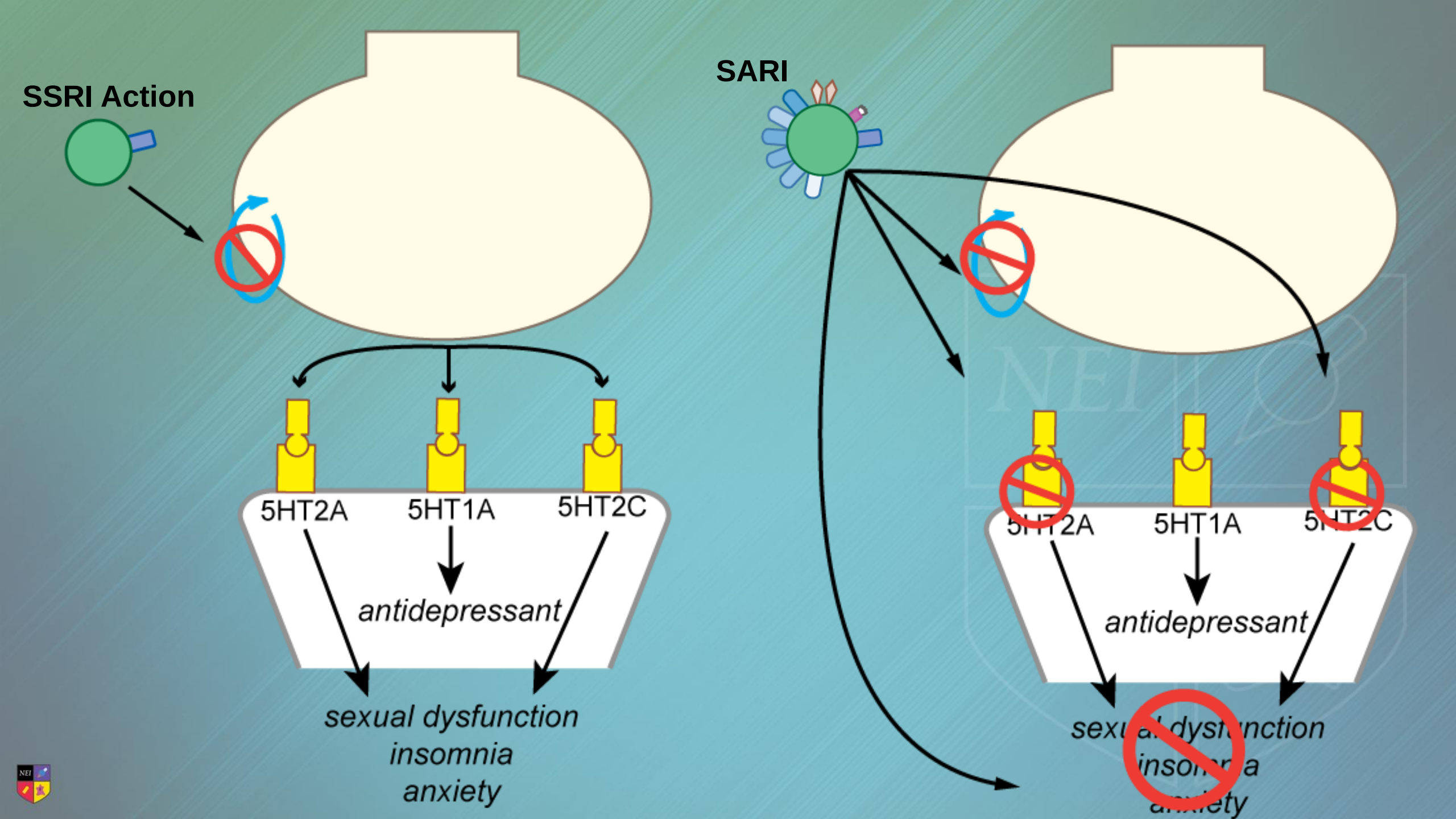


Stahl SM. Stahl's essential psychopharmacology, 5th ed; 2021.

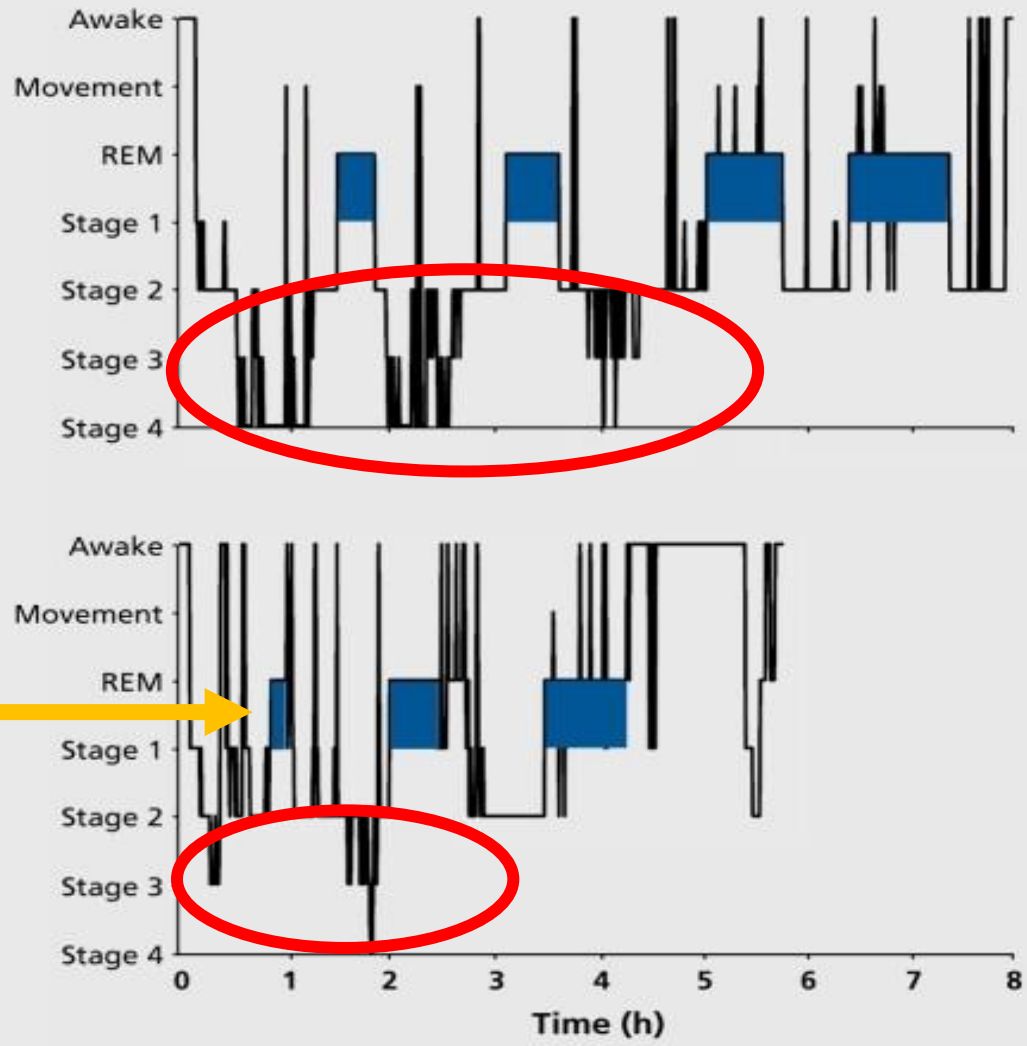
	Receptors									
	D2 Antag	D2/3 Partial Ag	5HT2A Antag	5HT1A Partial Agonism	5HT2C Antag	5HT7 Antag	NRI	SRI	H1 Antag	A1 Antag	AChm Antag
SGA											
Risperidone	x		x								
Paliperidone	x		x			x				x	
Ziprasidone	x		x				x	x			
Iloperidone	x		x							x	
Lurasidone	x		x			x					
Clozapine	x		x	x	x	x			x	x	
Olanzapine	x		x		x				x		x
Quetiapine	x		x	x	x	x	x		x	x	x
Asenapine	x		x		x	x					x
Aripiprazole	x	x	x	x		x					
Brexpiprazole	x	x	x	x							
Cariprazine	x	x	x	x							
Lumateperone	x	x	x	x							
								x			
	Lowers Psychosis	Lowers MDD	Lowers EPS	Lowers MDD	Lowers MDD	Lowers MDD	Lowers MDD	Lowers MDD	Lowers Agitation	Increases Sedation	Increases Antichol
	Lowers Mania	Lowers EPS	Lowers MDD	Lowers Anxiety	Increases Weight			Lowers Anxiety	Increases Weight	Increases Dizziness	
			Improves sleep						Increase Sedation	Improves sleep	
	DONES +++	PIPS, RIPS, RONES +++	PINES +++	PINES +++	PINES+++				Improves Sleep		
				PIPS, RIPS, RONES +++					PINES+++		PINES+++

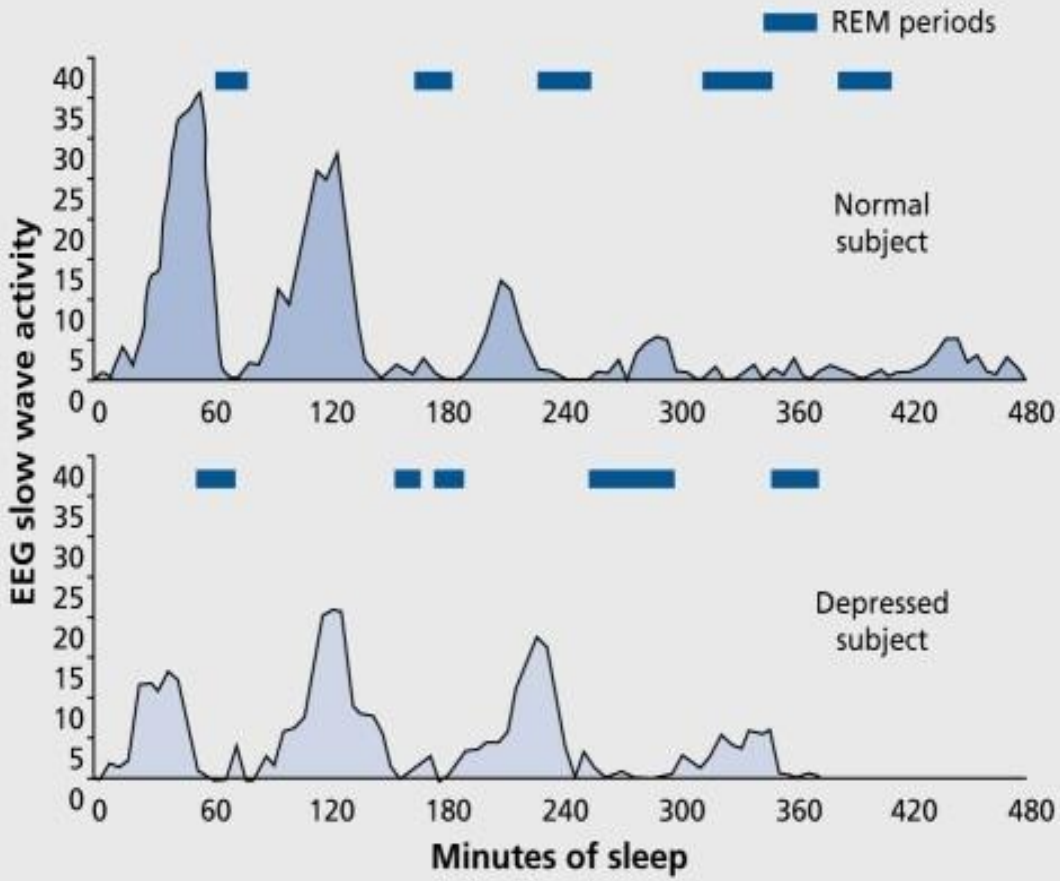
Schwartz T. Practical psychopharmacology: basic to advanced principles; 2017.

Is 5HT2A Antagonism Avoidance of Activation or a Direct Mood Treatment?


SSRI Action
5HT2A
5HT1A
5HT2C
antidepressant
sexual dysfunction
insomnia
anxiety
SARI
5HT2A
5HT1A
antidepressant

Sleep Architecture in MDD





Nutt D et al. Dialogues Clin Neurosci 2008;10(3):329-36.

5HT2A Antagonism: Does It Work Across Psychotropic Domains?

- Do antipsychotics help sleep?
- Yes, for improved efficiency and less arousals
- May increase SWS

Parameter	C (N=146; P=42.08%)	AD (N=105; P=30.26%)	ADAC (N=40; P=11.53%)	ADAP (N=28; P=8.07%)	ADACP (N=28; P=8.07%)	p
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
TIB (in minutes)	418.05 (44.83)	413.34 (49.00)	418.53 (36.03)	440.82 (59.04)	415.68 (33.66)	0.232
TSP (in minutes)	384.72 (58.99)	374.23 (71.64)	378.53 (69.95)	405.29 (63.37)	364.95 (94.29)	0.223
TST (in minutes)	309.95 (81.90)	327.34 (84.14)	334.61 (79.35)	**370.71 (74.94)**	326.07 (101.79)	0.002
SE (in %)	73.85 (17.44)	78.65 (18.40)	79.74 (16.94)	**84.31 (13.85)**	78.01 (22.75)	0.001
SOL (in minutes)	28.03 (28.43)	31.81 (31.93)	36.54 (54.83)	31.41 (36.88)	36.45 (48.68)	0.868
Number of REM periods	6.62(5.40)	**3.98 (3.50)**	**4.15 (4.02)**	5.71 (5.72)	**3.18 (3.55)**	<0.001
REM onset latency (in minutes)	151.94 (81.38)	**209.19 (88.81)**	189.84 (97.60)	169.28 (90.47)	**218.21 (84.22)**	<0.001
WASO (in minutes)	79.77 (65.23)	**54.15 (54.10**	**47.31 (39.73)**	**38.61 (46.74)**	**49.84 (56.73)**	<0.001
Total arousal index	19.19 (16.33)	20.21 (17.12)	15.53 (11.79	**15.08* (19.39)**	13.12 (12.44)	0.002
AHI	17.31 (20.77)	13.94 (18.44)	9.98 (14.67)	**9.37 (17.50)**	9.37 (11.84)	0.009
PLMI	19.44 (24.25	30.73* (39.32)	22.07 (26.06)	17.91 (15.25)	17.59 (32.81)	0.042
Minimal SaO2 (in %)	82.65 (11.70)	84.58 (8.29	86.38 (5.17)	86.21 (9.04)	83.86 (9.55)	0.168
HR in NREM sleep	67.41 (9.87)	**71.77 (11.29)**	**74.61 (11.37)**	71.97 (15.25)	**80.26 (14.32)**	<0.001
Sleep stage distribution(in percent)						
Stage 1	15.82 (12.98)	13.93 (10.56)	10.66 (6.53)	**8.32* (4.80)**	10.28 (7.23)	<0.001
Stage 2	54.67 (12.53)	**60.19 (12.26)**	55.60 (16.74)	60.45 (15.29)	**63.05 (14.35)**	0.001
SWS	16.12 (10.79)	15.89 (10.99)	21.66 (15.25)	19.01 (16.39)	18.85 (13.76)	0.286
REM	13.40 (7.22)	**10.01 (7.54)**	12.08 (10.36)	12.20 (8.05)	**8.27 (6.31)**	<0.001

Monti JM. Sleep medicine 2016;23:89-96; Ghossoub et al. Sleep Science 2021;14(3)236-44.

Summary

- 5HT2A receptors reside across a variety of neural circuits and may directly stimulate glutamate or dopamine activity or alter activity by agonizing inhibitory GABA interneurons—Uggh, it is complicated!
- Psychotropics that antagonize 5HT2A may increase or decrease downstream activity of other transmitters depending on specific 5HT2A receptor location and subsequent blockade
- All atypical antipsychotics and some antidepressants block 5HT2A
- We have reviewed the basic neurophysiology and anatomy in these areas that allows clinicians to better understand why psychotropics work as indicated for certain DSM-5 Disorders and why off-label applications can sometimes help for others

Posttest Question 1

Which classes of psychotropics antagonize 5HT2A receptors?

1. Atypical antipsychotics
2. Sedating antidepressants (SARI & NASSA)
3. Tricyclic antidepressants
4. Buspirone anxiolytics
5. 1 and 2
6. All of the above

Posttest Question 2

5HT2A receptor antagonism can serve the atypical antipsychotics by clinically improving…

1. EPS
2. Psychosis
3. Sleep
4. Depression
5. 1 and 2
6. All of the above

Posttest Question 3

A 30-year-old male is treated to remission with haloperidol, a typical antipsychotic, for his psychosis but develops akathisia. He does not want to relapse and go back to the hospital so refuses to change medications. Which agent below theoretically might be able to lower EPS by lending its 5HT2A blockade, thus making the haloperidol seem more atypical in nature?

1. Vortioxetine
2. Imipramine
3. Mirtazapine
4. Paroxetine
5. All of the above
6. None of the above