Neuroscience Education Institute

HO HUM TO AHA! TREATING ANHEDONIA AND EMOTIONAL BLUNTING

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Presented at the 2023 NEI Congress meeting

Learning Objectives

- Delineate the transdiagnostic epidemiology, proposed neurobiology, and differential diagnosis of emotional blunting and anhedonia
- Implement treatment strategies for anhedonia and emotional blunting in depressive states to improve patient outcomes
- Assess clinical evidence for current and emerging treatments of anhedonia

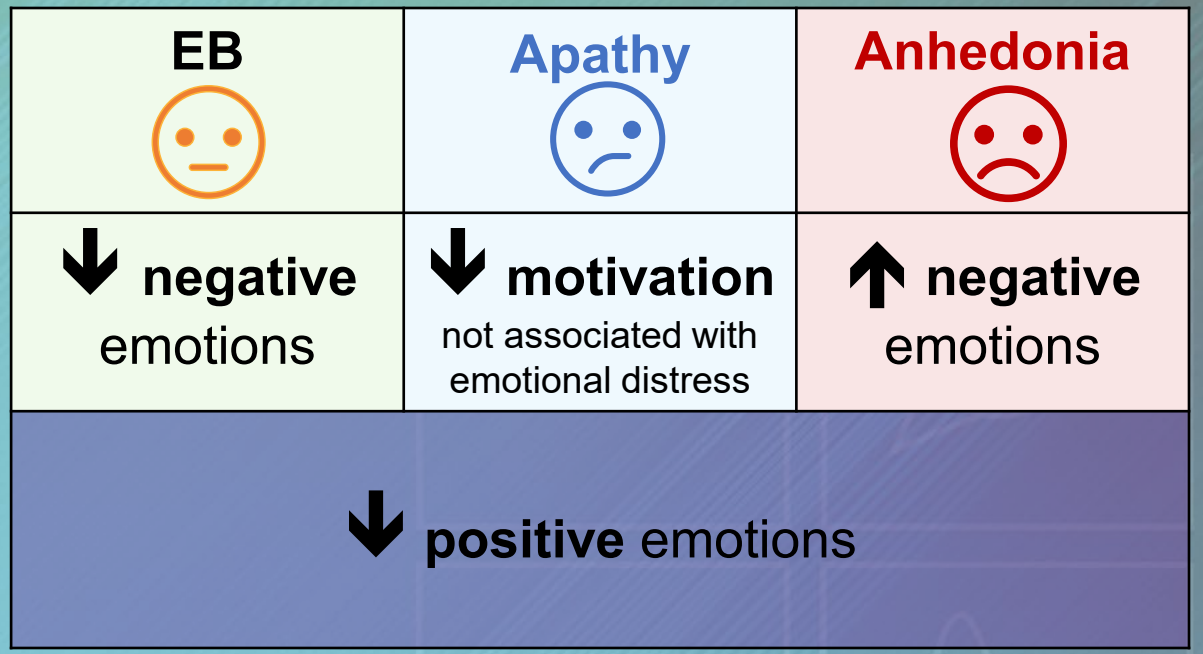
Anhedonia, Emotional Blunting, and Apathy

What Are Emotional Blunting, Apathy, and Anhedonia?

- **WHAT IS Emotional Blunting?** Diminished sensitivity and responsiveness to a broad range of emotions
- Inability to laugh or cry in fitting circumstances

WHAT IT IS NOT

- **Anhedonia**; in which positive emotions and motivation are reduced
- **Apathy**; in which lack of motivation is not secondary to a mental health disorder?



Ma H et al. Front Psychiatry 2021;12:792960.

What Causes Emotional Blunting?

Adverse effect of antidepressants?

- EB often coincides with use of SSRIs, leading many to make a causal inference
- No studies have evaluated occurrence of EB in control patients taking antidepressants, limiting the ability to confirm directionality

Residual symptom of MDD?

- Loss of interest/pleasure are known symptoms of MDD
- EB may be linked to the dysregulation of dopamine and norepinephrine seen in MDD
- It is possible that EB is a symptom of MDD that is incompletely treated with SSRIs

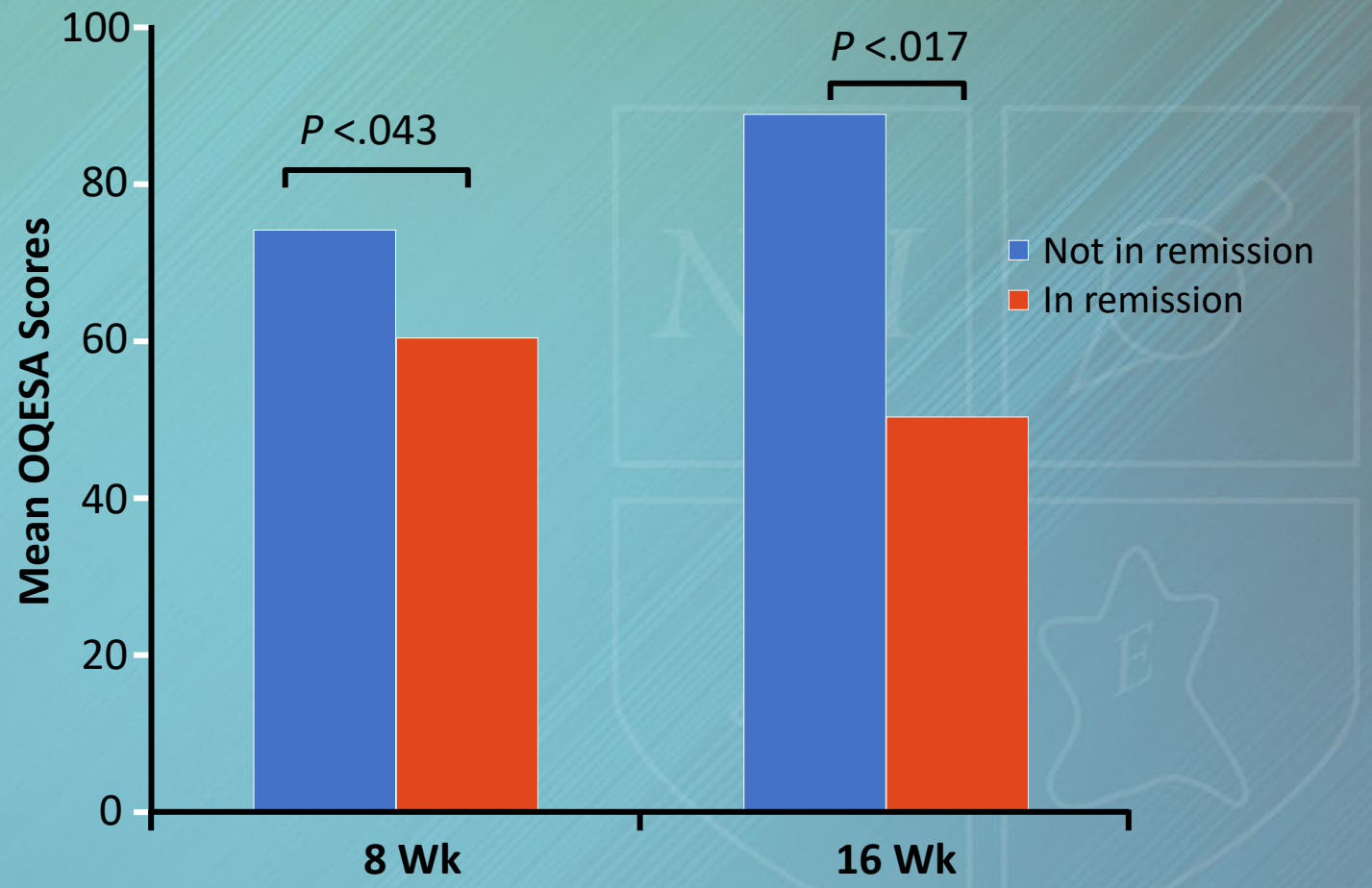
Ma H et al. Frontiers Psychiatry 2021;12:792960;
Goodwin GM et al. J Affect Disord 2017;221:31-5.

Is Emotional Blunting a Residual Symptom of Depression or an Adverse Effect of Antidepressant Treatment?

- Inclusion: N = 98 patients with MDD
- Patients were assessed with MADRS (at Wk 2, 4, 8, 12, and 16)
- **OQESA***: Wk 8 and Wk 16 visits

Symptomatic remission was associated with reduced emotional blunting.

*OQESA—Oxford Questionnaire on the Emotional Side-effects of Antidepressants.



Ascibasi K et al. J Clin Psychopharmacol 2020;40(6):594-8.

Is Emotional Blunting Related to Antidepressant Class?

Participants

- N = 669 patients with depression on antidepressant monotherapy were surveyed

Results

- 46% of participants reported EB
- Similar range of occurrence with SSRIs (45%) and SNRIs (48%*)
- **EB is slightly less common with bupropion (33%; not statistically significant)**

Clinical Implication

- EB is not specific to SSRIs

Limitation

- Rates of EB in some agents may be overstated by small group numbers

*Duloxetine was a statistical outlier (36, 75%) and has been removed.

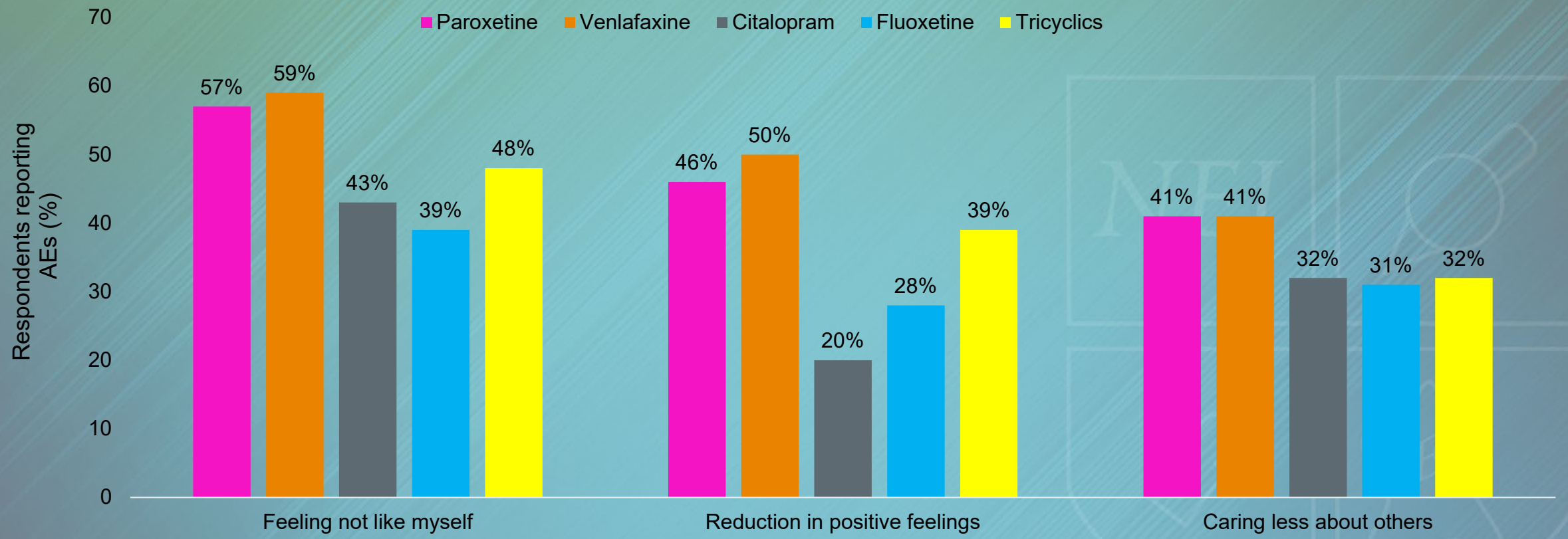
Rate of EB by Agent / Class

	Patients Receiving, n	Patients With EB, %	Agents Included
SNRI/SNDRI*	131	48	Desvenlafaxine, venlafaxine, mirtazapine
SSRI	416	45	Citalopram, fluoxetine, sertraline, paroxetine, escitalopram
Tricyclic	17	47	Amitriptyline
NDRI	40	33	Bupropion
Others	29	48	
Total	669	46	

Emotional blunting was measured by Oxford Questionnaire on the Emotional Side-Effects of Antidepressants (OQESA).

Goodwin GM et al. J Affect Disord 2017;221:31-5.

Emotional Adverse Events Are Frequently Reported by Patients While Taking Commonly Used Antidepressants

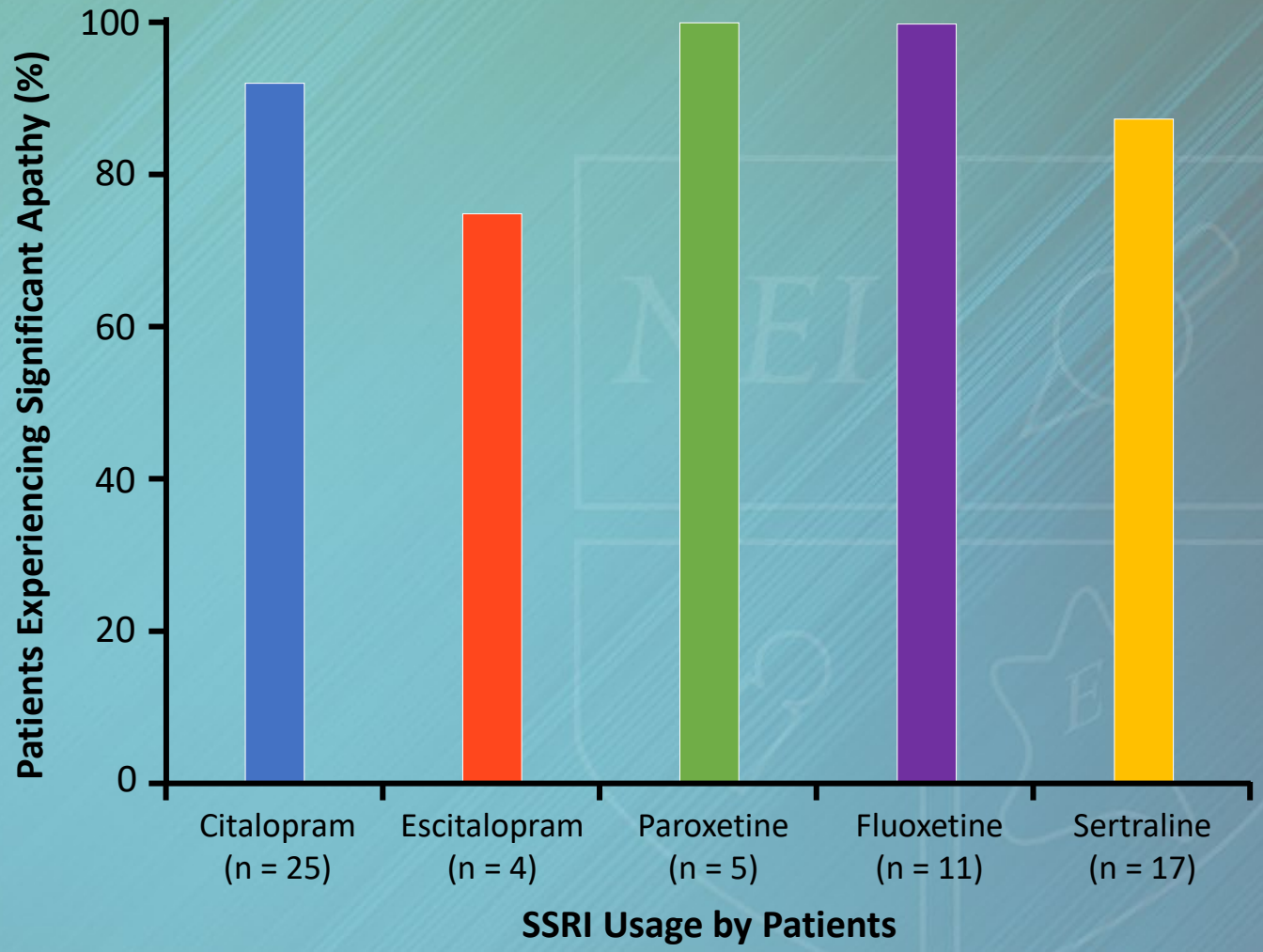


Read J et al. Psychiatry Res 2014;216:67-73.

Apathy Is Commonly Associated With SSRI Use

- N = 119 patients (retrospective chart review)
- **Apathy scores significantly higher in those treated with SSRIs than in those not treated with SSRIs**
- **42.5 ± 9.2 vs 31.3 ± 6**, *P* <.0001
- Apathy was assessed using the Apathy Evaluation Scale-clinician version
- Score = 18–72; higher score, worse apathy
- Clinically significant apathy: score >30

92% of SSRI-treated patients showed apathy!



Padala PR et al. Medicine 2020;99(33):e21497.

Defining Anhedonia

Patients with anhedonia have a reduced ability to experience pleasure or interest in things previously enjoyable

"without"

Anhedonia

"pleasure"

Anhedonia has both consummatory and anticipatory elements

Consummatory

Inability to feel pleasure during current events

↓

Reduced joy or interest in interpersonal or social interactions and natural rewards, including eating and sexual behaviour

Anticipatory

Inability to predict future experience of pleasure

↓

Lower reward responsiveness and reduced motivation to act towards future pleasure

Gillissie ES et al. J Psychiatr Res 2023;158:209-15.

Apathy and Anhedonia Are Common in Multiple Neuropsychiatric Disorders

Disorder, %	Apathy in Population	Anhedonia in Population
Alzheimer disease	49	61
Frontotemporal dementia	72	–
Huntington's disease	47	–
Major depressive disorder	38	37
Parkinson's disease	40	46
Schizophrenia	47	45
Stroke	36	–
Traumatic brain injury	61	22

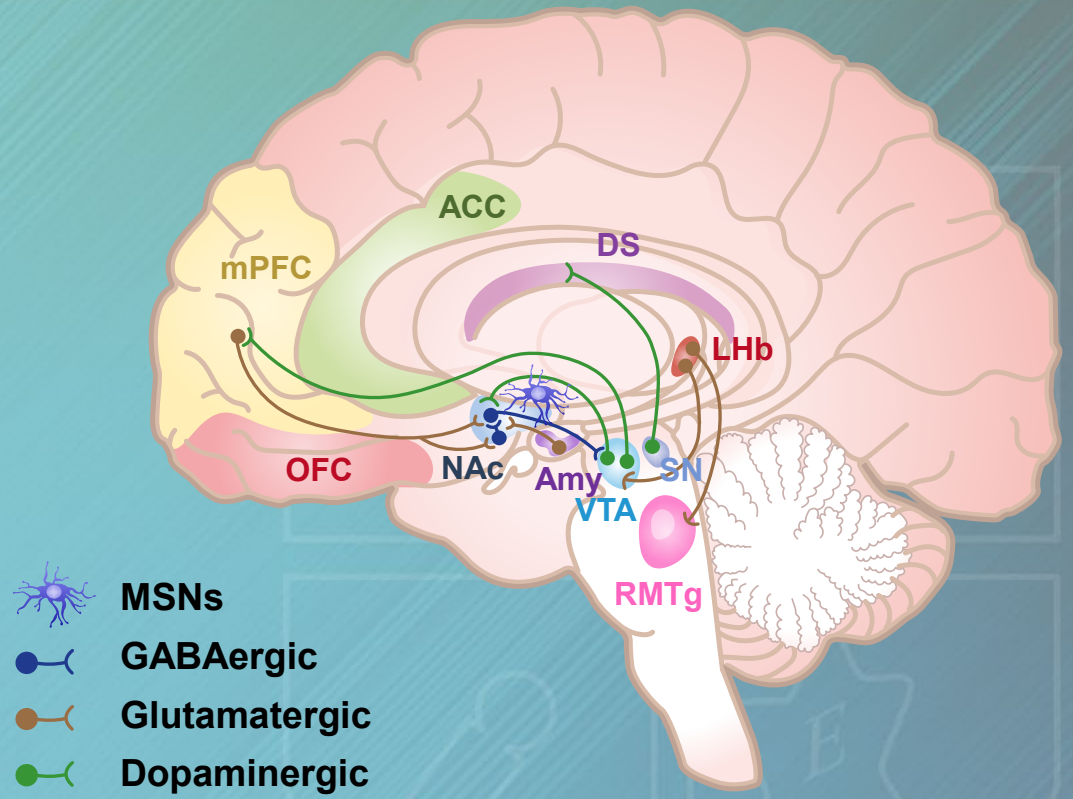
≈40% of MDD patients suffer from apathy and anhedonia!

Husain M et al. Nat Rev Neurosci 2018;19(8):470-84.

Neurocircuitry and Neurobiology of Anhedonia

Anhedonia Is Associated With Disturbances in Reward Circuit Pathways

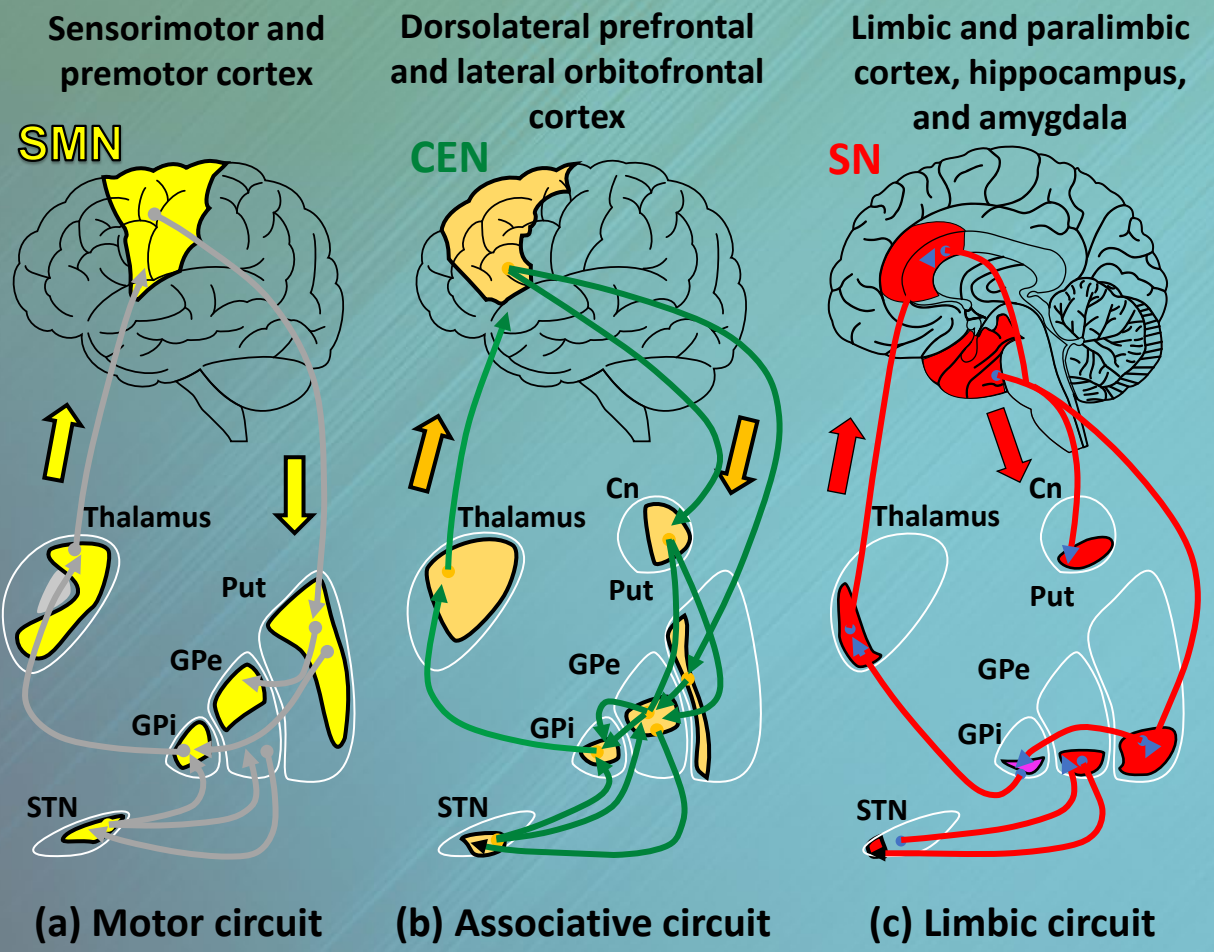
- Anhedonia has been implicated in disturbances of central dopaminergic, mesolimbic, and mesocortical reward circuit pathways
- These pathways are involved with hedonic drive, motivation, cognition, and perception

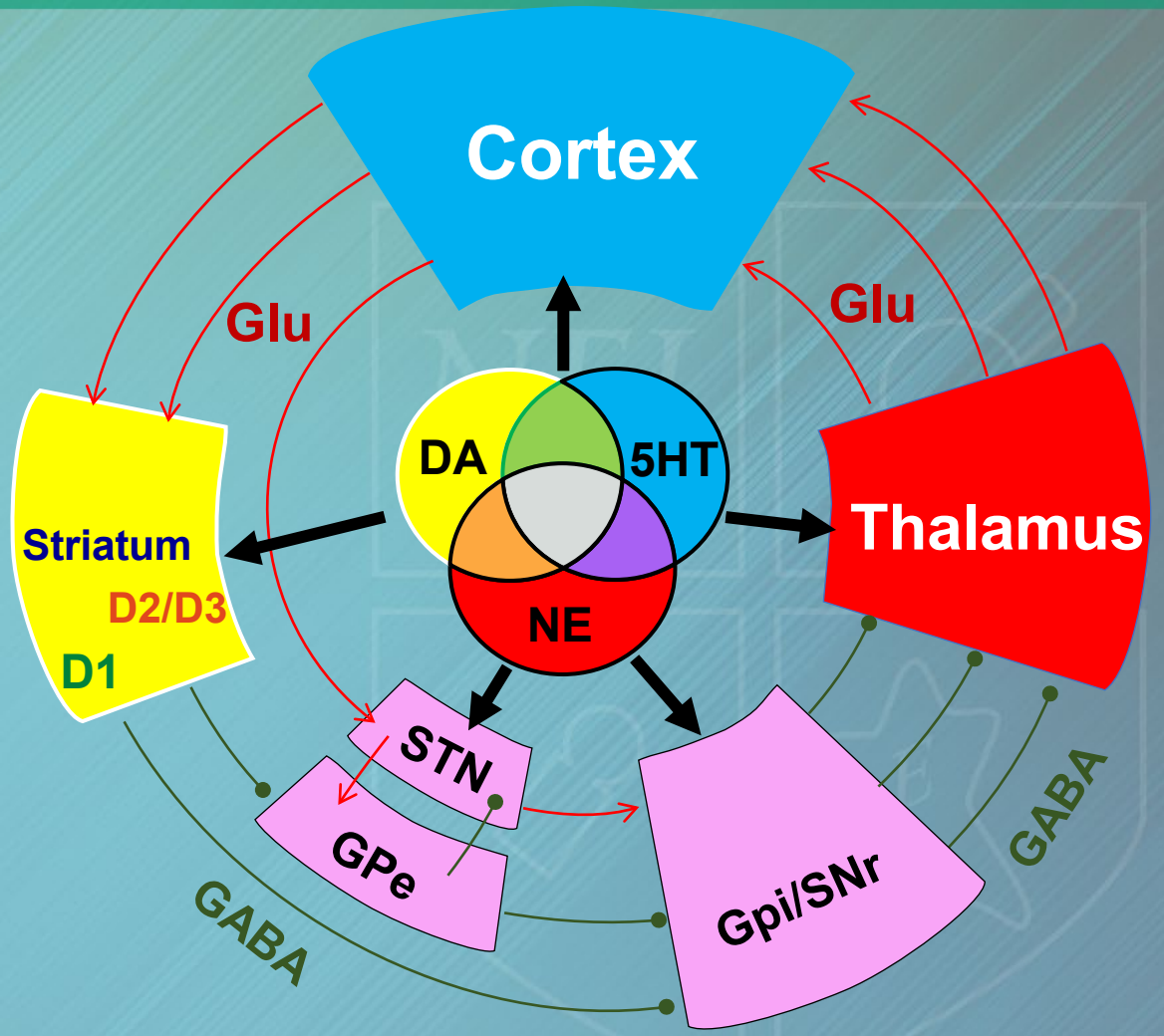


mPFC, medial prefrontal cortex; ACC, anterior cingulate cortex; DS, dorsal striatum; LHb, lateral habenula; OFC, orbitofrontal cortex; NAc, nucleus accumbens; Amy, amygdala; VTA, ventral tegmental area; SN, substantia nigra; RMTg, rostromedial tegmental nucleus; MSN, medium spiny neuron; GABA, gamma-aminobutyric acid

Pan Z et al. Curr Pharm Des 2017;23:2065-72; Su Y-A, Si T. Gen Psychiatr 2022;35:e100724.

Motor, Associative, and Limbic Divisions of Cortico-Striatal-Thalamo-Cortical Loop: An "Updating System"

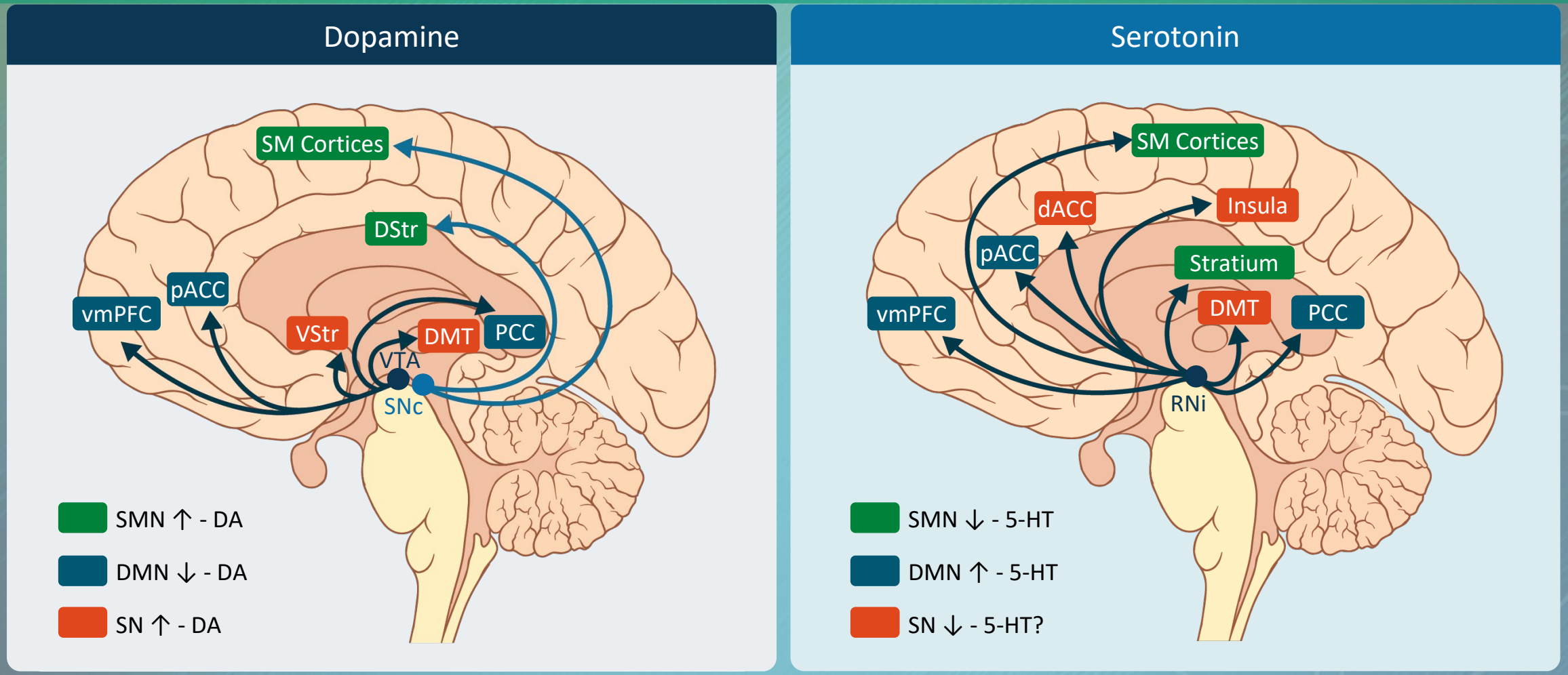




Cn, caudate nucleus; CEN, central executive network; D2-ENK, dopamine receptor D2 and enkephalin; D1-DYN, dopamine receptor D1, substance P and dynorphin; GPi, globus pallidus pars interna; GPe, globus pallidus pars externa; Put, putamen; SMN, sensorimotor network; STN, subthalamic nucleus; SN, salience network; SNr, substantia nigra pars reticulata; SNc, substantia nigra pars compacta.

Modified from: Lapidus KAB et al. Neurotherapeutics 2014;11(3):485-95; Shipp S. Brain Struct Funct 2017;222(2):669-706.

5-HT and DA Have a Role in Networks Associated With Anhedonia



5-HT, serotonin; DA, dopamine; dACC, dorsal anterior cingulate cortex; DMN, default mode network; DMT, dorsomedial thalamus; DStr, dorsal striatum; pACC, perigenual anterior cingulate cortex; PCC, posterior cingulate cortex; RNi, raphe nuclei; SM, sensorimotor; SMN, sensorimotor network; SN, salience network; SNc, substantia nigra pars compacta; vmPFC, ventromedial prefrontal cortex; VStr, ventral striatum; VTA, ventral tegmental area.

Conio B et al. Mol Psychiatry 2020;25(1):82-93.

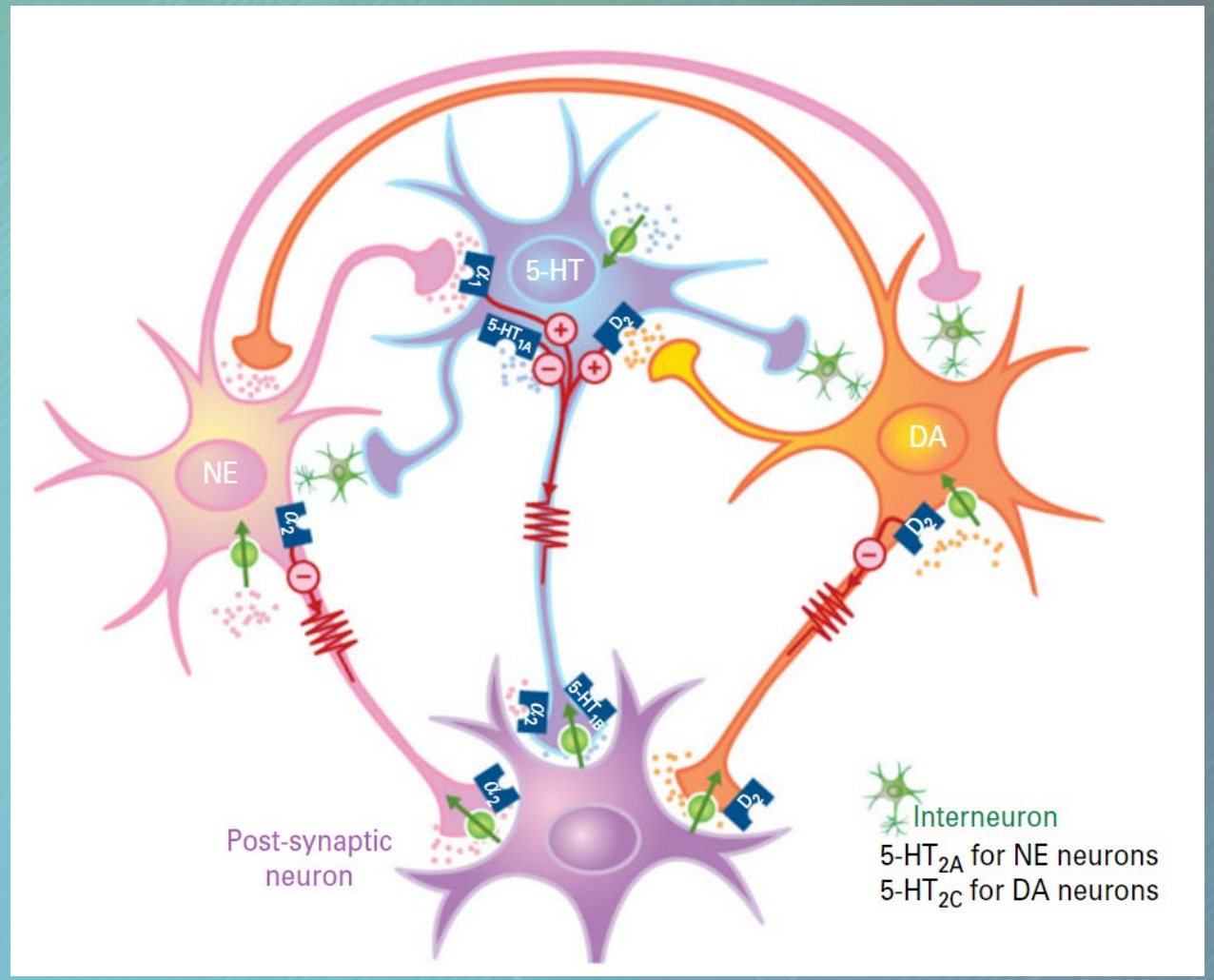
What's serotonin got to do with it?

ROLES OF SEROTONIN (5-HT) IN DISEASE PATHOLOGY

- Role of 5-HT, once considered central to MDD, has come into question:
  - **MDD**: Depletion can enhance emotions
  - **EB**: Excess may diminish emotions

ROLES OF SSRIS IN EMOTIONAL BLUNTING (EB) PATHOLOGY

- **SSRIs** can diminish midbrain DA/NE activity in response aversive/rewarding stimuli
  - *Individuals with lower baseline DA/NE modulation may be predisposed to EB*
- **SSRIs** may directly alter frontal lobe activity where 5-HT receptor density is high



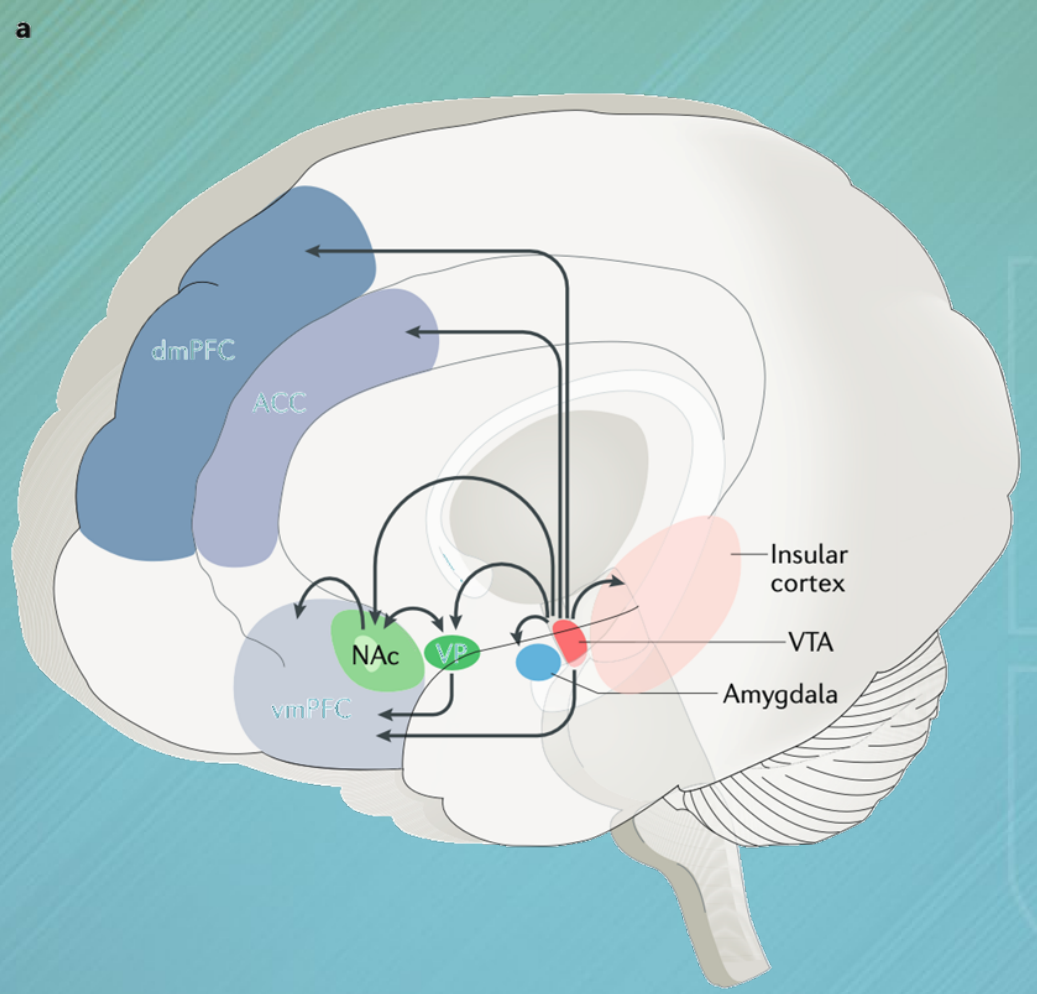
Marazziti D. F1000Res 2017;6(F1000 Faculty Rev):180; Kanen JW et al. Transl Psychiatry 2021;11(1):81; Sternat T, Katzman MA. Neuropsychiatr Dis Treat 2016;12:2149-64; Barnhart WJ et al. J Psychiatric Pract 2004;10:196-9; McCabe C et al. Biol Psychiatry 2010;67(5):439-45; Blier P. Int J Neuropsychopharm 2014;17(7):997-1008.

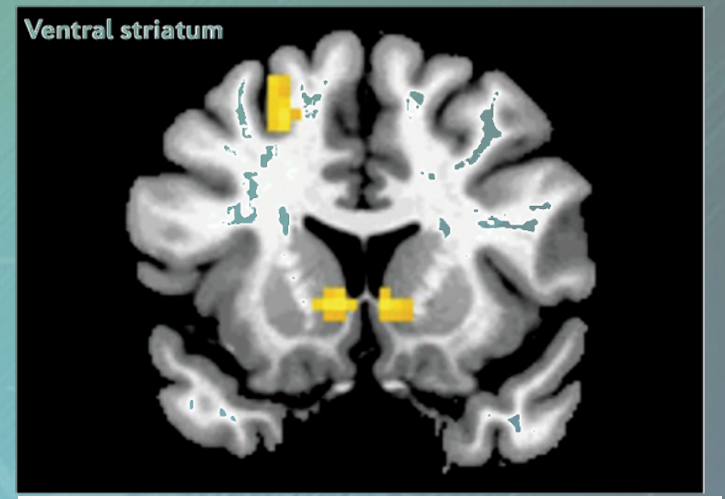
Brain Regions Implicated in Motivation, Apathy, and Anhedonia

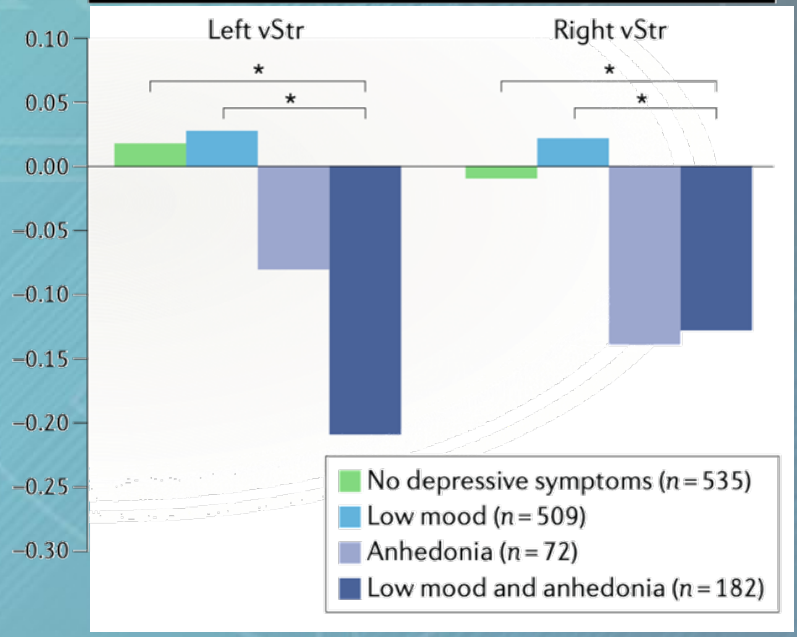
Frontostriatal circuits involved in motivation and effort-based decisions include:

- Dopaminergic projection from ventral tegmental area to ventral striatum
- Striatal regions projecting via thalamus to medial prefrontal cortex

These regions in turn project back to the basal ganglia.







Husain M, Roiser JP. Nat Rev Neurosci 2018;19(8):470-84.

Factors Impacting Anhedonia

Vicious Cycle of Anhedonia

1

Patients with depression expect to respond less positively to their environment

2

Patients respond less to helping behavior

3

Patients undergo social withdrawal

4

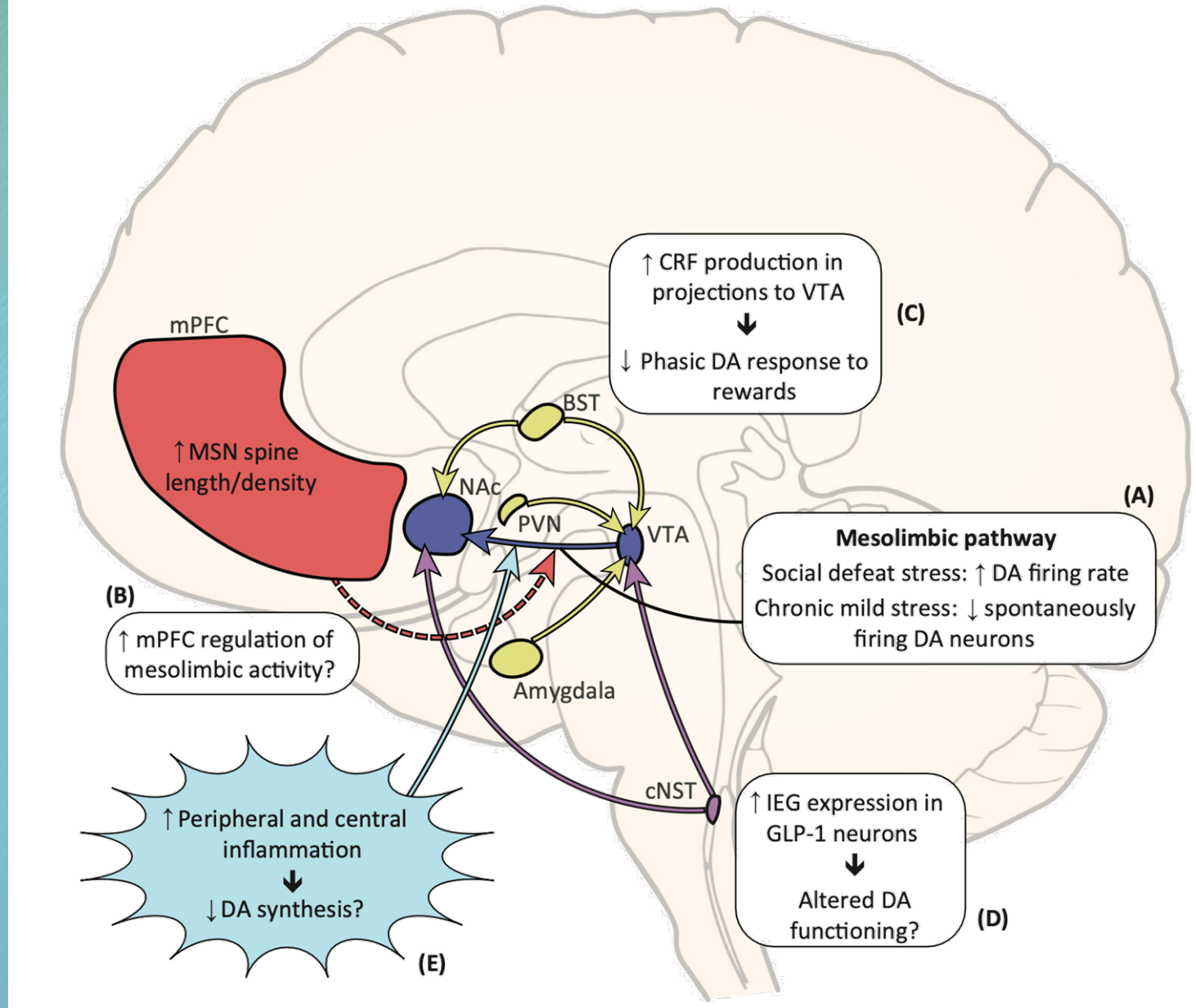
Patients experience less exposure to potentially positive feedback

- **Restrictions and continued social distancing** due to the COVID-19 quarantine measures likely **propagate the anhedonia cycle[2]**
- Anhedonia is frequently reported in **COVID-19 survivors[3]**
- Anhedonia/reduced hedonic tone may **predict COVID-19-related depression severity[4]**

Setterfield M et al. J Affect Disord 2016;205:372-7.

Is chronic stress the silent partner of anhedonia?

- **Stress alters mesolimbic reward processing** in humans and animals; these changes are linked to anhedonic behavior
- **Stress also produces dendritic remodeling in mPFC**, and co-occurring functional changes in the mPFC-mesolimbic circuit appear to contribute to anhedonic-like outcomes
- In prolonged stress, **proinflammatory cytokines** appear to **filter across the blood–brain barrier** to interact with mesolimbic circuitry and increase susceptibility to anhedonic-like behavior
- **Inflammatory responses** could also interfere with **dopamine synthesis**



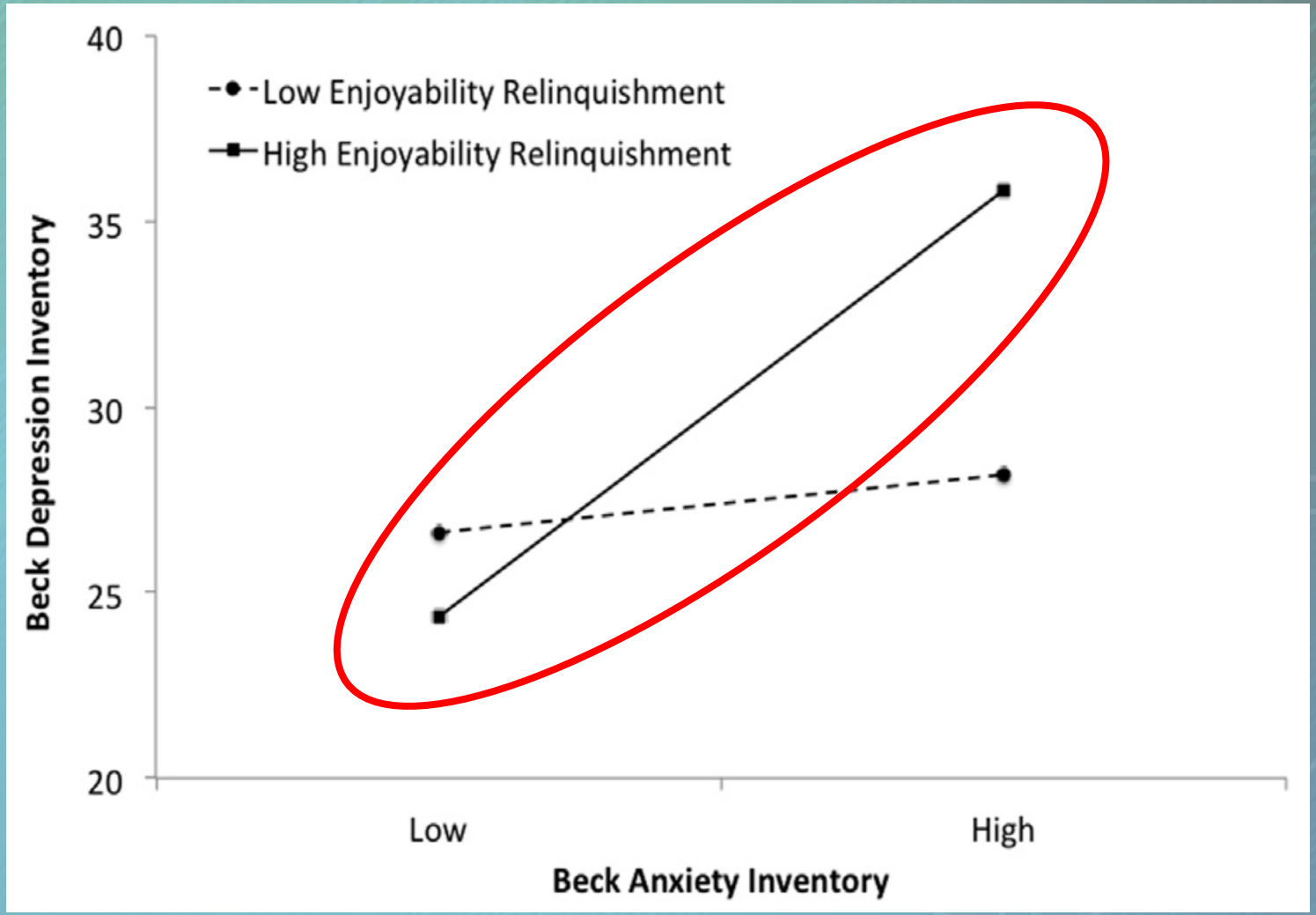
CRF: corticotropin-releasing hormone; GLP-1: glucagon-like peptide-1; IEG: Immediate Early Gene ; MSN: medium spiny neuron

Stanton et al. Trends Neurosci 2019;42(1):23-42.

Anhedonia and Anxiety Are Common Travelling Companions on the Path to Depression

Anxiety and anhedonia are intertwined origins of depression.

Study 1 (n=109), symptoms of anxiety and depression were positively related only in individuals who relinquished potential enjoyment due to their anxiety-related avoidance; in Study 3 (n=216), anxiety led to anhedonia and then depression over time and anhedonia led to anxiety and then depression at both 5 and 11 months.

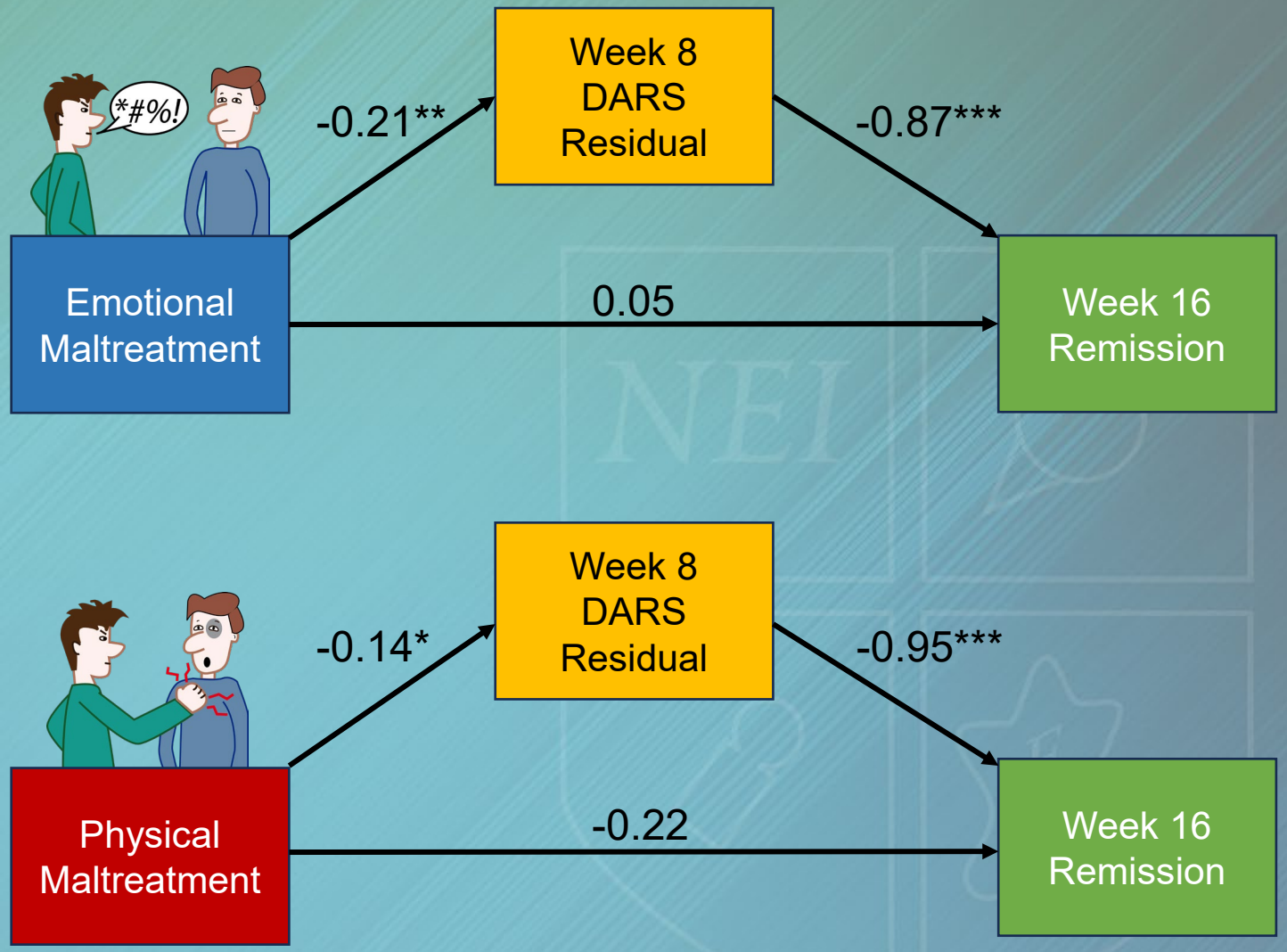


Winer ES et al. J Affect Disord 2017;221:289-96.

Early Life Abuse and Anhedonia

CAN-BIND-1 Trial

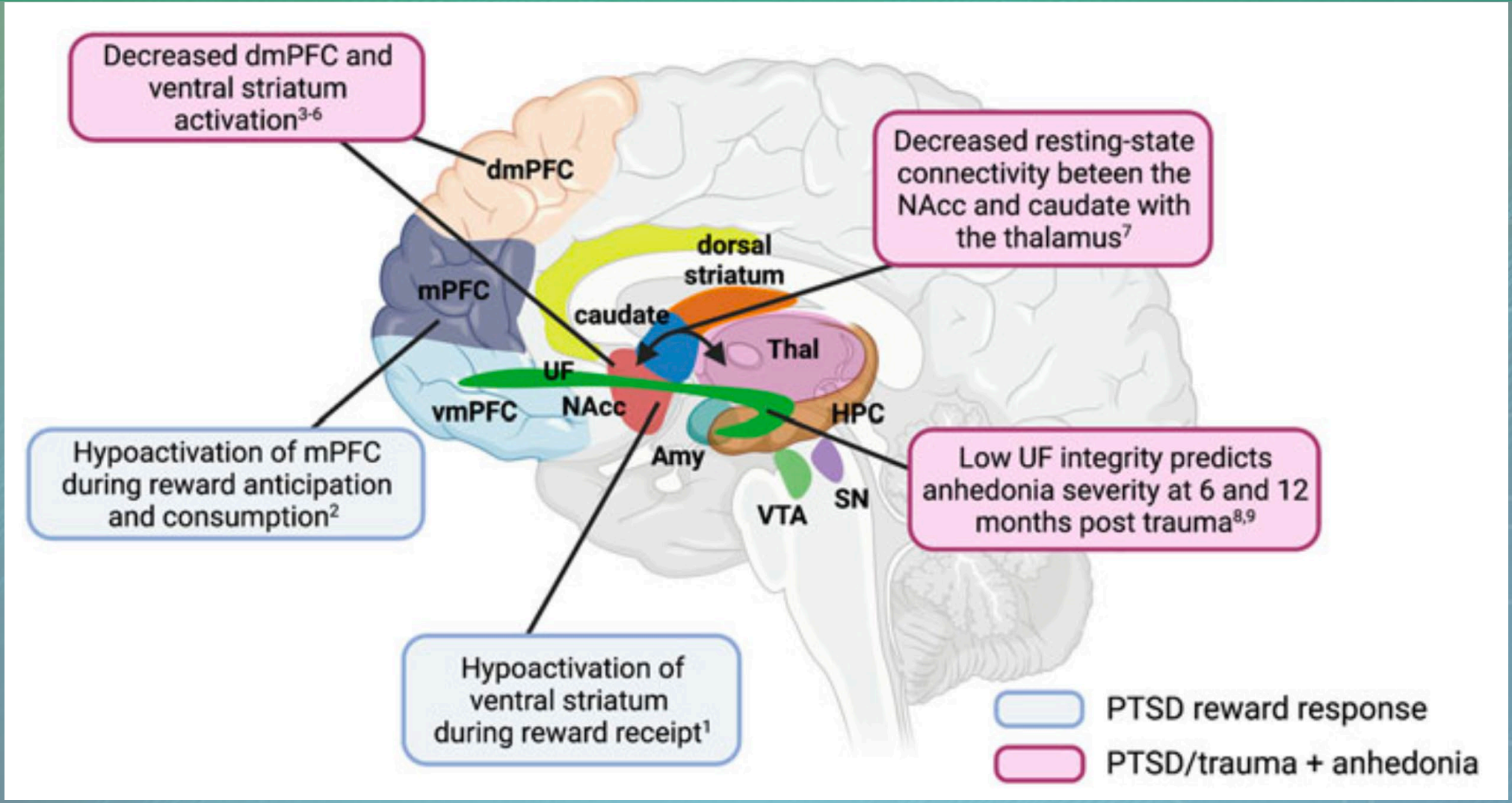
- **164 patients with MDD**
- Childhood Experience of Care and Abuse **(CECA)** structured interview
- All patients received **escitalopram**
- At 8 wks, **non-responders augmented with aripiprazole**
- **Greater severity of emotional & physical maltreatment predicted less change in anhedonia from baseline** to week 8, which subsequently significantly predicted a greater likelihood of nonremission to escitalopram or escitalopram + aripiprazole at week 16



DARS: Dimensional Anhedonia rating Scale

Harkness KL et al. Can J Psychiatry 2023;68(8):586-95.

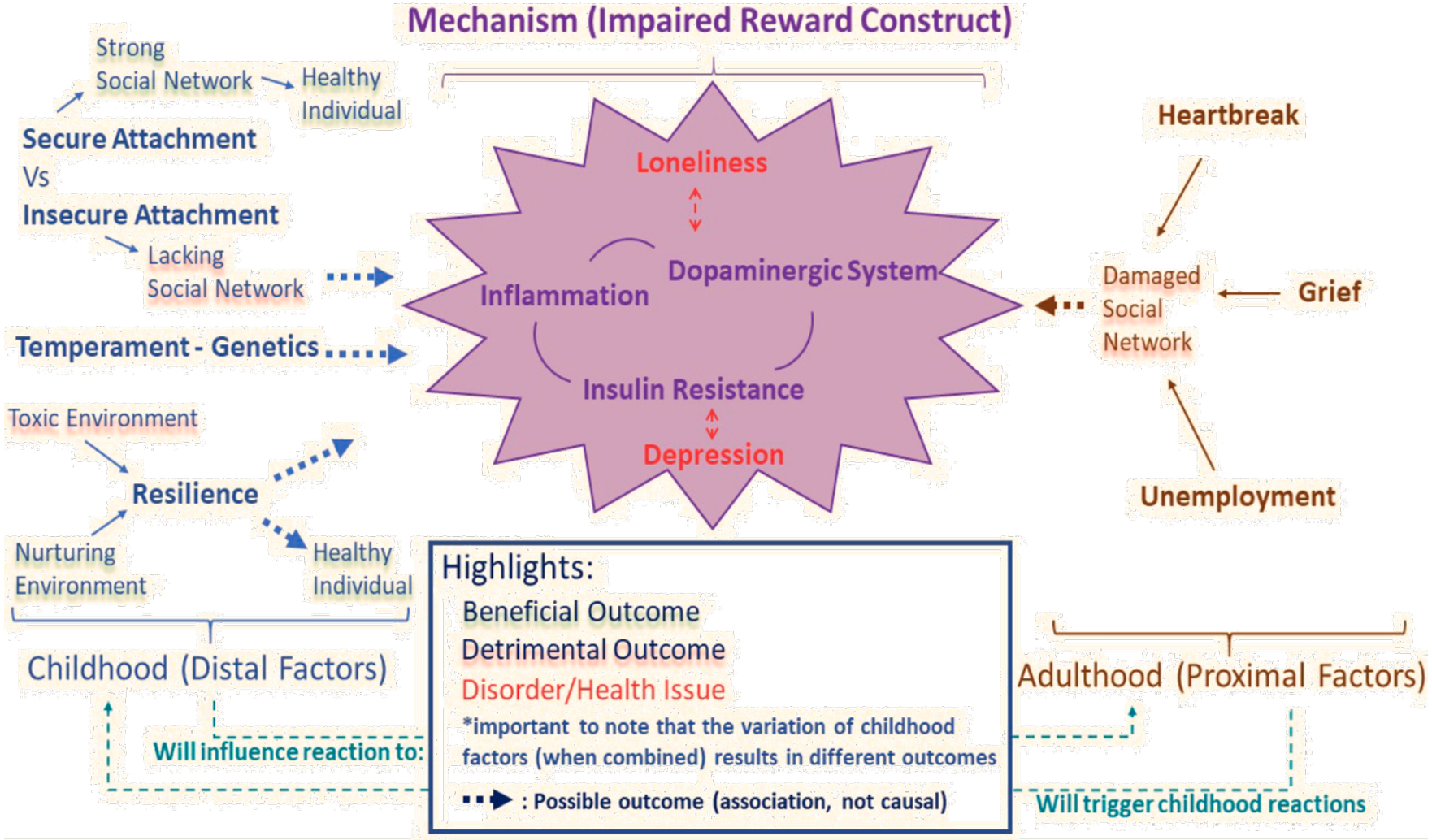
PTSD and Anhedonia



dmPFC dorsomedial prefrontal cortex, mPFC medial prefrontal cortex, vmPFC ventromedial prefrontal cortex, NAcc nucleus accumbens, Amy amygdala, Thal thalamus, HPC hippocampus, VTA ventral tegmental area, SN substantia nigra, UF uncinate fasciculus.

Vinograd et al. Curr Topics Behav Neurosci 2022;58:185-200.

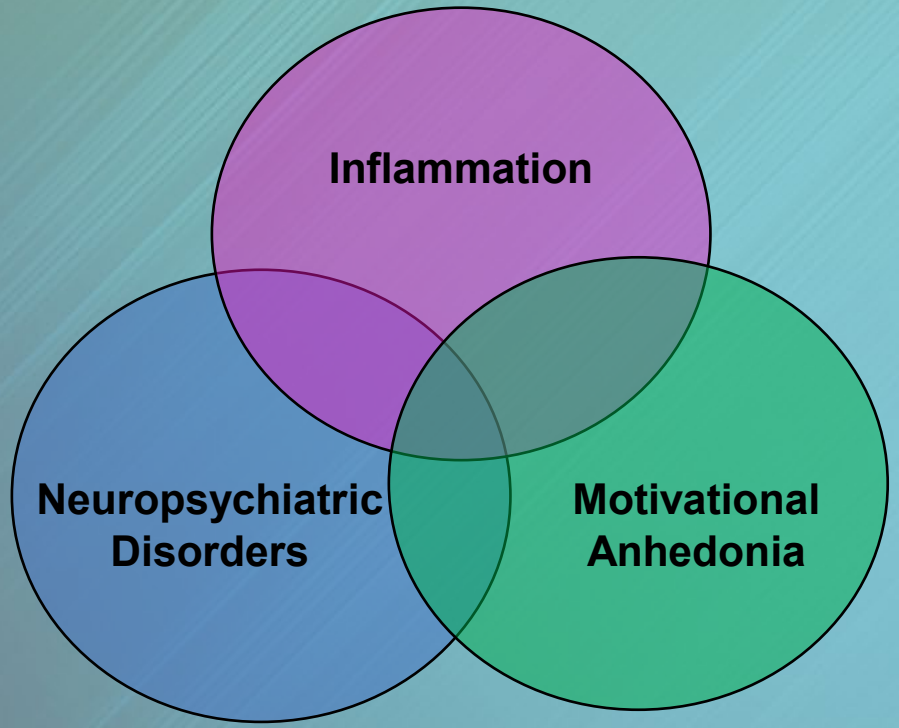
Birds of a Feather: Loneliness, Altered Dopamine Signaling, Inflammation, Metabolic Abnormalities, and Depression

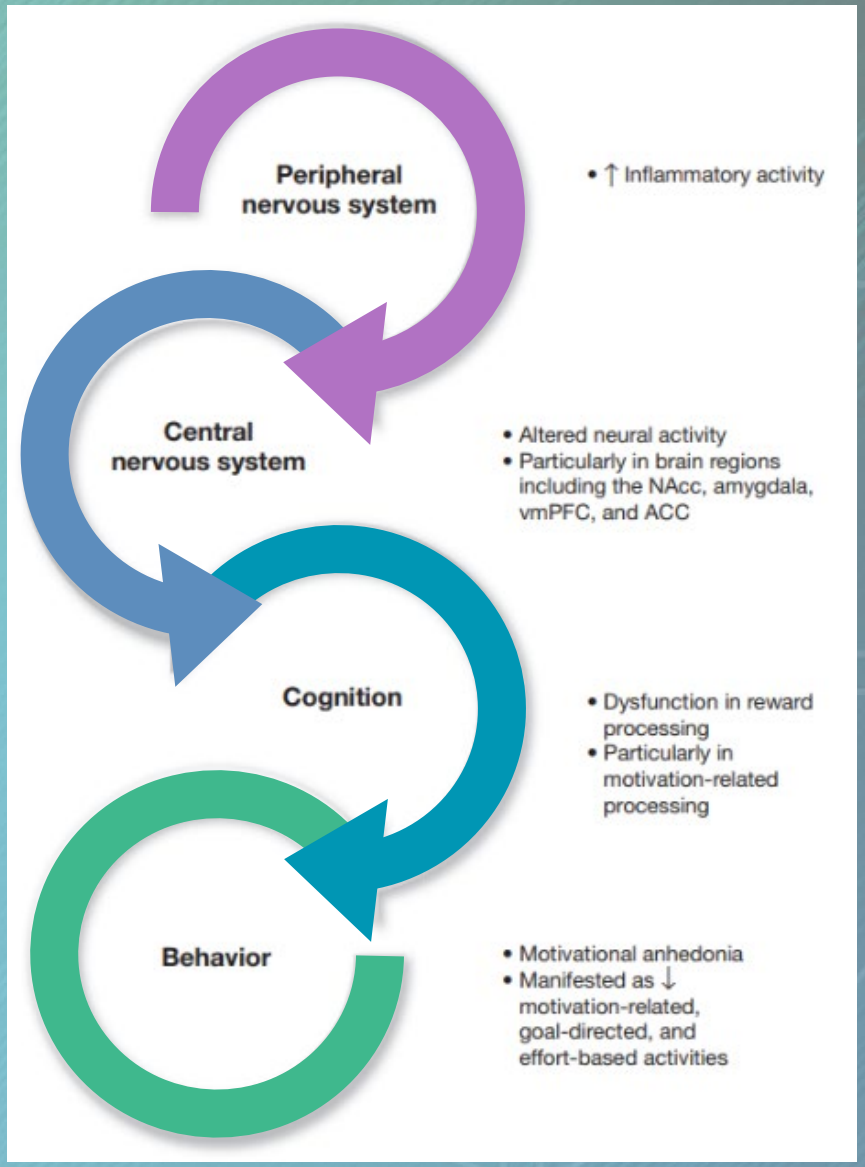


Wilkialis L et al. Psychiatry Res 2021;298:113800.

Inflammation and Motivational Anhedonia

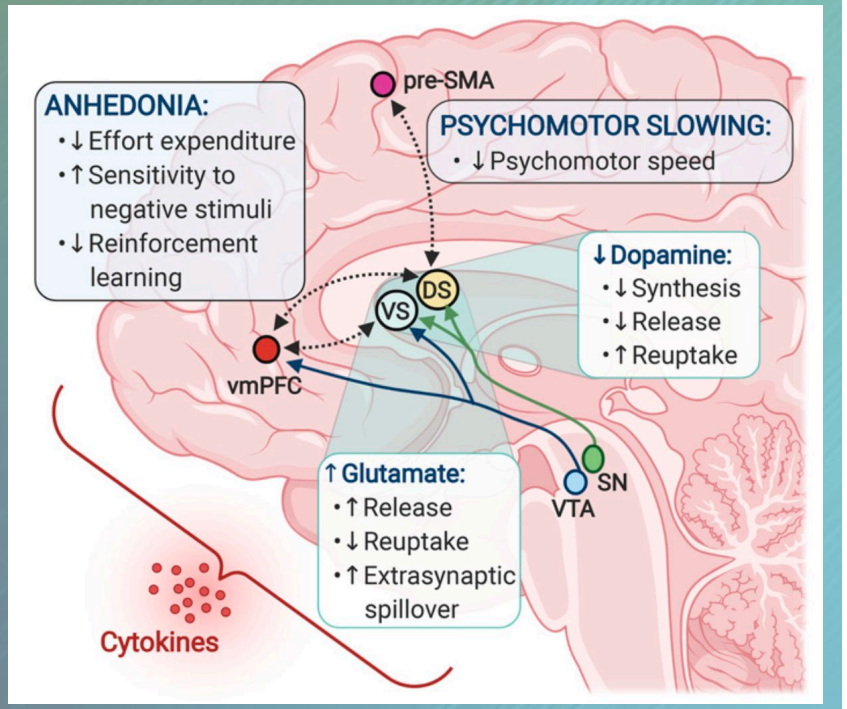
- Motivational processes may be vulnerable to persistent inflammatory activity
- Causal interactions need further elucidation

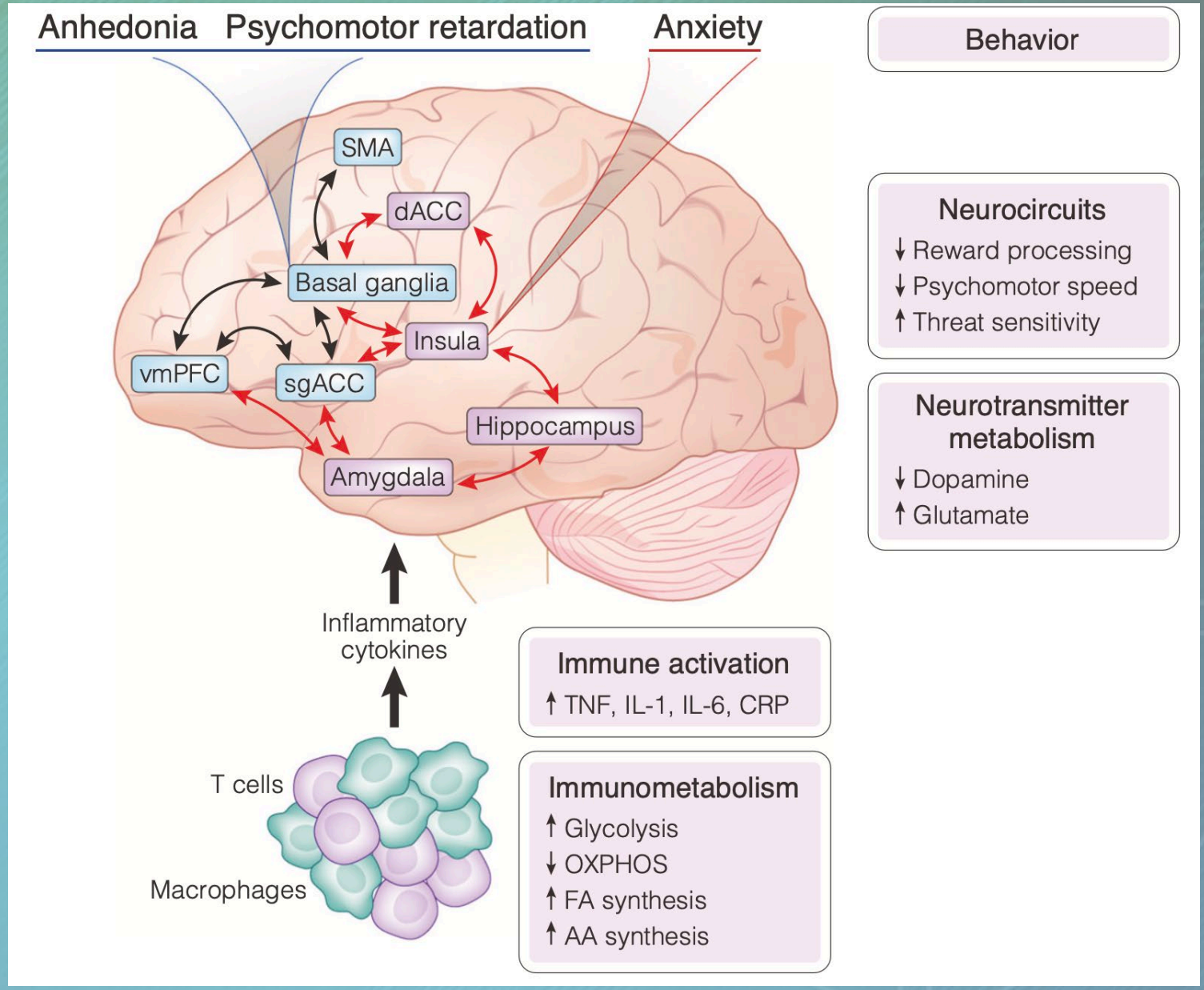




Nogo D et al. Ann Clin Psychiatry 2021;33(3):193-206.

Inflammation-Induced Psychiatric Symptoms

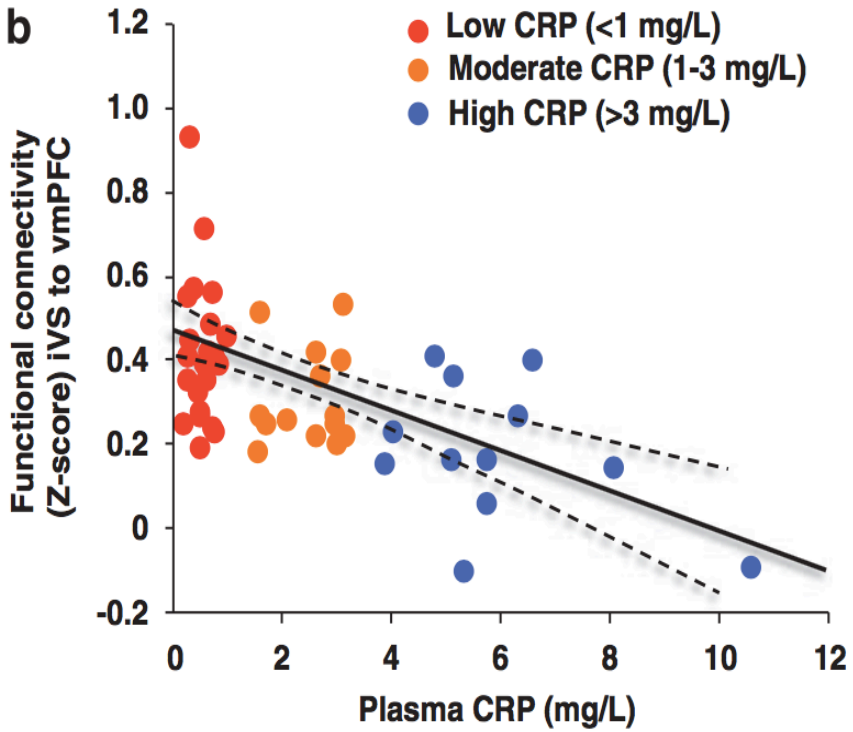




Abbreviations: tumor necrosis factor (TNF), interleukin (IL)-1,IL-6, C-reactive protein (CRP), oxidative phosphorylation (OXPHOS), ventromedial prefrontal cortex (vmPFC), subgenual anterior cingulate cortex (sgACC), supplementary motor area (SMA), dorsal ACC (dACC).

Miller AH, Raison CL. Mol Psychiatry 2023;28(1):68-75; Lucido MJ et al. Pharmacol Rev 2021;73(3):1084-117.

Peripheral Inflammation in MDD Is Associated With Diminished Connectivity in Reward Circuitry



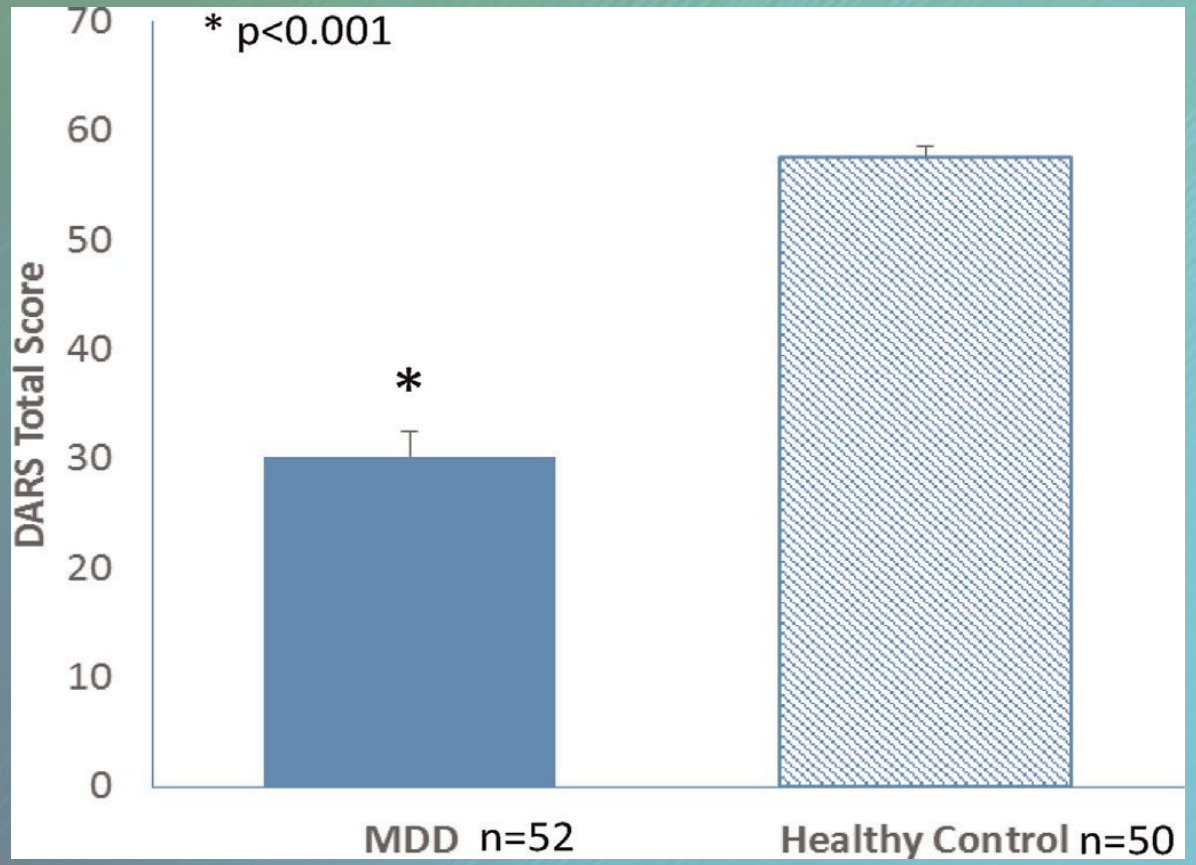
In 48 medically stable, unmedicated outpatients with major depression, plasma CRP was negatively associated with functional connectivity between left inferior ventral striatum (iVS) and ventromedial prefrontal cortex (vmPFC; BA32)

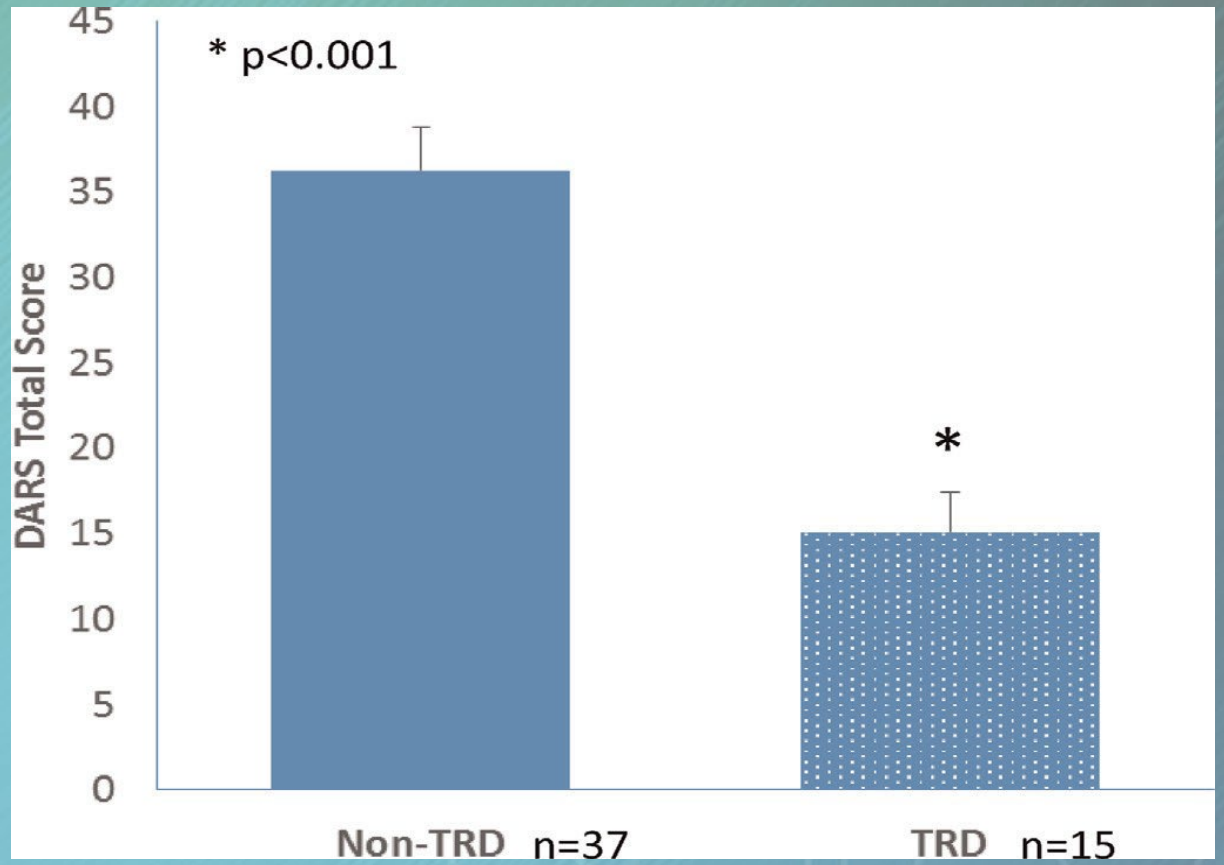
CRP, C-reactive protein; MDD, major depressive disorder

Felger JC et al. Mol Psychiatry 2016;21(10):1358-65.

Impact of Anhedonia

TRD has a strong association with anhedonia

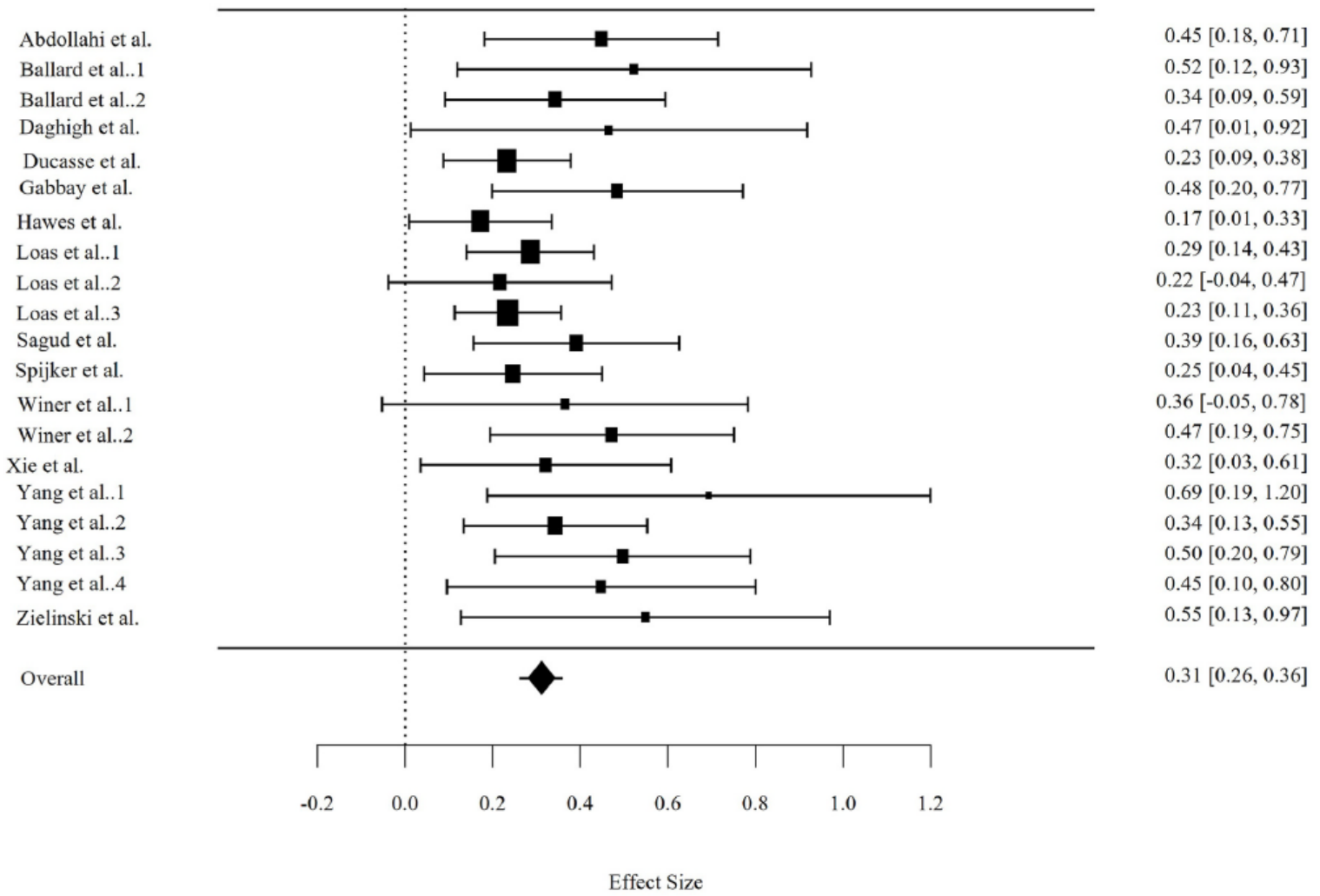




Dimensional Anhedonia Rating Scale (DARS), a dynamic scale that measures desire, motivation, effort and consummatory pleasure across hedonic domains.

Rizvi et al. Psychiatry Res 2015;229:109–119.

Anhedonia as a Risk Factor for Suicide: Meta-Analysis



(Heart) BREAKING NEWS

Approximately
50,000
lives lost to suicide in 2022

Anticipatory anhedonia

was the highest risk factor (r = 0.40; p<0.001), with a moderate to large effect size

Gillissie ES et al. J Psychiatr Res 2023;158:209-15;
Suicide data and statistics. https://www.cdc.gov/suicide/suicide-data-statistics.html Published Aug. 10, 2023.

Treating Anhedonia and Emotional Blunting

Pharmacological Treatments Under Investigation for Anhedonia

Monoaminergic

TREATMENT	*MOA*
Vortioxetine*	Various 5HT receptor modulation/SRI
Dextromethorphan-bupropion*	NMDA antag//SNDRI/ sigma-1 agonist
Bupropion*	NDRI
Agomelatine	MT1+MT2 agonist/5HT2C antag
Escitalopram*	SSRI
Sertraline*	SSRI
Fluoxetine*	SSRI
Vilazodone*	SSRI/5HT1A agonist
Venlafaxine ER*	SNRI
Levomilnacipran ER*	SNRI
Amitifadine	SNDRI
Moclobemide	MAOI-A
Clomipramine	TCA

Glutamatergic

TREATMENT	*MOA*
Ketamine	NMDA antag
Riluzole	Glu reuptake enhancer

"Antipsychotics"

TREATMENT	*MOA*
Cariprazine*	D2+D3 partial agonist
Pramipexole	D2+D3 partial agonist
Aripiprazole*	D2 partial agonist
Lumateperone*	D2+5HT2A antag/D1 modulator/SRI

Opioid Agents

TREATMENT	*MOA*
Navacaprant	Kappa opioid antag
Aticaprant	Kappa opioid antag

Psychedelics

TREATMENT	*MOA*
Psilocybin	5HT2A agonist

Anti-inflammatory Agents

TREATMENT	*MOA*
Infliximab	TNFα antag

Stimulants

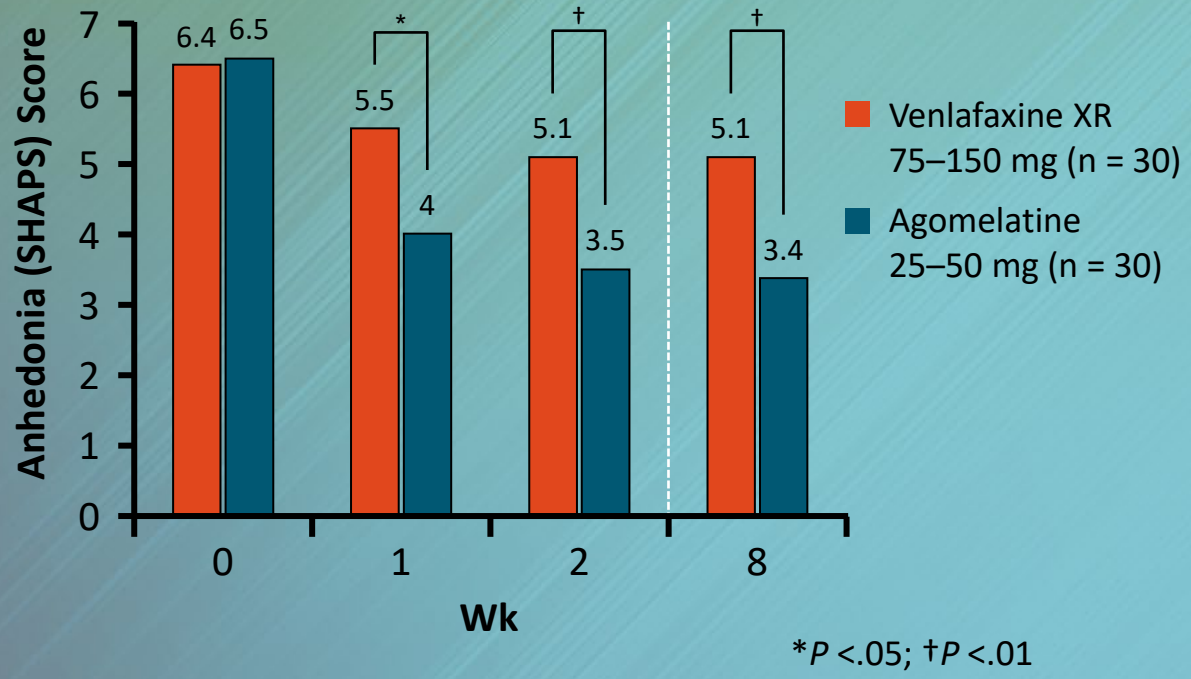
TREATMENT	MOA
Amphetamine	NDRI
Methylphenidate	NDRI

**FDA-approved for depression*

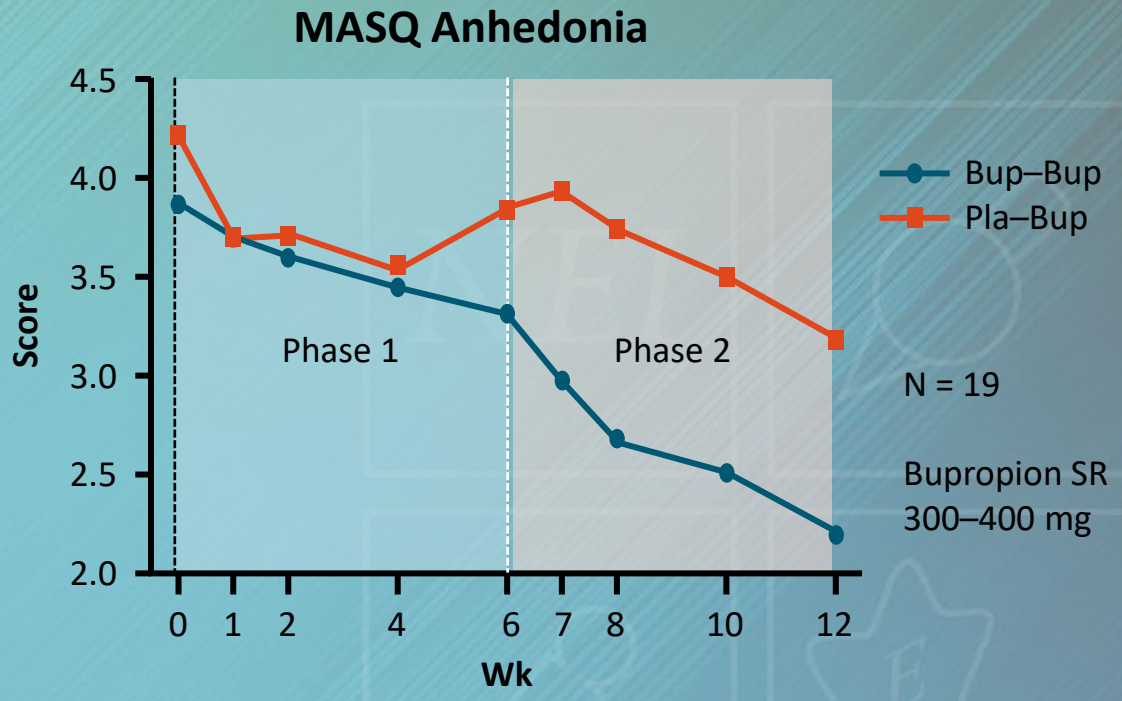
Presentation Focus

Serretti A. Clin Psychopharmacol Neurosci 2023;21(3):401-9;
Cao B et al. Prog Neuropsychopharmacol Biol Psychiatry 2019;92:109-17.

Bupropion and Agomelatine Significantly Improved Anhedonia in MDD



*P <.05; †P <.01



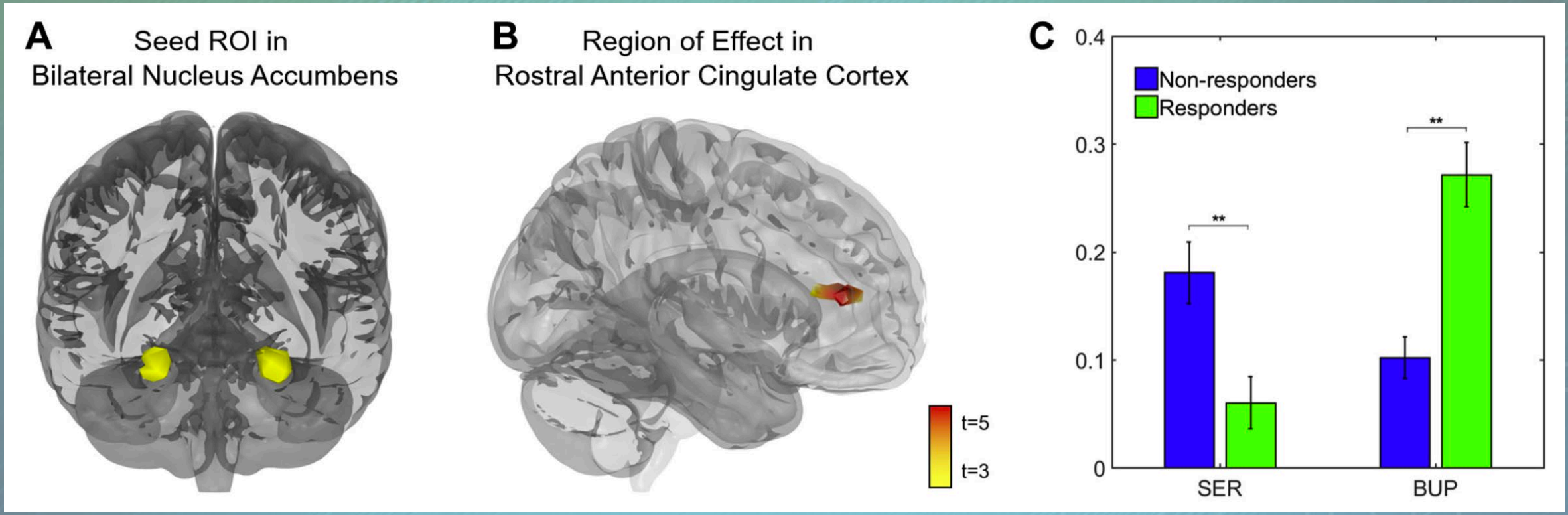
Agomelatine is MT_1/MT_2 melatonergic receptor agonist and $5\text{-}HT_{2C}$ antagonist.

Bupropion is an NDRI.

MASQ, Mood and Anxiety Symptoms Questionnaire; SHAPS, Snaith–Hamilton Pleasure Scale.

Di Giannantonio M et al. Eur Neuropsychopharmacol 2012;22(Suppl 3):S505-10; Tomarken AJ et al. J Affect Disord 2004;78(3):235-41.

Fronto-Striatal Connectivity Is Associated With Response to Bupropion in MDD Patients

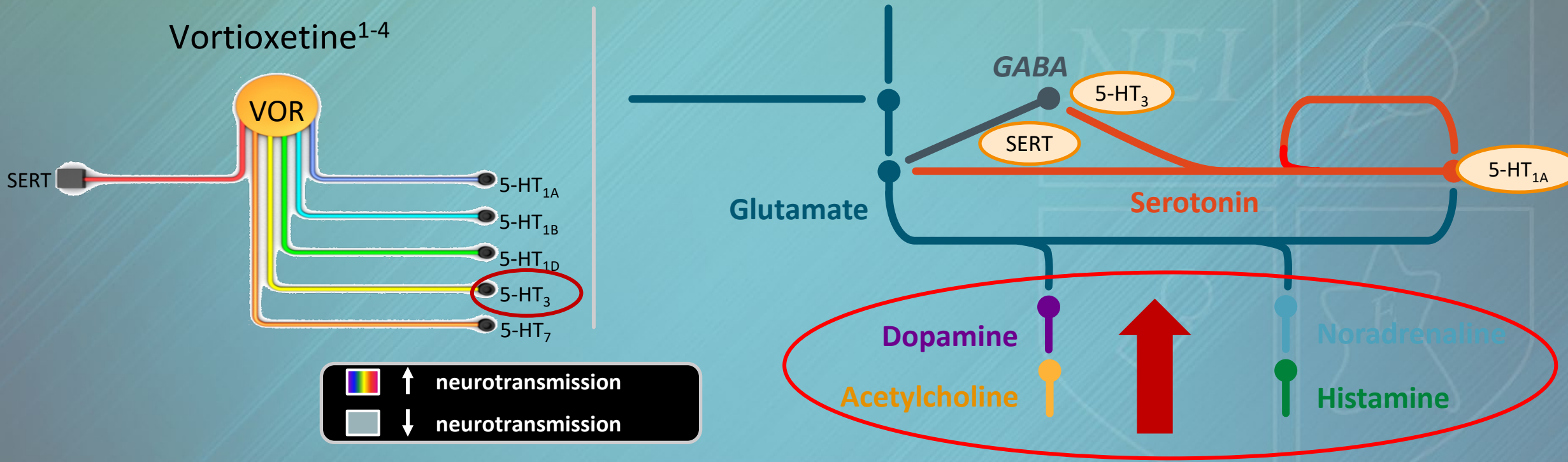


Greater pretreatment reward sensitivity and higher resting-state functional fronto-striatal connectivity (connectivity between bilateral nucleus accumbens and rostral anterior cingulate cortex) were associated with positive response to bupropion but not sertraline.

Ang YS et al. Biol Psychiatry 2020;88(8):657-67.

Vortioxetine for Emotional Blunting?

- **SSRIs** increase serotonergic signaling, down-regulating noradrenergic and dopaminergic signaling → **emotional blunting**
- **Vortioxetine** offers serotonin receptor activity modulation and SERT inhibition in one molecule,[1,2] with preclinical research indicating activation of additional pathways:



1. Guilloux JP et al. Neuropharmacology 2013;73:147-59. 2. Pehrson AL et al. Eur Neuropsychopharmacol 2013;23(2):133-45.
3. Mørk A et al. Pharmacol Biochem Behav 2013;105:41-50. 4. Pehrson AL et al. CNS Spectr 2014;19(2):121-33.

Antidepressants That May Reduce EB: Serotonin Modulation

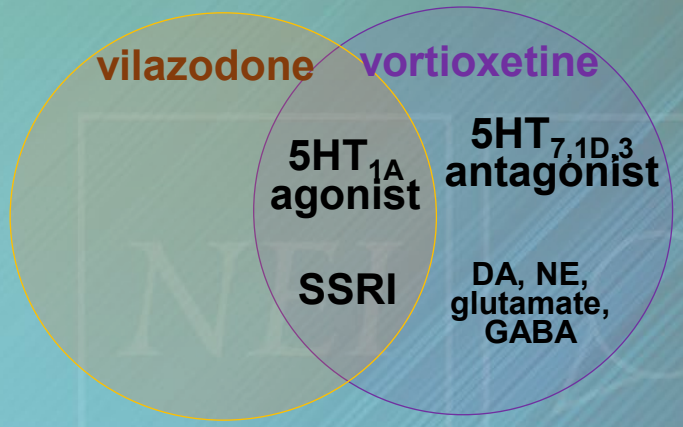
STUDY INTERVENTION

- Survey of 3243 online user reviews from popular websites
- Reported AEs were coded and correlated with user satisfaction with treatment

PROPOSED ROLES IN REDUCING EB

- Users of **vilazodone, vortioxetine less likely to report emotional blunting**
- Emotional AEs were moderately to substantially **associated with users' satisfaction**
- Drawbacks: Mechanisms associated with reduced EB were also associated with greater emotional instability

MECHANISMS OF ACTION



FREQUENCY OF ADVERSE EFFECTS

	EMOTIONAL NUMBING*	AGGRAVATED DEPRESSION, CRYING*	SEXUAL CHANGES*
VILAZODONE	**4.1%**	11.7%	7.1%
VORTIOXETINE	**5.9%**	10.8%	8.1%
DULOXETINE	8.2%	8.5%	12.8%
ESCITALOPRAM	10.7%	5.2%	23.1%

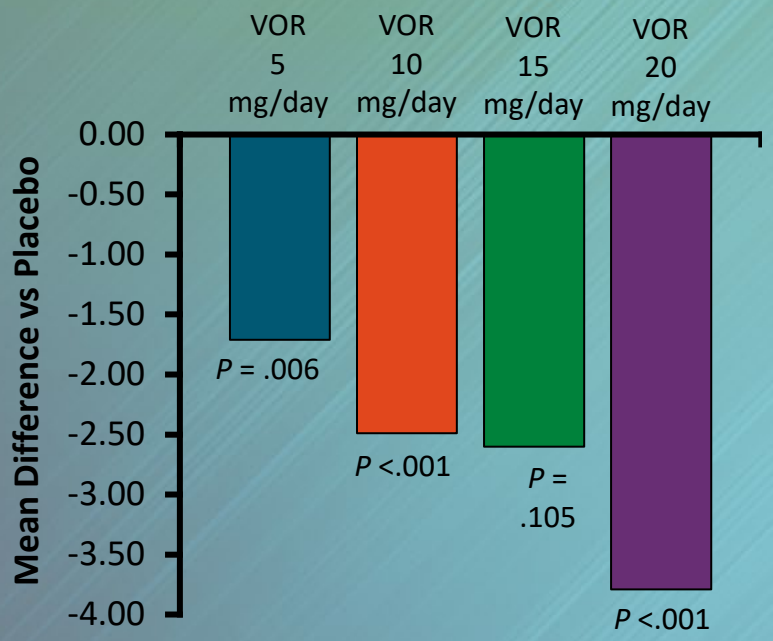
*$p<0.001$

Hughes S et al. Psych Res 2017;255:78-86.

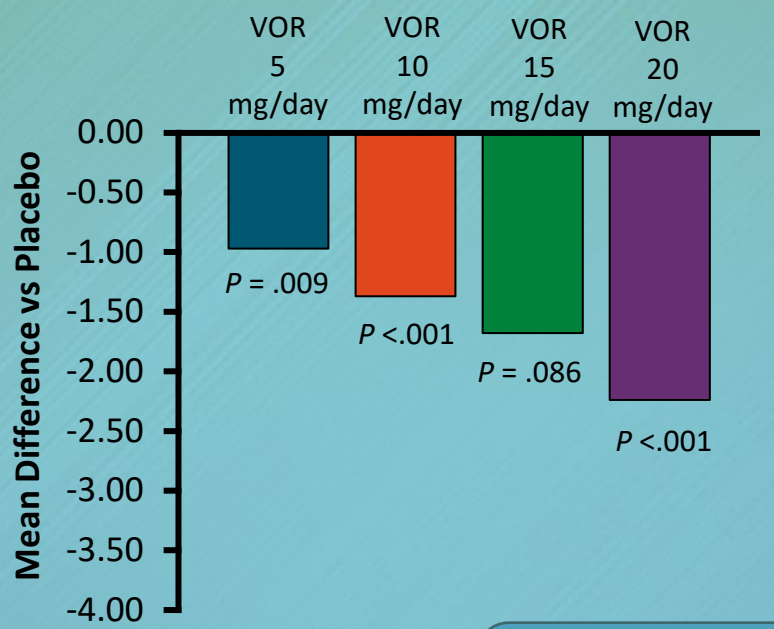
Vortioxetine Significantly Improved Depressive Symptoms, Functioning, and Anhedonia

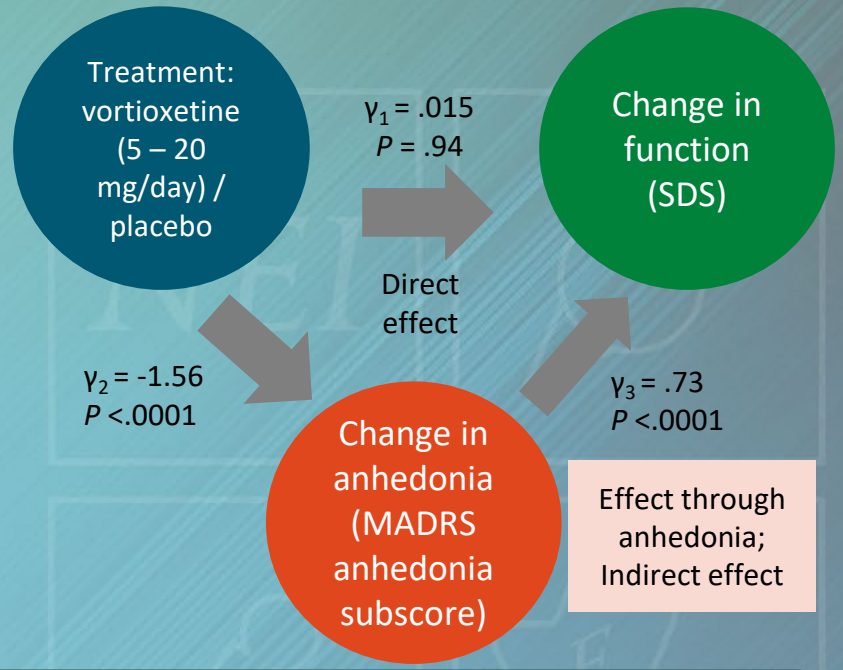
Pooled analysis of all 11 short-term, placebo-controlled studies

MADRS total score



MADRS anhedonia subscale score





Vortioxetine-associated improvements in functioning appear to be driven mostly by the effect of vortioxetine on anhedonia.

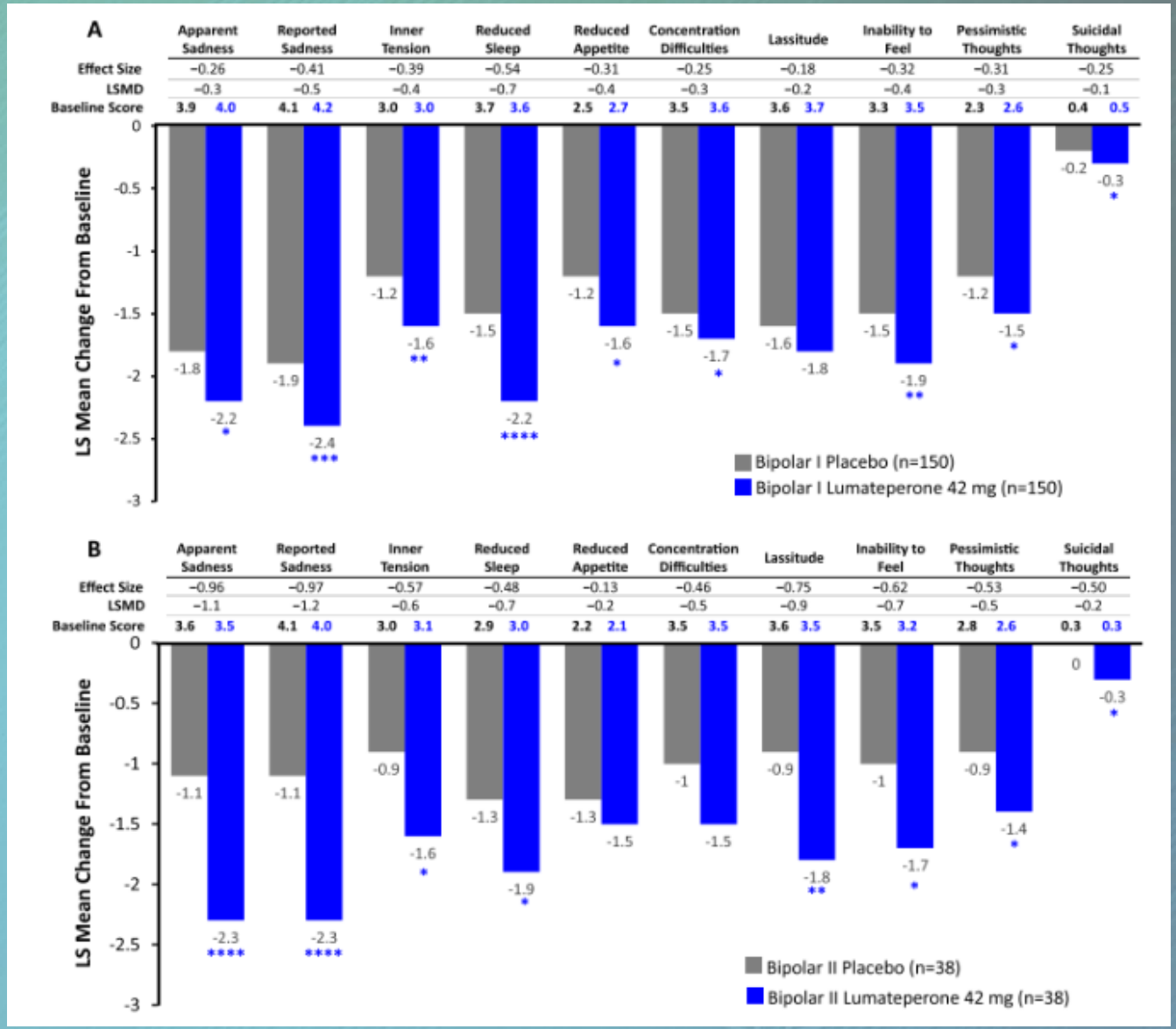
- n = 4988 patients with MDD and n = 495 in the active-comparator study
- Improvements in functioning associated with vortioxetine were driven by the effect of treatment on MADRS anhedonia factors

SDS, Sheehan Disability Scale.

McIntyre RS et al. Neuropsychiatr Dis Treat 2021;17:575-85.

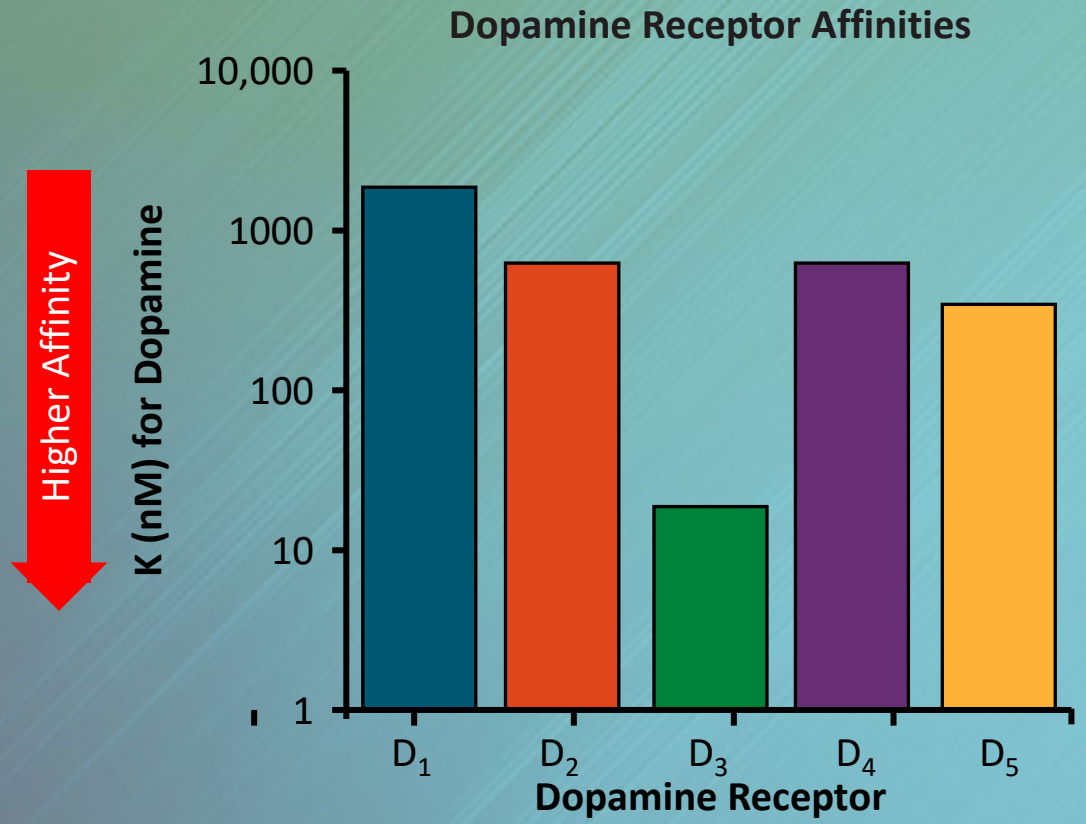
Lumateperone in Bipolar I and II Depression: Post Hoc Analyses

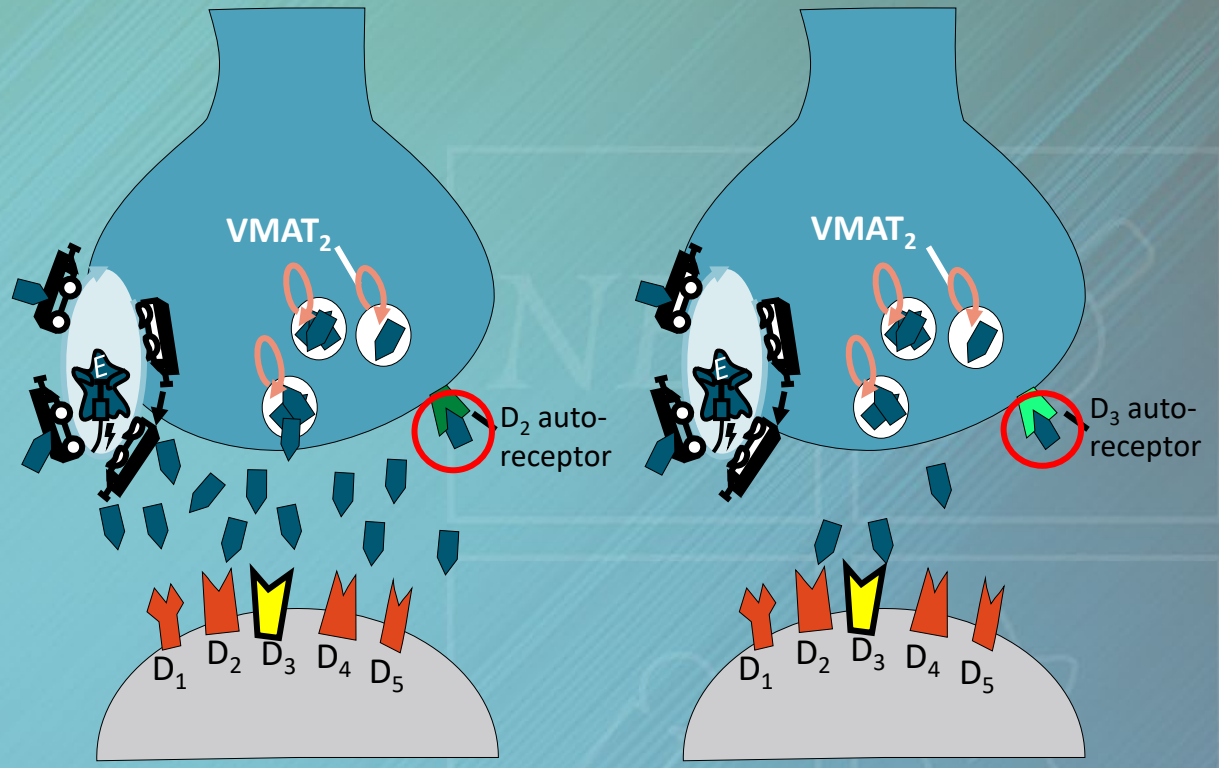
- Serotonin 5HT2A antagonist and dopamine D2 presynaptic partial antagonist/postsynaptic antagonist
  - Actions also at D1, AMPA, NMDA, and SERT
- Significant improvement in Montgomery-Asberg Depression Rating Scale (MADRS) anhedonia factor from baseline to Day 43 vs. placebo



McIntyre RS et al. Eur Neuropsychopharmacol 2023;68:78-88.

Regulation of Synaptic DA Concentration

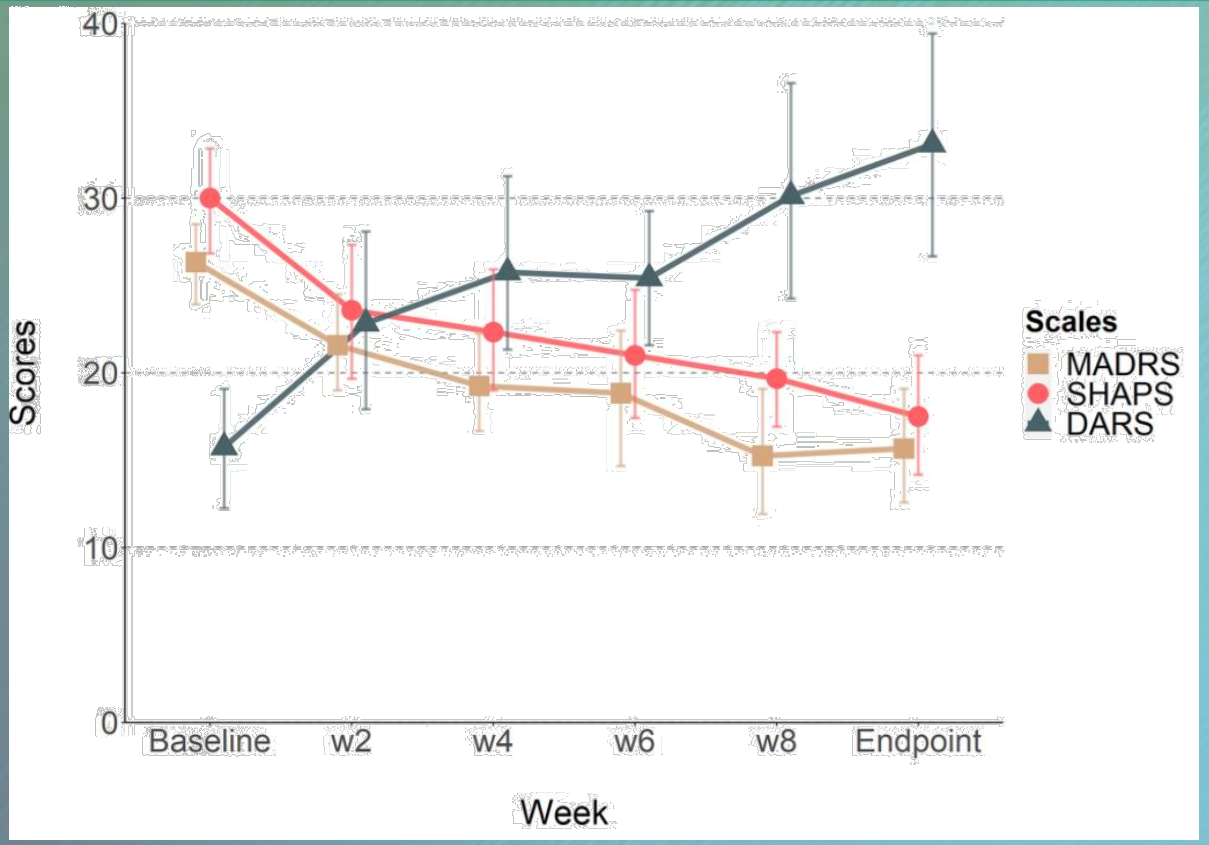


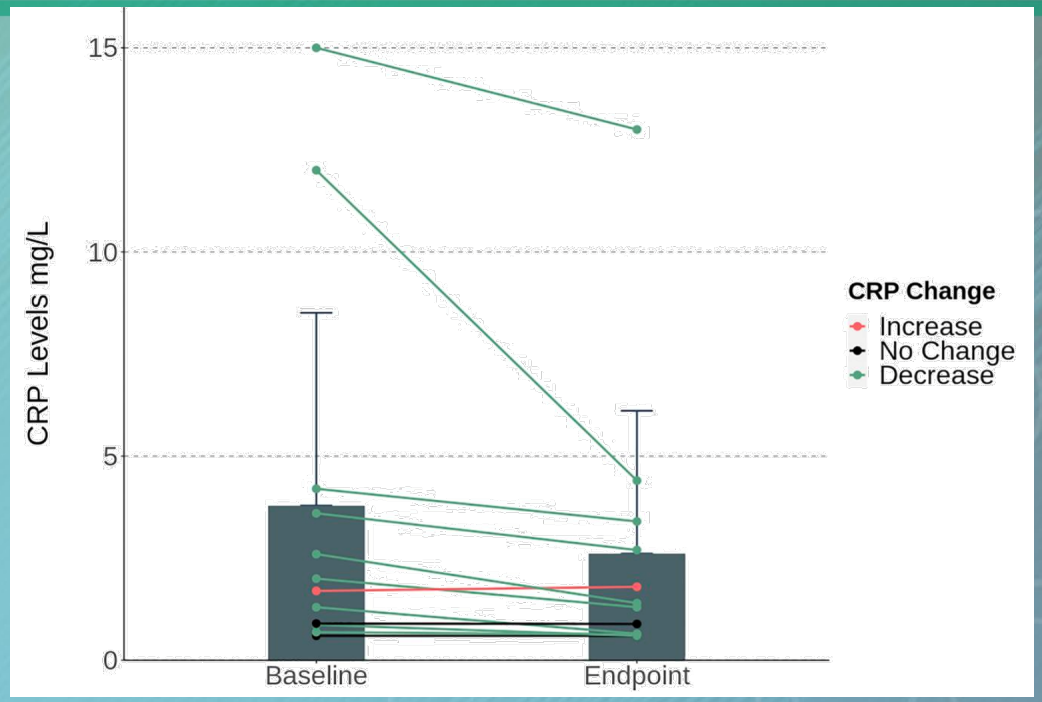


D_3 presynaptic receptors provide more refined control of tonic dopamine release (tonic) than D_2 (phasic) because they are the higher affinity receptors.

Stahl SM. CNS Spectr 2017;22(4):305-11.

Pramipexole (D3/D2 Partial Agonist) for Anhedonic Depression (MDD and Bipolar)





Mean levels of hs-CRP (mg/L) at baseline versus endpoint (week 10). The mean levels decreased during the study period from mean 3.8 mg/L at baseline to 2.6 mg/L at endpoint. P<0.01. CRP= C-reactive protein.

N=12 patients with unipolar or bipolar, moderate-to-severe depression and with significant anhedonia symptoms were on a stable dose of one or a combination of antidepressants and/or mood stabilizers and received 10 weeks of adjunctive pramipexole ER titrated to a maximum dose of 4.5 mg salt/day. All patients were rated with the Dimensional Anhedonia Rating Scale (DARS), the Montgomery-Åsberg Depression Rating (MADRS), and the Snaith-Hamilton Pleasure Scale (SHAPS).

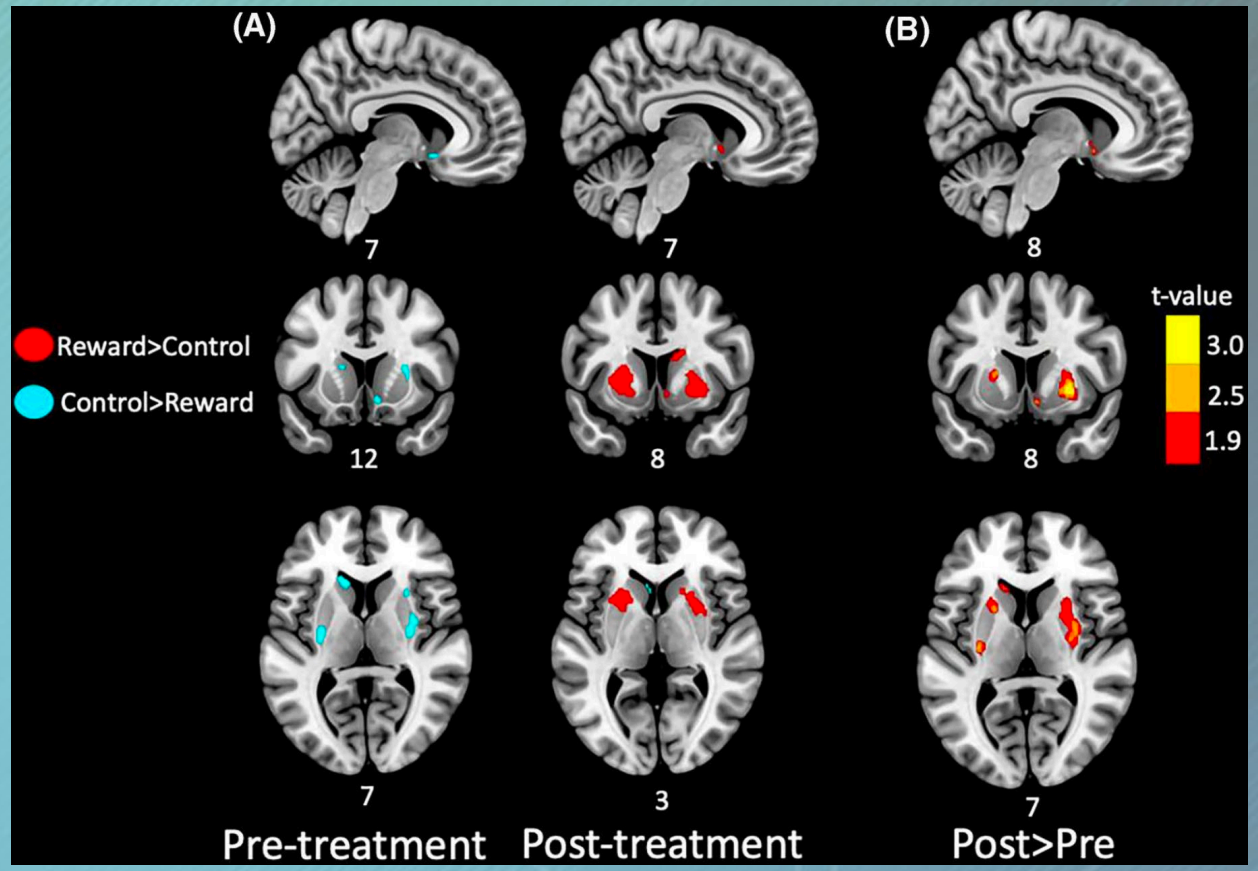
Ventorp F et al. Psych Res Clin Pract 2022;4(2):42-7.

Pramipexole (D3/D2 Partial Agonist) Treatment Improves Anhedonic Depression (MDD and Bipolar)

N=12 patients with unipolar or bipolar, moderate-to-severe **depression** and with **significant anhedonia symptoms** were on a stable dose of one or a combination of antidepressants and/or mood stabilizers and received **10 weeks of adjunctive pramipexole ER** titrated to a maximum dose of 4.5 mg/day.

All patients were rated with the Dimensional Anhedonia Rating Scale **(DARS),** the Montgomery-Åsberg Depression Rating **(MADRS),** and the Snaith-Hamilton Pleasure Scale **(SHAPS).**

Prior to treatment—deactivation in the left posterior putamen, right dorsal putamen, left dorsal caudate, and right nucleus accumbens. **After treatment—**substantial **reward-related activation** encompassing the **right nucleus accumbens, lateral putamen, and right dorsal caudate.**



Ventorp F et al. Psych Res Clin Pract 2022;4(2):42-7.

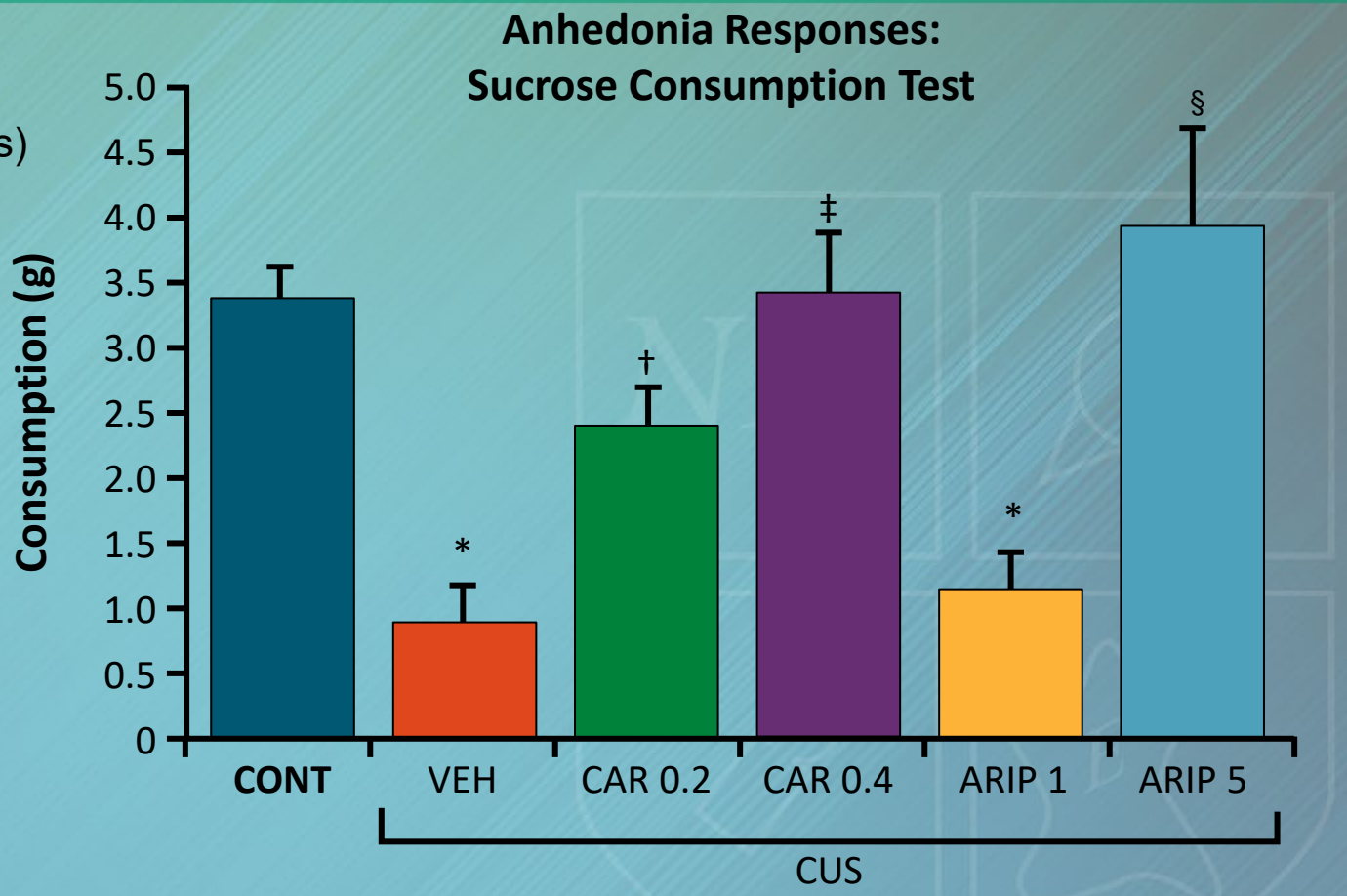
D2/D3 Partial Agonism/Antagonism May Diminish Anhedonia

CUS (*chronic unpredictable stress)* model

- Mice exposed to CUS model (controlled conditions)
- 10 different stressors 2/d for up to 26 days
- Stressors included:
  - Restraint stress (1 hr)
  - Cold (1 hr)
  - Forced swim (10 min)
  - Light/dark cycle disturbance
  - Strobe light
  - Odor
  - No/wet bedding
  - Cage tilt
- Administered either vehicle (1% sucrose solution)

or

- Medications: cariprazine or aripiprazole (i.p)



*P <.0001 compared to nonstressed control group. †P <.05 compared with CUS + vehicle group. ‡P <.001 compared with CUS + vehicle group. §P <.0001 compared with CUS + vehicle group

Duric et al. Int J Neuropsychopharmacol 2017;20:788.

Cariprazine for Anhedonia in Bipolar I Depression

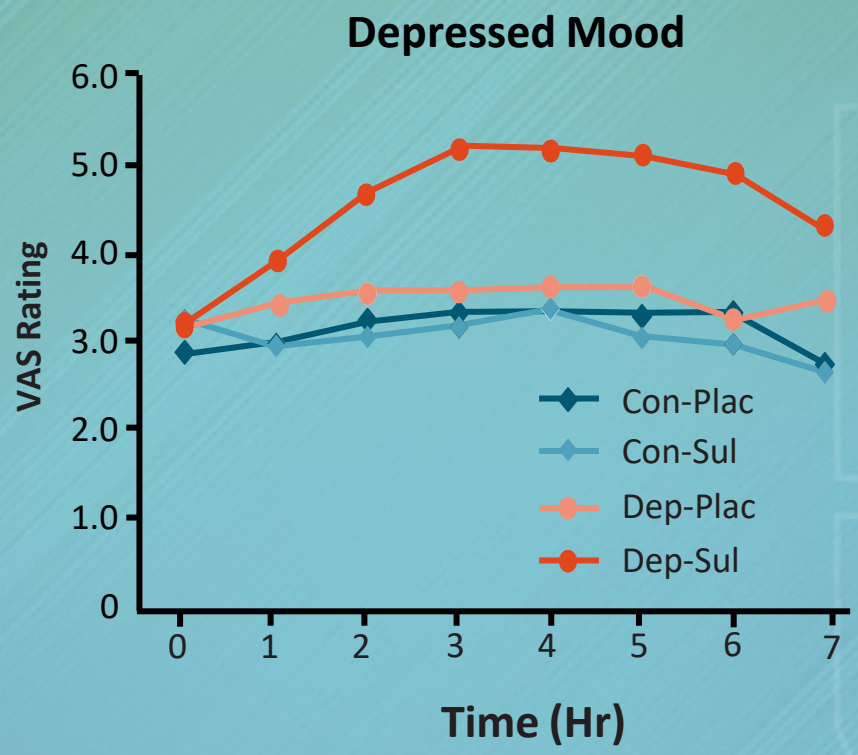
- Dopamine D3-preferring D3/D2 receptor partial agonist and serotonin 5HT1A receptor partial agonist
- Post hoc analyses of pooled data from 3 RCTs
- Cariprazine 1.5 mg/d and 3 mg/d improved 6 wk MADRS total score and MADRS anhedonia score in patients with higher anhedonia (1.5 mg/d was effective in lower anhedonia group)

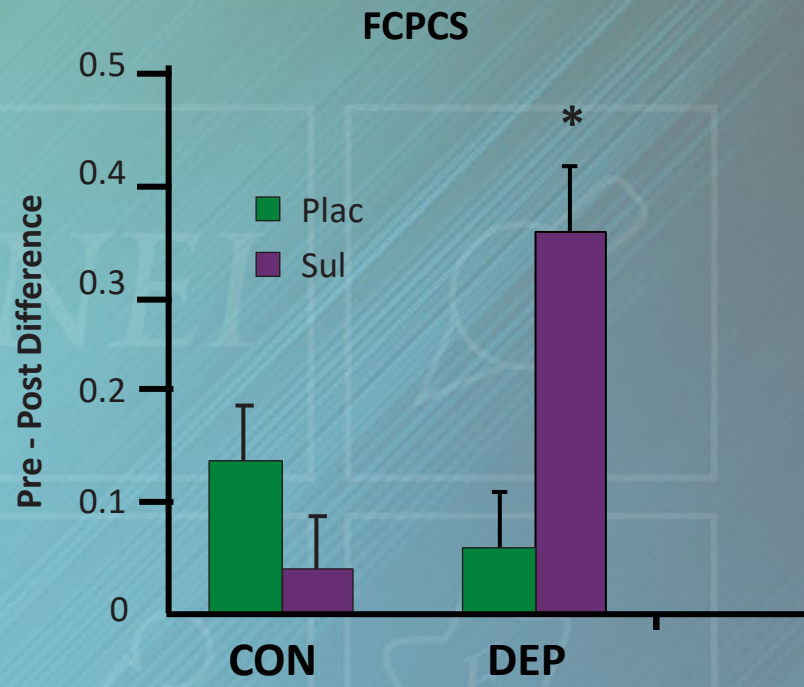
Cariprazine demonstrated antidepressant effects in BPI patients with or without anhedonia AND had an anti-anhedonic effect even when adjusting for other depressive symptoms

McIntrye RS et al. ECNP 2023.

D_2/D_3 Antagonism Has Different Impact on Mood in Patients With MDD vs Healthy Controls

- Volunteers (Con) or patients with depression (Dep) who had remitted (HAM-D ≤10) following SSRI treatment:
  - fluoxetine 20 mg (n = 5)
  - citalopram 30 mg (n = 2)
  - paroxetine 30 mg (n = 1)
- Dep were administered acutely either placebo (Plac) or a low dose of the **DA D_2/D_3 receptor antagonist sulpiride (Sul)**
- Sulpiride 200 mg caused a return of severely depressed mood in the patients (Dep) but not in controls (Con)
- Subjective well-being



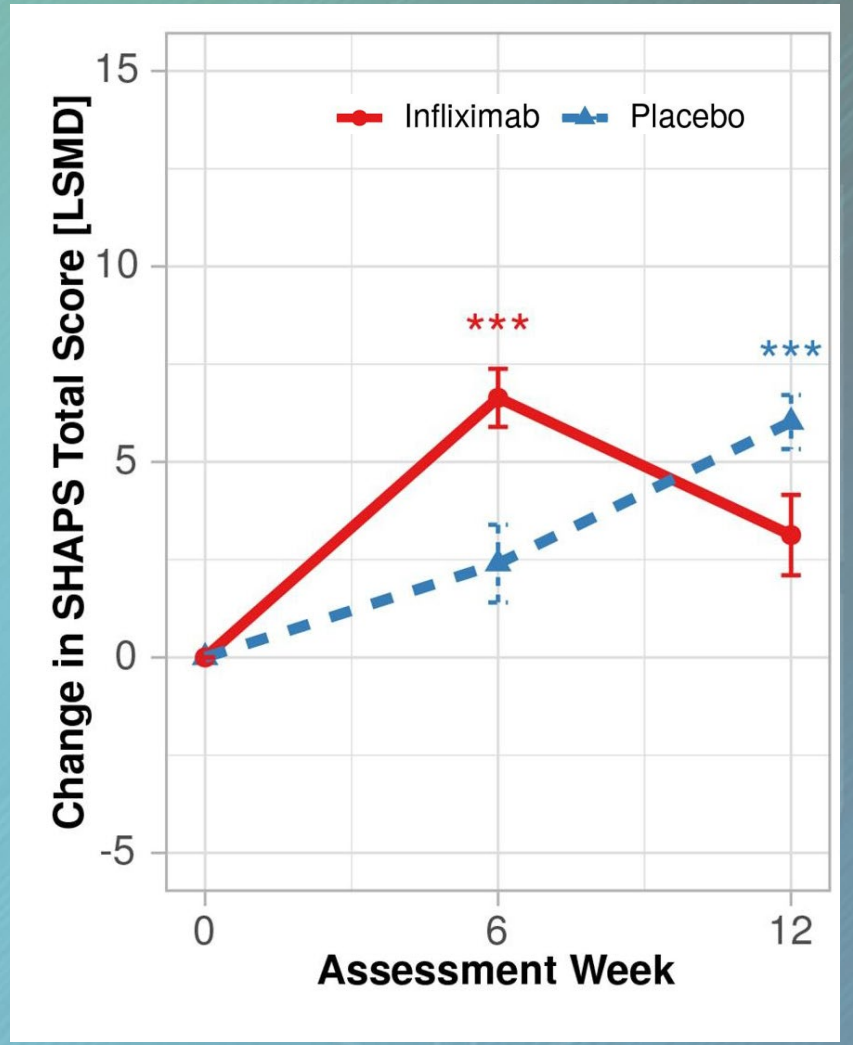


*P <.001 relative to placebo

Willner P et al. J Affect Disord 2005;86(1):37-45; Willner P et al. Neurosci Biobehav Rev 2013;37(10 Pt 1):2331-71.

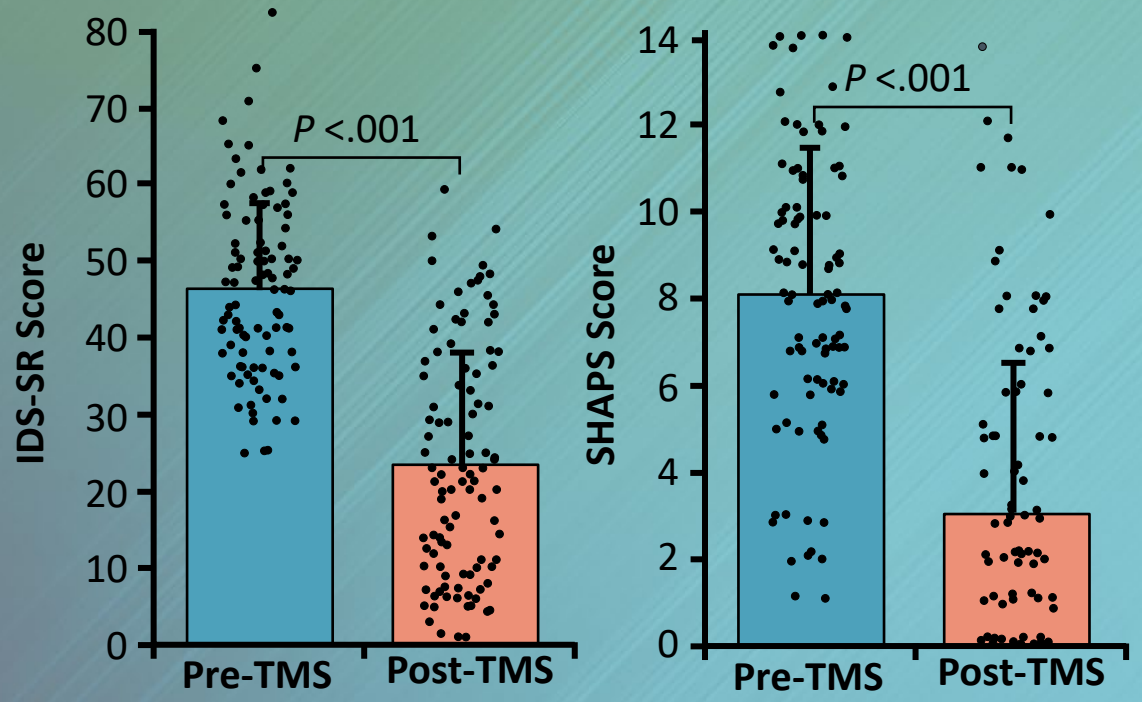
Adjunctive Infliximab in the Treatment of Anhedonia in Bipolar Depression

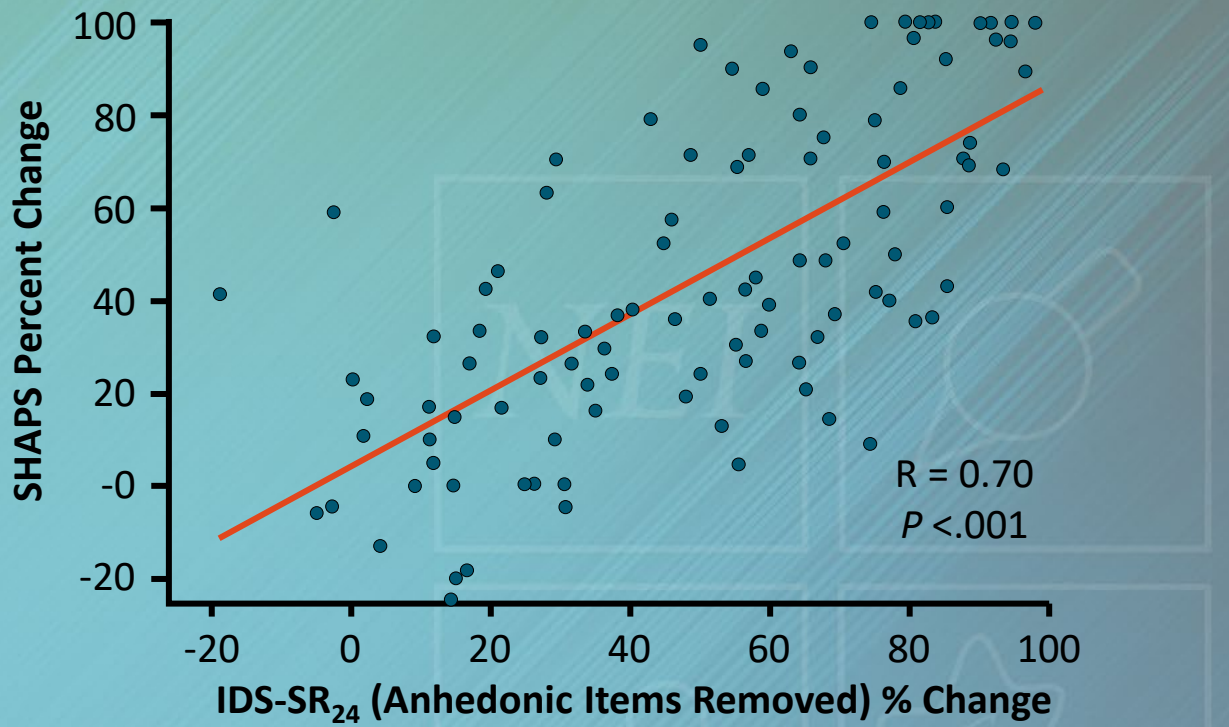
- Tumor necrosis factor alpha **(TNF-α) antagonist**
- Patients **aged 18–65 yo with bipolar I or II depression** (n=47)
  - Currently experiencing depressive episode
  - With higher probability of inflammatory activity
    - Obesity and dyslipidemia/hypertension, daily cig smoking, diabetes, migraine, IBS, and/or C-reactive protein level ≥5 mg/L
- **12-wk trial of 5mg/kg infliximab (n=21) or saline (n=26)**
- **Infliximab-treated patients had greater reductions in anhedonic symptoms (Snaith-Hamilton Pleasure Scale; SHAPS) at 6 weeks**
  - Moderated by baseline TNF-α and soluble TNF receptor (sTNFR1) levels
  - Improvements not sustained 6 weeks after final infusion



Lee Y et al. Brain Beh Immun 2020;88:631-9.

rTMS Benefits Anhedonia in Patients With MDD





Improvement in anhedonia is strongly correlated with improvement in other depressive symptoms (r = .55, *P* <.001)

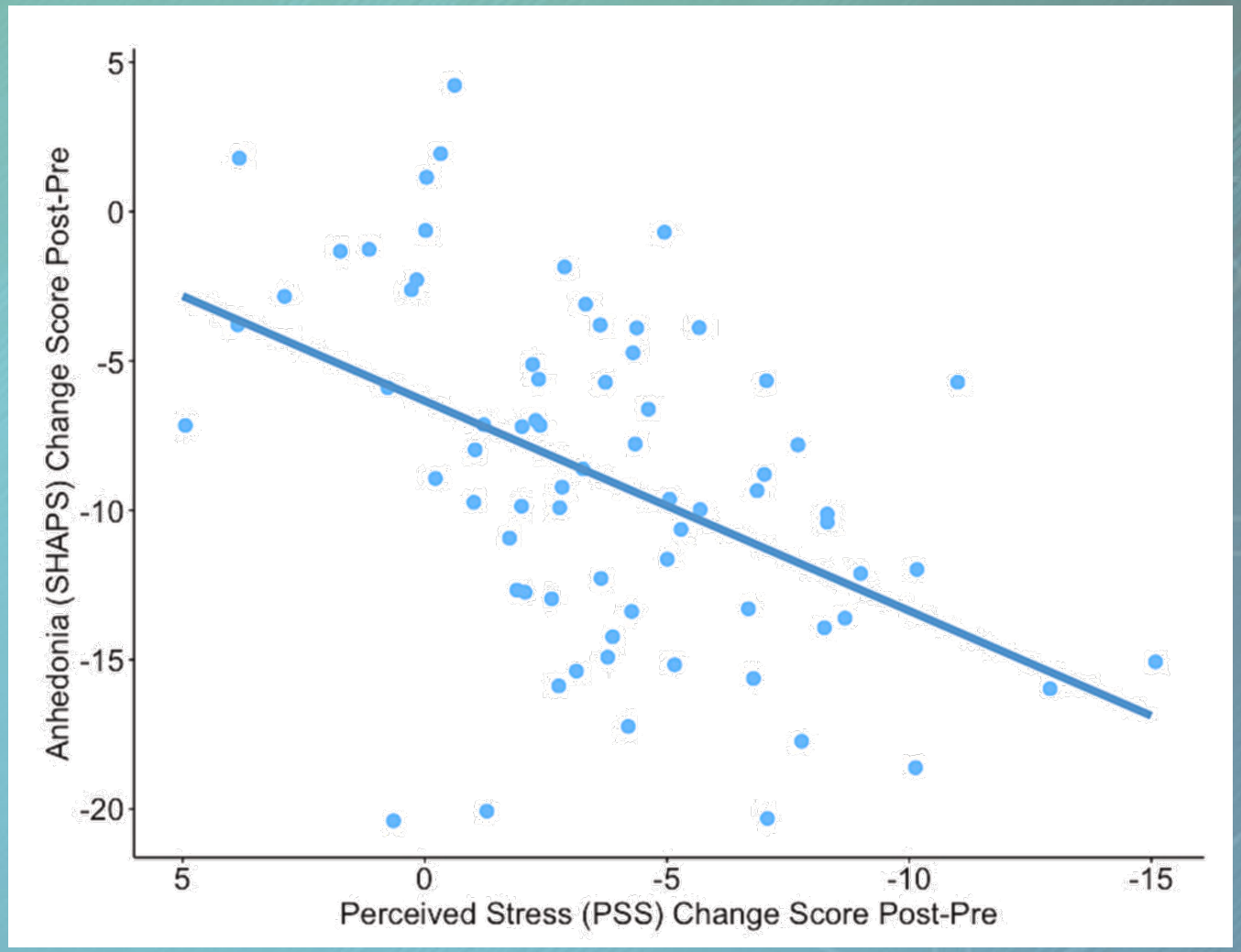
There was a significant improvement in depressive symptoms measured by IDS-SR scores from pre-TMS (46.36 ± 11.19) to post-TMS (25.40 ± 16.00), (*P* <.001, Cohen's *d* = 1.49) and a significant improvement in anhedonia symptoms reflected in a decrease in SHAPS scores from pre-TMS (8.10 ± 3.46) to post-TMS (3.06 ± 3.49), (*P* < .001, Cohen's *d* = 1.45). N = 144 patients with MDD who have failed at least 1 adequate antidepressant trial.

Fukuda AM et al. Brain Behav 2021;11(9):e2329.

Stress and anhedonia, two sides of the same coin? Psychotherapy works for both!

15-week clinical trial examining the effects of Behavioral Activation Treatment for Anhedonia **(BATA), a novel psychotherapy to treat anhedonia, compared to a Mindfulness-Based Cognitive Therapy (MBCT)** comparison intervention.

Treatment completers (n = 72) experienced significant reductions in anhedonia (M = − 8.94, SD = 5.66) on the Snaith-Hamilton Pleasure Scale (t(71) = 13.39, p < .0001), and **significant reductions in perceived stress** (M = − 3.71, SD = 3.88) on the Perceived Stress Scale (t(71) = 8.11, p < .0001)



Phillips R et al. J Affect Disord 2023;330:206-13.

Important Clinical Issues Regarding the Treatment of Anhedonia and Emotional Blunting in MDD

- **Are all emotions, positive and negative, similarly attenuated** or are only positive emotions diminished?
- **If positive emotions are diminished while negative are accentuated**, our patient is likely experiencing **anhedonia**
- Anhedonia is **associated with lower treatment response, functional impairment, and suicide risk**
  - Consider **optimizing current treatment, adding CBT, adjunctive treatment, or switch to an agent with greater efficacy** for anhedonia symptoms
- **If both positive and negative emotions are blunted**, we are possibly dealing with **treatment-related emotional blunting**
  - Consider an **agent that has lower risk of emotional blunting**
  - **Pursue treatment to remission**

Pharmacologic and Nonpharmacologic Interventions That May Benefit MDD Patients With Anhedonia

- Agents that increase DA/NE transmission
- Agents that block 5-HT_{2C} and 5-HT_3 receptors (indirectly increasing DA and glutamate transmission in salience network areas?)
- NMDA antagonists (decreasing burst signaling from lateral habenula)
- D_2/D_3 partial agonists
- Kappa opioid receptor antagonists
- Neuromodulation: rTMS
- Nonpharmacologic interventions: CBT; exercise

Summary

- Anhedonia is distinguishable from apathy and emotional blunting, which are often exacerbated with antidepressant use
- Anhedonia is a transdiagnostic phenomenon that is a common manifestation of neuropsychiatric disorders
- The presence of anhedonia is associated with worse outcomes in patients with depression—including more severe and longer depressive episodes as well as suicidality
- Evolving research is elucidating the role of aberrant neurocircuitry and neurotransmitter systems in apathy and anhedonia
- A variety of pharmacological and non-pharmacological agents have shown efficacy in reducing anhedonia

Posttest Question 1 of 3

What is the difference between anhedonia and apathy?

1. Anhedonia does not involve loss of interest in previously enjoyable activities
2. Apathy is defined as diminished sensitivity and responsiveness to a broad range of emotions
3. Anhedonia involves a reduction in positive emotions/pleasure
4. The primary feature of both anhedonia and apathy is the inability to laugh or cry in fitting circumstances

Posttest Question 2 of 3

Which of the following is associated with the highest risk of suicidality?

1. Anticipatory anhedonia
2. Consummatory anhedonia
3. Anticipatory and consummatory anhedonia are equally associated with suicidality

Posttest Question 3 of 3

Which of the following treatments have shown efficacy in reducing anhedonia?

1. Dopamine D2/D3 partial agonists
2. 5HT1A antagonists
3. NMDA agonists
4. Repetitive transcranial magnetic stimulation (rTMS)
5. 1 and 2 only
6. 1 and 4 only
7. All of the above