BRAI3N

UNIVERSITY of OTAGO

SAPERE AUDE

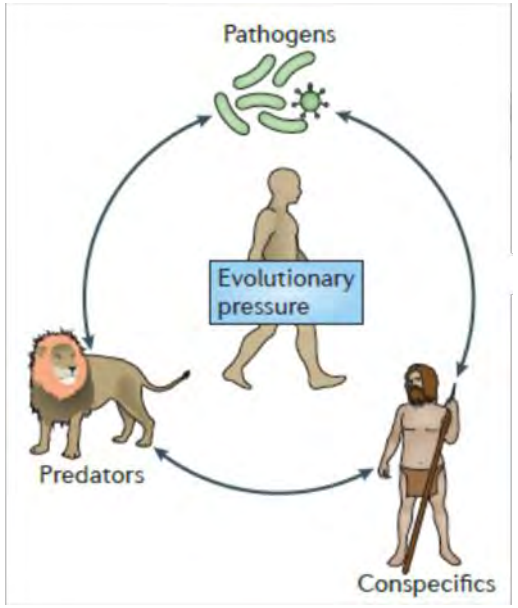
Te Whare Wānanga o Otāgo

PTSD

Dirk De Ridder

Brain Research consortium for Advanced International, Innovative & Interdisciplinary Neuromodulation

Self in the environment

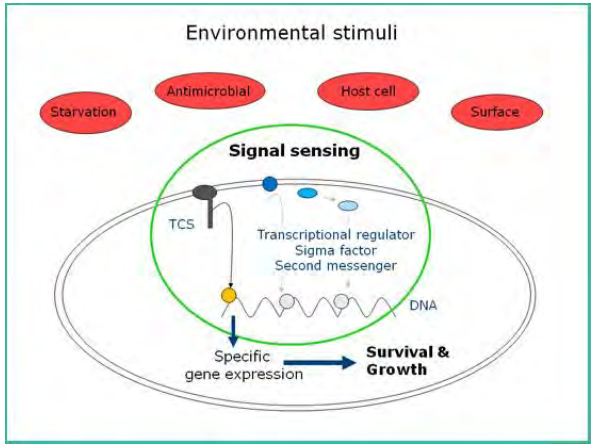


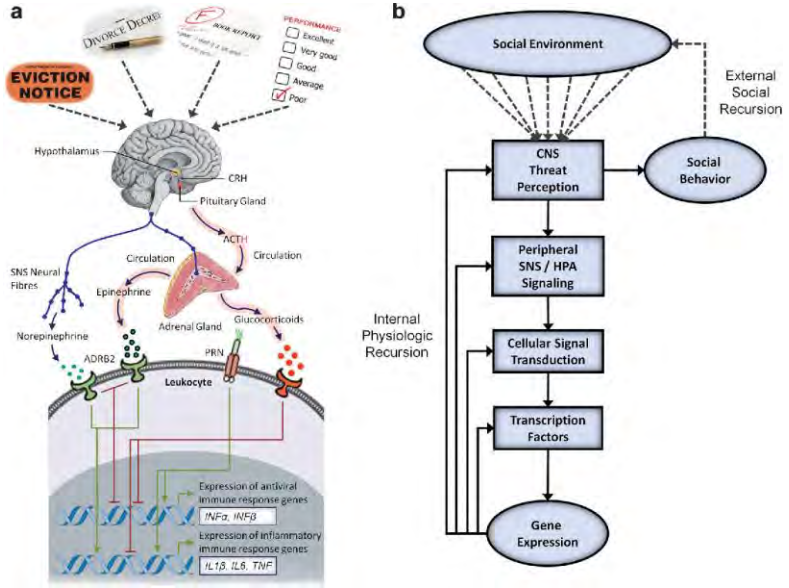
Two ways for body to communicate with outside world

Genetic response to environment

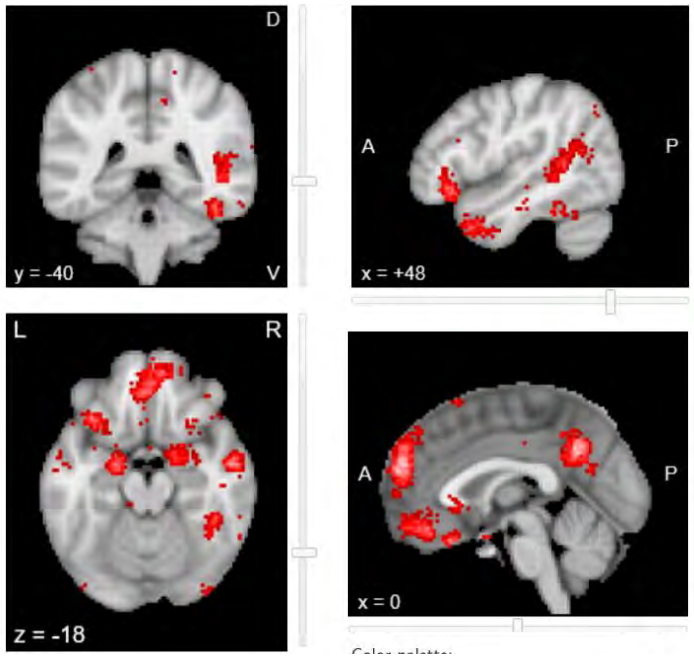
Bacteria respond to environment by activating or suppressing genes (Jacok & Monod 1961)

Humans respond to social stimuli by activating or suppressing genes (=sociogenomics) (Robinson 2005, Cole 2007)

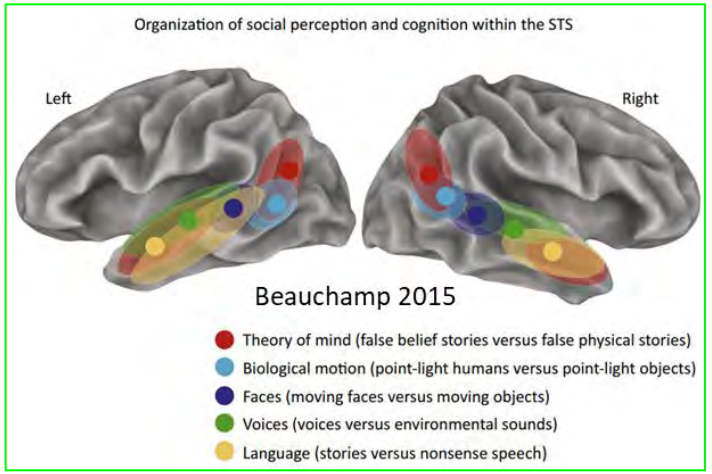


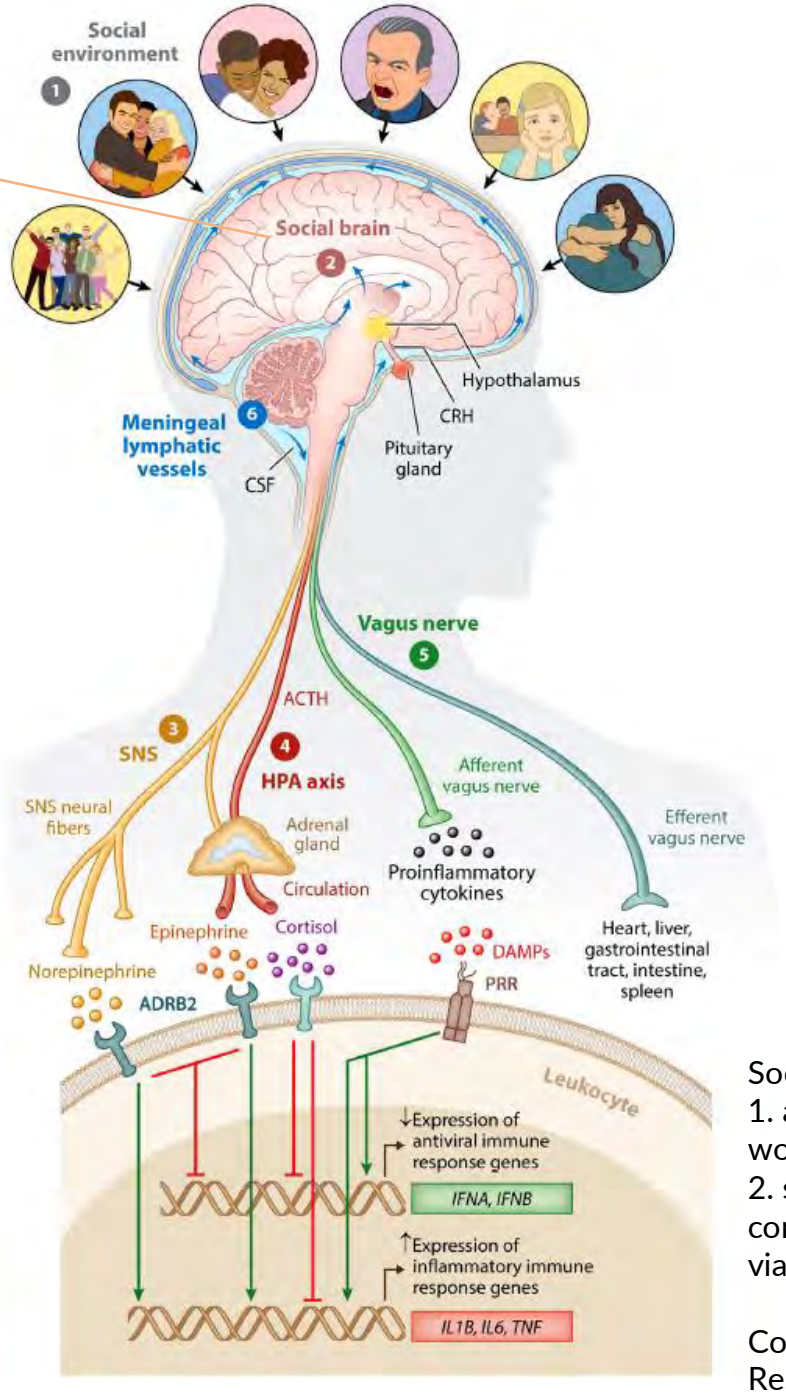


Social brain network (n=1000 studies)



Amygdala, sgACC, OFC= emotional network
+ DMN + VLPFC = Theory of mind
+ STS (social cortex)





Social threat (risk of tissue damage)
1. activates pro-inflammatory genes to heal wounds and antibacterial
2. suppresses default antiviral genes (social contact increases risk for viral infections) via adrenaline receptors

Conserved Transcriptional Response to Adversity (CTRA) Slavich 2023

Predictable changes in environment and clock genes

Predictable changes

Day-night, tides/moon, seasons

~50% of mammalian genes are expressed with 24-hour rhythms (Zhang 2014, Mure 2018)

Reason: time energy expenditure wisely (Straub 2010)

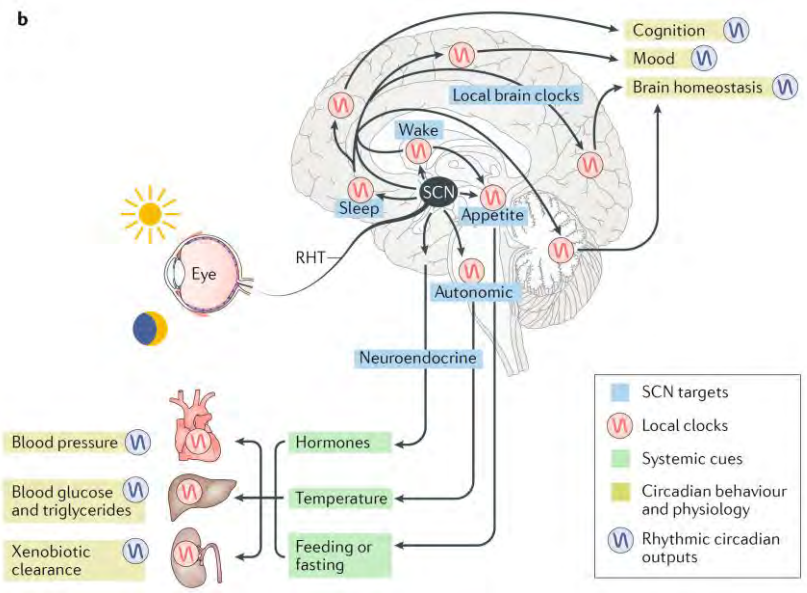
Brain consumes 25% of total energy

Immune system 20%

Heart and lungs 25%

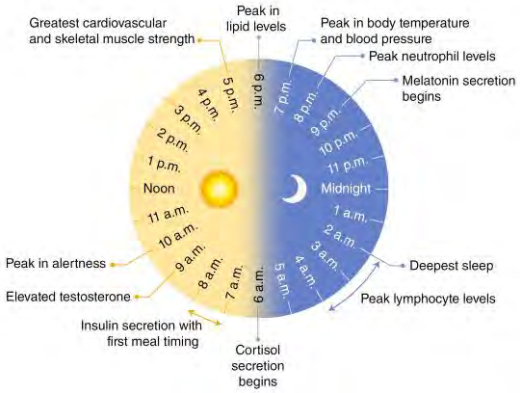
Internal organs 30%

+ Muscles: extra 20%

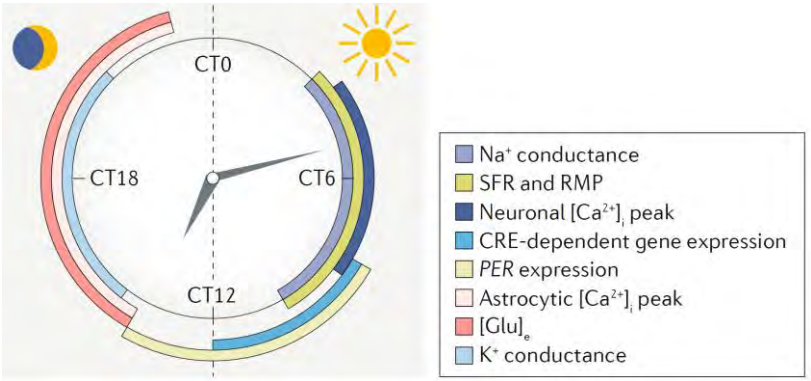


During day nervous system and metabolism are active, at night immune system, repair and growth (Masri 2018, Hastings 2018, Li 2022)

Insomnia= 63% in PTSD (Ahmadi 2022 meta-analysis)



Masri 2018



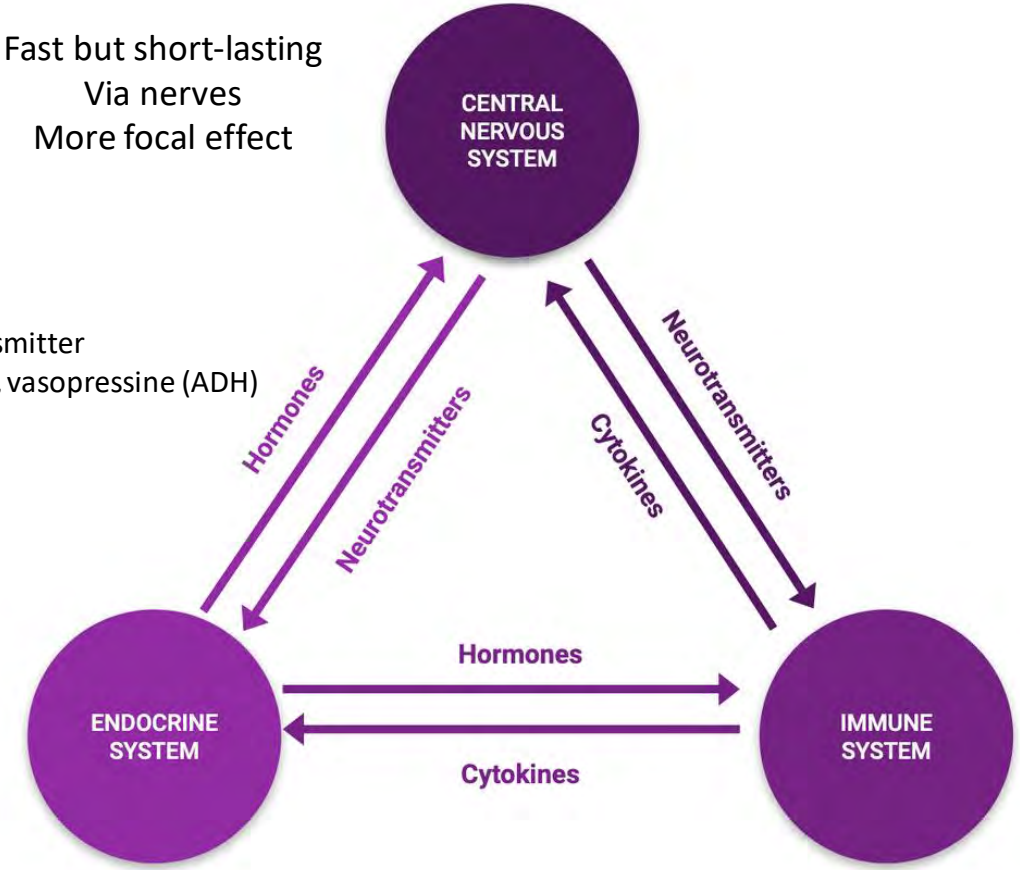
Hastings 2018

Signal molecules

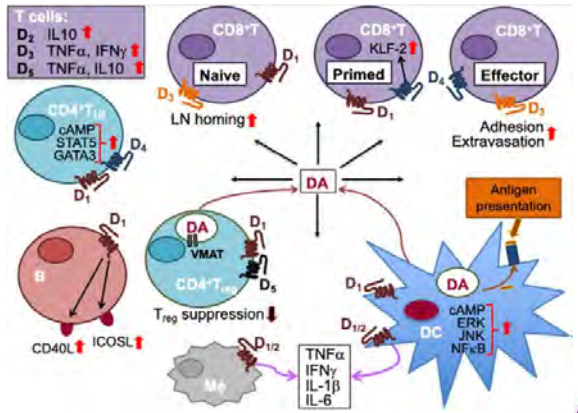
Fast but short-lasting
Via nerves
More focal effect

Some are both hormone and neurotransmitter
Eg noradrenaline, adrenaline, oxytocine, vasopressine (ADH)

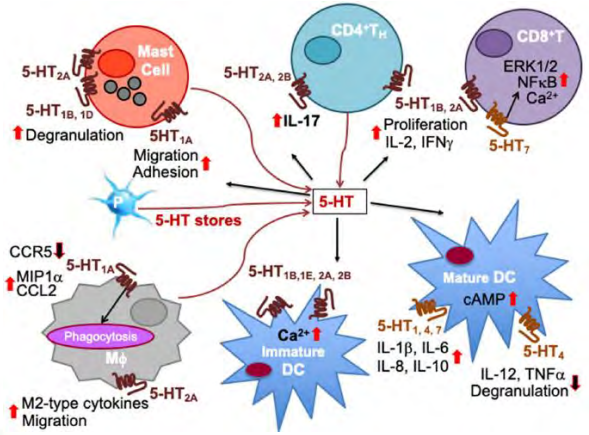
Slow but long-lasting
Via blood
'action at a distance'
More general effect



Cytokines = Lymphokines + IL
+ chemokines + interferons + TNFα

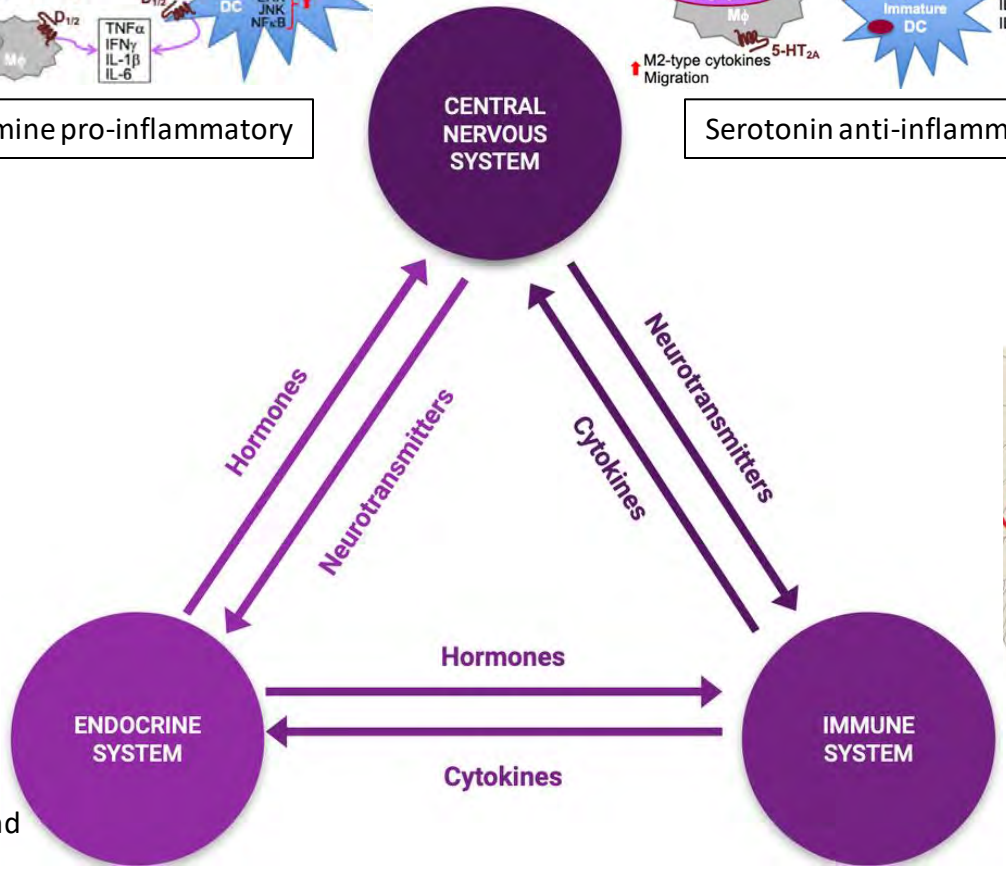


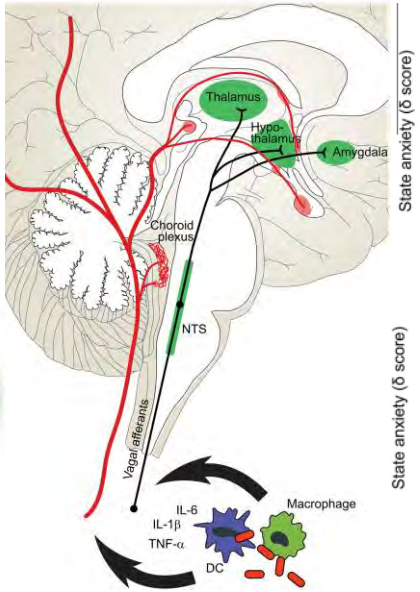
Dopamine pro-inflammatory

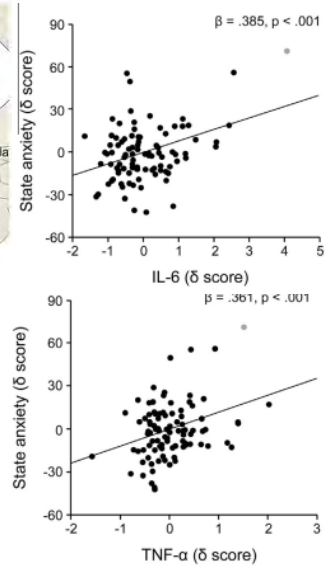


Serotonin anti-inflammatory

Hodo 2020





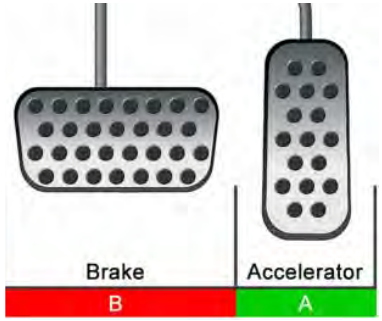


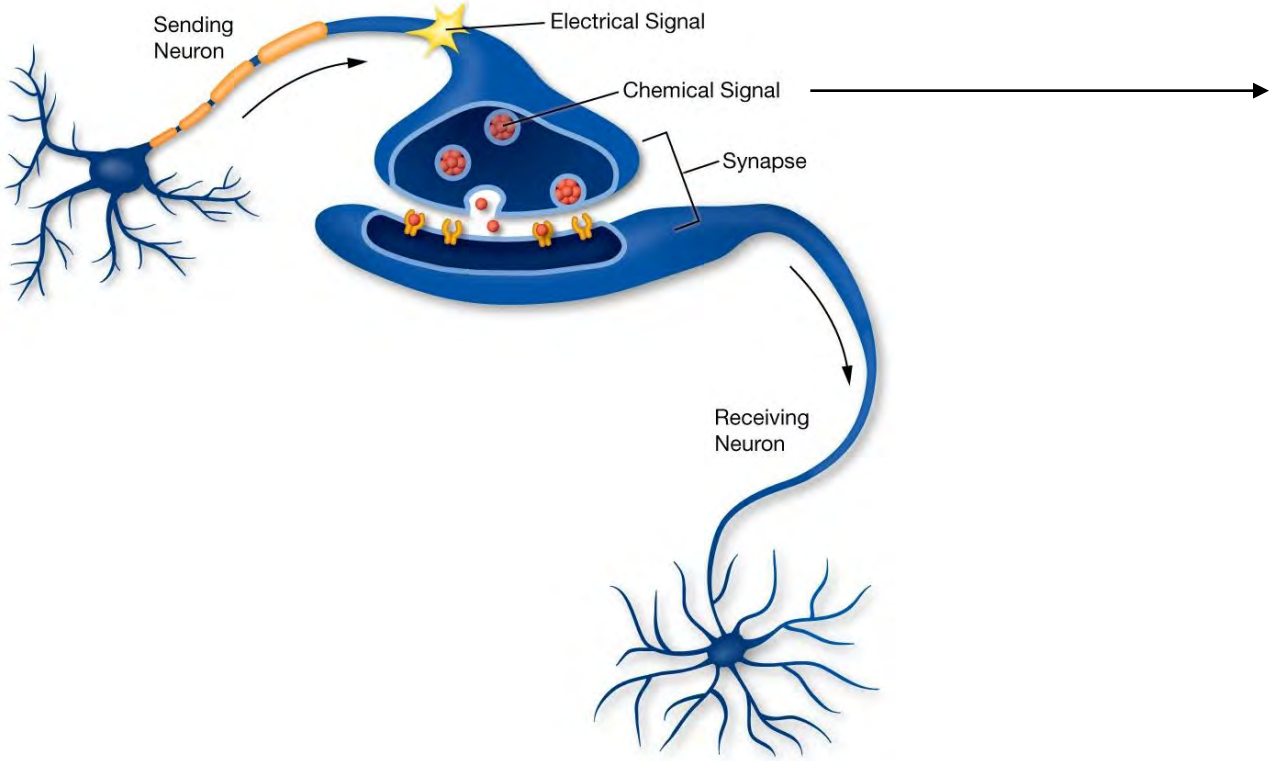
Lasselin 2016

Cortisol is anti-inflammatory
Testosterone is anti-inflammatory (Bianchi 2019) and increases libido in men and women
Estrogen is anti-inflammatory (Vegeto 2008)
Thyroid hormone and glucagon are anti-inflammatory (Garcia-Leme 1993)

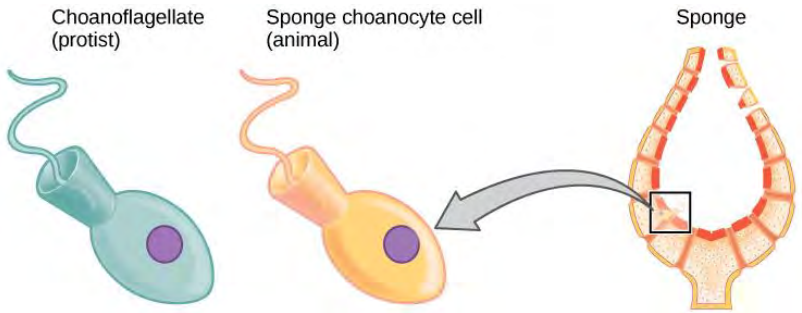
Cytokines induce sickness behaviour (sleep, fatigue, anxiety, social and sexual withdrawal,…)
Saves energy and prevents transmission (Shakhar 2015)

Brains are electrical and chemical



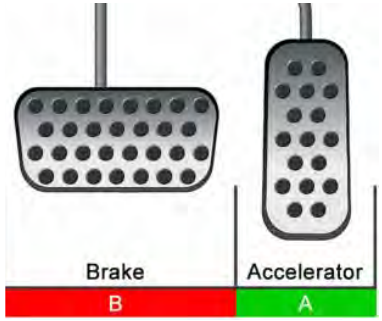


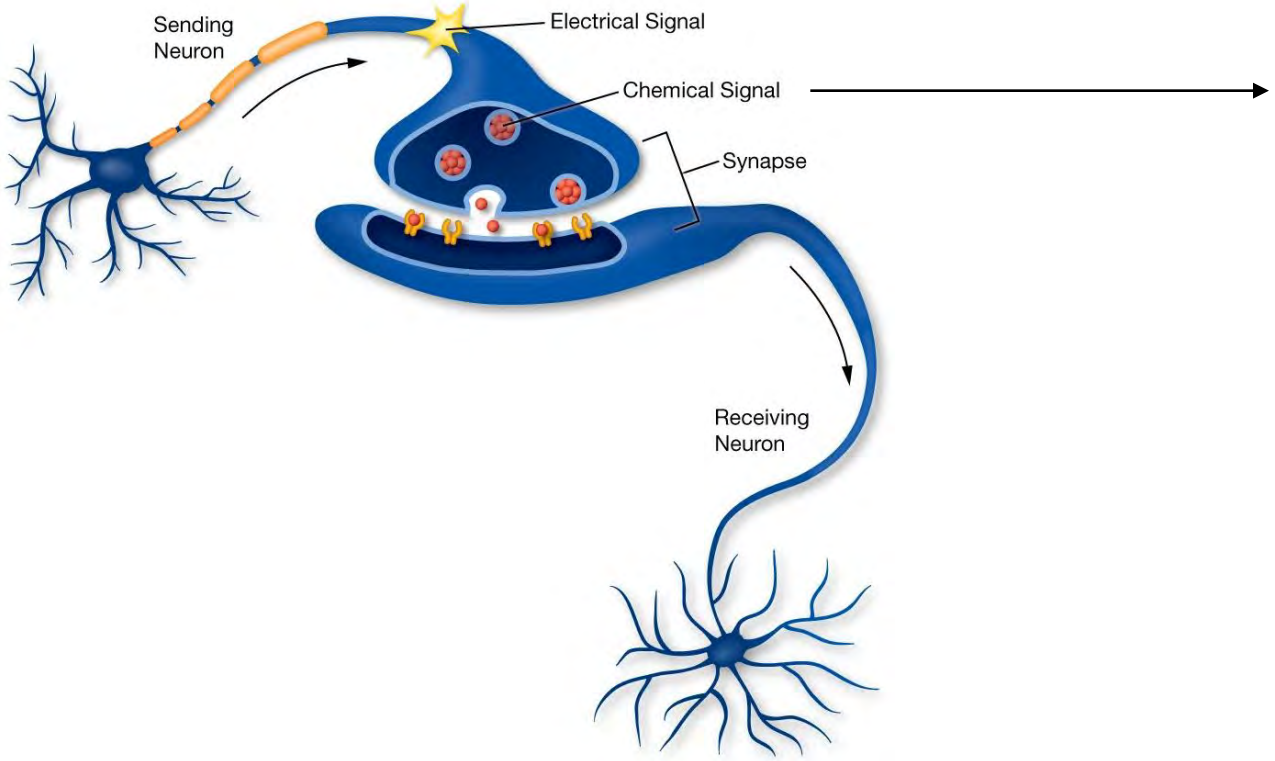
GABA/glycine ⟷ Glutamate

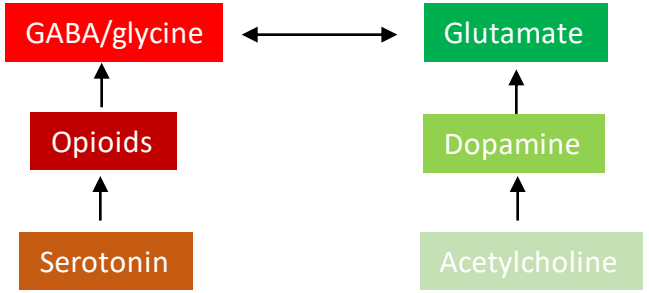


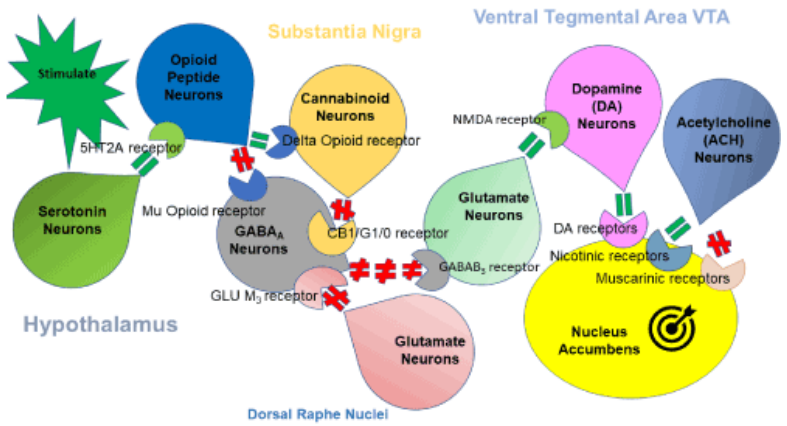
Choanoflagellates use glutamate and GABA as signal molecules
Same signal molecules later repurposed as neurotransmitters

Brains are electrical and chemical

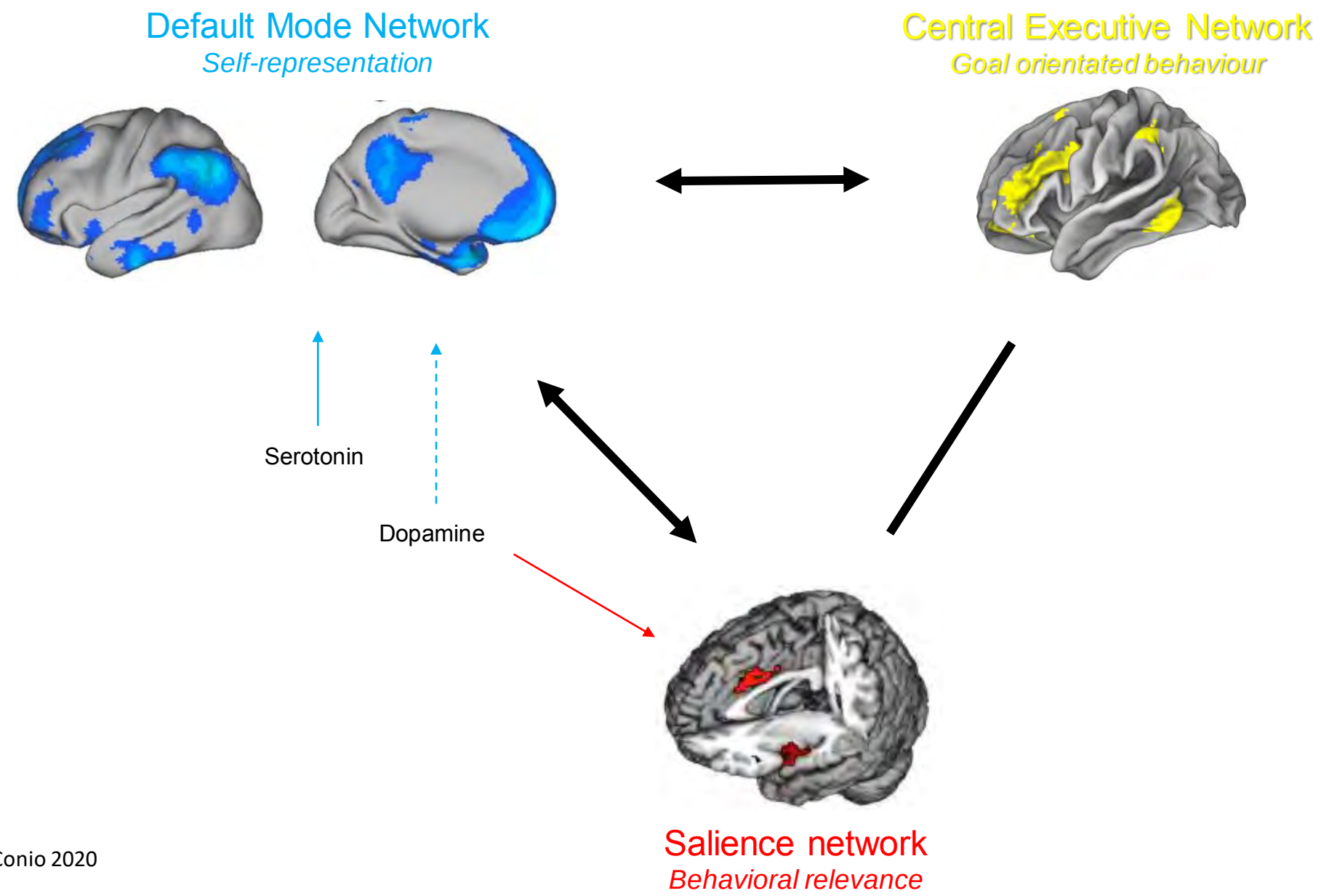




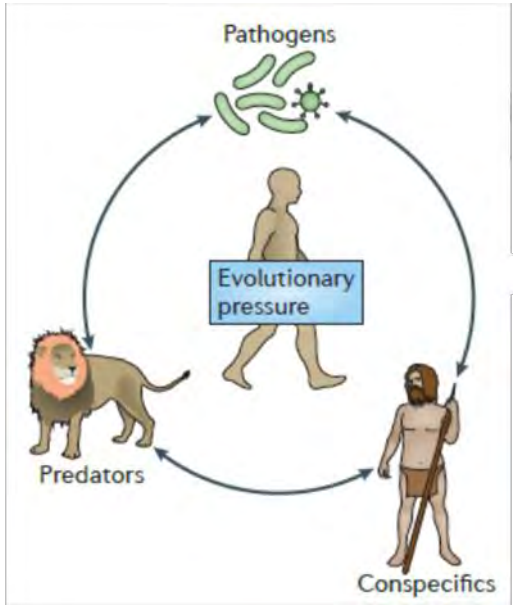




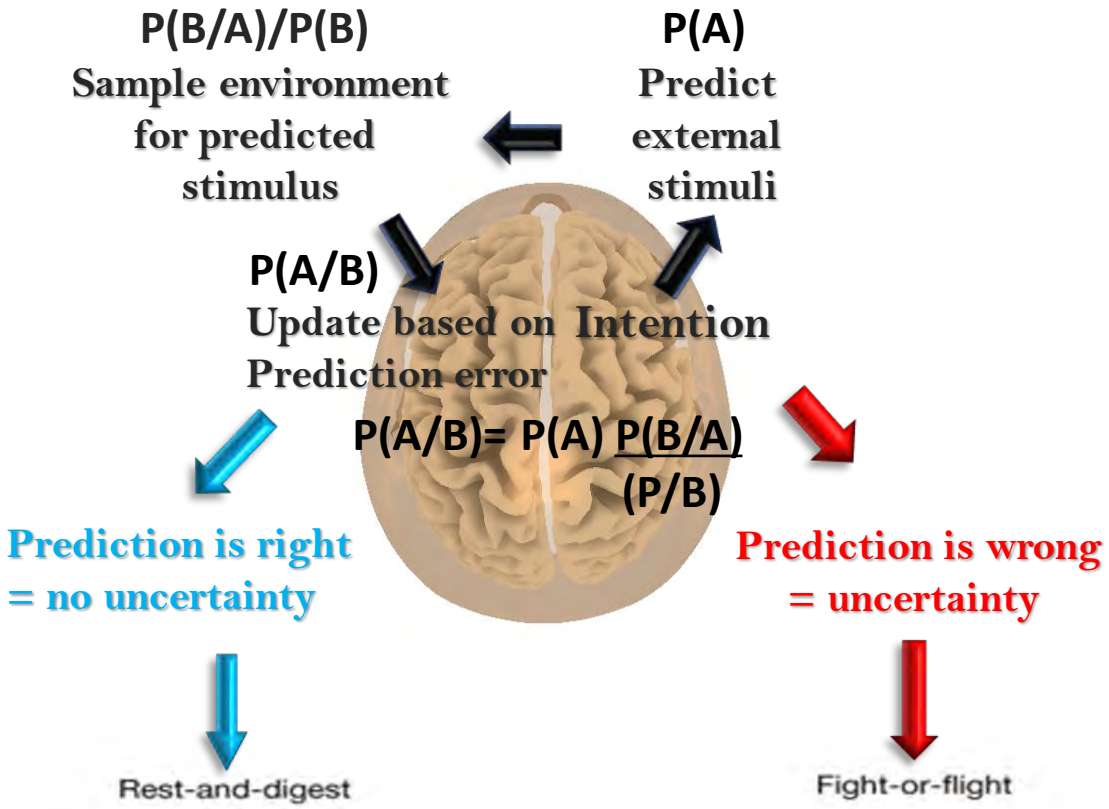
Blum 2020


Default Mode Network
Self-representation
Central Executive Network
Goal orientated behaviour
Serotonin
Dopamine
Salience network
Behavioral relevance

Conio 2020

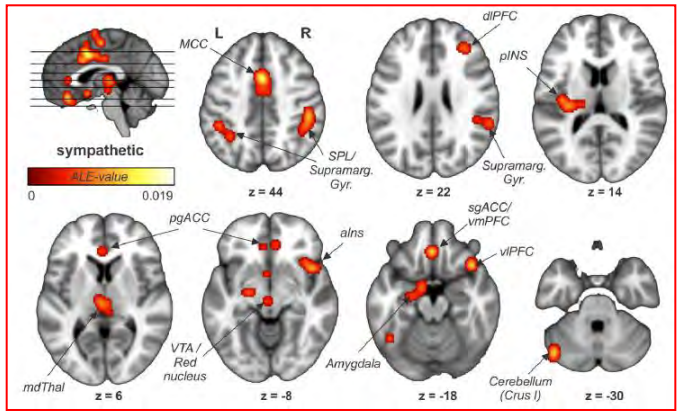


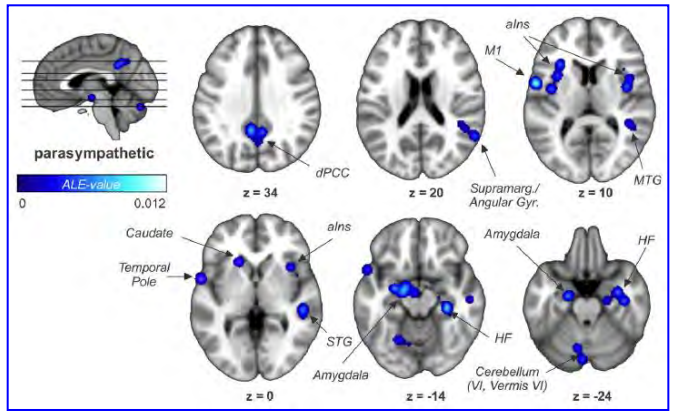
Brain networks for interaction of self with environment



$$P(A/B) = P(A)\,\frac{P(B/A)}{(P/B)}$$

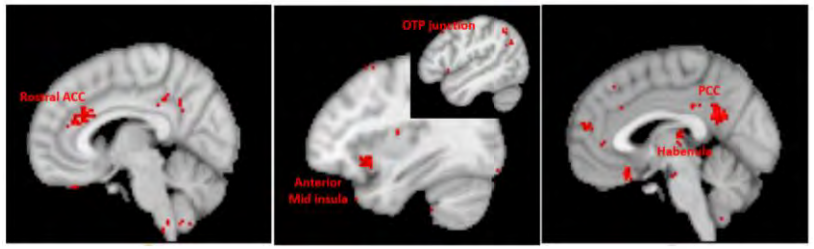
Evolution of ANS

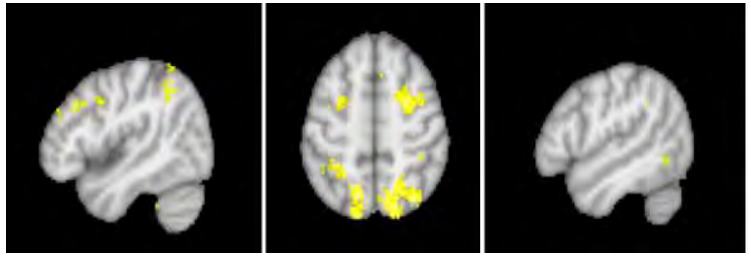


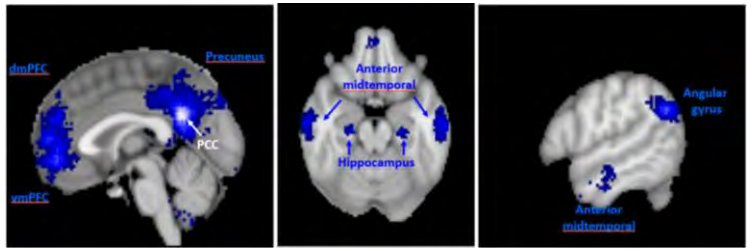


Salience + Central executive

Default mode





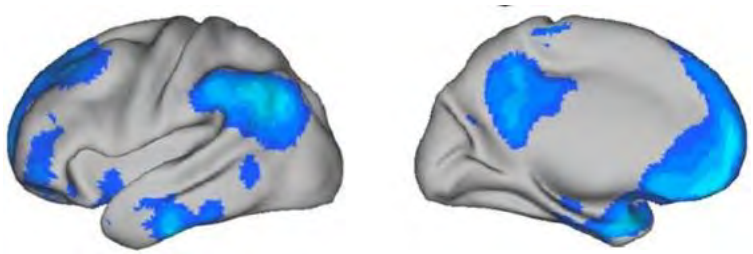


Self

Environment

Default Mode Network

Self-representation

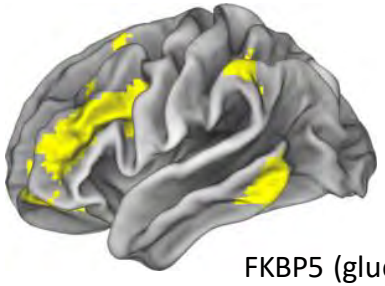


FKBP5 (glucocorticoid regulator) (Zhang 2020)
APOE-ε4 (Foo 2020)
BDNF (Schweiger 2019, Thomason 2009)
COMT (Dang 2013)
HTR2A, HTR1B (Miller 2016)
HTR1A (Zheng 2017)

FKBP5 (Zhang 2020)
BDNF (Thomason 2009)

Central Executive Network

Goal orientated behaviour



FKBP5 (glucocorticoid regulator) (Bryant 2016)

OXTR (Wang 2016)
BDNF (Thomason 2009)
COMT (Meyer 2016)

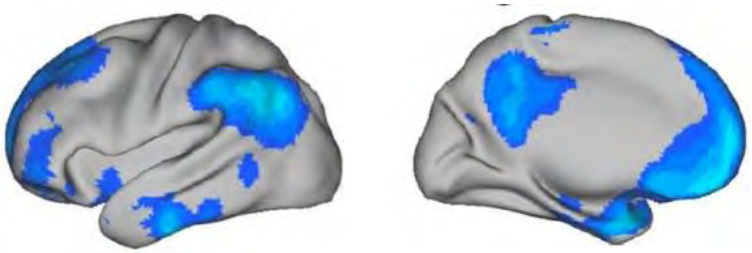
HTR1A (Zheng 2017)

Salience network

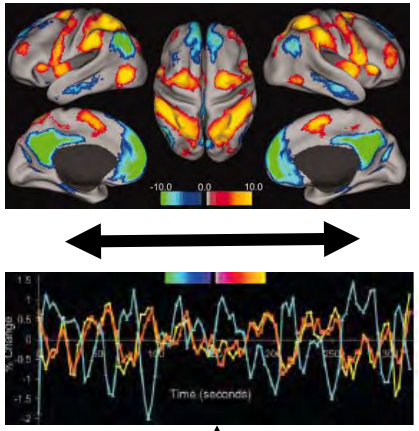
Behavioral relevance

Default Mode Network

Self-representation

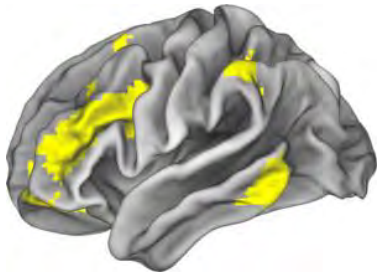


Fox 2005



Central Executive Network

Goal orientated interaction with environment



Rest, digest, restore

parasympathetic

Urge for action

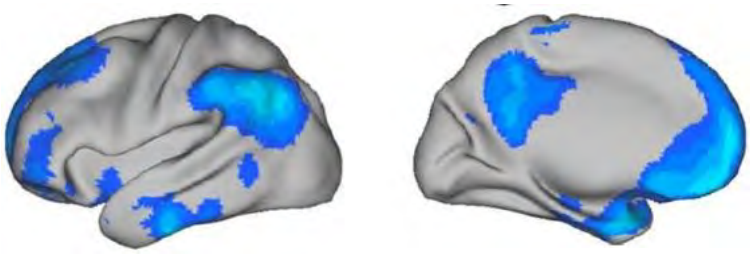
sympathetic

Salience network

Behavioral relevance

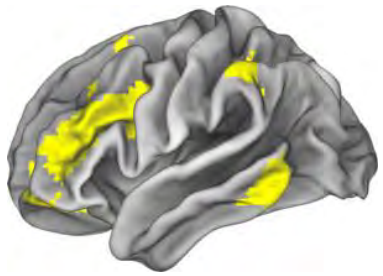
Default Mode Network

Self-representation



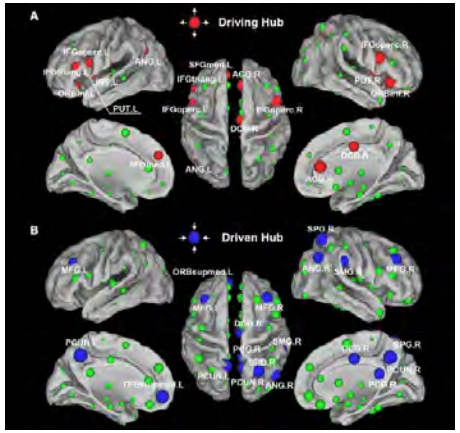
Central Executive Network

Goal orientated behaviour



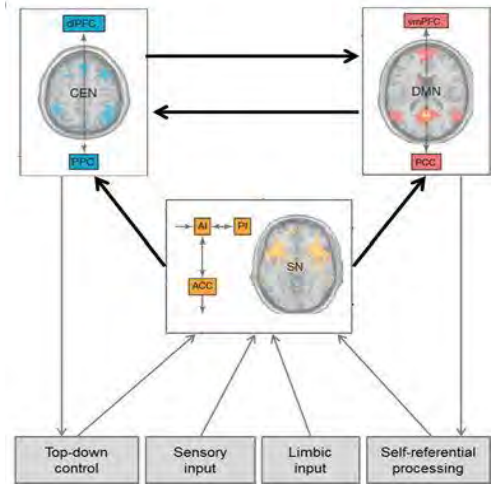
Salience network drives DMN

Yan 2011



Salience network switches between DMN and CEN

Menon 2010



Salience network

Behavioral relevance

Networks and network interactions change

Adaptive and maladaptive

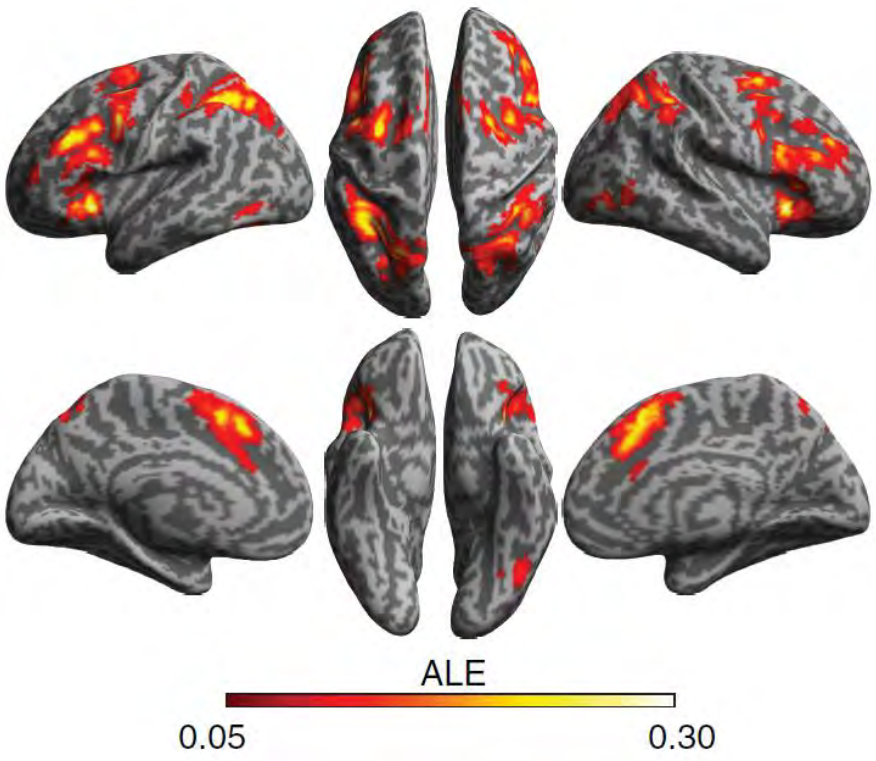
Stress & uncertainty

Stress & uncertainty

Stress = individual state of uncertainty about what needs to be done to safeguard physical, mental or social well-being (Peters 2017)

Uncertainty = state in which a given representation of the world cannot be adopted as a guide to subsequent behavior, cognition, or emotional processing (Harris 2008)

Uncertainty is processed by combined activity of CEN and SN (meta-analysis Wu 2020)



Wu 2020

Stress = uncertainty

Acute stress (adaptive)

Activity: increased in SN

Connectivity: Δ

Chronic stress (maladaptive)

Activity

Connectivity

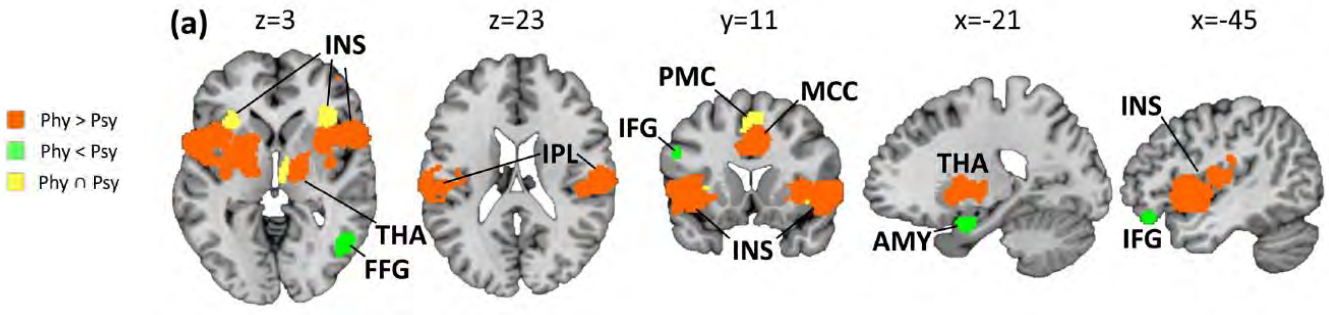
Inflammatory

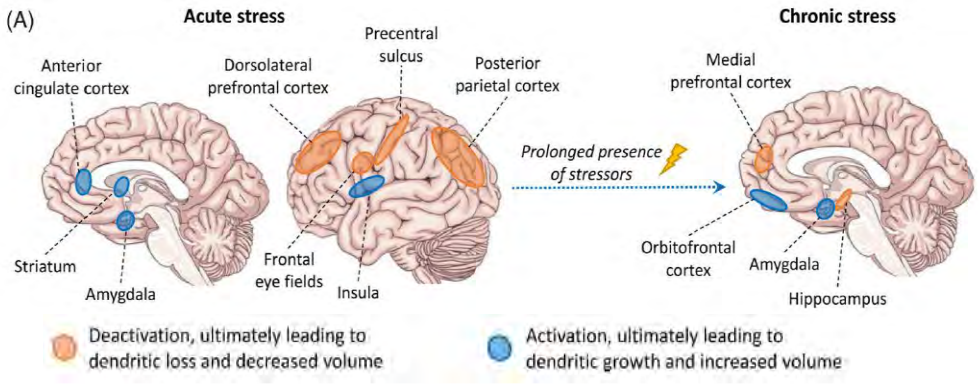
Exhaustion = mental disorder

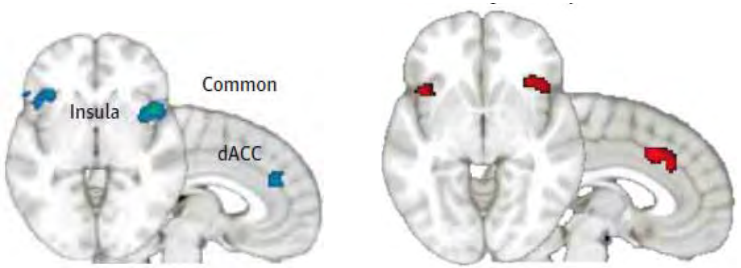
Activity

Connectivity

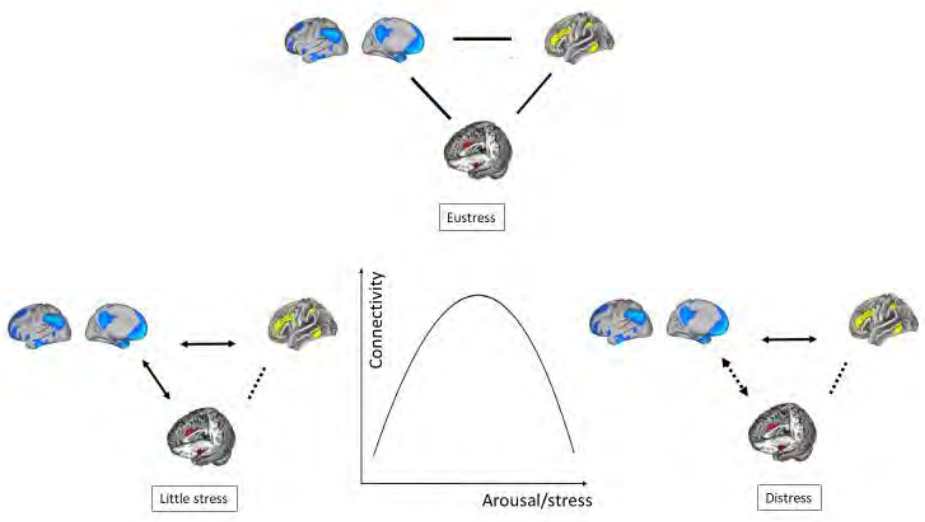
Atrophy







Stress = uncertainty



Acute stress (adaptive)

Activity: increased in SN

Connectivity: Δ

Chronic stress (maladaptive)

Activity

Connectivity

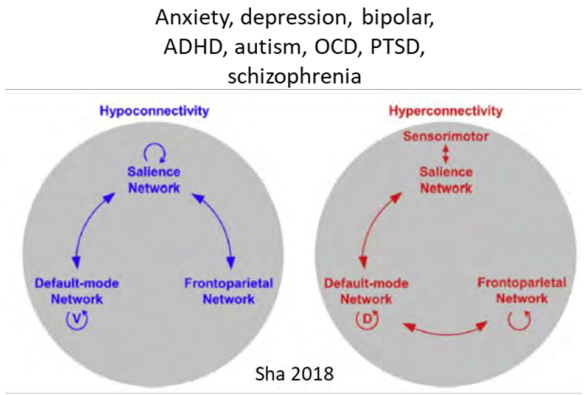
Inflammatory

Exhaustion = mental disorder

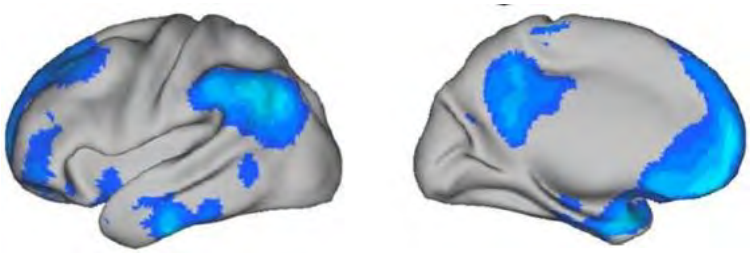
Activity

Connectivity

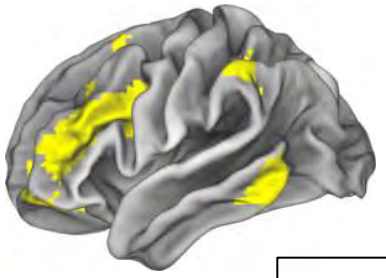
Atrophy



Default Mode Network
Self-representation



Central Executive Network
Goal orientated behaviour

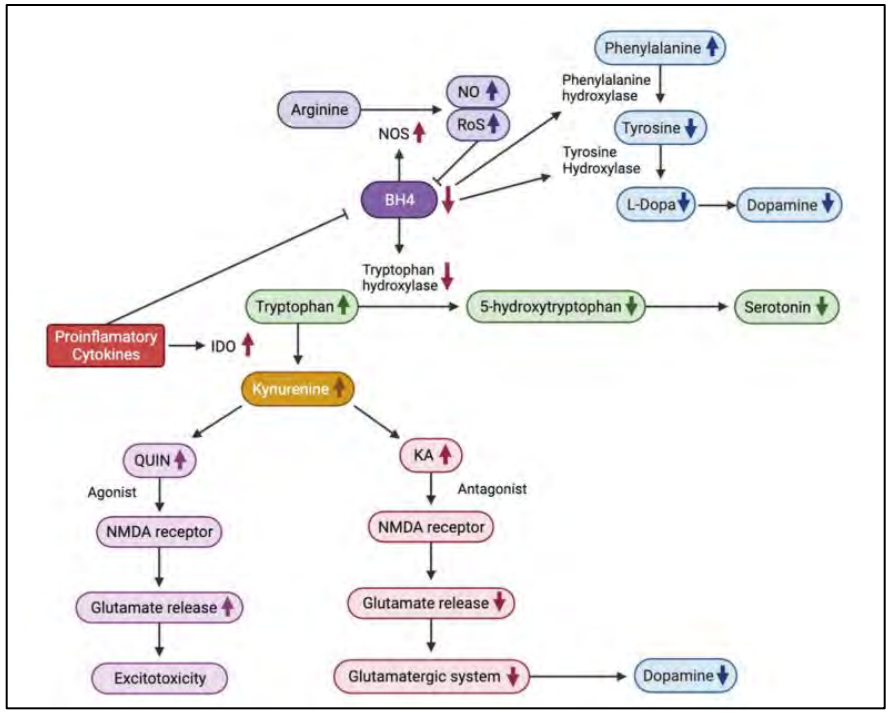


Serotonin

Dopamine

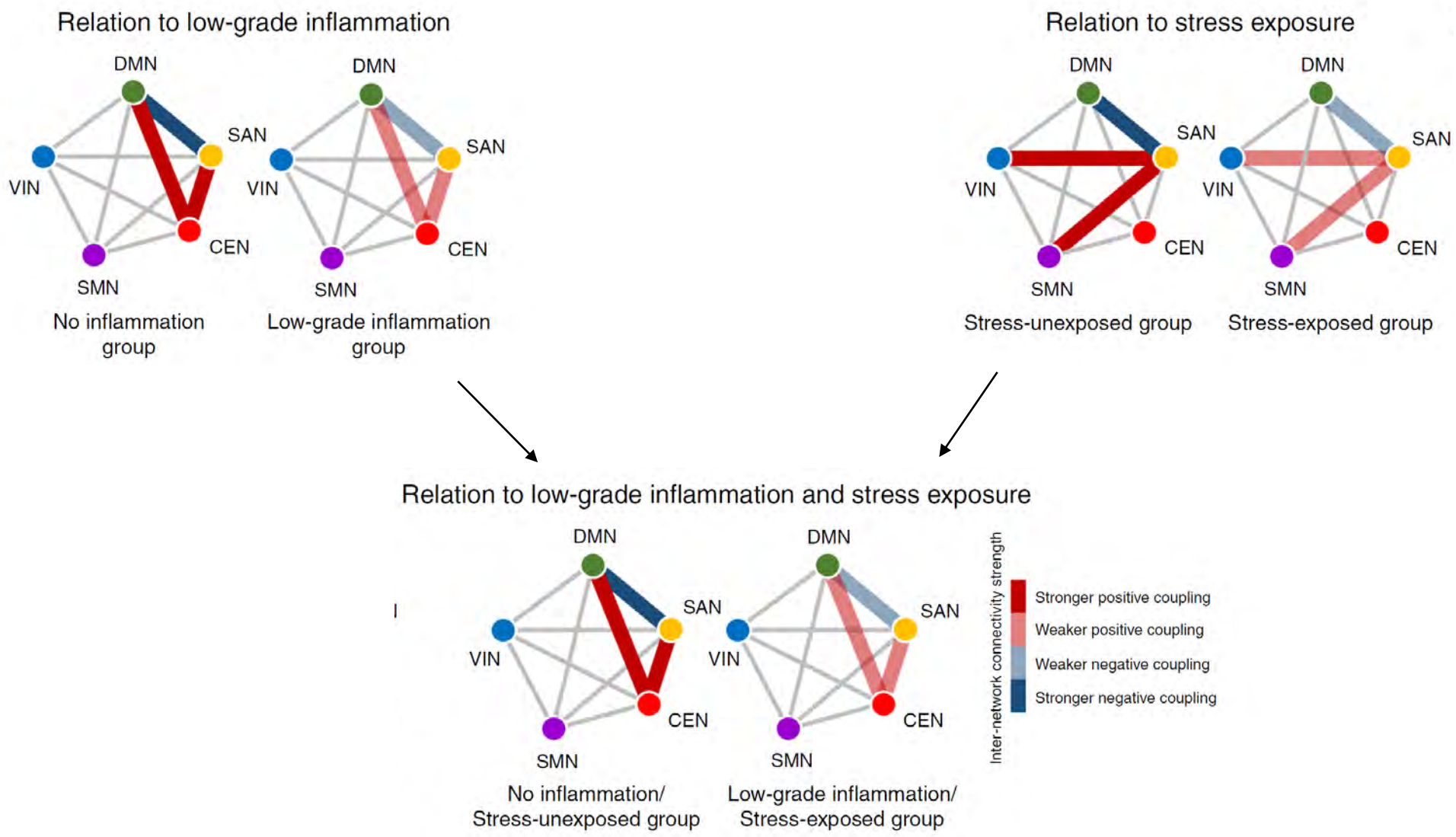
Salience network
Behavioral relevance

Neuroinflammation changes serotonin and dopamine (Katrinli 2022)



Conio 2020

Stress and neuroinflammation



Kim 2020

Genetic factors
- Immune response
  Cytokines
- Nervous system
  Neurotransmitters
  Growth factors

*

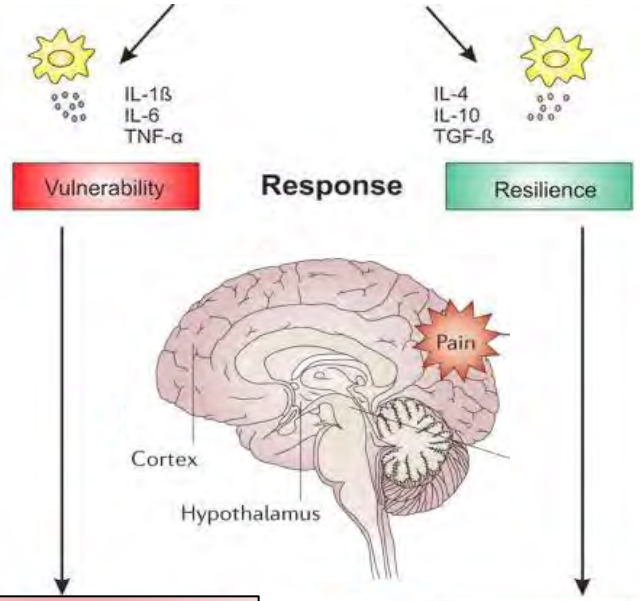
Microbiome

#

Environmental factors
- Psychological stress
- Physical stress
- Trauma
- Childhood adversity
- Toxins, medication, diet

Epigenetics
Regulates gene expression

Neuroinflammation



Fear	→	Anxiety
Sadness	→	Depression
Stress	→	PTSD
Pain	→	Chronic pain
Tinnitus	→	Chronic tinnitus
…		

Outcome

Mental health

*Martins-Silva 2020, # Watson 2017

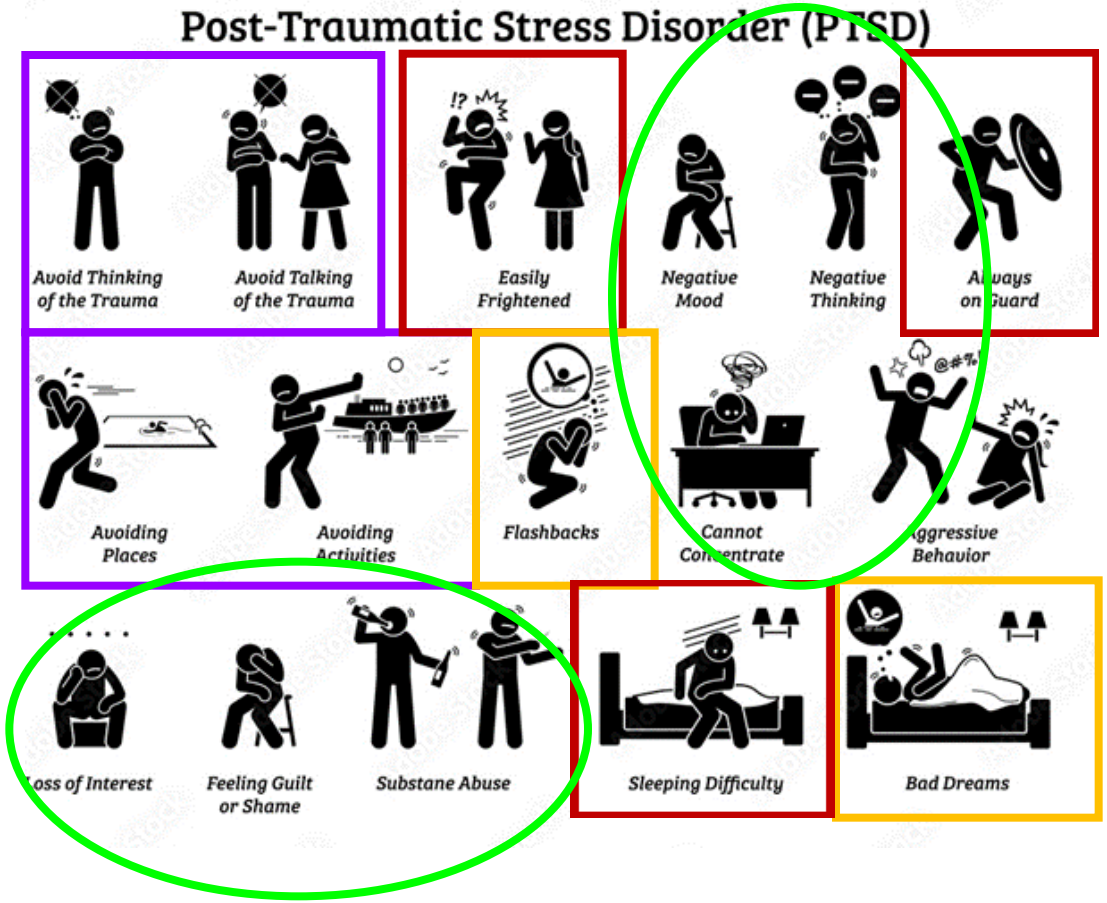
PTSD

What is PTSD?

Core symptoms of PTSD

1. Reliving (flashbacks, nightmares,...)
2. Avoidance of traumatic reminders
3. Sense of current threat (hyperarousal, sleep problems, ...)

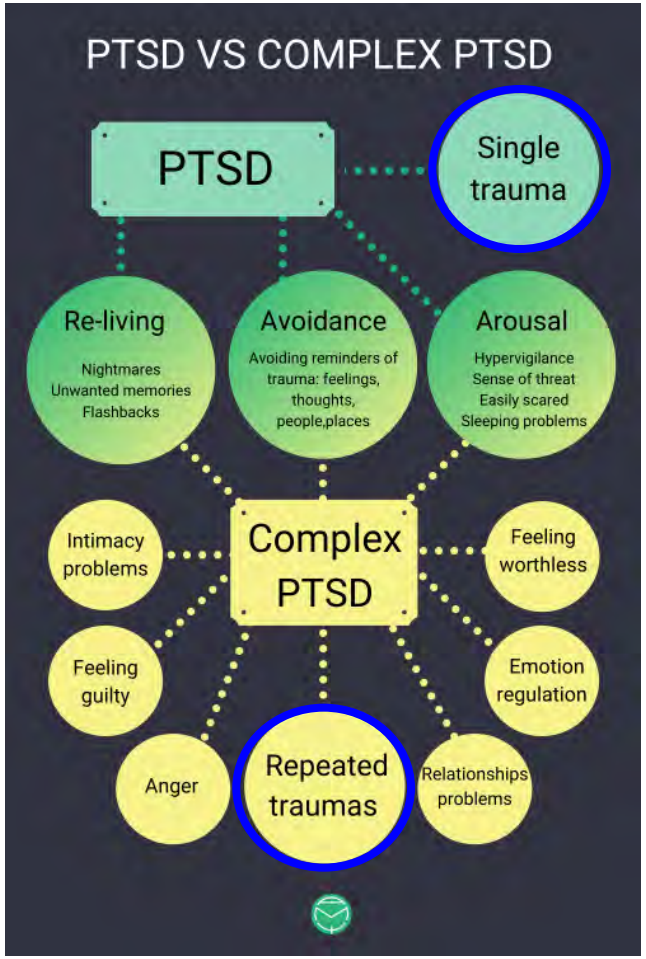
?



What is PTSD?

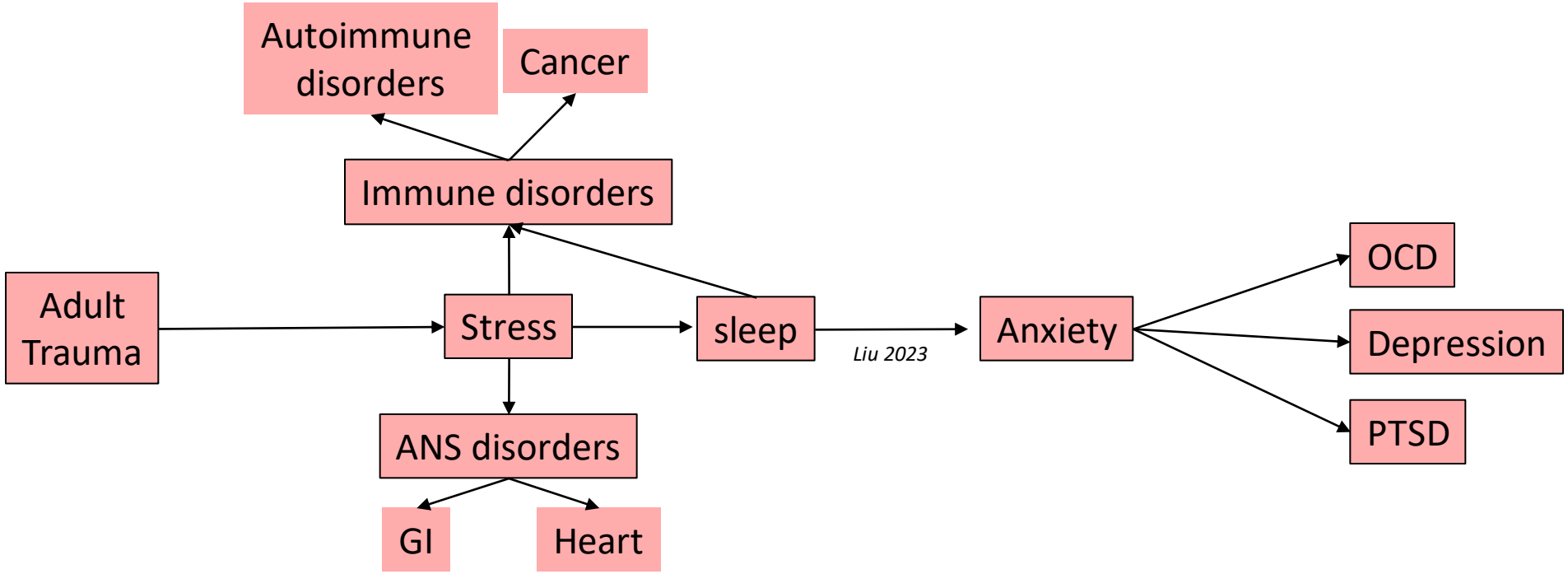
Core symptoms of PTSD

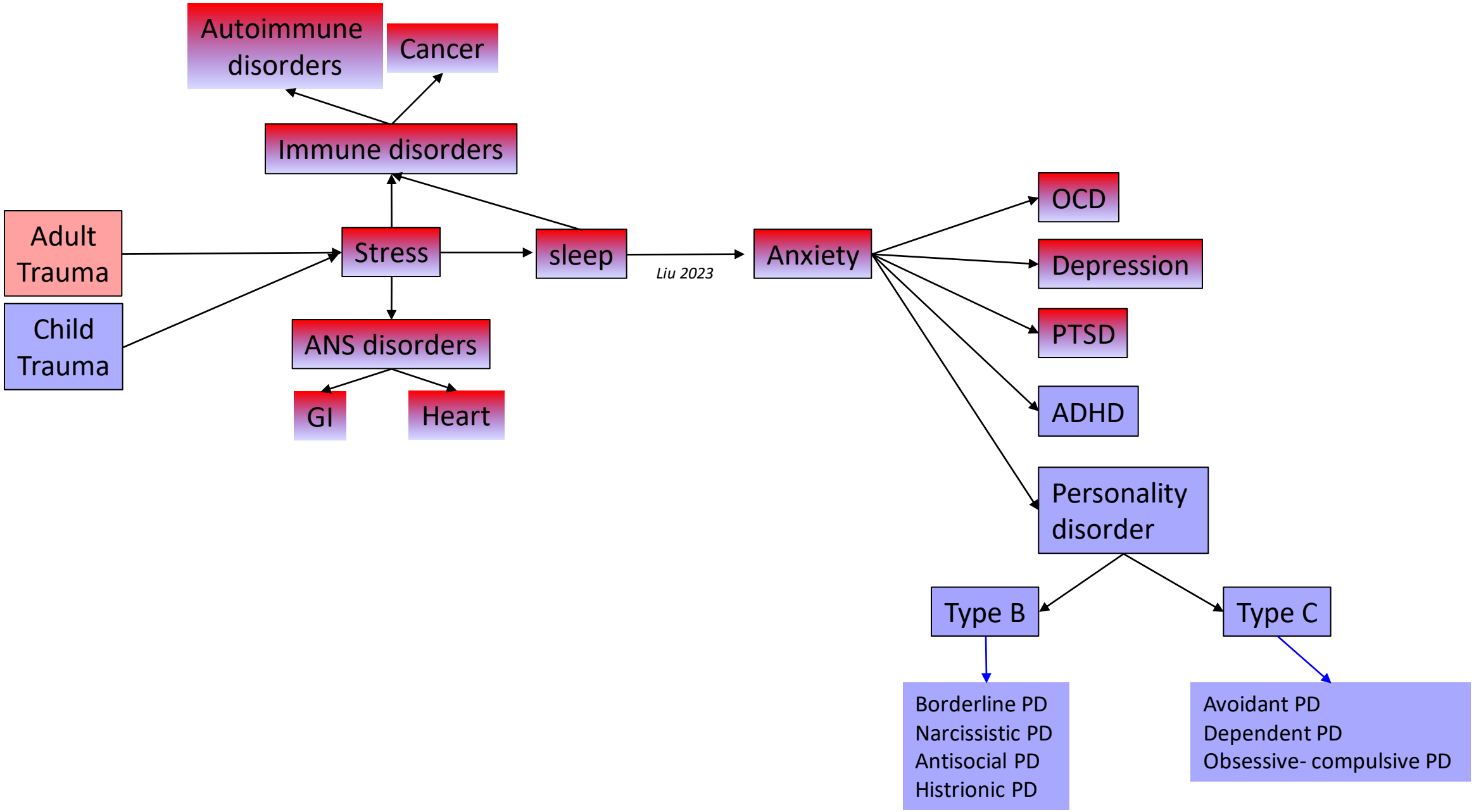
1. **Reliving** (flashbacks, nightmares,…)
2. **Avoidance of traumatic reminders**
3. **Sense of current threat** (hyperarousal, sleep problems, …)



Repeated or prolonged without possibility to escape

childhood abuse, child soldier, torture, slave trade, sex trafficking, genocide…
(Hermann 1992)


Autoimmune disorders
Cancer
Immune disorders
Adult Trauma
Stress
sleep
Liu 2023
Anxiety
OCD
Depression
PTSD
ANS disorders
GI
Heart


Autoimmune disorders
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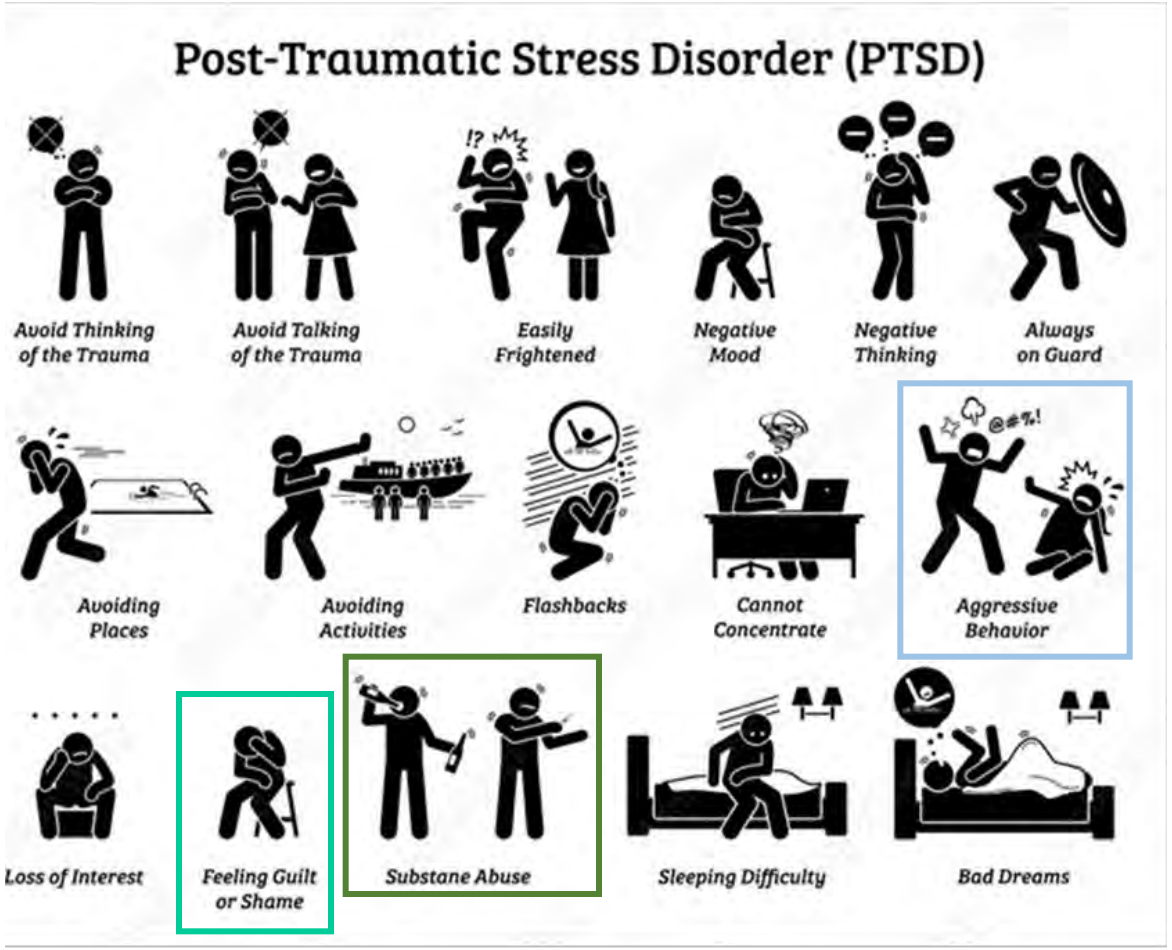
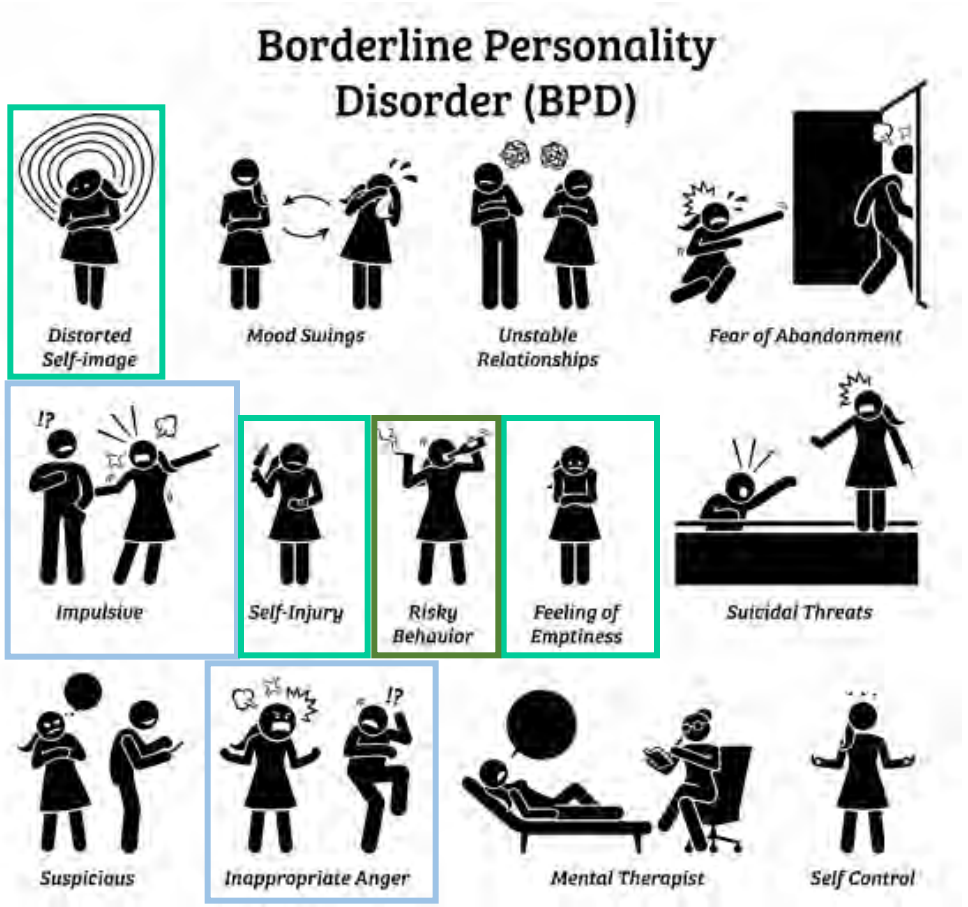
sleep
Liu 2023
Anxiety
ANS disorders
GI
Heart
OCD
Depression
PTSD
ADHD
Personality disorder
Type B
Type C
Borderline PD
Narcissistic PD
Antisocial PD
Histrionic PD
Avoidant PD
Dependent PD
Obsessive- compulsive PD

complex PTSD at X-road of PTSD and Borderline Personality Disorder?

81% of BPD have childhood trauma (Hermann 1989)
(71% physical abuse, 69% sexual abuse, 62% witness domestic violence)

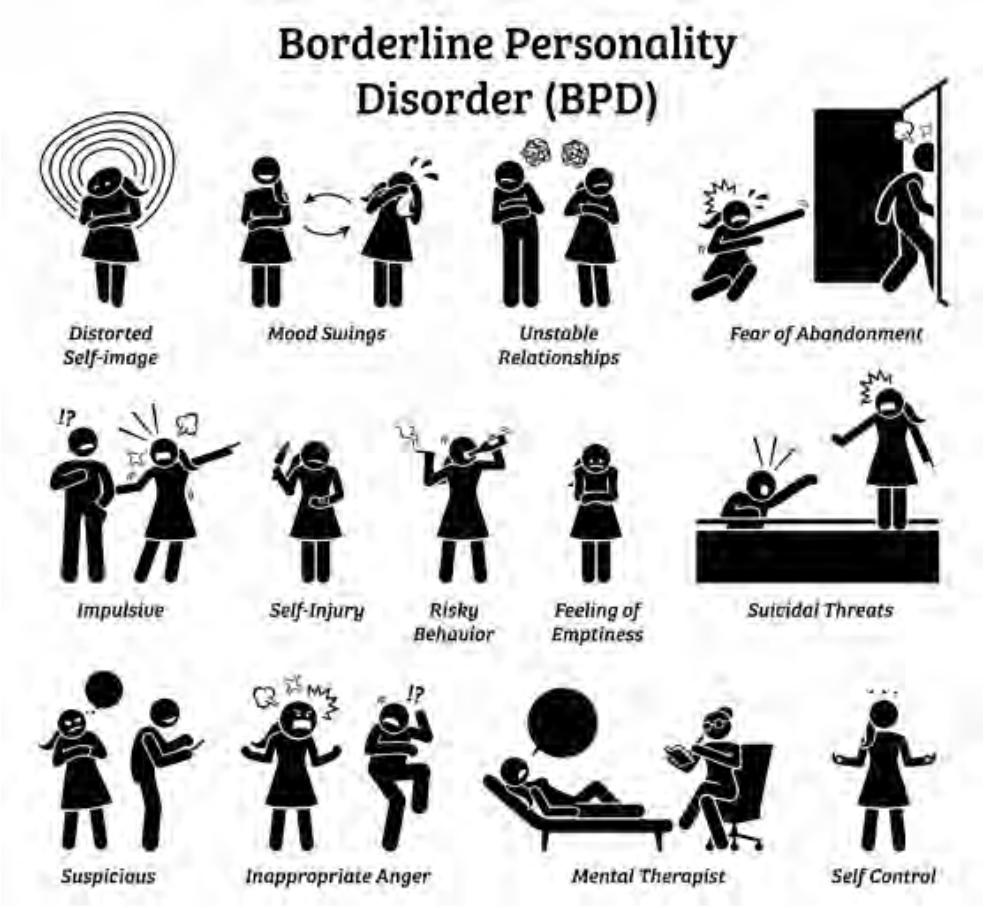




complex PTSD at X-road of PTSD and Borderline Personality Disorder?

Post-Traumatic Stress Disorder	Complex Post-Traumatic Stress Disorder	Borderline Personality Disorder
		Dissociation and paranoia
		Avoidance of real or imagined abandonment
		Shifting self-identity
	Interpersonal disturbances	Interpersonal disturbances
	Negative self-concept	Negative self-concept
	Affect Dysregulation	Affect Dysregulation
Sense of threat	Sense of threat	
Persistent avoidance of stimuli associated with the traumatic events	Persistent avoidance of stimuli associated with the traumatic events	
Recurrent, involuntary and intrusive distressing memories of the traumatic event	Recurrent, involuntary and intrusive distressing memories of the traumatic event	
Exposure to actual or threat of death, serious injury or sexual violence	Exposure to actual or threat of death, serious injury or sexual violence	

81% of BPD have childhood trauma (Hermann 1989)
(71% physical abuse, 69% sexual abuse, 62% witness domestic violence)



Prevalence of PTSD (meta-analyses): **20%**

Prevalence of PTSD

- Life-time prevalence: 5%
  - varies per country: 1-7% (Duckers 2018, Ressler 2022)
  - Women experience PTSD more frequently (2:1) and more intensely (Ressler 2022)
- Major traumatic events: 20% (Utzon-Frank 2014)
- Floods: 16% (Chen 2015)
- War-zone: 23.5% (Lim 2022)
- Post-pandemic (SARS, ZIKA, Ebola, Polio, …) : 22.6% (Yuan 2021)
  - Health care workers: 26.9%
  - Infected people: 23.8%
  - General public: 19.3%
  - No difference between men and women

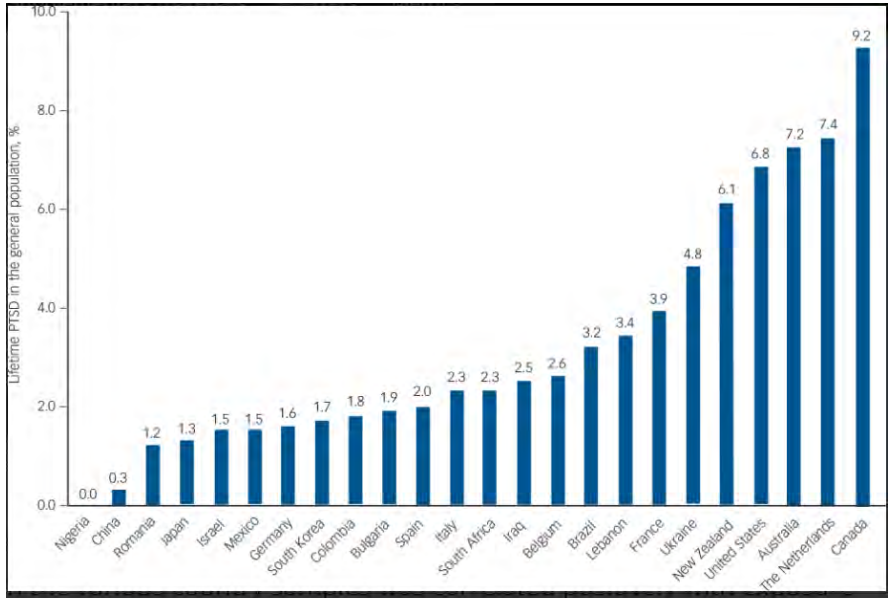
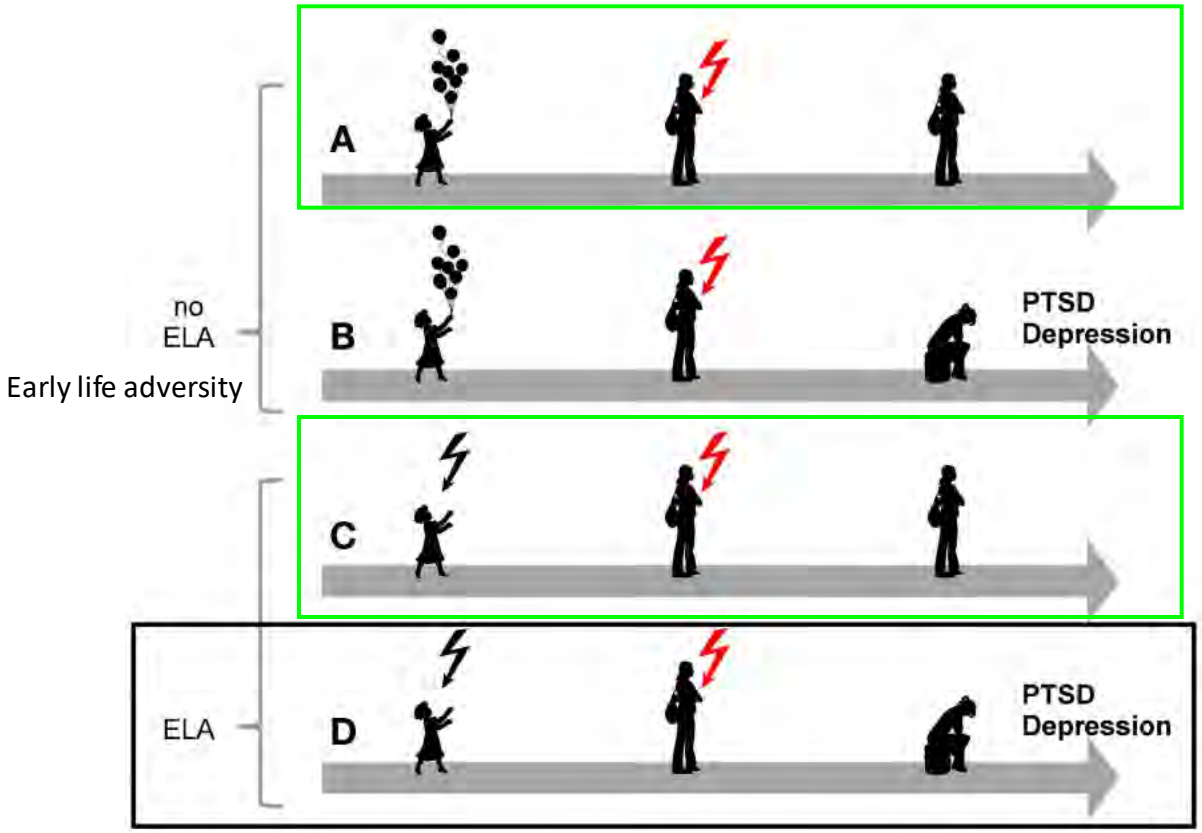
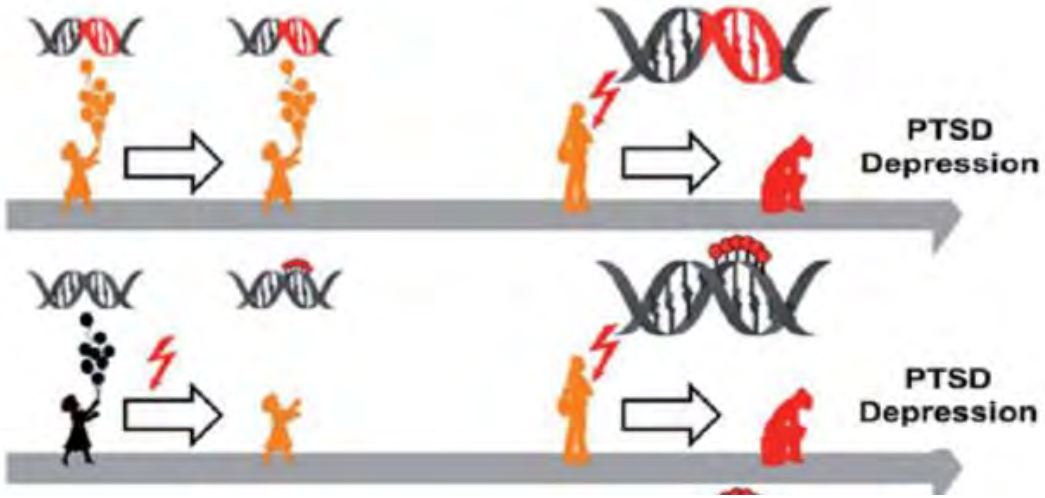


Fig. 1 Lifetime post-traumatic stress disorder (PTSD) prevalence in 24 countries (%, *n* = 86 687).

20% develop PTSD, what about the other 80%?

Resilience


A
B
C
D
no
ELA
Early life adversity
ELA
PTSD
Depression
PTSD
Depression


PTSD
Depression
PTSD
Depression

Raabe 2013

Resilience

= capacity of a dynamic system to **adapt** successfully to disturbances that **threat**en system function, viability, or development (Masten 2018)

= ability to cognitively or emotionally **cope with stress, trauma or adversity** without long-term negative consequences

Measured/quantified by

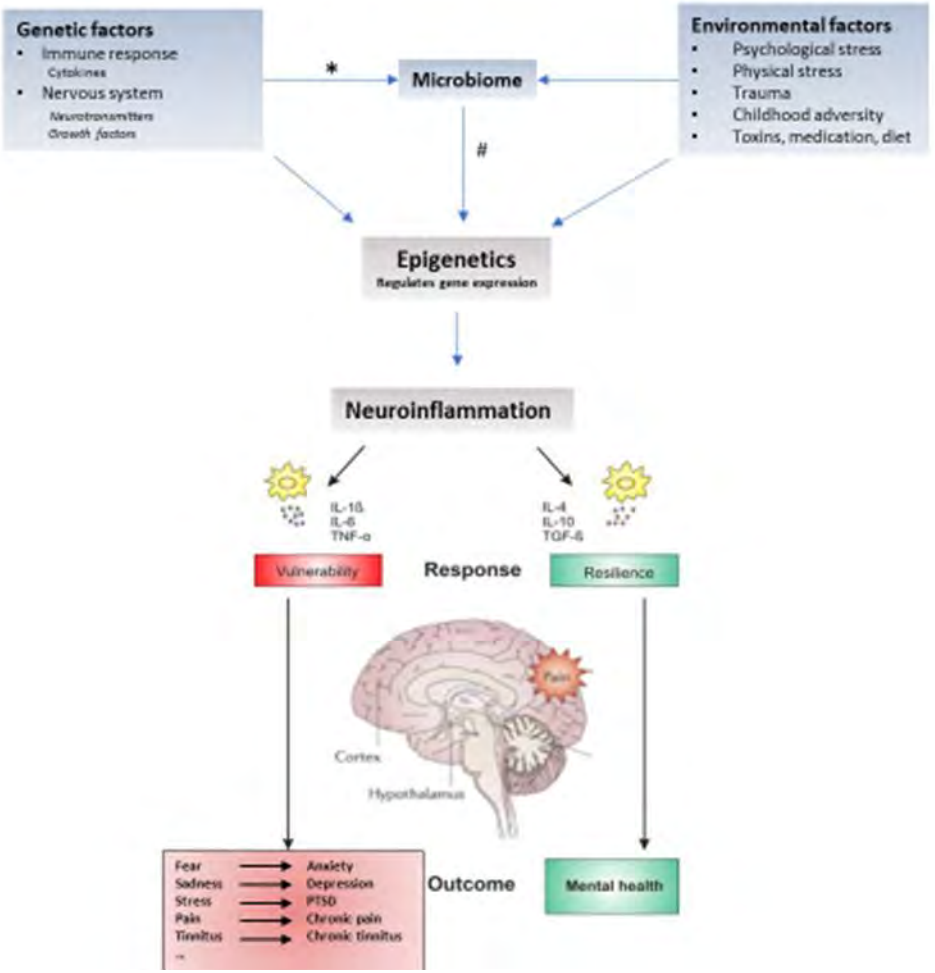
Adult Resilience Measure and

Child and Youth Resilience Measure

Connor-Davidson Resilience Scale

Genetics: 5-HTTLPR (=SLC6A4 = serotonin transporter), DRD4, BDNF, OXTR, CRHR1 (corticotropin releasing hormone receptor 1), RGS2 (= regulator of G-protein signaling 2) (Niitsu 2019)

Epigenetics: serotonin transporter (SLC6A4; 5-HTTLPR), melatonin receptor 1A (MTNR1A), brain-derived neurotrophic factor (BDNF), tyrosine hydroxylase (TH), and the protein family of DNA methyltransferases (DNMTs)

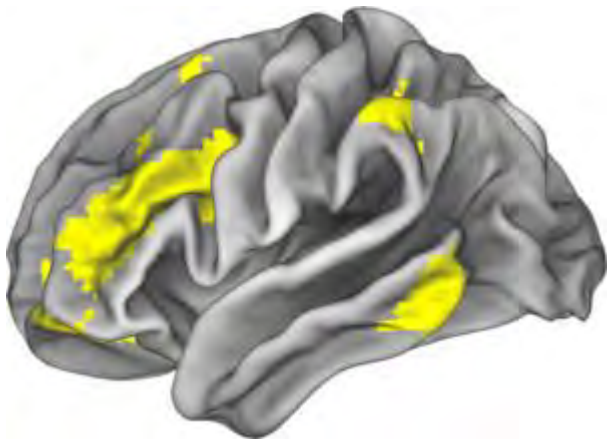


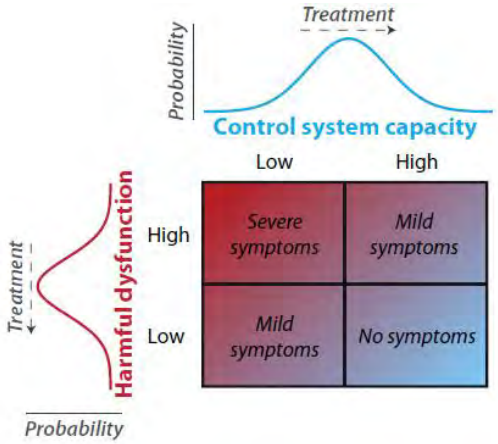
Central executive network = frontoparietal control network

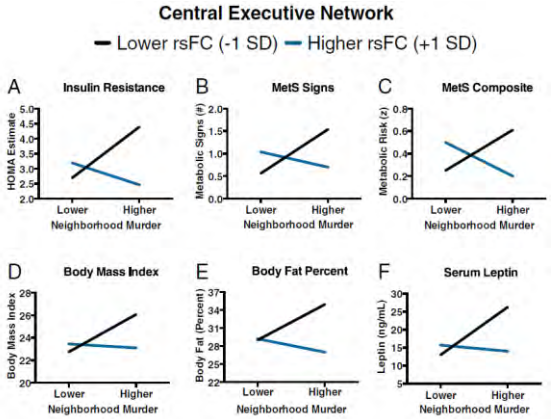
Like the body's immune system is protective against symptoms of bodily disease, the **FP control system is postulated to be protective against symptoms of mental disease** (Cole 2014)

Higher neighbourhood murder rate is associated with greater cardiometabolic risk (obesity, insulin resistance, and metabolic syndrome), but this relationship is apparent only among youth who displayed lower CEN resting-state connectivity (Miller 2018)

Intrinsic CEN connectivity is neurobiological contributor of stress resilience.





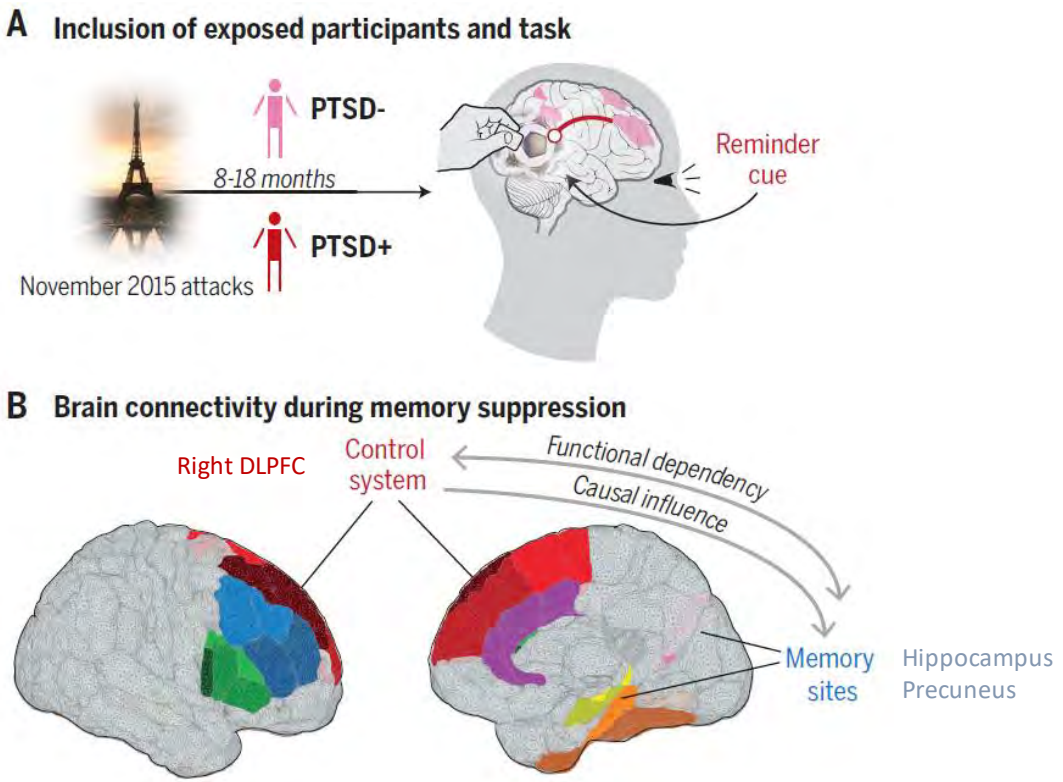


In PTSD DLPFC fails to suppress memories

In healthy individuals (PTSD– and nonexposed) preventing the unwanted emergence of intrusive memory into consciousness is associated with a significant reduction of the functional coupling between control (right DLPFC) and memory systems (hippocampus and precuneus), compared with situations where the reminder did not trigger such intrusion.

In contrast, there was a near-absence of such a decrease in connectivity in PTSD+.

Thus the CEN (DLPFC) cannot suppress the DMN-memory network



Mary 2020

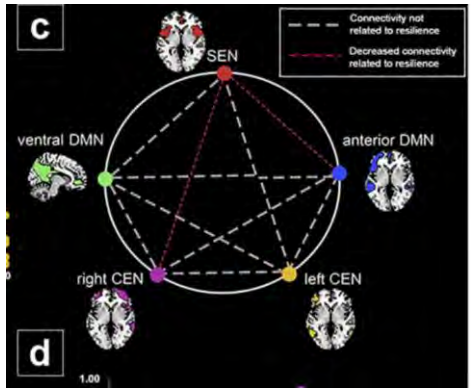
Resilience

Stronger **intra CEN connectivity** (bilaterally) is associated with more resilience (Miller 2018)

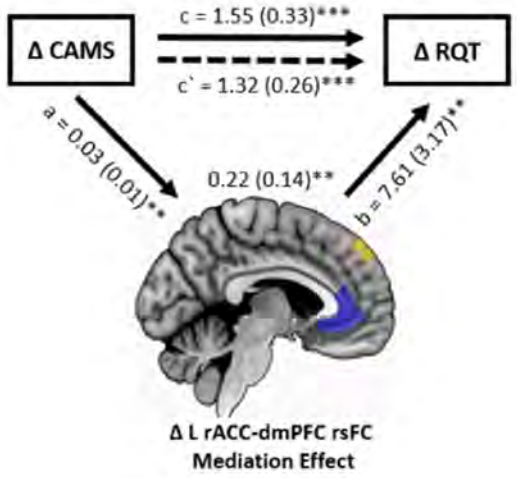
This stress reduction network connects to **pgACC/vmPFC** which results in better coping (Sinha 2016)

- The more the pgACC is active the more resilience (RQT), which can be enhanced by mindfulness (CAMS) (Kwak 2019)
- Resilience is associated with lower rsFC of the SN with the right CEN and anterior DMN (Iadipaolo 2018, Brunetti 2017)

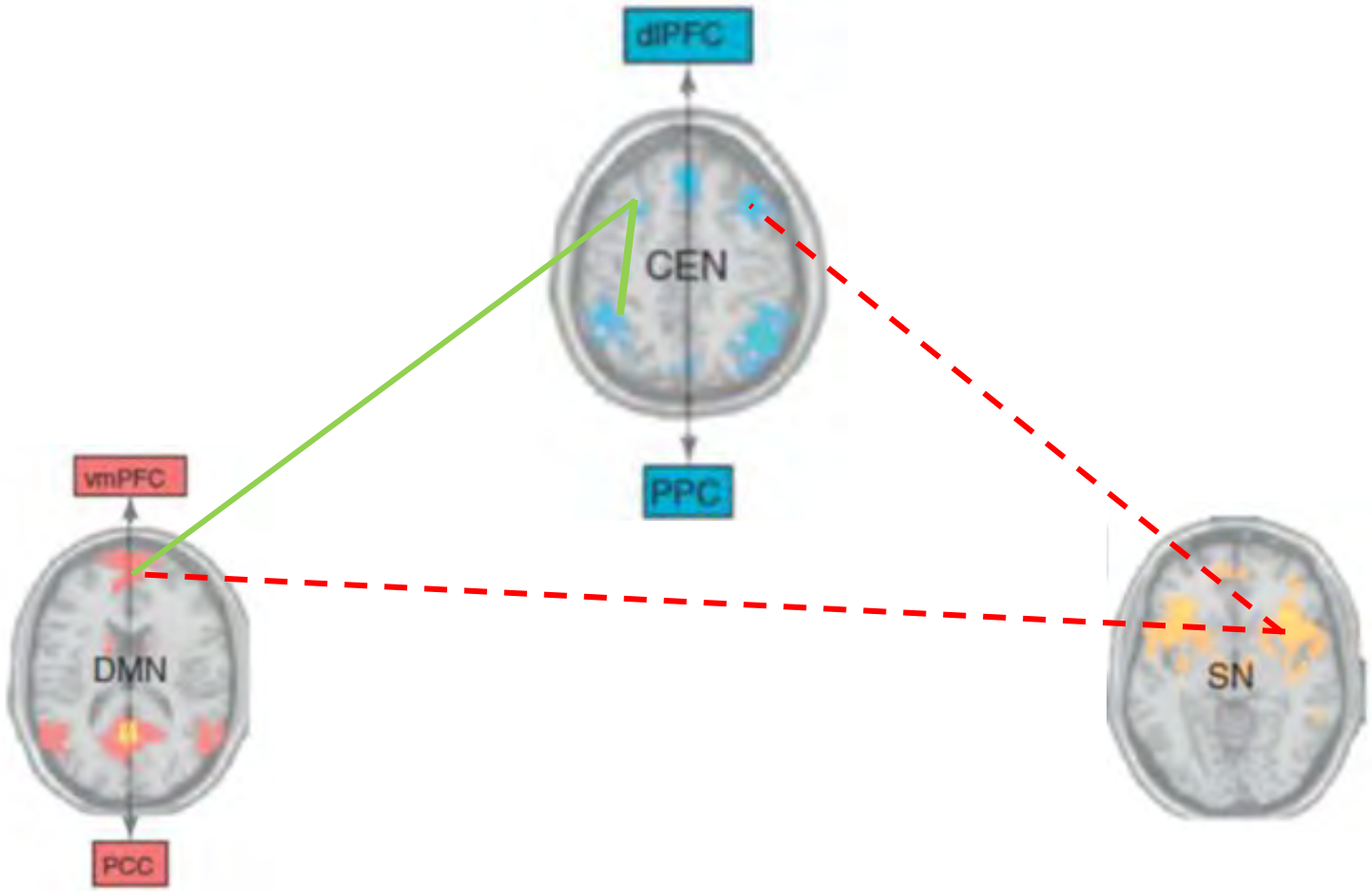
Summary: **resilience is capacity to inhibit irrelevant stimuli and launch goal oriented behaviour**



Iadipaolo 2018

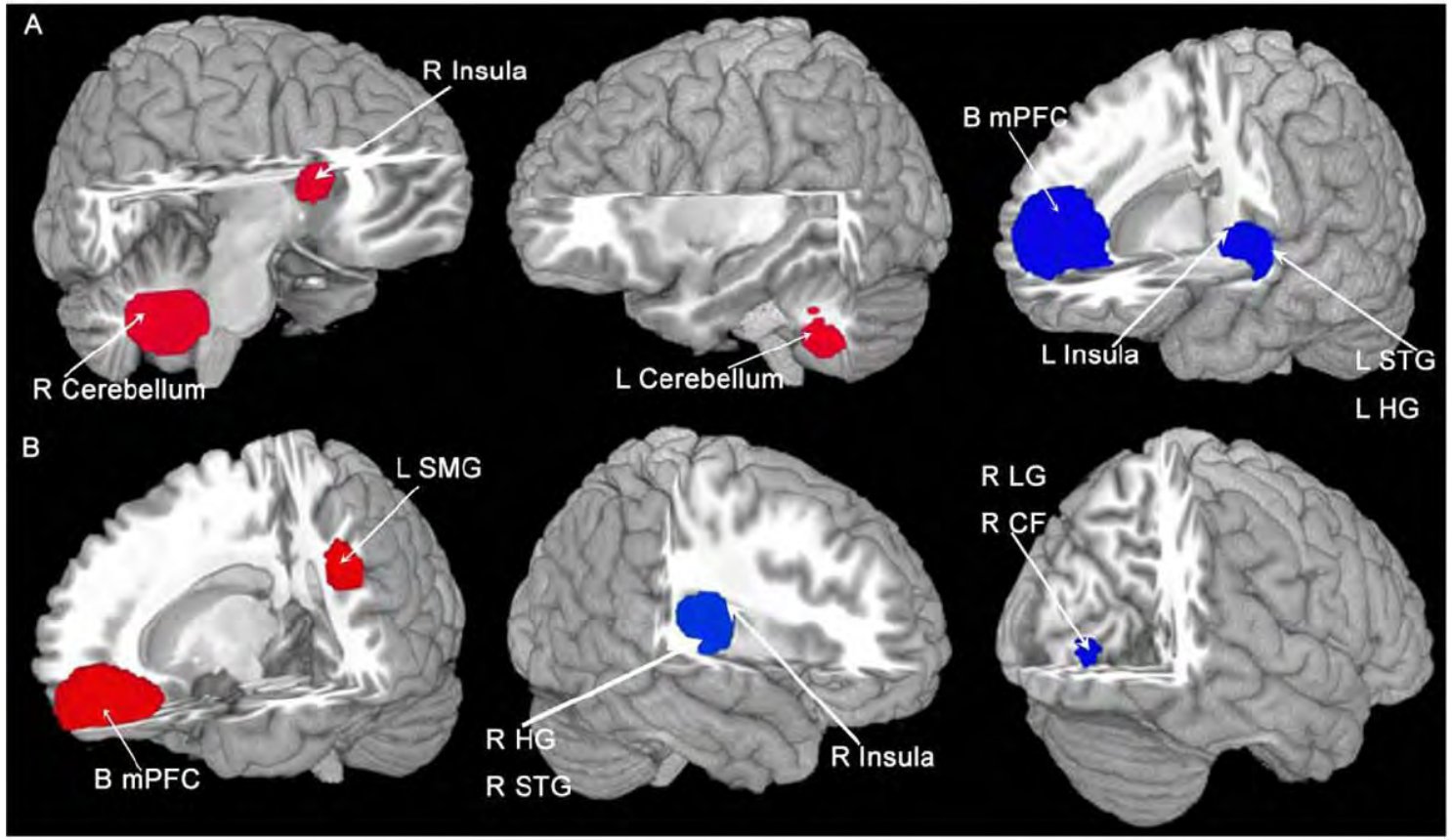


Triple network model for resilience



Resilience = increased FC between left CEN and vmPFC/pgACC
= decreased FC between right CEN and SN and vmPFC/pgACC

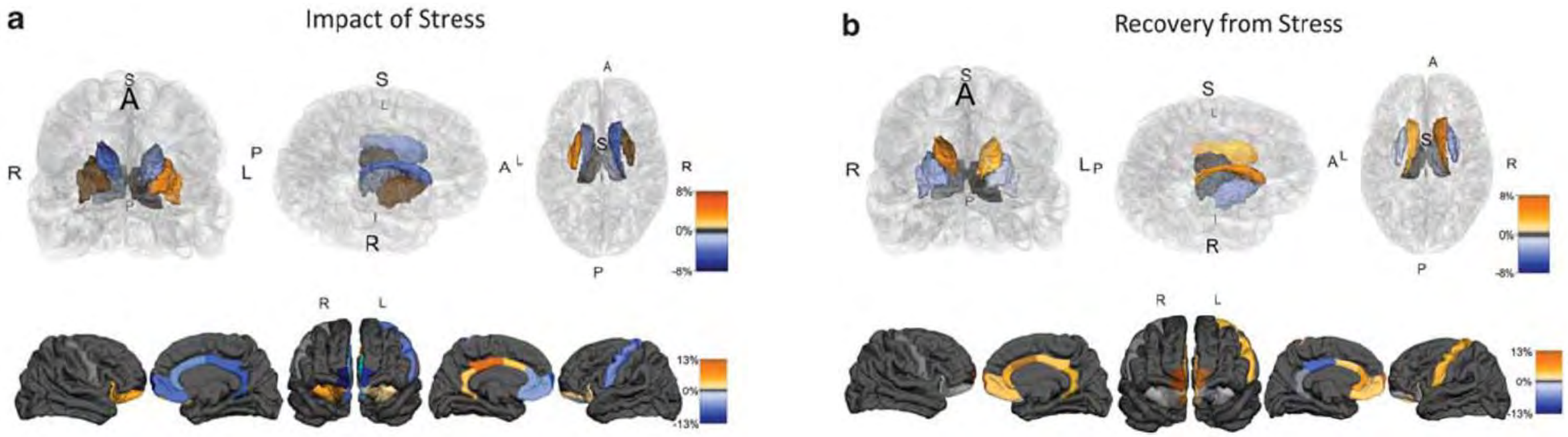
Brain activity in PTSD (meta-analysis)



Increased and decreased activity

Wang 2016

Stress and reversible vmPFC/caudate atrophy (inhibition decrease)

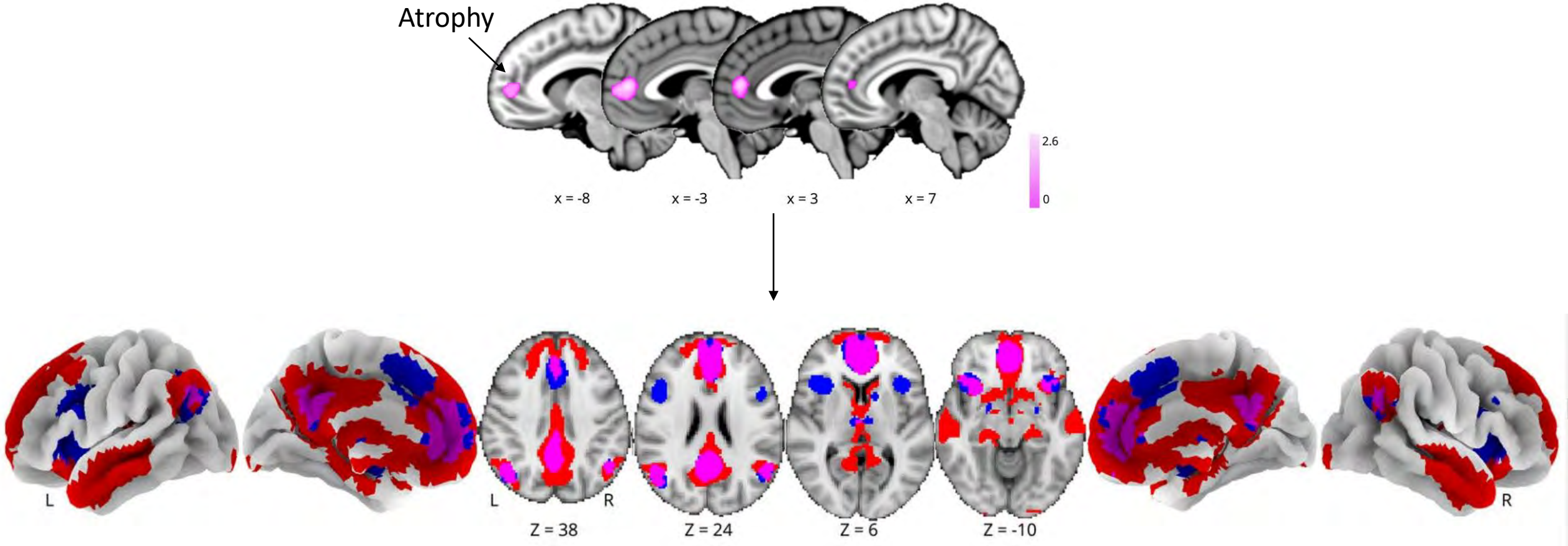


Atrophy of vmPFC and caudate
Volume increase of putamen

→ Reverse of atrophy and hypertrophy

Soares 2012

PTSD: pgACC atrophy and FC changes (meta-analysis)



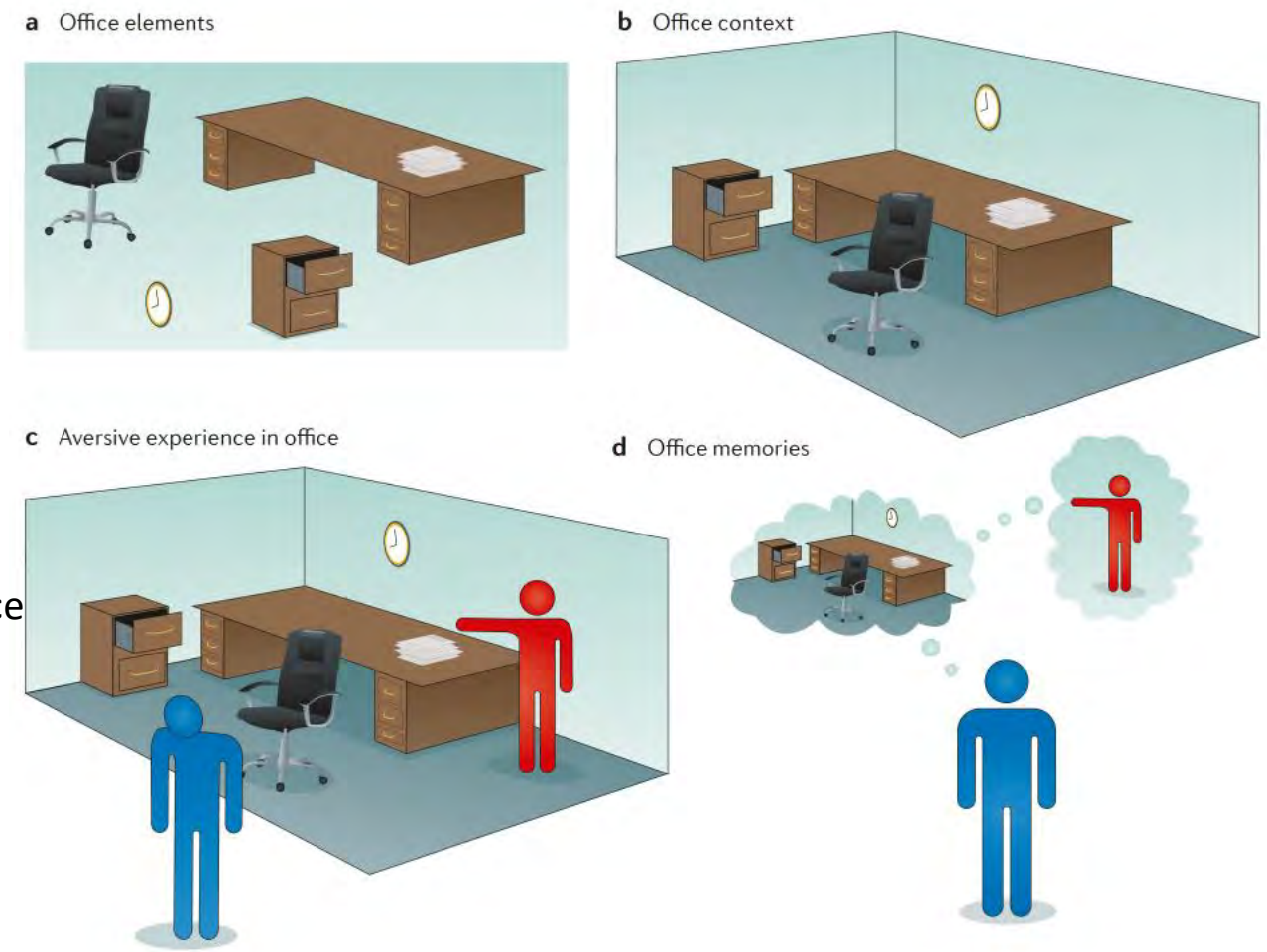
Resting state FC no task (SN and CEN) = at rest SN and CEN active

Meta-Analytic Co-activation Modeling (MACM with task) (DMN) = at task DMN active (freezing?)

Overlap (DMN)

Pankey 2022

PTSD is conditioned fear



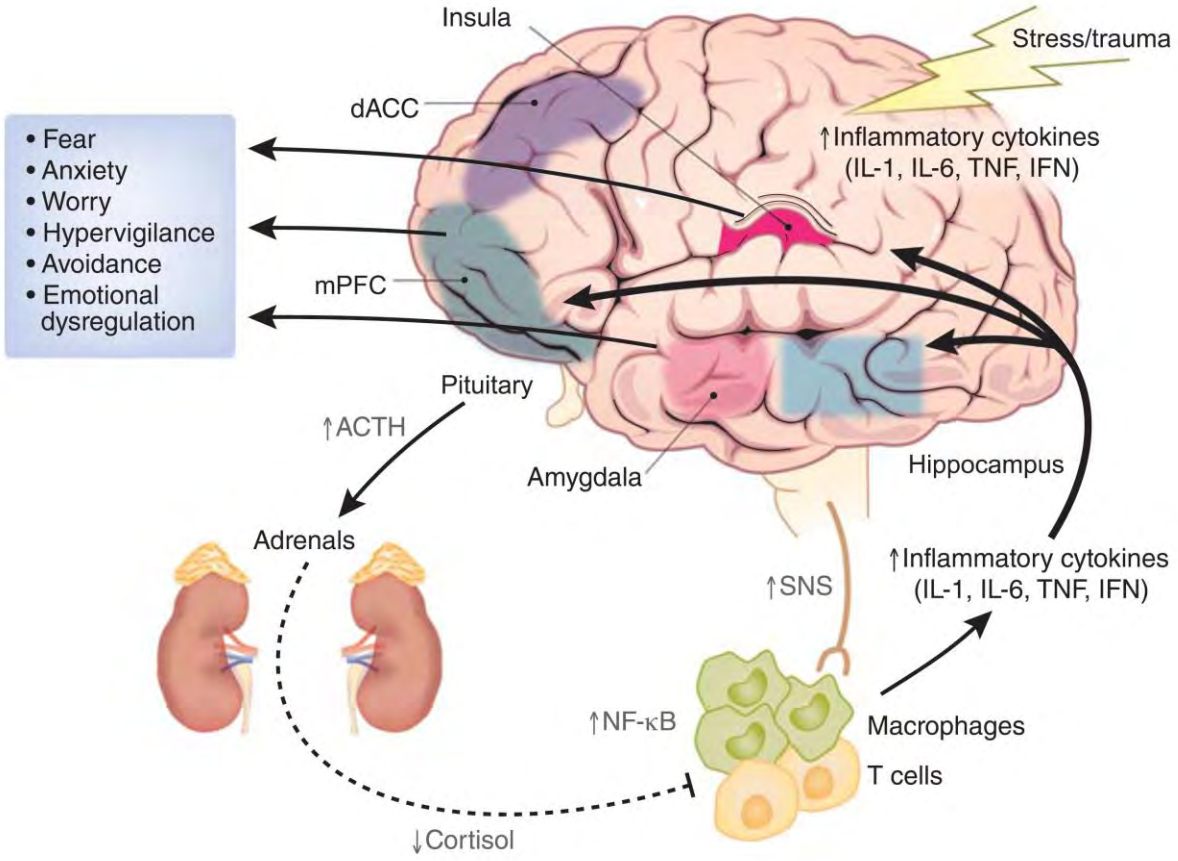
Fear conditioning:
Neutral stimulus/context = office
becomes linked to angry boss

The office/context may become generalized: any office may trigger fear
Thus the office or context predicts negative consequences
= anxiety in PTSD, GAD,

Maren 2013

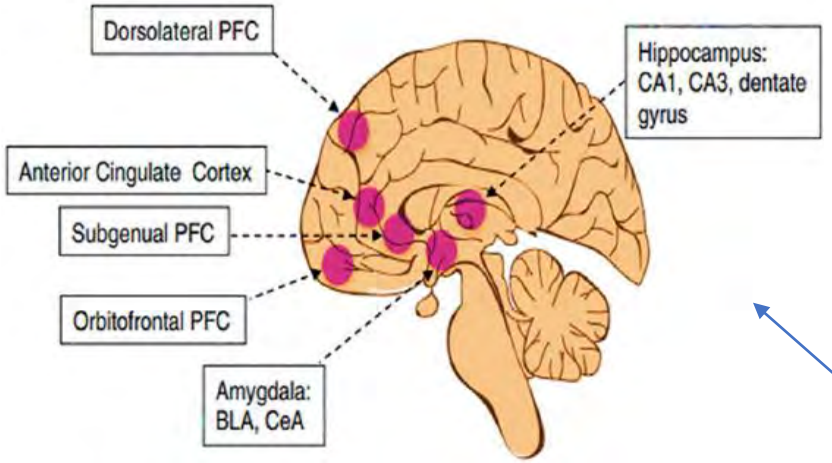
Neuroinflammation turns (physiological) fear into (pathological) anxiety

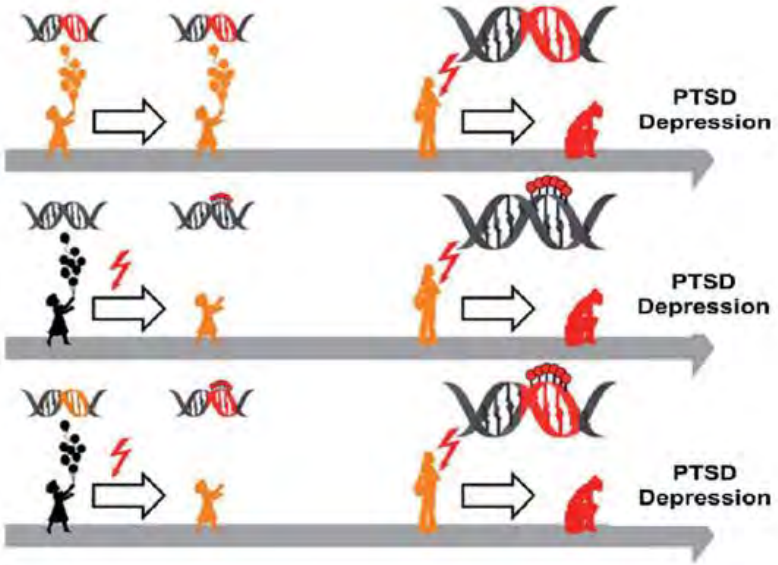
Immune biomarkers	Relationship to anxiety disorders
Interleukin-6	Increased in PD
Interleukin-1β	Increased in PD
Interleukin-2	Decreased in GAD Increased in PD
C-reactive protein	Increased in GAD Increases over time in agoraphobia
Tumor necrosis factor-α	Increased in GAD and PD Increases over time in agoraphobia

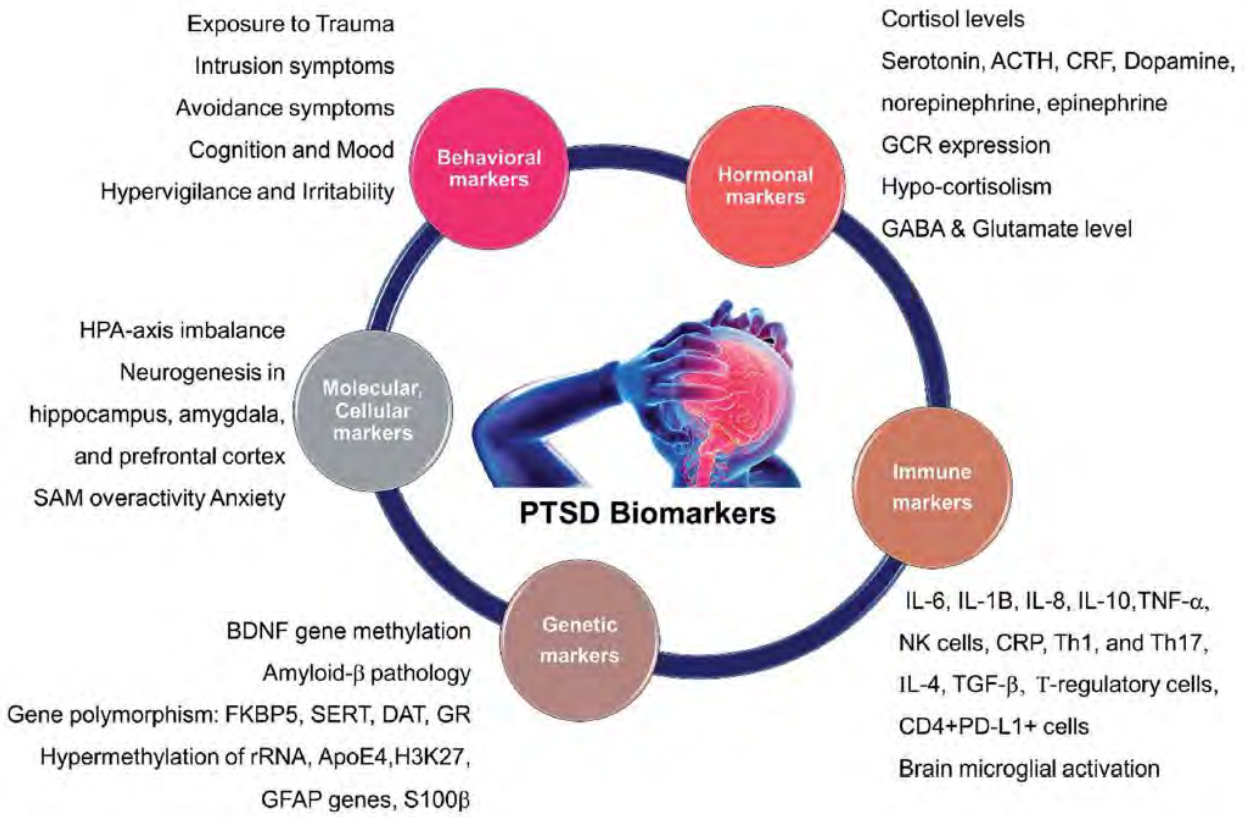


Michopoulos 2017

PTSD







Prasad 2019

Genetic factors
- Immune response (?)
- Nervous system
  MAOA, COMT, 5HT1A, ADORA2A, NPSR1

Microbiome

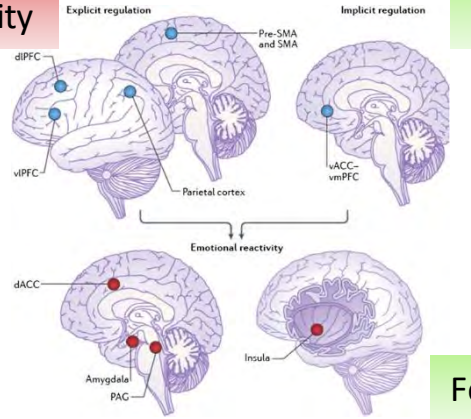
Environmental factors
- Psychological stress
- Physical stress
- Trauma
- Childhood adversity
- Toxins, mediation, diet

Epigenetics
Regulates gene expression

Neuroinflammation
Central sensitization

IL1, IL6, TNFα

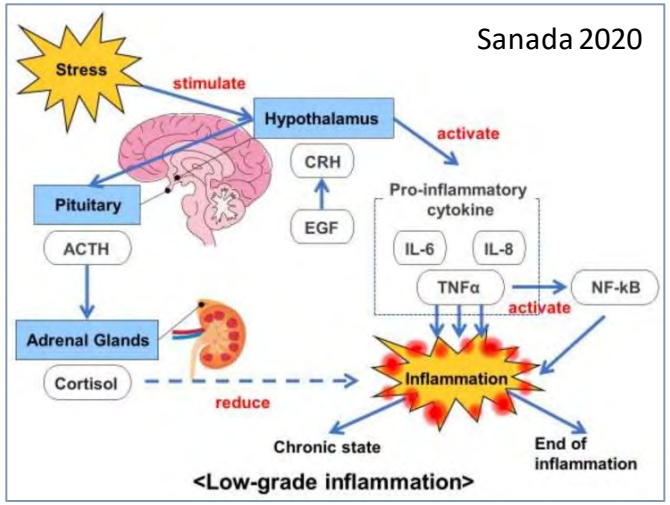
Vulnerability



Resilience

Anxiety

Fear resolves



Treatment

Psychological treatments for PTSD: network meta-analysis

Start and end of study

Changes in PTSD symptom scores between baseline and treatment endpoint
N total = 4700; *k* total = 71; 151 study arms

Intervention	*N*	*k*	Mean SMD (95% CrI) *v.* waitlist	Mean rank (95% CrI)
Metacognitive therapy	10	1	**−3.04 (−5.09 to −0.98)**	
Couple intervention	22	1	−2.67 (−5.41 to 0.06)	
EMDR	260	11	**−2.07 (−2.70 to −1.44)**	1.78 (1–5)
Combined somatic/cognitive therapies	237	4	**−1.69 (−2.66 to −0.73)**	3.64 (1–9)
Resilience-oriented treatment	20	1	−1.63 (−3.59 to 0.32)	
TF-CBT	903	29	**−1.46 (−1.87 to −1.05)**	4.51 (2–8)
Self-help with support	198	5	**−1.46 (−2.33 to −0.59)**	4.72 (1–10)
Present-centred therapy	99	3	**−1.42 (−2.45 to −0.40)**	
Non-TF-CBT	209	7	**−1.22 (−1.95 to −0.49)**	6.07 (2–10)
TF-CBT + SSRI	115	3	**−1.21 (−2.35 to −0.07)**	6.14 (1–11)
Psychoeducation	152	2	−1.21 (−3.13 to 0.71)	6.19 (1–12)
IPT	55	2	−1.19 (−2.54 to 0.15)	
SSRI	166	5	**−1.14 (−2.09 to −0.19)**	6.55 (2–11)
Self-help without support	335	11	**−0.91 (−1.67 to −0.15)**	7.77 (3–11)
Relaxation	25	2	−0.73 (−2.15 to 0.70)	
Counselling	278	9	**−0.73 (−1.41 to −0.05)**	
Attention placebo	221	9	−0.39 (−1.42 to 0.63)	10.12 (5–12)
Waitlist	1312	43	Reference	11.61 (10–12)
Attention bias modification	83	3	2.14 (0.63 to 3.65)	

Start and 4 months after study

Changes in PTSD symptom scores between baseline and 1–4-month follow-up
N total = 2315; *k* total = 28; 57 study arms

Intervention	*N*	*k*	Mean SMD (95% CrI) *v.* waitlist	Mean rank (95% CrI)
Couple intervention	21	1	**−2.04 (−3.72 to −0.36)**	
Self-help with support	85	3	**−1.27 (−2.12 to −0.42)**	
Self-help without support	40	2	−1.19 (−2.52 to 0.13)	
Behavioural therapy	47	2	**−1.19 (−2.16 to −0.21)**	
Combined somatic/cognitive therapies	23	1	−1.17 (−2.75 to 0.43)	
EMDR	121	4	**−1.12 (−1.94 to −0.27)**	1.50 (1–4)
TF-CBT	753	13	**−0.73 (−1.23 to −0.25)**	2.47 (1–4)
Psychoeducation	183	3	−0.51 (−1.47 to 0.44)	3.46 (1–6)
Non-TF-CBT	123	4	−0.43 (−1.35 to 0.53)	3.80 (1–6)
IPT	32	1	−0.39 (−1.76 to 0.97)	
Counselling	205	4	−0.30 (−1.12 to 0.53)	4.31 (2–6)
Present-centred therapy	70	2	−0.15 (−1.29 to 1.01)	
Attention placebo	44	2	−0.02 (−1.35 to 1.33)	
Waitlist	496	14	Reference	5.46 (4–6)
Family therapy	72	1	0.15 (−1.13 to 1.43)	

Remission at end of study

Remission at treatment endpoint
N total = 2249; *k* total = 34; 76 study arms

Intervention	*N*	*k*	Mean LOR (95% CrI) *v.* waitlist	Mean rank (95% CrI)
Psychodynamic therapy	49	1	**4.61 (1.87 to 7.57)**	
EMDR	132	5	**3.38 (2.04 to 4.84)**	1.17 (1–3)
Non-TF-CBT	65	2	**3.30 (1.48 to 5.29)**	
Relaxation	57	2	**2.65 (0.77 to 4.59)**	
IPT	72	2	**2.53 (0.71 to 4.40)**	
Present-centred therapy	75	2	**2.50 (0.75 to 4.36)**	
TF-CBT	601	21	**2.46 (1.79 to 3.19)**	2.15 (1–3)
Couple intervention	49	2	2.14 (−0.51 to 4.83)	
Self-help with support	105	2	**1.76 (0.03 to 3.49)**	3.07 (1–4)
TF-CBT + SSRI	57	1	1.65 (−0.61 to 4.00)	
Self-help without support	74	3	1.52 (−0.16 to 3.32)	
SSRI	87	2	1.42 (−0.45 to 3.42)	
Counselling	150	6	**1.34 (0.20 to 2.51)**	3.66 (3–4)
Attention placebo	23	1	1.09 (−1.97 to 4.24)	
Psychoeducation	28	1	−0.75 (−4.66 to 3.07)	
Waitlist	625	23	Reference	4.97 (4–5)

Mavranezouli 2020

Psychological treatments for complex PTSD (Meta-analysis)

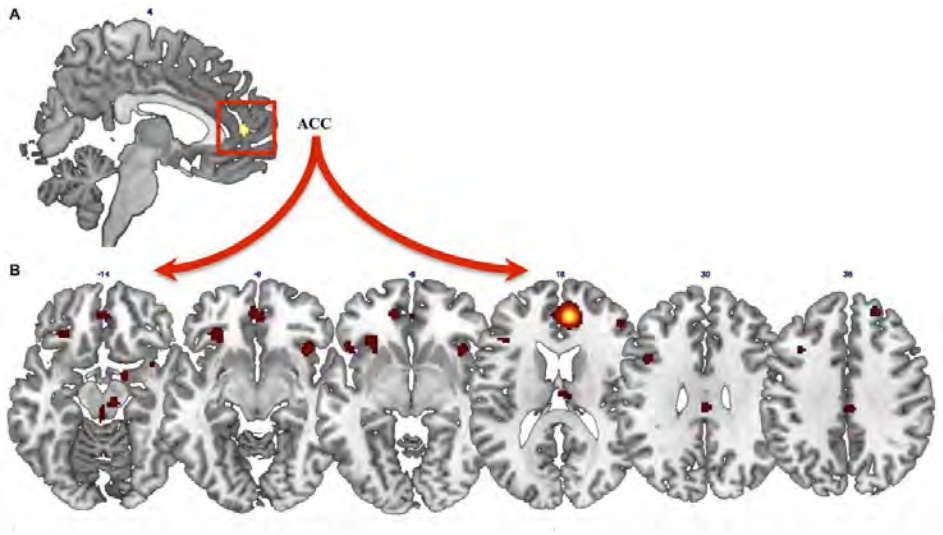
Meta-analysis (Karatzias 2019)

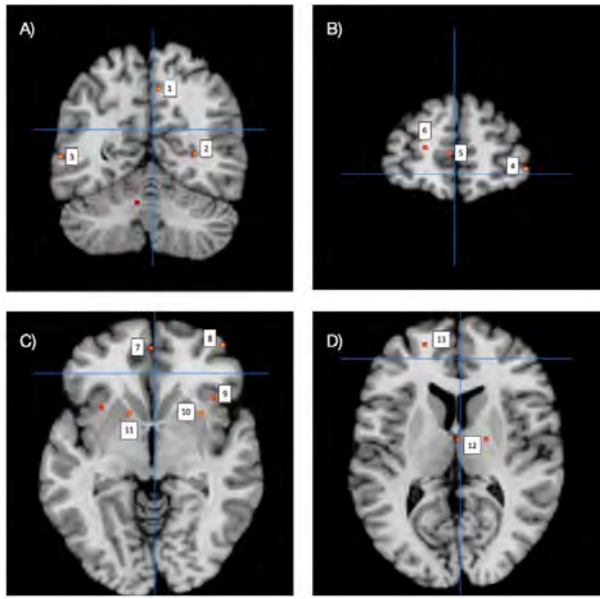
- CBT: NNT 8-14
- Exposure therapy: NNT 3-7
- EMDR: NNT 5-8
- Worse if associated childhood aversity

EMDR

EMDR improves FC between pgACC and insula (Meta-analysis, Boccia 2015), as well as thalamus, putamen (Pierce 2023)

Equally good as other psychological interventions
(Wright 2024, meta-analysis)

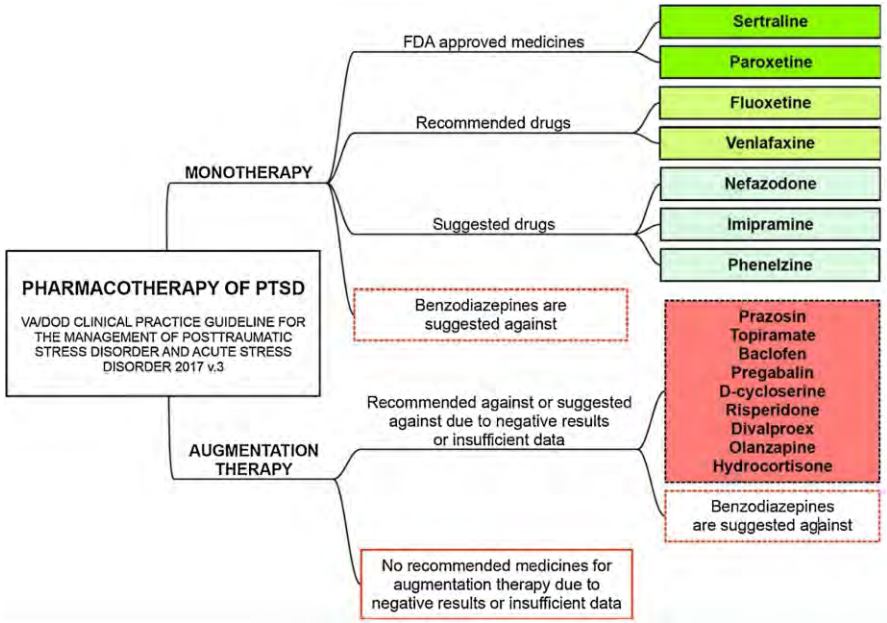




Pharmacological treatment meta-analyses

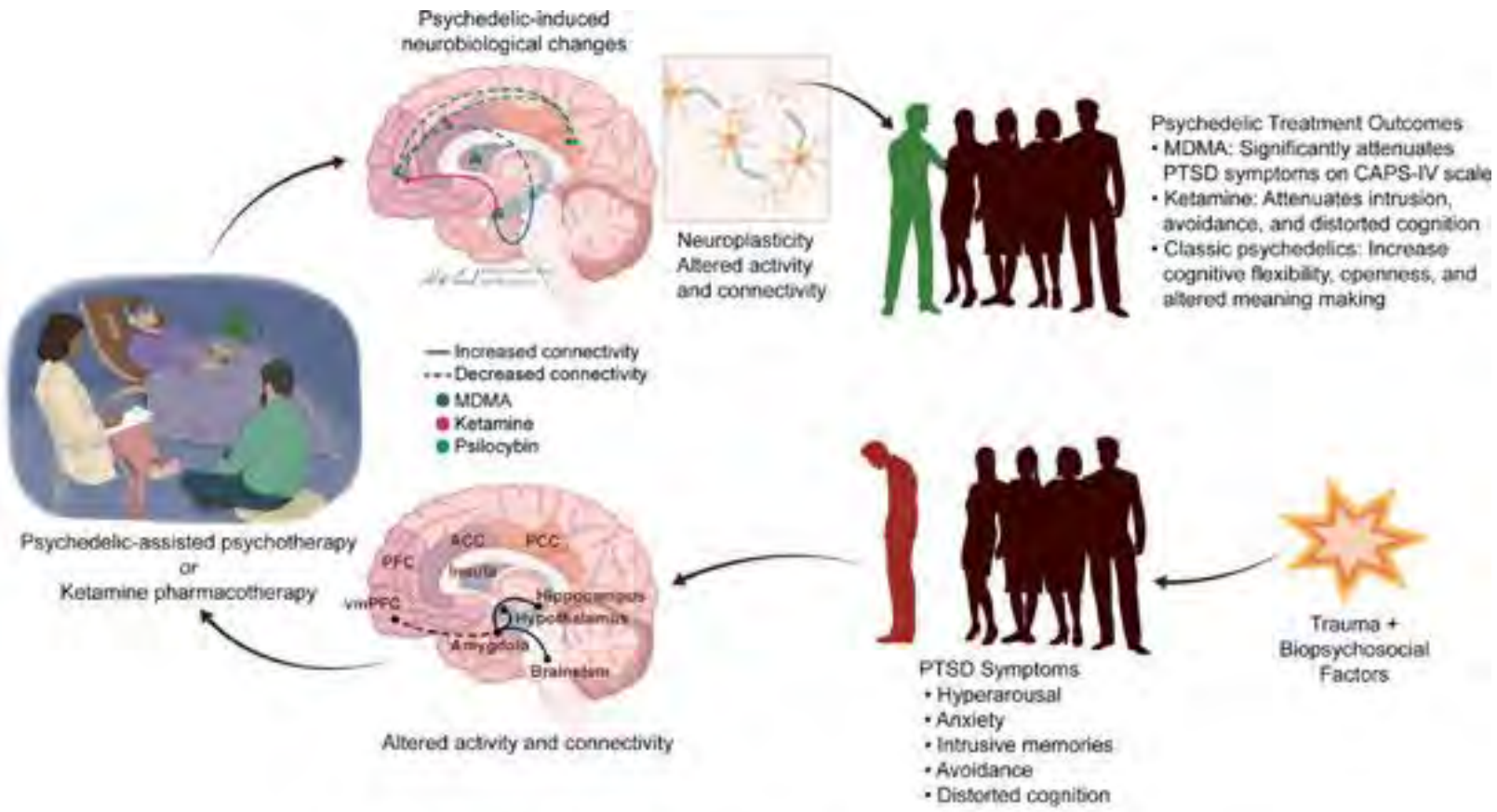
Pharmacological therapy (de Moraes Costa 2020, Zhang 2023)

topiramate, risperidone, quetiapine, paroxetine, venlafaxine, fluoxetine, sertraline



Malikowska-Racia 2019

Psychedelics and dissociatives for PTSD



Hypothesized therapeutic mechanism of psychedelics to treat PTSD.

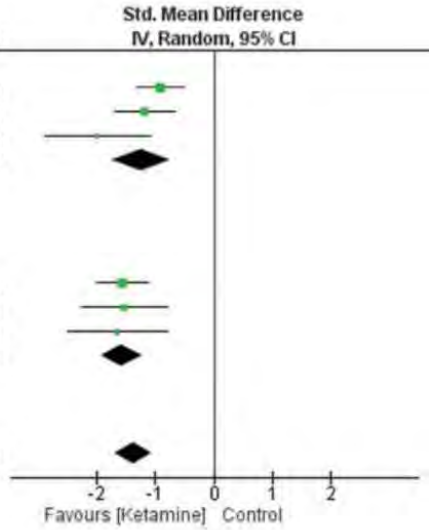
Zaretsky 2023

Ketamine and PTSD meta-analysis

Ketamine for PTSD (de Albuquerque 2022, AlFaran 2022))

- Has beneficial effect on PTSD
- Large effect size

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.2.1 CAPS-5								
Abdallah et al. (2022)	27,3	16,5	51	39,76	9,57	51	25,0%	-0,92 [-1,33, -0,51]
Feder et al. (2014)	59,34	21,18	35	80,09	12,36	35	20,0%	-1,18 [-1,69, -0,67]
Feder et al. (2021)	21,35	11,58	15	40,1	5,9	15	9,2%	-1,99 [-2,88, -1,09]
Subtotal (95% CI)			**101**			**101**	**54,2%**	**-1,23 [-1,73, -0,74]**
Heterogeneity: Tau² = 0,11; Chi² = 4,59, df = 2 (P = 0,10); I² = 56%								
Test for overall effect: Z = 4,87 (P < 0.00001)								
2.2.2 MADRS								
Abdallah et al. (2022)	12,03	12,71	51	29,66	9,5	51	23,1%	-1,56 [-2,00, -1,11]
Feder et al. (2014)	12,35	1,86	19	21,92	8,5	19	12,6%	-1,52 [-2,25, -0,79]
Feder et al. (2021)	13,7	9,29	15	27,4	6,7	15	10,2%	-1,65 [-2,49, -0,80]
Subtotal (95% CI)			**85**			**85**	**45,8%**	**-1,57 [-1,91, -1,22]**
Heterogeneity: Tau² = 0,00; Chi² = 0,05, df = 2 (P = 0,98); I² = 0%								
Test for overall effect: Z = 8,85 (P < 0.00001)								
Total (95% CI)			**186**			**186**	**100,0%**	**-1,37 [-1,67, -1,06]**
Heterogeneity: Tau² = 0,05; Chi² = 8,11, df = 5 (P = 0,15); I² = 38%								
Test for overall effect: Z = 8,78 (P < 0.00001)								
Test for subgroup differences: Chi² = 1,17, df = 1 (P = 0,28), I² = 14,5%								



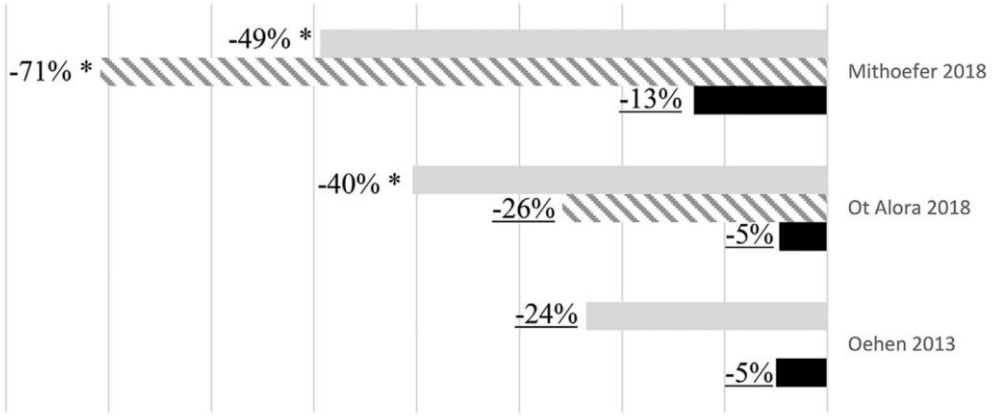
Psychedelic enhanced psychotherapy meta-analysis

MDMA assisted psychotherapy is efficacious (Jerome 2020, Smith 2021, Tedesco 2021, AlFaran 2023)

- 85% no longer criteria of PTSD vs 15% placebo
- Very large effect size: 2.78
- -22 points on CAPS
- 84% had improved feelings of well-being
- 72% had less excess vigilance
- 71% had fewer nightmares
- 69% had less avoidance
- 69% had less anxiety
- 66% had improved sleep
- 1.2% feeling worse or worse sleep
- 2.4% increased nightmares, avoidance, excessive vigilance, and anxiety

Cave! SSRI may dampen effect of MDMA assisted psychotherapy (Price 2022), and SNRI reduce effects in healthy volonteers (Hysek 2012)

2B. MDMA Dose Response (% Reduction CAPS-IV Scores)



Source	MDMA Mean	MDMA SD	MDMA Total	Control Mean	Control SD	Control Total	MD [95%-CI]	Favors MDMA	Favors Control	Weight
Mithoefer 2011	-53.70	7.2000	12	-20.50	8.8000	8	-33.20 [-40.53; -25.87]			24.3%
Mitchell 2021	-24.40	11.6000	42	-13.90	11.5000	37	-10.50 [-15.60; -5.40]			25.5%
Mithoefer 2018	-49.50	24.2000	19	-11.40	12.7000	7	-38.10 [-52.48; -23.72]			19.4%
Ot'Alora 2018	-24.40	24.2000	21	-11.50	21.2000	6	-12.90 [-32.77; 6.97]			15.5%
Oehen 2013	-15.60	18.1000	7	-3.20	15.3000	4	-12.40 [-32.51; 7.71]			15.3%
Random effects model			**101**			**62**	**-22.03 [-38.53; -5.52]**			**100.0%**

Heterogeneity: $I^2 = 88\%$, $\tau^2 = 141.3706$, $p < 0.01$

-60 -40 -20 0 20 40 60
Mean Difference (95% CI)

Source	MDMA Events	MDMA Total	Control Events	Control Total	RR [95%CI]	Favors Control	Favors MDMA	Weight
Mithoefer 2011	10	12	2	8	3.33 [0.98; 11.37]			11.4%
Mitchell 2021	28	42	12	37	2.06 [1.23; 3.43]			65.6%
Mithoefer 2018	13	19	2	7	2.39 [0.71; 8.03]			11.7%
Ot'Alora 2018	9	21	2	6	1.29 [0.37; 4.42]			11.3%
Random effects model	**60**	**94**	**18**	**58**	**2.10 [1.37; 3.21]**			**100.0%**

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.75$

0.1 0.2 0.5 1 2 5 10
Risk Ratio (95% CI)

Neuromodulation for PTSD

rTMS

tDCS

Neurofeedback

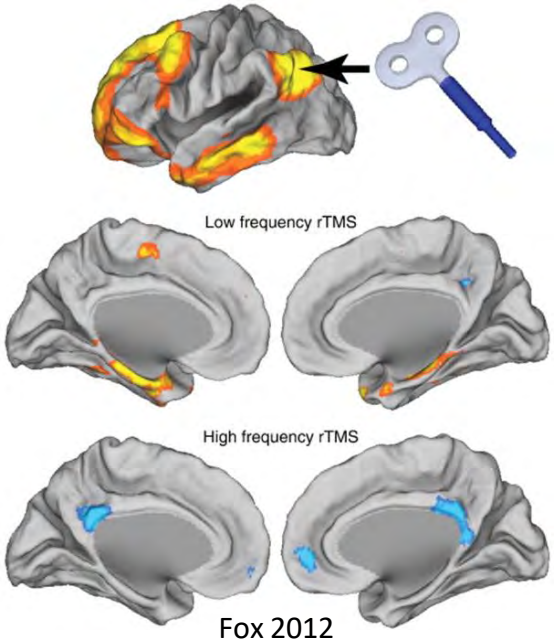
rTMS for PTSD meta-analysis

rTMS (Xu 2024)

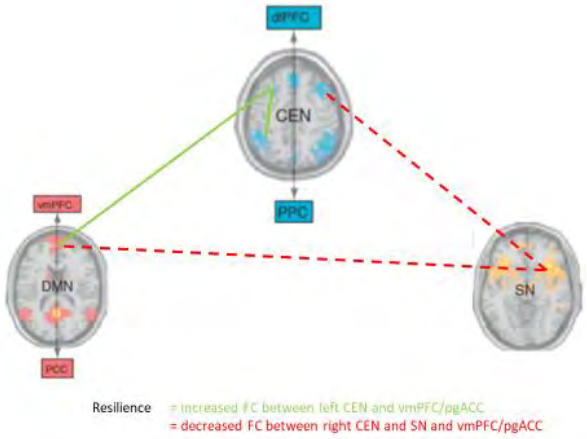
- Verum vs sham
- 8 studies, 309 patients
- Effect size = 1.75
- Long term effect
- Right DLPFC
- 10 Hz > 1 Hz (reduce connectivity = resilience)

NNT	Cohen's d[a]	Effect size
1	–	Perfect[b]
2.3	0.8	Large
3.6	0.5	Medium
9.0	0.2	Small

Sullivan2021



Fox 2012



tDCS for PTSD

Double blind placebo controlled RCT (Ahmadizadeh 2019)

- Significant reduction in
  - PTSD symptoms
  - hyper-arousal and
  - negative alterations in cognition and mood (depression and anxiety

Variables	Active (n = 18)			Sham (n = 16)		
	Baseline	Post-test	Follow-up	baseline	Post-test	Follow-up
PCL-5	54.39 ± 2.93	37.44 ± 10.77	41.28 ± 8.86	54.81 ± 2.79	52.00 ± 11.19	52.81 ± 5.07
BDI-II	31.55 ± 3.73	20.55 ± 7.84	21.55 ± 8.03	29.75 ± 9.43	27.62 ± 6.53	32.31 ± 6.89
BAI	26.61 ± 7.58	20.94 ± 6.38	21.44 ± 8.24	32.12 ± 4.42	31.43 ± 4.90	33.62 ± 5.03
Re-experiencing	13.55 ± 3.20	7.94 ± 3.26	10.38 ± 3.46	14.31 ± 2.60	12.68 ± 3.07	12.12 ± 2.98
Avoidance	5.83 ± 1.38	5.77 ± 1.62	5.44 ± 1.82	5.81 ± 1.80	5.93 ± 1.48	5.75 ± 1.57
NACM	18.22 ± 2.51	13.22 ± 6.02	13.94 ± 5.01	17.56 ± 2.89	17.43 ± 3.91	18.75 ± 3.06
Hyper-arousal	16.77 ± 4.00	10.50 ± 5.00	11.50 ± 3.29	17.12 ± 3.13	15.93 ± 4.28	16.18 3.72

Neurofeedback for PTSD meta-analysis

Meta-analysis (Steingrimsson 2020, Ashkovic 2023)

- 7 RCTs
- SMD -1.75
- 80% remission
- Certainty of evidence is very low
- Different protocols, different targets

Table 3. Summary of findings with estimated certainty of evidence.

Outcome	Number and type of studies (participants), risk of bias	Absolute effect estimates	Certainty of evidence – GRADE a
PTSD symptoms	2 RCTs ($n = 88$) with Low Risk of Bias	**CAPS** Standardised mean difference at end of treatment in favour of NFB – 0.88 (95% CI −1.42, −0.35), $p = .001$	⊕⊕⊕◯ b
	5 RCTs ($n = 127$) with High Risk of Bias	**IES-R/PCL-5/MMPI-PTSD/Non-validated PTSD Questionnaire** Standardised mean difference at end of treatment in favour of NFB −2.39 (95% CI −3.87. −0.90), $p = .00001$	⊕◯◯◯ c
Symptoms of Depression	2 RCTs ($n = 49$) and 1 NRSI ($n = 26$) with High Risk of Bias	**Beck Depression Inventory/HSCL-D** Standardised mean difference at end of treatment in favour of NFB −1.37 (95% CI −2.21 to −0.53), $p = .001$	⊕◯◯◯ d
Symptoms of Anxiety	1 RCT ($n = 19$) and 2 NRSI ($n = 49$) with High Risk of Bias	**Beck Anxiety Inventory /HSCL-A** Standardised mean difference at end of treatment in favour of NFB −1.00 (95% CI −1.51 to −0.49), $p = .0001$	⊕◯◯◯ e
Medication use	1 RCT (28) and 1 NRSI ($n = 13$)	Number of patients with decreased medication use NFB vs CL: Decrease: 22/22 vs. 1/18 Between-group difference: Chi2 = 36.14, $p < .001$	⊕◯◯◯ f

⊕⊕⊕⊕ – High certainty (we are very confident that the true effect lies close to that of the estimate of the effect)
⊕⊕⊕◯ Moderate certainty (we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different)
⊕⊕◯◯ Low certainty (our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect)
⊕◯◯◯ Very low certainty (we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect)

a, certainty of evidence; b, downgraded one step for imprecision (due to a small number of participants and only 2 events); c,d,e,f downgraded three steps for serious risk of bias and study limitations (missing outcome data, unclear randomisation, deviation from intended intervention and bias in measurement of outcomes), high heterogeneity, indirectness, and serious imprecision.

How I treat PTSD evidence informed?

Phase 1: treat PTSD symptoms

Psychotherapy
+
Pharmacology
+
Neuromodulation

Nervous system

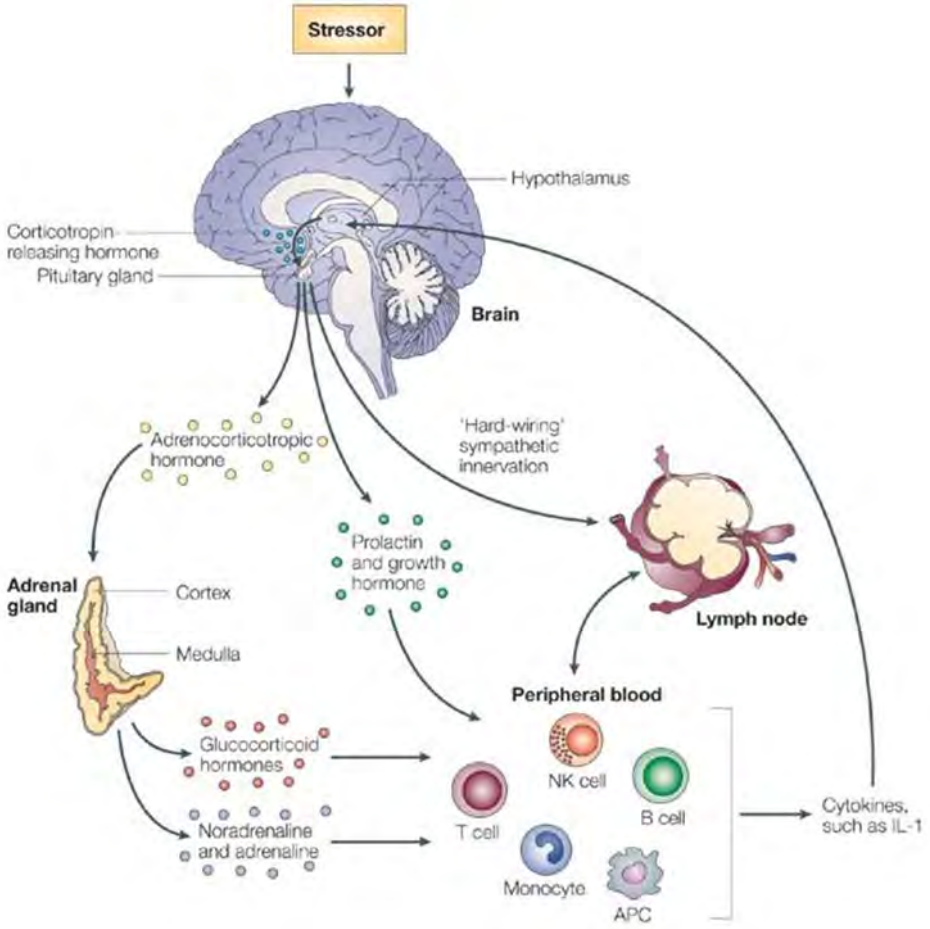
Deanxit + rivotril 0.5 mg
Naltrexone 5 mg (SUD)
Aripirazole 2mg
Oxytocin nose spray for panic attacks
+
rTMS (19=0 Hz right DLPFC)
(tDCS bifrontal)

Endocrine system

Clonidine 0.15 mg 1/4

Immunological system

Naltrexone 5 mg
NAC 1200 mg 2dd (Back 2016)



Glaser 2005 Nature Reviews | Immunology

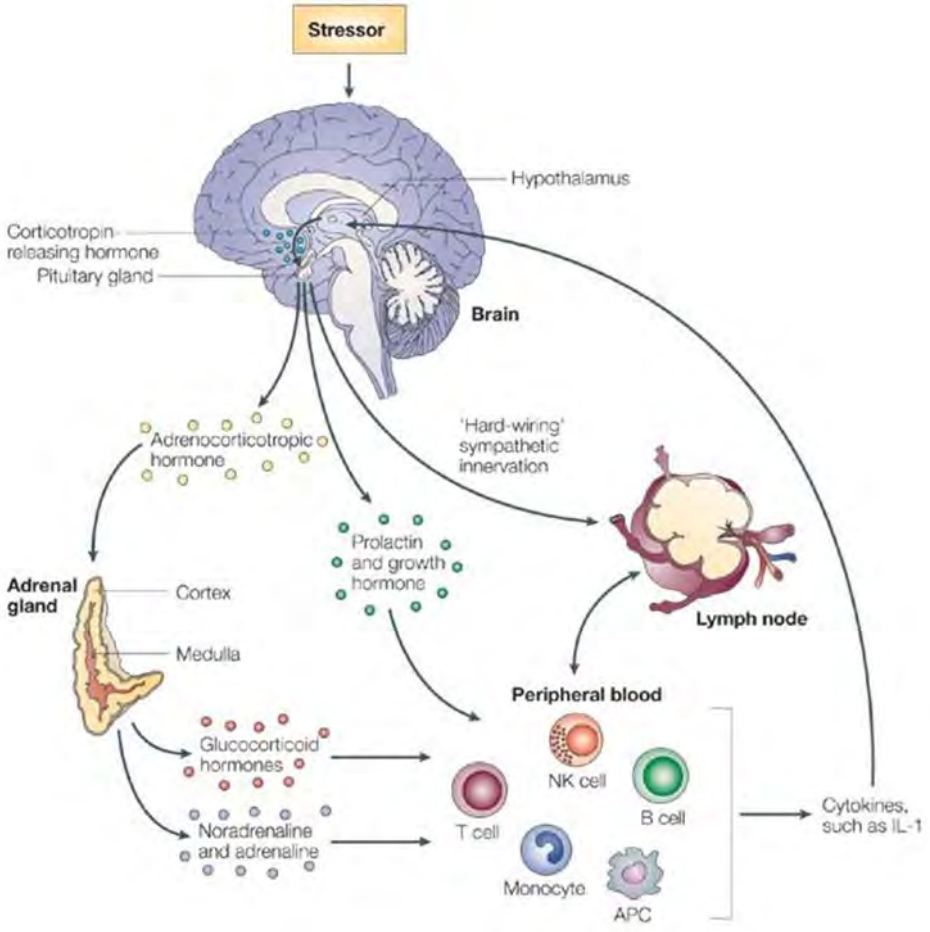
How I treat PTSD evidence informed?

Phase 2: maintenance

Psychotherapy
+
Pharmacology
+
Neuromodulation

Nervous system
- Microdosing
- Neurofeedback: IFS treatments
  - pgACC uptraining
  - pgACC-PCC anticorrelated with insula=-dACC
  - Right CEN

Pharmacology: lowest comfortable dose



Glaser 2005 Nature Reviews | Immunology

Conclusion

PTSD is result of deficient resilience network
By genetic and epigenetic influences on trauma processing
Involves pgACC-amygdala-hippocampal-putamen network
Neuroinflammation turns fear into PTSD
Treatment consists of treating brain, endocrine and immune system
Including psychotherapy/EMDR, pharmacology and neuromodulation

Dirk De Ridder