Neuromodulation & Psychedelics

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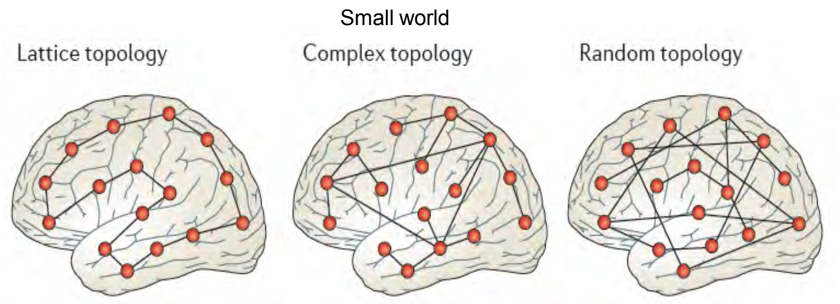
Brain Research consortium for Advanced International, Innovative & Interdisciplinary Neuromodulation

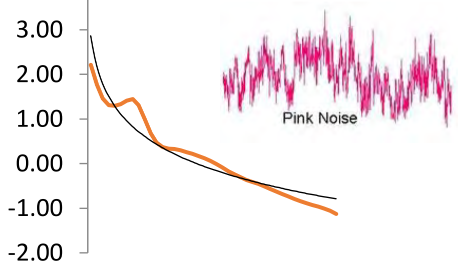
Brain = complex adaptive system

Complex adaptive systems (CAS)

Arise when 2 conditions are fulfilled (Amaral 2004)

1. Structure has small world topology
2. Presence of noise





Graph = mathematical representation of a system/network composed of interconnected elements
Graph theory = mathematical study of graphs (= networks)
Network topology = the mathematical study of shapes and spaces (concerned with the invariant properties of space that are preserved under continuous deformations (bending, stretching))

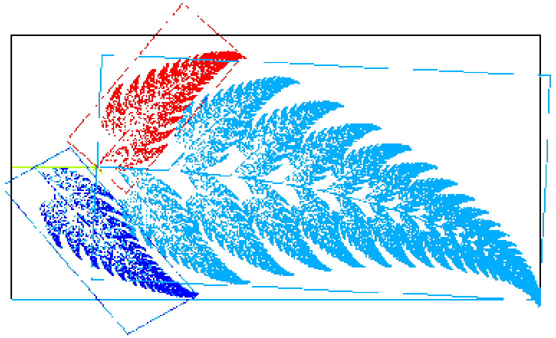
Brain = complex adaptive system

Complex adaptive systems (CAS)

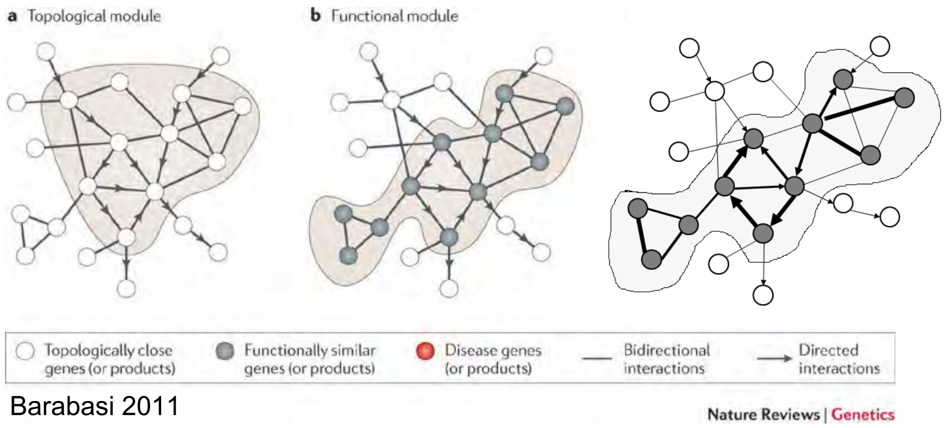
are characterized by

1. Complex : containing many parts in intricate arrangement
2. Adaptive: capacity to change and learn from experience

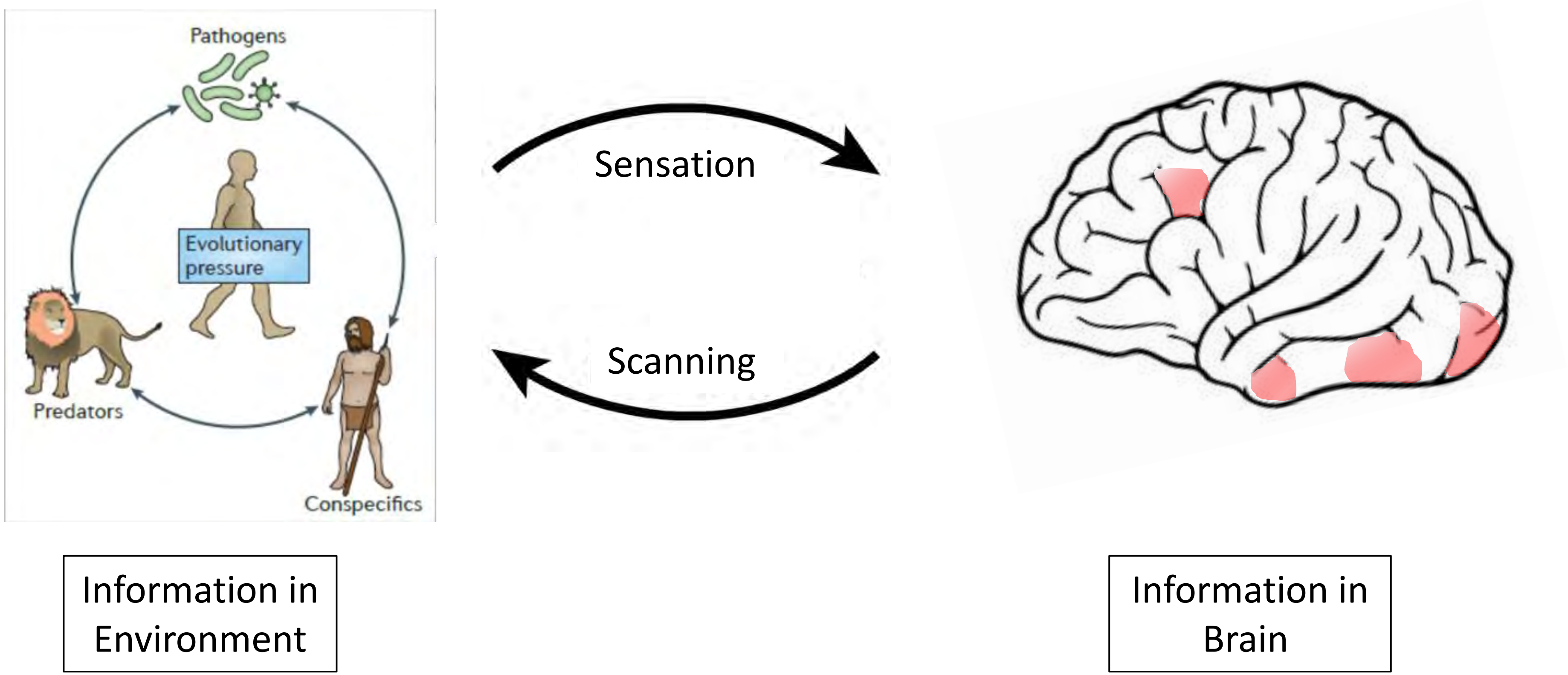
   giving them resilience in the face of perturbation (homeostasis)
3. Self-organization : complexity of the system increases without external organizer
4. Self-similarity: the whole has the same shape as one or more of the parts (fractal)
5. **Emergence** : whole is more than sum of components, new property



Each pattern has emergent characteristic



Code = activity + connectivity


Pathogens
Evolutionary pressure
Predators
Conspecifics
Sensation
Scanning
Information in Environment
Information in Brain

Two ways for body to communicate with environment

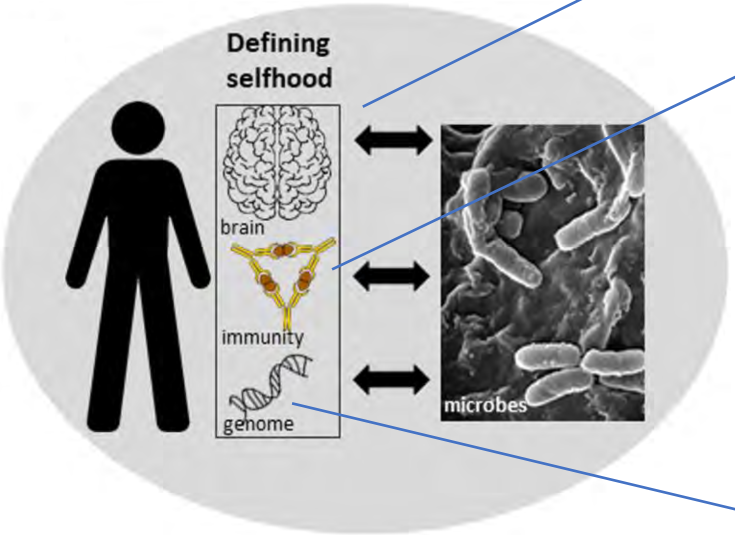
Nervous system developed as a way to distinguish bacteria as from beneficial symbiontic bacteria from pathogenic bacteria and viruses and engage with microbes (detect, move to or fight) (Klimovich 2018)

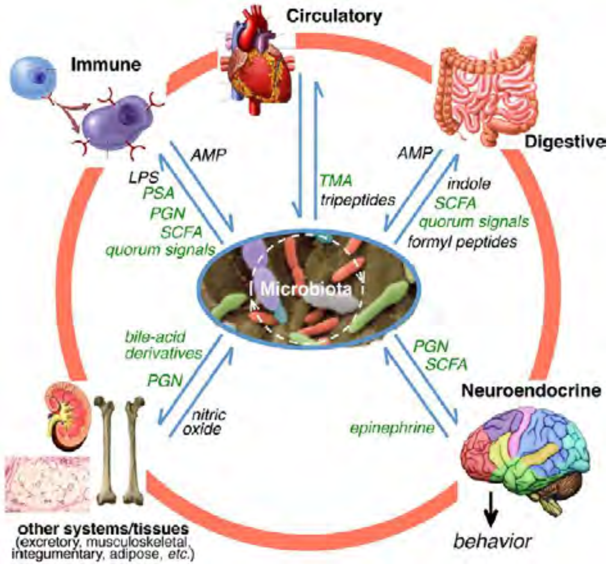
Microbiome and self

Self

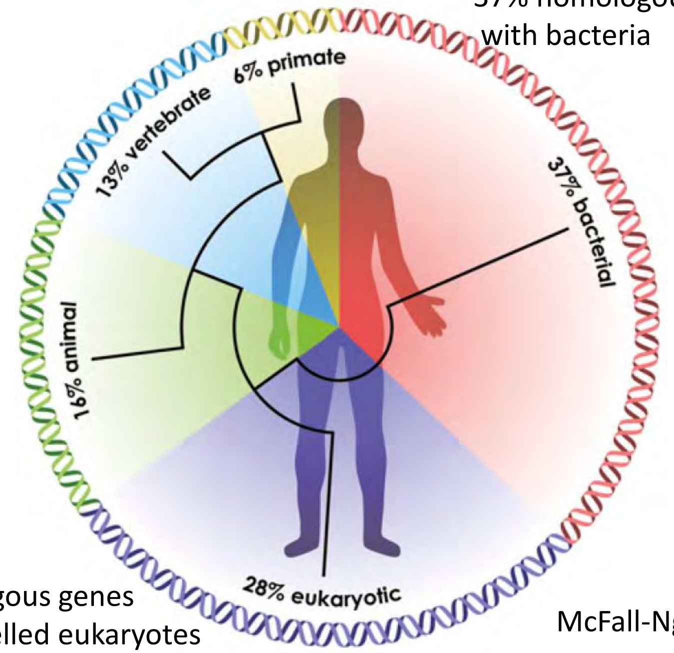
Traditional view

Current view





37% homologous genes with bacteria



28% homologous genes with single celled eukaryotes

Rees 2018

McFall-Ngai 2013

Brain and immune system are energy expensive

Selfish brain (Straub 2010)

Brain consumes 25% of total energy

Immune system 20%

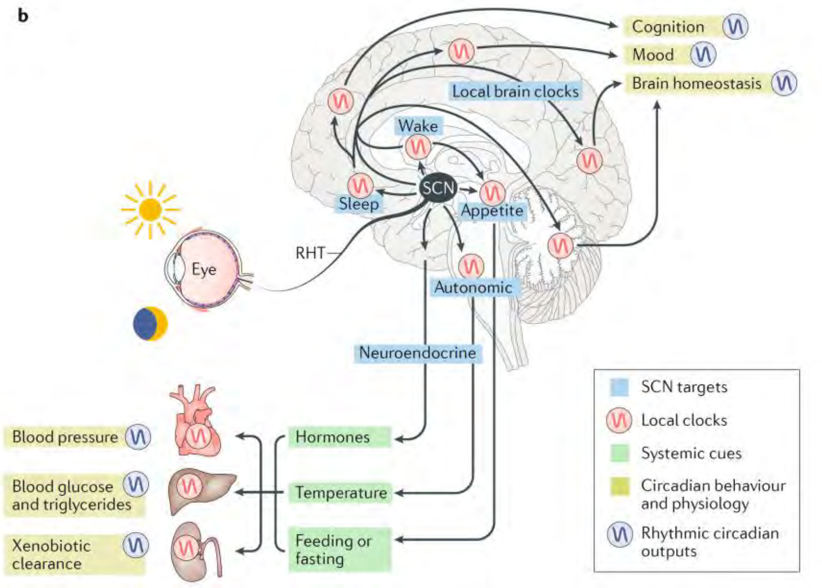
Heart and lungs 25%

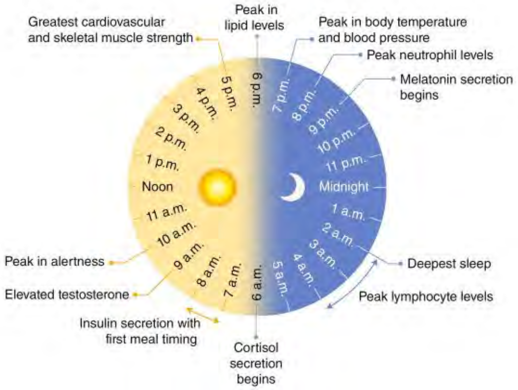
Internal organs 30%

+ Muscles: extra 20%

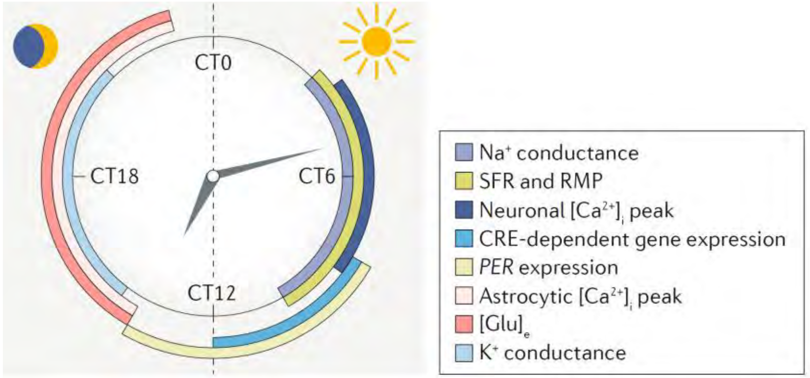
~50% of mammalian genes are expressed with 24-hour rhythms (Zhang 2014, Mure 2018)

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





Masri 2018

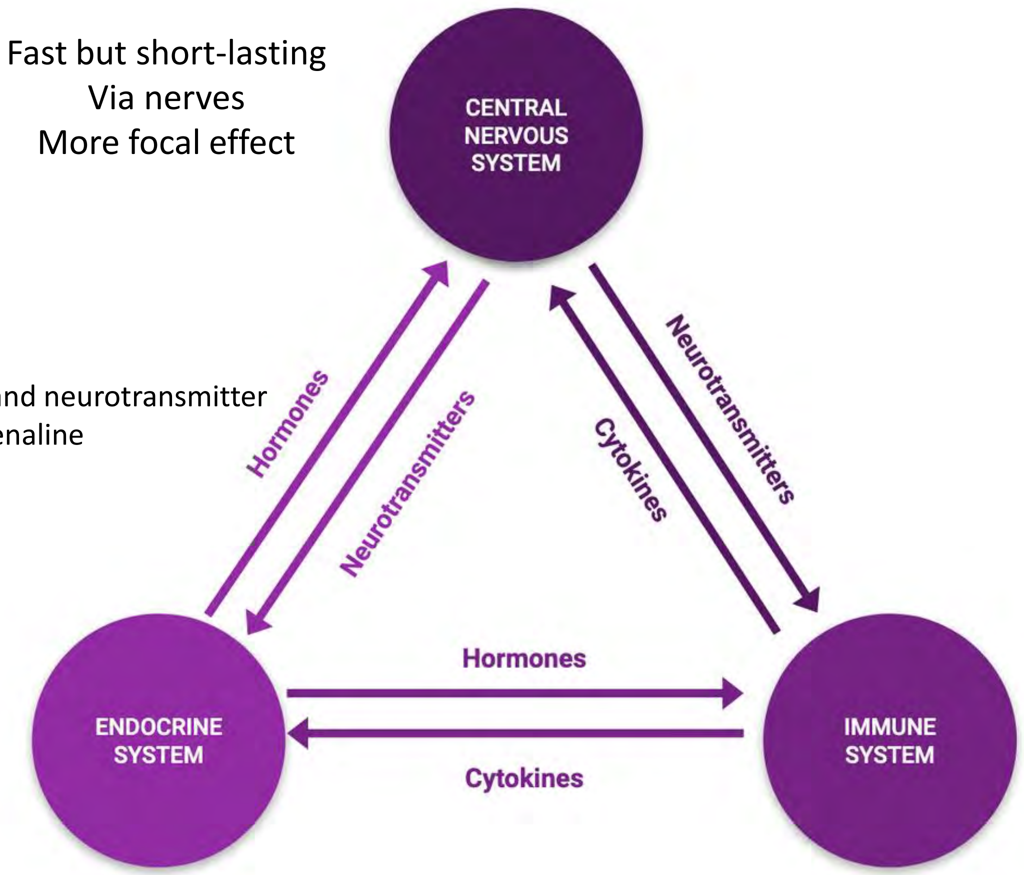


Hastings 2018

Signal molecules

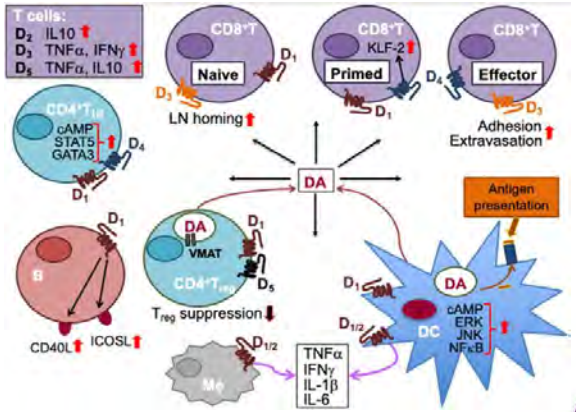
Fast but short-lasting
Via nerves
More focal effect

Some are both hormone and neurotransmitter
Eg noradrenaline and adrenaline

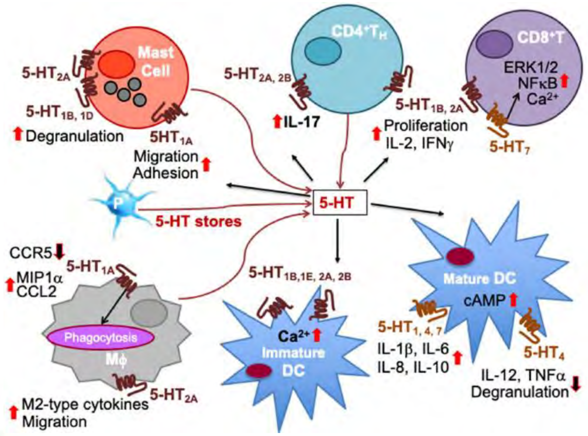


Slow but long-lasting
Via blood
More general effect

Cytokines = Lymphokines + IL
+ chemokines + interferons + TNFα

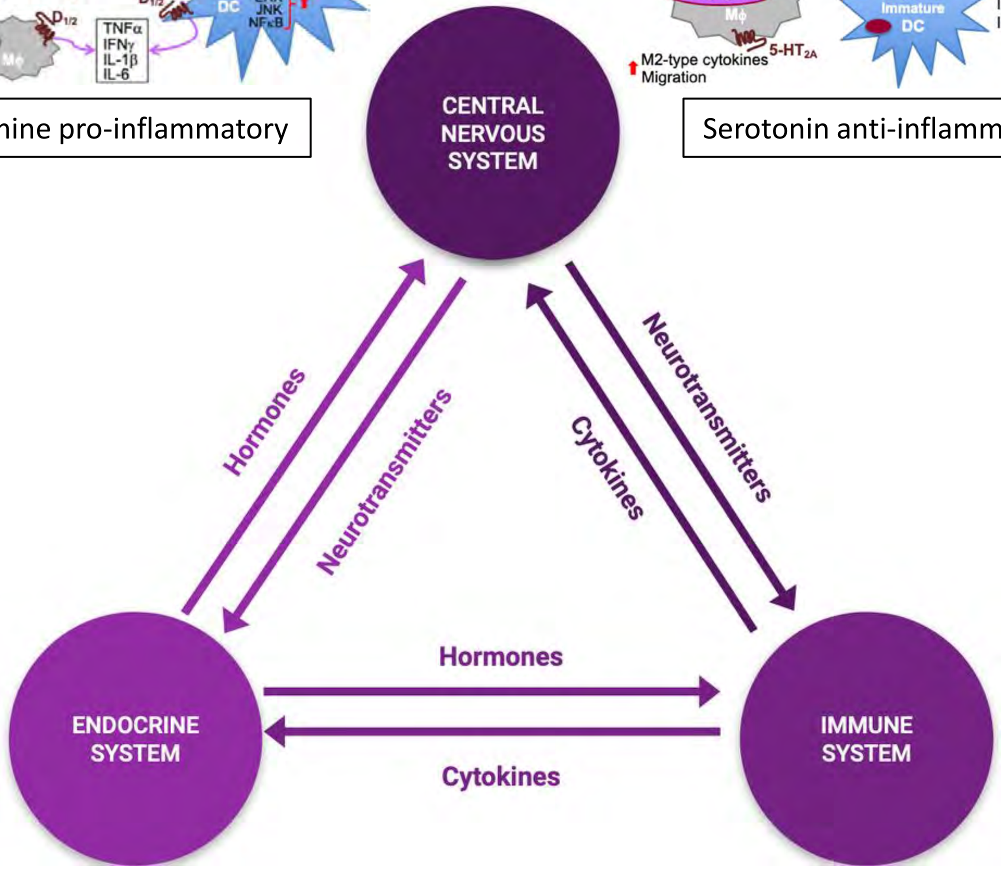


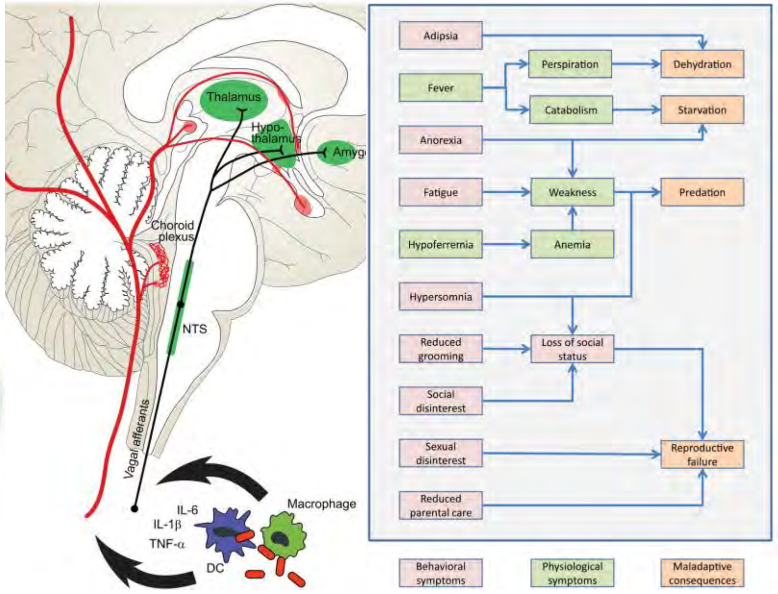
Dopamine pro-inflammatory



Serotonin anti-inflammatory

Hodo 2020

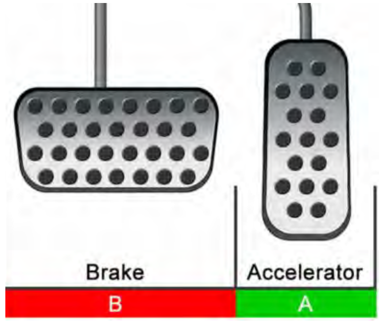


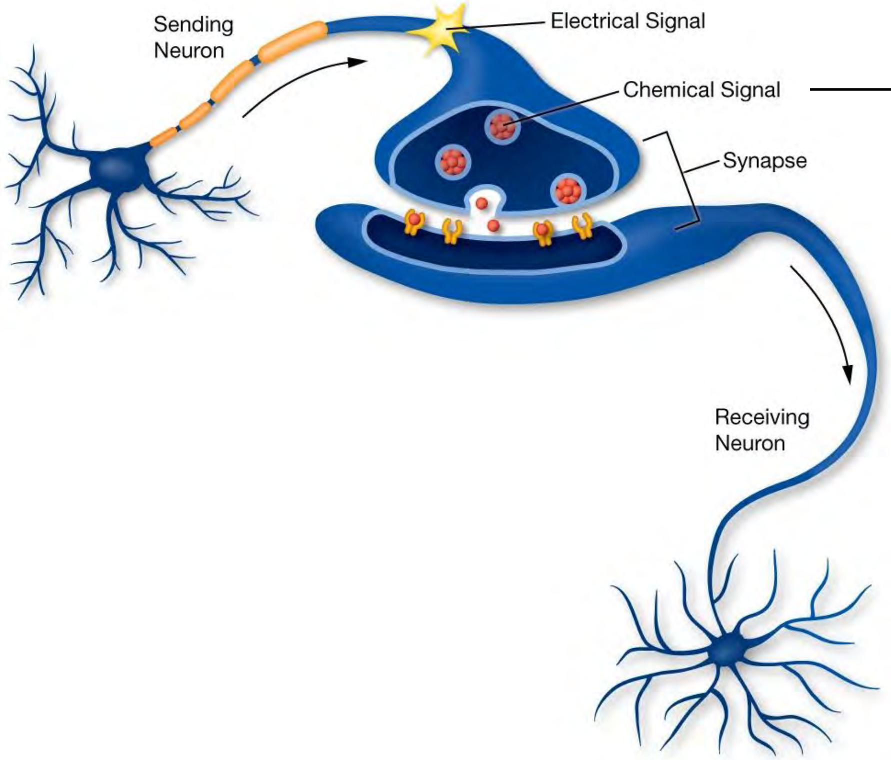


Cortisol is anti-inflammatory
Testosterone is anti-inflammatory (Bianchi 2019)
Estrogen is anti-inflammatory (Vegeto 2008)
Thyroid hormone and glucagon are anti-inflammatory (Garcia-Leme 1993)

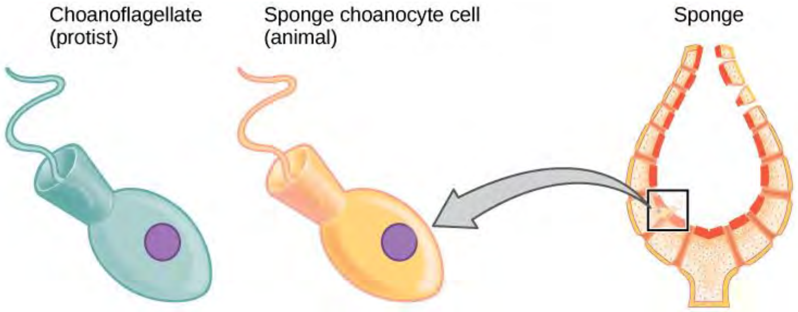
Cytokines induce sickness behaviour (sleep, fatigue, social and sexual withdrawal,…)
Saves energy and prevents transmission (Shakhar 2015)

Brains are electrical and chemical



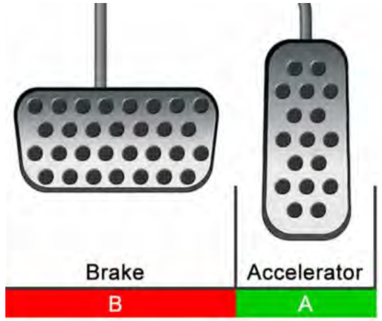


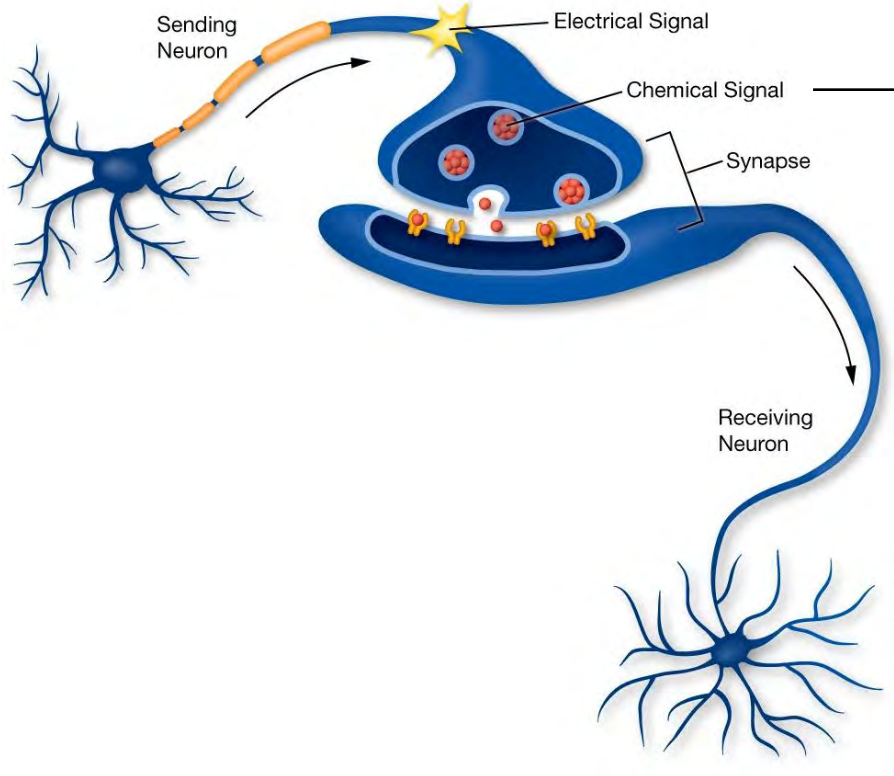
GABA/glycine ⟷ Glutamate

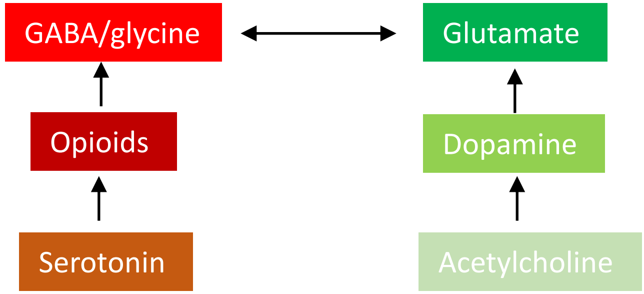


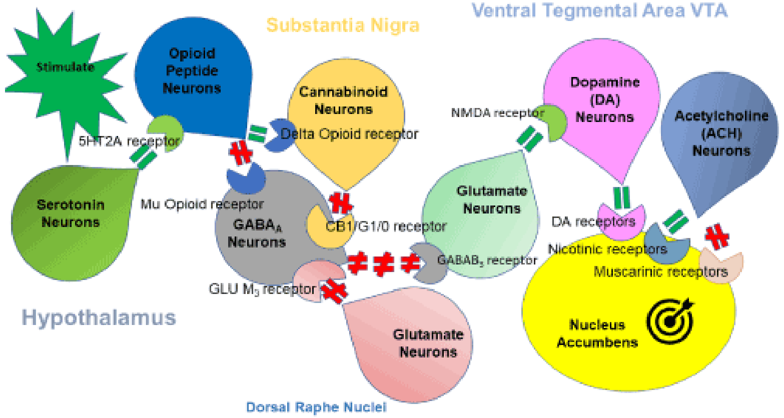
Choanoflagellates use glutamate and GABA as signal molecules
Same signal molecules later repurposed as neurotransmitters

Brains are electrical and chemical

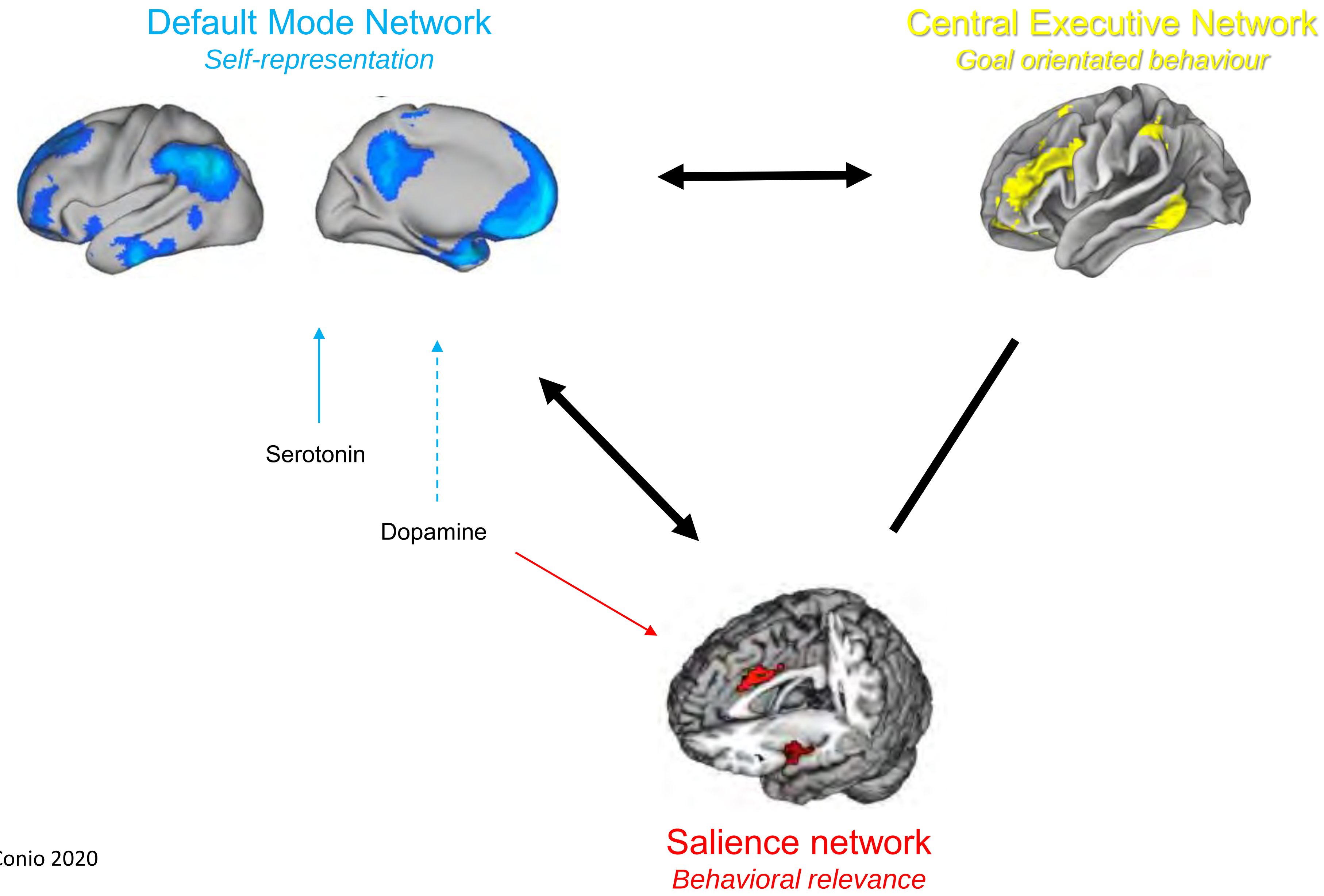




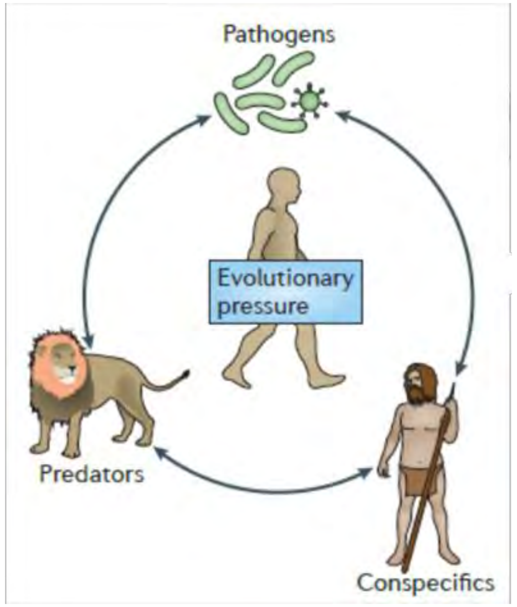




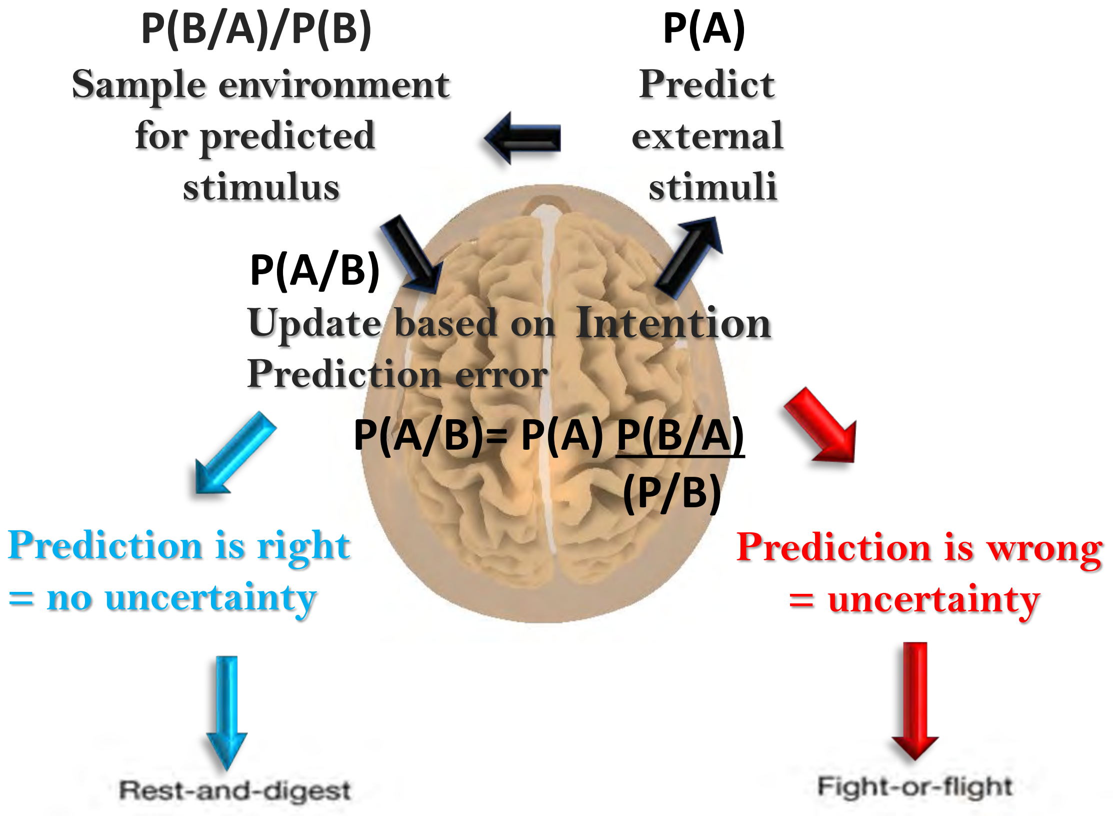
Blum 2020


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

Conio 2020

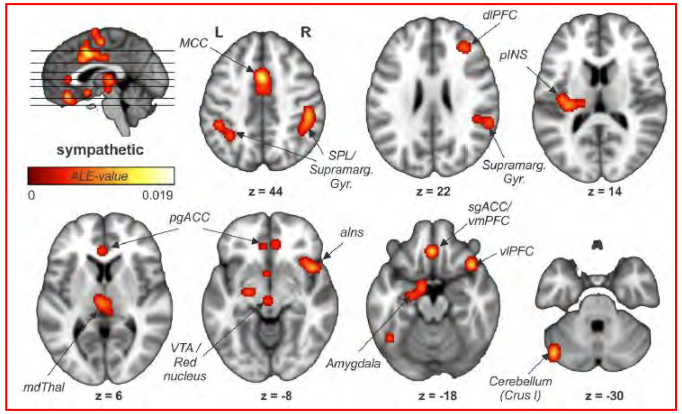


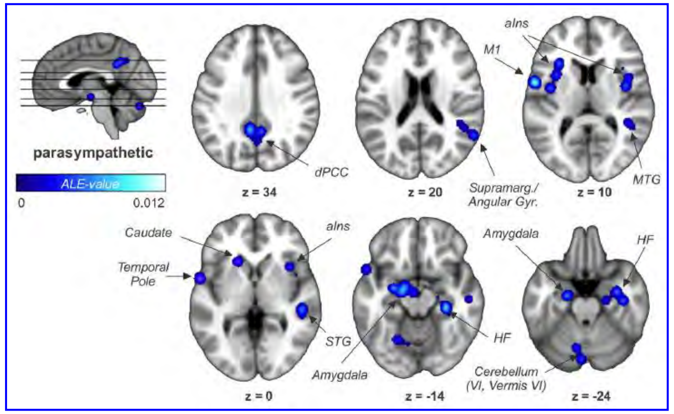
Brain networks for interaction of self with environment



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

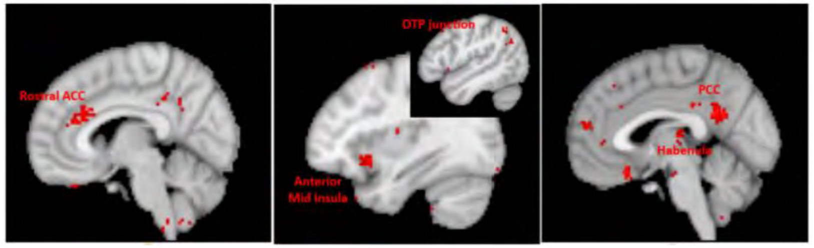
Evolution of ANS

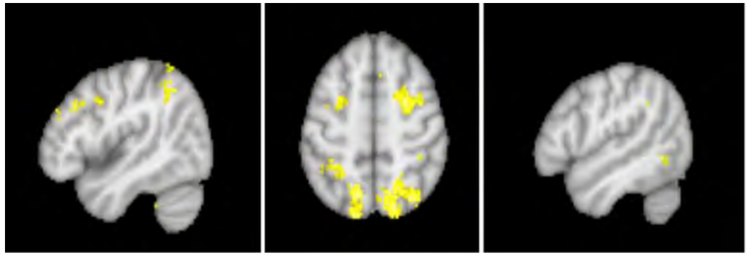


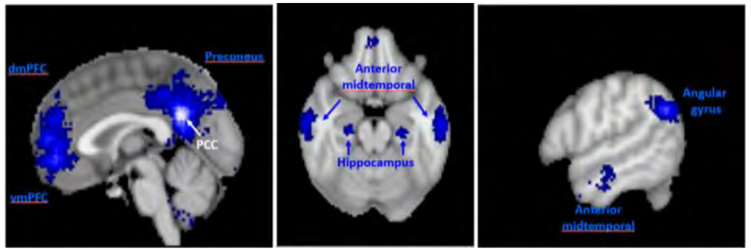


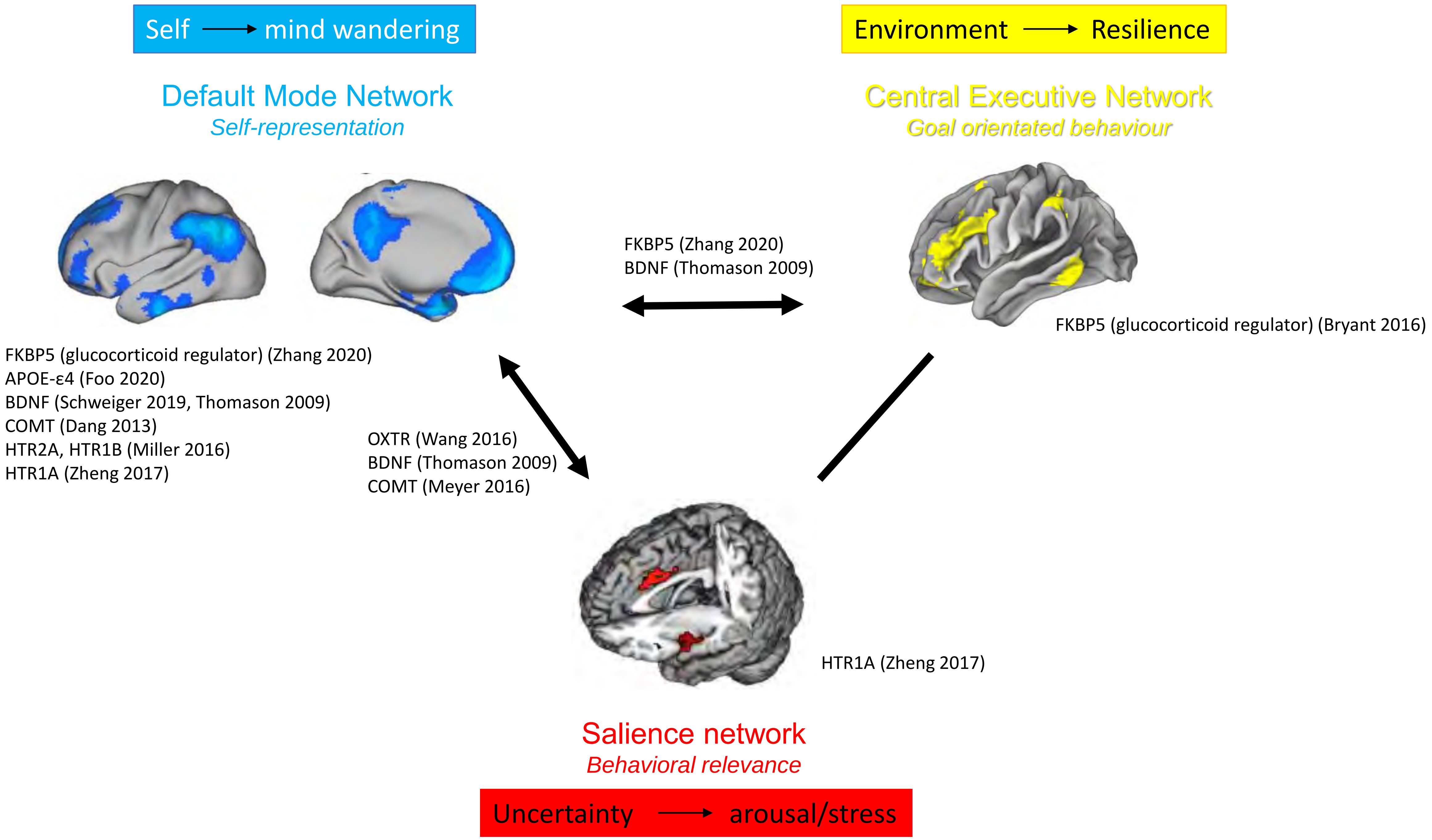
Salience + Central executive

Default mode



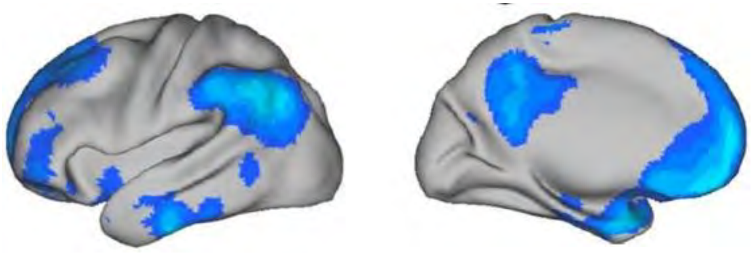





Self → mind wandering
Environment → Resilience
Default Mode Network
Self-representation
Central Executive Network
Goal orientated behaviour
FKBP5 (Zhang 2020)
BDNF (Thomason 2009)
FKBP5 (glucocorticoid regulator) (Bryant 2016)
FKBP5 (glucocorticoid regulator) (Zhang 2020)
APOE-ε4 (Foo 2020)
BDNF (Schweiger 2019, Thomason 2009)
COMT (Dang 2013)
HTR2A, HTR1B (Miller 2016)
HTR1A (Zheng 2017)
OXTR (Wang 2016)
BDNF (Thomason 2009)
COMT (Meyer 2016)
HTR1A (Zheng 2017)
Salience network
Behavioral relevance
Uncertainty → arousal/stress

Default Mode Network

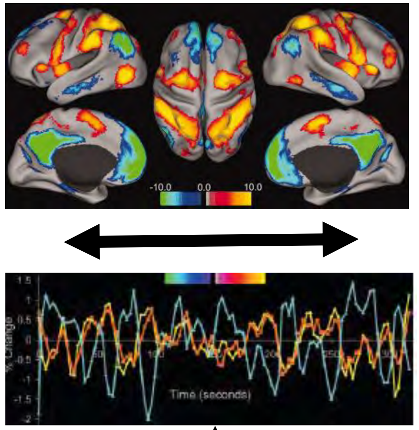
Self-representation



Rest, digest, restore

parasympathetic

Fox 2005

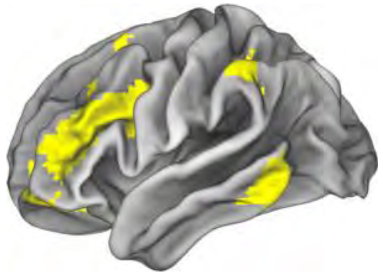


Salience network

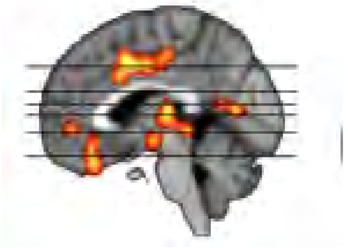
Behavioral relevance

Central Executive Network

Goal orientated interaction with environment

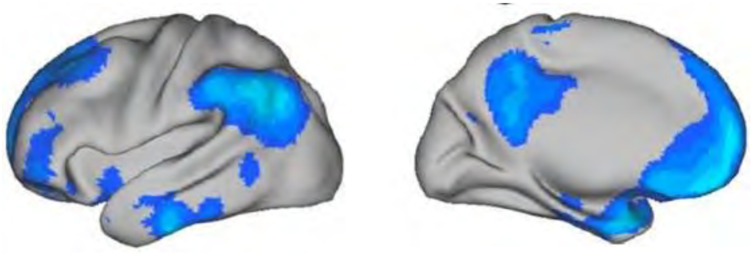


Urge for action

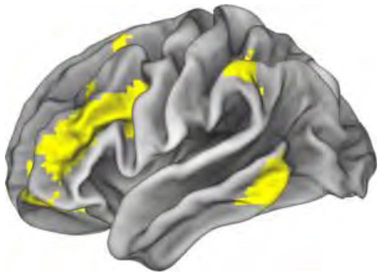


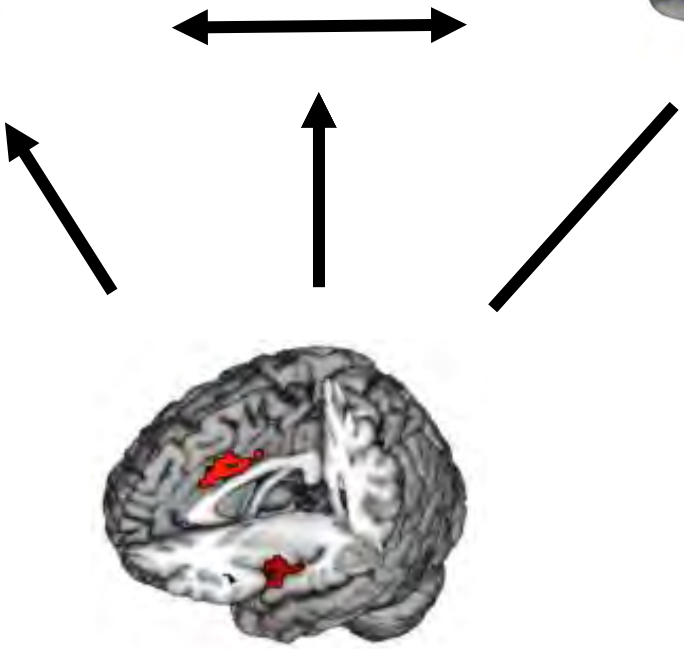
sympathetic

Default Mode Network
Self-representation



Central Executive Network
Goal orientated behaviour

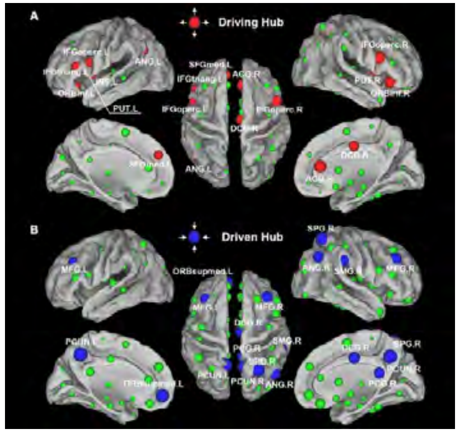




Salience network
Behavioral relevance

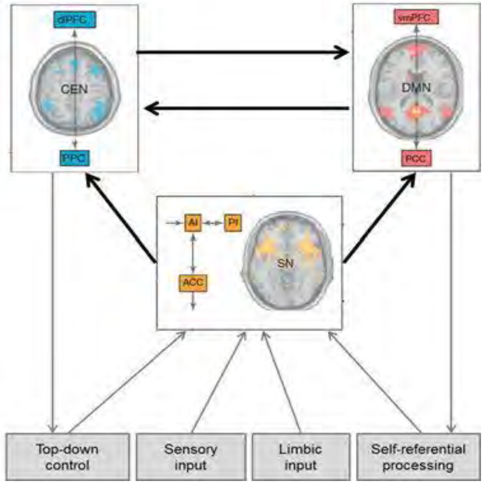
Salience network drives DMN

Yan 2011



Salience network switches between DMN and CEN

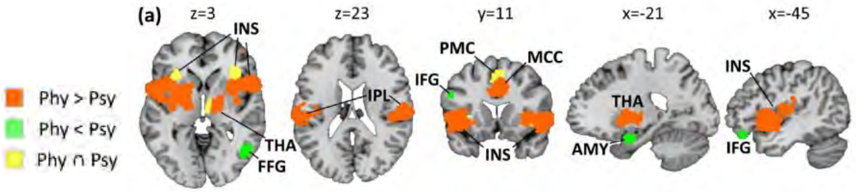
Menon 2010

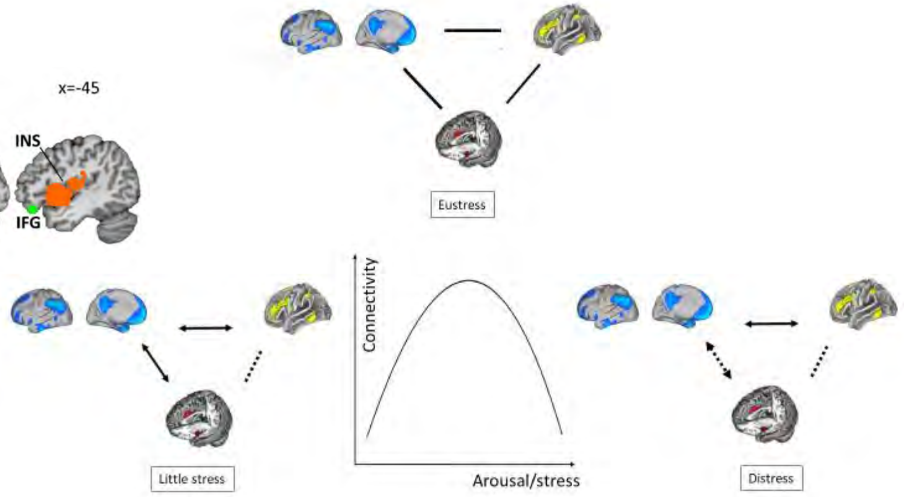


Networks and network interactions change

Adaptive and maladaptive

Stress = uncertainty

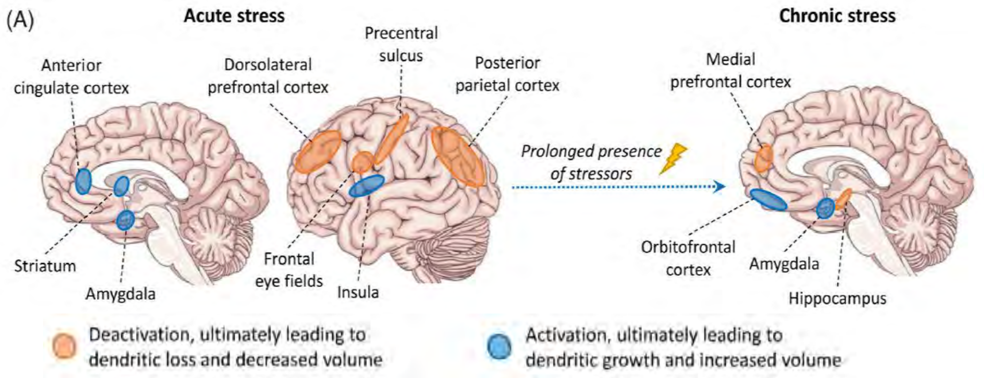


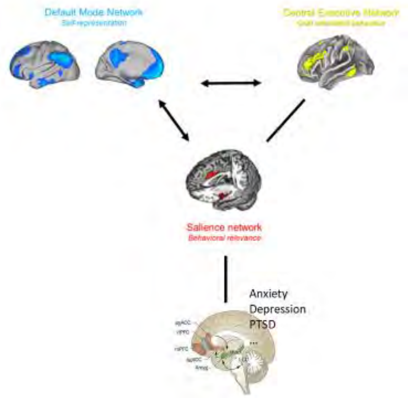


Acute stress (adaptive)

Activity: increased in SN

Connectivity: Δ





Chronic stress (maladaptive)

Activity

Connectivity

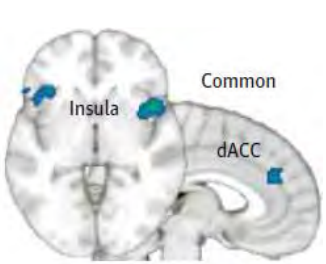
Inflammatory

Exhaustion = mental disorder

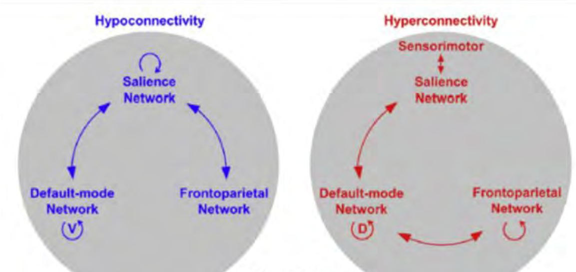
Activity

Connectivity

Atrophy



Anxiety, depression, bipolar, ADHD, autism, OCD, PTSD, schizophrenia

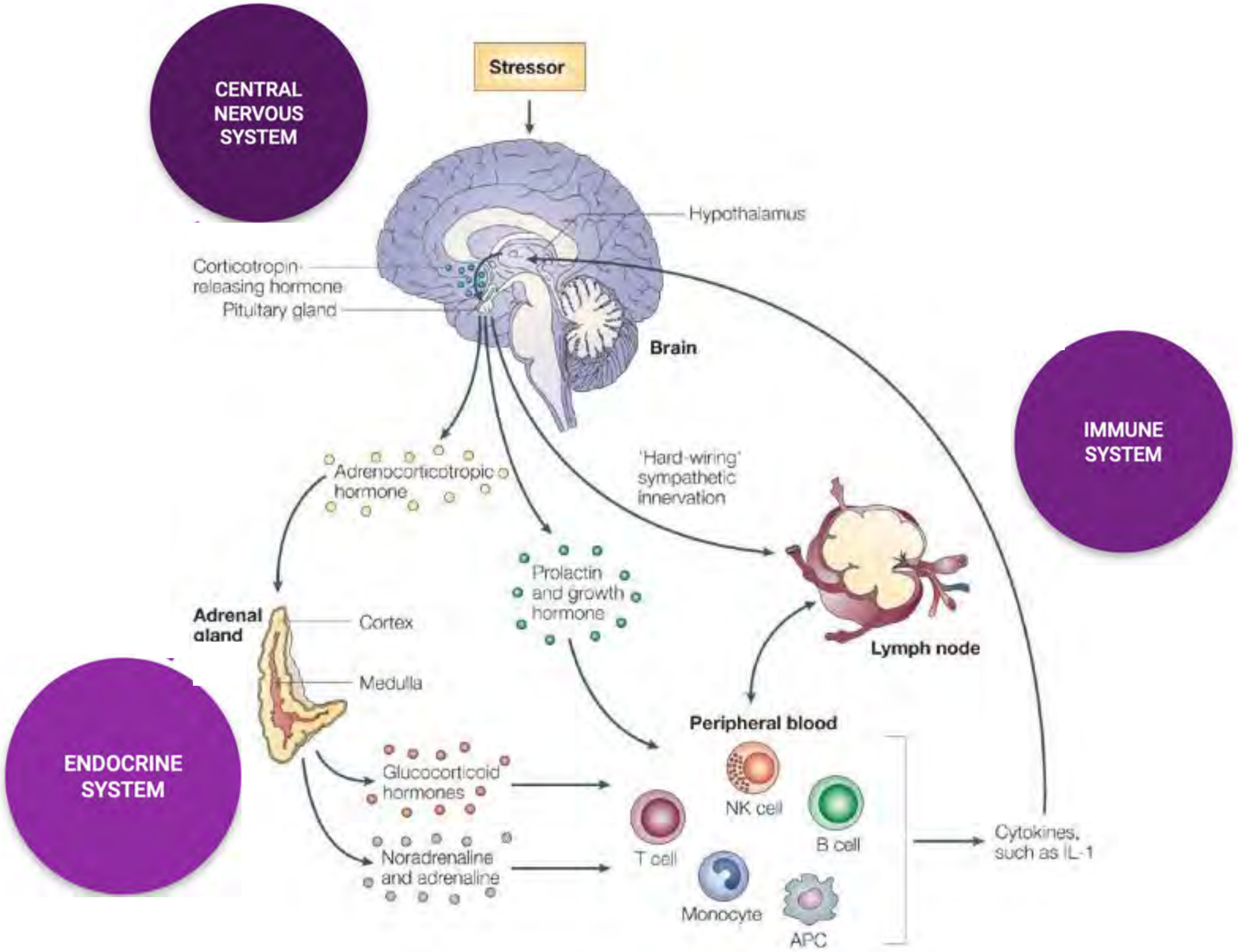


Sha 2018

Chronic stress related diseases

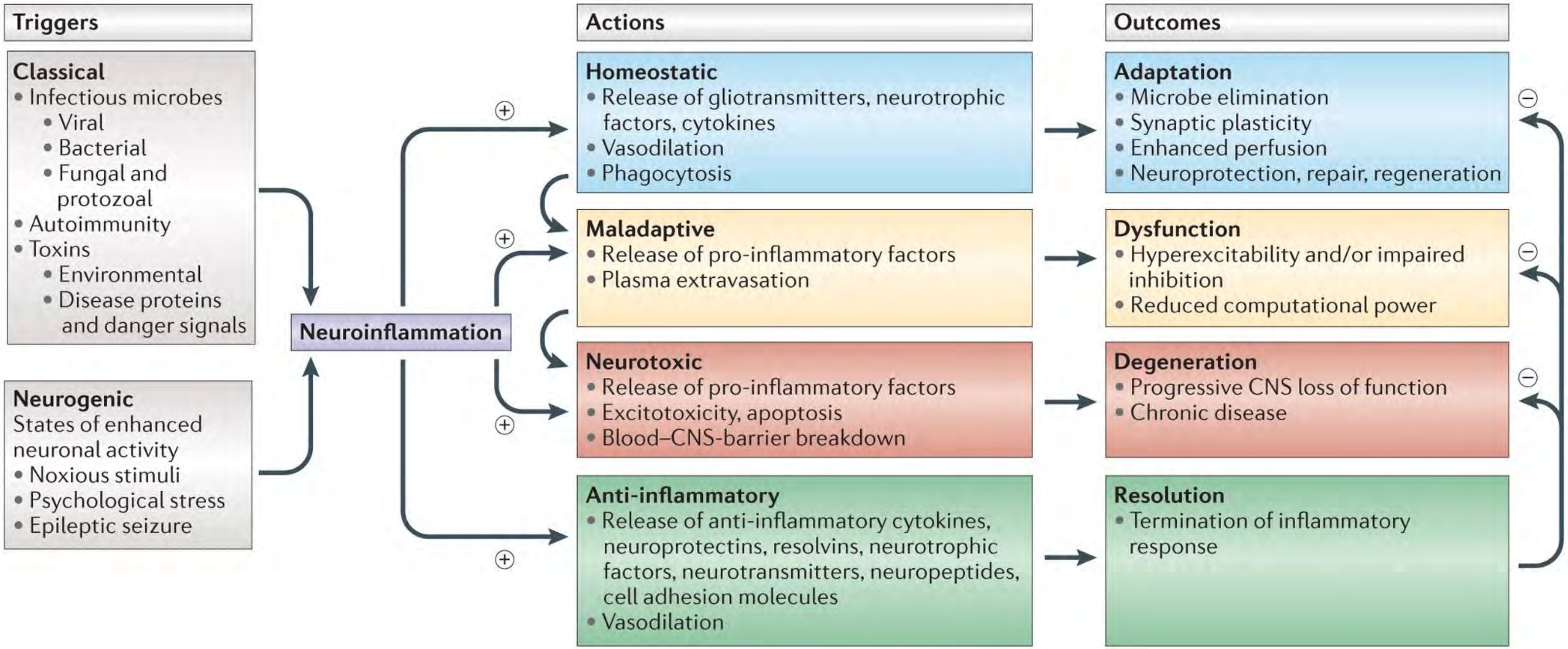
Stress is associated with (Cohen 2007)

1. Depression and anxiety
2. Cardiovascular disorders
3. HIV to AIDS progression
4. Cancer progression or relapse



Glaser 2005

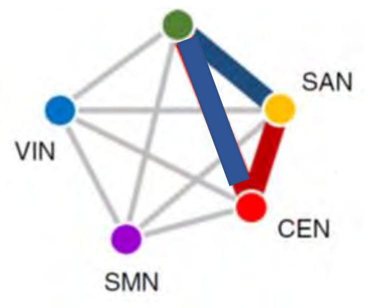
Neuroinflammation



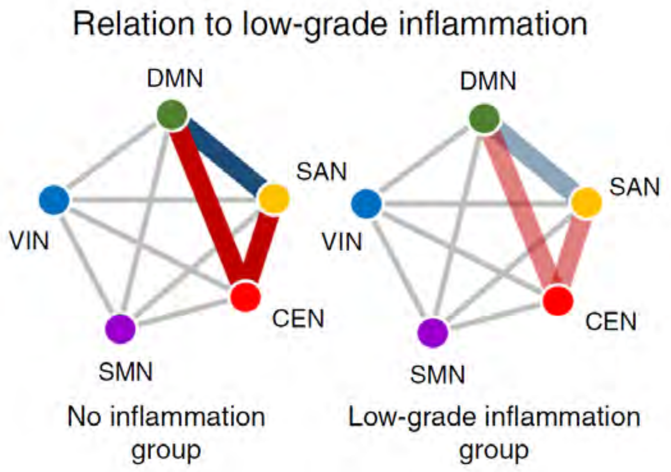
Xanthos 2014

Stress and neuroinflammation

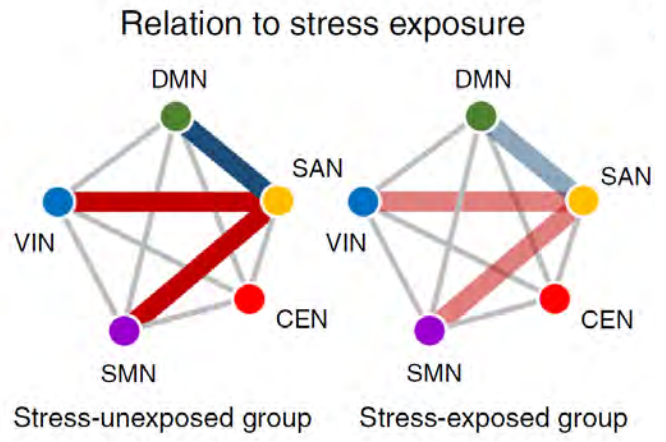
No stress

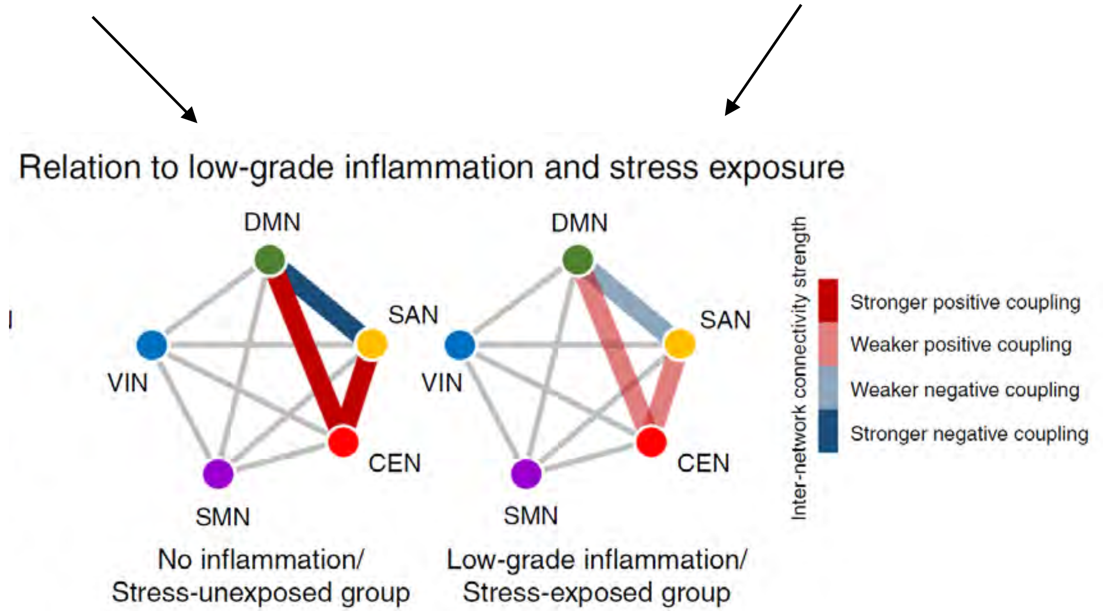


PTSD



PTSD



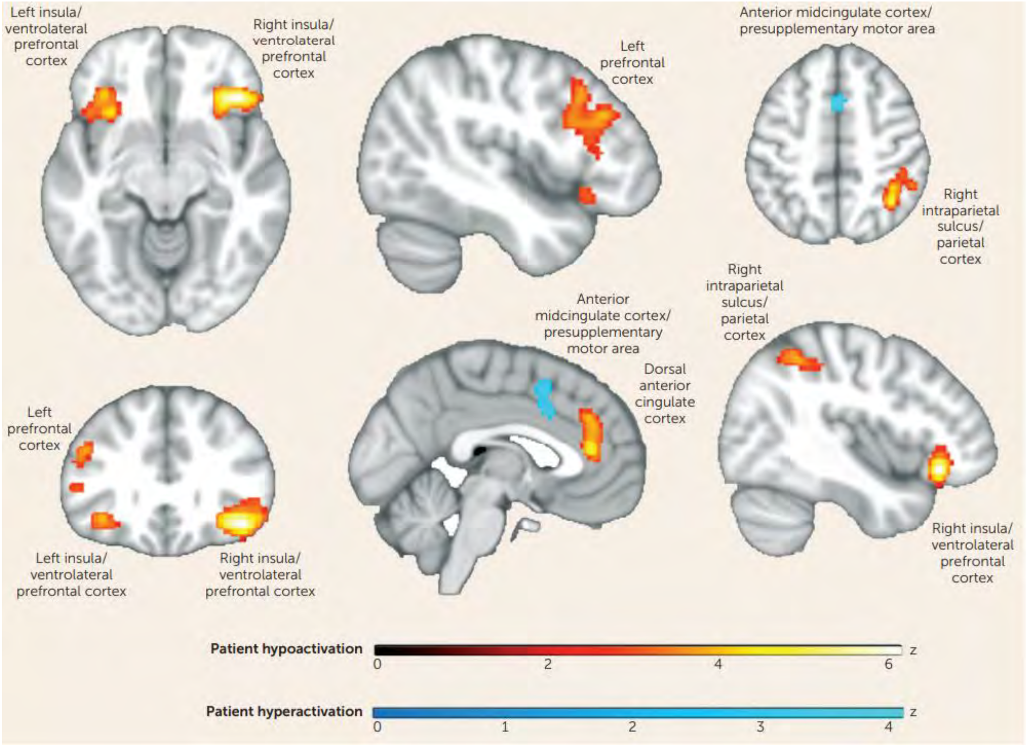


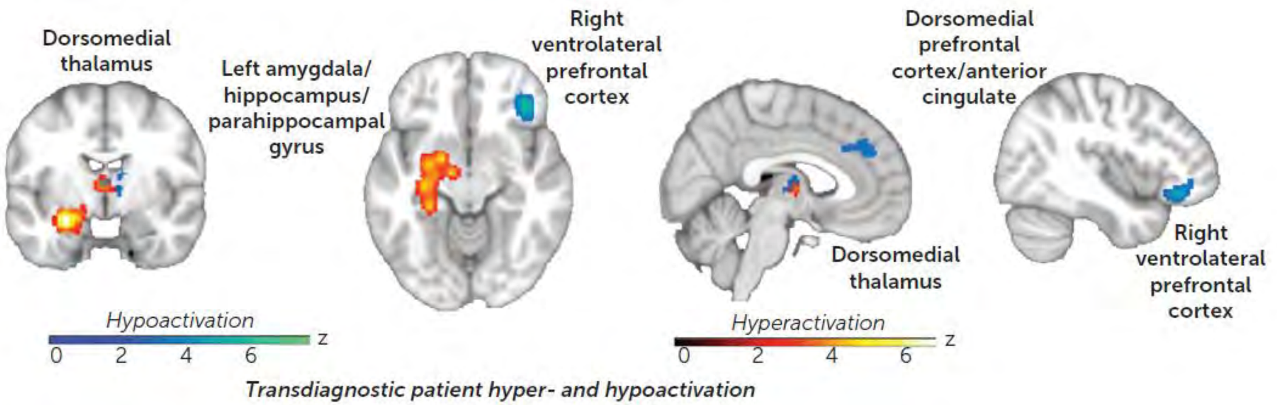
Kim 2020

Common activity changes in schizophrenia, bipolar or unipolar depression, anxiety, and substance use disorder

Cognitive dysfunction

Emotional dysfunction

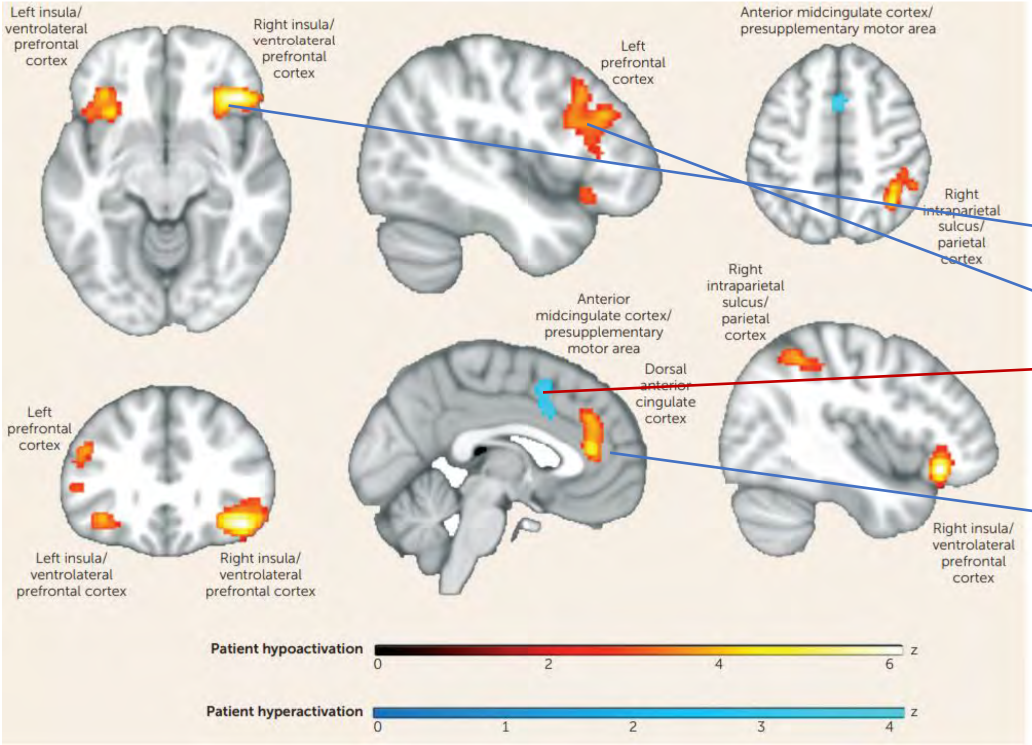




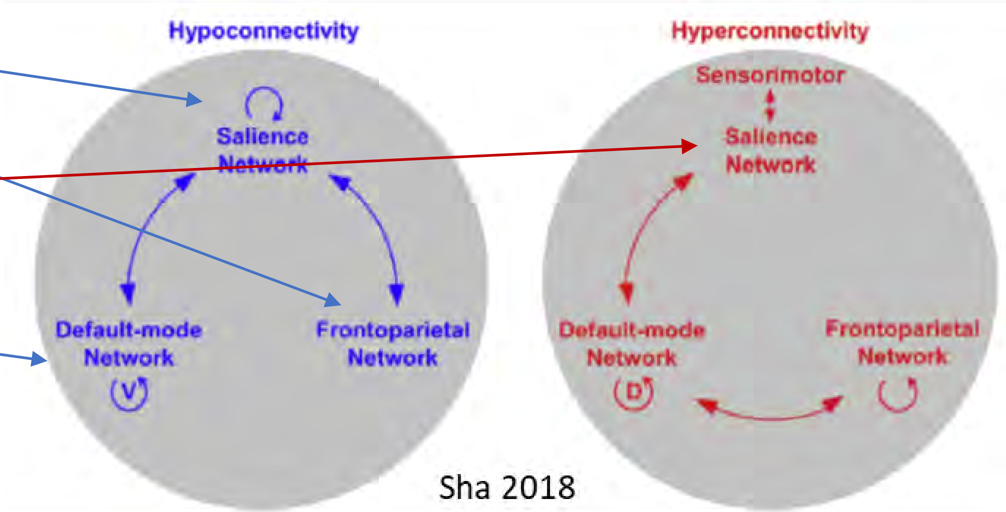
McTeague 2017

McTeague 2017

Triple network model and mental disorders

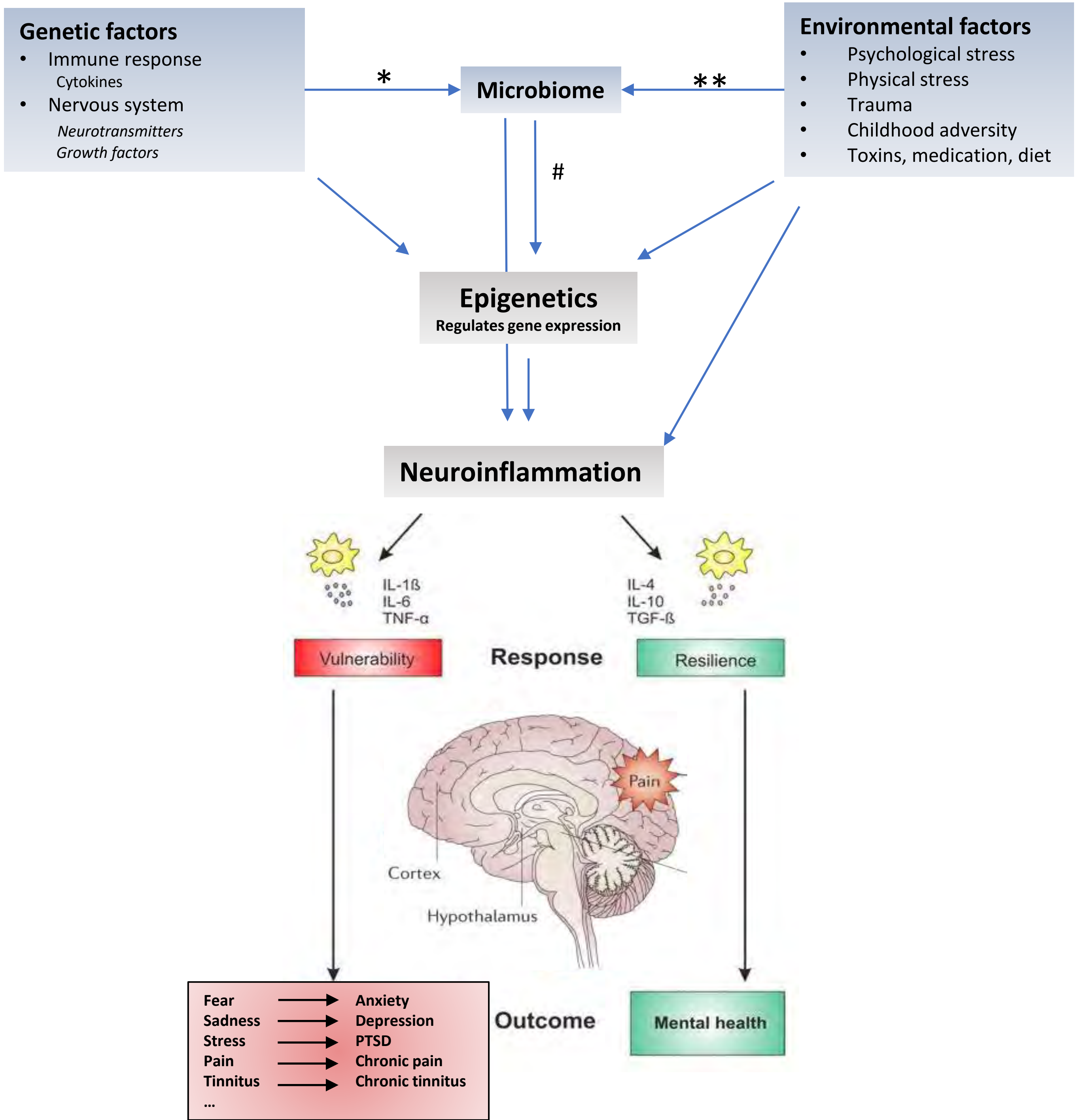


Anxiety, depression, bipolar, ADHD, autism, OCD, PTSD, schizophrenia



Sha 2018

McTeague 2017



*Martins-Silva 2020, # Watson 2017

** Hantsoo 2021

Neuroplasticity

= capacity of the nervous system to modify its organization (structure and function), adjusting itself to changes in the environment

Brain disorders

= maladaptive neuroplasticity

Adaptive reconfiguration of dynamically interacting brain networks

Neuroplasticity

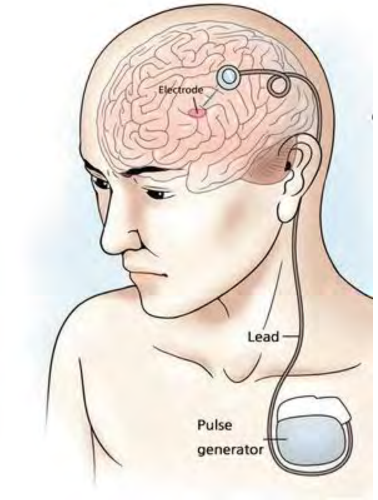
= capacity of the nervous system to modify its organization (structure and function), adjusting itself to changes in the environment

↓

Neuromodulation

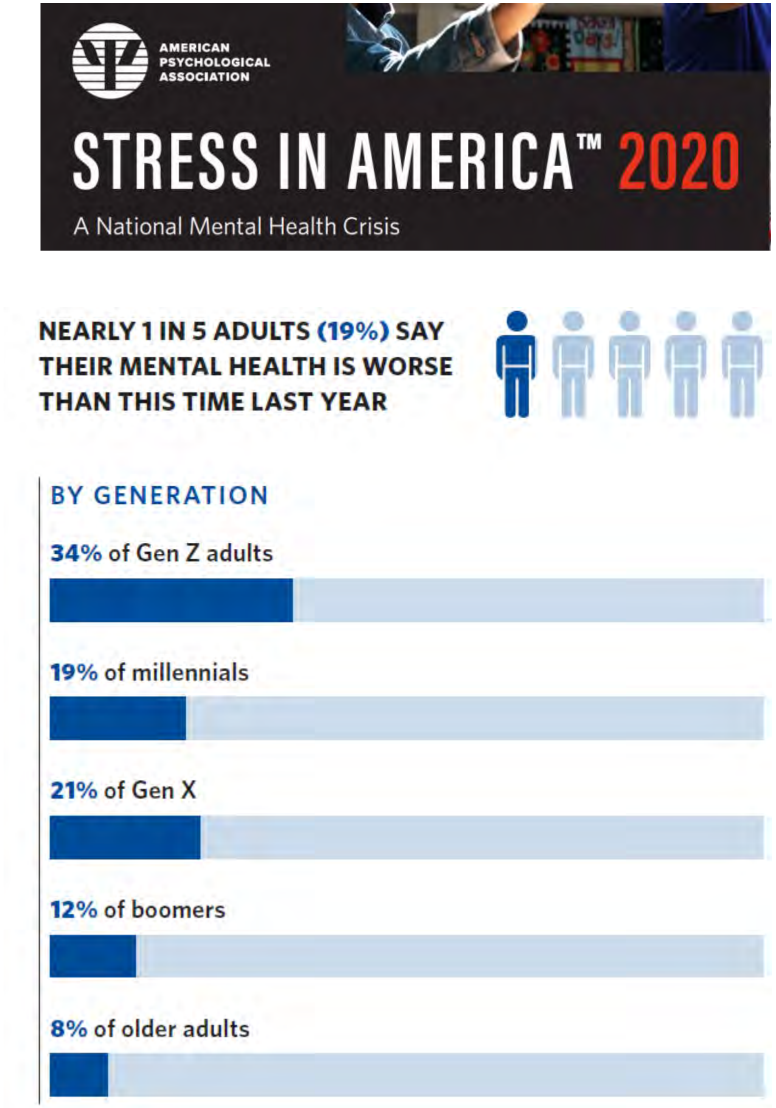
= induction of neuroplastic changes via local application of electrical, magnetic, sound, pharmacological or optic stimuli

Why neuromodulation?



Covid related psychological impact: esp younger people

Population	Stress	Anxiety	Depression	Sleep	Reference
College students	23%	29%	37%		Wang 2021
Pregnant women	56%	33%	27%		Demissie 2021
Health care workers	29%	34%	31%	36%	Sahebi 2021
General population	36%	27%	28%	27%	Nochaiwong 2021
Pre-covid		6.6% 12.9% lifetime	5.4% 9.6% lifetime		Steel 2014



Efficacy of psychotherapy and psychopharmacology

3,782 RCTs and 650,514 patients (Leichsenring 2022)

MDD, anxiety, PTSD, OCD, somatoform disorders, eating disorders, ADHD, SUD, insomnia, schizophrenia spectrum disorders, and bipolar disorder.

Psychopharmacology and psychotherapy are equally effective (Cuijpers 2017)

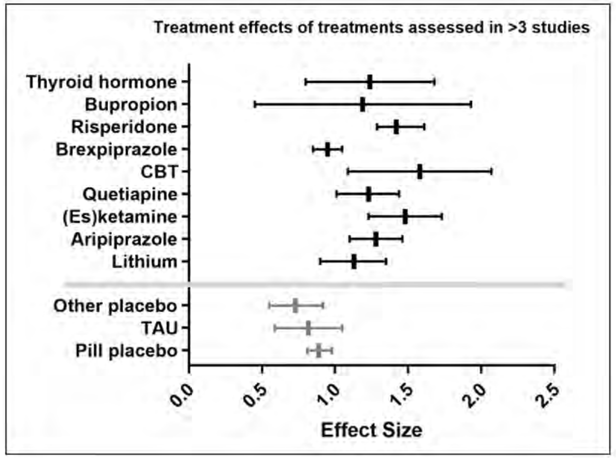
NNT	Cohen's d[a]	Effect size
1	–	Perfect[b]
2.3	0.8	Large
3.6	0.5	Medium
9.0	0.2	Small

Sullivan2021

Small effect sizes (Standard Mean Difference) (Leichsenring 2022)

- 0.34 SMD for psychotherapy > control
- 0.36 SMD for pharmacology > placebo
- NNT for psychotherapy is 7.4 (Schefft 2019)
- NNT for SSRI and TCA is 7 and 9 (Arroll 2009)

Augmentation for treatment resistant depression



Combined is better than monotherapy

- 0.31 SMD of combined vs monotherapy
- Combination in treatment resistant depression is better (Scott 2022)

Scott 2022

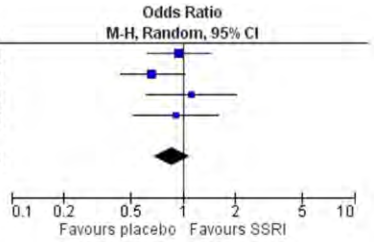
Antidepressants in >65

Antidepressants for MDD >65 yo (Tham 2016)

- No better than placebo for response or remission
- Better for prevention relapse

Study or Subgroup	SSRI Events	SSRI Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Random, 95% CI
Kasper (Escitalopram)	78	170	85	180	33.7%	0.95 [0.62, 1.44]
Kasper (Fluoxetine)	61	164	85	180	32.0%	0.66 [0.43, 1.02]
Roose (Citalopram)	34	84	34	90	16.0%	1.12 [0.61, 2.06]
Schatzberg (Fluoxetine)	39	99	40	96	18.2%	0.91 [0.51, 1.61]
Total (95% CI)		**517**		**546**	**100.0%**	**0.86 [0.67, 1.10]**
Total events	212		244			

Heterogeneity: Tau² = 0.00; Chi² = 2.38, df = 3 (P = 0.50); I² = 0%
Test for overall effect: Z = 1.20 (P = 0.23)



2. Response to acute treatment with SSRIs versus a placebo in elderly subjects, aged 65 years and older, with depressive disorder: Odds Ratio.

Study or Subgroup	SSRI Events	SSRI Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Random, 95% CI
Kasper (Escitalopram)	78	170	85	180	33.7%	0.95 [0.62, 1.44]
Kasper (Fluoxetine)	61	164	85	180	32.0%	0.66 [0.43, 1.02]
Roose (Citalopram)	34	84	34	90	16.0%	1.12 [0.61, 2.06]
Schatzberg (Fluoxetine)	39	99	40	96	18.2%	0.91 [0.51, 1.61]
Total (95% CI)		**517**		**546**	**100.0%**	**0.86 [0.67, 1.10]**
Total events	212		244			

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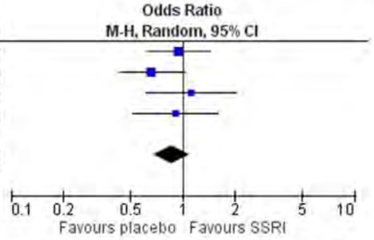
Test for overall effect: Z = 1.20 (P = 0.23)



3. Remission after acute treatment with SSRIs versus a placebo in elderly subjects, aged 65 years and older, with depressive disorder: Odds Ratio.

Study or Subgroup	SSRI Events	SSRI Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Random, 95% CI
Gorwood 2007	13	152	50	153	56.7%	0.19 [0.10, 0.37]
Klysner 2002	18	60	38	61	43.3%	0.26 [0.12, 0.55]
Total (95% CI)		212		214	100.0%	0.22 [0.13, 0.36]
Total events	31		88			

Heterogeneity: Tau² = 0.00; Chi² = 0.34, df = 1 (P = 0.56); I² = 0%
Test for overall effect: Z = 5.97 (P < 0.00001)

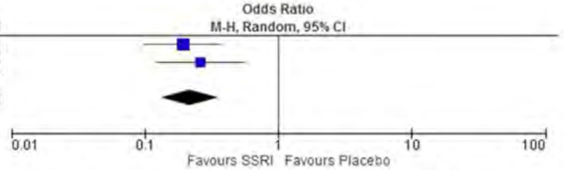


Fig. 4. Relapse in depressive disorder after maintenance treatment with SSRIs or a placebo for up to one year: Odds Ratio.

Non-Surgical Neuromodulation

TMS

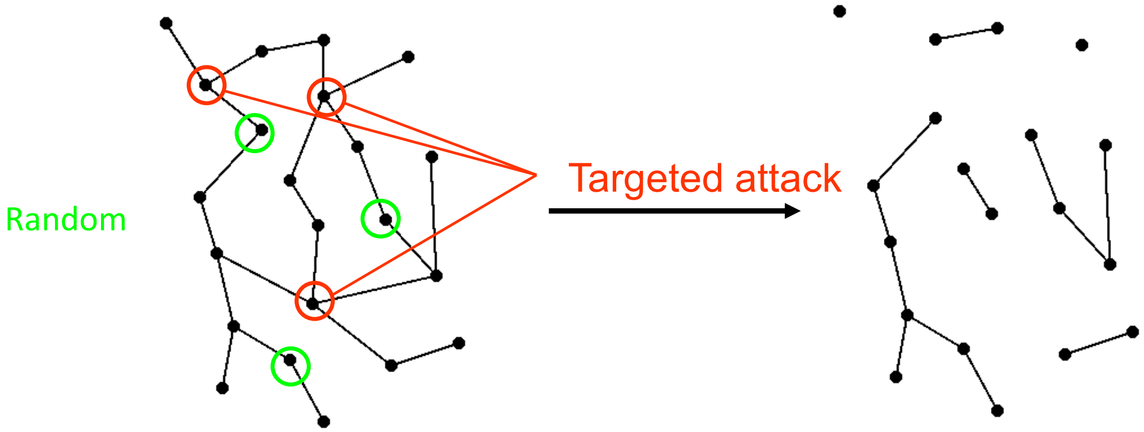
TENS

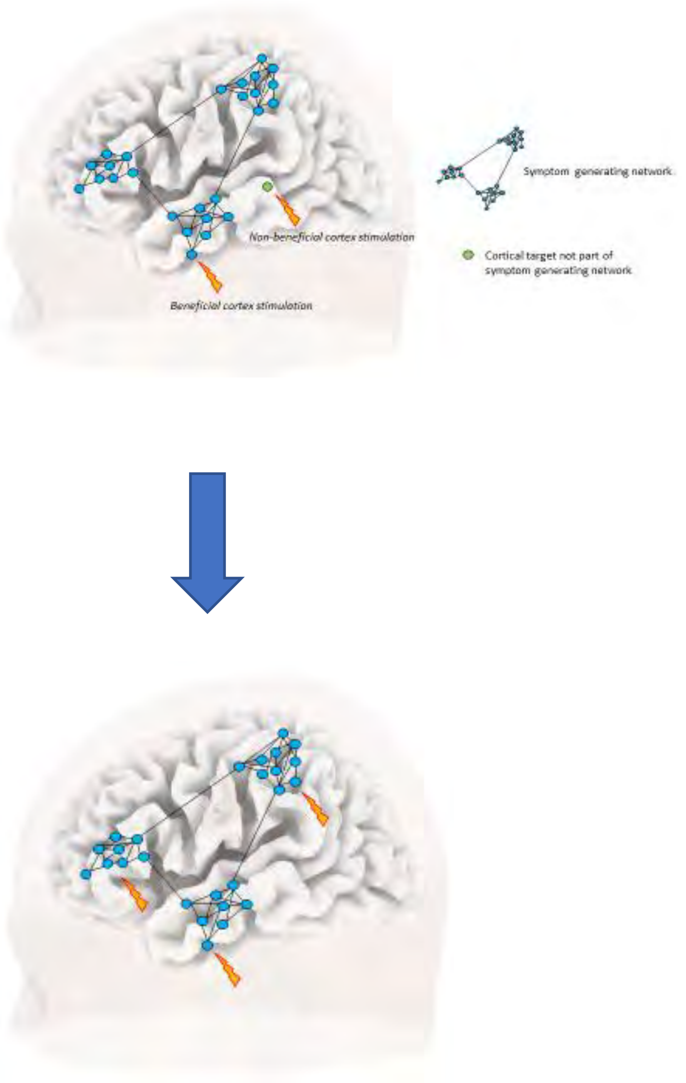
tDCS
tACS } tES
tRNS

Neurofeedback

ECT

Network stimulation





Albert 2000

De Ridder 2017

Neuromodulation techniques

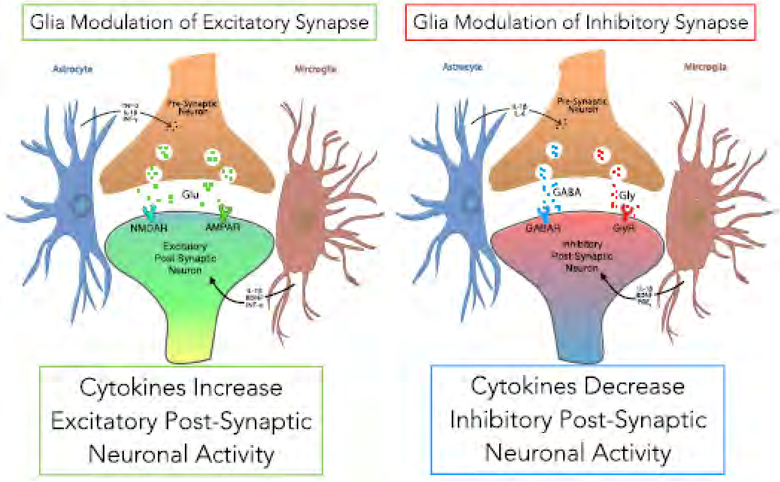
	TMS	tDCS	tACS*	tRNS*	implants	ECT	NFB
Putative mechanism	A & β synchronization Suprathreshold for AP	Depolarize Hyperpolarize Subthreshold for AP	Entrain at specified frequency Subthreshold for AP	Desynchronize ? Subthreshold for AP	Virtual lesion Subthreshold for AP	Epileptic reset	Train oscillations Subthreshold for AP
Functional connectivity	changes	changes	changes	changes	changes	changes	changes
Effective connectivity	changes	changes	changes	?	changes	changes	changes

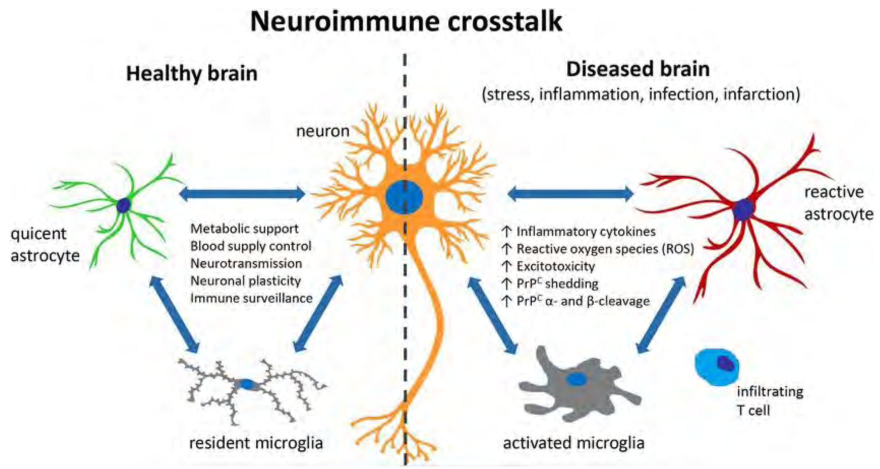
Electrical stimulation modulates neuroinflammation

All kinds of electrical stimulation modulate neuroinflammation (Chakravarthy 2018)

- SCS, DBS, VNS, DRG, PNS, TENS, tDCS
- Tonic and burst stimulation
  - Via modulation of inflammatory cytokines (Chakravarthy 2018, Caylor 2019)
  - Via modulation of astrocytes and microglia (Vedam-Mai 2012, Fenoy 2014, Campos 2010, Etievant 2016, Caylor 2019)

Therapy	Involved Cytokines	Role of Cytokines	Effect of Therapy
Tonic spinal cord stimulation	IL-15, IL-2, IL-12	Proinflammatory	Reduction in pro-inflammatory cytokines after SCS in CRPS patients (20)
	IL-4, IL-5, IL-10	Anti-inflammatory	Reduction in anti-inflammatory cytokines after SCS in CRPS patients (20)
Burst spinal cord stimulation	IL-10	Anti-inflammatory	Increase in level of IL-10 after burst SCS in back pain patients (22)
Dorsal root ganglion stimulation	IL-Iβ, TNF-α	Proinflammatory	Inhibition of pro inflammatory expression *in vitro* using light-induced injury model of microglia (31)
Vagus nerve stimulation	TNF, IL-1β, IL-8, HMGB1	Proinflammatory	Reduction in proinflammatory cytokines in cervical VNS in humans (50,51)
Peripheral nerve stimulation	IL-1B, IL-6, IL-1β	Proinflammatory	Reduction in proinflammatory cytokines with electroacupuncture in inflamed skin tissues (69)
TENS and subcutaneous electrical stimulation	IL-1, IL-6, TNF-α	Proinflammatory	Reduction in proinflammatory cytokines in a rat model (11)



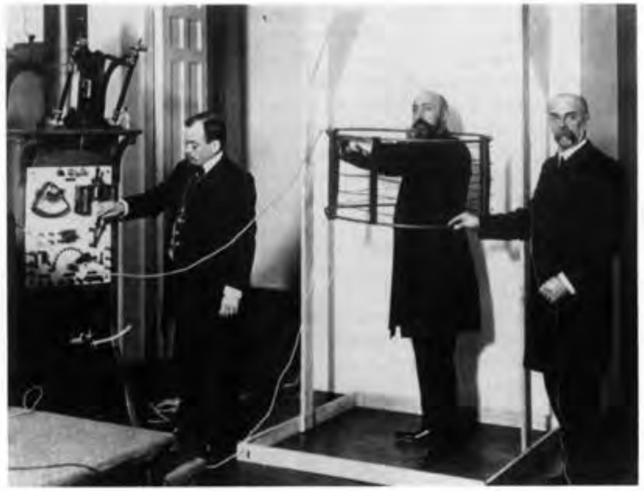


Caylor 2019

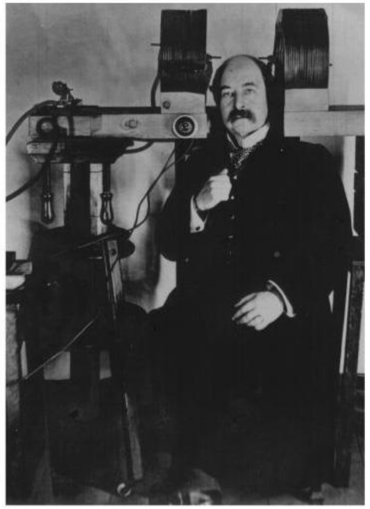
Salvesen 2018

Transcranial Magnetic Stimulation

d'Arsonval (1896)



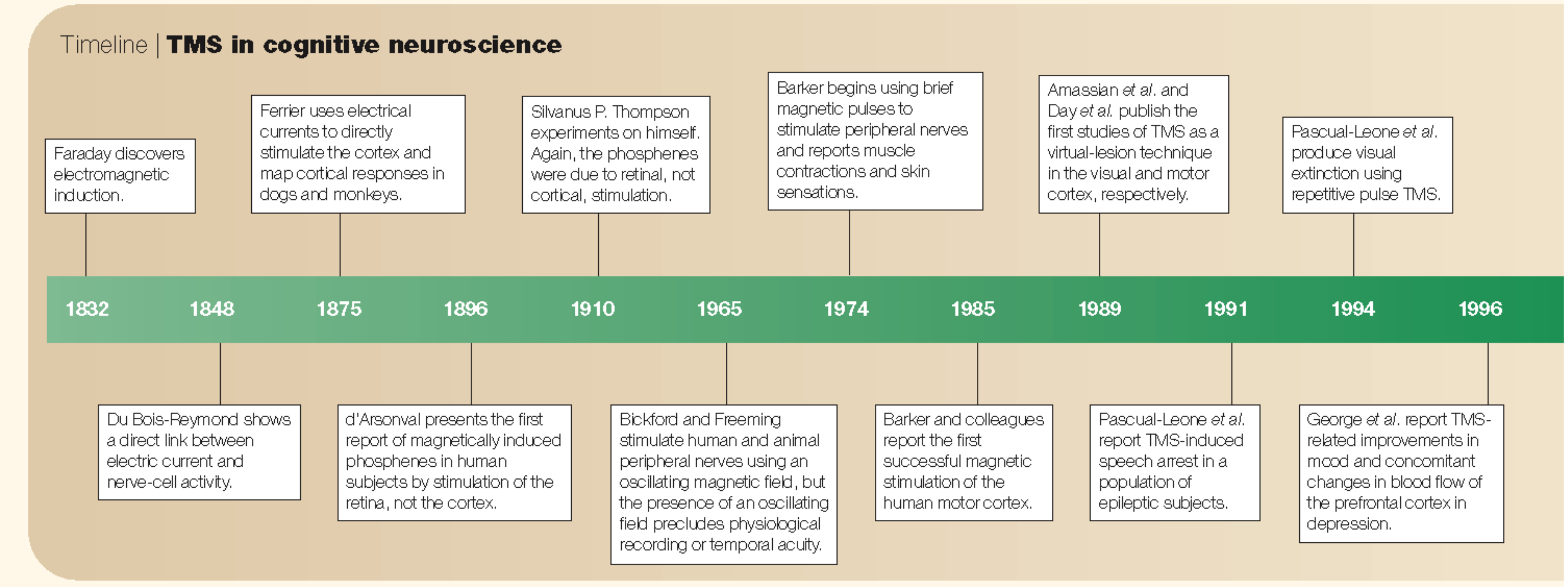
Thompson, 1910



Magnusson & Stevens, 1911

Barker 1985

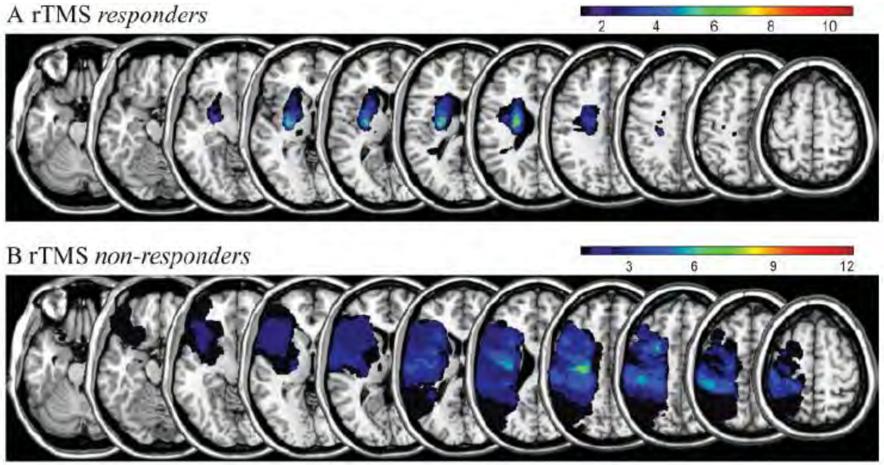
Figure- Barker demonstrating TMS [1].

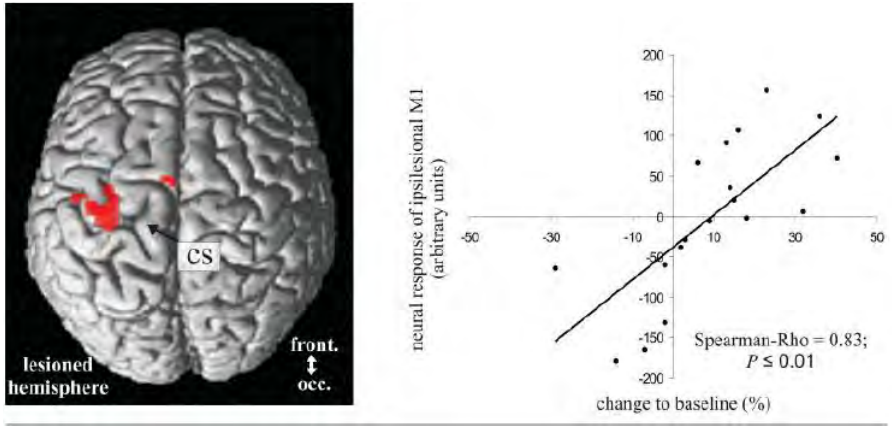


What does TMS do in the brain ?

TMS and stroke

- HF TMS of stroke side only efficacious for subcortical stroke (Ameli 2009)
- Improvement correlates with fMRI BOLD change
  - ie with how much the cortex can be activated





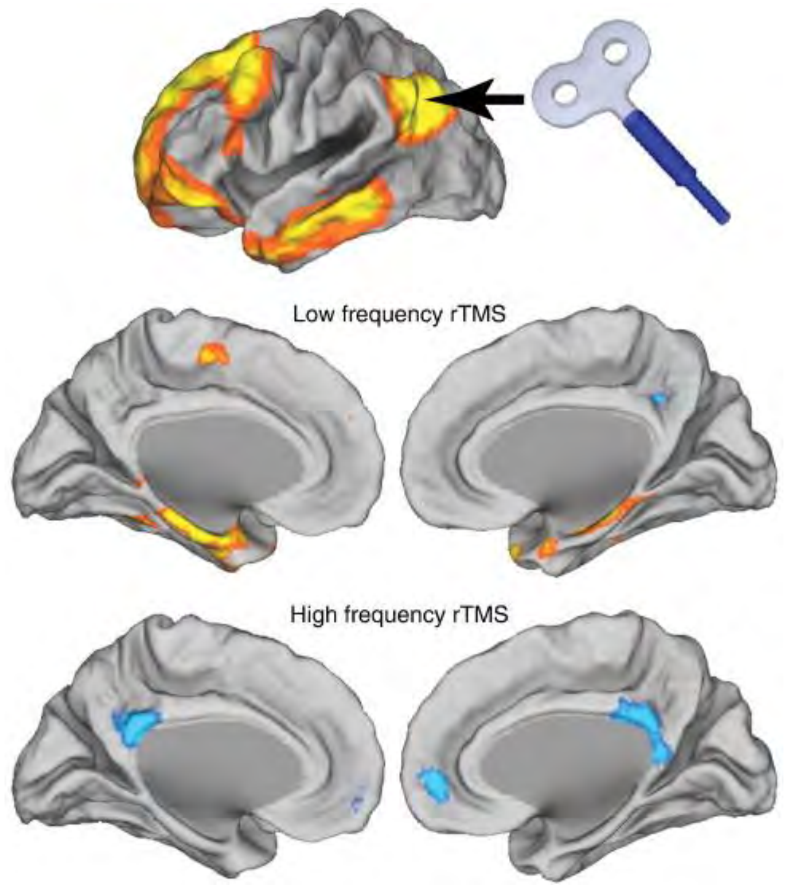
What does TMS do in the brain ?

TMS and FC

TMS changes functional connectivity (Fox 2012)

LF rTMS increases FC

HF rTMS decreases FC



rTMS in mental disorders

Large to very effect size
2 to 5 times effect size of medication (0.36) or psychotherapy (0.34)

Effect size	*d*	Reference
Very small	0.01	[10]
Small	0.20	[9]
Medium	0.50	[9]
Large	0.80	[9]
Very large	1.20	[10]
Huge	2.0	[10]

						Heterogeneity			Egger's	
	K	N	SMD (95% CI)	Z	*p* values	Q	*p* values	I^2	*t*	
Core symptom severity										
TMS										
ADHD	2	51	−0.50 (−1.33 to 0.33)	1.18	0.237	2.11	0.146	52		
Depression	76	3366	−0.45 (−0.57 to −0.33)	7.16	<0.001	197.91	<0.001	62	1.95	0.055
Unipolar	42	2336	−0.60 (−0.78 to −0.42)	6.45	<0.001	154.91	<0.001	74	2.85	0.007
Bipolar	4	145	−0.20 (−0.52 to 0.11)	1.26	0.209	1.84	0.606	0		
GAD	3	111	−1.80 (−2.60 to −1.00)	4.40	<0.001	5.37	0.068	63		
OCD	26	760	−0.66 (−0.91 to −0.41)	5.10	<0.001	72.18	<0.001	65	3.31	0.003
PTSD	10	255	−1.09 (−1.61 to −0.57)	4.10	<0.001	42.44	<0.001	79	0.59	0.572
Schizophrenia										
Positive symptoms	33	1474	−0.11 (−0.33 to 0.11)	0.96	0.338	153.20	<0.001	77	2.27	0.029
Negative symptoms	31	1266	−0.49 (−0.73 to −0.26)	4.07	<0.001	133.98	<0.001	78	2.45	0.020
Total symptoms	29	1334	−0.50 (−0.66 to −0.33)	5.81	<0.001	58.67	<0.001	52	2.42	0.022
Auditory hallucinations	16	545	−0.19 (−0.36 to −0.02)	2.19	0.029	12.62	0.632	0	2.64	0.020
SUD	4	100	−1.46 (−3.35 to 0.42)	1.52	0.128	49.44	<0.001	92		

NNT for depression is 3.4 (Liu 2014) vs 7 for medication and psychotherapy

Hyde 2022

Chou 2020
Vacas 2018

rTMS for cognitive functioning

Effect size	d	Reference
Very small	0.01	[10]
Small	0.20	[9]
Medium	0.50	[9]
Large	0.80	[9]
Very large	1.20	[10]
Huge	2.0	[10]

Cognitive functioning									
TMS									
Attention									
Depression	3	146	−0.10 (−0.44 to 0.23)	0.67	0.538	0.97	0.617	0	
Schizophrenia	3	126	−0.18 (−0.64 to 0.29)	0.74	0.457	3.26	0.196	39	
Executive functioning									
Depression	8	292	−0.41 (−0.39 to 0.08)	1.35	0.176	7.46	0.383	6	
Schizophrenia	5	142	−0.28 (−0.74 to 0.18)	1.19	0.233	6.82	0.146	41	
Processing speed									
Depression	7	276	0.07 (−0.17 to 0.31)	0.59	0.553	4.71	0.582	0	
Schizophrenia	5	168	−0.26 (−0.57 to 0.04)	1.70	0.090	1.84	0.765	0	
Working memory									
Depression	7	306	0.02 (−0.21 to 0.25)	0.19	0.848	3.88	0.694	0	
Schizophrenia	10	313	−0.65 (−0.39 to 0.06)	1.42	0.156	9.18	0.421	2	1.86
SUD	2	69	−0.66 (−1.87 to 0.55)	1.07	0.285	5.95	0.015	83	
AD & MCI (memory)	**13**	**293**	**0.77**						
AD & MCI (behavior, psychology)			**0.58**						

Chou 2020
Vacas 2020

Hyde 2022

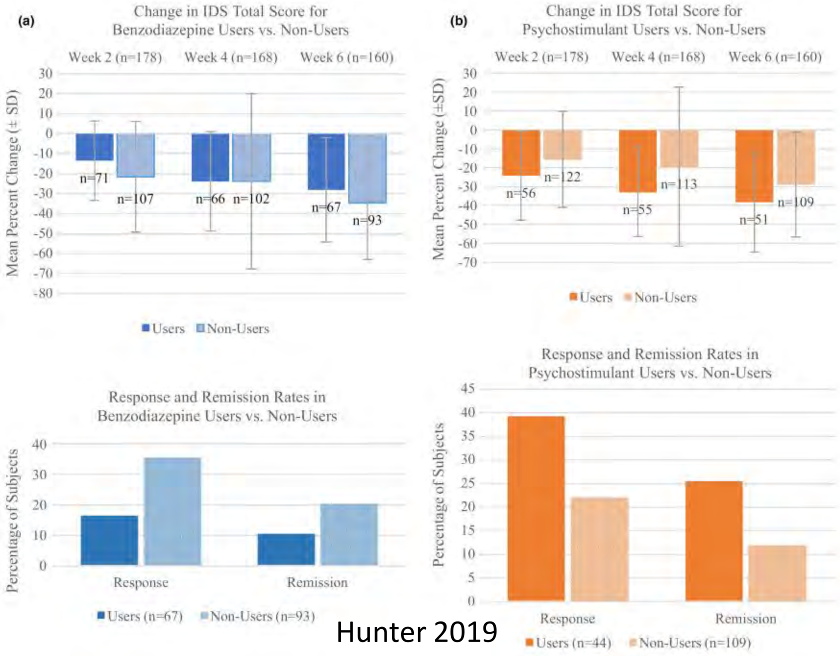
rTMS and concomitant medication

rTMS influenced by concomitant medication

Better with **psychostimulants** (Hunter 2019) and **antidepressants** (Sehatzadeh 2019, Wei 2017)

Worse with *antipsychotics* (Hebel 2020) and unknown for *benzodiazepines* (worse: Hunter 2019 & Kaster 2019, no difference: Fitzgerald 2020).

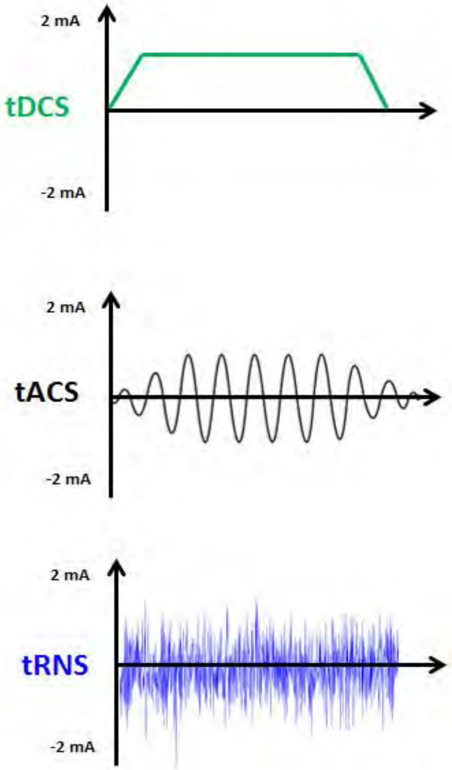
No influence of lithium or antiepileptics (Hebel 2021)



Hunter 2019

+

Transcranial Electrical Stimulation



tDCS

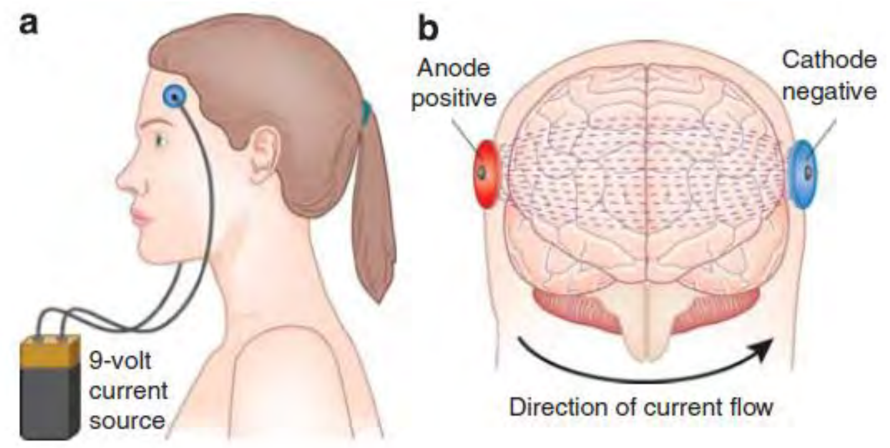
Transcranial direct current stimulation

In contrast to TMS does not evoke motor response on motor cortex stimulation

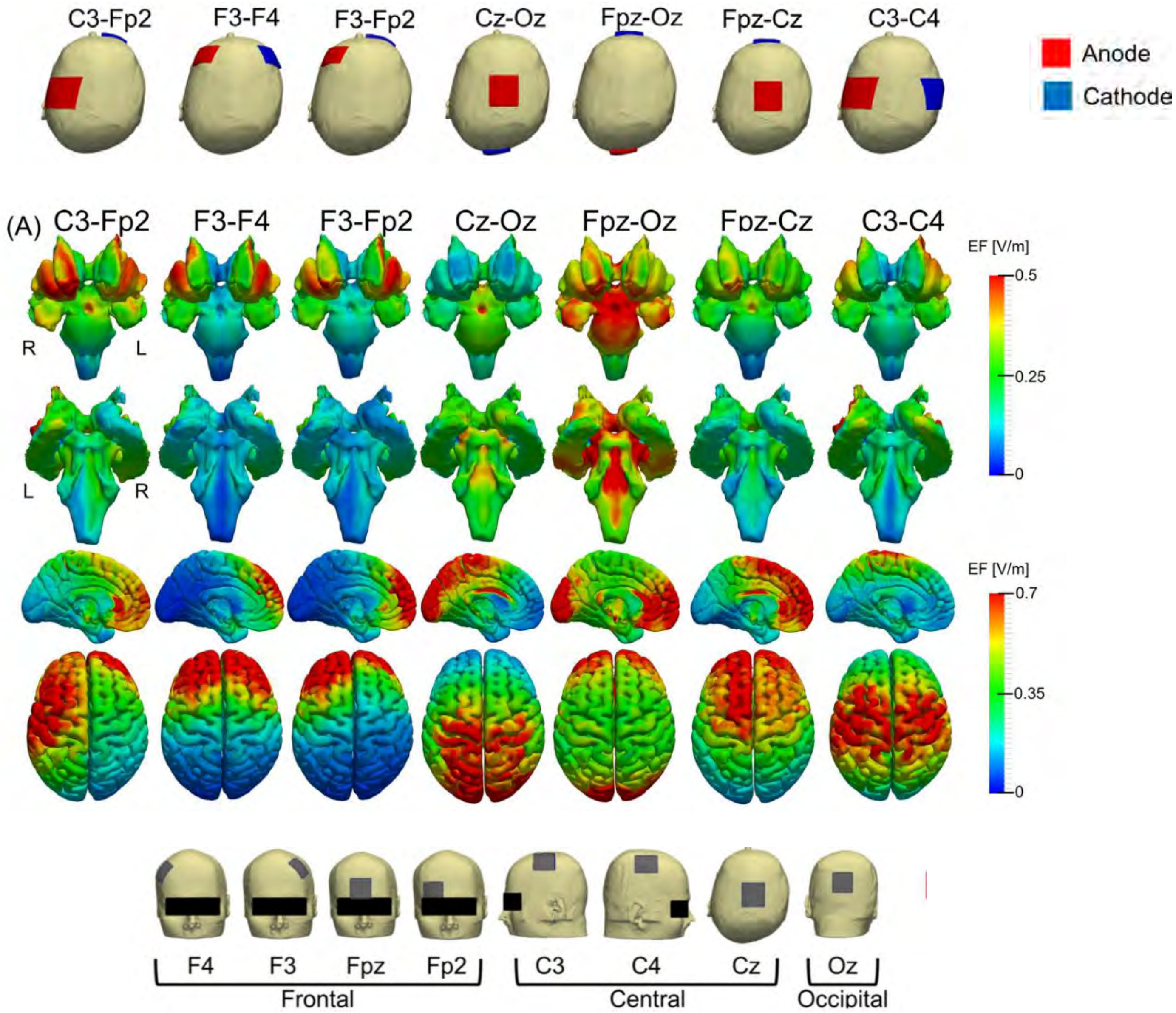
tDCS

tDCS basics

- 25% of transcranially applied direct current reaches the brain (Vöröslakos 2018)
  - *calculations on realistic head models*
  - *validation in animal experiments (Rush 1968)*
  - *validation in humans (Dymond 1975)*
- Current flows from anode to cathode (George 2010)
- Modulates underlying brain cells' resting state potential



tDCS targets



Gomez-Tames 2020

tDCS for mental disorders

Effect size	*d*	Reference
Very small	0.01	[10]
Small	0.20	[9]
Medium	0.50	[9]
Large	0.80	[9]
Very large	1.20	[10]
Huge	2.0	[10]

Large effect size
Almost triple effect size of medication (0.36) or psychotherapy (0.34)

TDCS								
Depression	9	419	−0.87 (−1.51 to −0.24)	2.70	0.007	67.89	<0.001	88
Unipolar	5	148	−1.04 (−2.17 to 0.08)	1.82	0.069	40.39	<0.001	90
GAD	2	42	−0.55 (−1.17 to 0.07)	1.74	0.083	0.55	0.457	0
OCD	2	46	−0.37 (−0.95 to 0.22)	1.23	0.218	0.003	0.953	0
Schizophrenia								
Positive symptoms	8	367	−0.12 (−0.33 to 0.08)	1.18	0.237	3.59	0.826	0
Negative symptoms	7	267	−0.54 (−0.95 to −0.14)	2.61	0.009	14.98	0.020	60
Total symptoms	9	386	−0.63 (−1.03 to −0.23)	3.10	0.002	26.14	0.001	69
Auditory hallucinations	7	312	−0.42 (−0.81 to −0.02)	2.06	0.040	16.50	0.011	64
SUD	7	224	−0.73 (−1.00 to −0.46)	5.29	<0.001	2.95	0.815	0

Much better than rTMS

NNT for depression is 7 (Brunoni 2018) vs 3.4 for rTMS (Liu 2014) 7 for medication and psychotherapy

Hyde 2022

Effect size	*d*	Reference
Very small	0.01	[10]
Small	0.20	[9]
Medium	0.50	[9]
Large	0.80	[9]
Very large	1.20	[10]
Huge	2.0	[10]

tDCS for cognitive functioning

						Heterogeneity		
	K	**N**	**SMD (95% CI)**	**Z**	***p* values**	**Q**	***p* values**	I^2
TDCS								
Attention								
Schizophrenia	6	247	−0.30 (−0.55 to −0.05)	−2.31	0.021	6.15	0.292	19
Executive functioning								
Depression	3	154	−0.19 (−0.51 to 0.12)	1.20	0.231	0.12	0.942	0
Schizophrenia	7	261	−0.13 (−0.37 to 0.12)	1.00	0.317	3.76	0.710	0
Processing speed								
Depression	3	123	0.05 (−0.31 to 0.41)	0.29	0.771	1.34	0.512	0
Schizophrenia	7	261	−0.38 (−0.78 to 0.18)	1.87	0.061	14.23	0.027	58
Working memory								
Depression	5	198	−0.11 (−0.42 to 0.19)	0.73	0.465	4.54	0.338	12
Schizophrenia	7	279	−0.38 (−0.74 to −0.03)	2.14	0.032	12.24	0.057	51
AD & MCI (memory)			**0.99**					
AD & MCI (behavior and psychology)								

Chen 2022

Hyde 2022

tDCS + medication (McLaren 2018)

Glutamate
- Antagonist decreased
- Agonist increased

GABA
- Increased

Serotonin
- increased

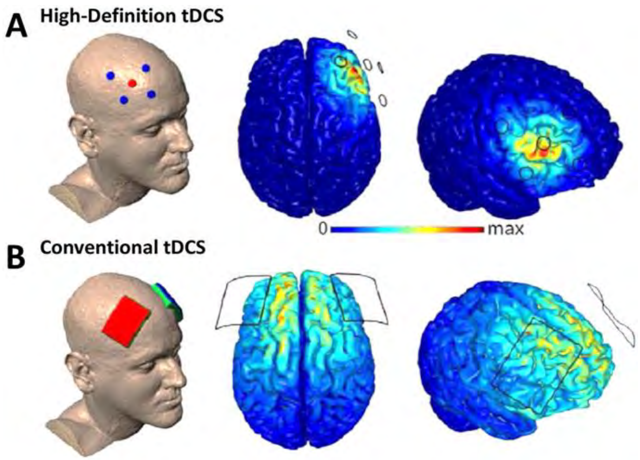
Dopamine
- Inverted U curve

Noradrenaline/adrenaline
- Agonist increased
- Antagonist decreased

Amphetamine
- increased

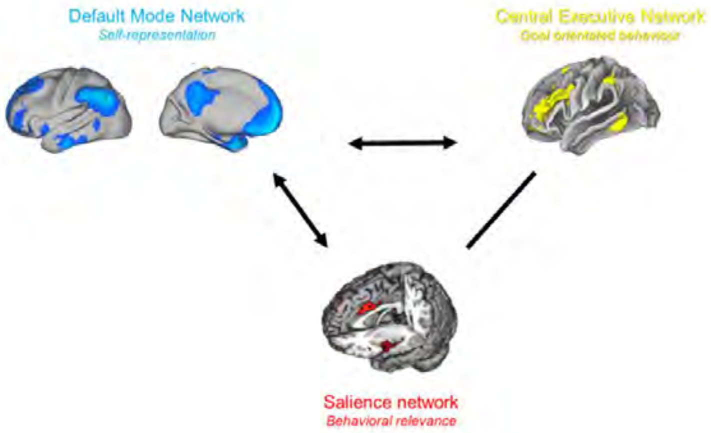
Calcium and sodium blockers
- Decreased

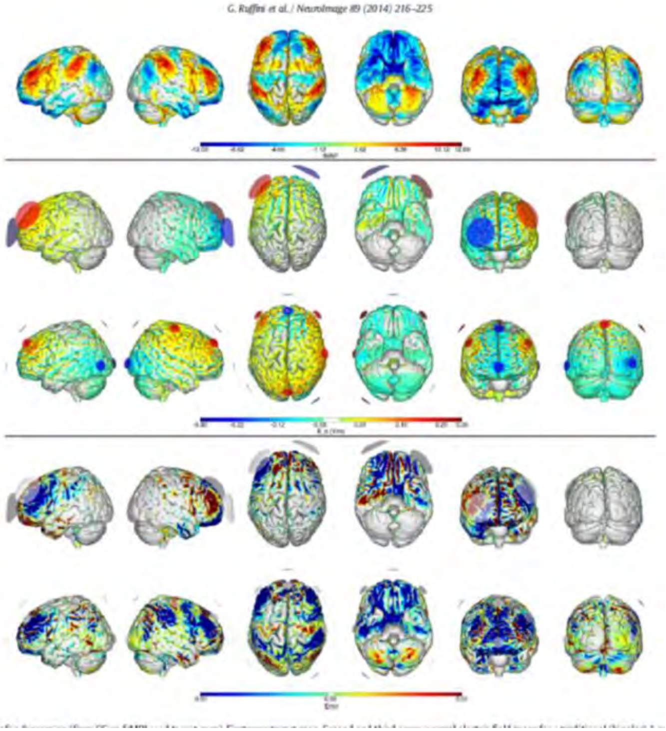
Why HD-tES?



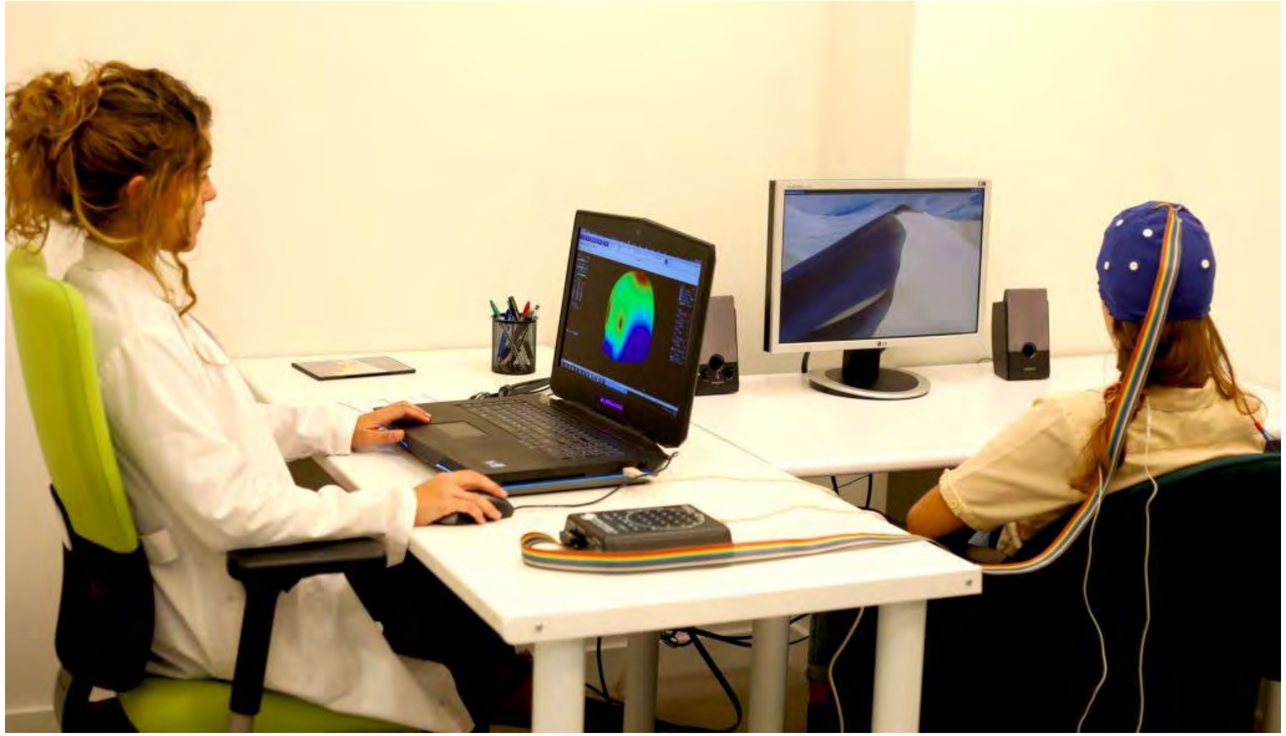
Two reasons

1. More focal stimulation (Edwards 2013, Ester 2021)
2. Multitarget = network stimulation (Ruffini 2014)

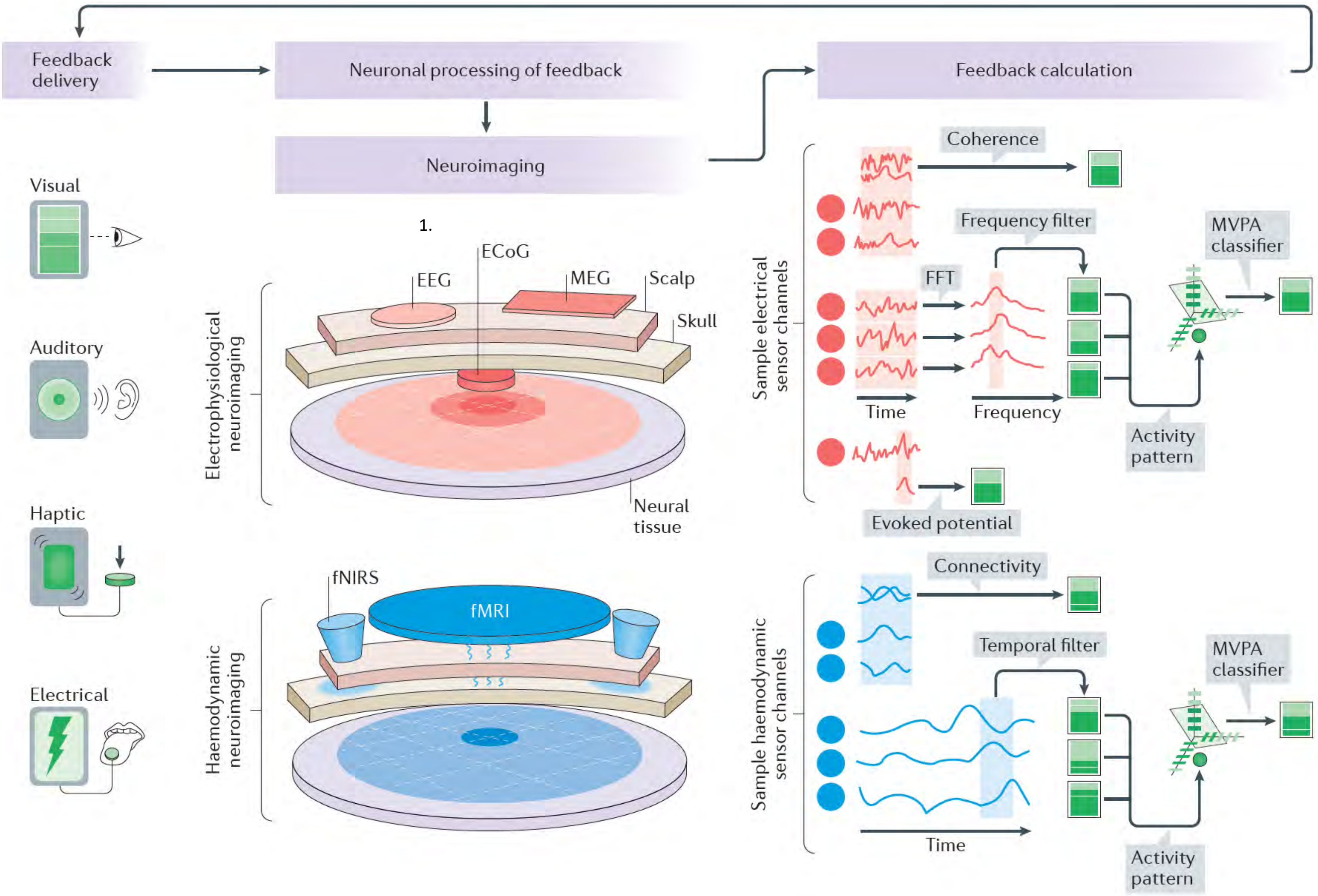




Neurofeedback



Neurofeedback



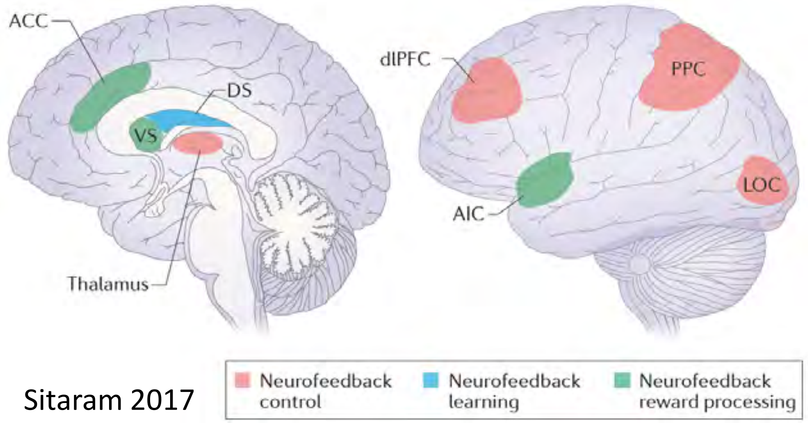
MVPA = MultiVariate Pattern Analysis

Sitaram 2017

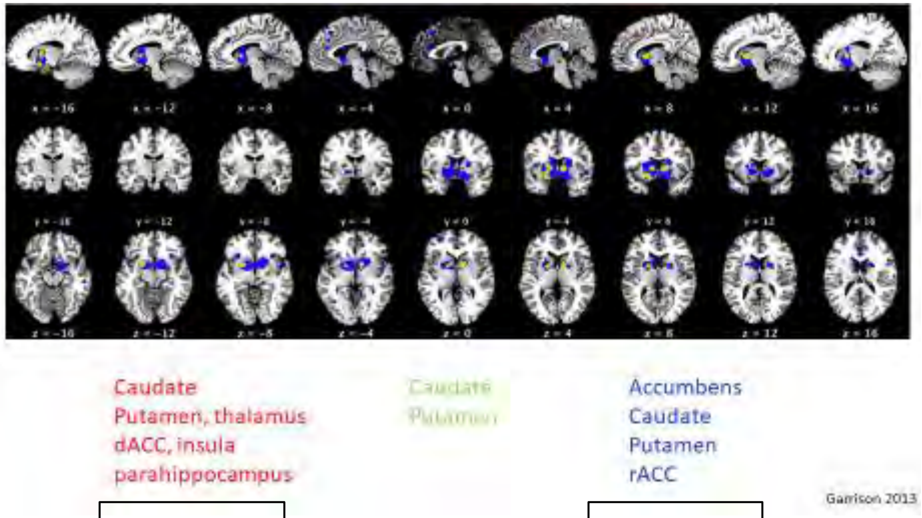
Neurofeedback

Neural correlates of Neurofeedback (Sitaram 2017)

- Paying attention to visual feedback involves visual cortex and FP attentional network = CEN
- The feedback itself involves accumbens as well as dACC and insula = SN
- The learning occurs in dorsal striatum (caudate & putamen)

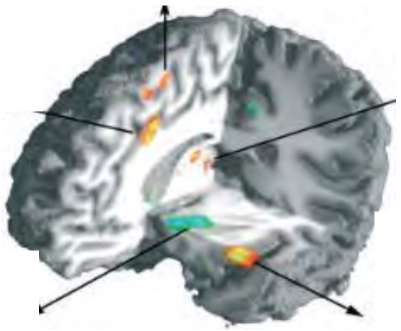


Sitaram 2017



Pavlovian

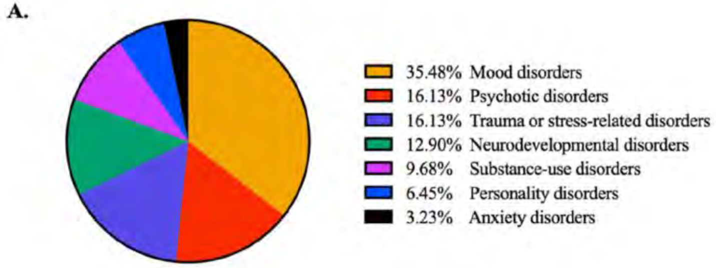
Operant



Ullsperger 2003

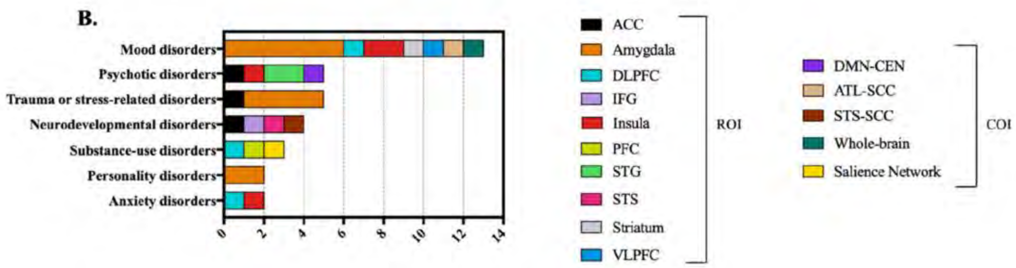
Is neurofeedback evidence based?

1. fMRI neurofeedback meta-analysis (Pindi 2022)

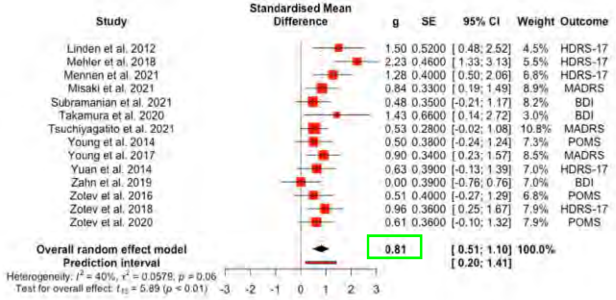


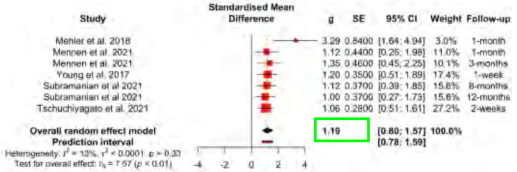
ROIs

COIs

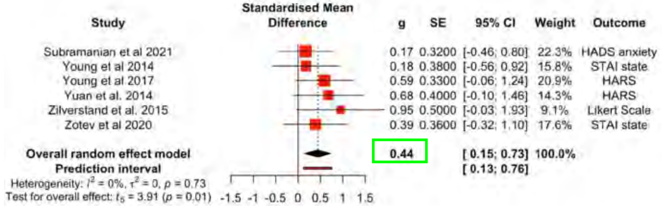


depression

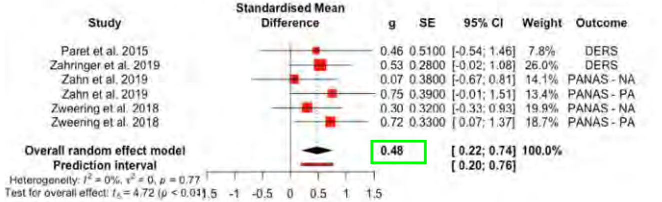




anxiety



Emotion regulation



Effect size	*d*	Reference
Very small	0.01	[10]
Small	0.20	[9]
Medium	0.50	[9]
Large	0.80	[9]
Very large	1.20	[10]
Huge	2.0	[10]

Is neurofeedback evidence based?

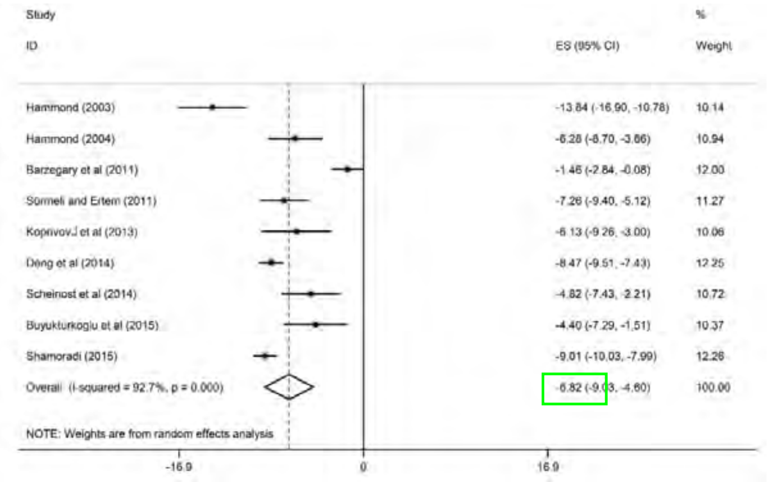
1. fMRI neurofeedback
2. EEG neurofeedback meta-analyses
    1. ADHD (Fan 2022)

        Improves inattention, not hyperactivity
    2. OCD (Zafarmand 2021)

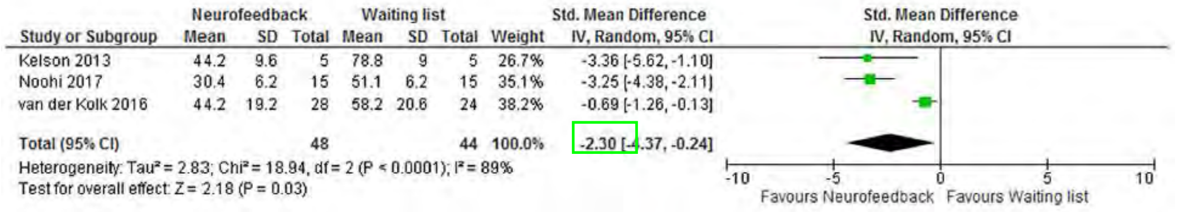
        Improves OCD
    3. PTSD (Steingrimsson 2019)

        Large effect size, low certainty
    4. Internalizing disorders (Perez 2022)

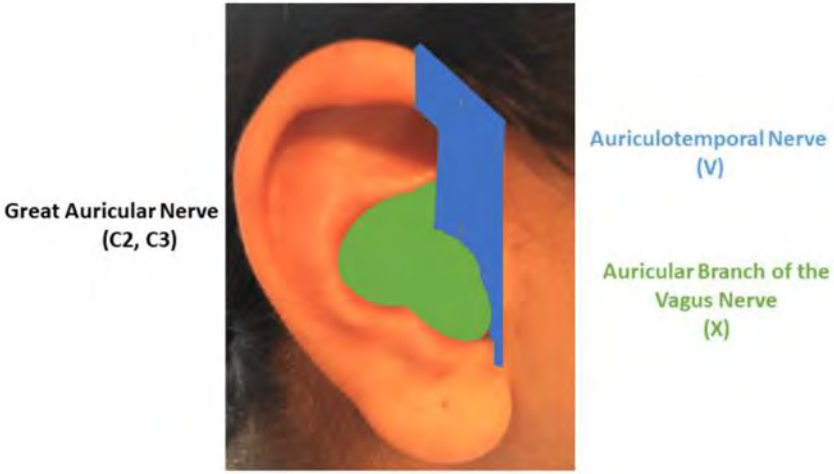
        Small to moderate effect sizes, low certainty



MCID 5?
Strauss 2018



Vagus nerve stimulation

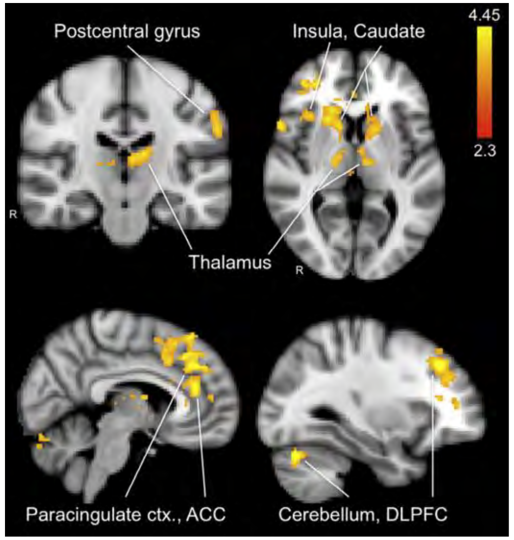


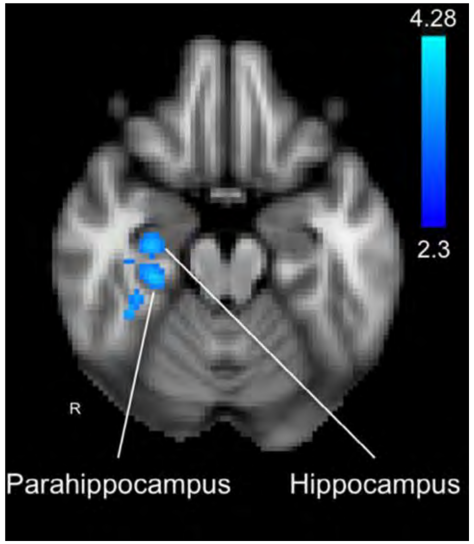
Non-invasive VNS modulates triple network

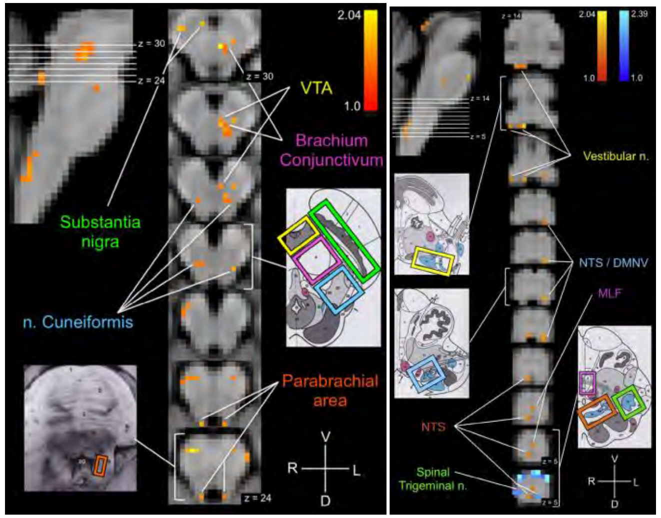
Non-invasive VNS (Frangos 2016)

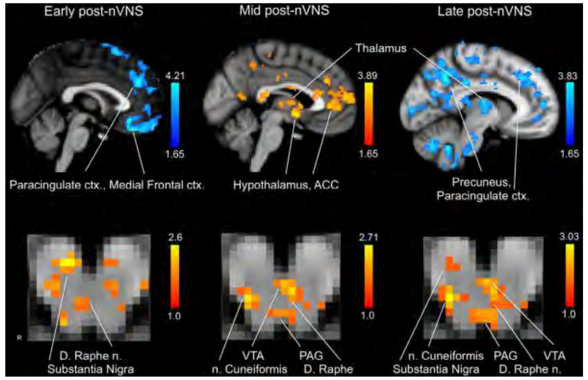
- Activates
  - **rdACC + insula + caudate = SN**
  - **Thalamus & DLPFC (CEN)**
  - NTS, dorsal raphe, VTA, Subst Nigra
- Deactivates
  - Hippocampus, **parahippocampus (DMN)**

- On stopping stimulation
  - **Early deactivation of SN**
  - **Activation of DMN (13-15 min)**
  - **Late deactivation of DMN**

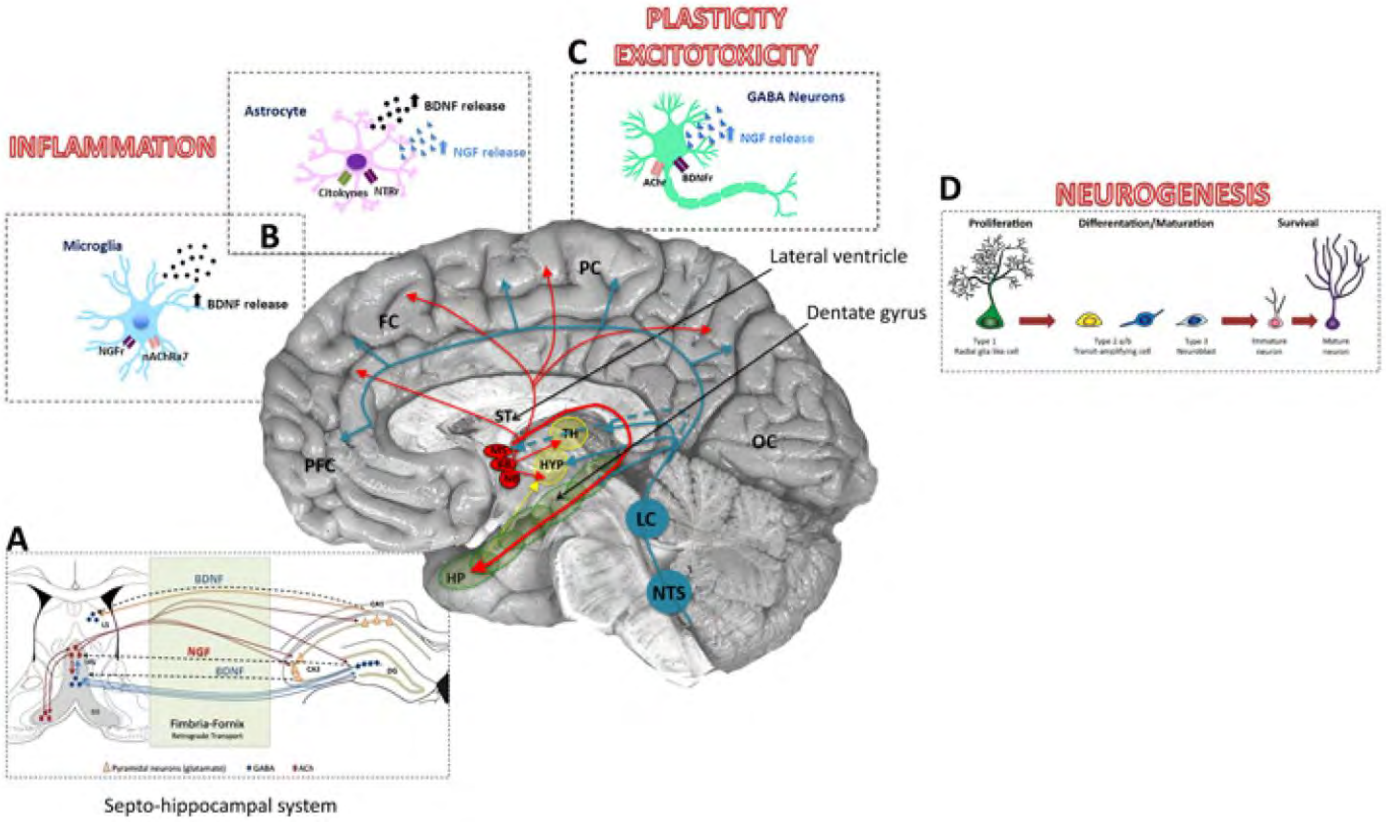








VNS modulates plasticity, inflammation and neurogenesis



Brain Areas	NGF Protein	NGF mRNA	BDNF Protein	BDNF mRNA
Hippocampus 5Hz	⇧⇧	⇧⇧	—	—
Hippocampus 20Hz	—	⇧	—	⇩
Cerebral Cortex 5Hz	⇧⇧	⇧	—	⇧
Cerebral Cortex 20Hz	⇧⇧⇧	⇧⇧	⇧⇧	⇧⇧
Hypothalamus 5Hz	⇧	⇧⇧	—	⇧⇧
Hypothalamus 20Hz	—	⇧⇧	⇧⇧	⇧⇧

Difference respect to Fasted unstimulated control rats.
— = no changes ⇧ = >20% ⇧⇧ = >40%

Rosso 2020

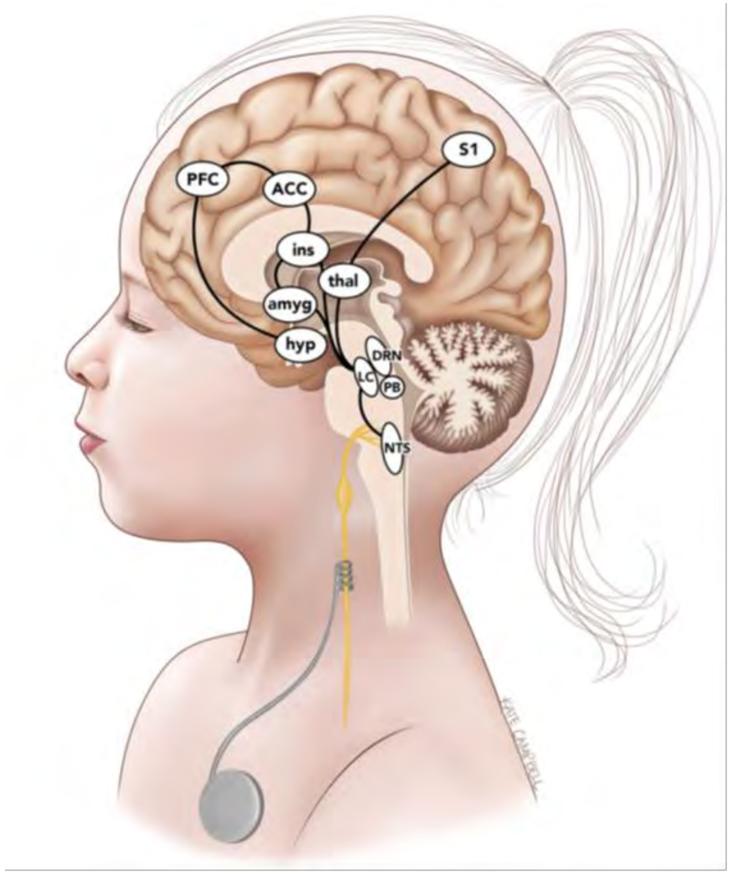
VNS clinically

Reimbursed for (Johnson 2018)

- Depression
- Epilepsy

Other indications (Johnson 2018, Patel 2021, Wang 2021)

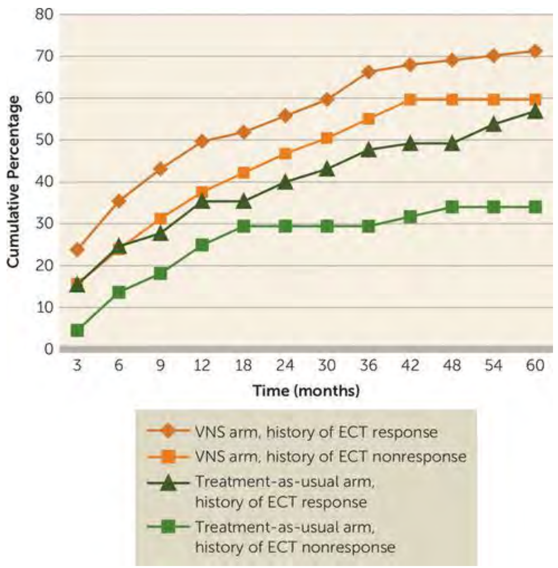
- Anti-inflammatory disorders
    - sepsis,
    - lung injury
    - rheumatoid arthritis (RA)
    - Diabetes
- Pain (Patel 2021)
- Cognition (Patel 2021)
- Cardiovascular function (Patel 2021)
- Parkinson’s disease (Wang 2021)
- Autism (Wang 2021)
- Stroke (Wang 2021)
- TBI (Wang 2021)

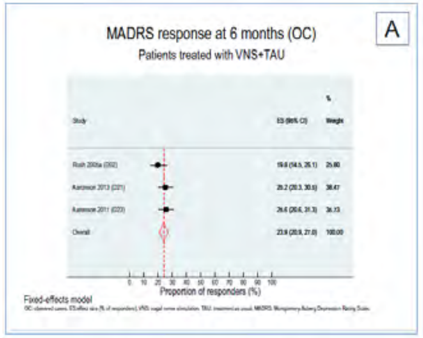


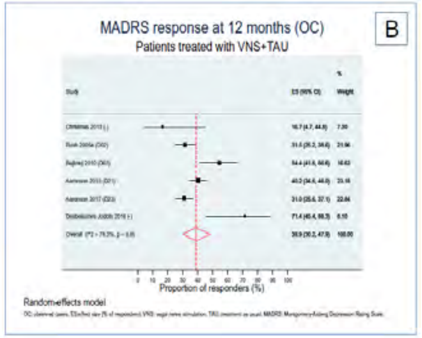
VNS for depression

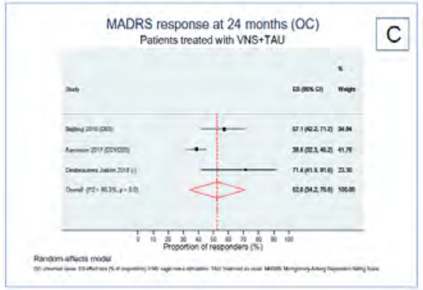
Meta-analytic proof of benefit (Bottomley 2020)

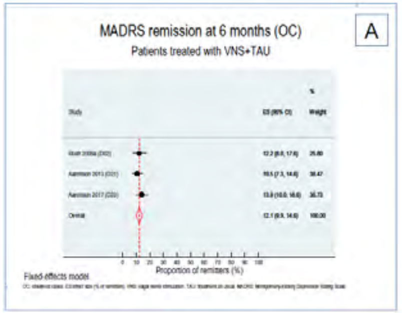
Efficacy improves in time (Aaronson 2017)

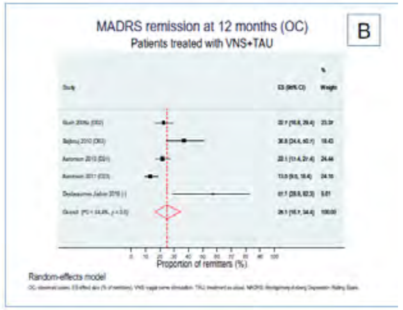


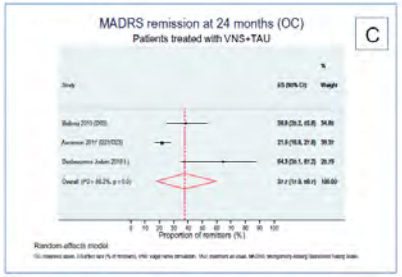












Chemical brain

Why do humans like drugs?

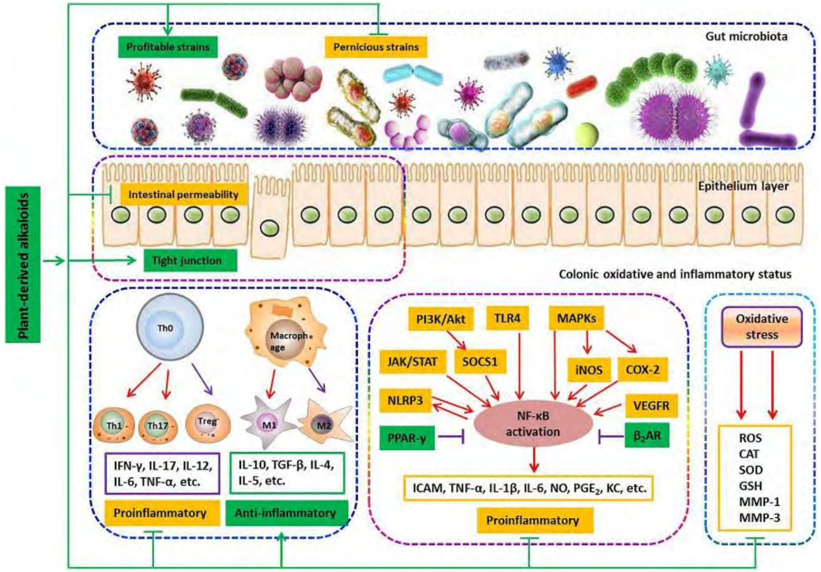
Plants defend themselves against bacteria, parasites and herbivores by producing toxins (alkaloids)

- Humans get reward (=incentive salience) to ingest these protective toxins against bacteria, parasites (Sullivan 2008) and viruses (Abookleesh 2022)

Plants alkaloids protect human microbiome (IBS) (Peng 2019)

- Inhibit pathogenic non-commensal bacteria and stimulate commensal bacteria
- Activate anti-inflammatory and inhibit pro-inflammatory responses

Toxin (typical source)	Receptor
Nicotine[a] (tobacco)	Nicotinic acetylcholine
Arecoline[a] (betel nut)	Muscarinic acetylcholine
Cocaine[c] (coca)	Adrenergic, Dopaminergic
Ephedrine[c] (khat)	Adrenergic, Dopaminergic
Caffeine[b] (coffee)	Adenosine
Theophylline[b] (tea)	Adenosine
Theobromine[b] (chocolate)	Adenosine
Morphine[a] (opium poppy)	Opioid
Δ9-THC[a] (cannabis)	Cannabinoid
Psilocybin	Serotonin
DMT	Serotonin
Ibogain	Serotonin
Mescaline	Serotonin



Hallicunogenics

Hallicunogenics

1. Delirants:
   1. Anticholinergics: atropine (belladonna)
   2. GABAergics: mushroom
2. Dissociatives: ketamine, NO, opioidergics (salvia divinorum)
3. Psychedelics
   1. Serotoninergics
      1. Act on 5-HT2A receptor
      2. 3 families
         1. Tryptamine:
            1. Psilocybin = magic mushrooms
            2. DMT = ayahuasca: vine, liana
         2. Phenetylamine:
            1. Mescaline = cactus (peyote)
            2. MDMA
         3. Lysergamide:
            1. LSD = ergot (fungus on rye)
   2. Cannabinoidergics
      1. Act on CB1 receptor: THC (cannabis)





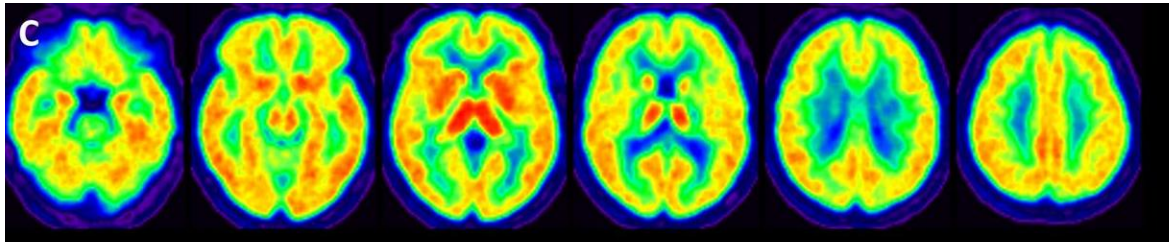


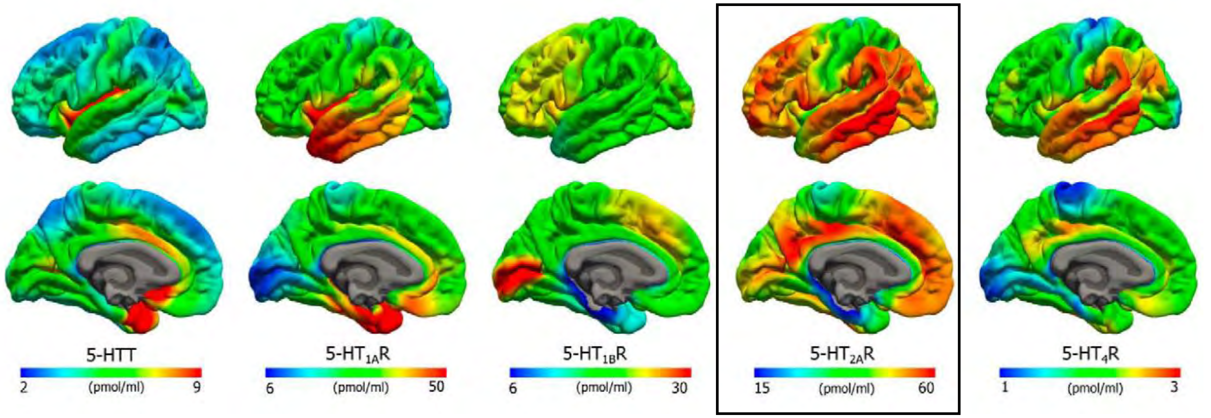

Psychedelics

Hallicunogenics

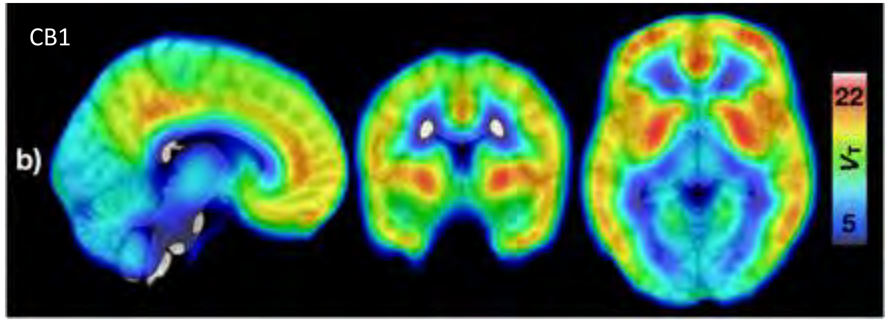
1. Delirants: anticholinergics, GABAergics
2. Dissociatives: ketamine, NO, opioidergics
3. Psychedelics
    1. Serotoninergics
        1. Act on 5-HT2A receptor
        2. 3 families
            1. Tryptamine: psilocybin, DMT(ayahuasca)
            2. Phenetylamine: mescaline, MDMA
            3. Lysergamide: LSD
    2. Cannabinoidergics
        1. Act on CB1 receptor: THC

NMDA receptors (McGinnity 2014)



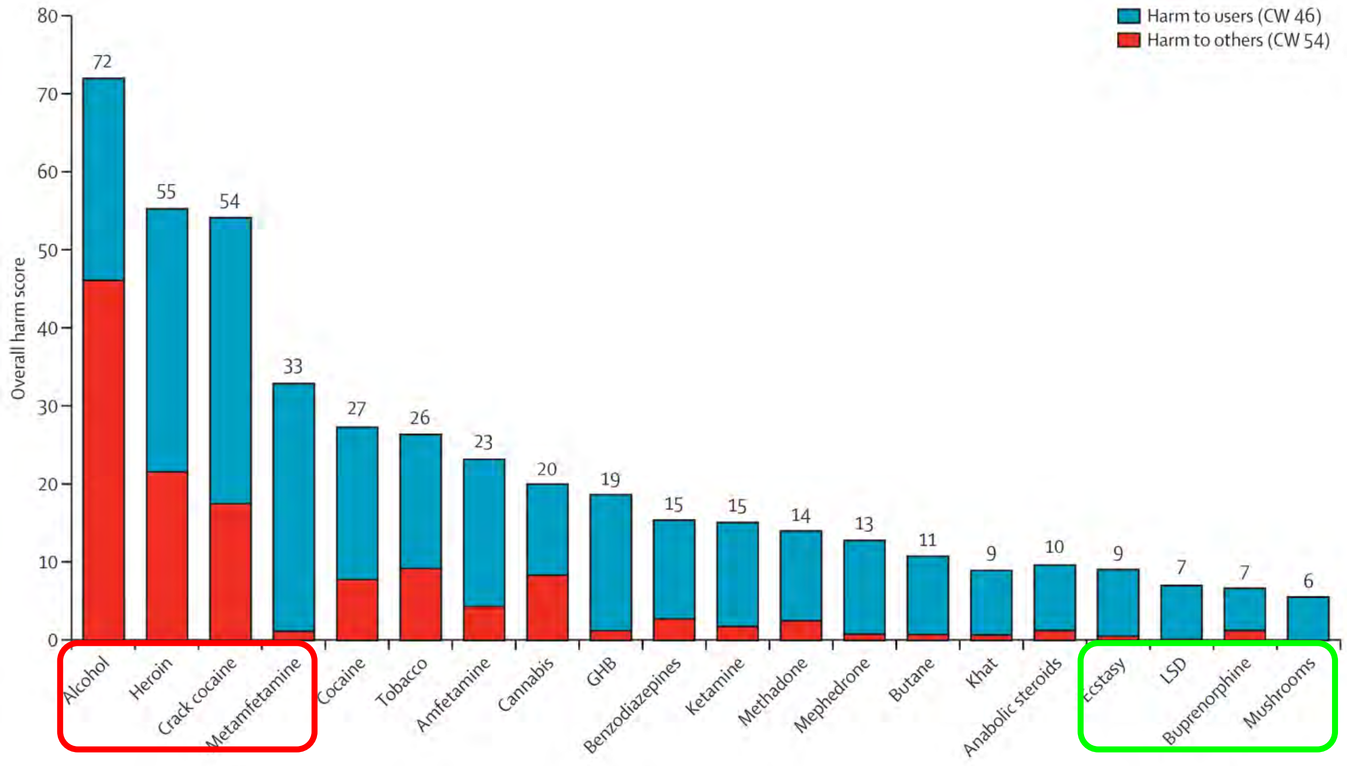


Beliveau 2017



Kantonen 2020

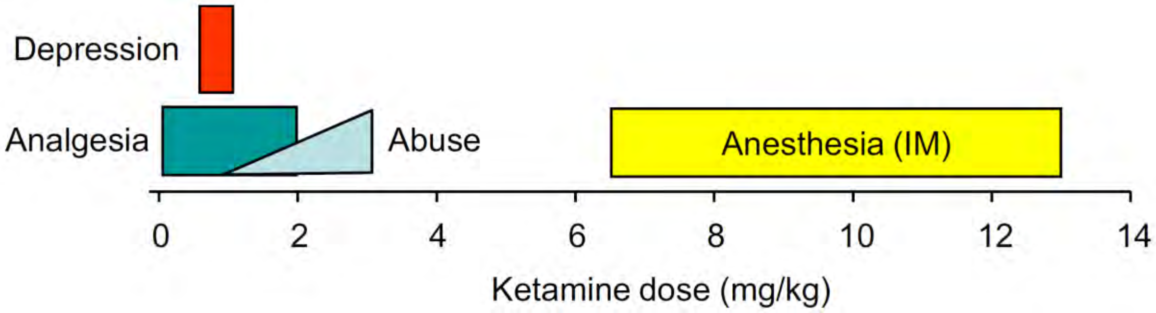
Harm scores



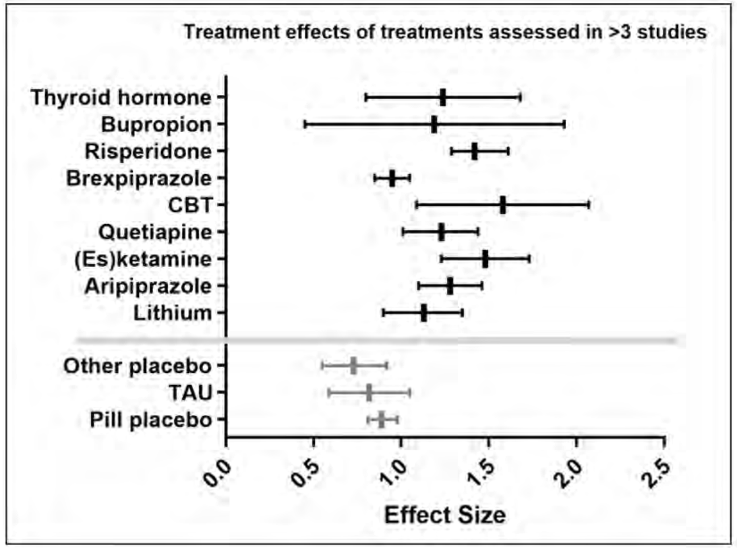
Nutt 2010

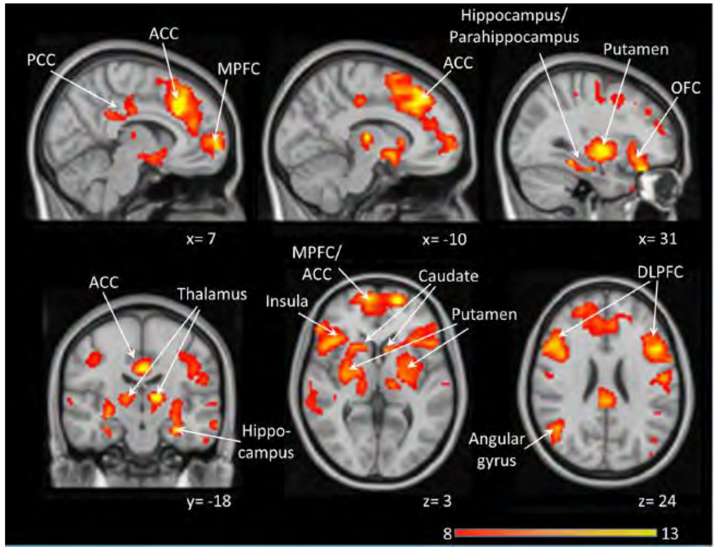
What do psychedelics do?

Ketamine

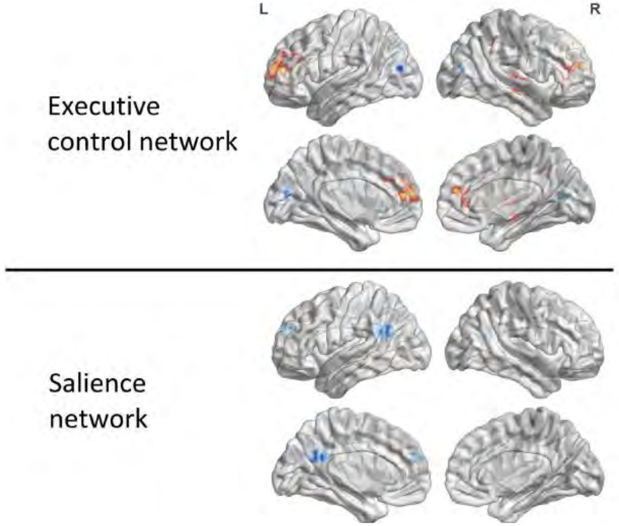


Augmentation for treatment resistant depression





Activity changes in SN, DMN, CEN



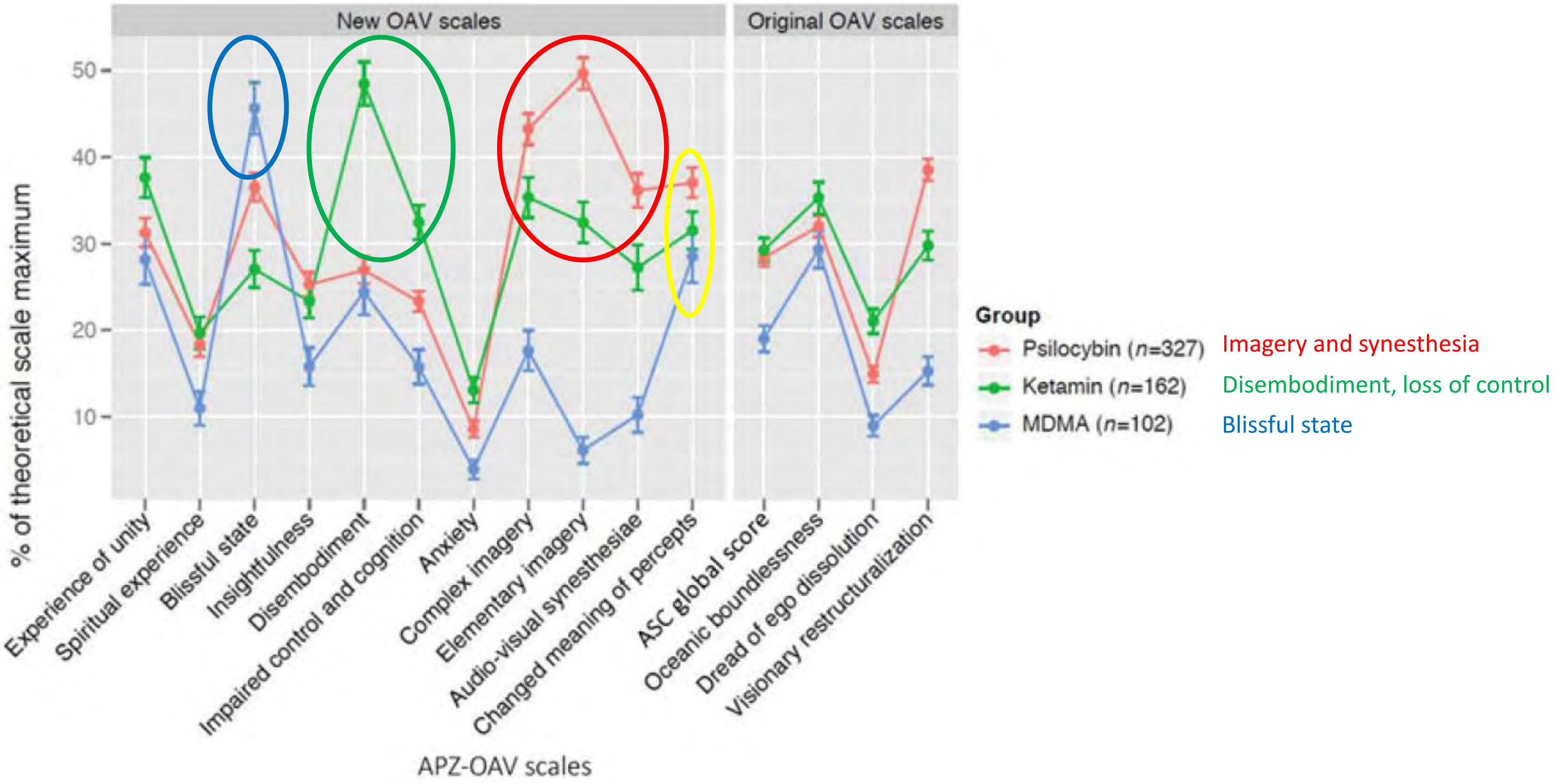
Connectivity increase CEN
Connectivity decrease DMN to SN

Bryant 2019

Mueller 2018

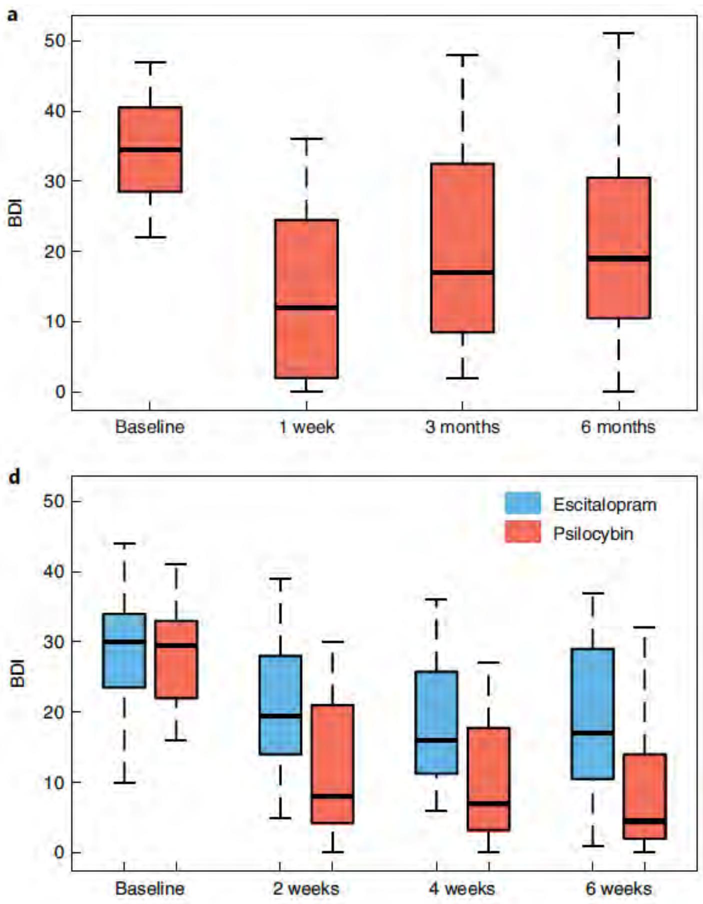
Scott 2022

Different drugs different clinical effects



Vollenweider 2018

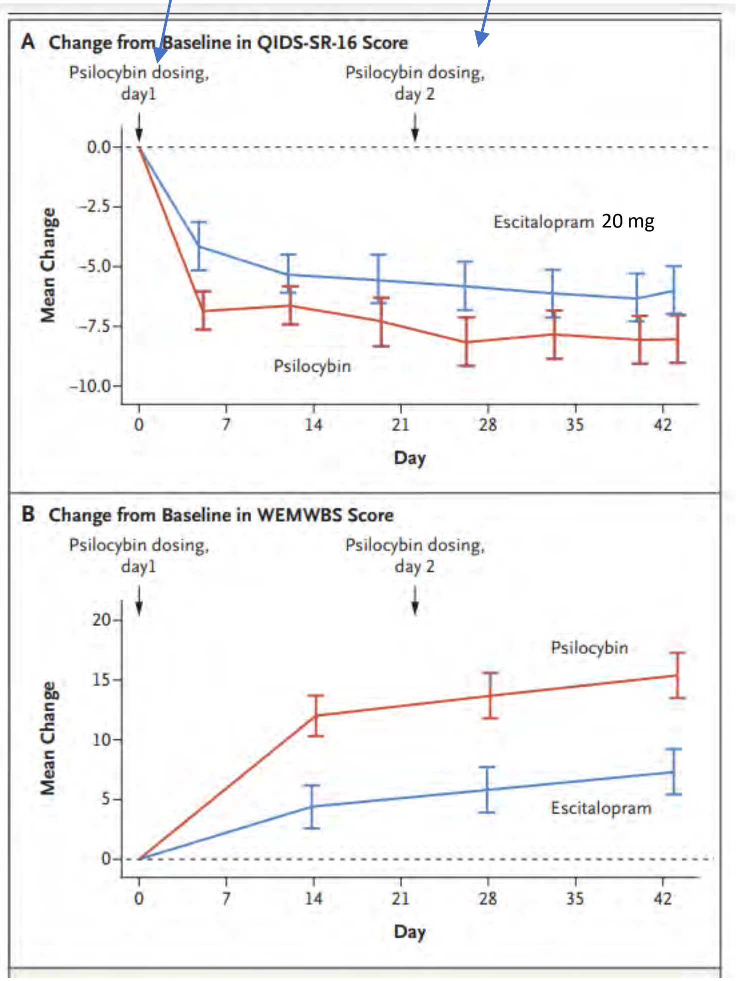
Psychedelics act fast and equal to SSRI



Daws 2022

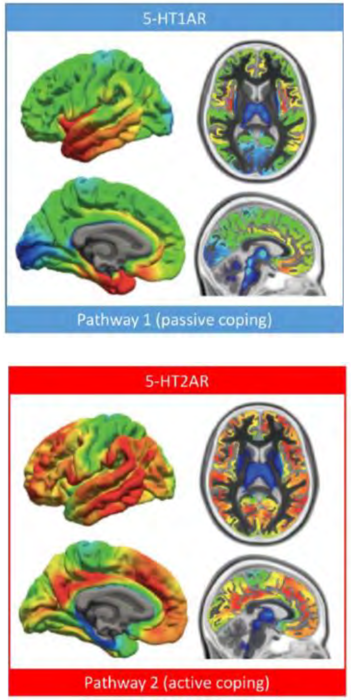
Escitalopram group receives 20 mg Escitalopram
Psilocybin group receives 25 mg

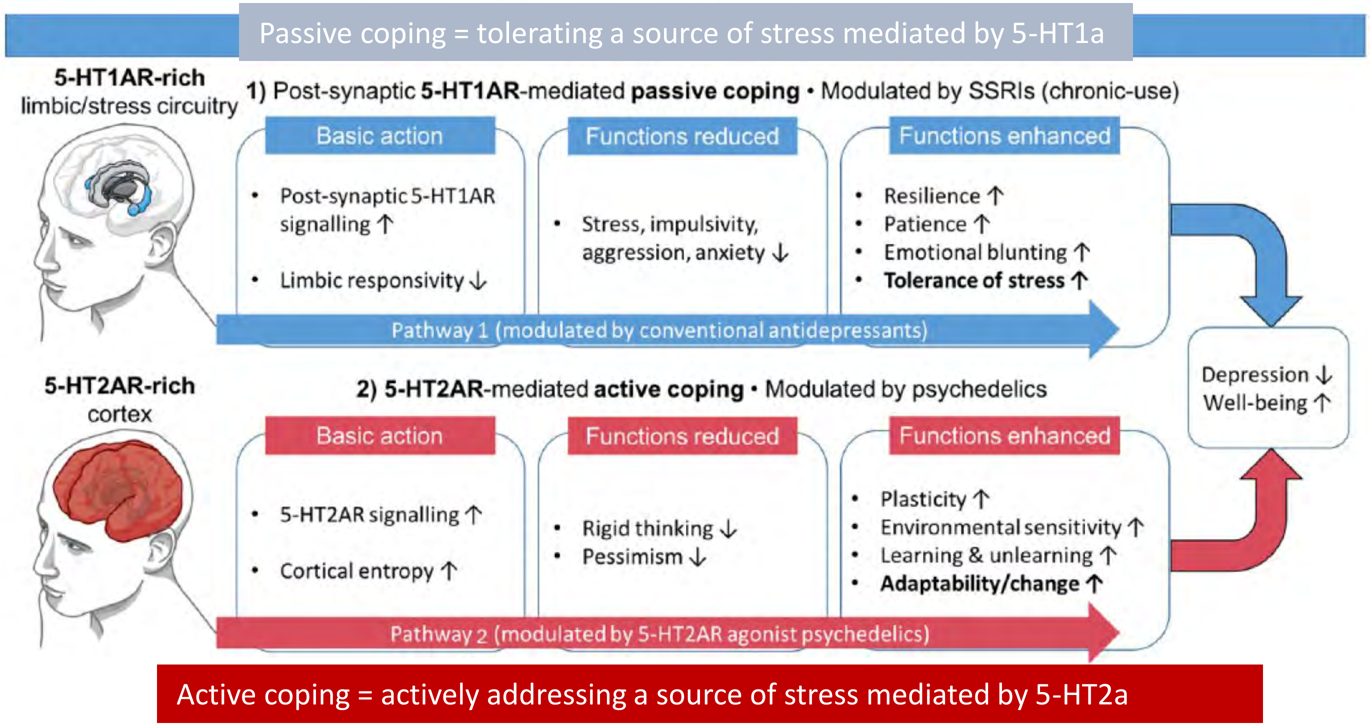
Escitalopram group receives 1 mg psilocybin
+ 10 mg escitalopram
Psilocybin group receives 25 mg psilocybin



Carhart-Harris 2021

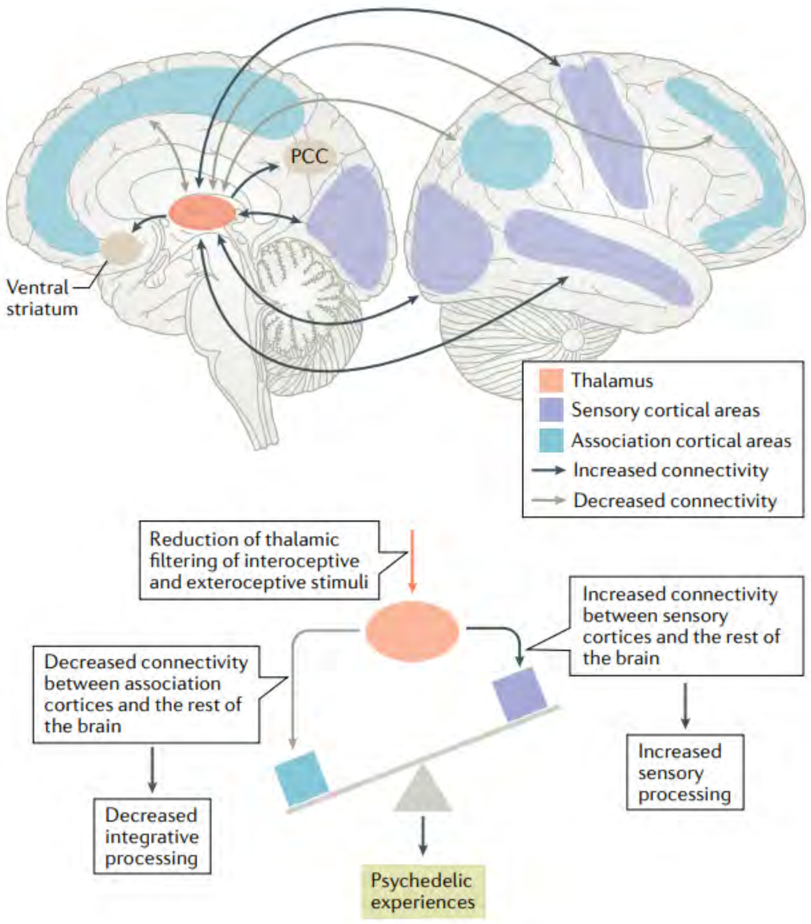
Serotonin and adaptation to stress





Carhart-Harris 2017

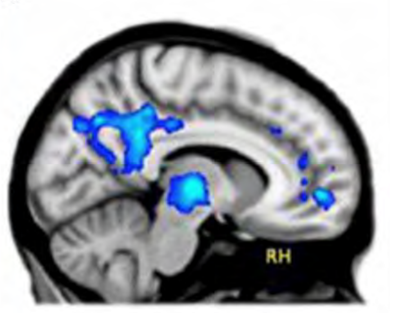
Psychedelics increase sensory but decrease integration processing



Vollenweider 2020

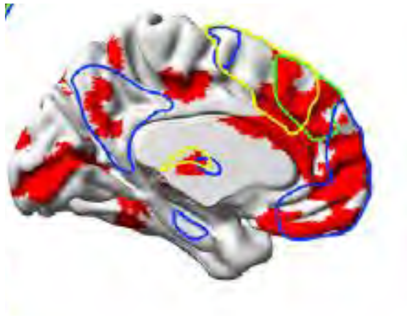
Self-dissolution with hallicunogenics

Psylocybin
Magic mushrooms



Carhart-Harris 2014

Lysergic acid diethylamide
LSD



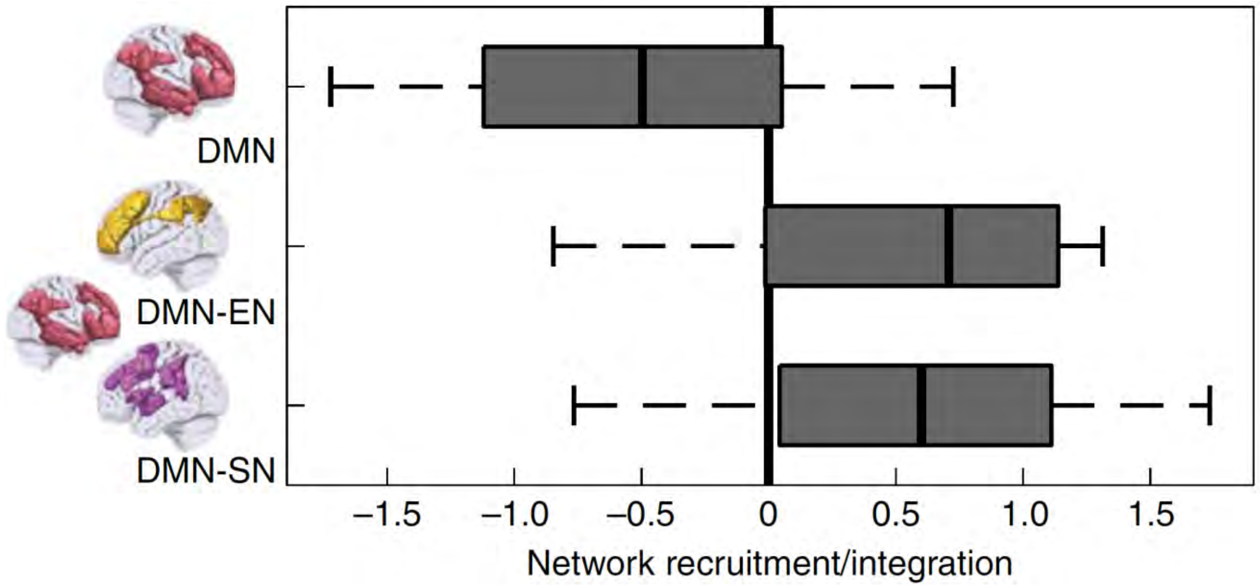
Tagliazucchi 2016

Ayahuasca

Palhano-Fontes 2014

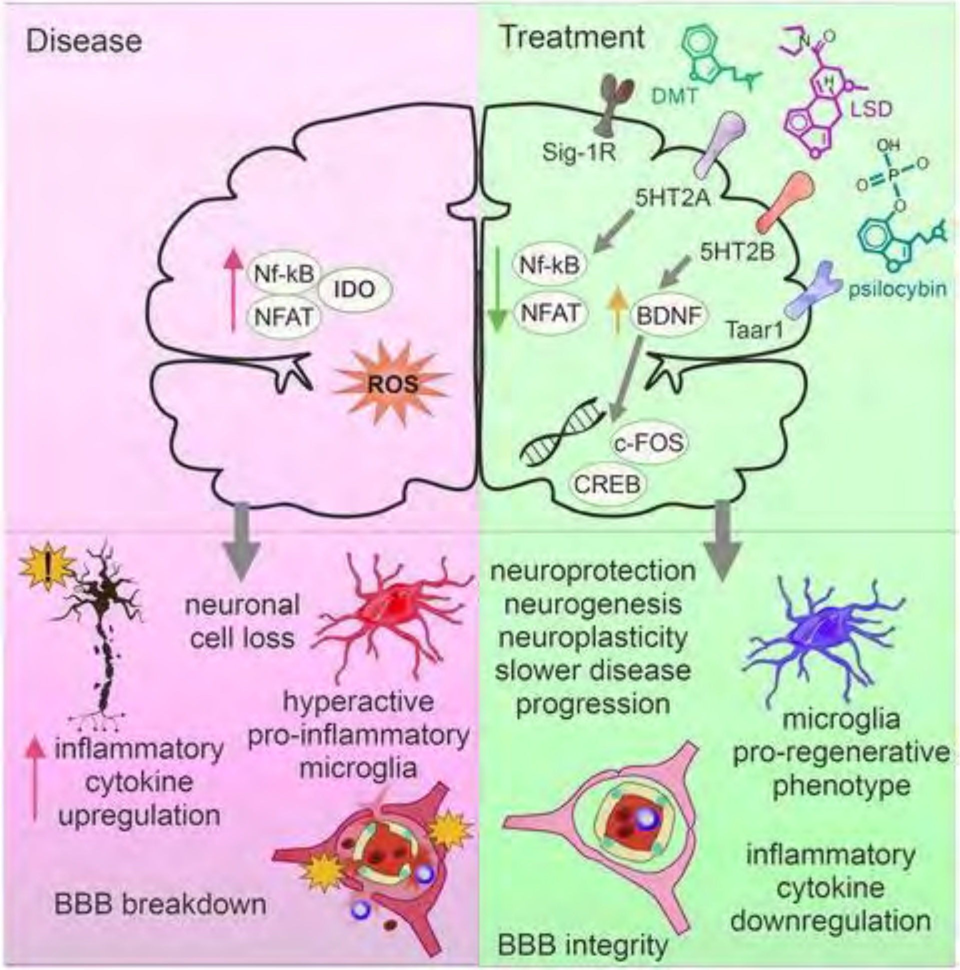
Ego dissolution also occurs in near death experience (Martial 2021)

Psychedelics: DMN disintegrates but connects with CEN and SN



Daws 2022

Psychedelics are anti-inflammatory



Kozlowska 2021

Macro vs microdosing

Plausible dose ranges for microdoses of various substances.

Compound	Typical recreational or therapeutic dose range	Intoxication threshold dose range	Plausible microdose dose range
Psilocybe cubensis dried mushroom: PO	3–5 g	0.5–1.5 g	0.1–0.5 g
Psilocybin synthetic: PO	17–30 mg[a]	3–8 mg[b]	0.8–5 mg[c]
Psilocybin synthetic: IV#	2 mg/70 kg – moderate dose[d]	1 mg[e]	0.5 mg[e]
LSD: PO	100–200 μg	20–25 μg[f]	6–20 μg[g]
DMT: IV#	14–28 mg/70 kg[h]	3.5 mg/70 kg	0.7–3.5 mg/70 kg
DMT: smoked	25 mg[i]		8–9 mg[j]
DMT: IM#	50–70 mg/70 kg	30 mg/70 kg[k]	6–25 mg/70 kg
Ibogaine synthetic: IV#	1000–2000 mg/70 kg (possibly starting at 200 mg/70 kg)	100–210 mg/70 kg[l]	20 mg/70 kg[m]

Note: PO, per oral; IV, intravenous; IM = intramuscular; LSD, lysergic acid diethylamide; # = depends on infusion rate.

Current evidence for microdosing effects.

Effects found in both self-report and lab studies	Effects found in self-report studies but not well investigated in lab studies	Effects found in self-report studies; investigated but not confirmed in lab studies[a]
• Altered time perception • Pain tolerance • Changes in conscious state	• Improved mental health • Reduced substance use • Increased absorption • Reduced mind wandering • Personality changes • Insight • Nature relatedness • Wellbeing • Improved creativity	• Improved mood • Social connection • Improved cognition • Enhanced emotional processing • Increased energy

[a] Note: Lab studies to date have investigated only acute effects. Sustained effects related to microdosing have not yet been explored in lab-based studies.

Polito 2022

Microdosing LSD

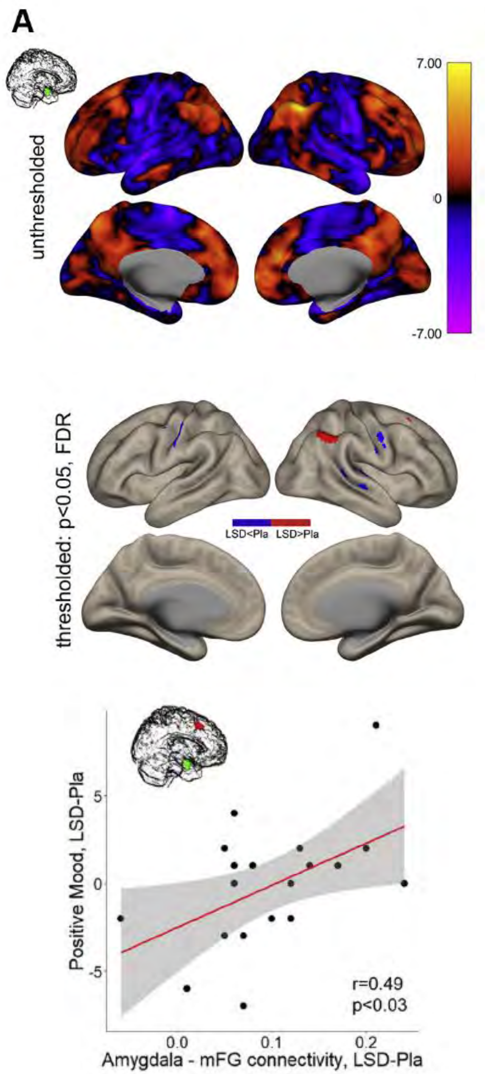
Microdosing LSD changes FC amygdala (Bershad 2019)

Increased to DMN and CEN (= synergy core)

Decreased to sensory and motor areas and SN

TPJ (DMN)

ACC/dmPFC related to mood



Placebo controlled

Bershad 2019

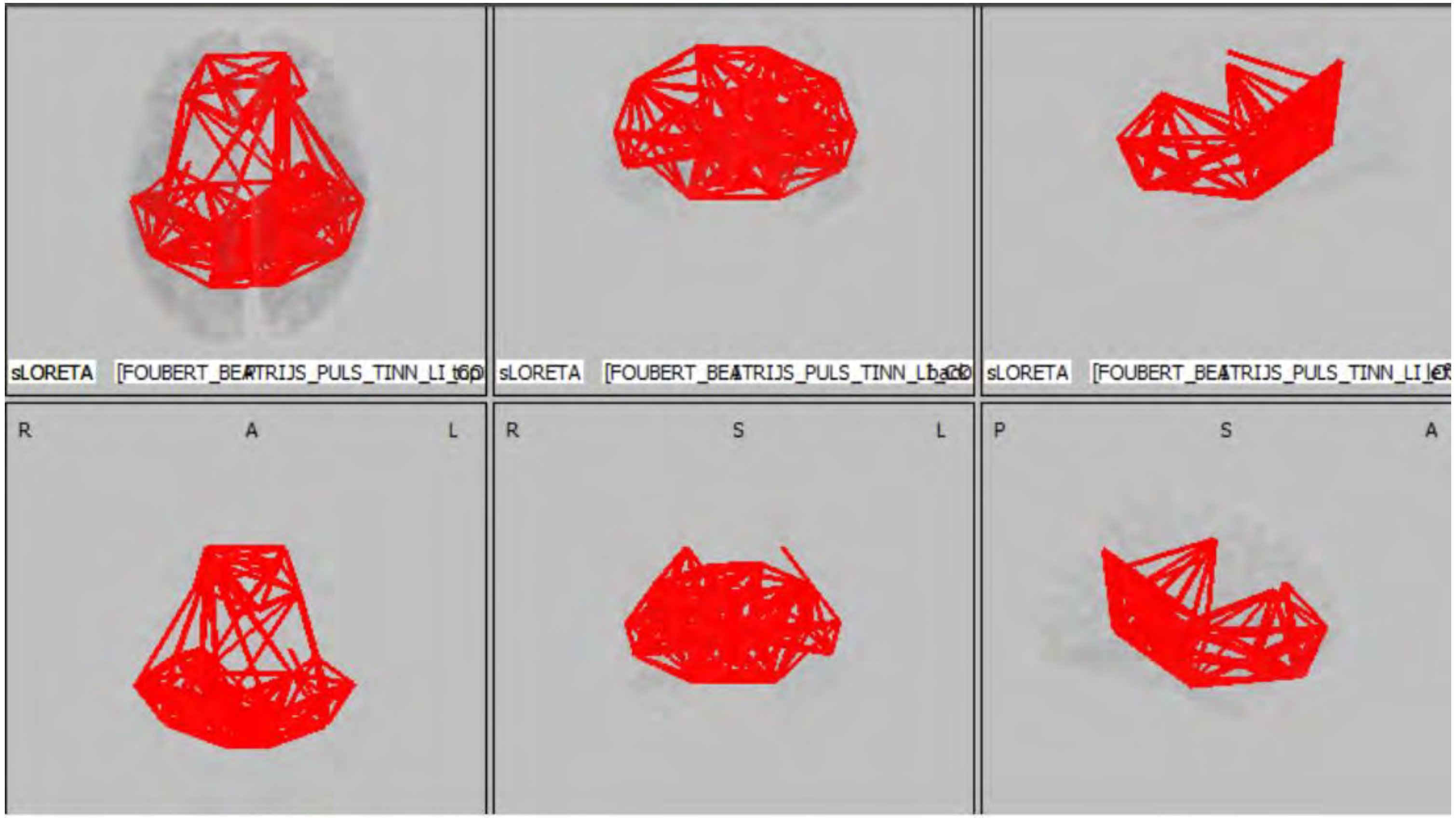
Exhausted brain

Phase 1: increased alpha connectivity

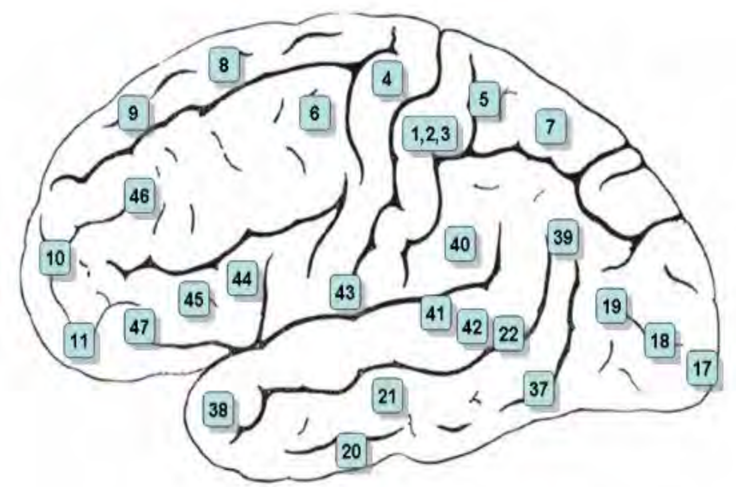
Phase 2: decrease in high frequency spectral power

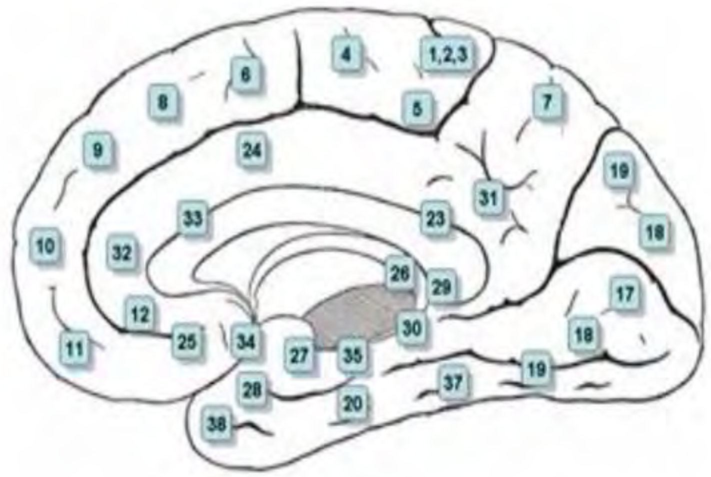
Phase 3: low voltage spectrum

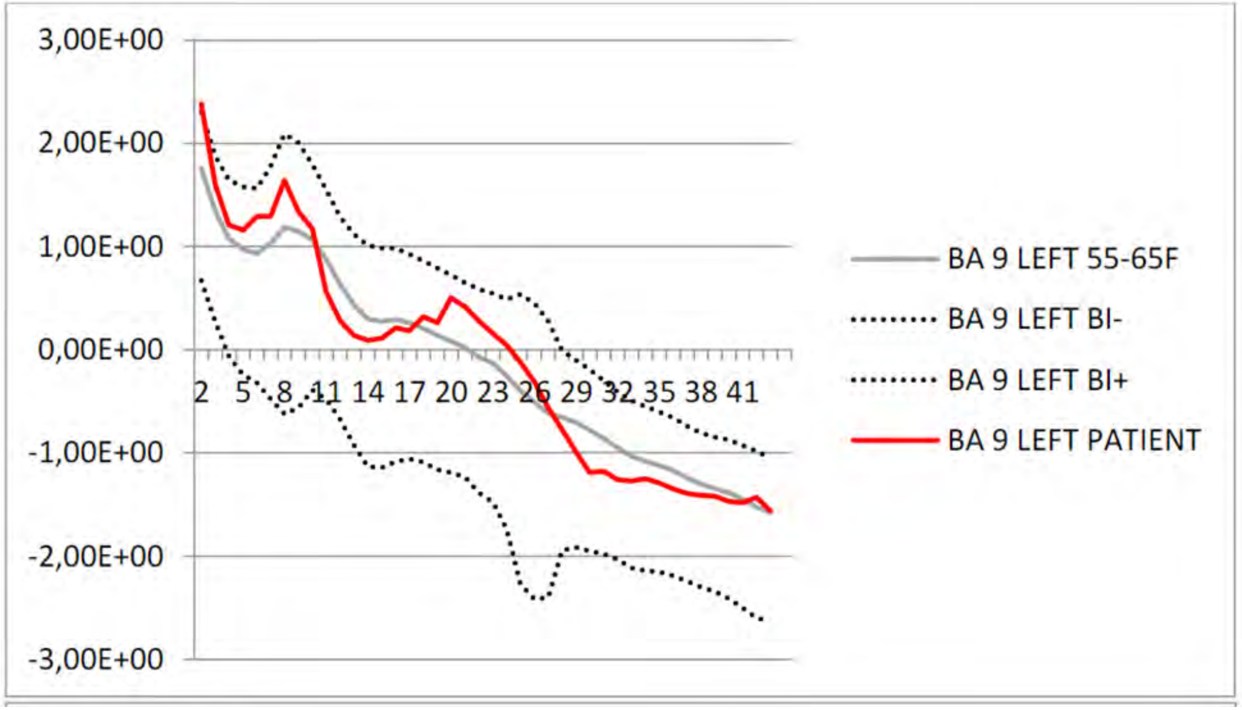
Increased alpha connectivity (vs norm group)



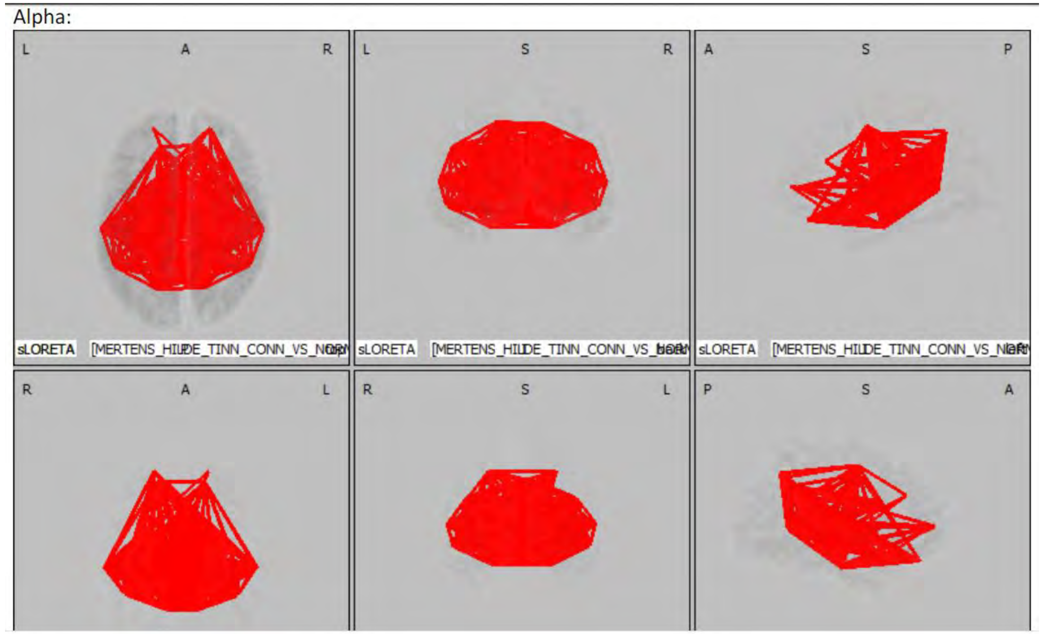
Normal spectral analysis

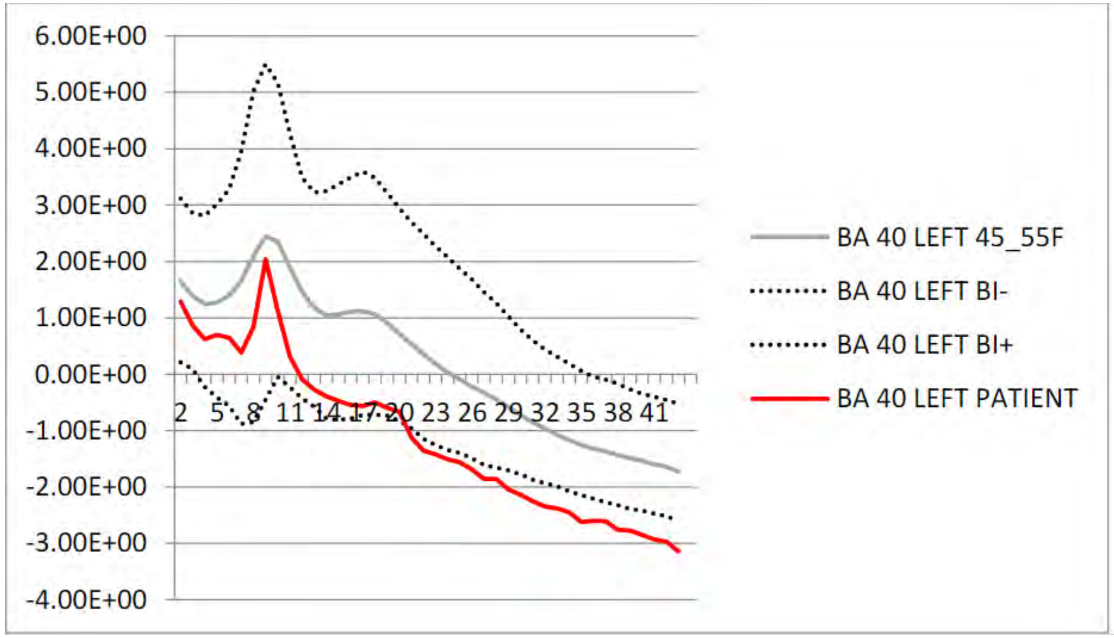






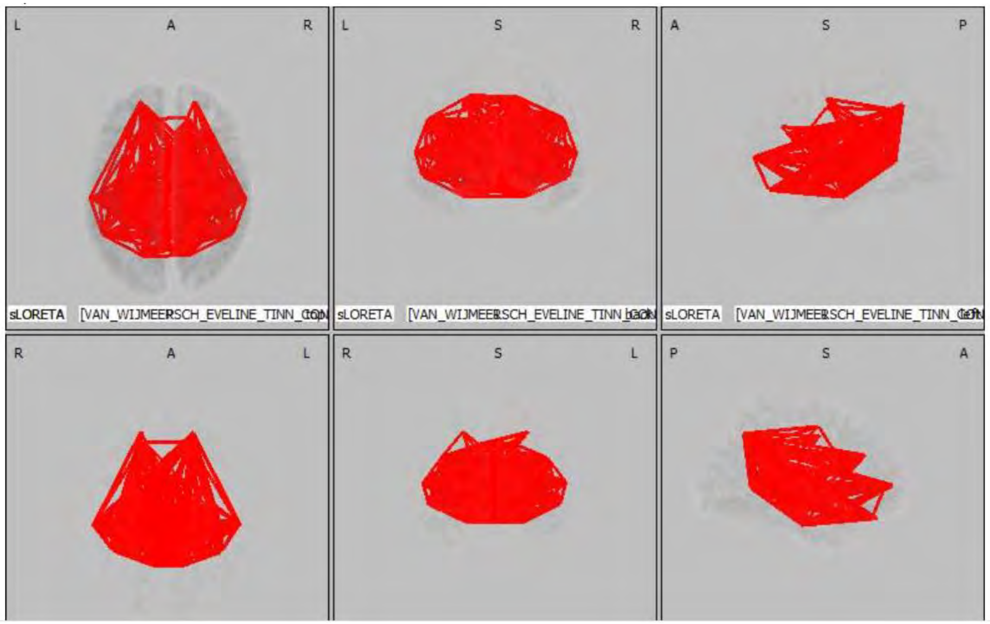
Low voltage for high frequencies in spectral analysis

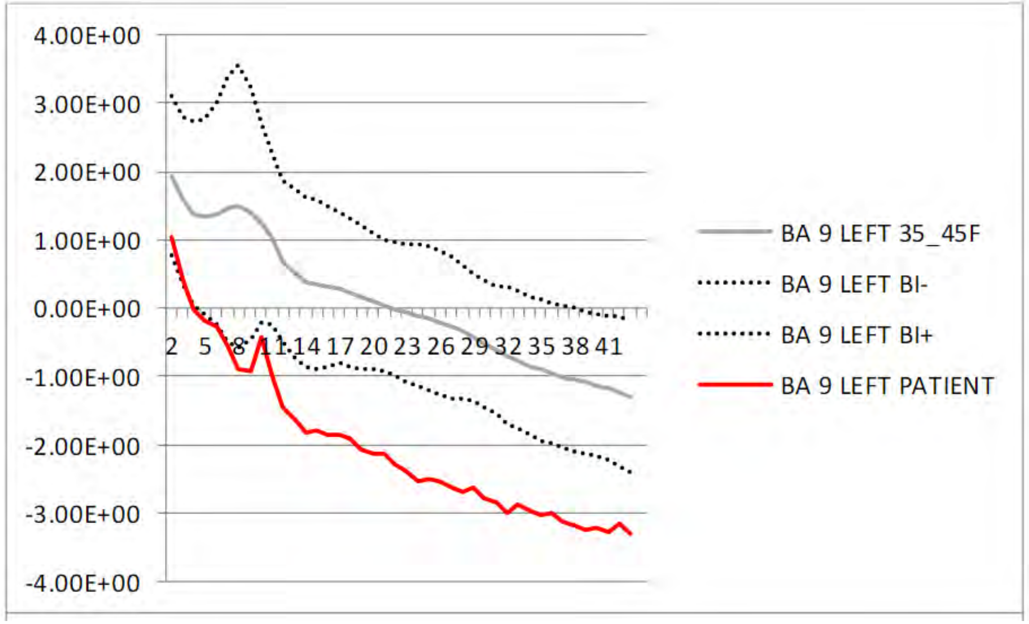




HRV: LF/HF = 0.80

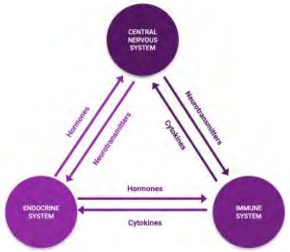
Increased alpha connectivity (vs norm group) + generalized low voltage spectral analysis





Treatment

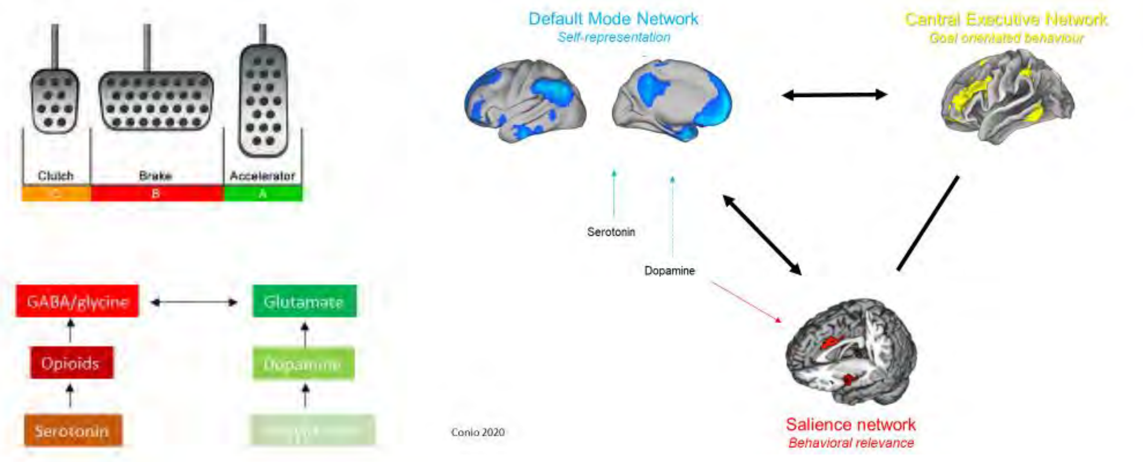
Phase 1: Force brain to rest

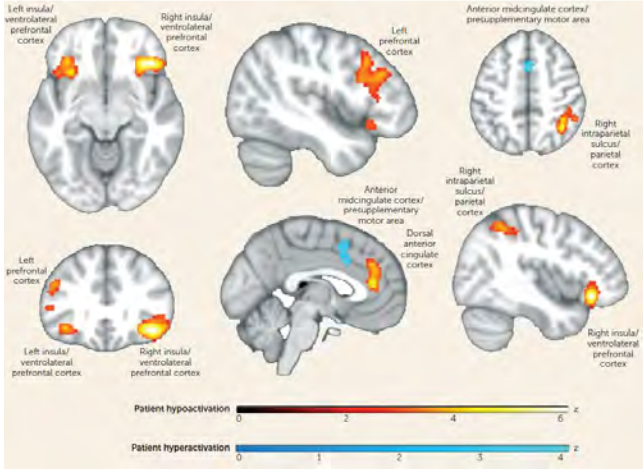


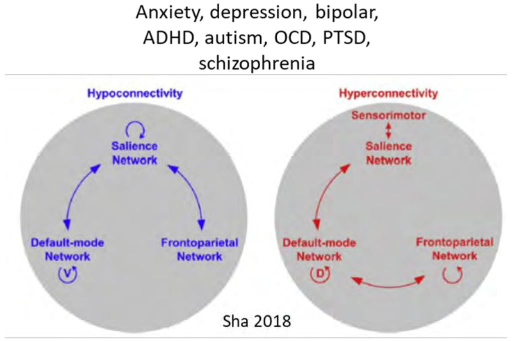
- Chemical
  - Nervous system
    - Block dopamine (deanxit), noradrenaline (clonidine), glutamate (ketamine)
    - Increase serotonin (SSRI, aripiprazole, macrodosis psychedelics), endorphins (naltrexone)
  - Immunological
    - Anti-inflammatory (NAC, LDN,…)
    - Probiotics
  - Hormonal ?
- Electrical
  - Activate left CEN: TMS 10 Hz left
  - Block SN: TMS 1 Hz

Phase 2: rebuild the brain

- Chemical: wean medication/hormones (Thyroid) or low maintenance dose: microdosing
- Electrical: start neurofeedback
  - Strengthen DMN
  - Strengthen anticorrelation DMN-SN
  - Strengthen CEN







Conclusion

Neuromodulation
All techniques have same underlying principle
(TES, TMS, electrodes, neurofeedback)

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Neuromodulation
changes activity of neurons & glia
thereby changes functional and effective connectivity
modulates neural networks functioning (eg efficiency)
thereby changing the network's emergent function

Psychedelics
Change activity and functional connectivity
Modulating neural networks
Changing the networks emergent function

Chemical and electrical neuromodulation interact (strengthen or weaken)