BRAI3N

UNIVERSITY of OTAGO
Te Whare Wānanga o Otāgo

INSPIRED BY LIFE
Manipal, India

Physical & psychological pain
The other side of the same coin?

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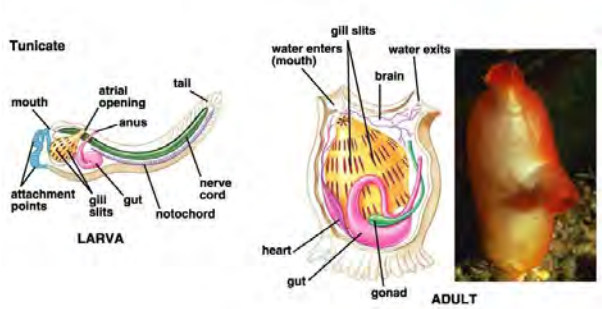
Why do we have a brain?

We have a brain because we need one



Sea squirt

Move around

Changing environment

Change = uncertainty but **predictable**

Intentionality

Brains = prediction machines
essential in navigation/movement
using information from previous experiences (memory)
to predict future events (intelligence)
based on current context
in relation to the self
to reduce uncertainty
important for survival and procreation
i.e. for natural, social and sexual selection

Hierarchy of needs

Animals need to decide moment by moment which needs (goal to survive & procreate) to pursue, for which energy and time needs to be allocated (Gros 2018, Sutton 2020)

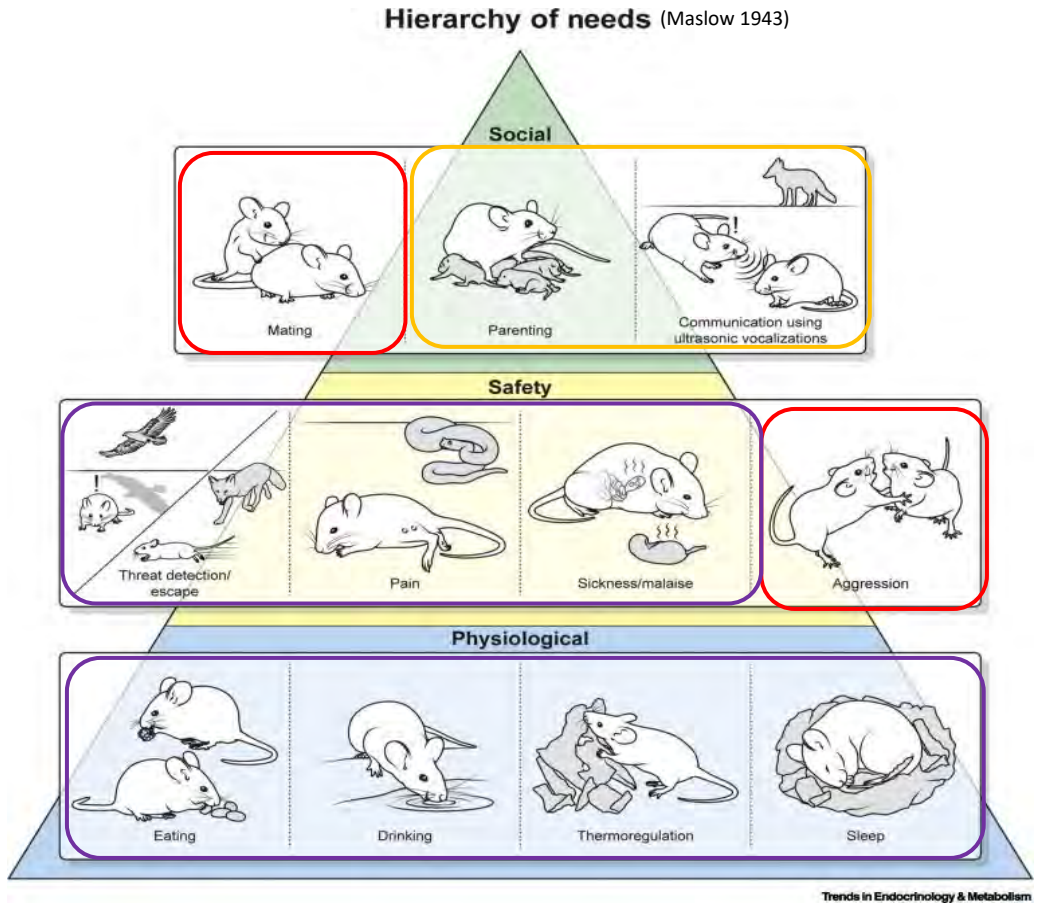
Each competing need is linked to a motivation to either **'do'** something or nothing

> Activates the sympathetic (arousal, do) or parasympathetic (rest/digest/restore) nervous system

When a need requires action, it triggers an **increase in noradrenergic sensory gain** to find/sample the stimuli that are needed to fulfil the need

Each competing need has different dopaminergic motivational **salience**, i.e. propels an organism to or away from an object/stimulus

Whether an object/stimulus is good (pleasure) or **bad (suffering)** to reduce the need is determined by the **context**



Natural – sexual – social selection

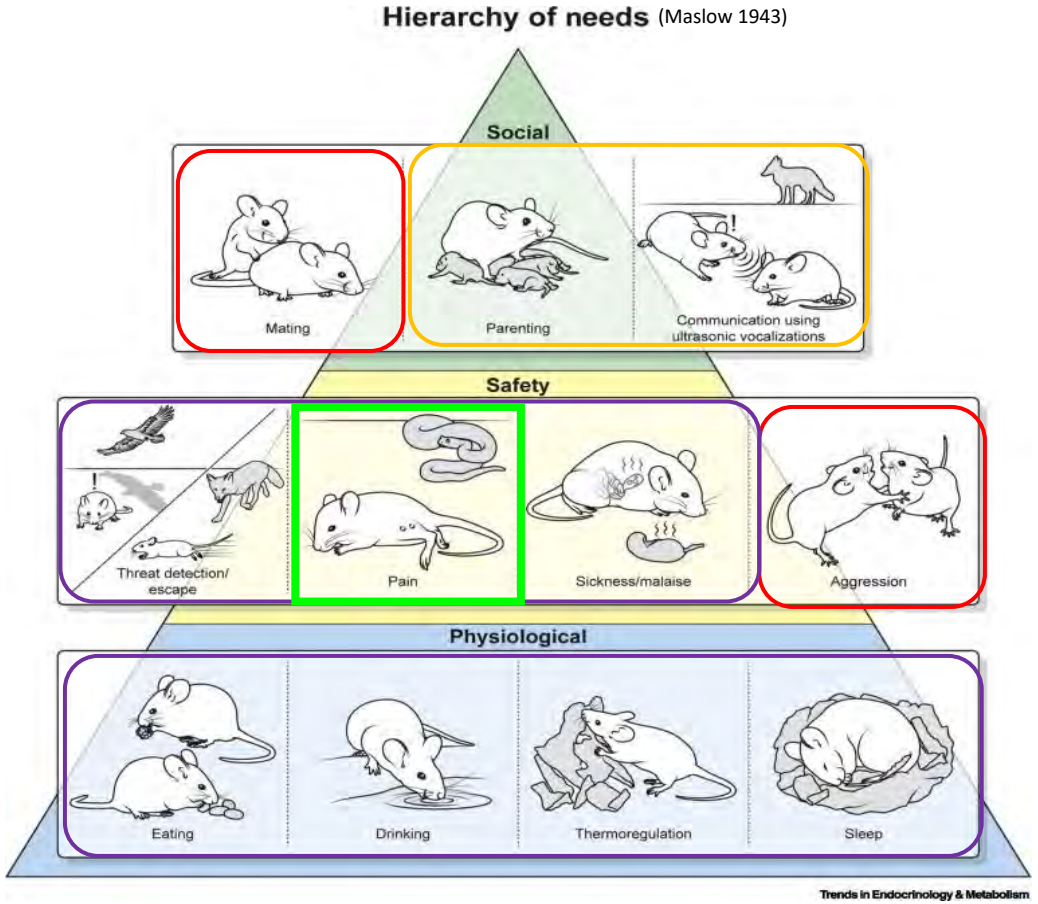
Sutton 2020

Hierarchy of needs

→ Motivation 1
(eg thirst)

→ Motivation 2
(eg fear)

→ Motivation 3
(eg lust)



Natural – sexual – social selection

Hierarchy depends on context, but in general '**safety first**'
In stress = uncertainty: '**better safe than sorry**'
In absence of stress = no uncertainty: '**no guts no glory**'

Pain & Pleasure

1. Determine priority in hierarchy of needs
2. Learn for the future

Philosophy of pleasure and pain

Epicurus (341-270 BC)

Pursuit of pleasure and abscence of pain is **purpose of life**, but without excesses (based on Plato and Aristotle)

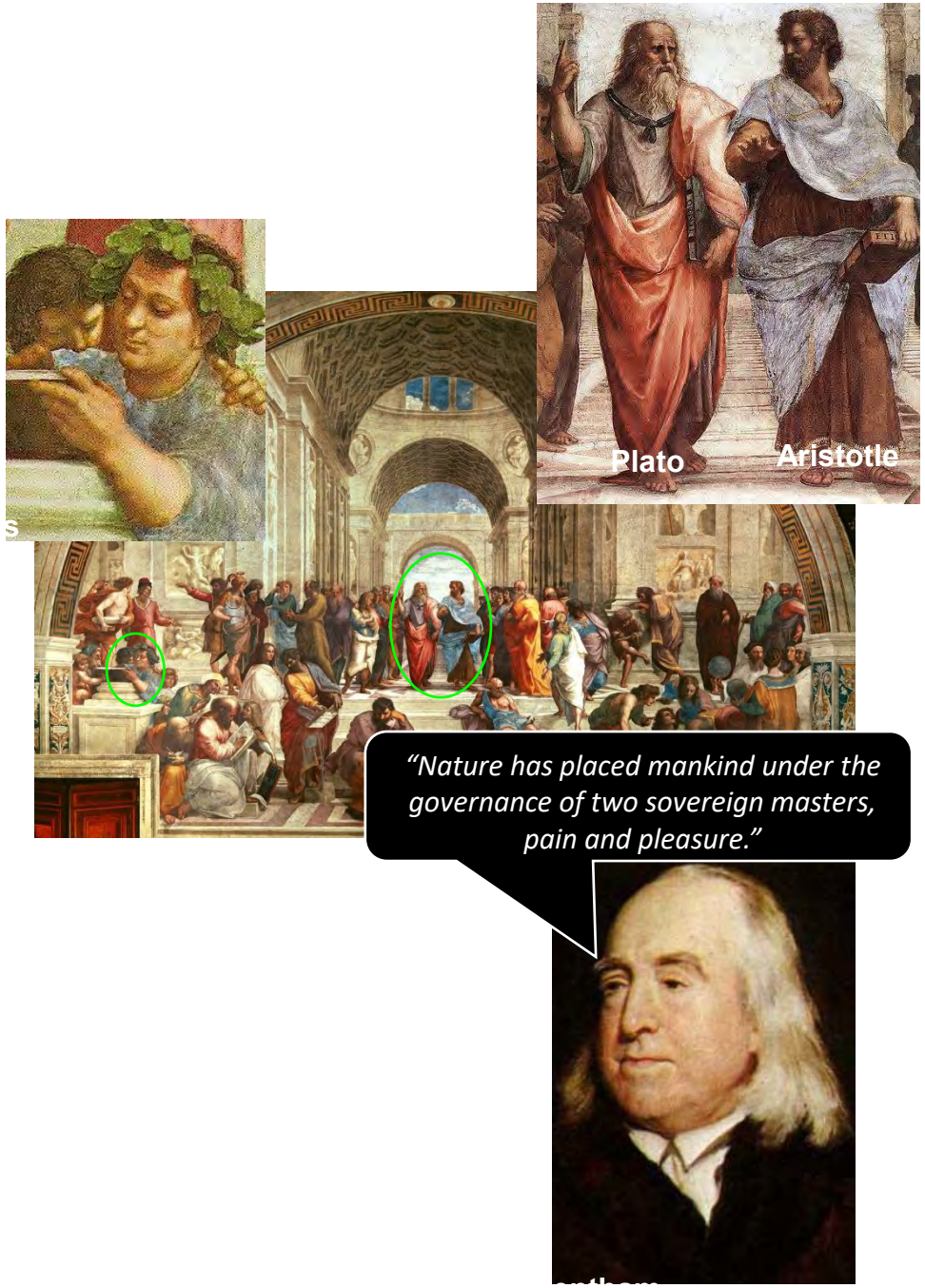
- Ataraxia: peace and freedom from fear
- Aponia: the absence of pain

Bentham (1748-1832)

Utilitarianism: One has to maximize pleasure and minimize pain...

Not only purpose of life but also **mechanism of life**

in order to reduce uncertainty

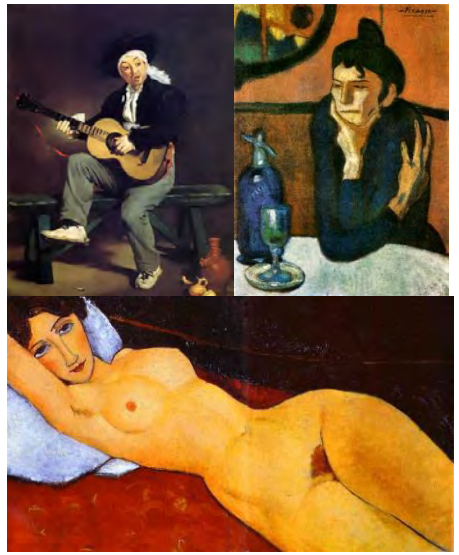


Pleasure and pain as mechanism of life

Brain is constantly bombarded by simultaneous stimuli (Seeley 2005)

Salient environmental events should be processed with **priority** (Dolan 2002, Seeley 2005,Fecteau 2006).

Emotions create **priority** mode for attentional perceptual processing (Dolan 2002).



P(B/A)/P(B)
Sample environment for predicted stimulus

P(A)
Predict external stimuli

P(A/B)
Update based on Intention
Prediction error

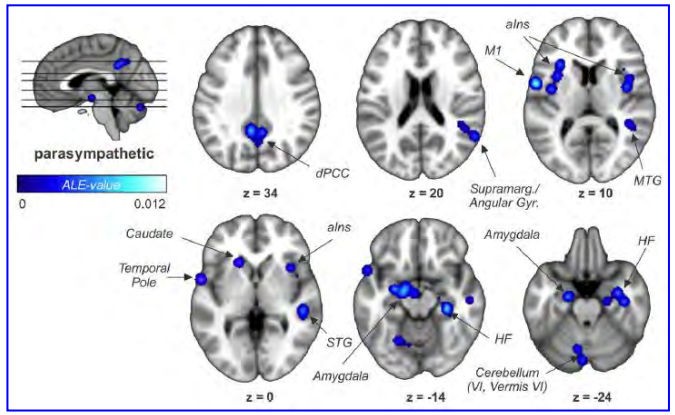
Prediction is right

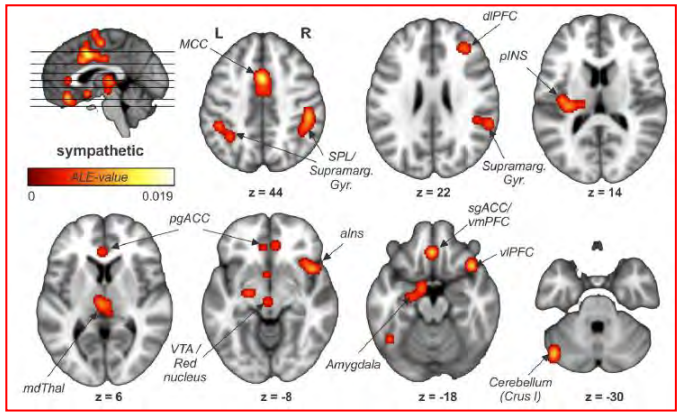
Prediction is wrong

'Rest & digest'
Parasympathetic

'Do'
Sympathetic

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





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Prediction error

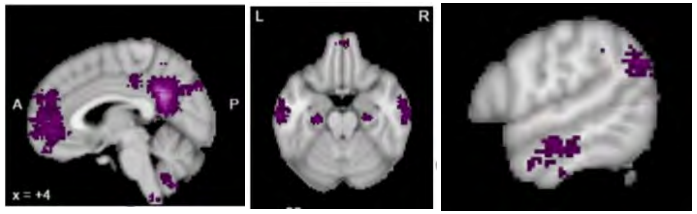
$$P(A/B) = P(A)\frac{P(B/A)}{P(B)}$$

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

Prediction is right

Prediction is wrong

No conscious perception
Rest & digest



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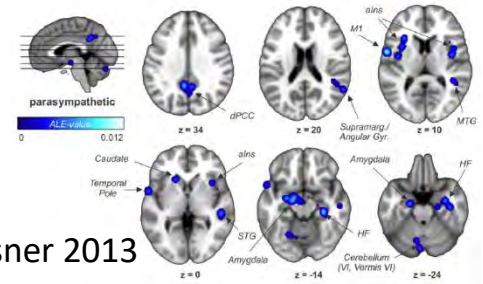


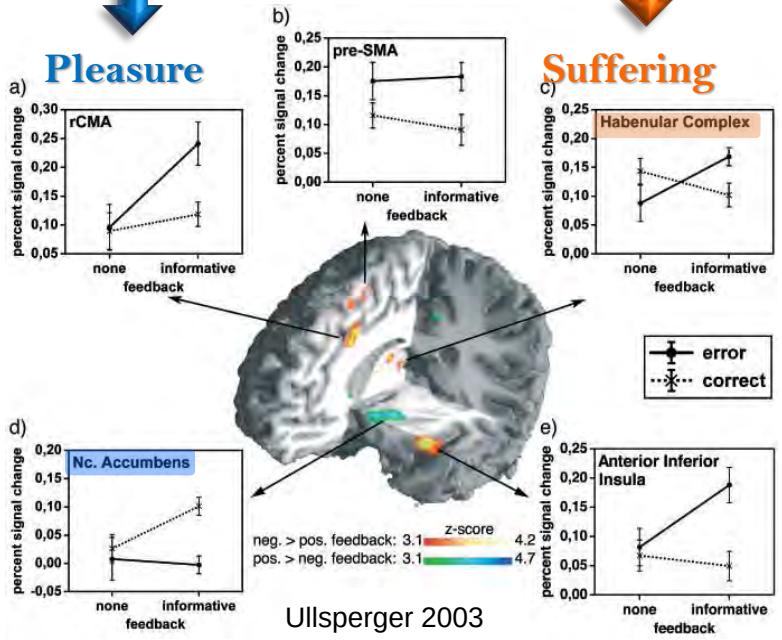
Beissner 2013

Better than prediction

Worse than prediction

Pleasure

Suffering



Ullsperger 2003

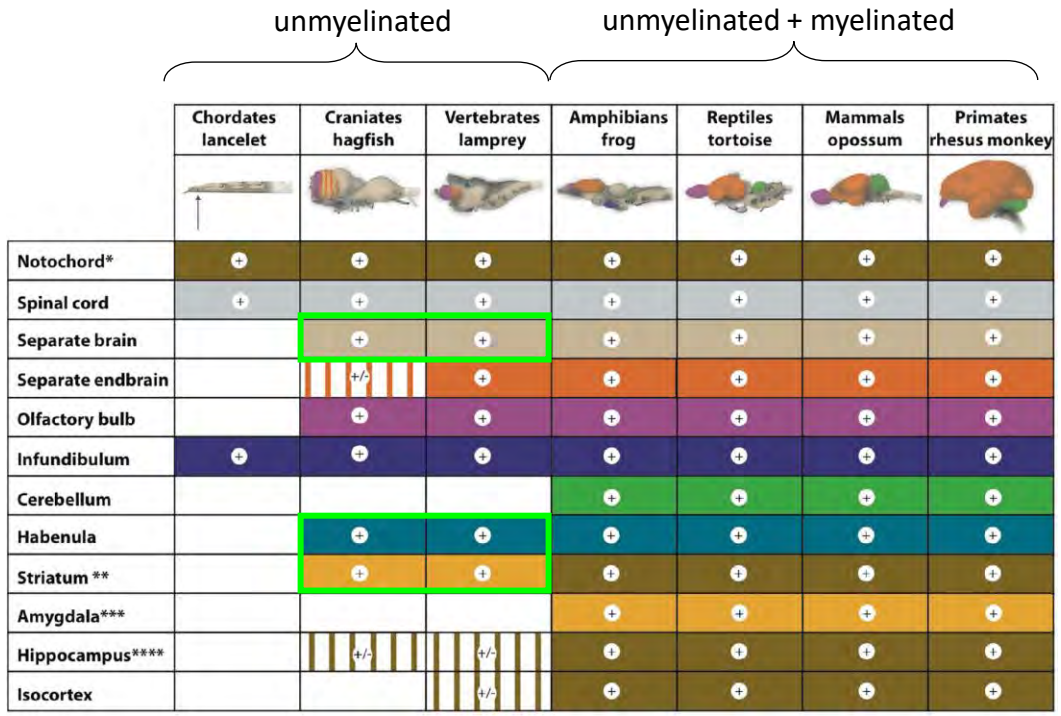
Evolution of reward seeking (food, partner) and misery fleeing (predator) brain circuitry

Cambrian explosion (540 million years ago)(Loonen 2015)

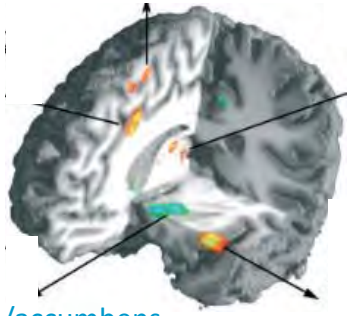
- Lancelet fish (amphioxus, 530 M) has no true brain
- First brain* arises in hagfish and lamprey
- Hagfish (300M) and lamprey (360M) have basic feedback circuitry
  1. Habenula
  2. Striatum/accumbens

This motivation to seek reward and flee from misery/punishment permits organism to learn what is beneficial and harmful for survival and procreation

Requires only unmyelinated (C-) fibers in CNS and PNS

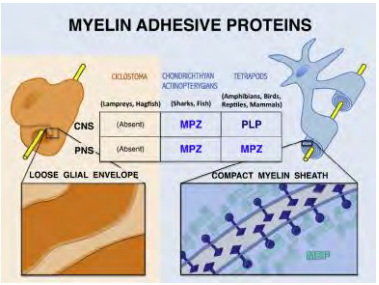


Loonen 2015



Habenula: suffering

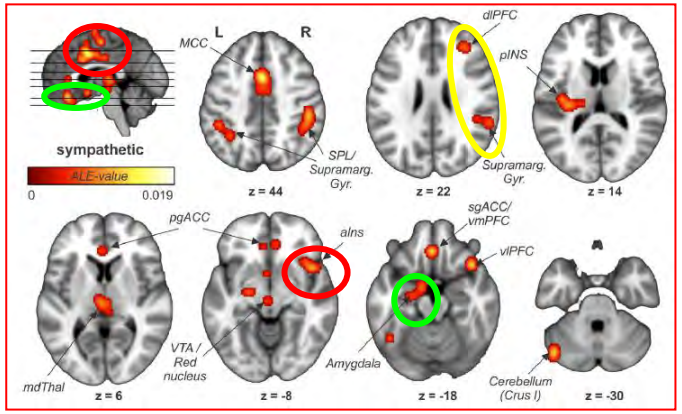
Striatum/accumbens
Pleasure



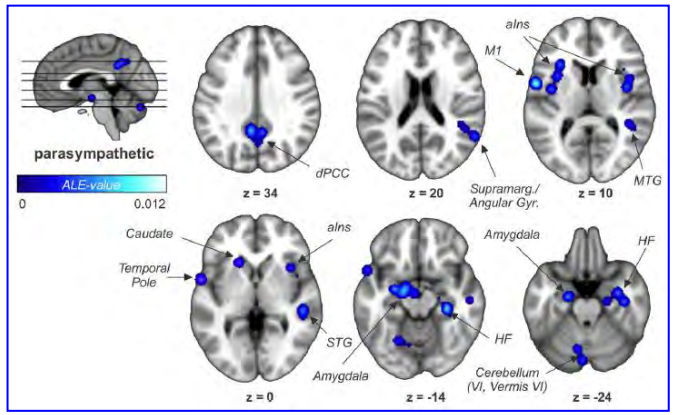
de Bellard 2016

* Brain subserves entire body, bilobar, specialized parts, multisynaptic (Sarnat 2002)

Sympathetic

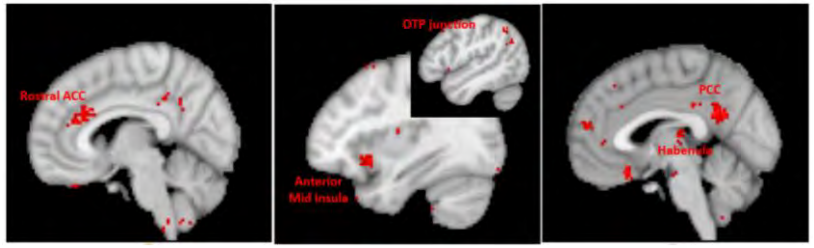


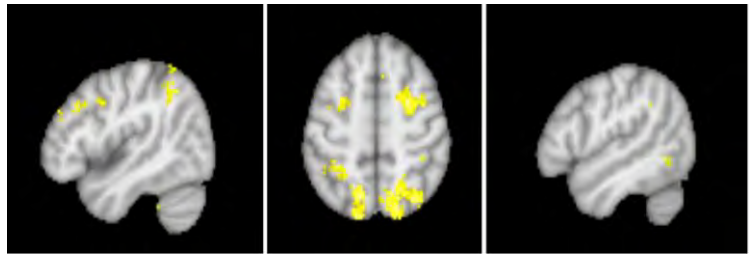
Parasympathetic



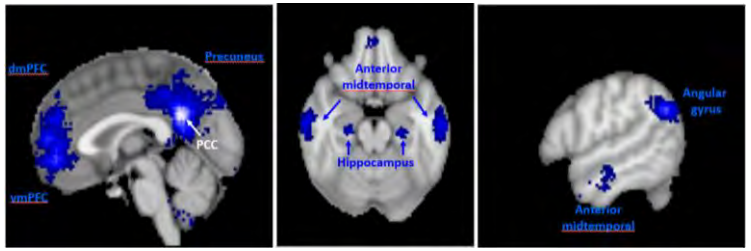
Beissner 2013

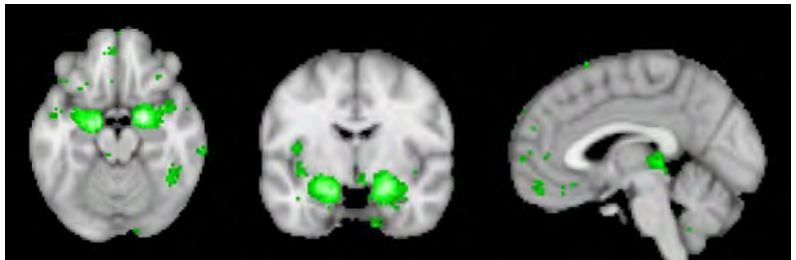
Salience + Central executive



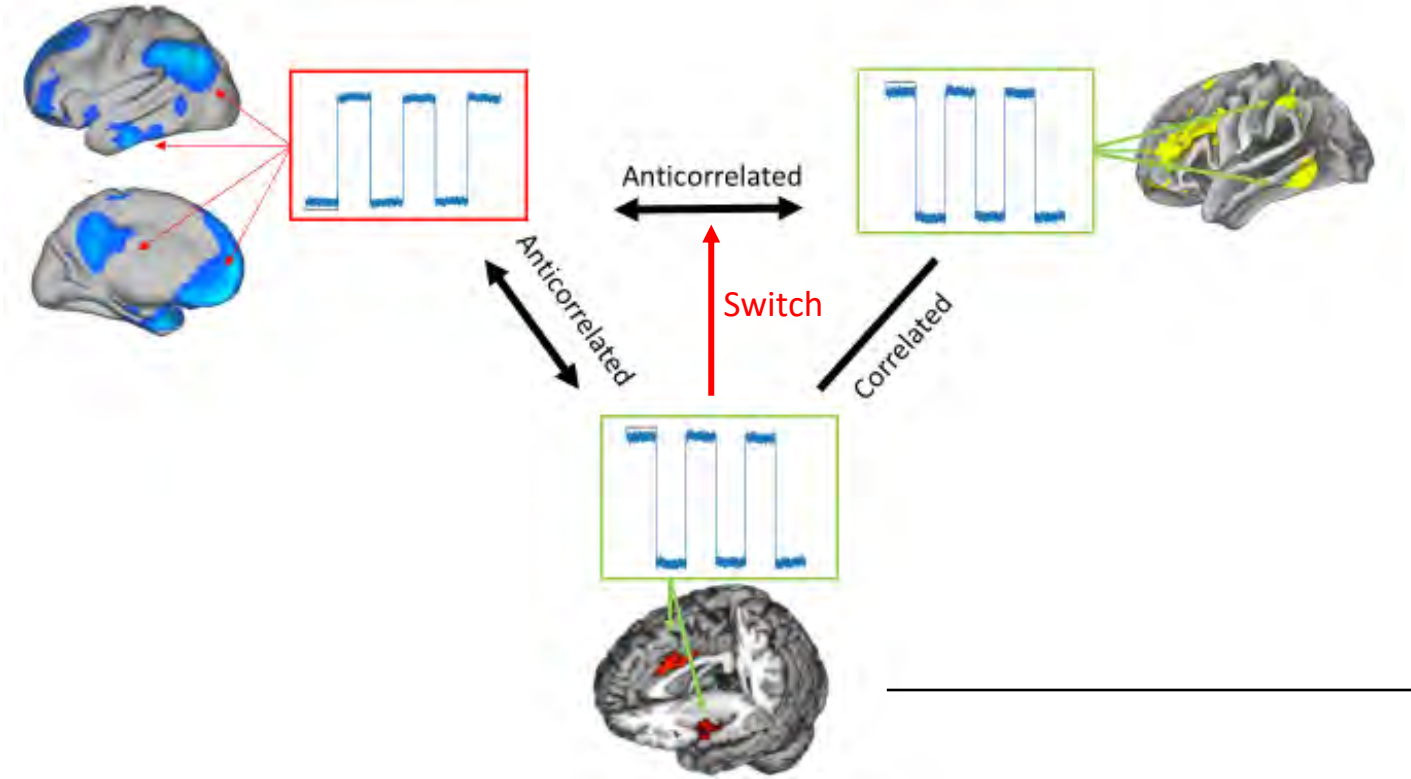


Default mode





Emotion



Cognition

Conductor

Emotion

Pain

Definition

Pain = as an unpleasant **sensory** and **emotional** experience associated with actual or potential **tissue damage** …(Bonica 1979)

Acute Pain

Acute pain depends on context and intention/goal

- Battle front (Beecher 1956)
  - No relationship between the extent of the injury (= stimulus intensity) and experienced pain in wounded soldiers evacuated from the frontline
  - Intensity of the suffering is largely determined by the salience of the pain in this specific context
- SM (Kamping 2016)
  - Pain is perceived pleasant only in erotic context
- Sports
  - "If I feel no pain I have not trained hard enough"

The Price, Tom Lea (1944)

Conclusions

Tissue damage ≠ pain

Pain ≠ suffering

Pain can be pleasant

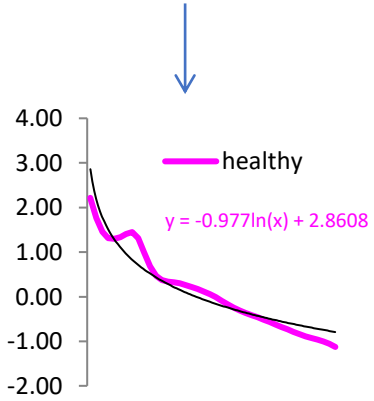
Pain and suffering are generated in the brain

Brain = complex adaptive system

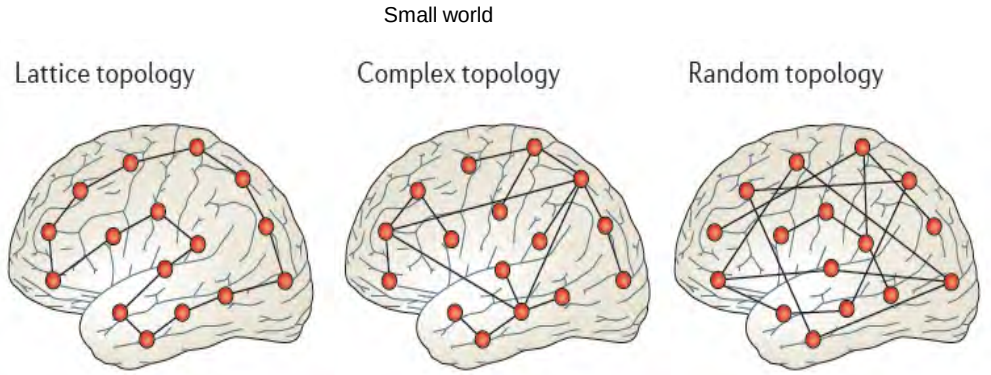
Complex adaptive systems (CAS)

Arise when 2 conditions are fulfilled (Amaral 2004)

1. Structure has small world topology
2. Presence of noise (= variability)



→ Brain is small world network (Liao 2017)



Brain = complex adaptive system

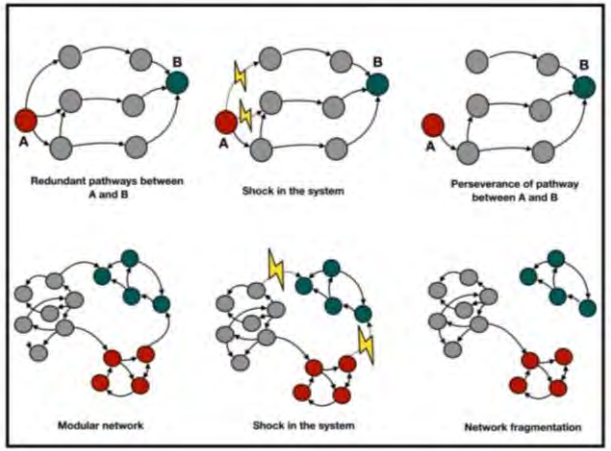
Complex adaptive systems (CAS)

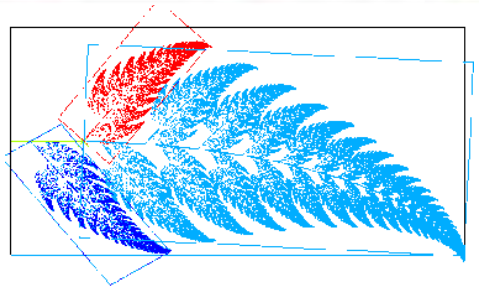
are characterized by

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

   Adding energy to matter results in overcoming 2nd law of thermodynamics and permits selective forces to work on it (Whitfield 2007)
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

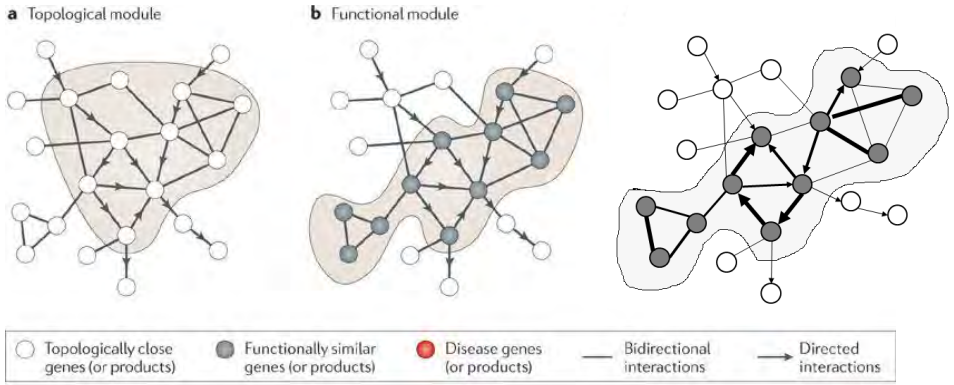




Interactions create emergence

Emergence

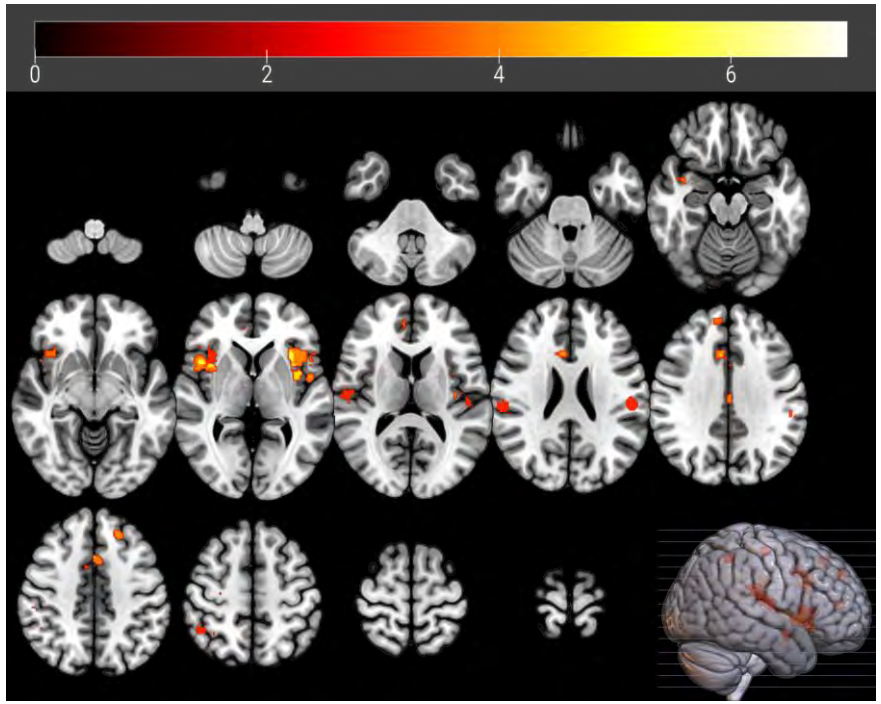
Each pattern has emergent characteristic



Barabasi 2011

Anatomy of pain and suffering

Meta-analysis conjunction pain and suffering



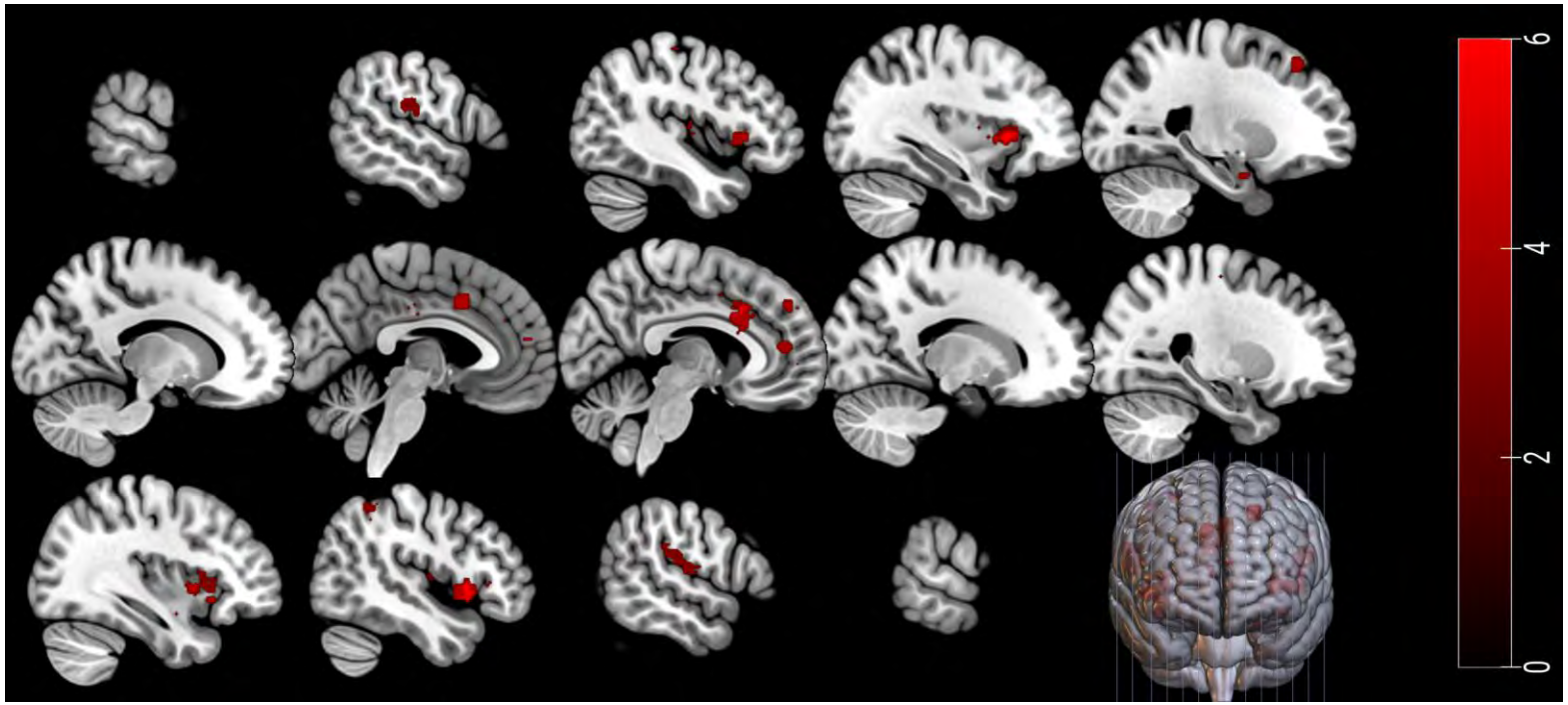
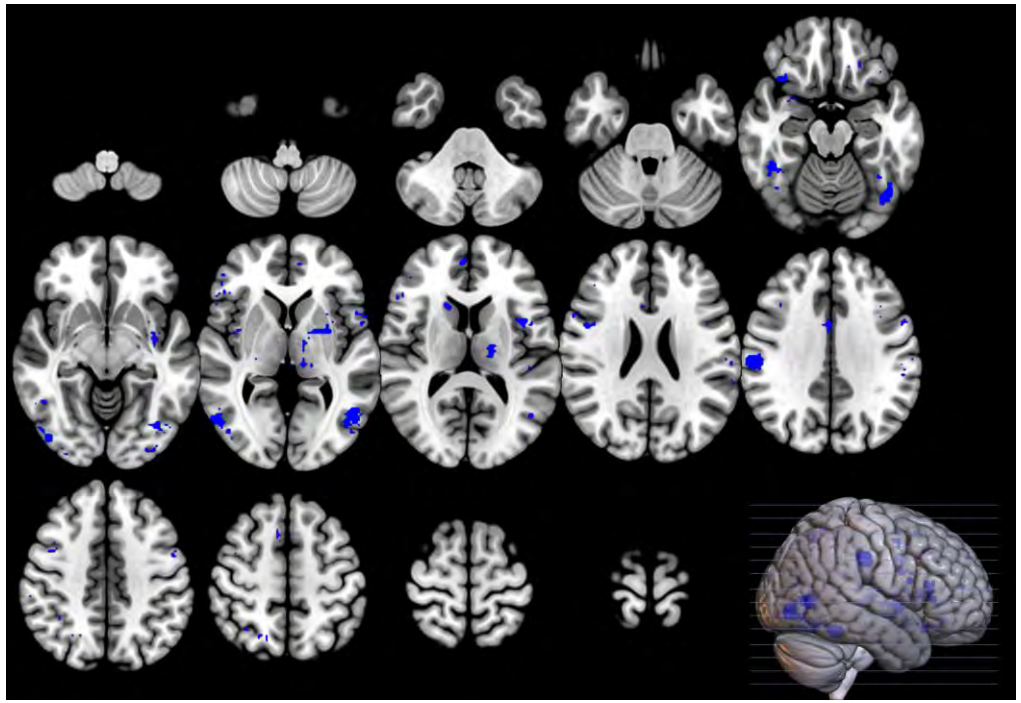


Image courtesy Vanneste

Meta-analysis subtraction pain and suffering



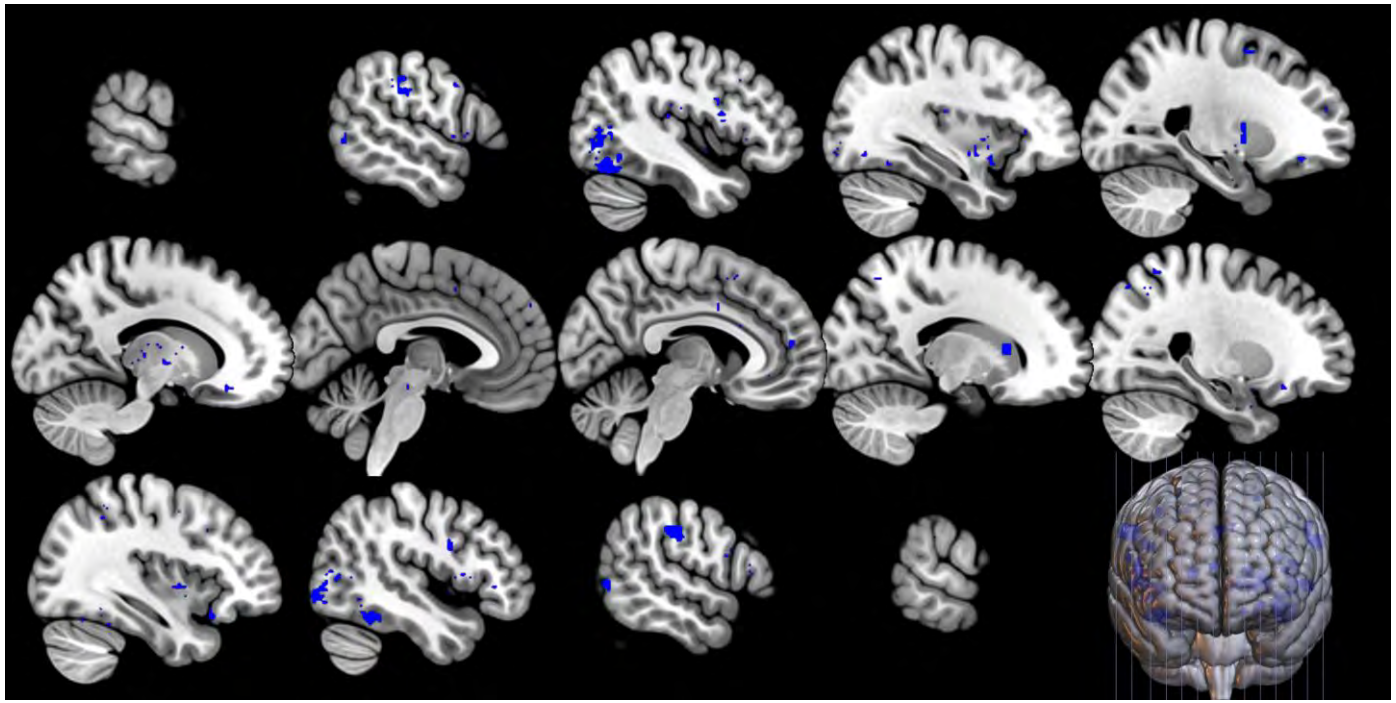
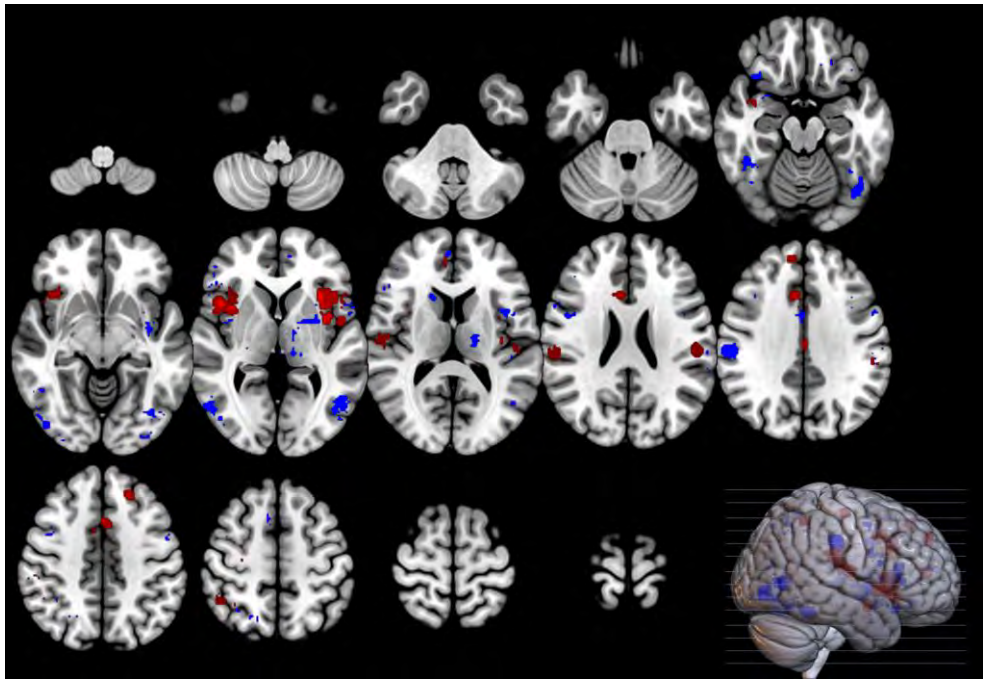


Image courtesy Vanneste

Meta-analysis: combination conjunction & subtraction



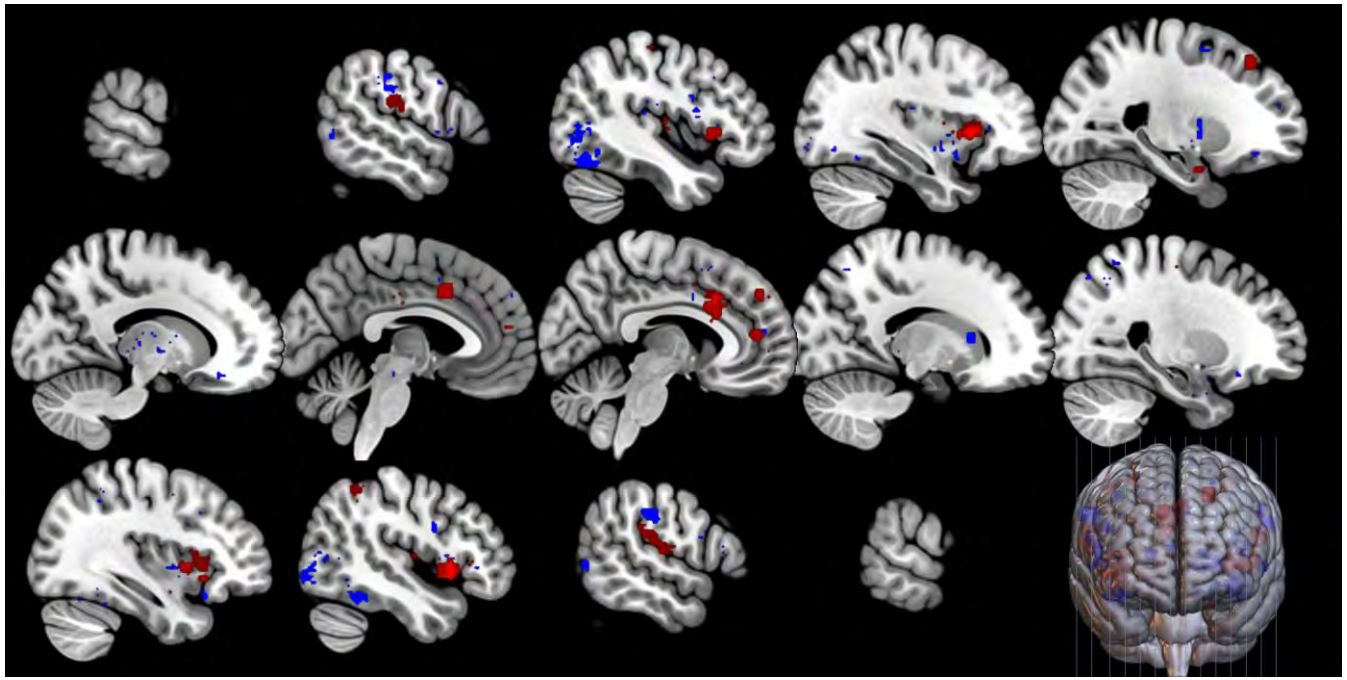
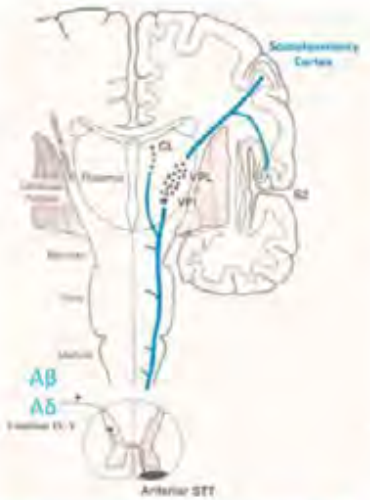
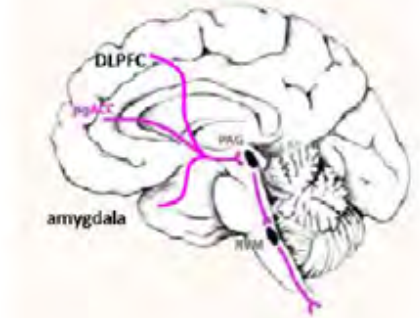


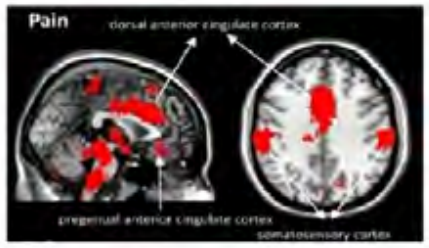
Image courtesy Vanneste

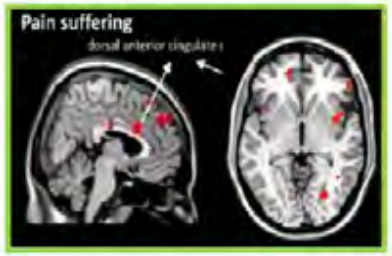
Summary

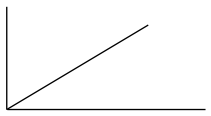
Global pain = *Lateral Pathway* **Painfulness** + *Medial Pathway* **Suffering** - *Inhibitory Pathway* **Pain suppression**

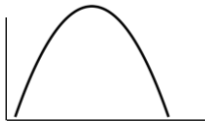


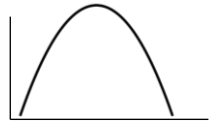












Viinikainen 2010, Marshall 2016, Schlund 2020

De Ridder 2021

Pain sensation

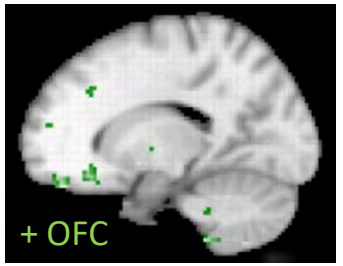
Cognitive reaction
(PCS, PVAQ)

Autonomic reaction
(stress, arousal)

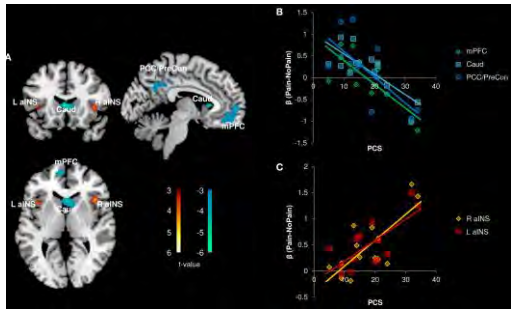
Emotional reaction
(unpleasantness, anger, fear, frustration)

Suffering

Chronic:
Anxiety
Depression
…

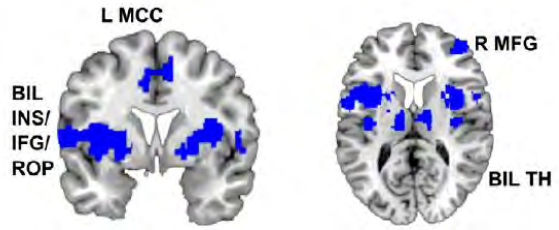


Catastrophizing = insula



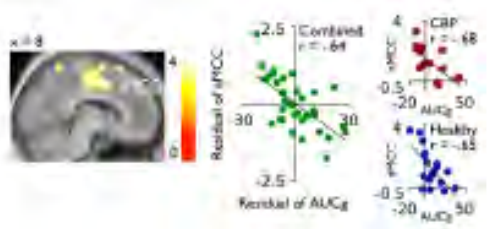
Mathur 2016

Stress = rdACC + insula



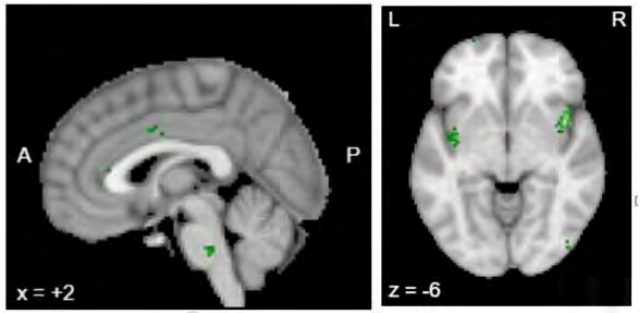
Kogler 2015

Unpleasantness = rdACC



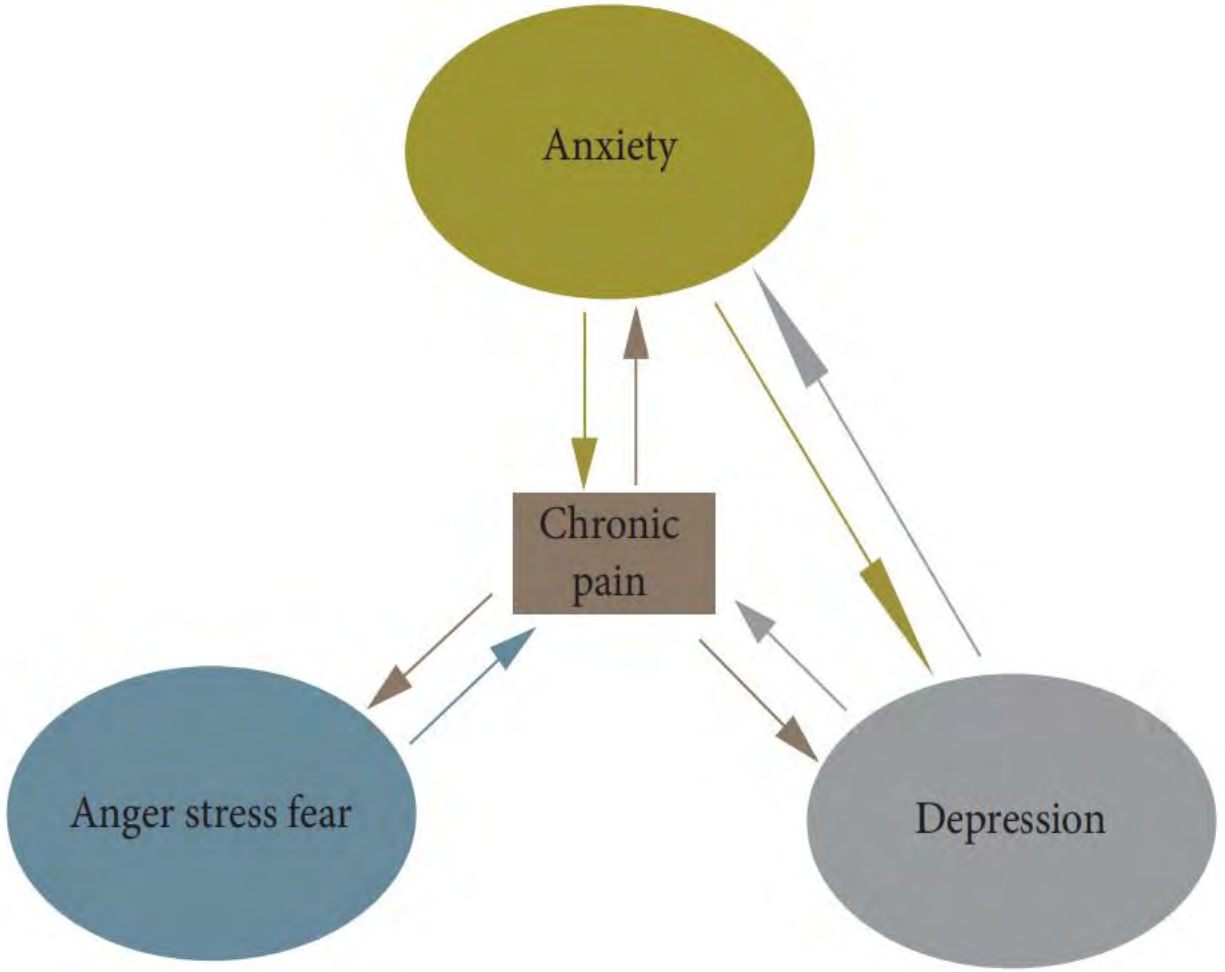
Vachon-Presseau 2013

Suffering = rdACC + insula



De Ridder 2021

Chronic pain & suffering



Feller 2017

Suffering

= unpleasant experience associated with negative cognitive, emotional and autonomic reaction

(De Ridder 2021)

Cognitive reaction
(PCS, PVAQ)

Pain

Autonomic reaction
(stress, arousal)

NRS = 5

Emotional reaction
(unpleasantness, anger, fear, frustration)

Suffering

NRS > 6

Embodiment

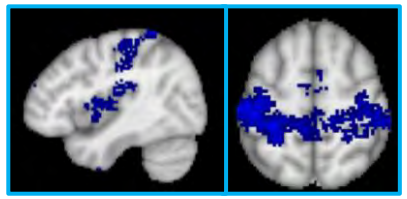
Disability, QOL
(ODI, EQ5, SF36)

Sleep
(PSQI)

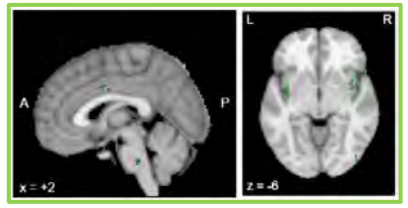
Functional/social impact

NRS > 7

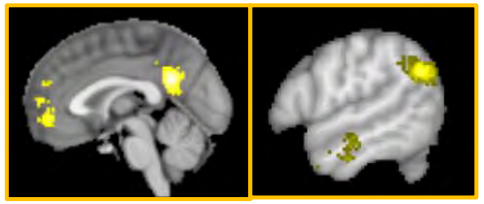
Somatosensory network



Salience network



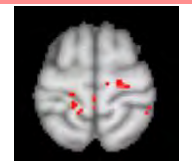
Default mode network



Central executive network

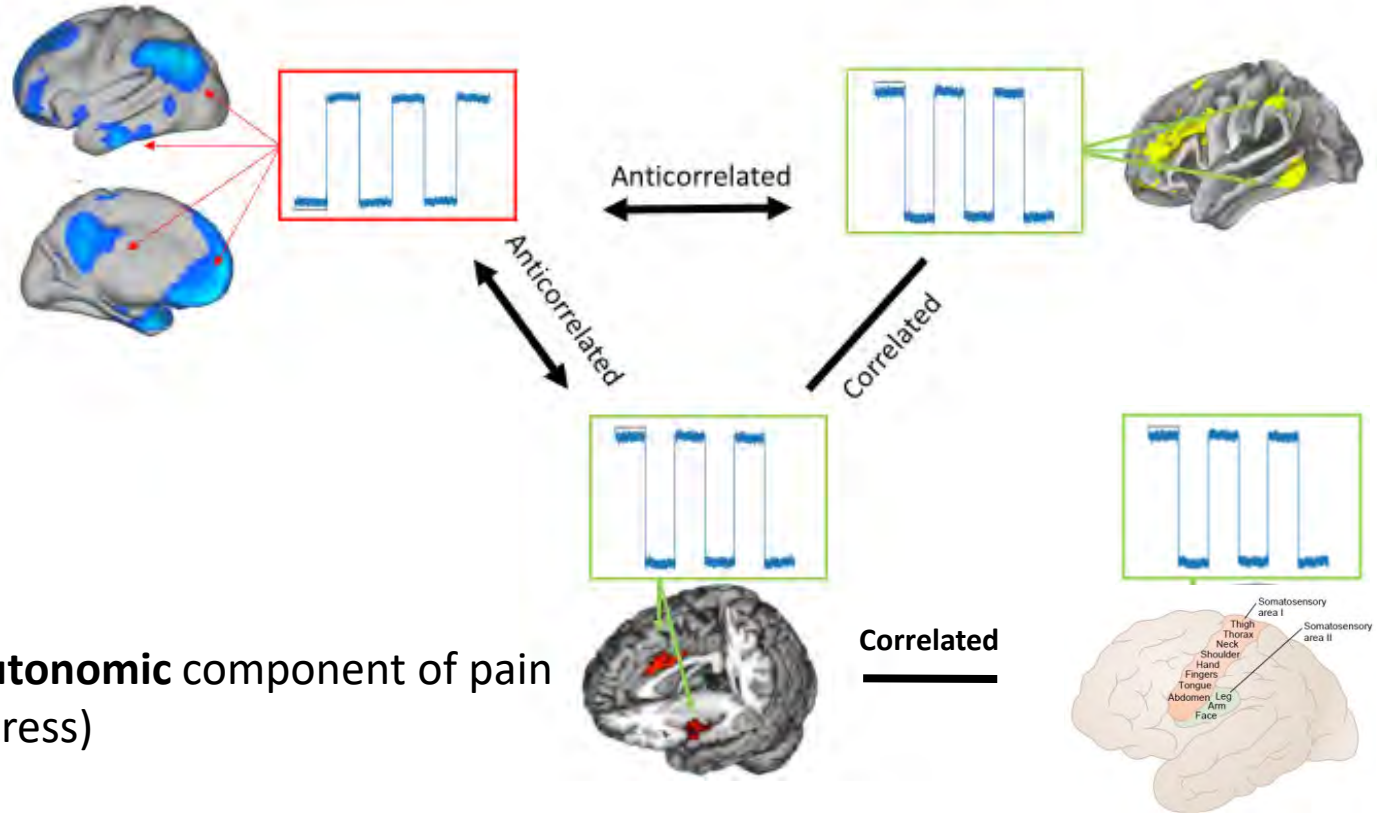
+

Sensorimotor network



De Ridder 2021

Raymaekers 2022

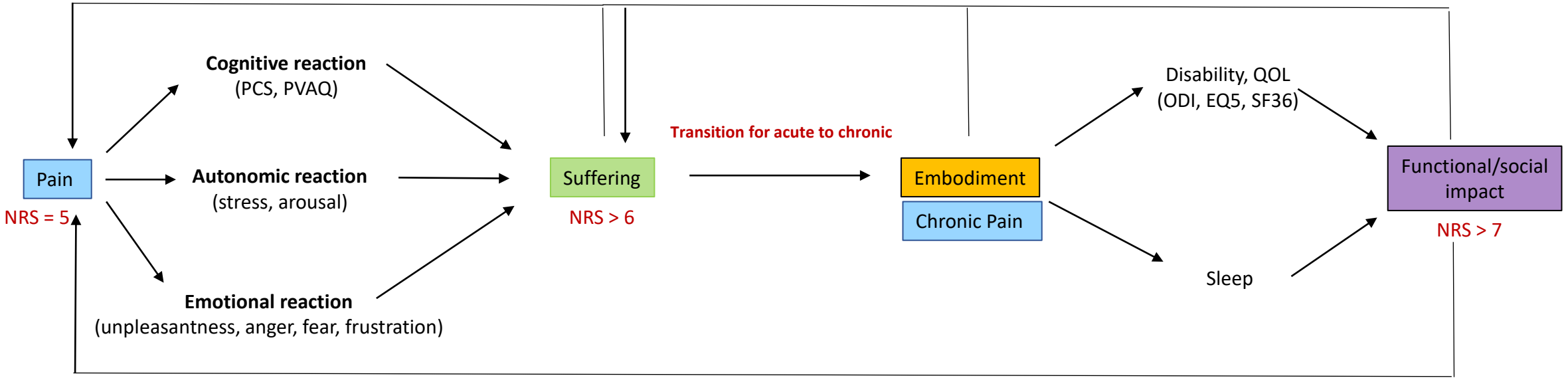


Cognitive component of pain
(rumination, attention,…)

Autonomic component of pain
(stress)

Perceptual component of pain
(Painfulness)

Emotional component of pain
(Fear, anger, frustration, unpleasantness)



Integrating pain in self saves energy

Chronic pain consumes less energy than acute pain (Straub 2017)

Sympathetic NS activation can increase energy expenditure by 15-35% (Sjostrom 1983, Fellows 1985, Matthews 1990, Ratheiser 1998)

➡ Allostasis is energy saving mechanism (Kleckner 2017)

Table 2 | **Activities causing a non-volitional increase in daily energy expenditure**

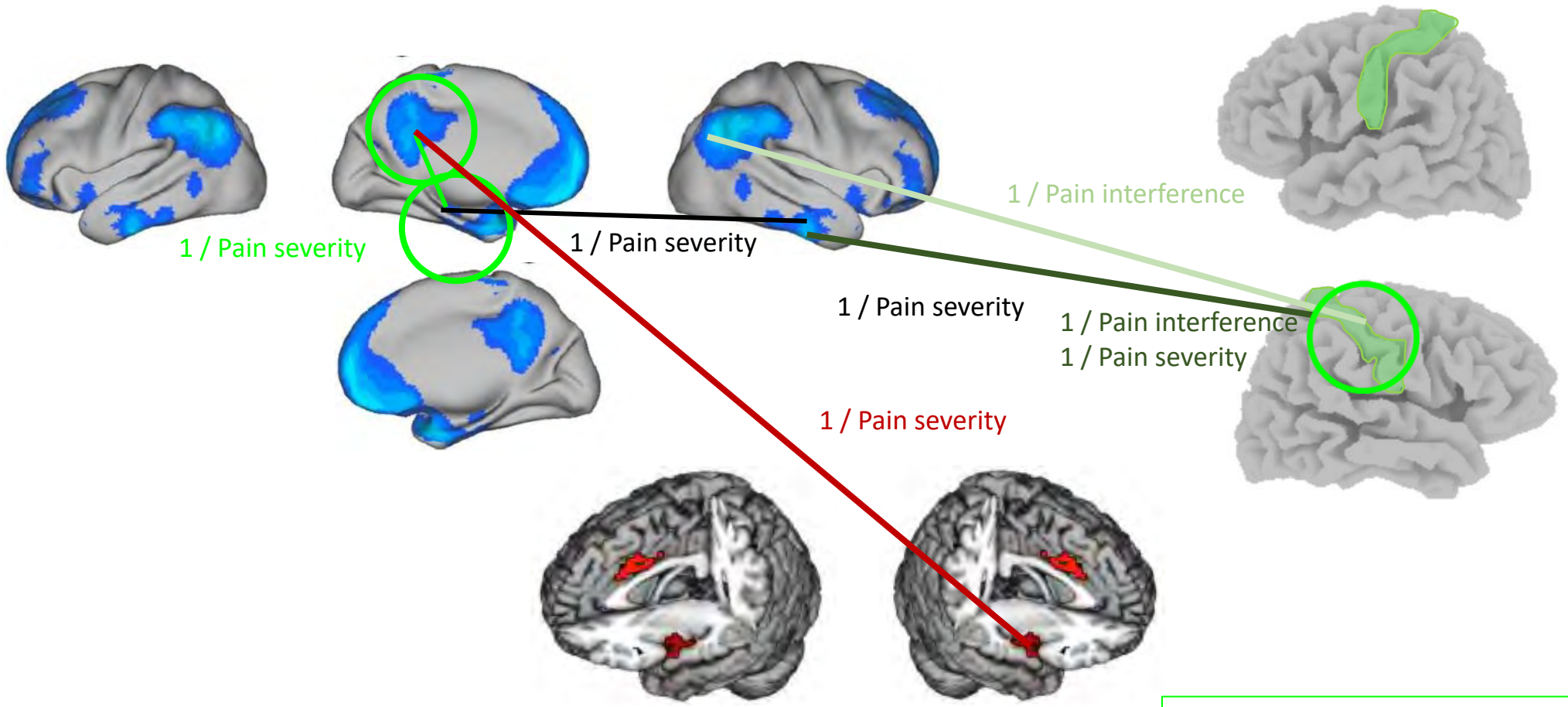
Non-volitional activity	Extra energy costs*	Refs
Inflammation	25–60%‡	1,57
Chronic low-grade infection§	10%	11
Acute pain	up to 60%	66
Chronic pain	15%	68
Psychological stress	up to 30%	63,69,70
Sleep alterations	up to 30%	72–74
Anxiety	up to 10%	75
Heavy smoking	up to 15%	64

*Extra energy costs are relative to total energy costs in healthy individuals, and are given as a percentage of the basal or total energy expenditure. ‡Range spans mild activation to sepsis. §Such as hepatitis C infection.

Straub 2017

Default Mode Network

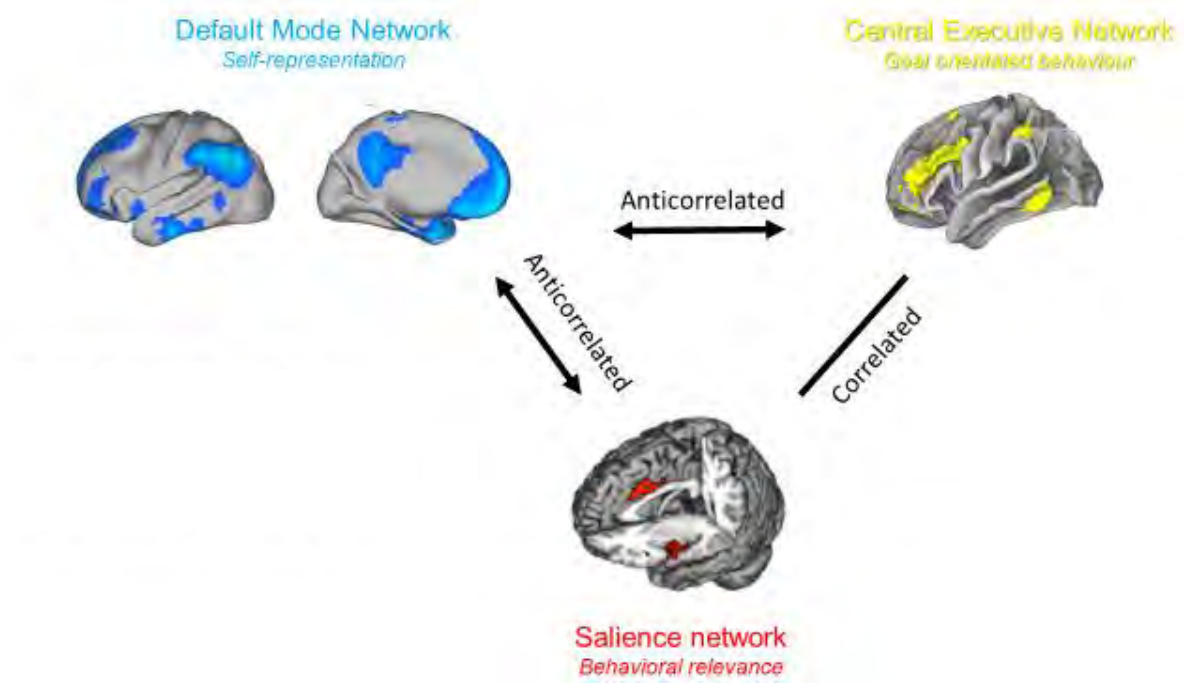
Somatosensory cortex



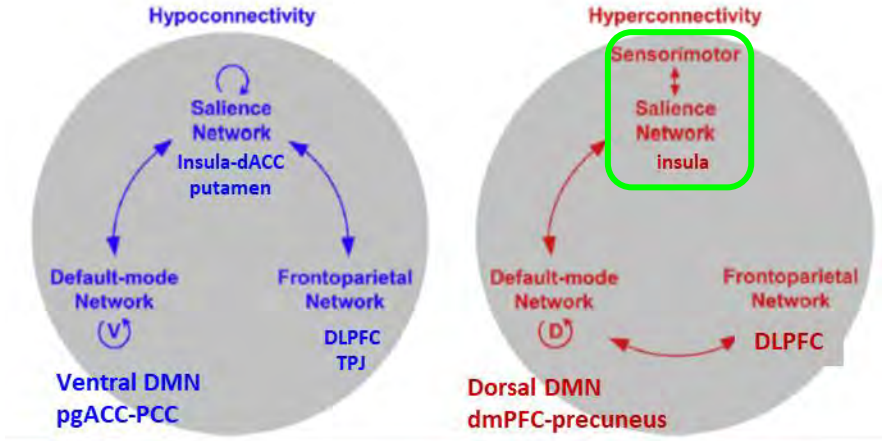
Salience network

Pain network: PCC- HC– S1

N=40



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

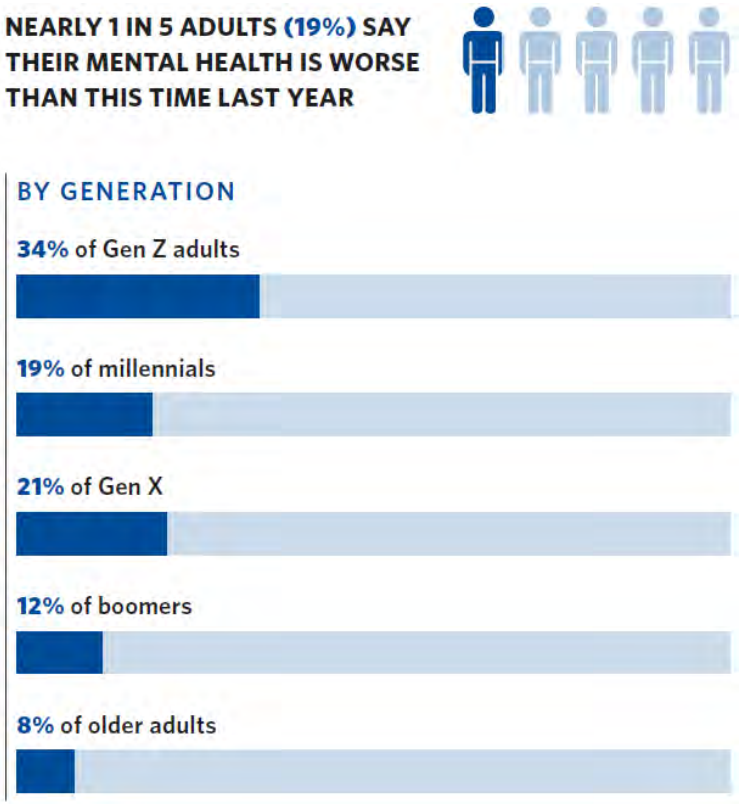


SN and DMN fall apart
SN disconnects from DMN and CEN
precuneus and dMPFC hyperconnect to insula, DLPFC and somatosensory

More psychological pain in society

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



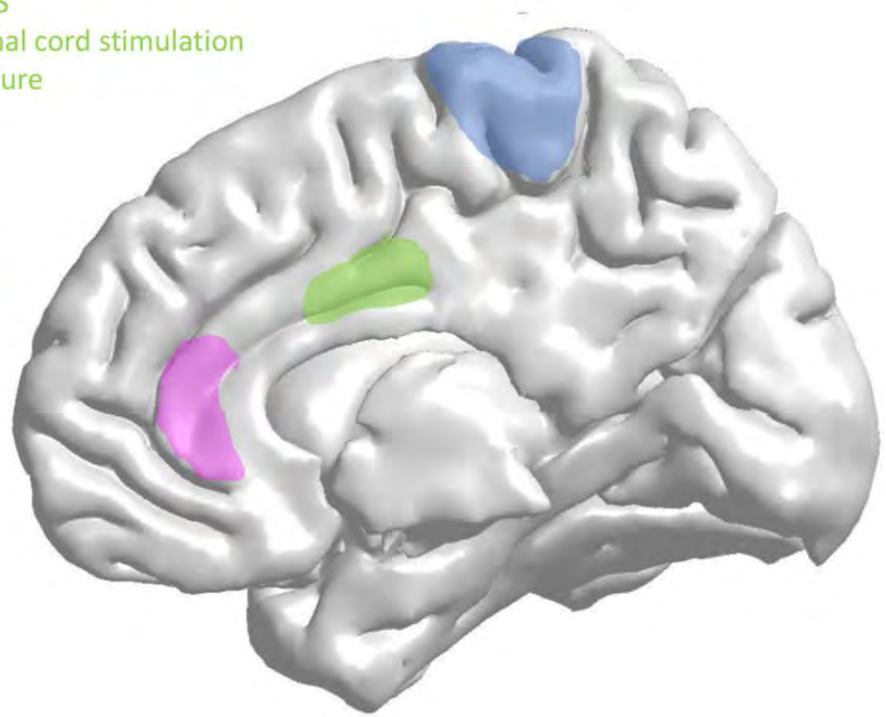
Treatment implications

Medial pathway

1. Pain killers (paracetamol, ibuprofen)
2. Oxytocin
3. Meditation
4. Yoga
5. Cingulotomy
6. Cingulum implants
7. TMS/tDCS
8. Burst spinal cord stimulation
9. Acupuncture

Lateral pathway

1. Aspirin
2. Gabapentin
3. Tonic spinal cord stimulation
4. Somatosensory cortex stimulation
5. Acupuncture



Descending pain inhibitory pathway

1. Psychopharmacology (SNRI)
2. Opioids
3. Testosteron
4. Placebo
5. Psychotherapy
6. Psychosurgery
7. TMS/tDCS
8. Spinal cord stimulation
9. Motor cortex stimulation
10. Exercise therapy
11. Acupuncture

De Ridder 2021

Psychotherapy

Efficacy of psychotherapy

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.

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

- 0.34 SMD for psychotherapy > control
- NNT for psychotherapy is 7.4 (Schefft 2019)

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

Efficacy of psychotherapy (meta-analyses)

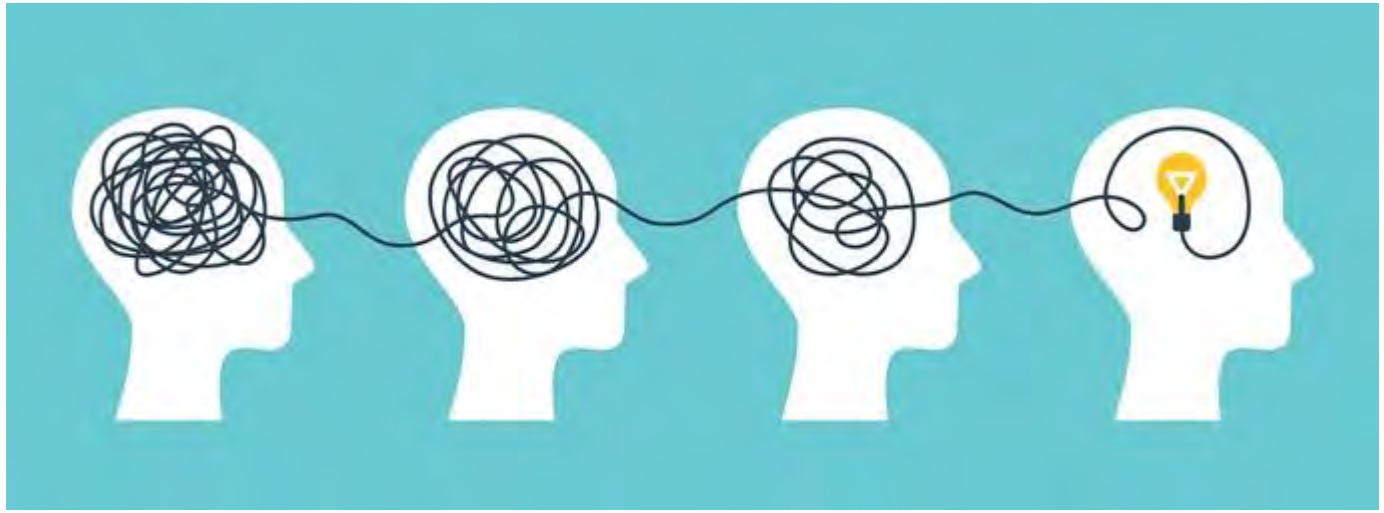
Is psychotherapy efficacious?(Wampold, meta-analysis 2001)

0.34 effect size (small to medium) (Leichsenring 2022)

7.4 = NNT for psychotherapy (Schefft 2019)

87% of therapeutic effect is unrelated to therapy (Wampold 2001)

1% of therapeutic success depends on type of psychotherapy (Wampold 2001)



What does matter in psychotherapy? Patients cure themselves (Sparks 2007)

Is the therapist important?

Experienced psychotherapists and untrained paraprofessionals have same outcome (Berman 1985, meta-analysis, n=32)

6% depends on psychotherapist (Crits-Christoph 1991)

Is the patient important?

40% depends on patient characteristics (Asay 1999)

15% improve before first consultation, decision to seek help (Howard 1986)

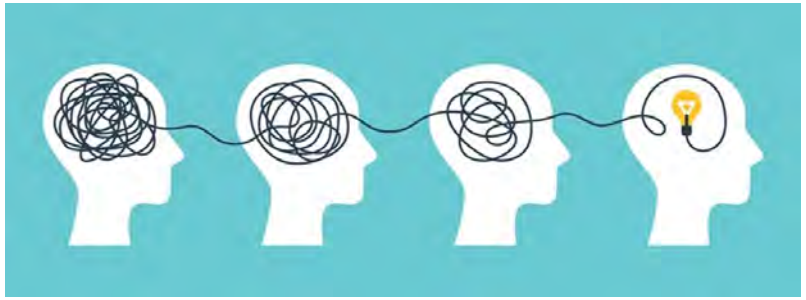
15% relates to hope, expectation (Asay 1999)

Is the patient – psychotherapist alliance important?

7-50% depends on therapeutic alliance (Wamplod 2001, Horvath 2001)

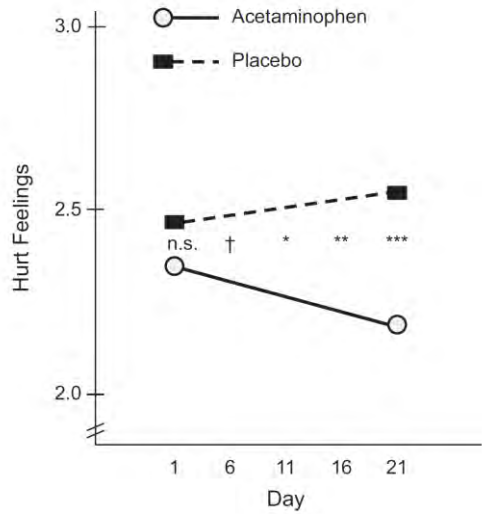
If no benefit by 3rd consultation, no benefit will follow (Brown 1999)

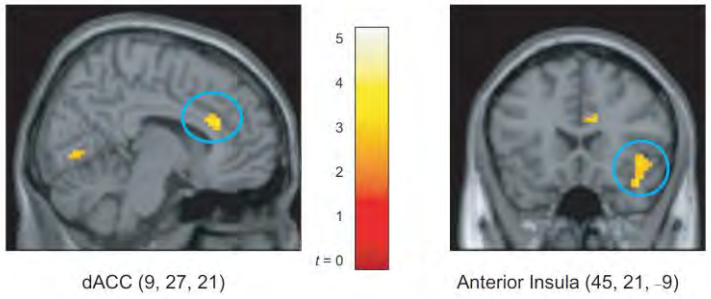
Conclusion: Patients cure themselves, psychotherapists create context (Sparks 2007)

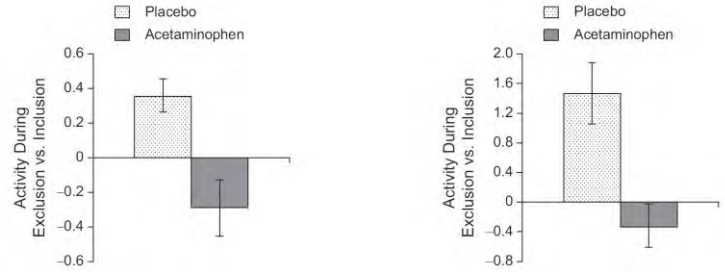


Medication

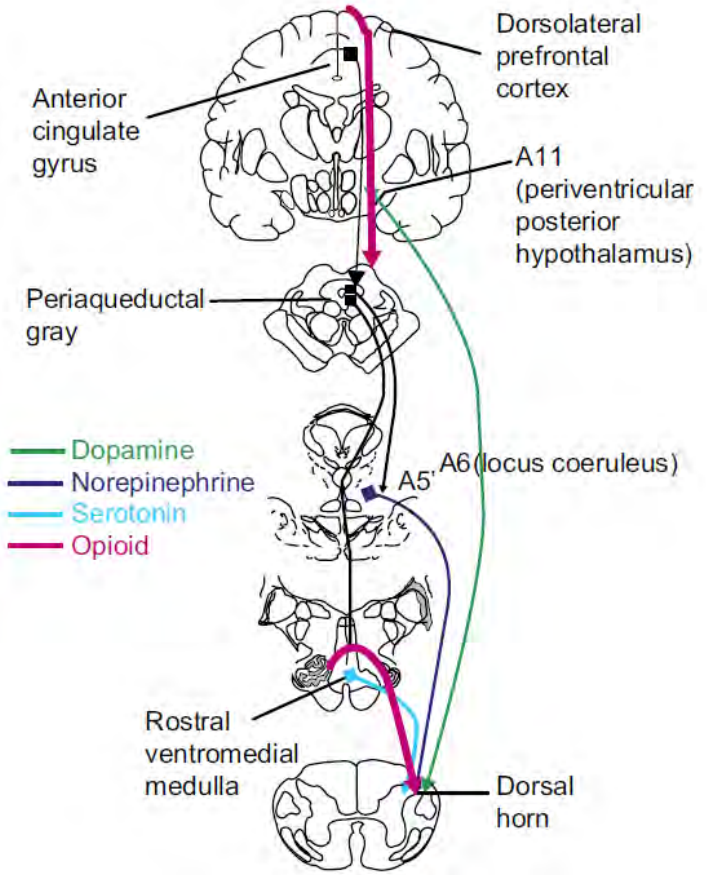
Paracetamol can treat psychological pain



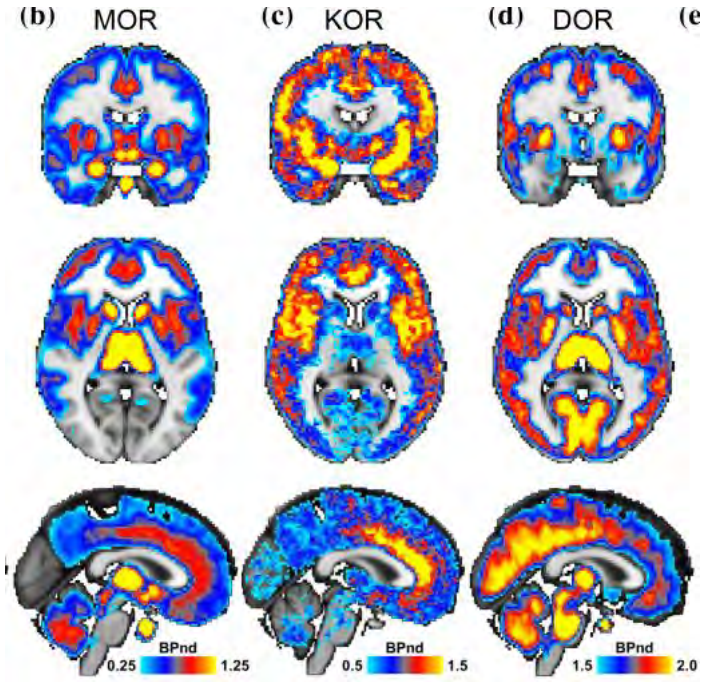




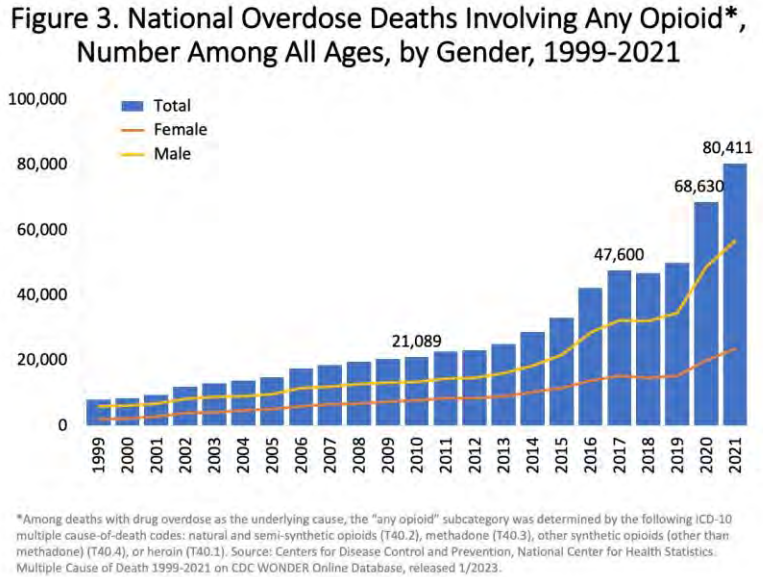
Psychopharmacology can treat painfulness



Opioid crisis



Shokri-Kojori 2021



Efficacy psychopharmacology

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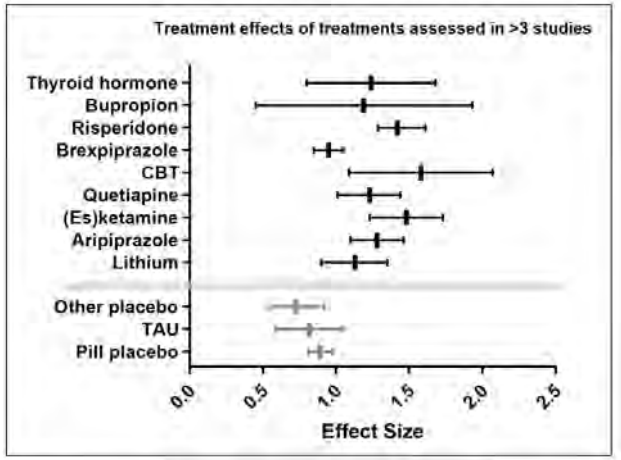
9.0	0.2	Small

Sullivan2021

Augmentation for treatment resistant depression

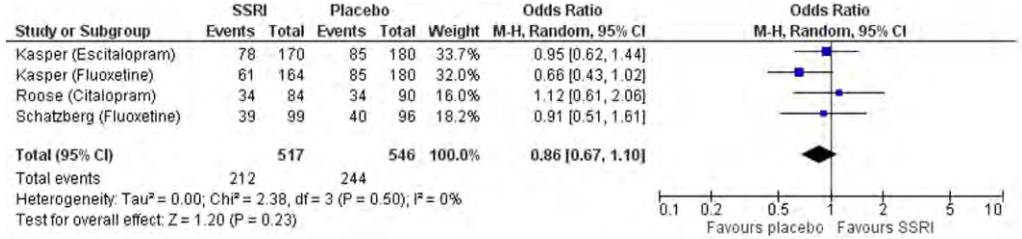


Scott 2022

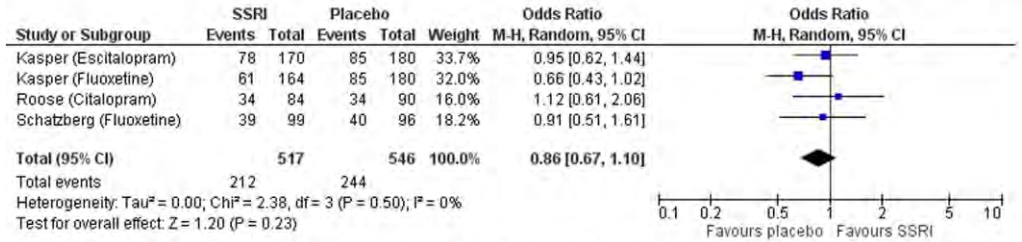
Antidepressants in >65

Antidepressants for MDD >65 yo (Tham 2016)

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



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



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

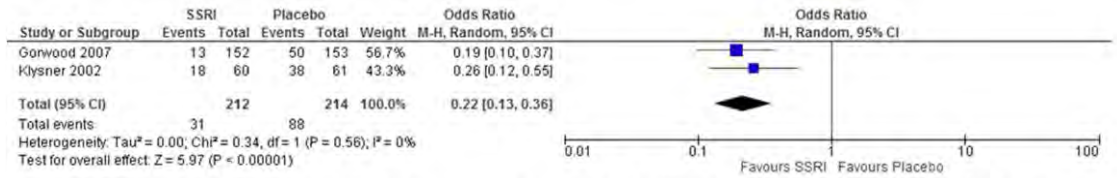


Fig. 4. Relapse in depressive disorder after maintenance treatment with SSRIs or a placebo for up to one year: Odds Ratio.

‘Neuropharma problem’

Old CNS drugs are dirty drugs:

- act on many different receptors, i.e. different networks
- found by serendipity or modification of known drugs

New CNS drugs are very specific

- Paul Ehrlich’s magic bullet (selective for 1 target) is problem (Prior 2014)

Big pharma not interested in drug development for CNS disorders

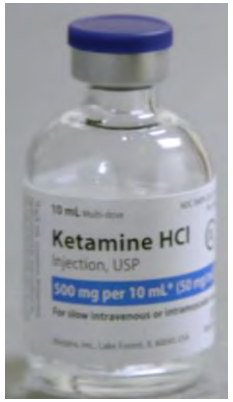
- Since 2011 GSK, AstraZeneca and Novartis have announced closures of neuroscience divisions globally.
- Pfizer, Sanofi, Janssen and Merck have begun to significantly downsize CNS operations (Pfizer stopped AD in 2017)

Developing medication for CNS has

- 50% less chance of making market (6.2% vs 13.3%)(Gribkoff 2017)
- Takes 30% longer (19.3 vs 14.7 months) (Gribkoff 2017)
- Cost 30% more than heart medication

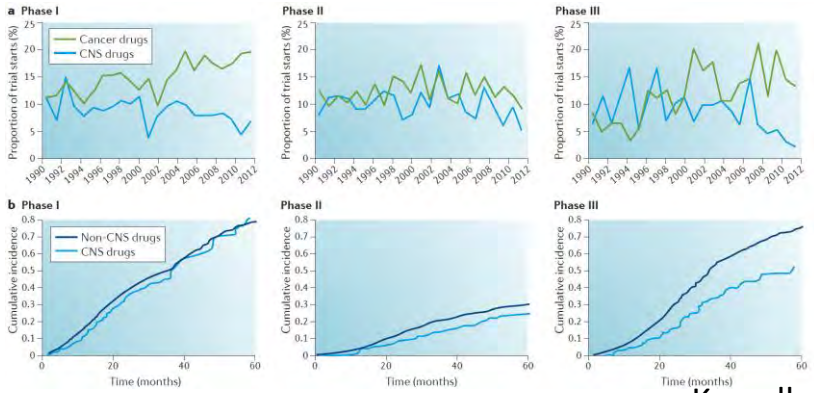
50% less medication developed for brain related diseases

- Too expensive
- Recent Failures: 4/5 medications fail phase III trials (Kesselheim 2015)
  - Most because no better than placebo (46%)



Site	Value (μM)	Type	Action	Species	Ref
NMDA (PCP)	0.25–0.66 0.35	K_i IC_{50}	Antagonist	Human	[89][90] [89]
$GABA_A$	IA	ND	ND	ND	[88]
MOR	26–42.1	K_i	Antagonist?	Various	[4][91]
MOR_2	12.1	K_i	Antagonist	Human	[92]
DOR	66.0–272	K_i	ND	Various	[4][91]
KOR	28.1–85.2	K_i	ND	Various	[4][91]
NOP	IA	ND	ND	Human	[91]
σ_1	66.0–140	K_i	Agonist	Rat	[93][88][90]
σ_2	26.3	K_i	Agonist?	Rat	[93][90]
D_2	>10	K_i	ND	Human	[90][94]
D_2^{High}	0.5 1.03	K_i EC_{50}	Agonist	Human Rat	[95][96] [97]
5-HT_{2A}	>10	K_i	ND	Human	[90]
5-HT_{2A}^{Hi}	≥15	K_i	Agonist?	Rat	[95][98]
5-HT_3	96.9	K_i	Potentiator	Mouse	[99][100]
M_1	45	K_i	Antagonist	Human	[4][101]
M_2	294	K_i	Antagonist	Human	[4][101]
M_3	246	K_i	Antagonist	Human	[4][101]
α7	20	IC_{50}	Antagonist	Human	[4]
α4β2	50	IC_{50}	Antagonist	Human	[4]
ERα	0.345 2.31	K_D IC_{50}	ND	Human Human	[102] [102]
ChE	494	K_i	Inhibitor	Human	[4]
SERT	>10 162 >10	K_i K_i IC_{50}	Inhibitor	Human Rat Human	[90] [103][104] [94]
NET	66.8 >10	K_i IC_{50}	Inhibitor	Human Human	[103][104][90] [94]
DAT	>10 62.9 >10	K_i K_i IC_{50}	Inhibitor	Human Rat Human	[90] [103][104] [94]
PCP_2	59.4	K_i	ND	Human	[105]
VGSC	mM	IC_{50}	Inhibitor	Human	[101]
VDCC	209	IC_{50}	Inhibitor	Human	[101]
HCN1	8–16	EC_{50}	Inhibitor	Mouse	[106]

The smaller the value, the stronger the interaction with the site



Kesselheim 2015

Neuromodulation to the rescue

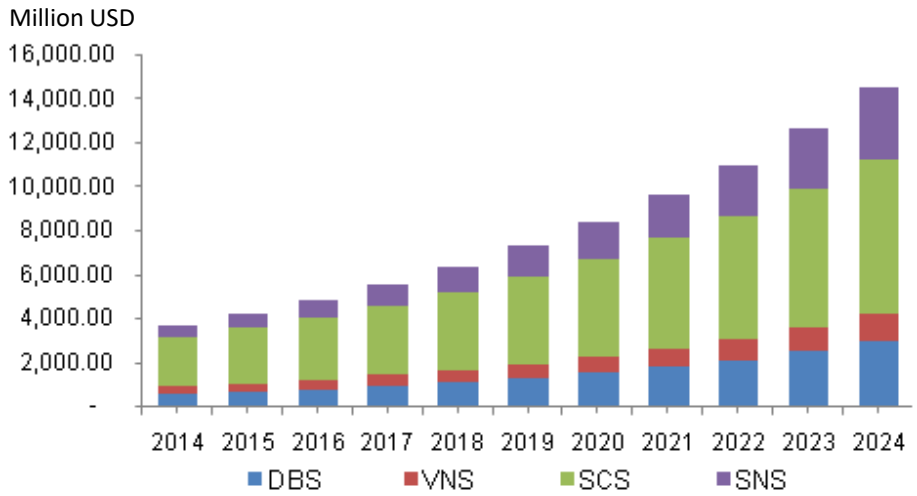
Neuropharma

Program	2009	2014	Percent Decrease
BMS	12	2	83.3%
Merck	32	7	78.1%
Pfizer/Wyeth	46	15	67.4%
AZ	21	7	66.7%
GSK	40	14	65.0%
Sanofi/Genzyme	29	12	58.6%
Lilly	16	9	43.8%
Abbott/Abbvie	17	10	41.2%
J&J	18	17	5.6%
Roche/Genentech	22	21	4.5%
Novartis	14	15	-7.1%
Total	267	129	51.7%

50% decline in pharma investment

Yokley 2016

Neuromodulation devices



Almost triple growth predicted

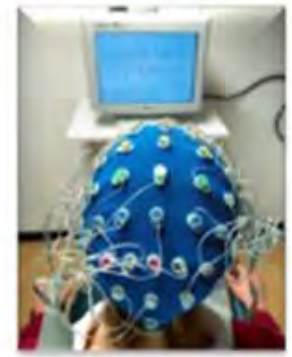
Market Research Report 2016

TMS

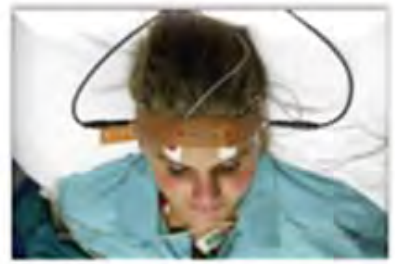
TENS

tDCS
tACS
tRNS
tES

Non-Surgical Neuromodulation



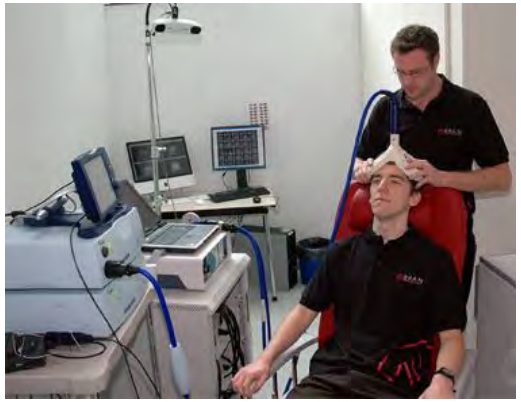
Neurofeedback



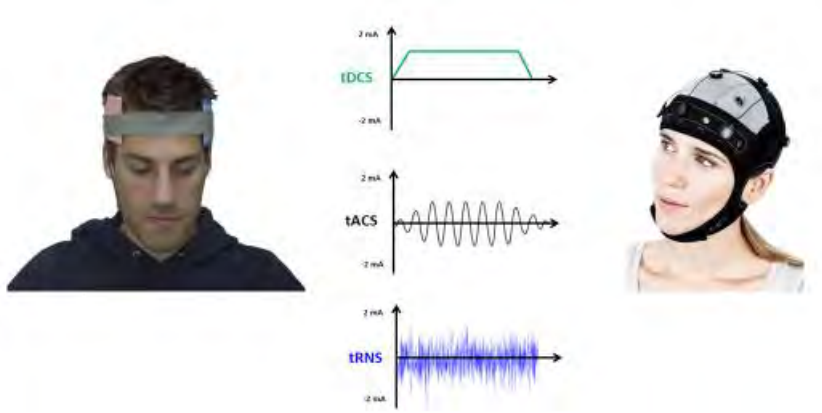
ECT

Target medial suffering pathway directly: non-invasive approach

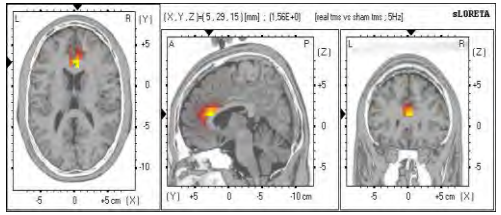
rTMS

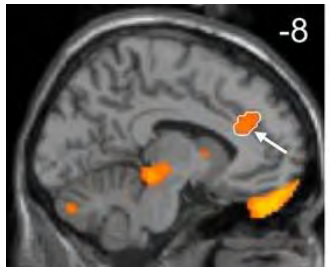


tES (tDCS-tRNS-tACS)

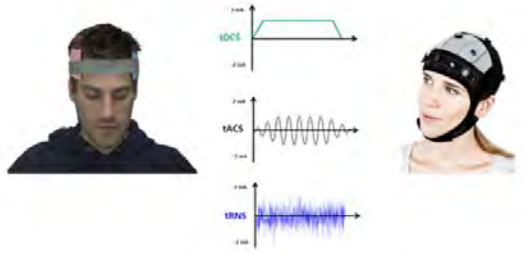


Real TMS vs sham TMS





Only difference is in beta2 ACC



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

rTMS in mental disorders

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

	K	N	SMD (95% CI)	Z	*p* values	Heterogeneity Q	Heterogeneity *p* values	Heterogeneity I^2	Egger's *t*	Egger's *p* values
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		

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]

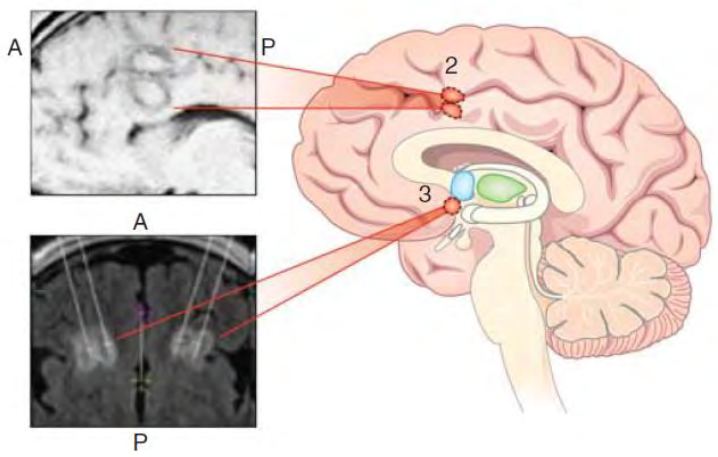
NNT for depression is 3.4 (Liu 2014) vs 7 for medication and psychotherapy

Hyde 2022

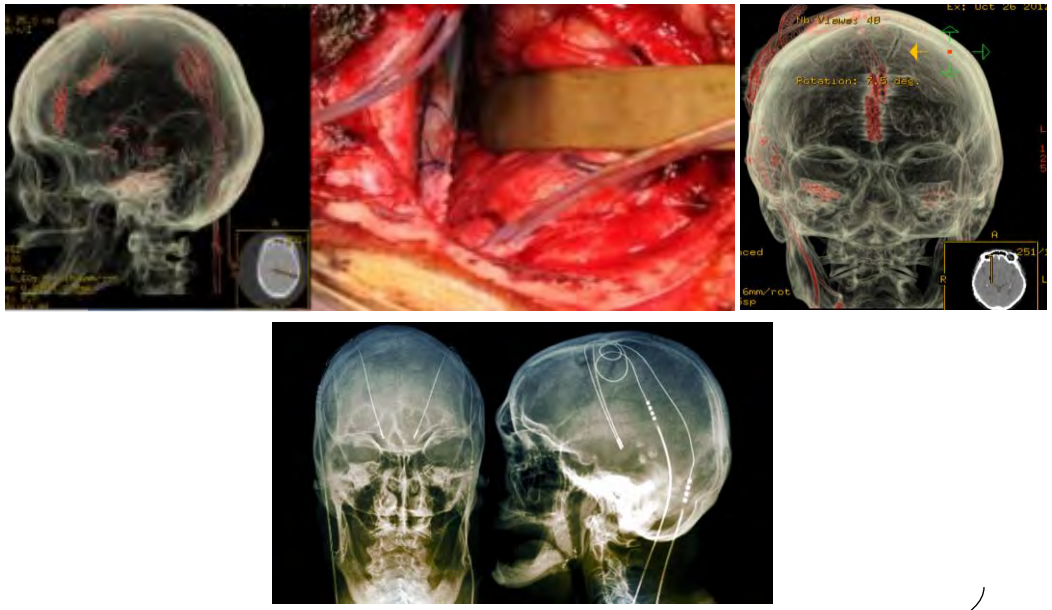
Brain surgery

Surgical treatment of suffering

Lesioning



DBS



Same outcome for OCD (Hageman 2021, meta-analysis)

Techniques

Lesioning

Only two remain

- Anterior Cingulotomy (dACC)
- Anterior Capsulotomy

Cingulotomy

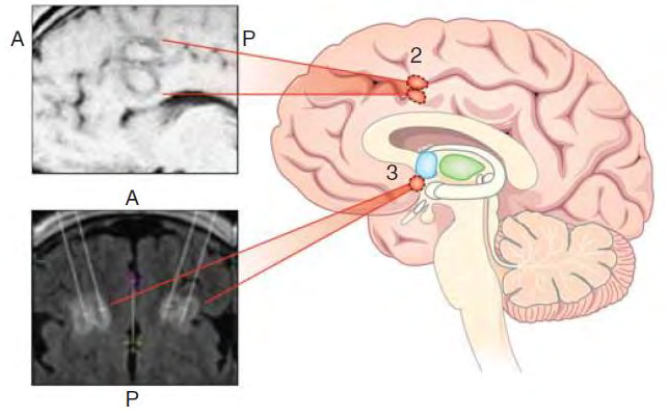
- No change in personality, general intelligence, memory or executive function (Christmas 2006)
- Reduces response intention and focused attention (Cohen 1999)

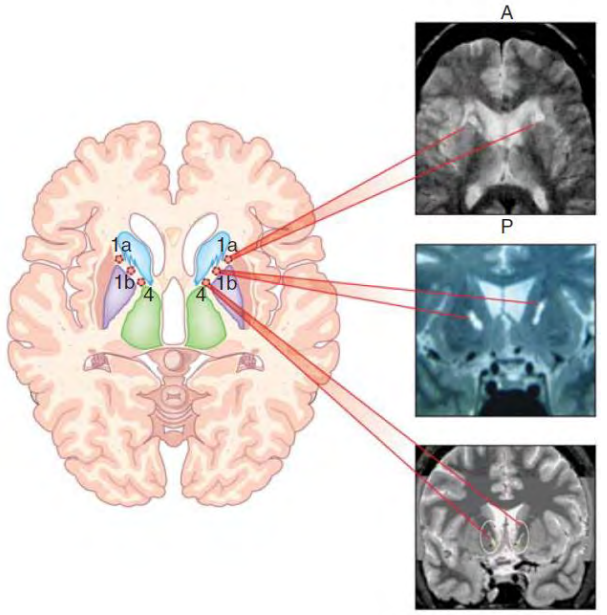
Capsulotomy

- Problems with executive functioning, apathy, or disinhibition. Weight gain (Rück 2008)

Same targets are used for DBS

1. dACC (n=3)
2. Anterior capsula (OCD)
3. + Nucleus accumbens
4. + subgenual/pregenual ACC
5. + VNS





Greenberg 2010

Psychosurgery for suffering (meta-analysis)

Psychosurgery has a large effect size for improvements in

1. depression ($g=1.27$; $p<0.0001$),
2. obsessive–compulsive symptoms ($g=2.25$; $p<0.0001$)
3. anxiety ($g=1.76$; $p<0.0001$)

The pooled clinical global impression improvement score = 2.36 ($p<0.0001$)

clinical global impression – improvement scale (**CGI-I**)

1. Very much improved
2. Much improved
3. Minimally improved
4. No change
5. Minimally worse
6. Much worse
7. Very much worse

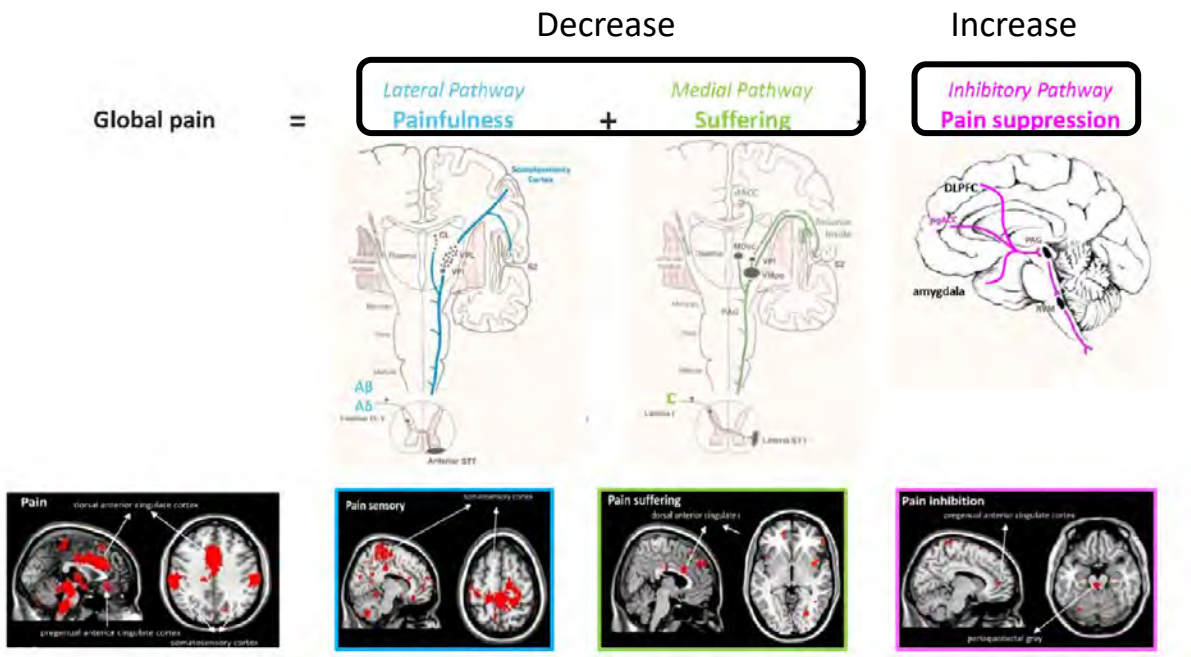
Davidson 2022

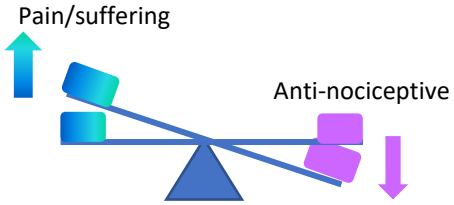
What about the future?

1. Spinal cord stimulation
2. Psychedelics + neuromodulation

Spinal cord stimulation for suffering

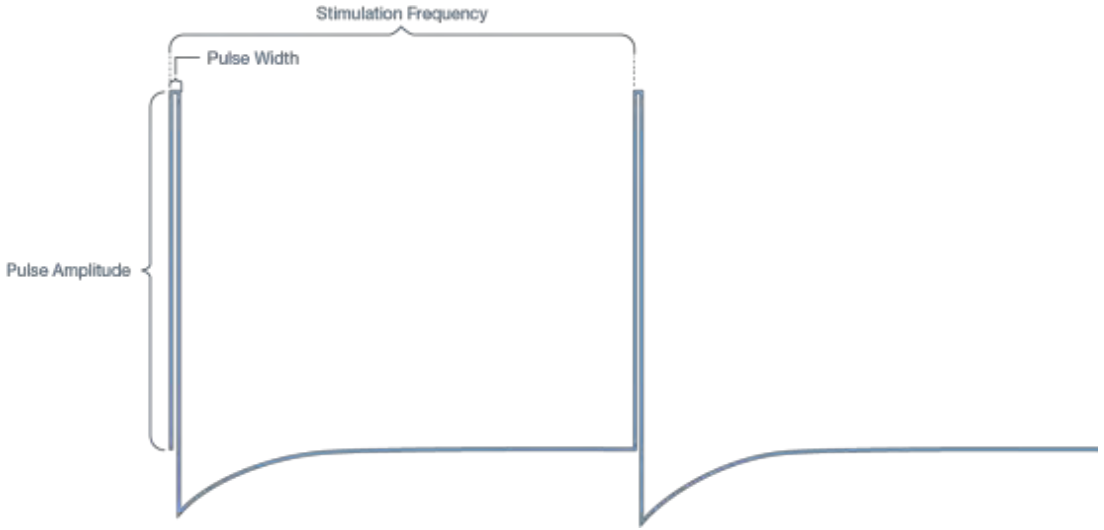
Concept = simple = normalize imbalance





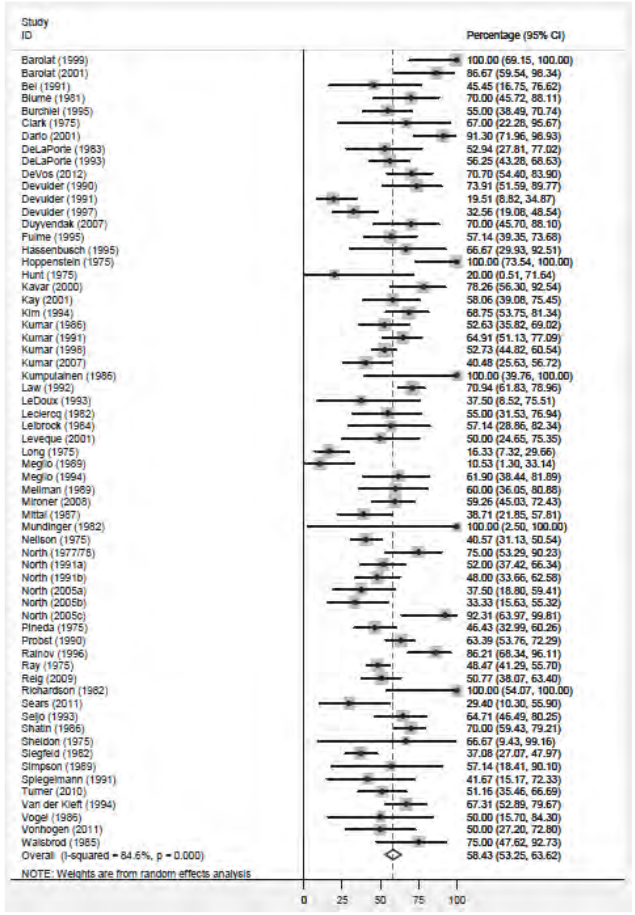
No Pain

Tonic spinal cord stimulation

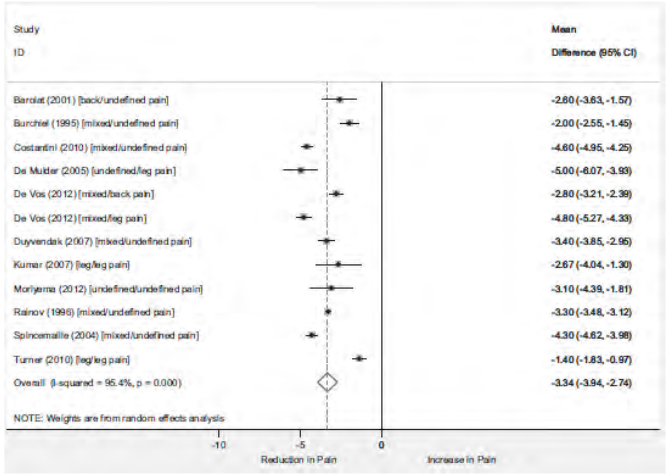


Benchmark: Meta-analysis for Tonic SCS for limb pain

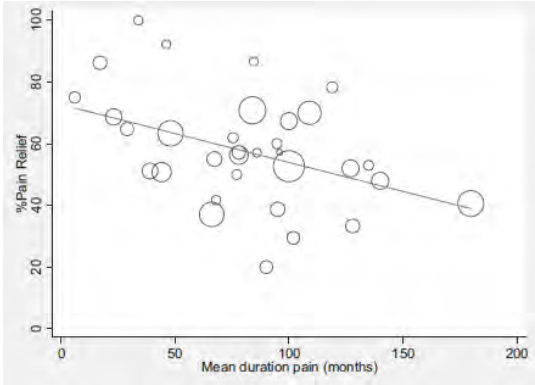
Pain suppression is 58% (Taylor 2013)



Pain reduction is 3 VAS (Taylor 2013)



Long standing pain is less suppressed



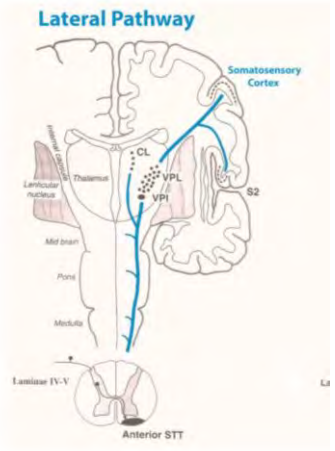
8 - 5

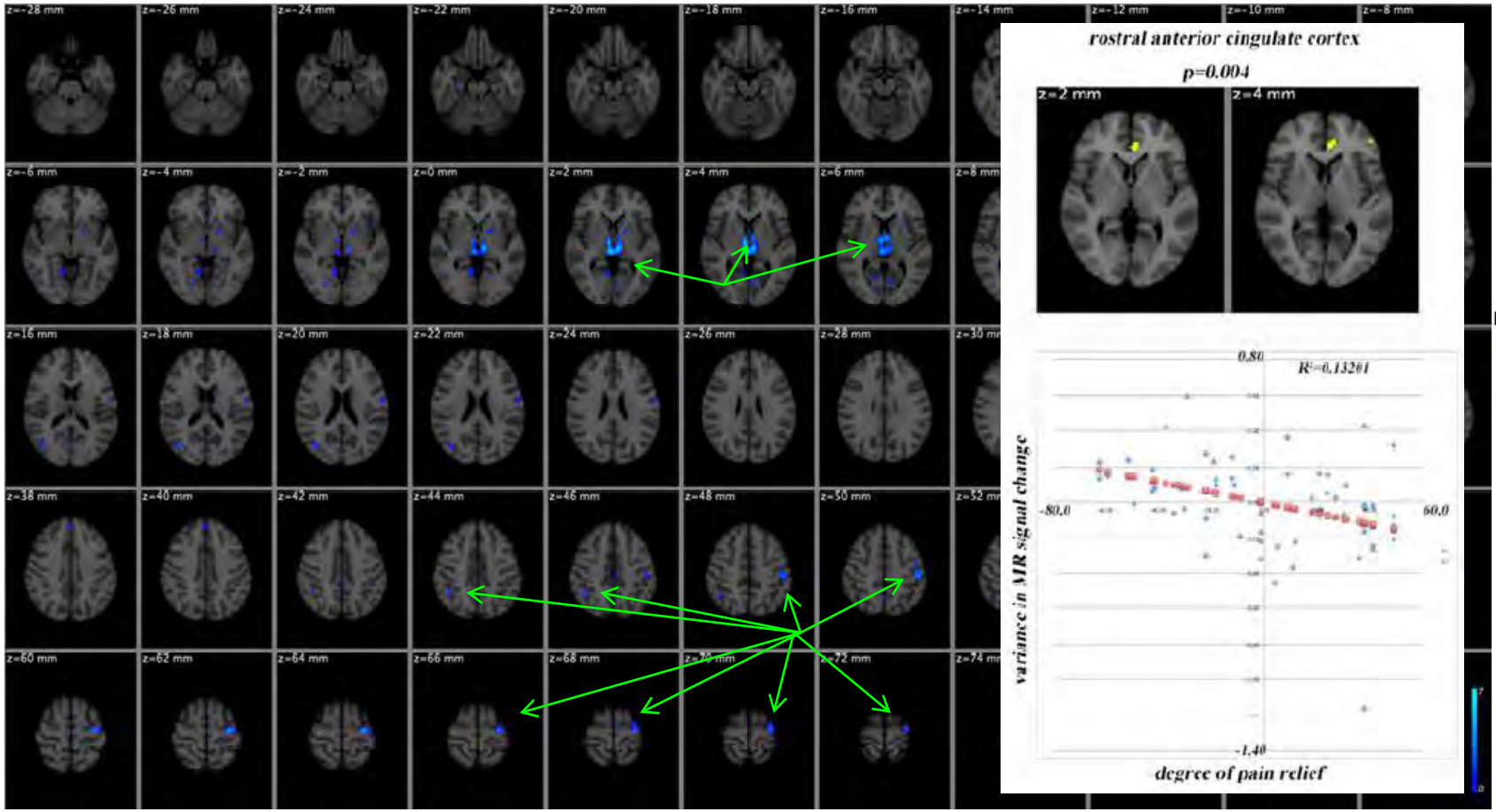
TABLE 3. Calculated MCID values for outcome instruments

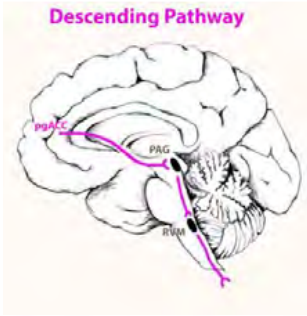
MCID Computation Method	NRS	ODI	BDI	PCS	MPQ
Average change method	2.4	6.9	3.8	8.3	2.3
MDC approach	0.9	3.8	5	1.9	1
Change difference calculation	2.7	5.4	5.9	13.6	2.2
ROC curve (AUC) analysis	1 (0.78)	3.5 (0.71)	2 (0.57)	3 (0.77)	1 (0.74)

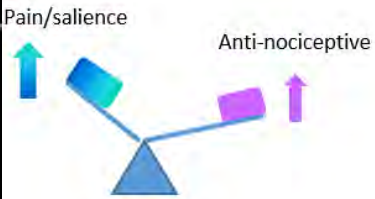
Sabourin 2021

Tonic stimulation in fMRI





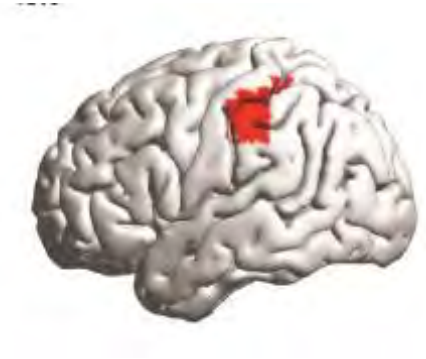


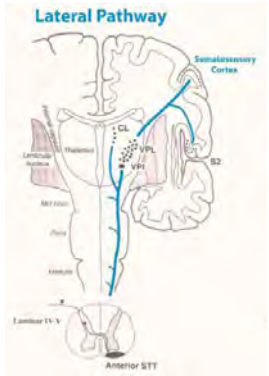


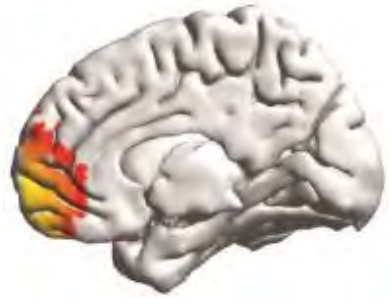
Especially thalamus (GABAergic, Moens 2012) &SSC, but also little in insula caudate, PHC, hypothalamus Moens 2012

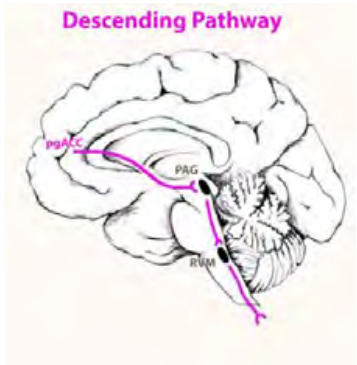
Rostral anterior cingulate cortex ~ pain relief (R^2= 0.13201)

Tonic & burst: common anti-nociceptive mechanism?





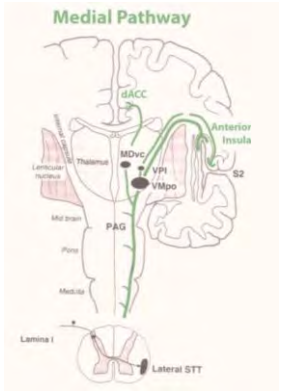


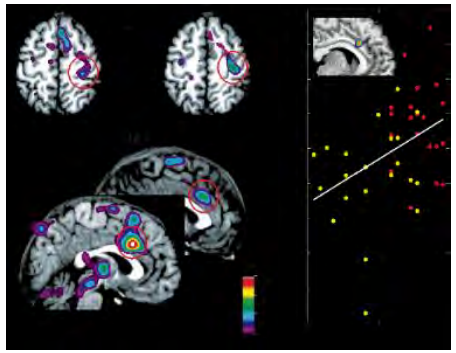


Both lateral and descending pathways modulated by tonic and burst stimulation

De Ridder 2016

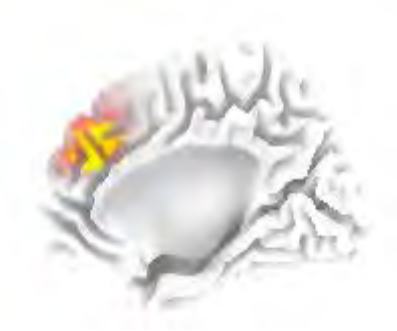
BurstDR™ Stimulation differs from tonic stimulation





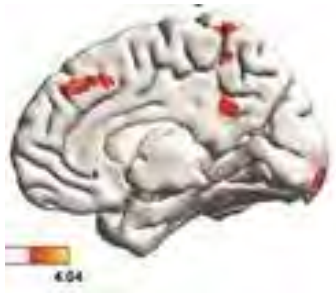
Rainville 1997

EEG



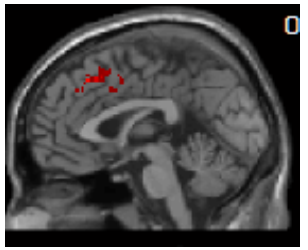
De Ridder 2013

PET



Yearwood 2018

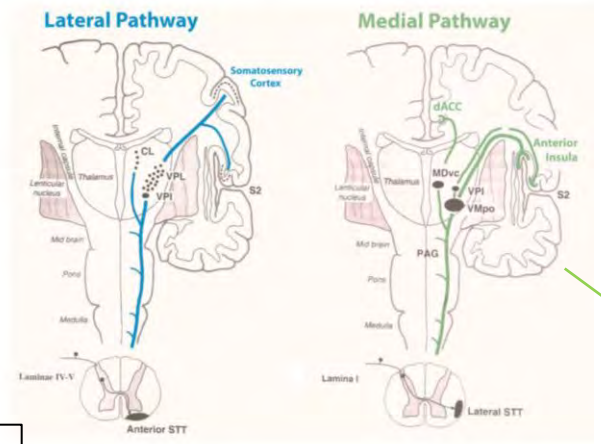
fMRI



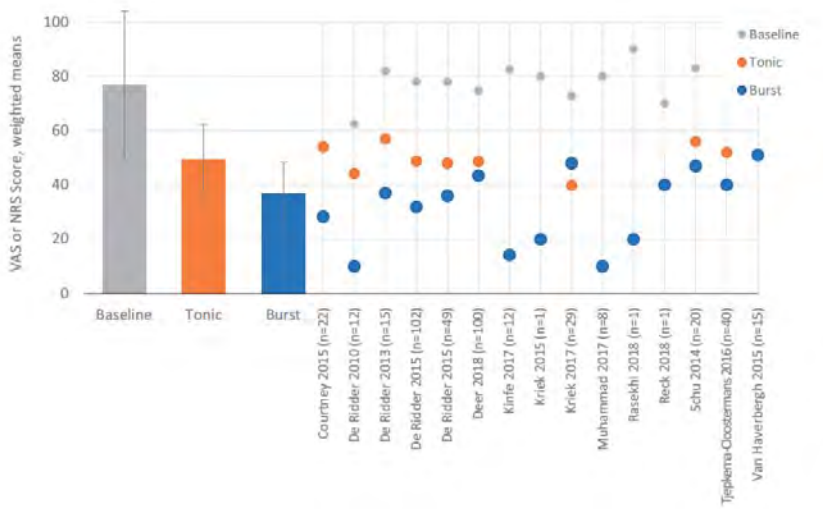
Vanneste, unpublished

BurstDR™ improves **suffering**

Global pain = painfulness + suffering -

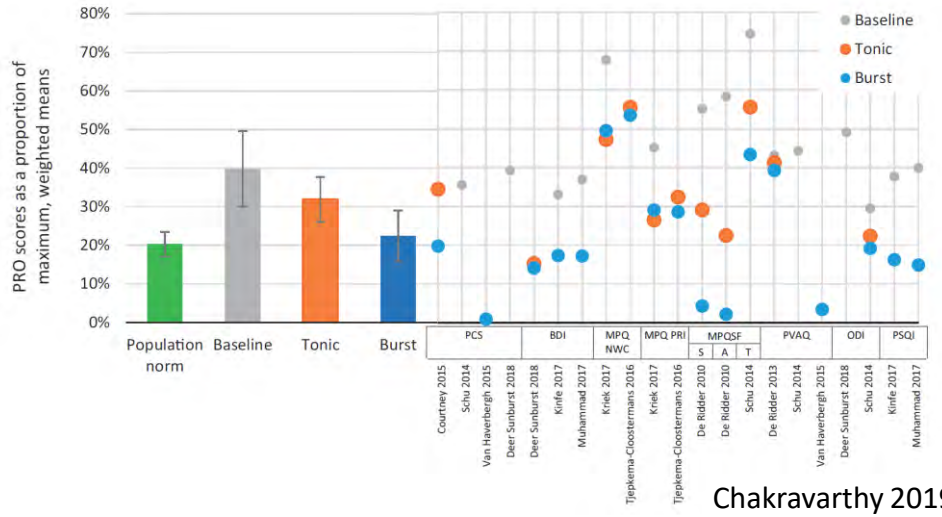


Painfulness 8 -5 -3 (Pooled analysis)



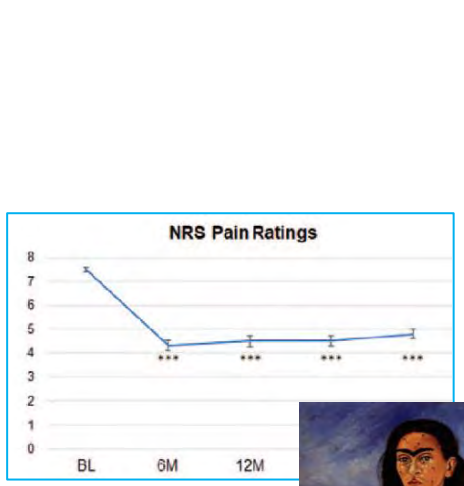
Suffering (pooled analysis)

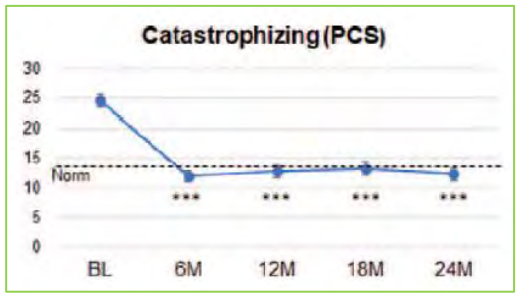
- Pain Catastrophizing Scale
- Beck Depression Inventory
- McGill Pain Questionnaire
- Pain Vigilance and Awareness Questionnaire
- Oswestry Disability Index
- Pittsburg Sleep Quality Index

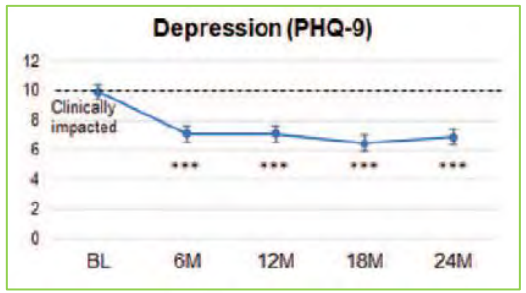


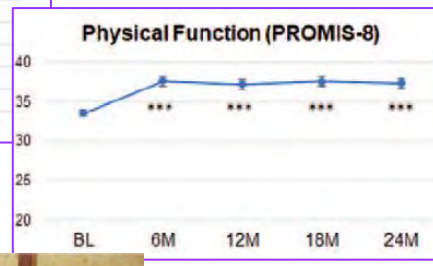
Chakravarthy 2019

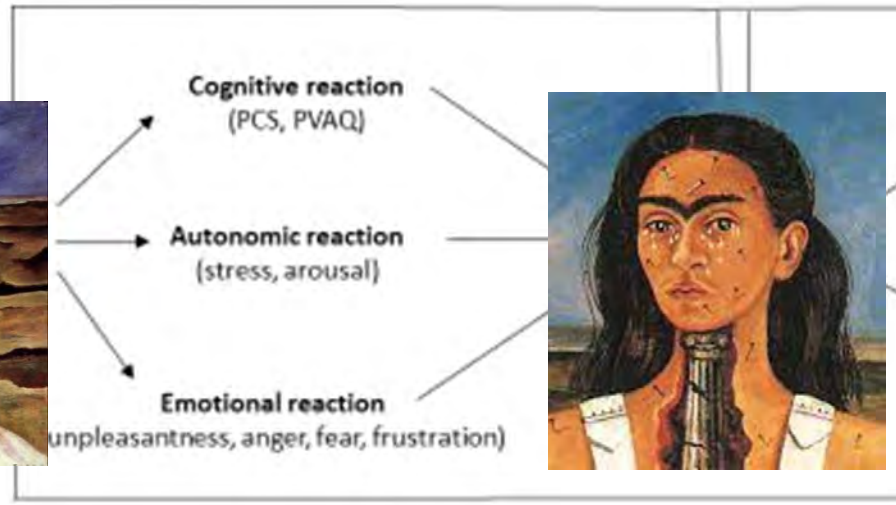
BurstDR™ improves **painfulness**, **suffering** and **quality of life/disability**

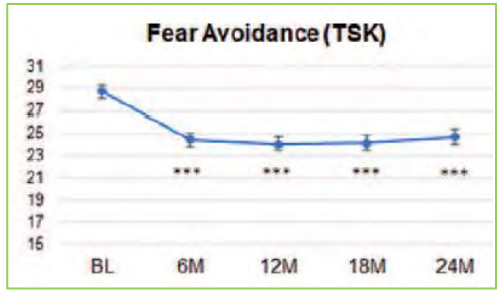


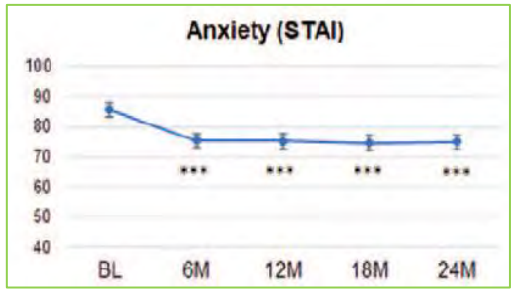


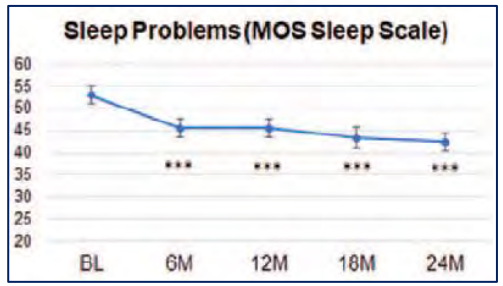












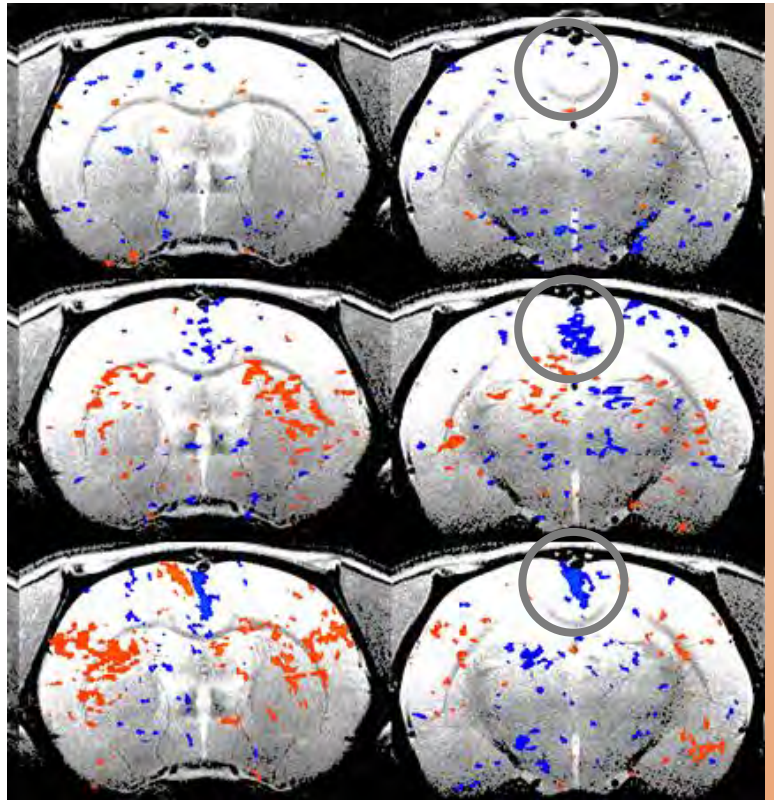
De Ridder 2021, 2022, Raymaekers 2022

Deer 2022

BurstDR™ stimulation for suffering without physical pain?

+1.00

-1.00

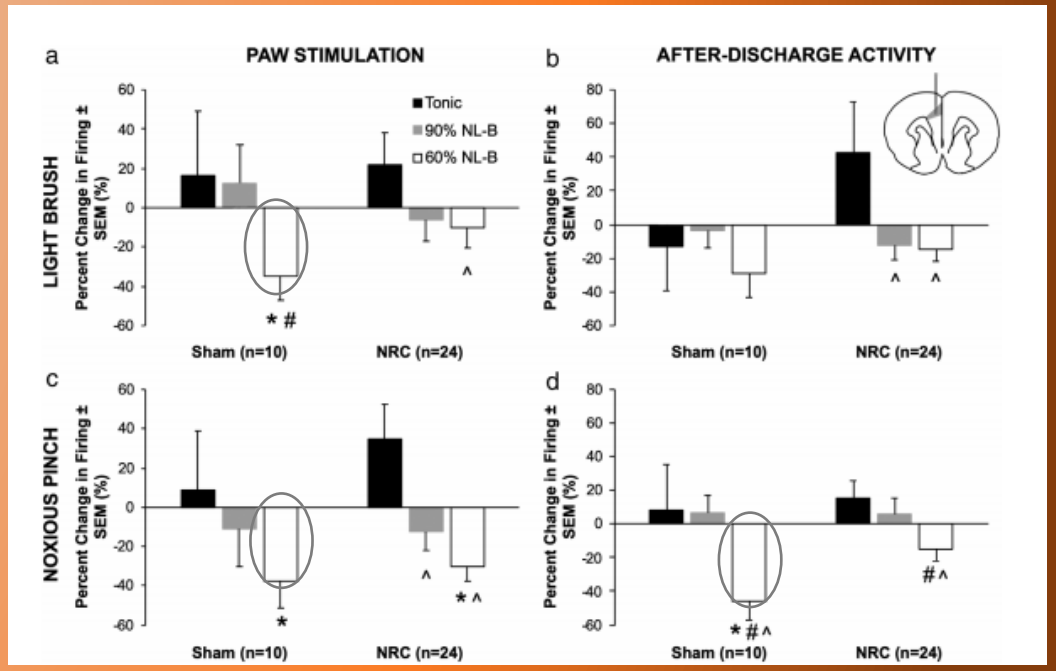


ANTERIOR CINGULATE
(medial pathway)

Tonic

BurstDR

Dosed BurstDR



BurstDR modulates ACC even without neuropathic pain

Quindlen-Hotek 2020

Psychedelics + neuromodulation

War on pain and suffering

Psychedelics & neuromodulation

Concept:

Disrupt abnormal connectivity associated with psychiatric disorder

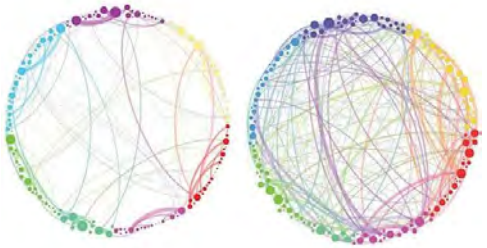
&

Rebuild with neuromodulation (rTMS, tES or neurofeedback)

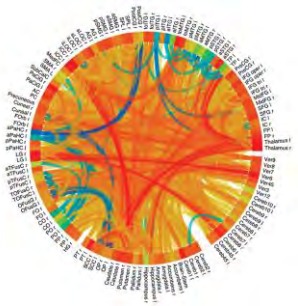
Concept

Disrupt pathological connectivity

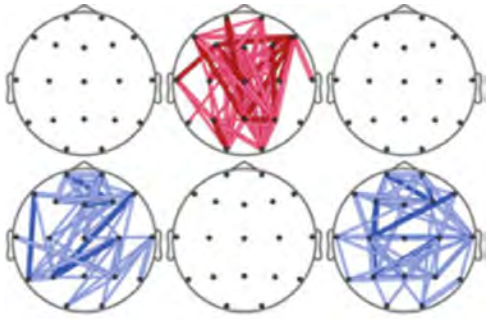
Psilocybin



LSD



Ayahuasca



+

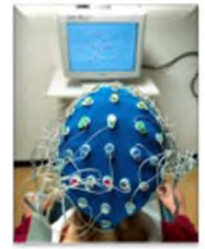
Rebuild normal network interactions

TMS

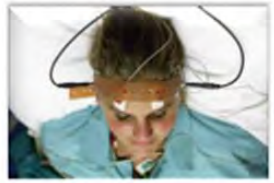
TENS

tDCS
tACS
tRNS
tES

Non-Surgical Neuromodulation

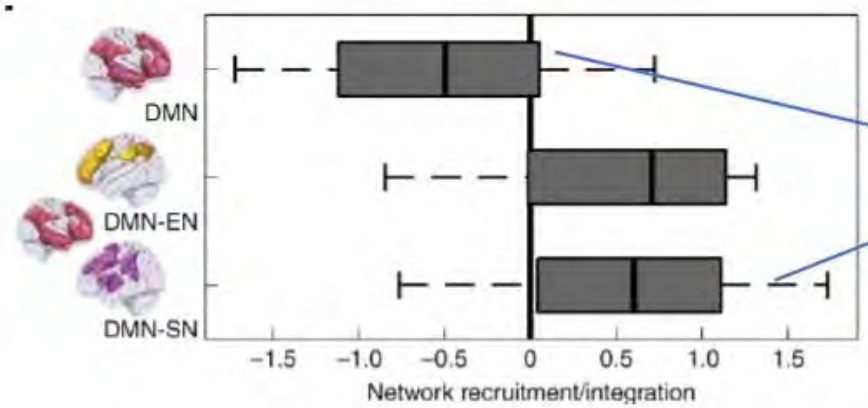


Neurofeedback



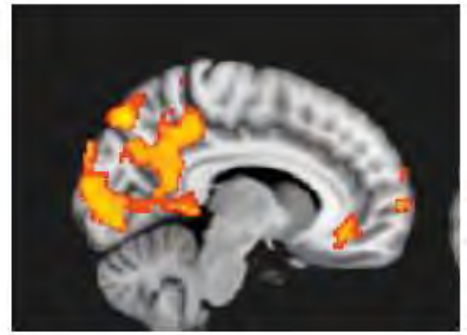
ECT

tDCS + psilocybin = complimentary

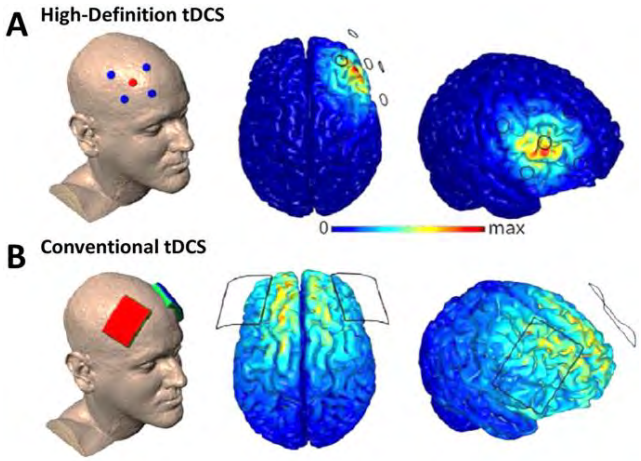


Anxiety, depression, bipolar, ADHD, autism, OCD, PTSD, schizophrenia

Sha 2018

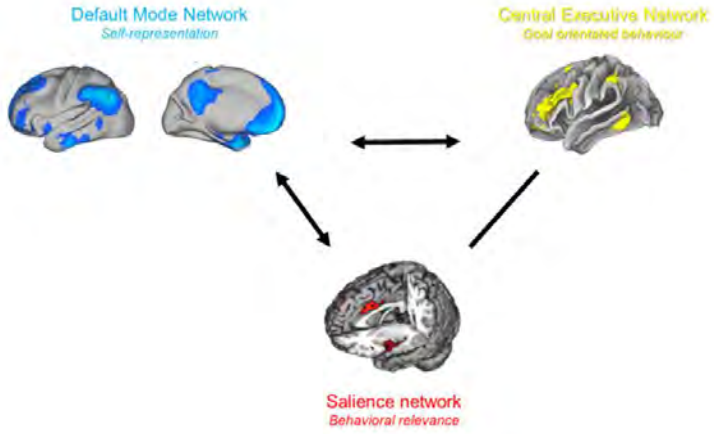


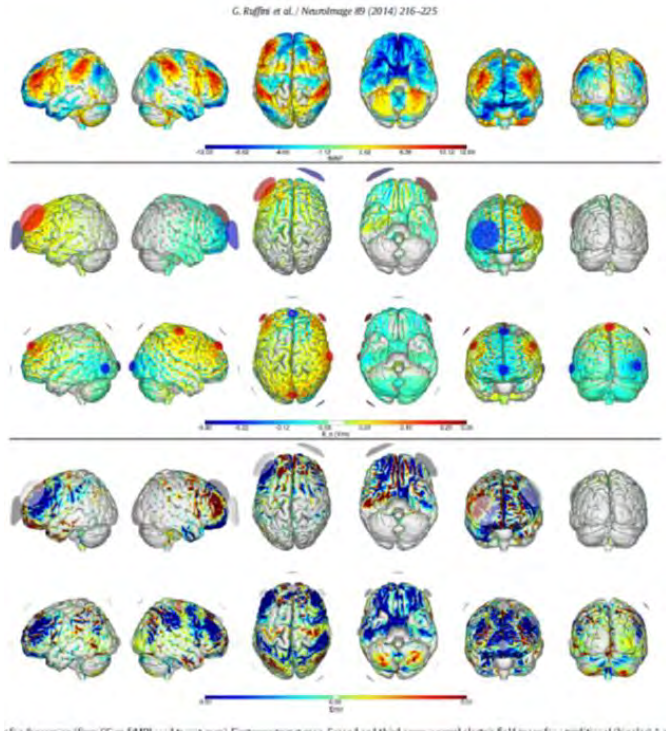
Why HD-tES?

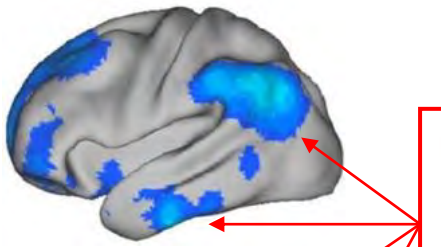


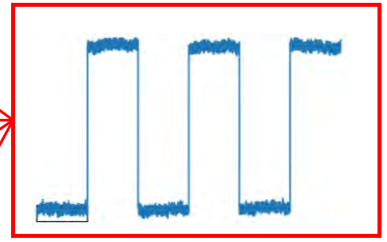
Two reasons

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

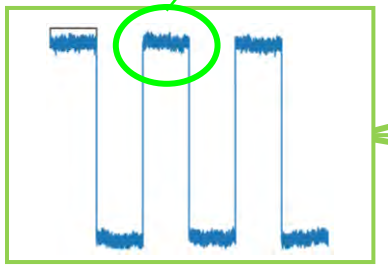


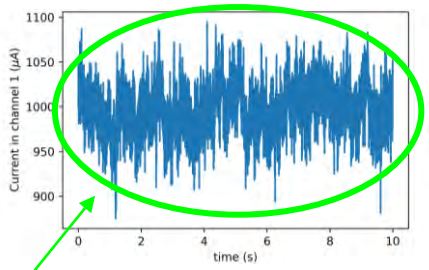


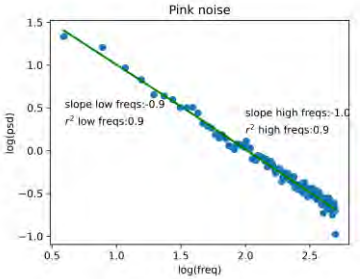


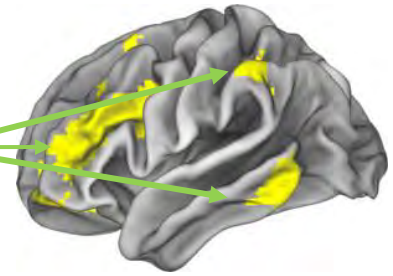


Anticorrelated



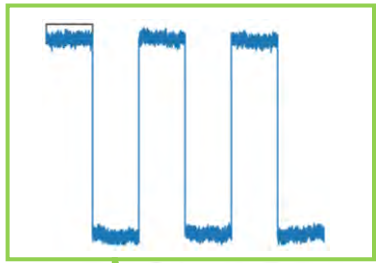


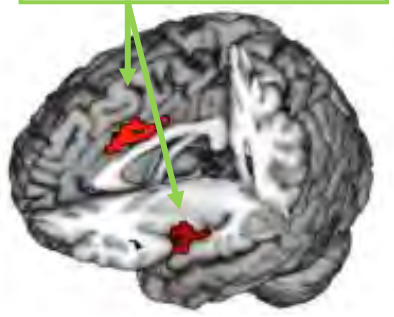




Anticorrelated

Correlated





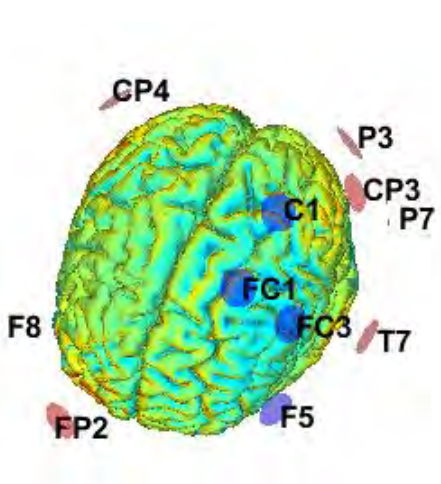
Active montage

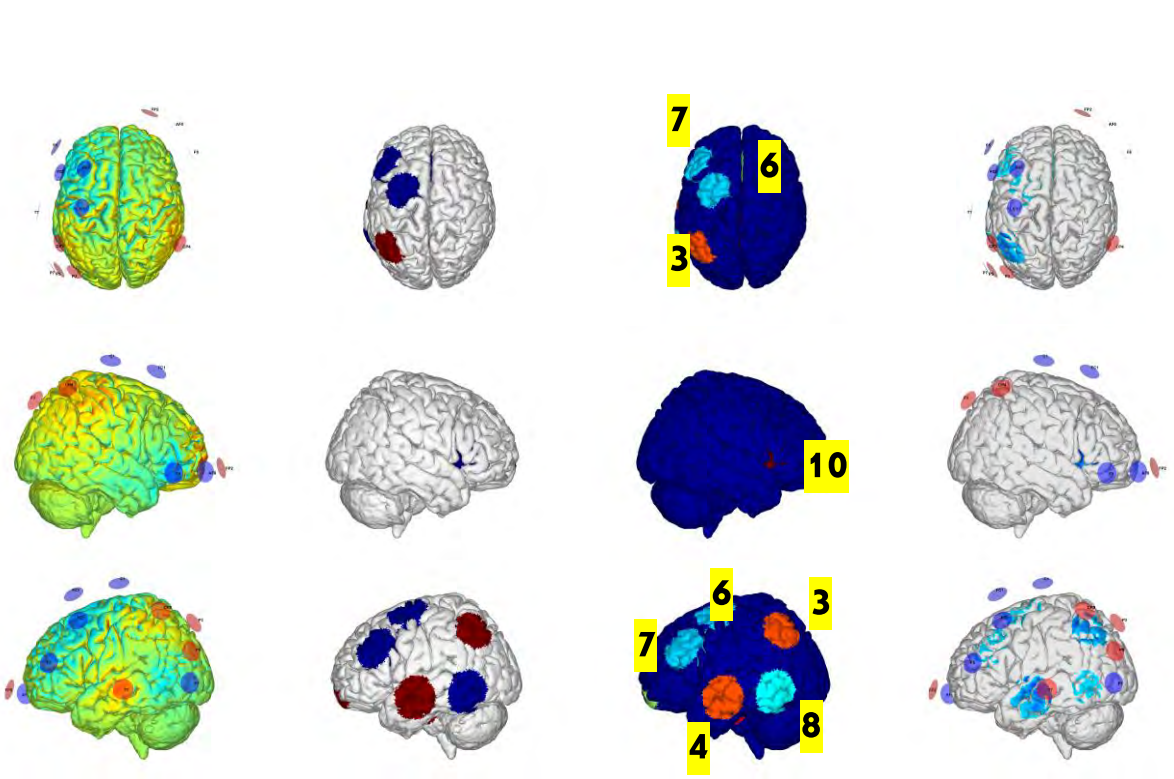
11 electrodes
Total injected current (uA): 3797 uA
Maximum current any electrode (uA): 1399 uA

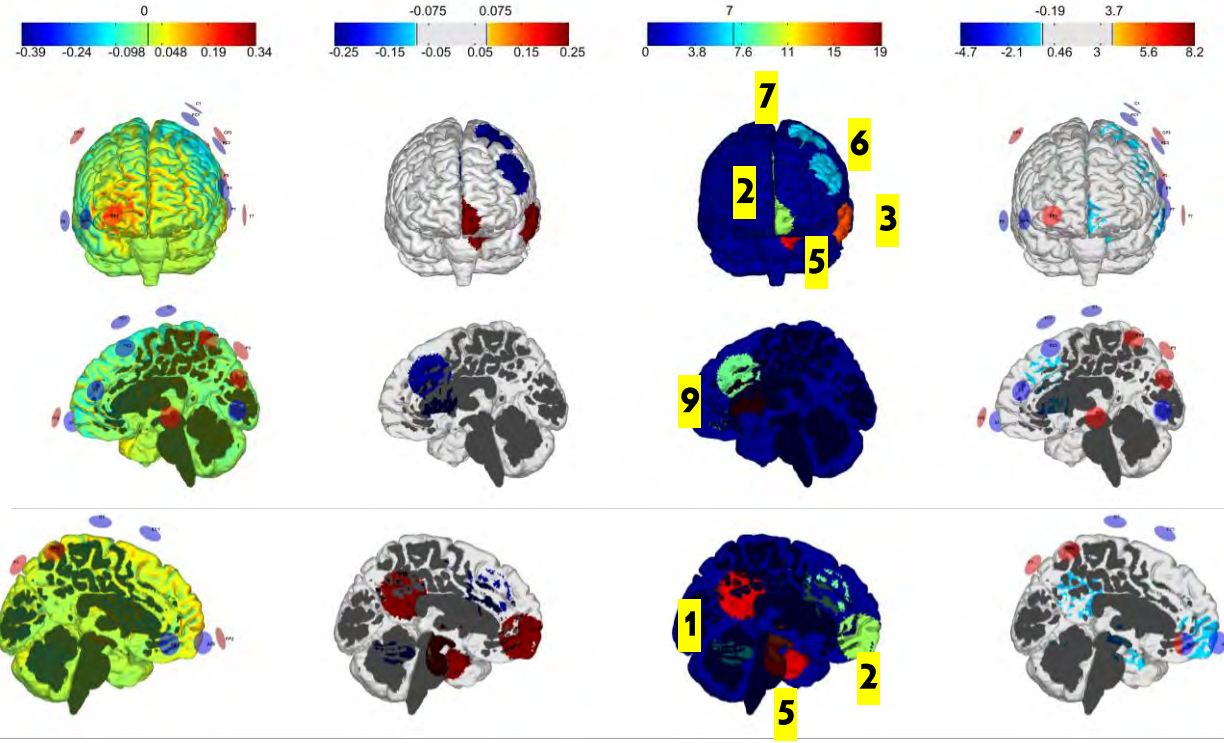
Fitness function (ERNI): -4137.005 mV^2/m^2 (98%)
WCC: 0.283 (98%)

C1: -452 uA
CP3: 511 uA
CP4: 869 uA
F5: -432 uA
F8: -1231 uA
FC1: -328 uA
FC3: -513 uA
FP2: 1399 uA
P3: 328 uA
P7: -841 uA
T7: 690 uA

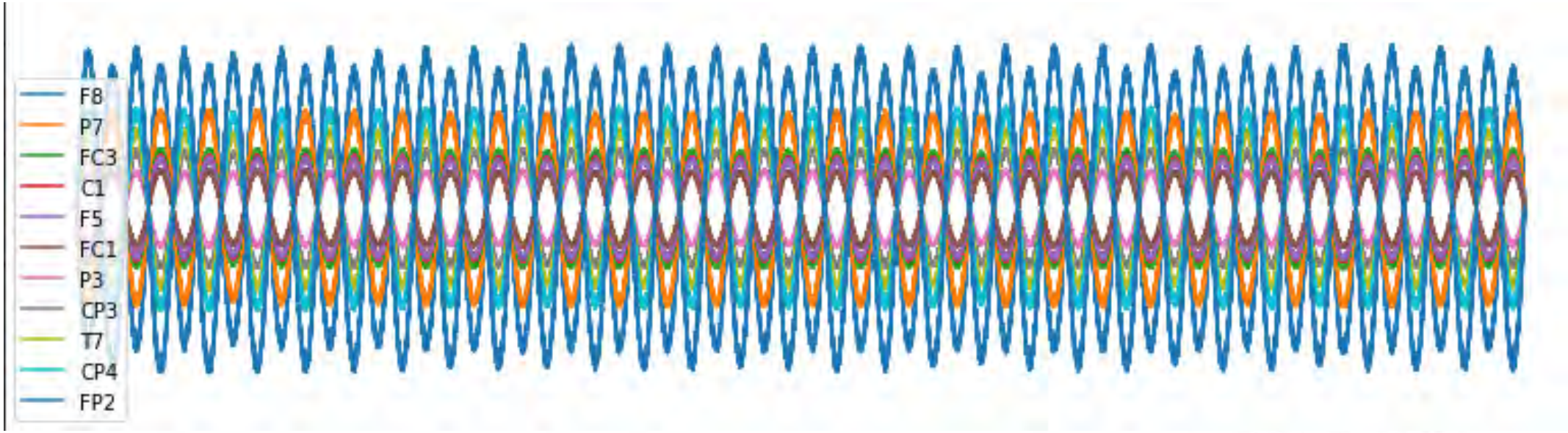
Idx	w5	<nE> (V/m)	
1	17	0.010	
2	10	0.021	
3	15	0.018	0.013
4	15	0.012	
5	17	0.003	
6	6	-0.038	
7	6	-0.032	
8	7	-0.024	-0.024
9	9	-0.013	
10	19	-0.007	

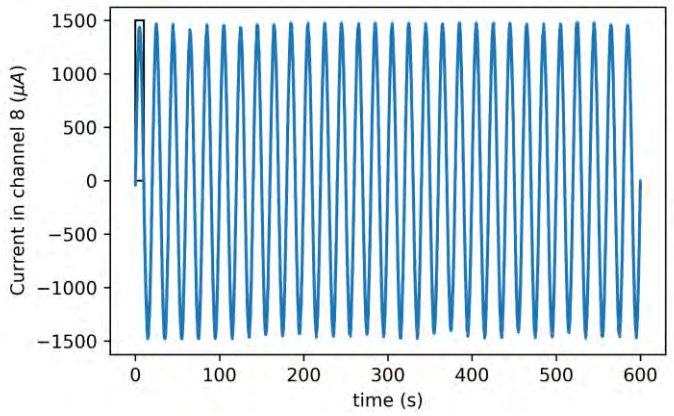


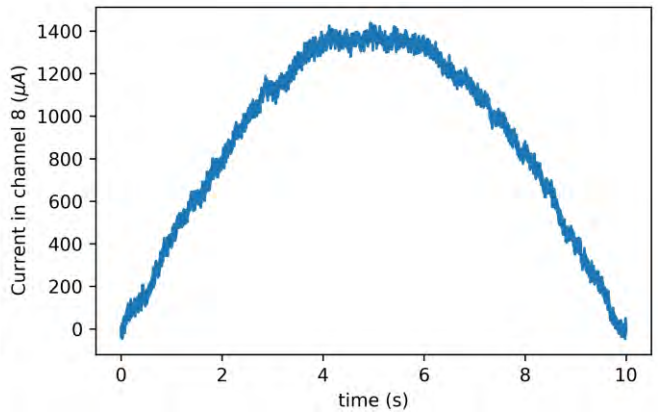


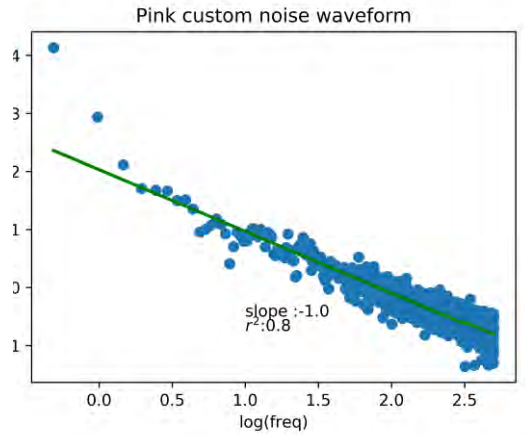


Active montage: pink noise







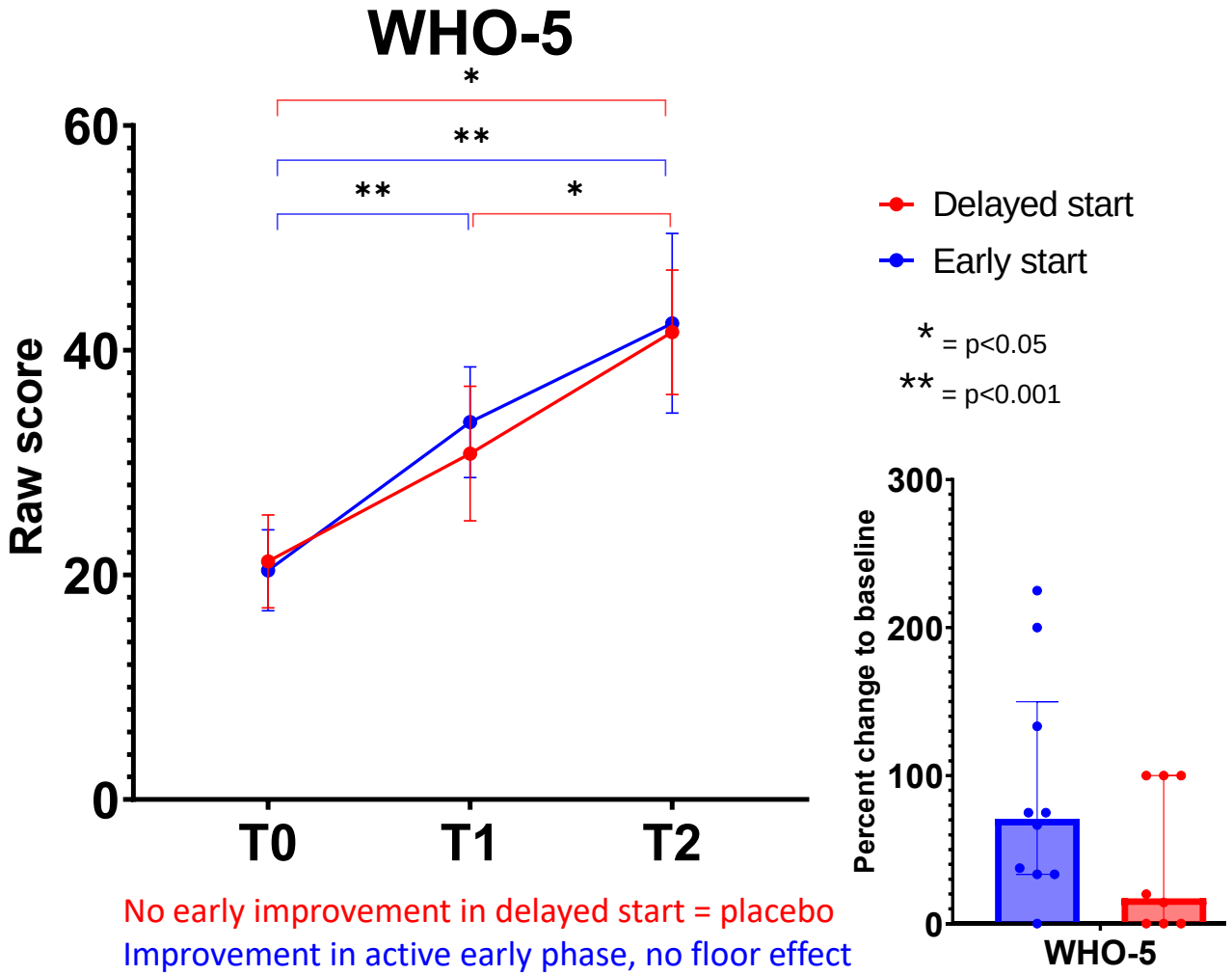


WHO-5

Scores from 0-100 (Elverrik 2014)

- No depression: >50
- Mild depression 28.7
- Moderate depression 22.9
- Severe depression 16.5

	Over the last two weeks	All of the time	Most of the time	More than half of the time	Less than half of the time	Some of the time	At no time
1	I have felt cheerful and in good spirits	5	4	3	2	1	0
2	I have felt calm and relaxed	5	4	3	2	1	0
3	I have felt active and vigorous	5	4	3	2	1	0
4	I woke up feeling fresh and rested	5	4	3	2	1	0
5	My daily life has been filled with things that interest me	5	4	3	2	1	0



No early improvement in delayed start = placebo

Improvement in active early phase, no floor effect

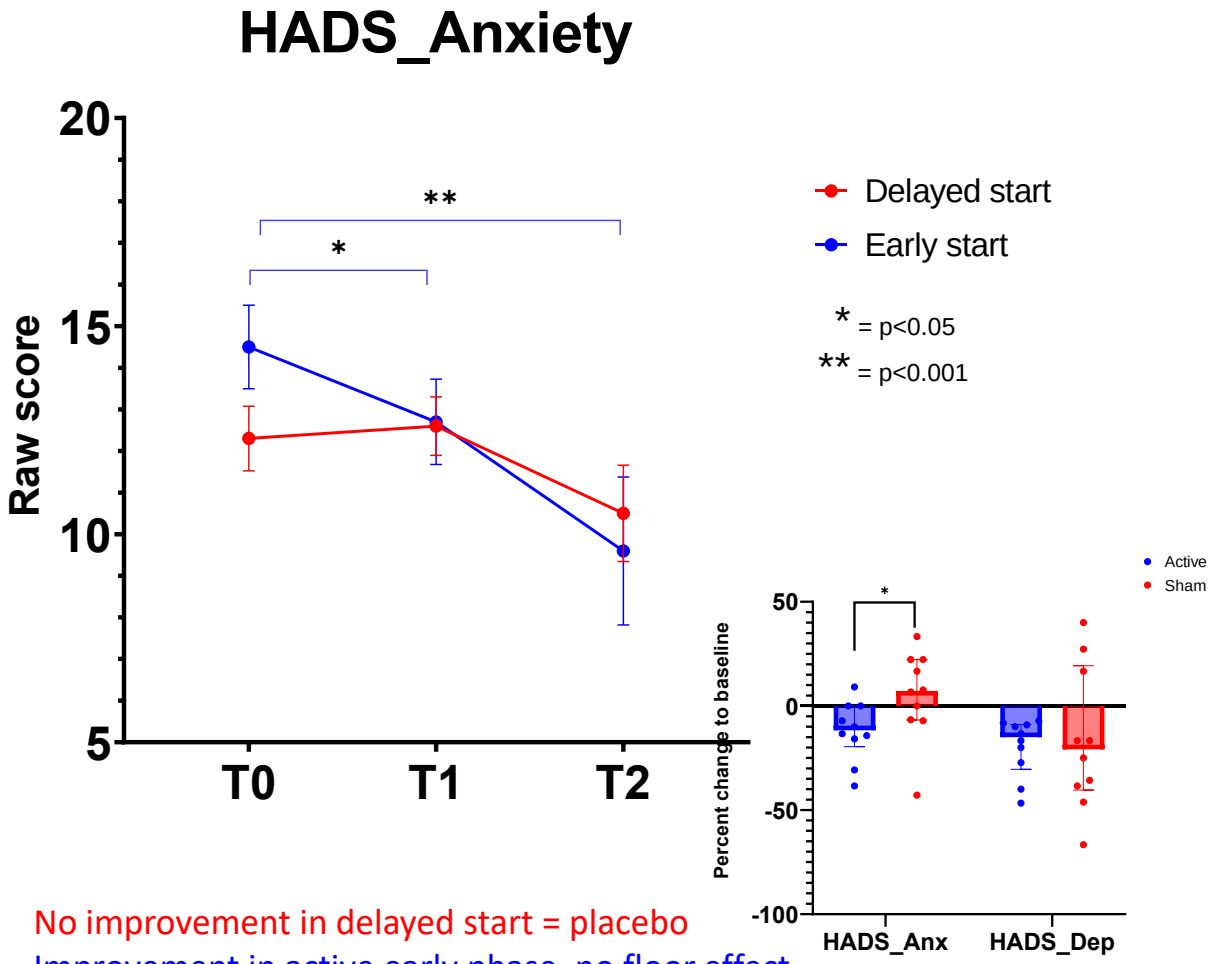
Hamilton Anxiety and Depression Scale

HADS

0-7	no anxiety, no depression
8–10	Mild
11–14	Moderate
15–21	Severe

MCID (+/- 1.5-2 points) (Lemay 2018, 2019)

Measure	Within-Patients	Between-Patients
Anxiety	1.67	1.29
Depression	1.85	1.21



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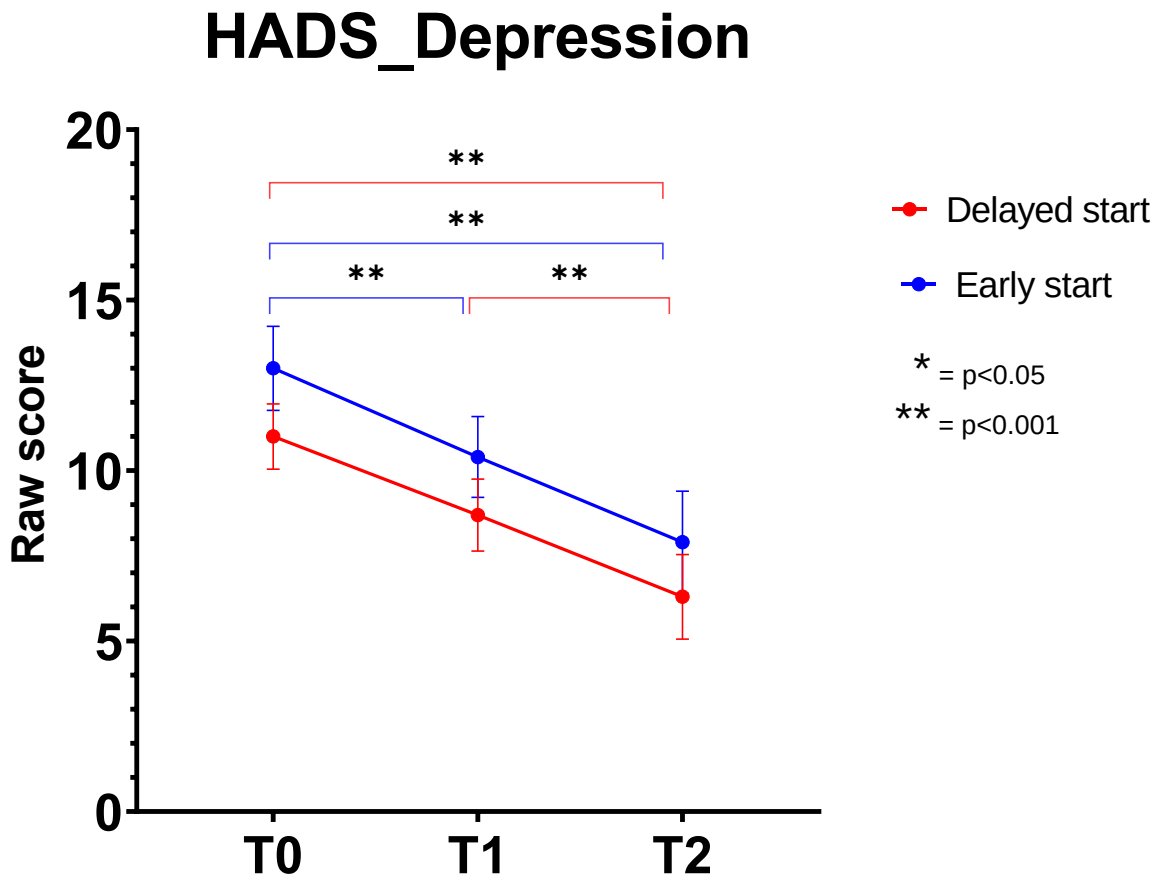
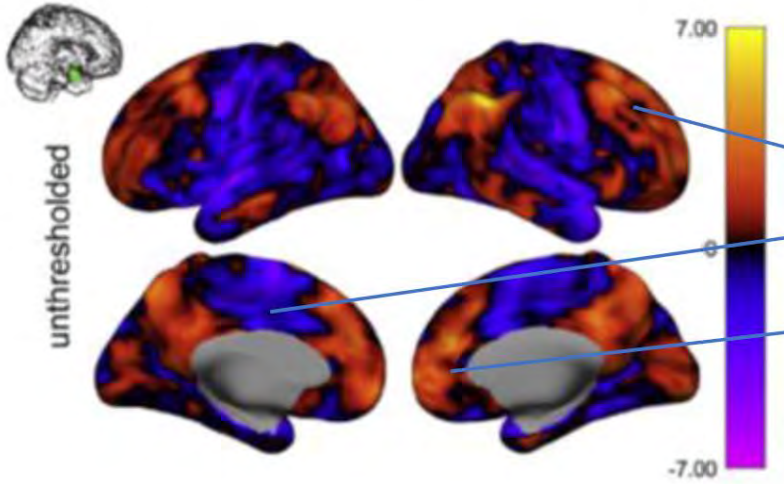


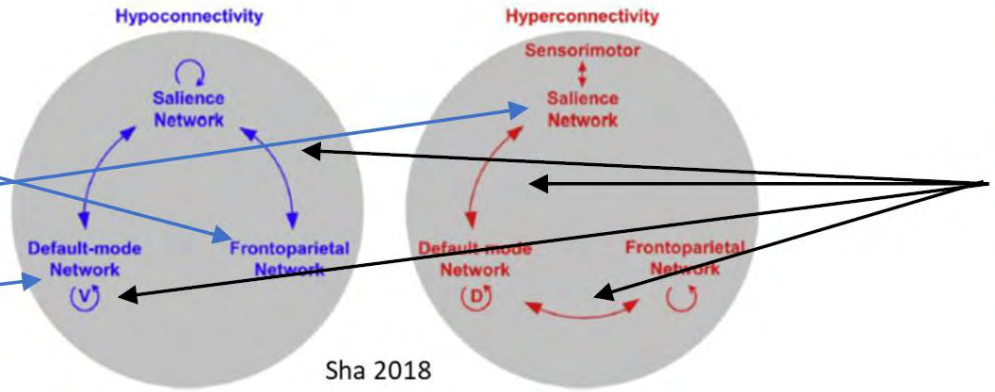
No early improvement in delayed start = placebo
Improvement in active early phase, no floor effect

Microdosing + HD-tDCS is also complimentary

Microdosing LSD



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

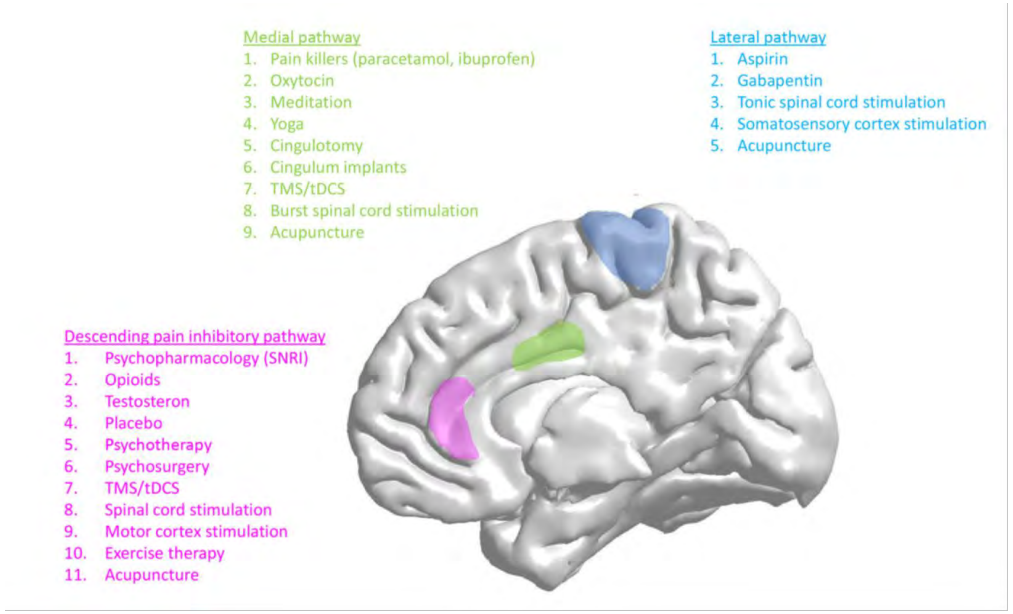


Sha 2018

HD-network tDCS

Pain and suffering

Pain = painfulness + suffering
Overlapping brain circuits
Treatment is multimodal
Medication + neuromodulation + …



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Brain Research consortium for Advanced International Innovative & Interdisciplinary Neuromodulation