Dipartimento
di Neuroscienze
e Riabilitazione

Dalla fatica fisica alla fatica mentale

Affaticamento cognitivo, stress e salute mentale: identificazione precoce

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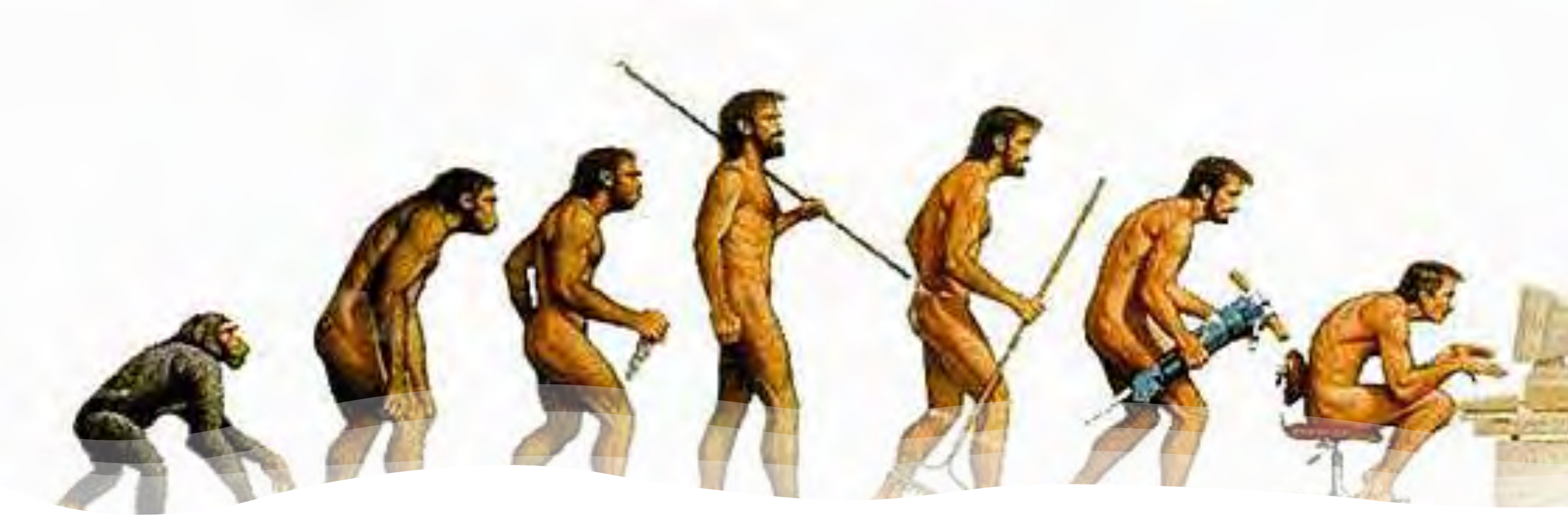


Affaticamento cognitivo, stress e salute mentale: ieri, oggi e domani

- Modelli storici in psichiatria e psicosomatica
- La depressione: ieri, oggi, domani
- Stress, sistemi omeostatici e depressione
- Dai modelli unidirezionali ai modelli integrativi
- Identificazione precoce del disagio psichico

Modelli storici in psichiatria e psicosomatica

History

- (500 BC) humoral theories of illness, Alcmaeon of Croton
- (400 - 300 BC) Socrates (know thyself), Plato and passions ….Aristotle and experience, Stoicism, Epicureanism…
- (100 - 200 AD) Areaetheus and mania, **Galen**, psychic pneuma and phrenitis, «rational, spiritual, and appetitive» soul
- Already debating and distinguishing between «insaniae» (psychoses) and «morbi animae», the mind-body problem
- Galen preconized psychotherapy: prompt pts to reveal their deepest passions and secrets, and cure passions. The “therapist”, had to be male, preferably older and wiser

History

- (400 – 1300) Medicine largely ignored during medioeval ages; mental illness considered within theological framework, hysteria "*Gaudet humore melancholico daemon"*
- (1233) Birth of the Inquisition and burning of witches, Malleus Maleficarum
- (1300) Reinassance Rebirth of sciences
- (1600s) : Descartes, Malpighi, Sydenham, Stahl. Organic psychiatry (neuroanatomy) and psychology «in the hands» of phylosophy. Distinction between organic and functional
- (1700 – 1800s) Illuminism and positivism, classifications, humanisation (Pinel), moral treatment: birth of modern psychiatry
- (1900s) hypnosis, psychoanalysis, phenomenology, social psychiatry, psychopharmacology: from asylums back to the community

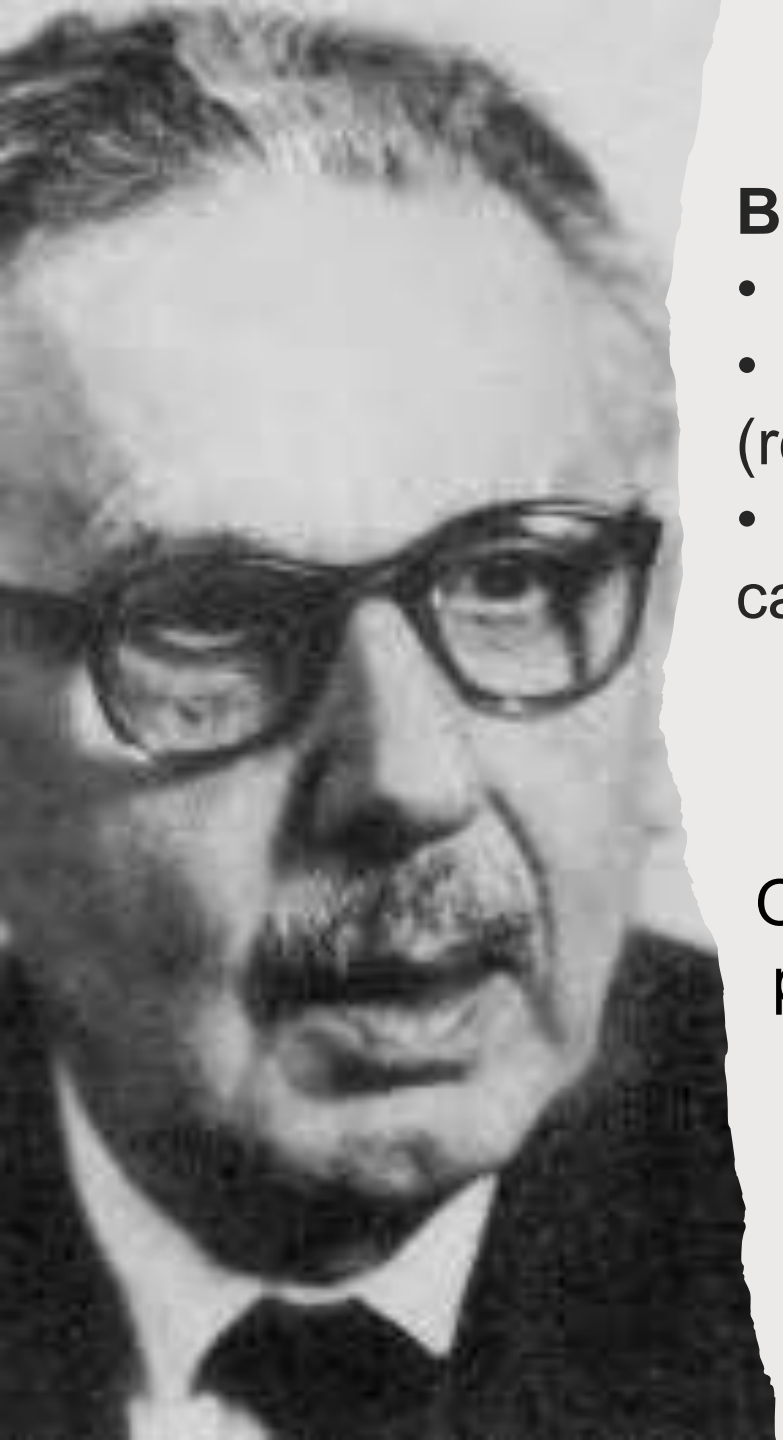
Descartes

Res cogitans e res extensa

Ghiandola pineale sede dell’anima

Melanconia

- Sentimento di mancanza di sentimento,
- Estraneità rispetto a se stessi
- Avvertire disperatamente di non esserci
- Venir meno della coscienza dell'esistenza
- Perdita del «sentimento dell'Io»
- Tuttavia, ancora nel reame del «comprensibile»



Binswanger

- Melanconia e mania
- Disturbo del processo temporale (retentio)
- Perdita della continuità che caratterizza l'esperienza naturale

Freud

Depressione, melanconia, lutto

Oggetto investito narcisisticamente, perduto; con esso si perde anche il soggetto

Mania come negazione

La psicosomatica in medicina

- The person is more than just the mere body as well as more than the mere soul: it is the whole human being'
- (Johann Christian Heinroth, Textbook of Disturbances of Mental Life, 1818)

- ...*le malattie rappresentano gli effetti somatici delle passioni e delle emozioni negative*) (Friedrich Groos, 1824)

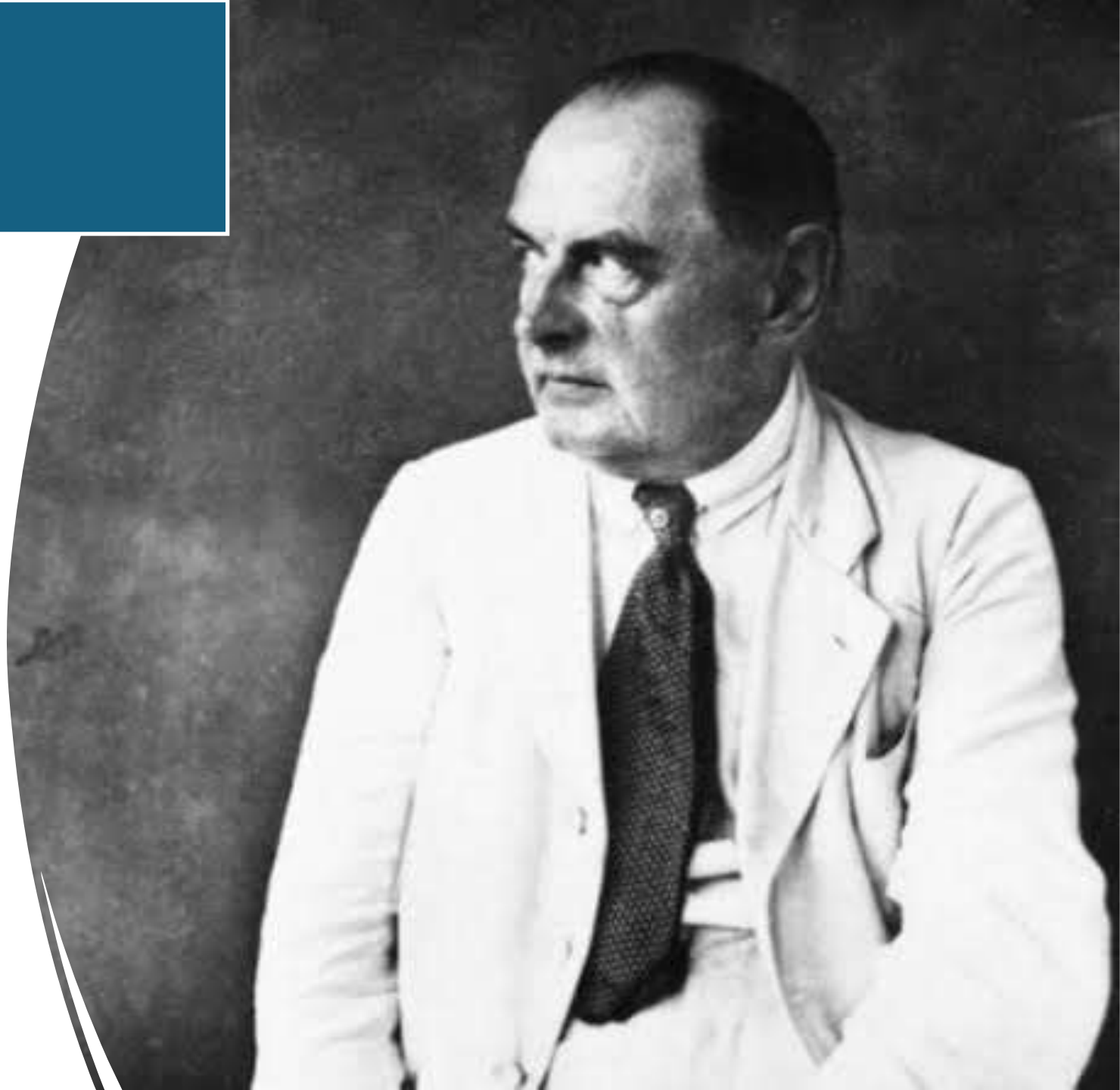
Psicosomatico → passioni sessuali esercitano un influsso sull'insorgenza di alcune patologie come tubercolosi, cancro ed epilessia

Somatopsichico → malattie fisiche influiscono sullo stato psichico dei malati, modificandolo

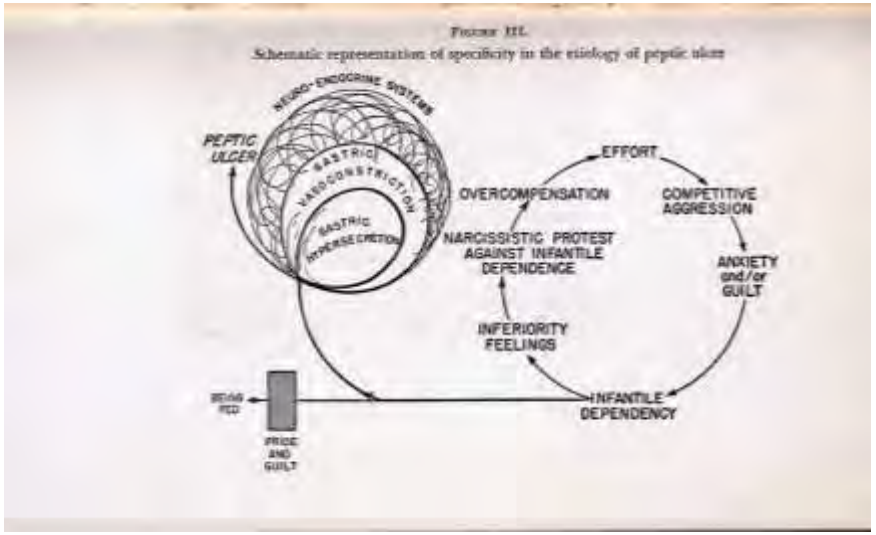
La psicosomatica in medicina

- La malattia fisica è un’espressione simbolica, secondo un linguaggio non mediato, di forze inconsce (“grammatica” fisica dell’inconscio) (Georg Walther Groddeck, Das Buch vom Es, 1923)

- La malattia riflette un’interazione tra una debolezza d’organo e impulsi nevrotici che “usano” quell’organo (Felix Deutsch, Selected Papers, 1940)

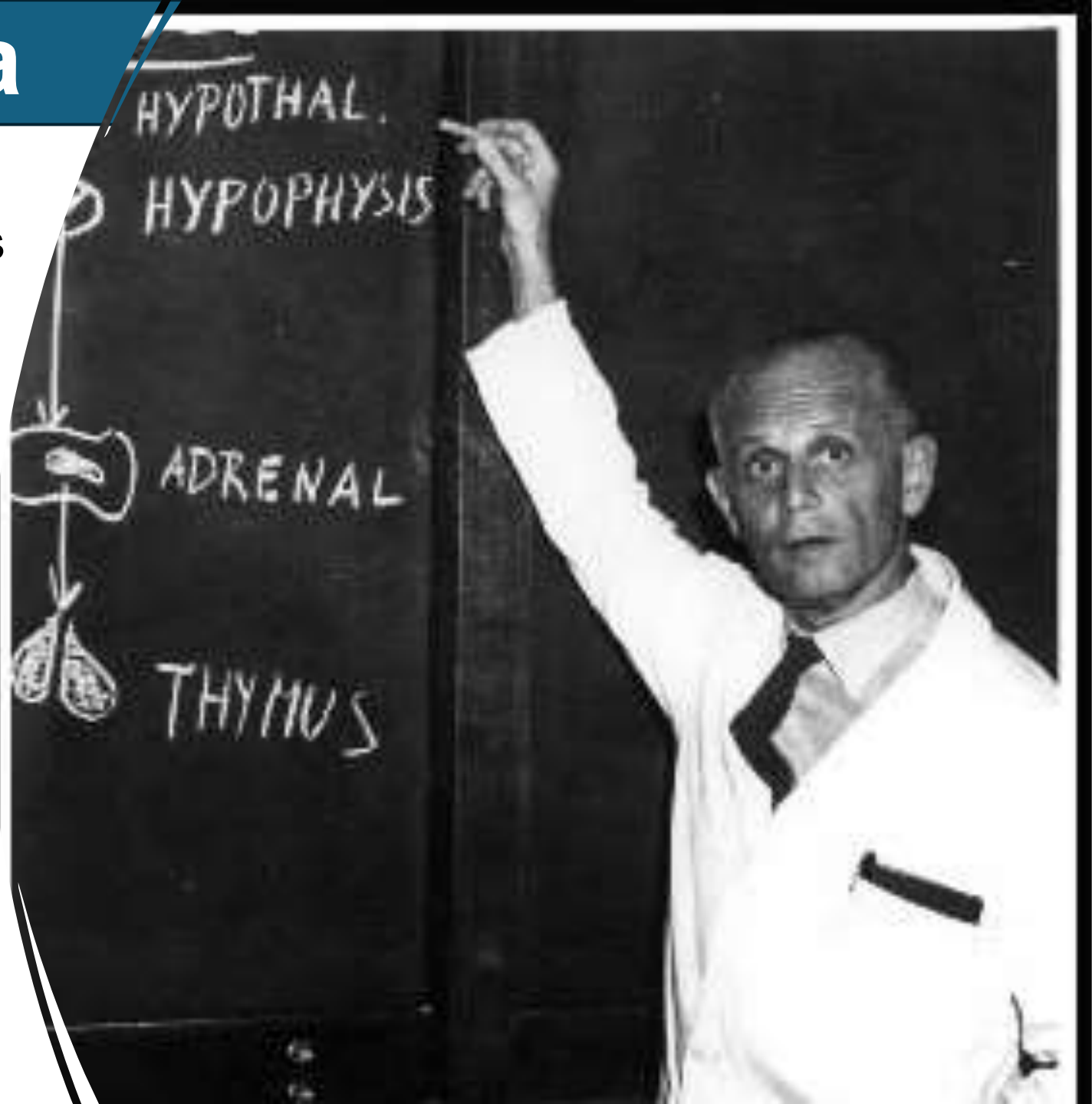


- “They (e.g. Groddeck) had interpreted everything too psychologically and had ignored the automatic physiological mechanisms that substantially controlled the expression of emotion as the body responded to stressful stimuli. However, specific unconscious wishes and infantile desires (e.g., the unconscious wish to be fed) may precipitate specific chains of physiological response and, ultimately, specific somatic diseases **(Holy Seven)” Franz Alexander**



La psico-fisiologia

Psychosomatic Medicine covers a different and broader field. Its object is to study in their **interrelation the psychological and physiological aspects of all normal and abnormal bodily functions and thus to integrate somatic therapy and psychotherapy**. It is not restricted to any specific field of pathology. Medical specialties such as internal medicine, pediatrics, dermatology, etc., may be so restricted. PM, however, is not a medical specialty of this kind; it designates a method of approach to the problems of etiology and therapy rather than a delimitation of the area" **Seyle**



The biopsychosocial approach in medicine

PSYCHOSOM MED 1967-1968

Review of Consultation Psychiatry and Psychosomatic Medicine

I. General Principles

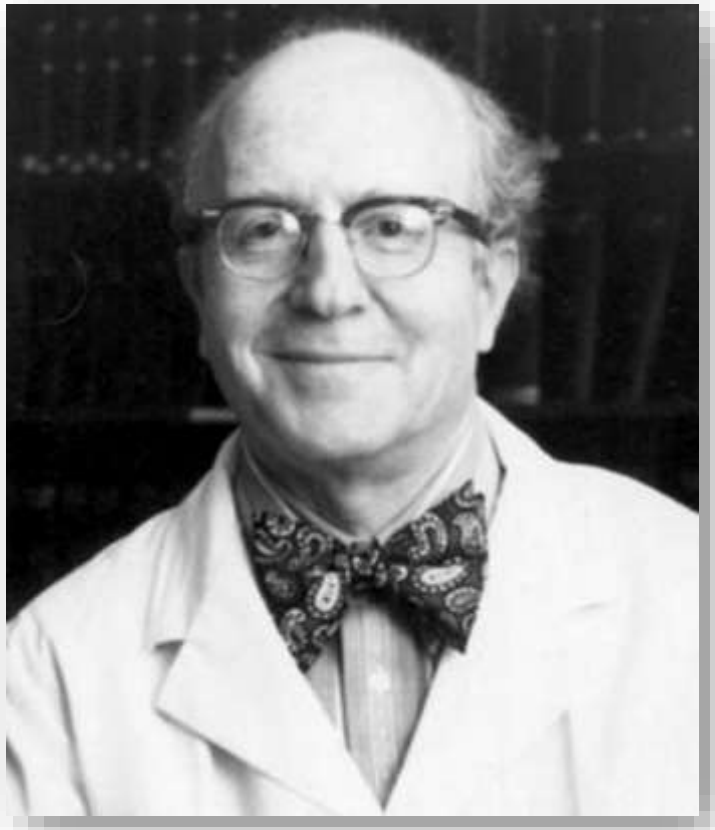
Z. J. LIPOWSKI, M.B., B.Ch., D. Psych.

SCIENCE, VOL. 196

The Need for a New Medical Model: A Challenge for Biomedicine

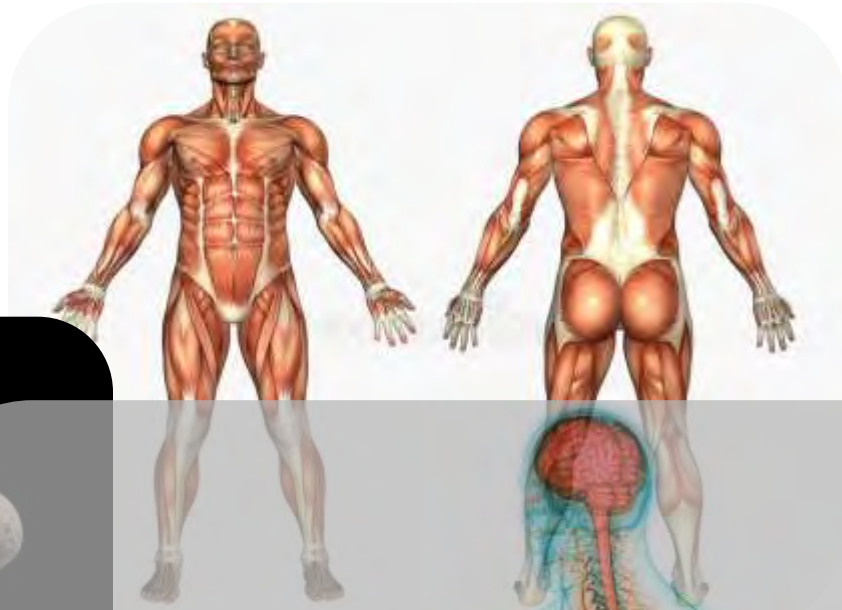
George L. Engel

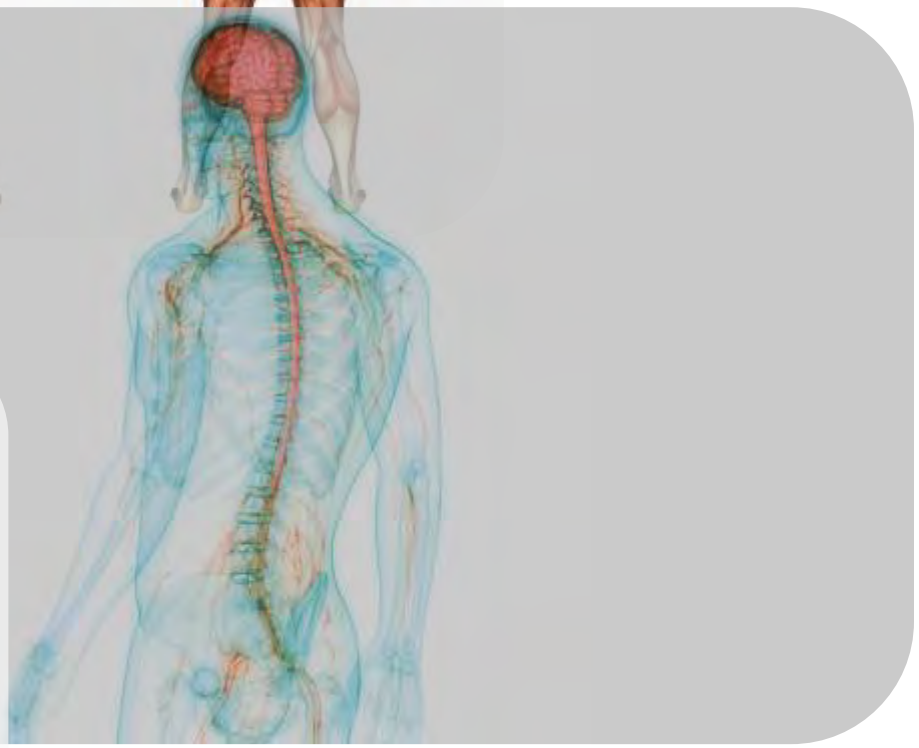
8 April 1977, Volume 196, Number 4286

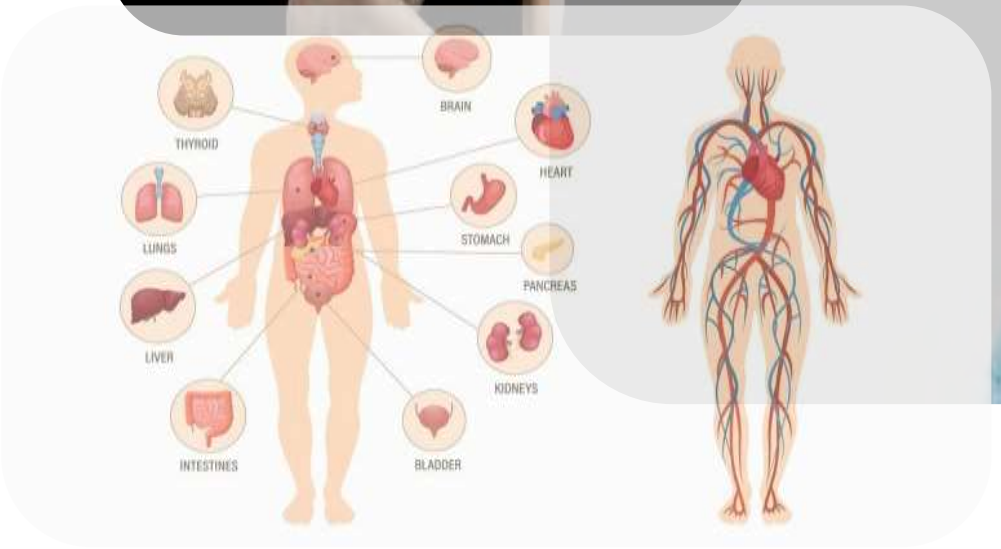


- «[…] delle singole scienze che si occupano della conoscenza dell'essere umano […] la psichiatria oggi, per ampi tratti, non fa più parte», rivolgendo essa le sue domande a un empirismo «orientato ai metodi delle **scienze naturali** applicate, le cui verifiche e falsificazioni computazionali rispondono soltanto al predicato della "scientificità"» (p. XV)

- H. **Tellenbach**, Melancolia, 1961







Corpo fisico

Corpo vissuto

La depressione: ieri, oggi, domani

- **Cinque o più dei seguenti sintomi sono stati contemporaneamente presenti durante un periodo di 2 settimane:**
  - Umore depresso per la maggior parte del giorno, quasi tutti giorni, come riportato dall'individuo o come osservato da altri.
  - Marcata diminuzione di interesse o piacere per tutte, o quasi tutte, le attività per la maggior parte del giorno, quasi tutti i gior
  - Significativa perdita di peso, non dovuta a dieta, o aumento di peso, oppure diminuzione o aumento dell'appetito quasi tutti i giorni.
  - Insonnia o ipersonnia quasi tutti i giorni.
  - Agitazione o rallentamento psicomotori quasi tutti i giorni.
  - Faticabilità o mancanza di energia quasi tutti i giorni.
  - Sentimenti di autosvalutazione o di colpa eccessivi o inappropriati, quasi tutti i giorni.
  - Ridotta capacità di pensare o di concentrarsi, o indecisione, qu tutti i giorni.
  - Pensieri ricorrenti di morte (non solo paura di morire), ricorrent ideazione suicidaria senza un piano specifico o un tentativo di suicidio o un piano specifico per commettere suicidioN.B. almeno uno dei sintomi è 1) umore depresso o 2) perdita di interesse o piacere. Non bisogna tener conto di sintomi chiaramente attribuibili ad un'altra condizione medica

Sintomi fisici nella LLMD

- perdita di energie, faticabilità,
- perdita o aumento di peso,
- disturbi del sonno,
- dolori fisici,
- senso di nausea, eccessiva sudorazione, tachicardia
- mancanza di desiderio sessuale

Sintomi cognitivi nella LLMD

ATTENZIONE

- Perdita del filo dei pensieri
- Incapacità di ascoltare
- Attenzione
- Concentrazione
- Mancanza di focalizzazione
- Cervello annebbiato

MEMORIA

- Mancanza di memoria a breve termine
- Dimenticanze
- Incapacità di fare calcoli

CONFUSIONE
INADEGUATEZZA
SENSO DI SOPRAFFAZIONE

VELOCITÀ PSICOMOTORIA

- Stanchezza/letargia
- Movimenti lenti

FUNZIONI ESECUTIVE

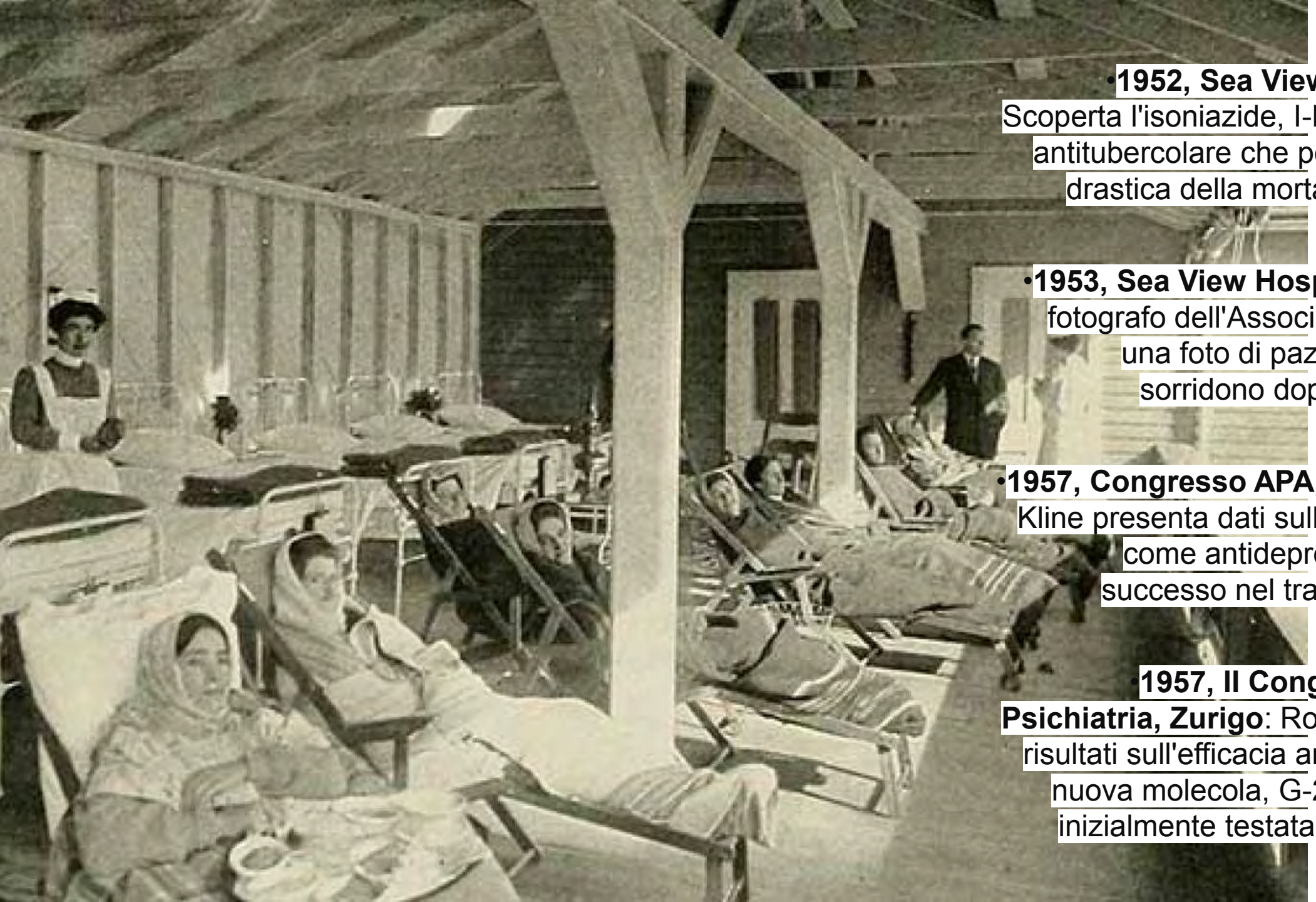
- Procrastinazione
- Mancanza di sicurezza
- Indecisione
- Incapacità di multitasking

Mental fatigue

- weariness, tiredness, lethargy, listlessness
- a psychobiological state of tiredness caused by prolonged periods of performing demanding, cognitive-load-inducing activities

- Burnout
- Work-related stress
- Exhaustion

- Kunasegaran et al. PeerJ 2023



- **1952, Sea View Clinic, New York**: Scoperta l'isoniazide, I-MAO come farmaco antitubercolare che porta a una riduzione drastica della mortalità a 4 decessi per 100.000 abitanti.
- **1953, Sea View Hospital, New York**: Un fotografo dell'Associated Press pubblica una foto di pazienti che danzano e sorridono dopo il trattamento con iproniazide.
- **1957, Congresso APA, Syracuse**: Nathan Kline presenta dati sull'uso dell'iproniazide come antidepressivo, mostrando il successo nel trattamento di pazienti depressi.
- **1957, II Congresso Mondiale di Psichiatria, Zurigo**: Roland Kuhn presenta risultati sull'efficacia antidepressiva di una nuova molecola, G-22355 (imipramina), inizialmente testata come antipsicotico.

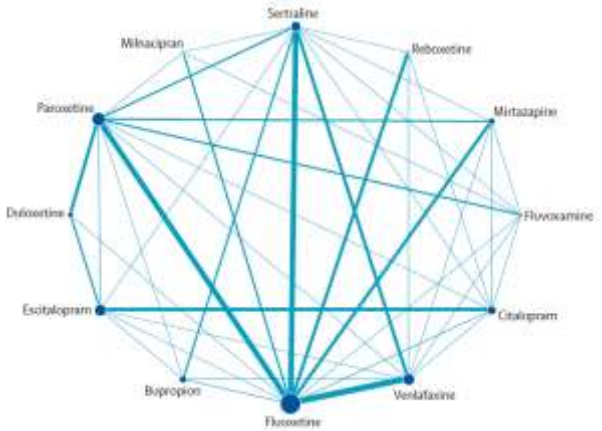
A un certo punto ci fu un'irruzione, chiamata G22355. Nel 1959 arrivarono, nella Clinica dove mi ero laureato e lavoravo, delle pilloline rosse che portavano questa sigla: era l'imipramina, il Tofranil. E noi vedevamo queste persone depresse e melanconiche che dopo due settimane cambiavano faccia, sorridevano, avevano un'aria propositiva: vedevamo, in altre parole, un cambiamento. Questo fu un colpo spaventoso per un povero psichiatra come ero io, un colpo fondamentale che significava l'ingresso della psichiatria nell'area della medicina. E ci si rese conto che si trattava di una ventata spaventosa che avrebbe cambiato ogni cosa.

Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis

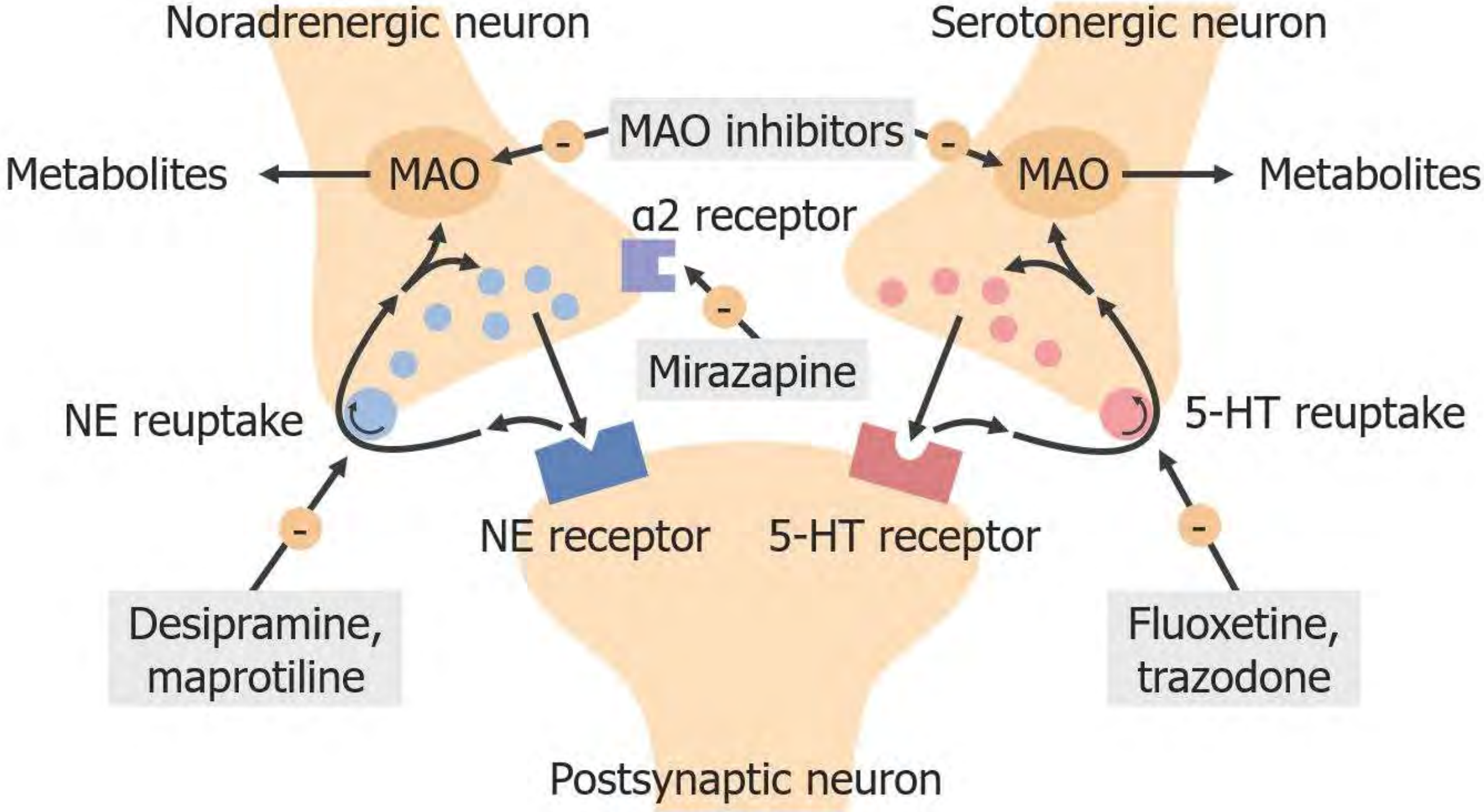
Andrea Cipriani, Toshiaki A Furukawa, Georgia Salanti, John R Geddes, Julian P T Higgins, Rachel Churchill, Norio Watanabe, Atsuo Nakagawa, Ichiro M Omori, Hugh McGuire, Michele Tansella, Corrado Barbui

117 trials. Mirtazapine, escitalopram, venlafaxine, and sertraline were significantly more efficacious than duloxetine (odds ratios [OR] 1·39, 1·33, 1·30 and 1·27), fluoxetine (1·37, 1·32, 1·28, and 1·25), fluvoxamine (1·41, 1·35, 1·30, and 1·27), paroxetine (1·35, 1·30, 1·27, and 1·22), and reboxetine (2·03, 1·95, 1·89, and 1·85). Reboxetine was significantly less efficacious than all the other antidepressants tested.

Escitalopram and sertraline showed the best profi le of acceptability, leading to significantly fewer discontinuations than did duloxetine, fluvoxamine, paroxetine, reboxetine, and venlafaxine.



Meccanismi d’azione


Noradrenergic neuron
Serotonergic neuron
MAO inhibitors
Metabolites
MAO
MAO
Metabolites
α2 receptor
Mirazapine
NE reuptake
5-HT reuptake
NE receptor
5-HT receptor
Desipramine,
maprotiline
Fluoxetine,
trazodone
Postsynaptic neuron

Molecular Psychiatry www.nature.com/mp

SYSTEMATIC REVIEW OPEN

The serotonin theory of depression: a systematic umbrella review of the evidence

Joanna Moncrieff[1,2✉], Ruth E. Cooper[3], Tom Stockmann[4], Simone Amendola[5], Michael P. Hengartner[6] and Mark A. Horowitz[1,2]

Prof Joanna Moncrieff

Professor of Critical and Social Psychiatry

Epidemiology & Applied Clinical Research

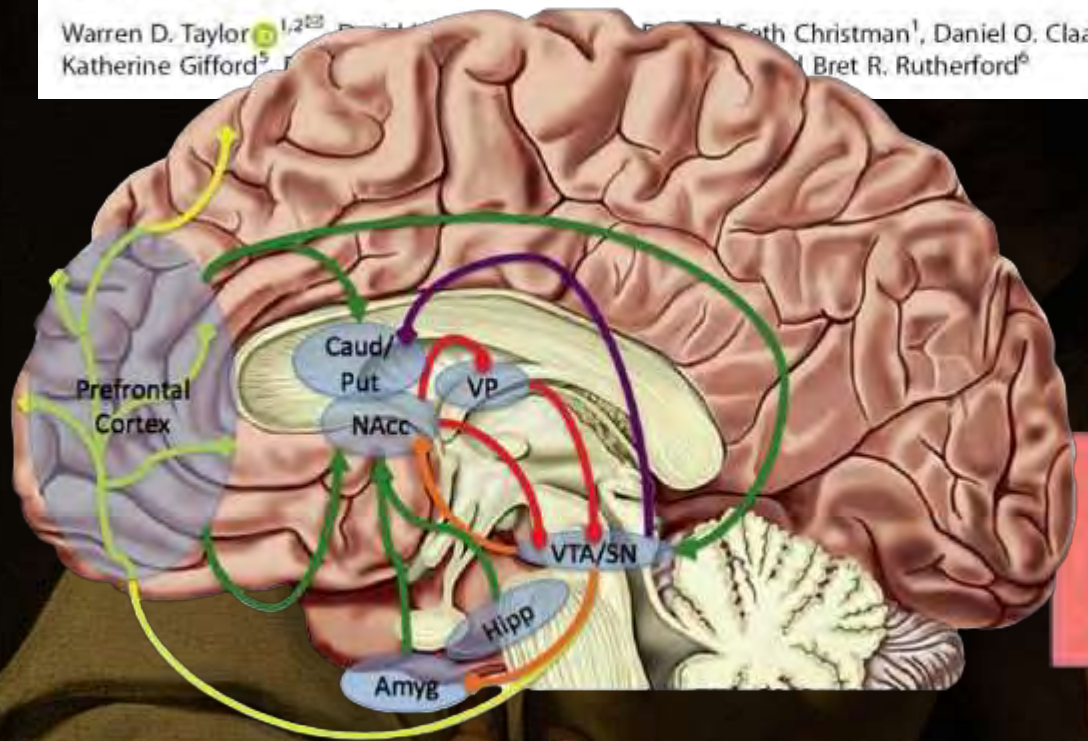
Division of Psychiatry

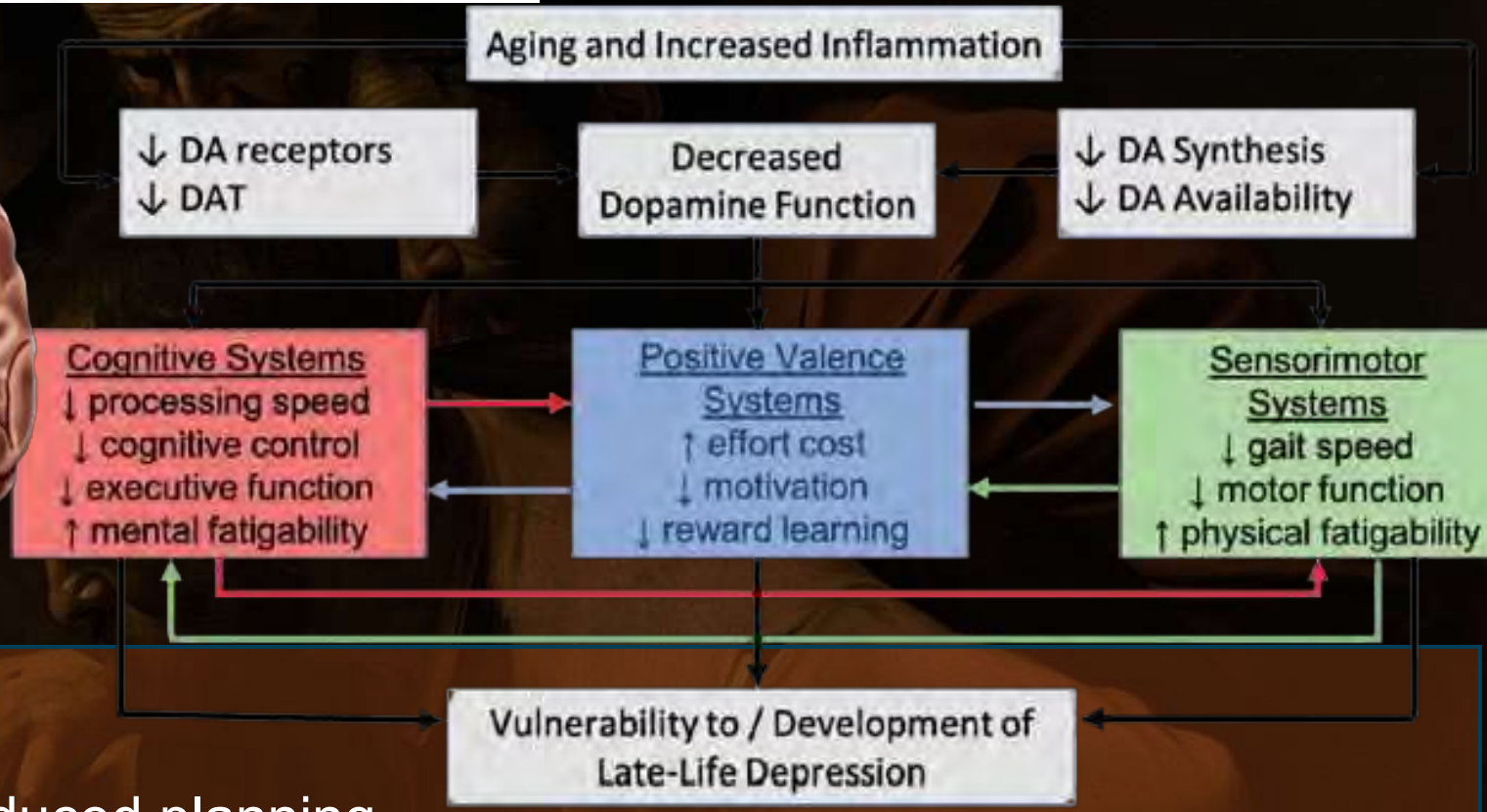
The main areas of serotonin research provide no consistent evidence of there being an association between serotonin and depression, and no support for the hypothesis that depression is caused by lowered serotonin activity or concentrations. Some evidence was consistent with the possibility that long-term antidepressant use reduces serotonin concentration.

REVIEW ARTICLE

Influences of dopaminergic system dysfunction on late-life depression

Warren D. Taylor[1,2✉], [illegible] Christman[1], Daniel O. Claassen[5], Guillermo Horga[6], Jeffrey M. Miller[6], Katherine Gifford[5], [illegible] Bret R. Rutherford[6]





Apathy, anhedonia,

psychomotor retardation, slowing, reduced planning

Slowed processing speed, Executive dysfunction, working memory deficits

Taylor et al., Mol Psychiatry 2021

Science

AAAS

Requirement of Hippocampal Neurogenesis for the Behavioral Effects of Antidepressants

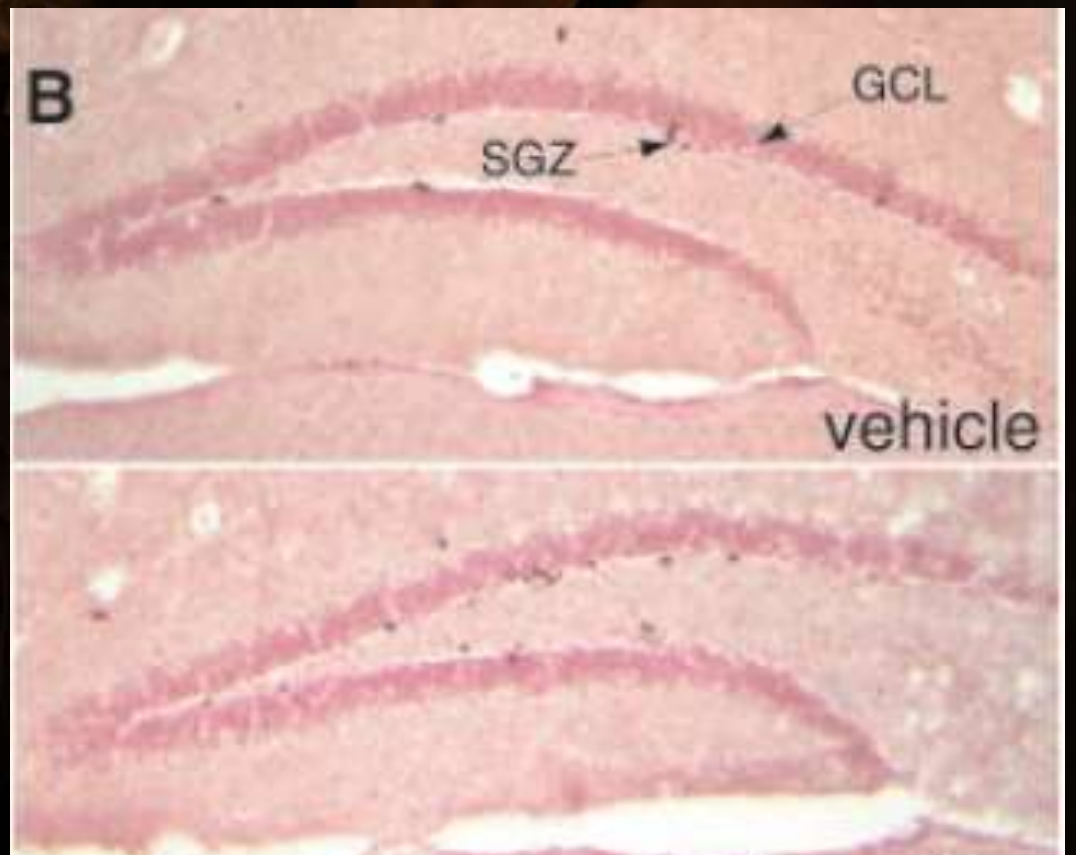
Luca Santarelli,[1*] Michael Saxe,[1*] Cornelius Gross,[1] Alexandre Surget,[2] Fortunato Battaglia,[3] Stephanie Dulawa,[1] Noelia Weisstaub,[1] James Lee,[1] Ronald Duman,[4] Ottavio Arancio,[3] Catherine Belzung,[2] René Hen[1†]

" … using genetic and radiological methods, we show that **disrupting AD induced neurogenesis blocks behavioral responses to AD**

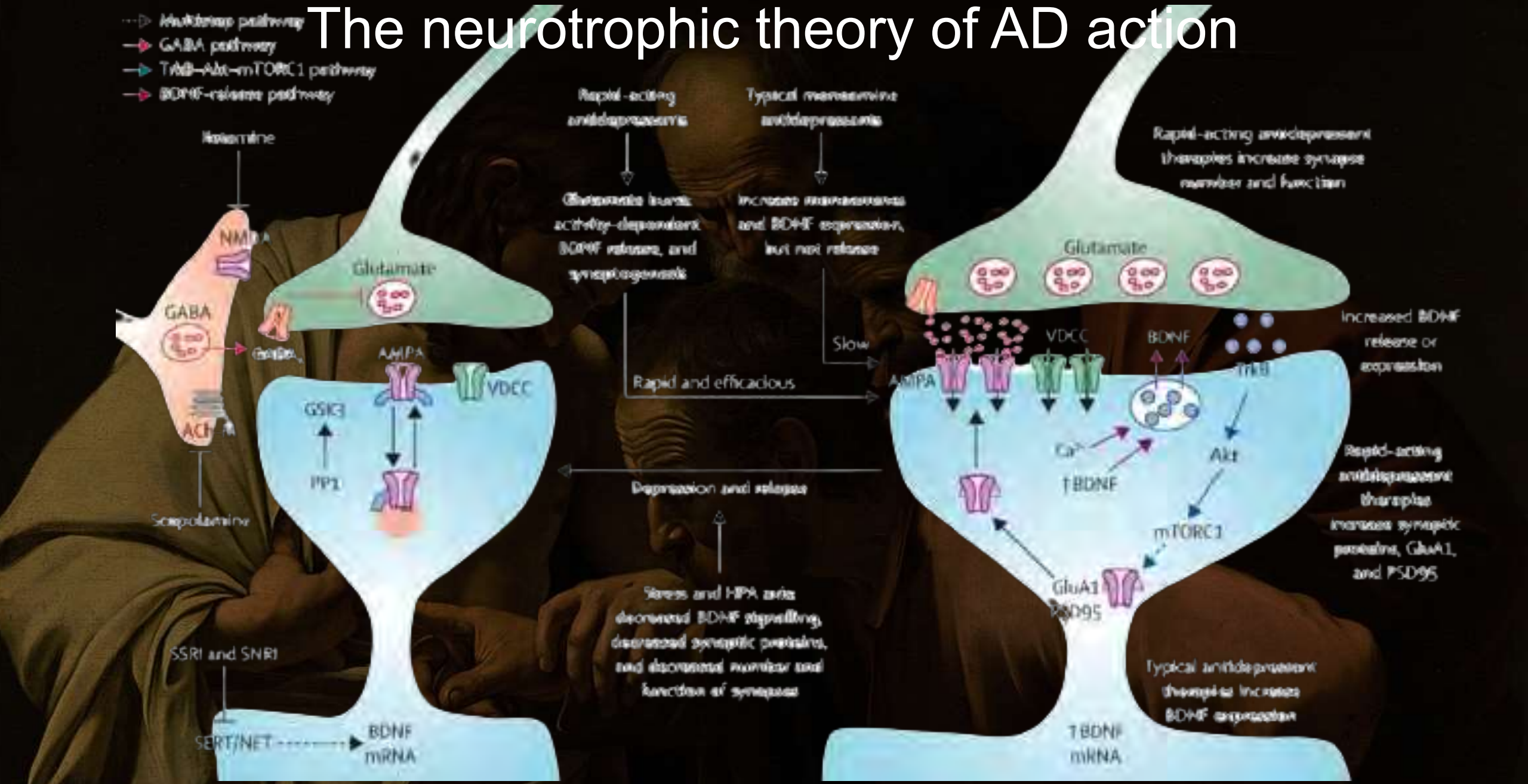
1) Serotonin 1A receptor null **mice** were insensitive to the neurogenic and behavioral effects of **fluoxetine**.

2) X-irradiation of a restricted region of mouse brain containing the hippocampus prevented the neurogenic and behavioral effects of two classes of AD "

Science ***301, 805 (2003)***

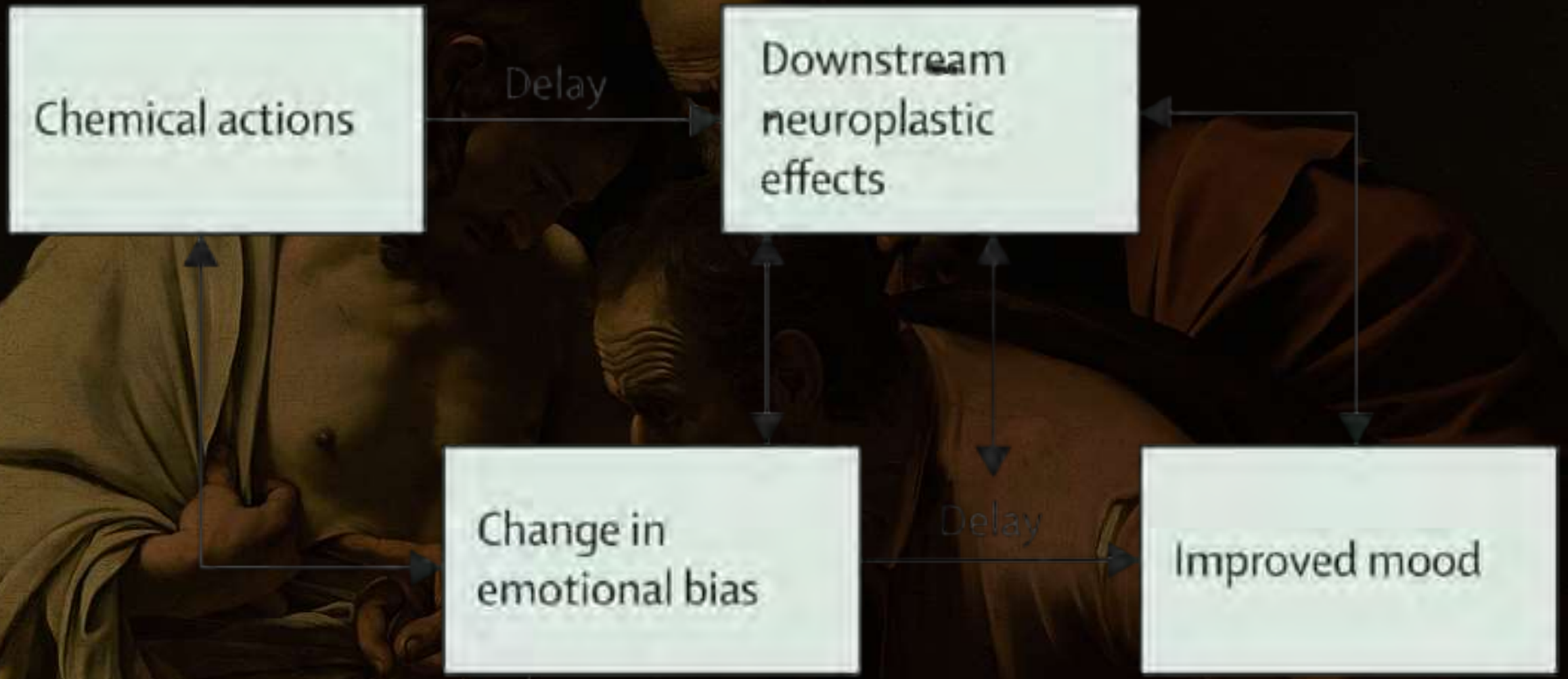


The neurotrophic theory of AD action



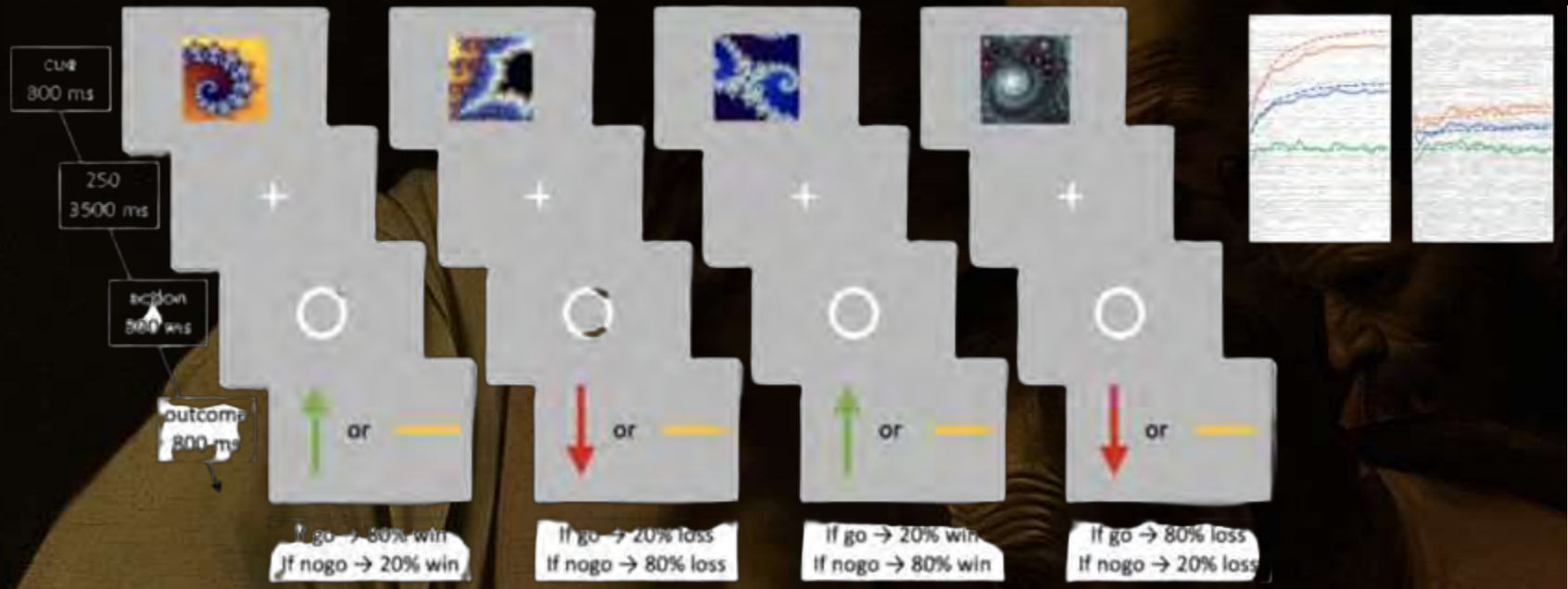
Harmer et al., Lancet Psychiatry. 2017

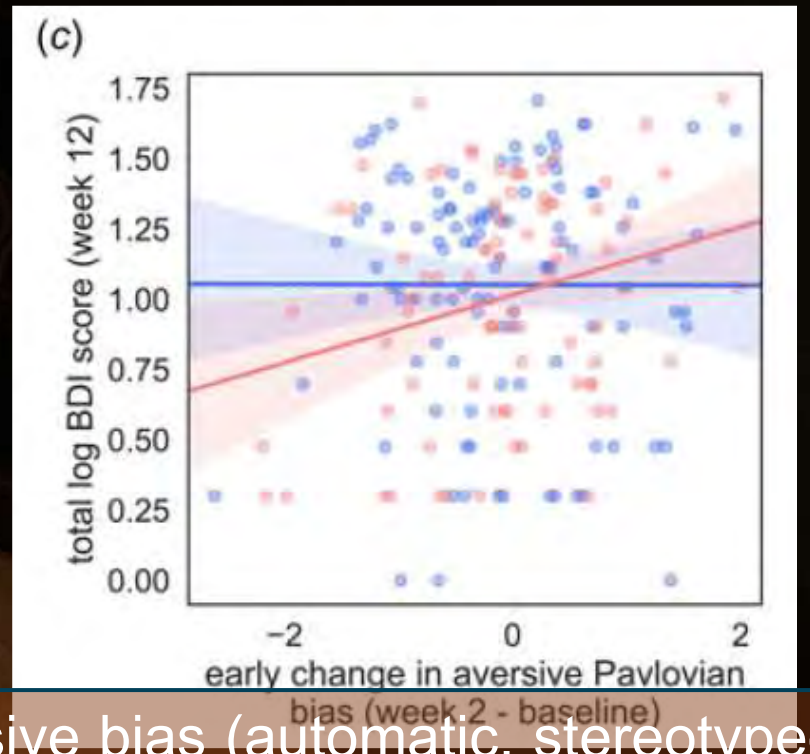
The cognitive neuropsychological theory of AD action



Harmer et al., Lancet Psychiatry. 2017

Computational psychiatry approach to AD action





Affective go-no go task. RL models to assess Pavlovian aversive bias (automatic, stereotyped inhibition of actions in the face of negative expectations) and learning from losses. Sertraline induced faster aversive learning from losses at 2 week (anxiety); early improvements of aversive Pavlovian bias predicted decrease in depression after 12 weeks.

SSRIs may facilitate learning faster in a punishing environment, thus leading to less negative and more positive (or neutral) prediction errors.

Malamud, Huys et al., Psychol Med. 2024

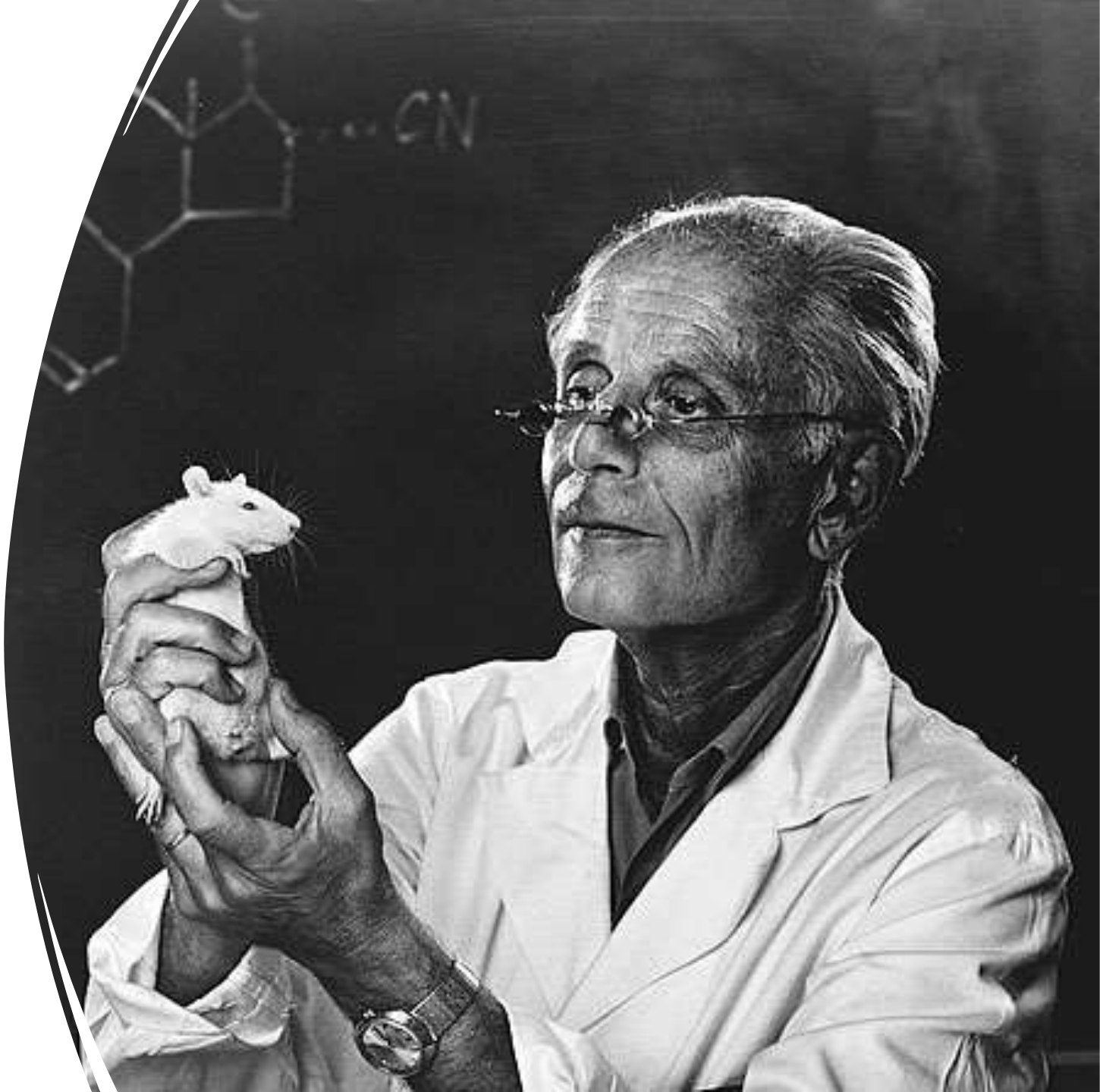
Modelli neurobiologici

What is **stress** ?

- **Hans Selye** (1907 – 1982)

- noticed that mice which were chronically injected with irritating substances or even with innocuous physiological solution exhibited a similar pattern of symptoms (***general adaptation syndrome***, GAS)

- In its biological meaning, stress is the body reaction to a real or imagined demand (environmental or psychological)



HPA axis

Pain
Infections
Physical threats
Exams, deadlines, talking in public

Immediate release of **adrenaline** - fight or flight response

(faster heartbeat, more blood to muscles, deeper breathing, higher attention and faster reflexes)

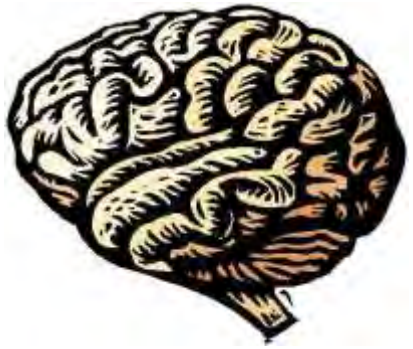
Release of **cortisol** - peak in 30 minutes

mantains blood pressure and glucose levels, saves body liquids, increases immunity, enhances memory

Chronic (dis)stress:
Hypertension, blood sugar imbalances, decreased bone density and muscle tissue, lowered immunity, loss of concentration

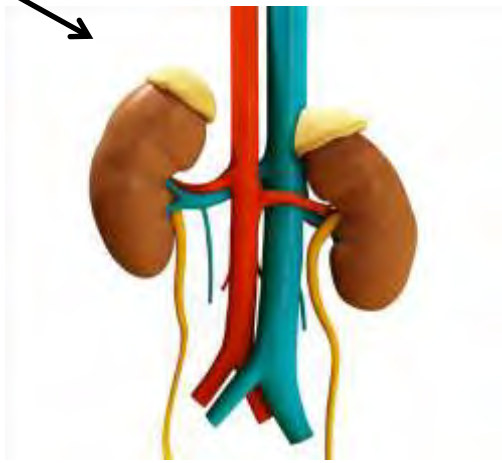
HPA axis

CRH



ACTH

(Negative feedback)



cortisol

A.G. Watts / Frontiers in Neuroendocrinology 26 (2005) 109–130
Bornstein and Chrousos, The Journal of Clinical Endocrinology & Metabolism ,1999
S. L. Lightman, Journal of Neuroendocrinology 2008

The usual suspects: HPA axis

Psychological stress

5HT, Nor, Dop,
GABA, Glut, opioids,
ACh

Prefrontal Cortex (+ -)
(Perception/judgement / emotional monitoring)

Hippocampus (+ -)
(memory processing)

Amygdala (+)
(fear conditioning)

Brainstem: NTS and VLM (+)
(sensory processing)

Physical stress

Hypothalamus (PVN)

CRH

Pituitary gland

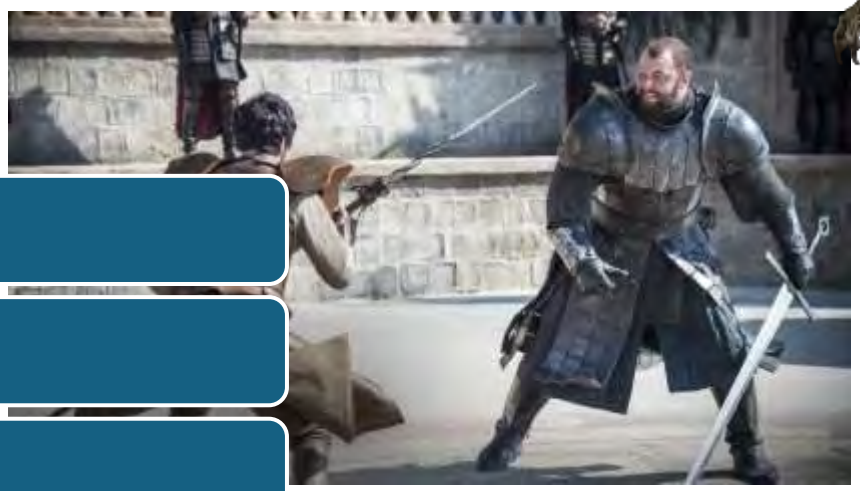
ACTH

cortisol

LHPA axis?

Dedovic et al., 2009; Belvederi Murri et al., 2015 PNEI

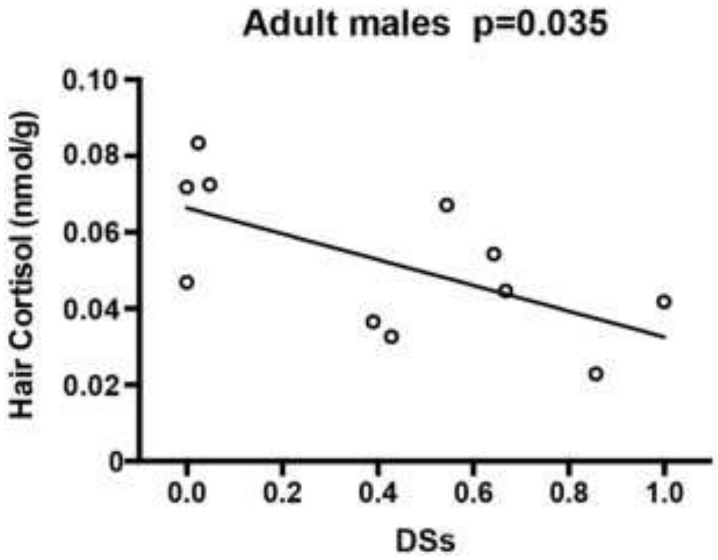
Drivers of HPA axis activity

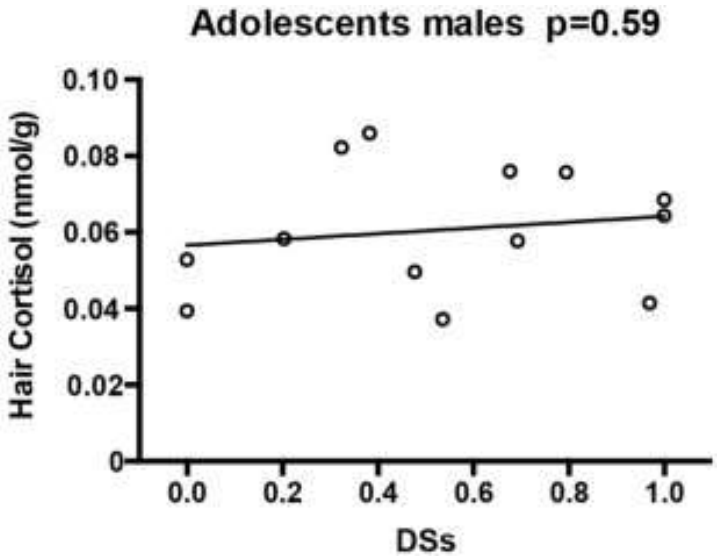


- Threat to physical integrity
- Social evaluation
- uncontrollability
- Evoking shame or loss
- Subjective distress
- MDD (+) or PTSD (-)
- time since onset (-)

Miller et al., Psychological Bulletin 2007

Drivers of HPA axis activity

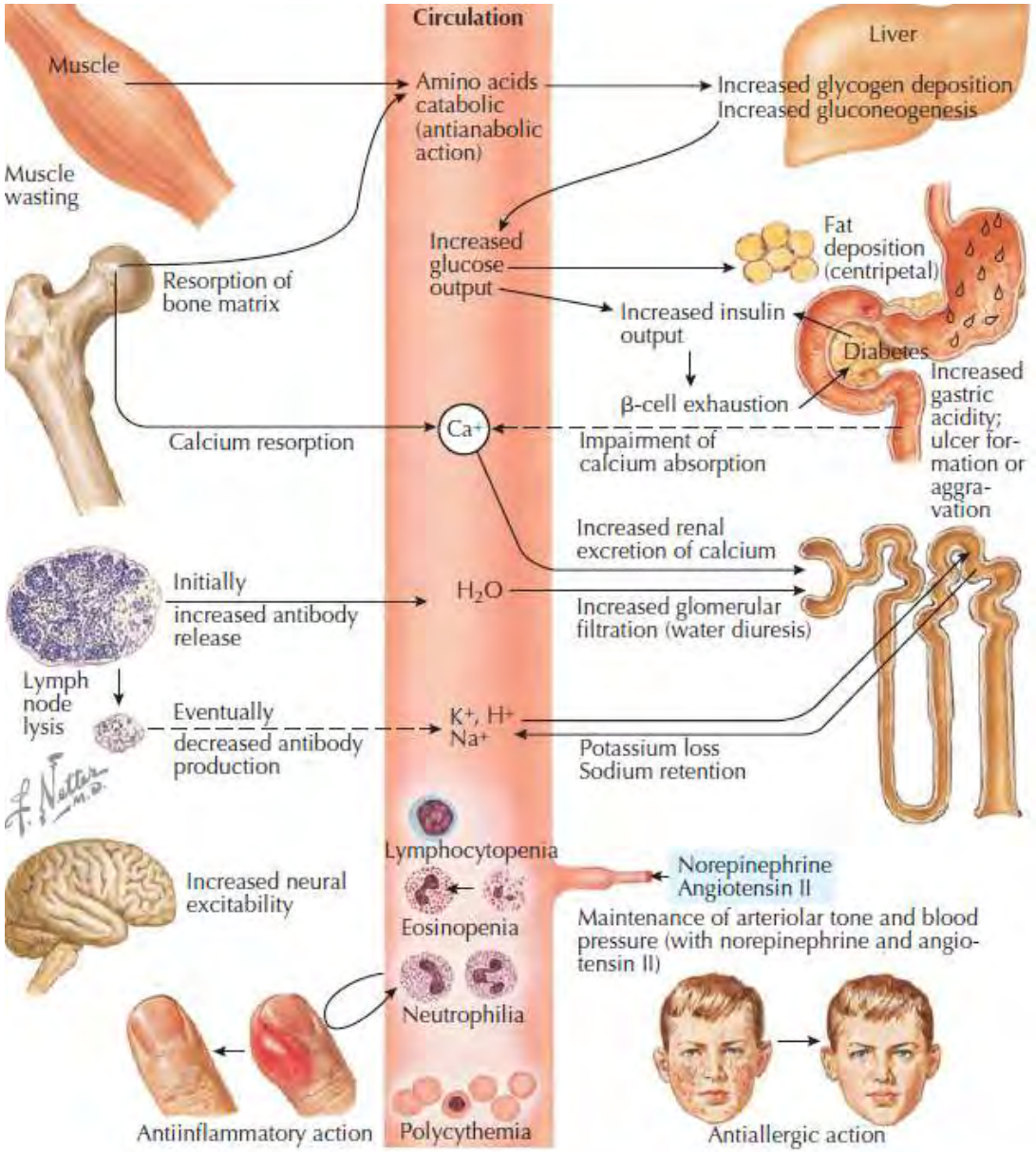




Resource inequity
Maintenance of dominance (despotism of the group)
Breeding style
Stability of social ranks
Subordinate coping strategies
Subordinate avoidance of dominants
Subordinants' use of alternative strategies

Sapolsky, Science, 2005; Feng et al. 2016

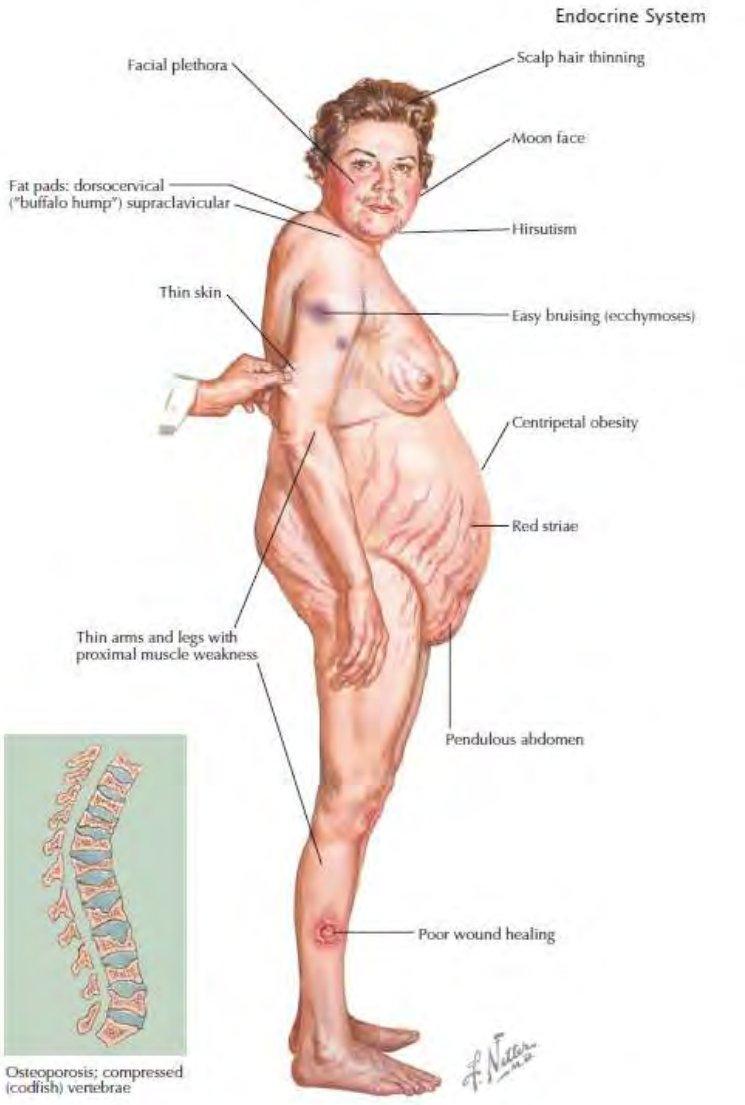
Actions of cortisol



"Glucocorticoids influence about 20% of the expressed human genome and their effects spare almost no organs or tissues."

Chrousos & Kino. Science STKE 2005

Cushing's syndrome



- 50 - 80% depression
- 30% episodes of mania-hypomania
- Over 50% anxiety / panic

Diffuse impairment in non-verbal, visual-ideational, visual-memory and spatial constructional abilities

Reversible if treated promptly but at 12 months correction of hypercortisolism results only in 2/3 of patients improved

Harvey Williams Cushing (1869 – 1939)

Fava and Sonino, CNS Drugs 2001; 15 (5): 361-373

Rapid actions of corticosteroids

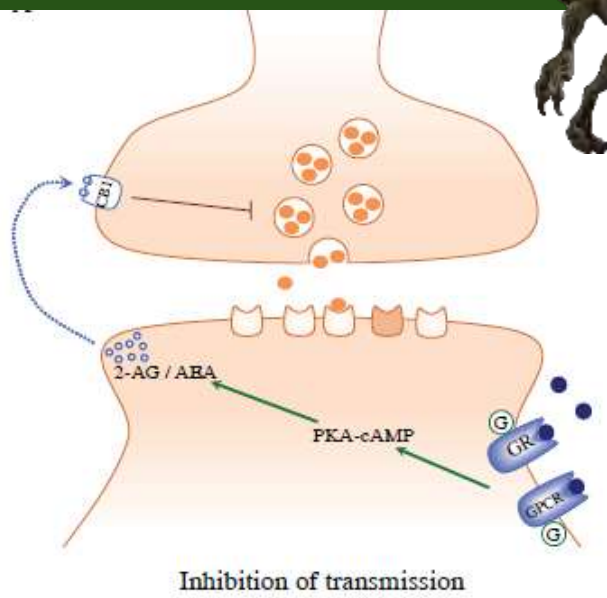
Rapid effects on the ***excitability and activation of neurons*** in the hypothalamus, hippocampus, amygdala and prefrontal cortex

HIPPOCAMPUS: mediated by pre- and postsynaptic membrane-located MRs and GRs → reduction of neural excitability, NMDA, AMPA signaling, LTP

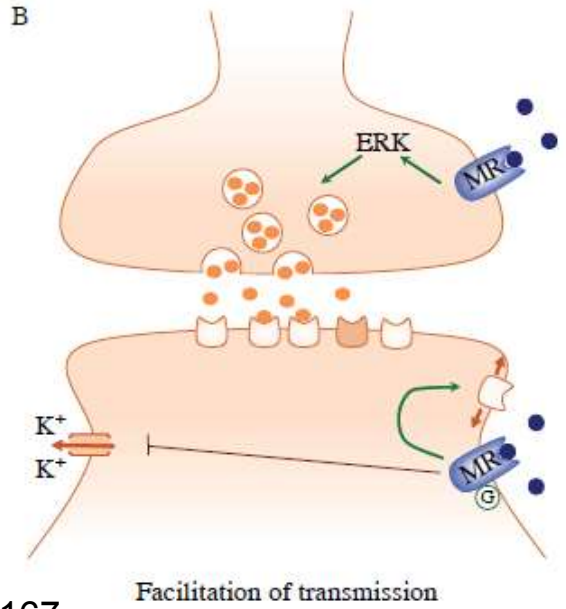
→**<u>Suppression of memory retrieval</u>**

AMYGDALA: stimulation of NA signaling, prolonged excitability in Basolateral nuclei

→ **<u>Consolidation of fear related memory</u>**



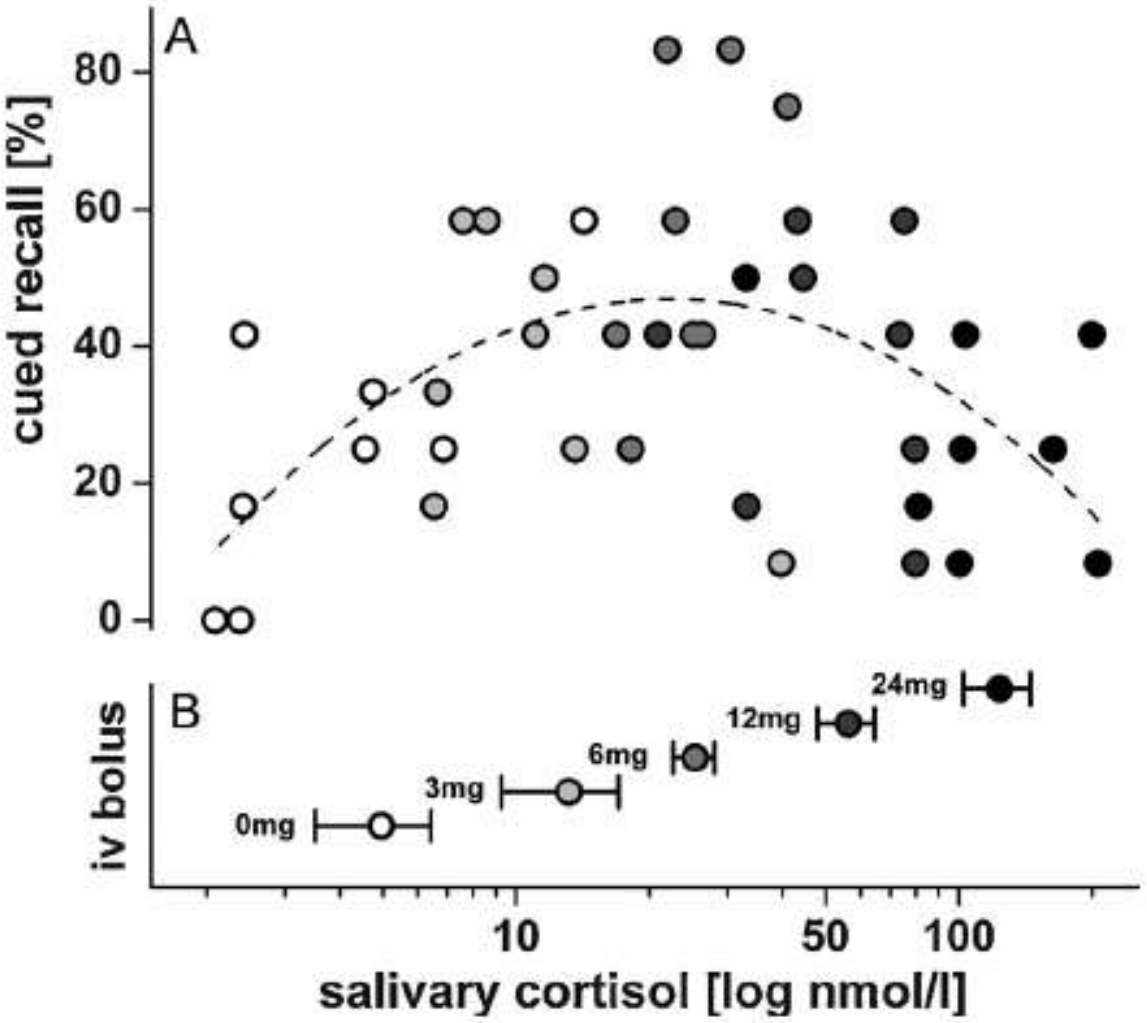
Inhibition of transmission



Facilitation of transmission

Groeneweg et al., Journal of Endocrinology (2011) 209, 153–167,

Rapid cognitive actions of GCs



DECLARATIVE MEMORY AND ASSOCIATIVE LEARNING

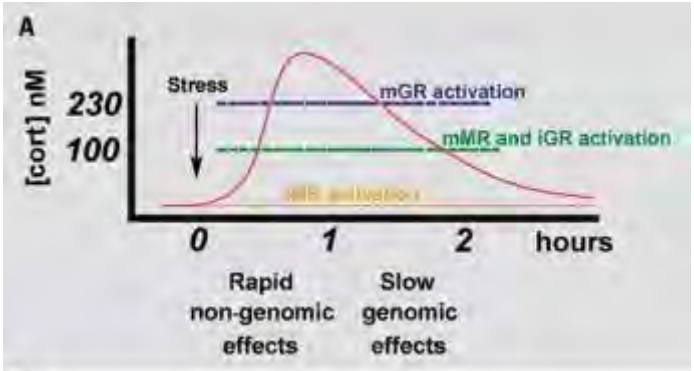
Also influence:

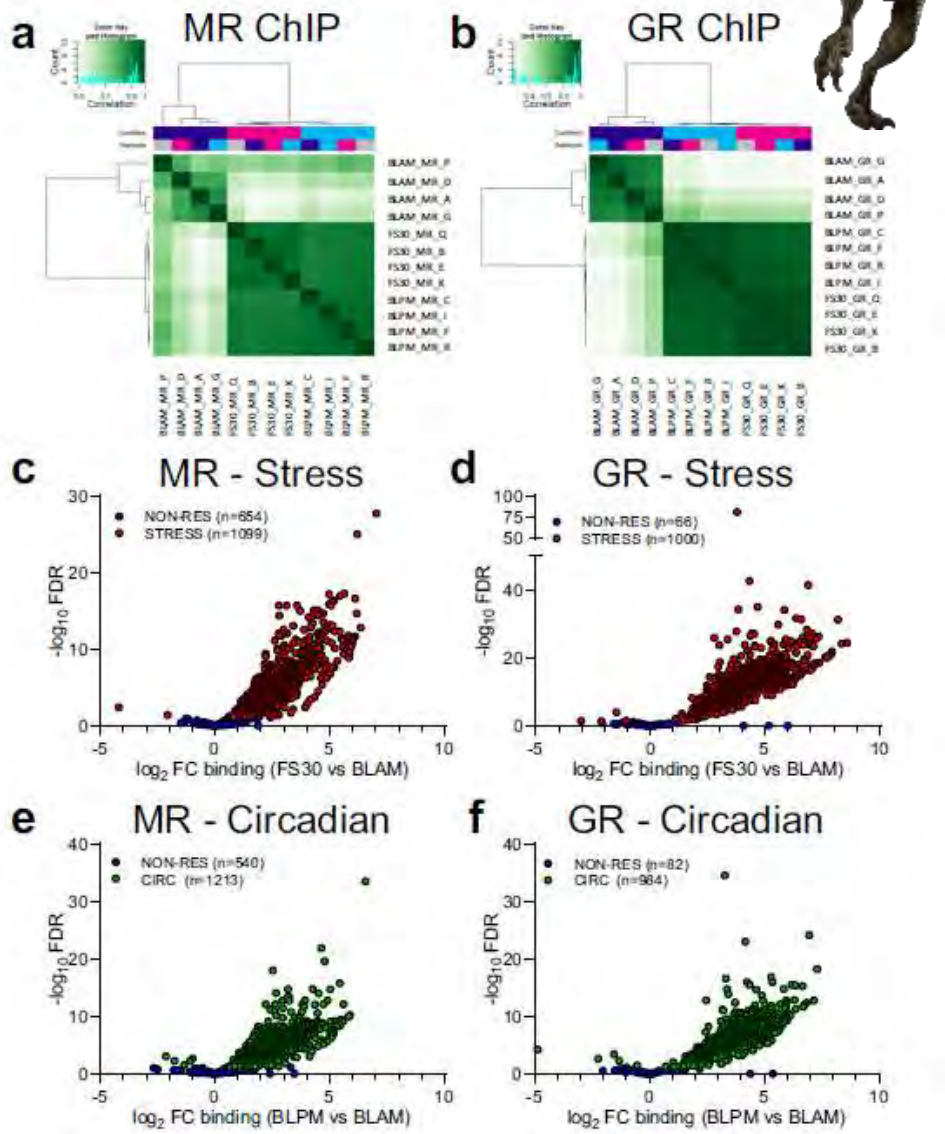
- Non verbal memory (recall)
- Selective attention
- Working memory
- Executive functions

Healthy subjects; cortisol IV infusion, memory retrieval testing shorter than 15 min, one week after learning

Belanoff et al., 2001; JPR; Shilling et al., 2013, PNEI

Corticosteroids: effect on neuroplasticity

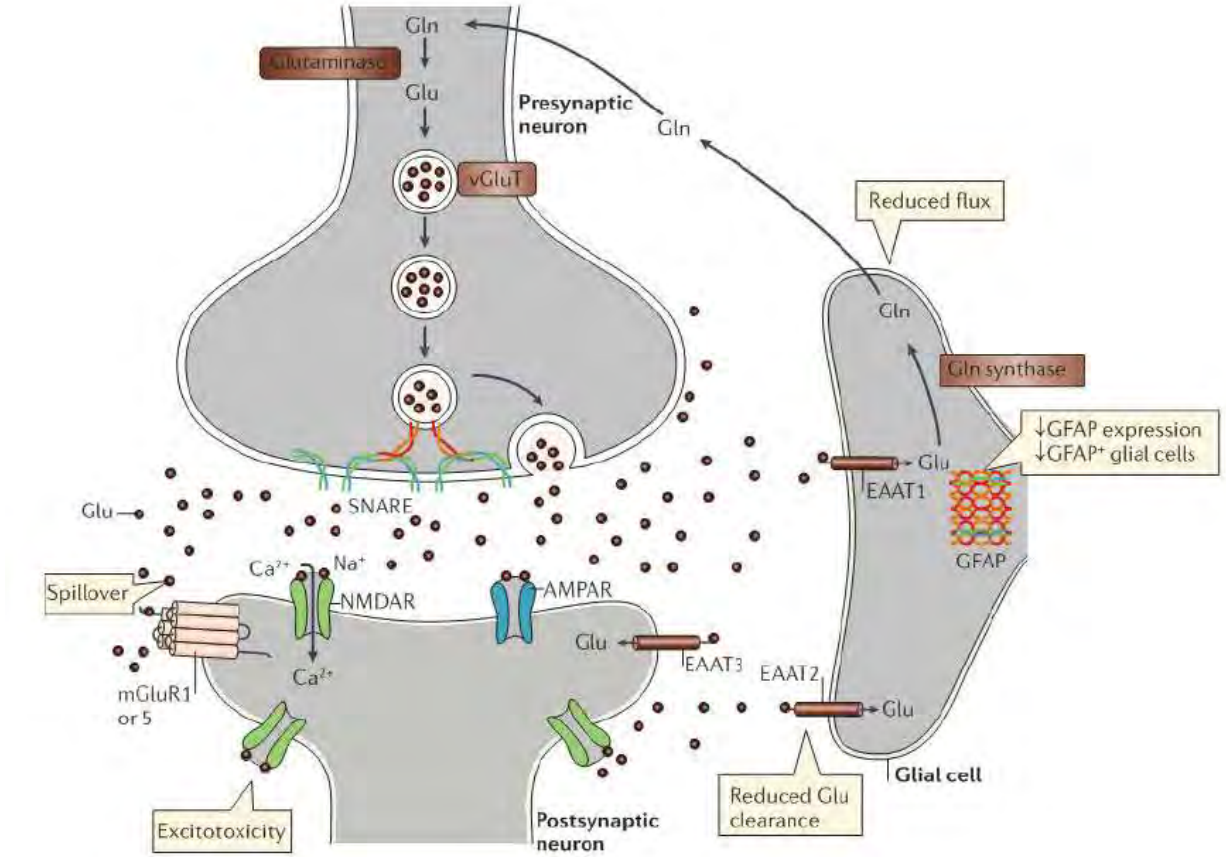


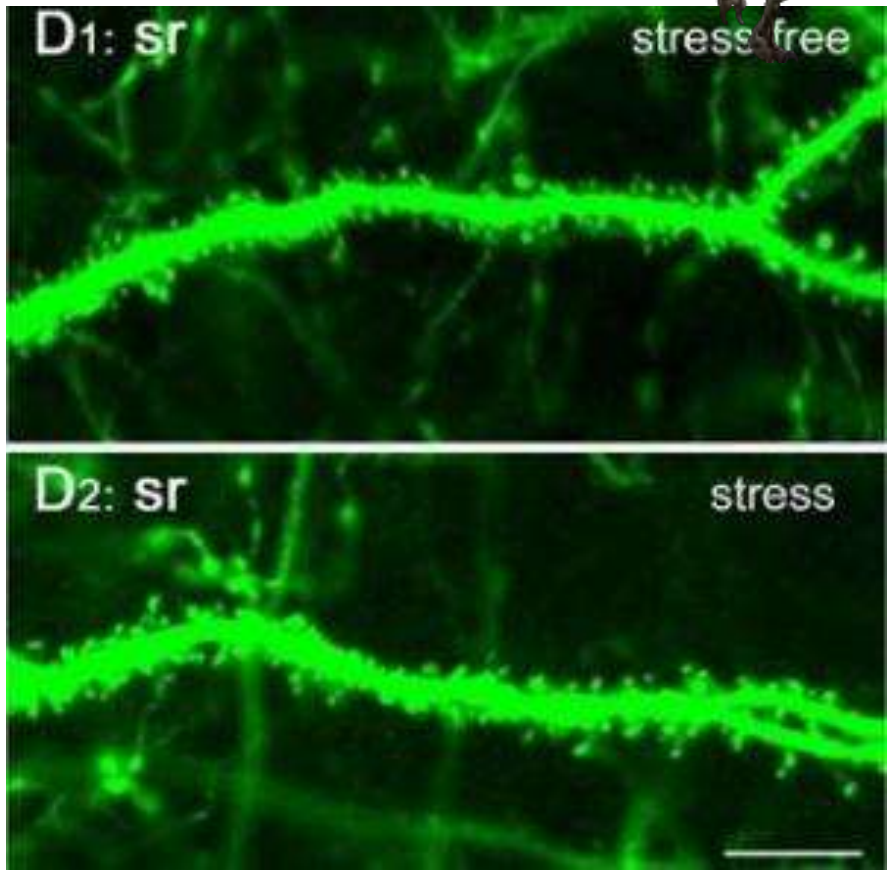


inverted u-shape relationship with LPT and general plasticity
MR and GR regulate genes involved in synaptic/ neuro-plasticity, cell morphology and development, behavior, and neuropsychiatric disorders

Maggio and Segal, **Front Cell Neurosci, 2012;** Mifsud et al., Nat Neurosci 2021

Glucocorticoid cascade hypothesis
(Sapolsky et al,1986)





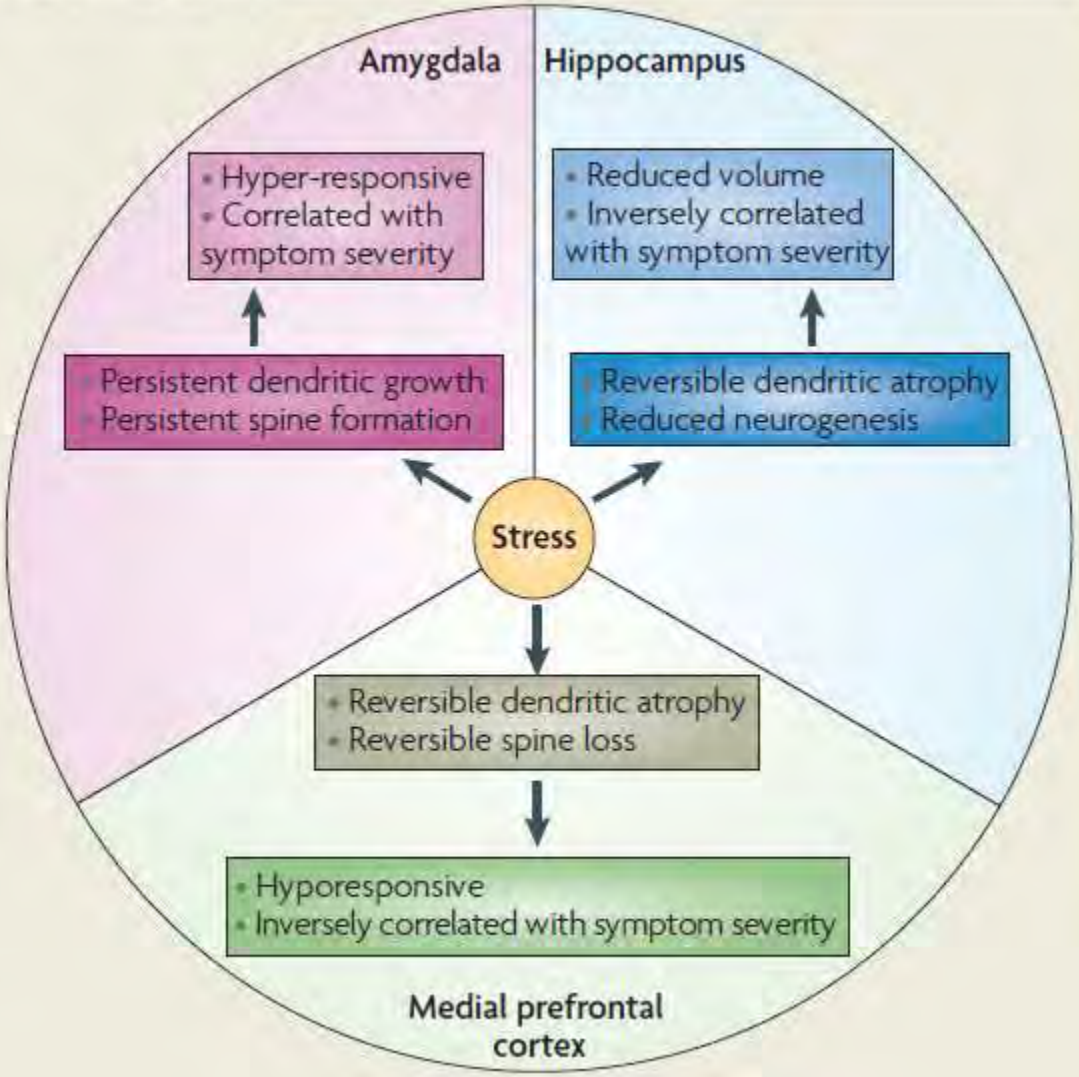
Chronic stress → GC-mediated enhanced glutamate transmission → retraction and simplification of dendritic spines → loss of neurons in Hippocampus

Hippocampal damage → HPA disinhibition → Hippocampal damage…

HPA axis: allostasis

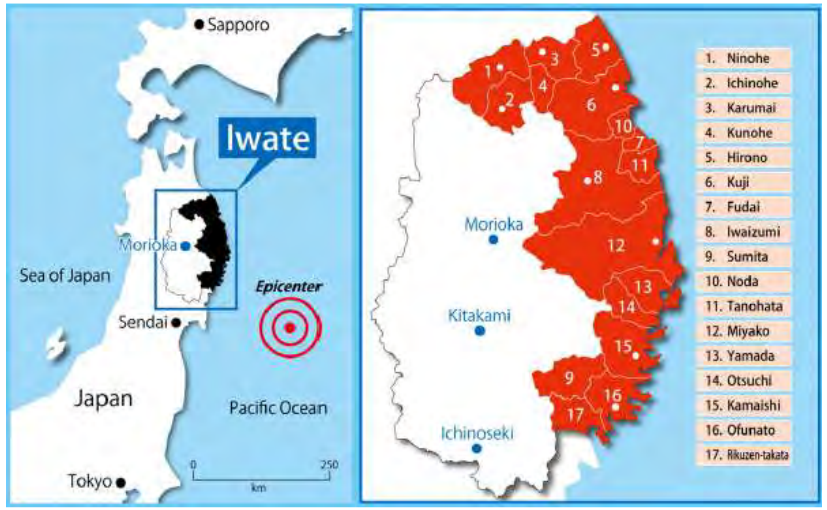
Box 1 | **Structural changes in interconnected brain regions**

Repeated stress of the type that causes remodelling of neurons and connections in the amygdala produces concurrent neuronal remodelling in the prefrontal cortex and hippocampus (see the figure), two structures that regulate the activity of the hypothalamus-pituitary-adrenal axis[117]. These changes include shrinkage of dendrites and a reduction of spine density in medial prefrontal cortex neurons and, in the hippocampus, shrinkage of dendrites in CA3 pyramidal neurons and dentate gyrus granule neurons. Chronic stress also decreases neurogenesis and neuron number in the dentate gyrus. However, dendritic branching in the orbitofrontal cortex increases as a result of chronic stress. For the most part, these stress-induced changes in the hippocampus and medial prefrontal cortex are reversible over time, at least in the animal models that have been investigated so far. As these brain regions are interconnected, it is likely that the structural remodelling in one region will influence the functions of other brain regions.



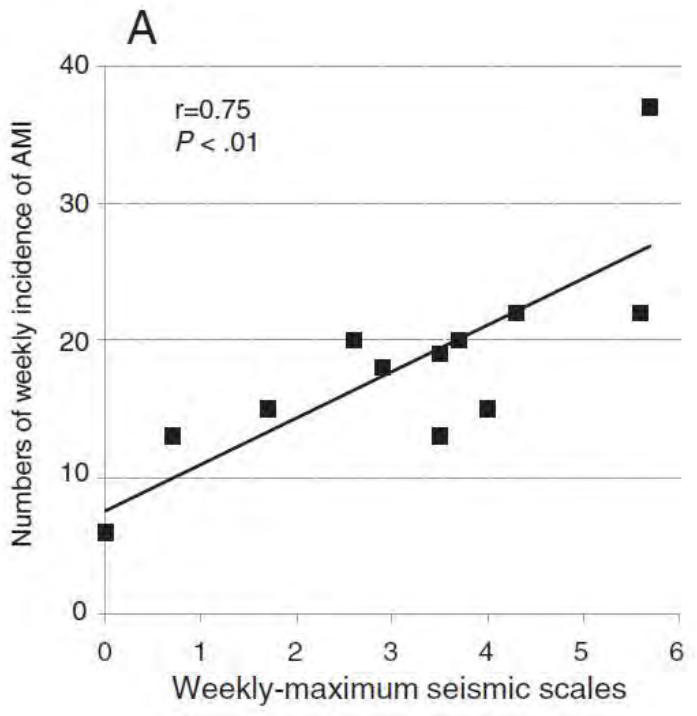
McEwen et al., NATuRE REvIEWS | **NeuroscieNce, 2009**

Autonomic Nervous System (ANS)



Relative risk of AMI was 2.03 (95% CI 1.55-2.66) for the 4-week period after the disaster compared with the corresponding periods in the preceding years.

The incidence of AMI was positively correlated with the seismic scale of the earthquake (r=0.75, p < .01).



Tanaka et al., Am Heart J. 2015 Jun;169(6):861-9.

Autonomic Nervous System (ANS)

Takotsubo syndrome (1991)

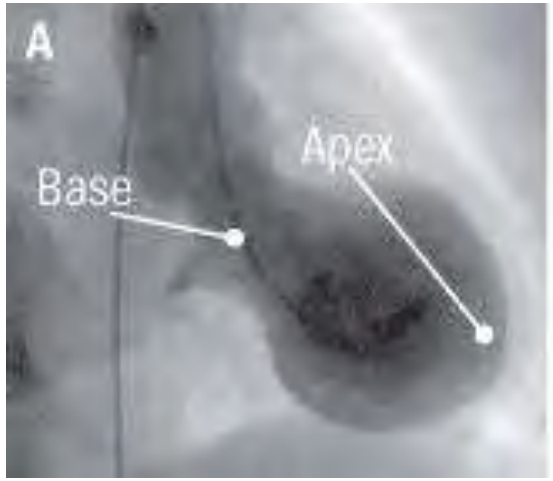
«Broken heart syndrome»; «Stress cardiomyopathy» after exposure to acute stressors (physical or psychological).

[Tako= octopus; Tsubo=basket]

Acute coronary syndrome + Ventricular ballooning of the left ventricular apex

→ 96% reversible; 4% MI / cardiac rupture

Wittstein et al., Heart Fail Clin, 2016

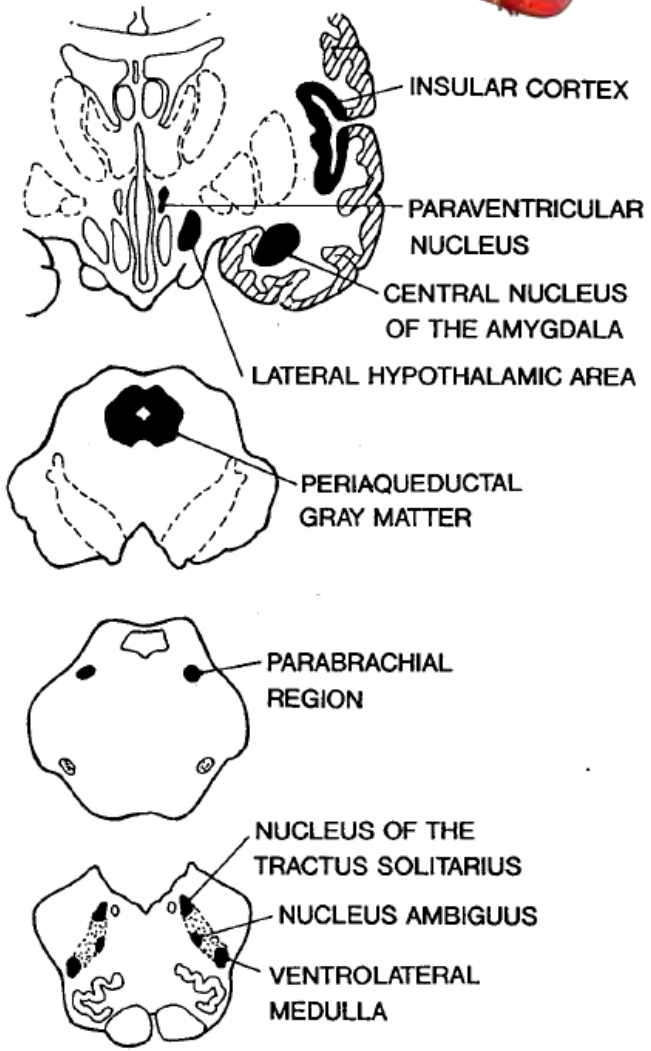


Autonomic Nervous System (ANS)

The Central Autonomic Network: Functional Organization. Dysfunction, and Perspective

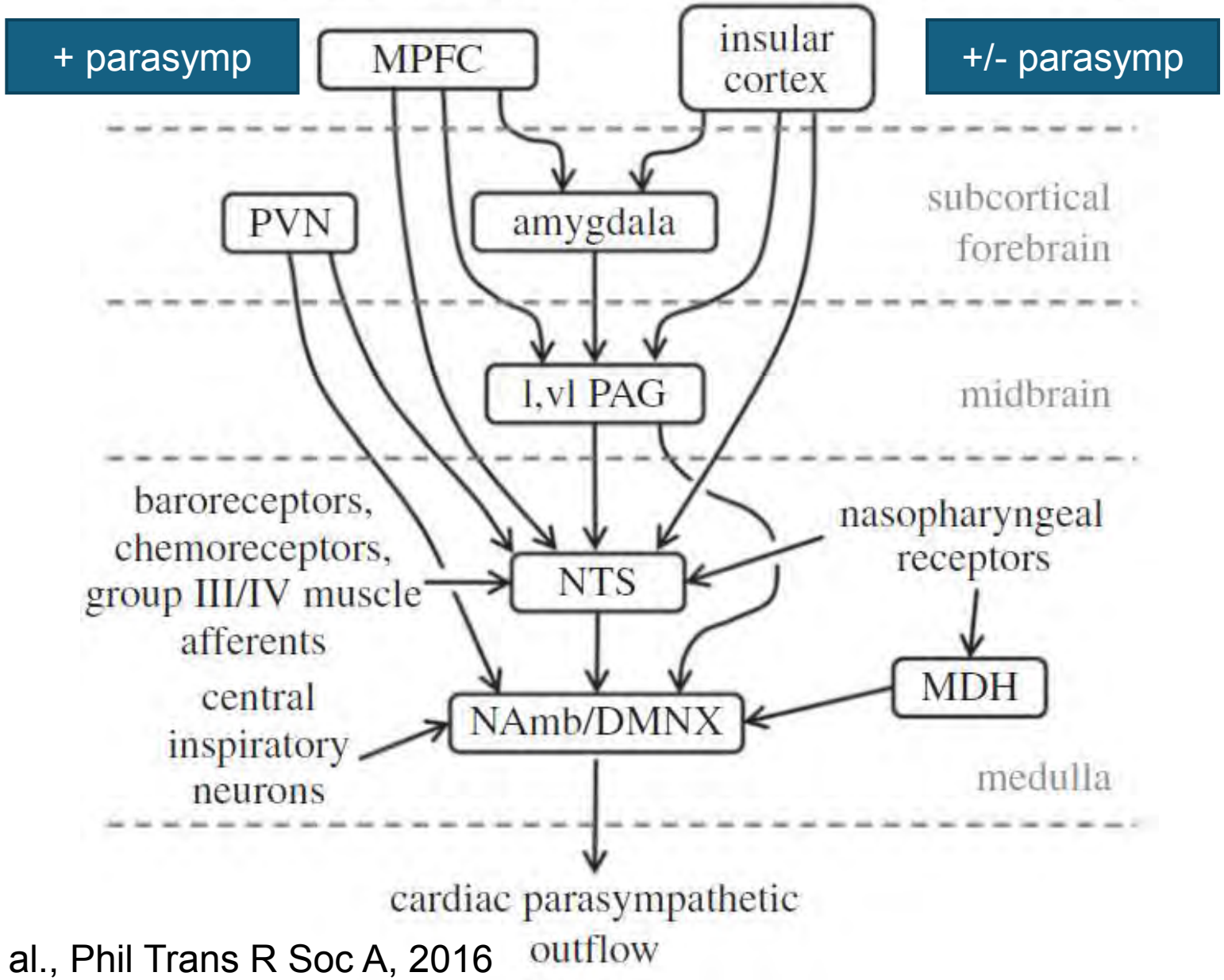
EDUARDO E. BENARROCH, M.D.

The central autonomic network (CAN) is an integral component of an internal regulation system through which the brain controls visceromotor, neuroendocrine, pain, and behavioral responses essential for survival. It includes the insular cortex, amygdala, hypothalamus, periaqueductal gray matter, parabrachial complex, nucleus of the tractus solitarius, and ventrolateral medulla.



Mayo Clin Proc 1993

Autonomic Nervous System (ANS)



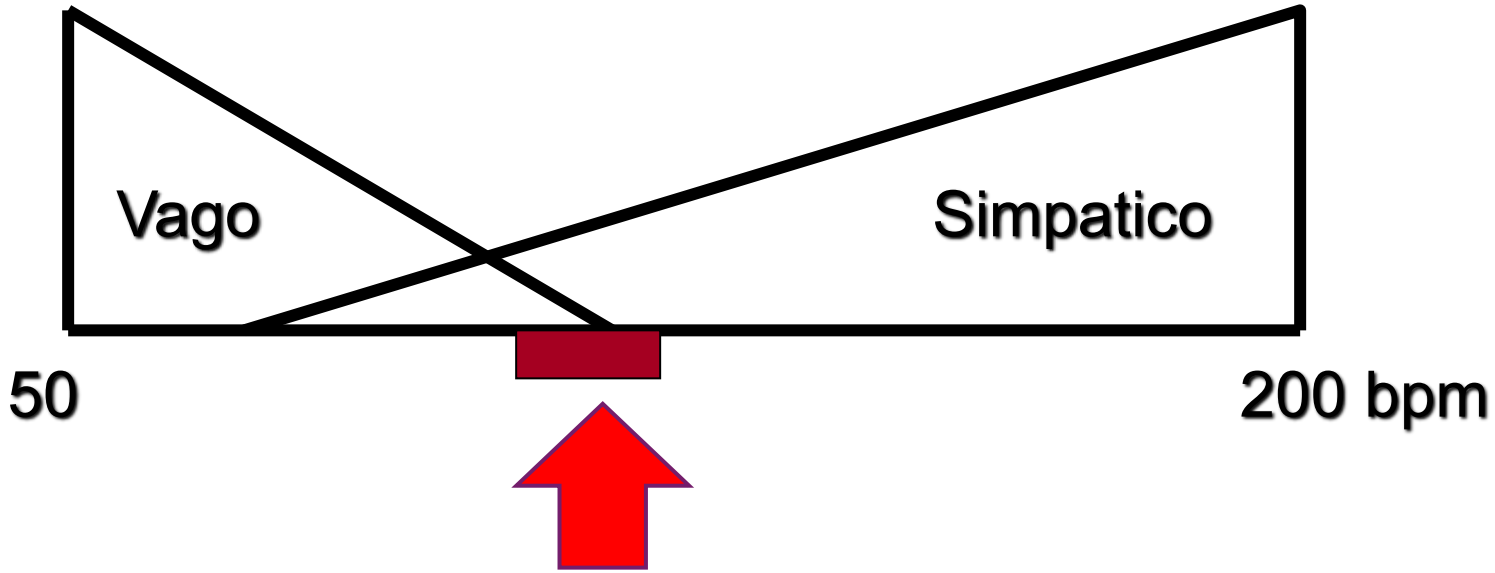
parasympathetic regulation

Silvani et al., Phil Trans R Soc A, 2016

Autonomic Nervous System (ANS)

Bilancia simpatovagale

Frequenza intrinseca NSA 100-110 BPM
"tono vagale": ca. 72 BPM – **riflesso barocettivo, Bainbridge**



Altri fattori che influenzano attività cardiaca

CATECOLAMINE CIRCOLANTI Ormoni tiroidei, cortisolo,
Concentrazione salina nel plasma (es. K+), Ipossia cellulare
→ depolarizzazione della membrana, farmaci

Heart Rate Variability (HRV)

REVIEW ARTICLE
published: 30 September 2014
doi: 10.3389/fpsyg.2014.01040

A healthy heart is not a metronome: an integrative review of the heart's anatomy and heart rate variability

Fred Shaffer[1], Rollin McCraty[2] and Christopher L. Zerr[1]*

[1] Center for Applied Psychophysiology, Department of Psychology, Truman State University, Kirksville, MO, USA
[2] HeartMath Research Center, Institute of HeartMath, Boulder Creek, CA, USA

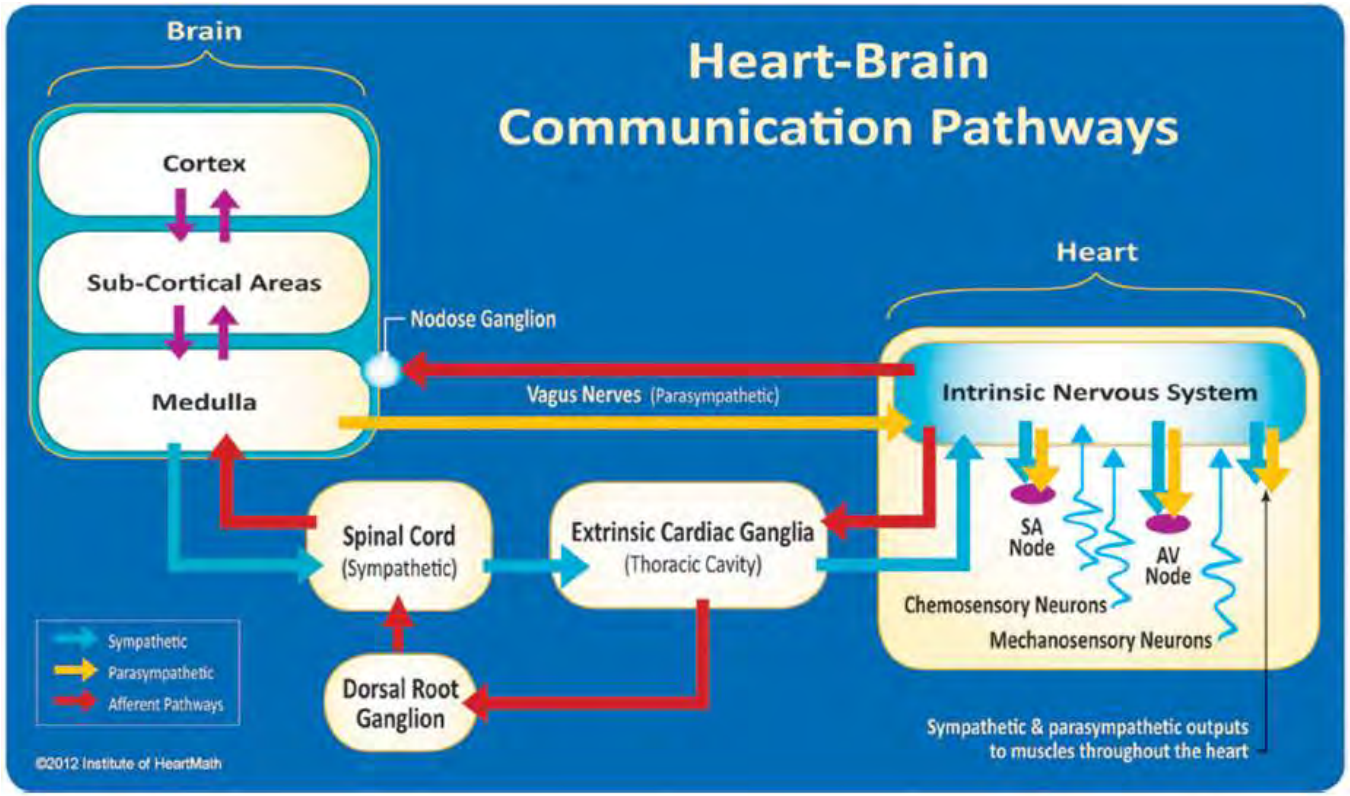
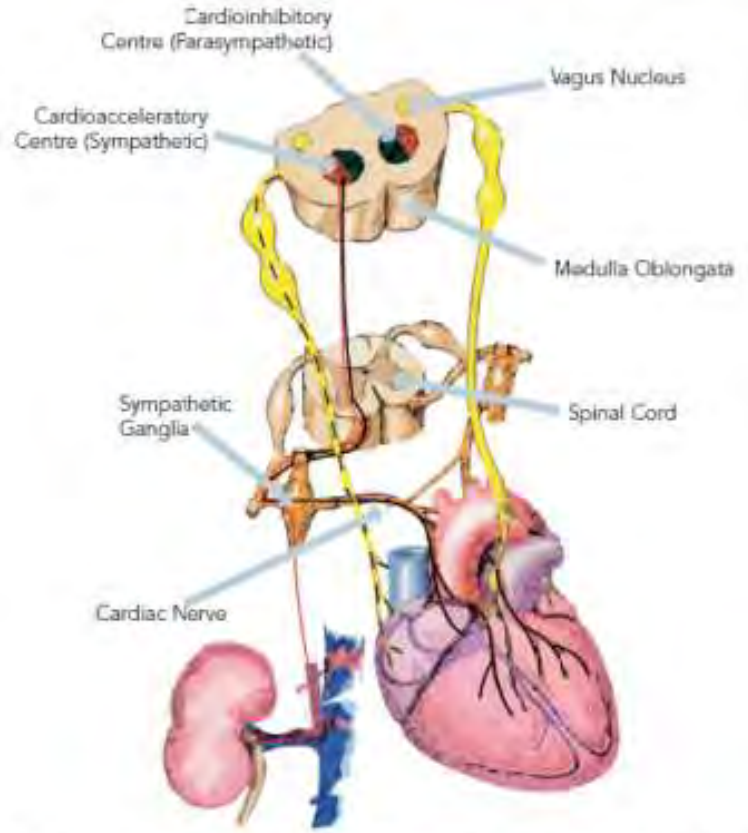


Figure 1: Schematic of Cardiovascular Aut[illegible]ontrol



Parasympathetic innervation exits the medullary centres via the vagus nerve, which then synapses with the intracardiac nervous system before providing post-ganglionic fibres to the myocardium. Sympathetic innervation exits the medulla and enters the spinal cord before exiting and traveling to the ganglia within the sympathetic chain. Post-ganglionic fibres travel along the major vessels prior to entering the myocardium. Sympathetic innervation also continues along the major vessels to the kidneys, supplying renal sympathetic innervation.

Activation of the CAN

Stress/arousal: orienting response with activation of both para- and sympathetic response.
Main center: AMI, dorsomedial hypothalamus (DMH) projection to raphe/RVMM

Physical exercise: progressive, ordered withdrawal of parasympathetic activity. Modulated by descending voluntary motor projections, baroceptor and other reflexes,
Main center: NTS, RVLM

Silvani et al., Phil Trans R Soc A, 2016

D-type personality

joint tendency towards negative affectivity (e.g. worry, irritability, gloom) and social inhibition (e.g. reticence and a lack of self-assurance).

Significant association of type D personality and hard endpoints (odds ratio (OR) of 2.28 (95% CI [1.43–3.62]), HR of 2.24 (95% CI [1.37–3.66]). The OR decreased over time (OR 5.02 to OR 1.54). There was no association in congestive heart failure patients.

Table 2
Summary of statistical data for individual analyses

Construct	*k*	*n* (Type-D)	*n* (non-Type-D)	OR	*d*	*Z*	*P*	*Q*	*P*(*Q*)	I^2
MACE	7	759	2144	3.16			<.001	4.35	.63	0%
QOL	5	393	870		-1.0	-3.66	<.001	58.37	<.001	93.15%
QOL (dichotomous data)	2	188	333	3.48			<.001	.21	.65	0%
QOL (continuous data)	3	205	537		-1.23	2.61	.01	51.88	<.001	96.15%
sTNFR-1, sTNFR-2, TNF-α, IL-10, IL-1ra, IL-6	3	105	200		-1.24	1.82	.07	49.11	<.001	95.93%

Versteeg et al., Eur J Prev Cardiol. 2012; Grande et al., Ann Behav Med. 2012

D-type personality

Risk factors tend to aggregate in clusters; higher neuroticism, hostility, cynicism, **Type D personality**, or anger are often associated with

- unhealthy diet
- Reduced physical activity
- smoking
- alcohol use
- Older age
- Lower socioeconomic status (SES
- Male gender

increased prevalence of metabolic syndrome

Framingham Heart Study

A Project of the National Heart, Lung, and Blood Institute and Boston University

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- Atrial Fibrillation
- Cardiovascular Disease
  - Cardiovascular Disease (10-year risk)
  - Cardiovascular Disease (30-year risk)
- Congestive Heart Failure
- Coronary Heart Disease
- Diabetes
- Hypertension
- Intermittent Claudication
- Stroke

Cardiovascular Disease (10-year risk)

(based on D'Agostino, Vasan, Pencina, Wolf, Cobain, Massaro, Profile for Use in Primary Care: The Framingham Heart Study')

Outcome

CVD (coronary death, myocardial infarction, coronary insufficien stroke, transient ischemic attack, peripheral artery disease, hea

Duration of follow-up

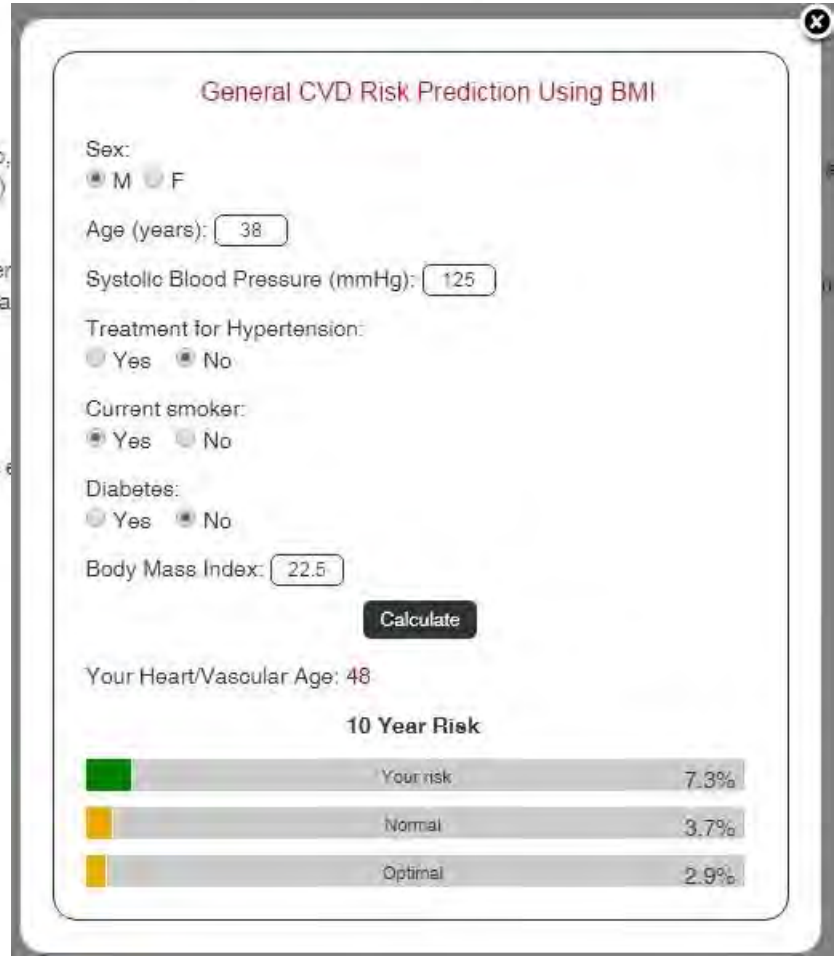
Maximum of 12 years, 10-year risk prediction

Population of interest

Individuals 30 to 74 years old and without CVD at the baseline e

Predictors

- Age
- Diabetes
- Smoking
- Treated and untreated Systolic Blood Pressure
- Total cholesterol
- HDL cholesterol



Outcomes:
CVD (coronary death, myocardial infarction, coronary insufficiency, angina, ischemic stroke, hemorrhagic stroke, TIA, peripheral artery disease, heart failure)

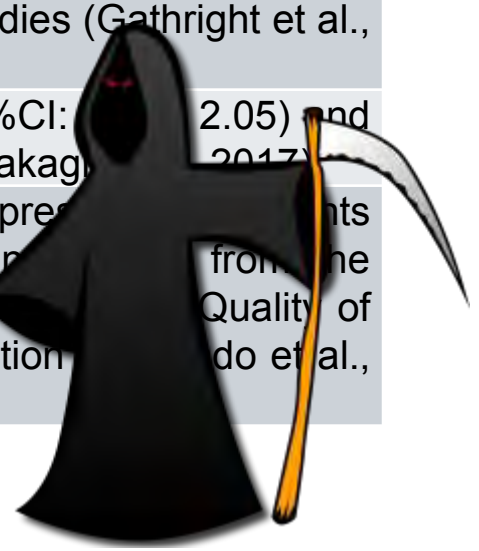
D'agostino et al., Circulation, 2008

https://www.framinghamheartstudy.org/risk-functions/cardiovascular-disease/10-year-risk.php#

Autonomic Nervous System (ANS)

Depression and cardiovascular mortality

Cardiovascular Mortality	Association between depression and mortality
Coronary Heart Disease	Depression was associated with increased risk of myocardial infarction-related (HR=1.31; 95%CI: 1.09 – 1.57) and coronary death (HR=1.36; 95%CI: 1.14 – 1.63). 19 prospective studies (Wu and Kling, 2016). Quality of evidences appraised as “highly suggestive” (Machado et al., 2018)
Arrhythmias related mortality	Depression was associated with increased risk of Sudden Cardiac Death (HR=1.62; 95%CI: 1.37–1.92), ventricular arrhythmias (HR=1.47; 95%CI: 1.23–1.76) recurrence of Atrial Fibrillation (HR=1.88; 95%CI: 1.54 – 2.30). 17 studies, of which 15 prospective (Shi et al., 2017)
Mortality in Heart Failure	Depression was associated with increased risk of all-cause mortality (HR=1.20; 95%CI: 1.10 – 1.31). Increased risk was driven by studies in participants older than 65. 14 prospective studies (Gathright et al., 2017). Quality of evidences appraised as “highly suggestive” (Machado et al., 2018)
Mortality after Cardiac Surgery	Perioperative depression was associated with increased risk of early (RR=1.44; 95%CI: 2.05) and late postoperative mortality (RR=1.44; 95%CI: 1.24 - 1.67). 16 prospective studies (Takag 2017)
Overall mortality	Depression was associated with increased risk of mortality relative to non-depre nts (RR=1.52, 95%CI: 1.45-1.59). Excess mortality risk was of similar magnitude in from he community vs. those with specific diseases. 293 prospective studies (Cuijpers et a Quality of evidence was however appraised as inadequate to support a direct causal association do et al., 2018; Miloyan and Fried, 2017)

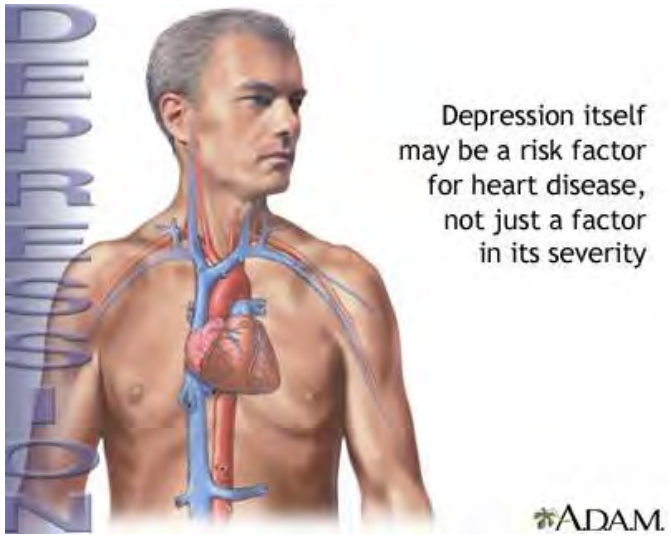


Belvederi Murri et al., Front Psych

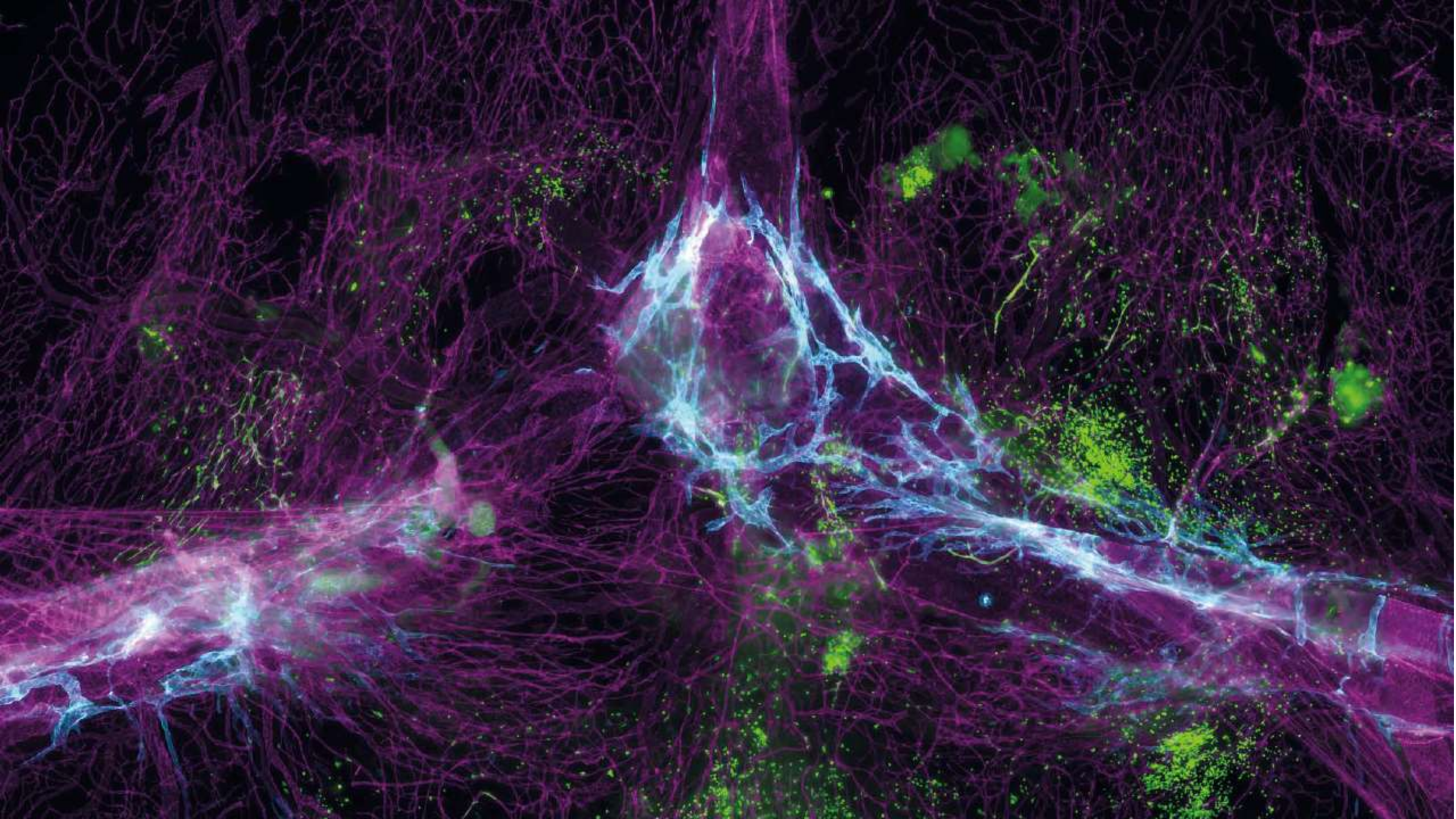
2010: Depressione Maggiore ufficialmente tra i FdR per CAD

The American Heart Association (AHA) elevates depression to the status of a risk factor for patients with acute coronary syndromes.

This statement is historic in that **it represents the first 'psychological' variable to be officially recognized by a major national health organization as a risk factor for vascular outcomes**

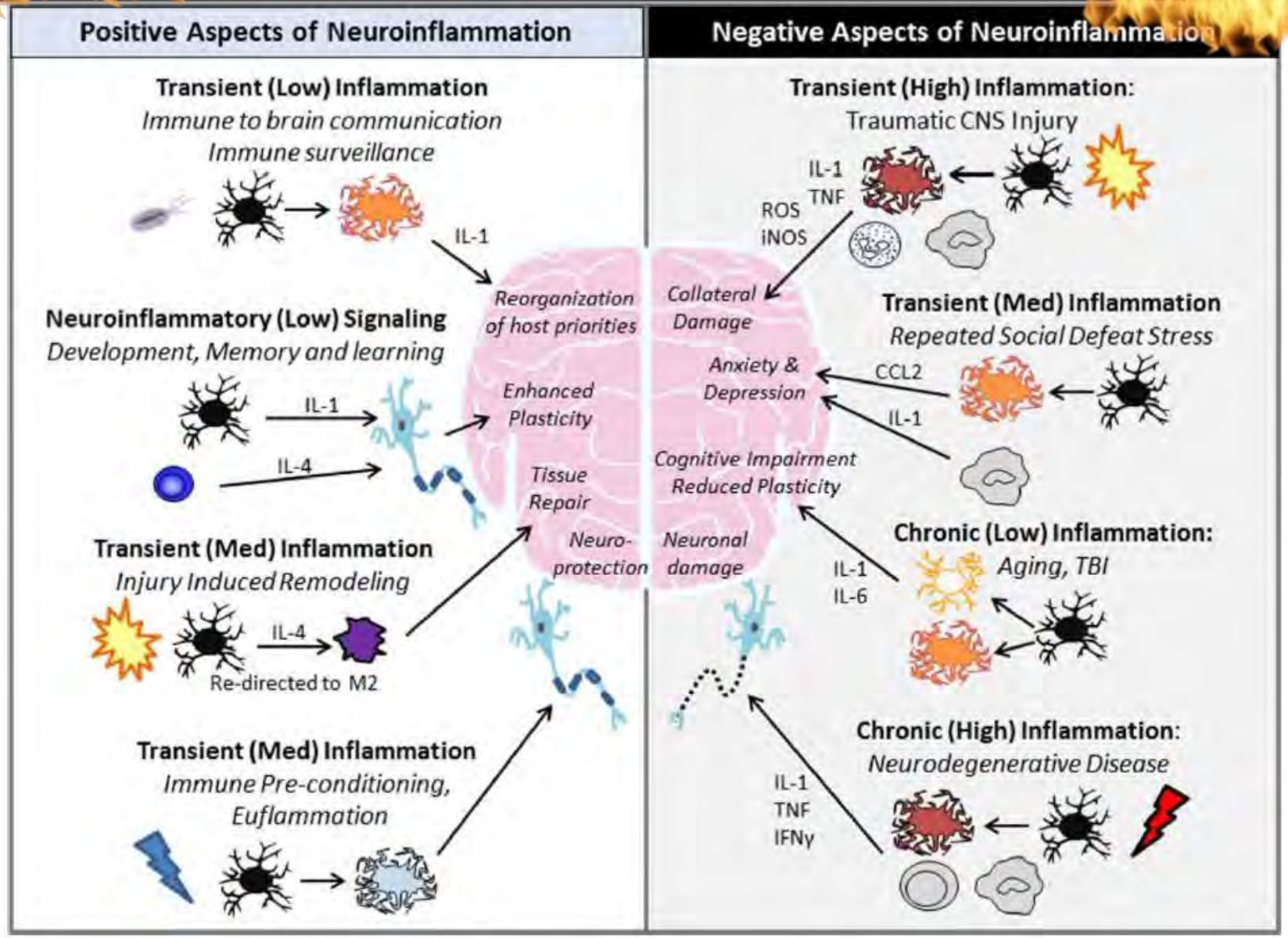


Global Burden of Disease Study 2010; Fiedorowski 2014



Neuroinflammation

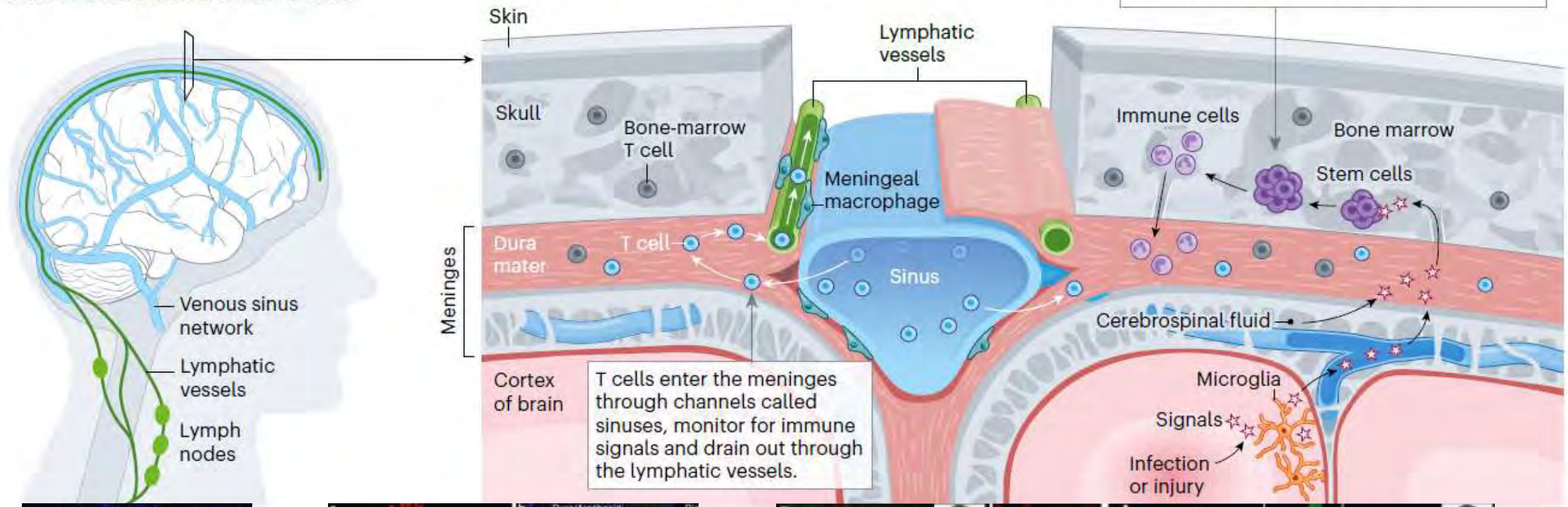
CNS infection
Stroke
Diseases
…

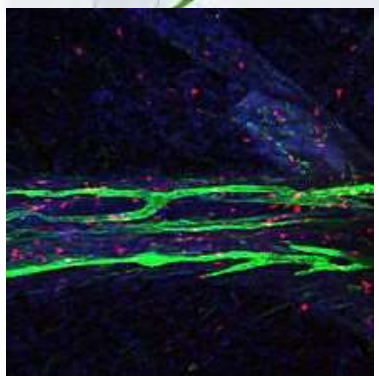


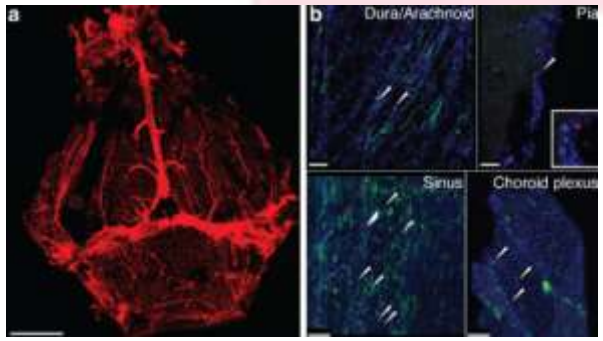
DiSabato et al. 2016

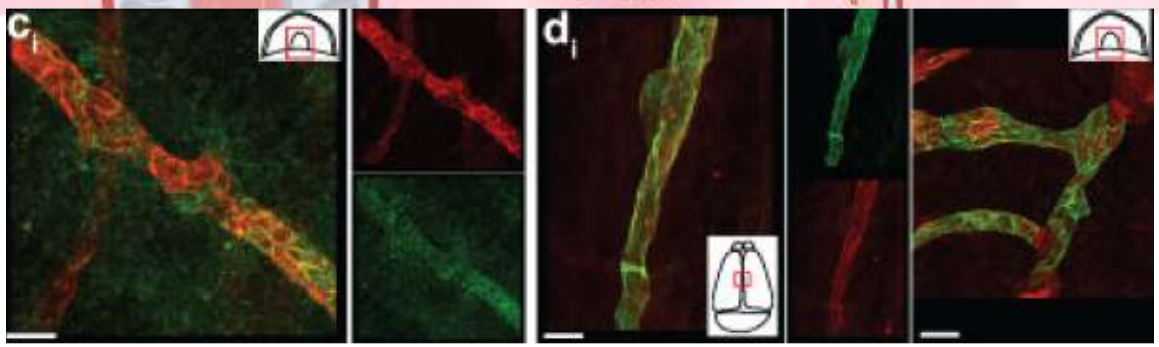
THE BRAIN'S IMMUNE DEFENCES

Long thought to be cut off from the body's immune system, the brain is now known to host its own immune cells while allowing others to circulate through its fluid-filled borders, the meninges. Cell types include microglia inside the brain and T cells and macrophages at the edges. Together, these help the healthy brain to function and defend it from disease.



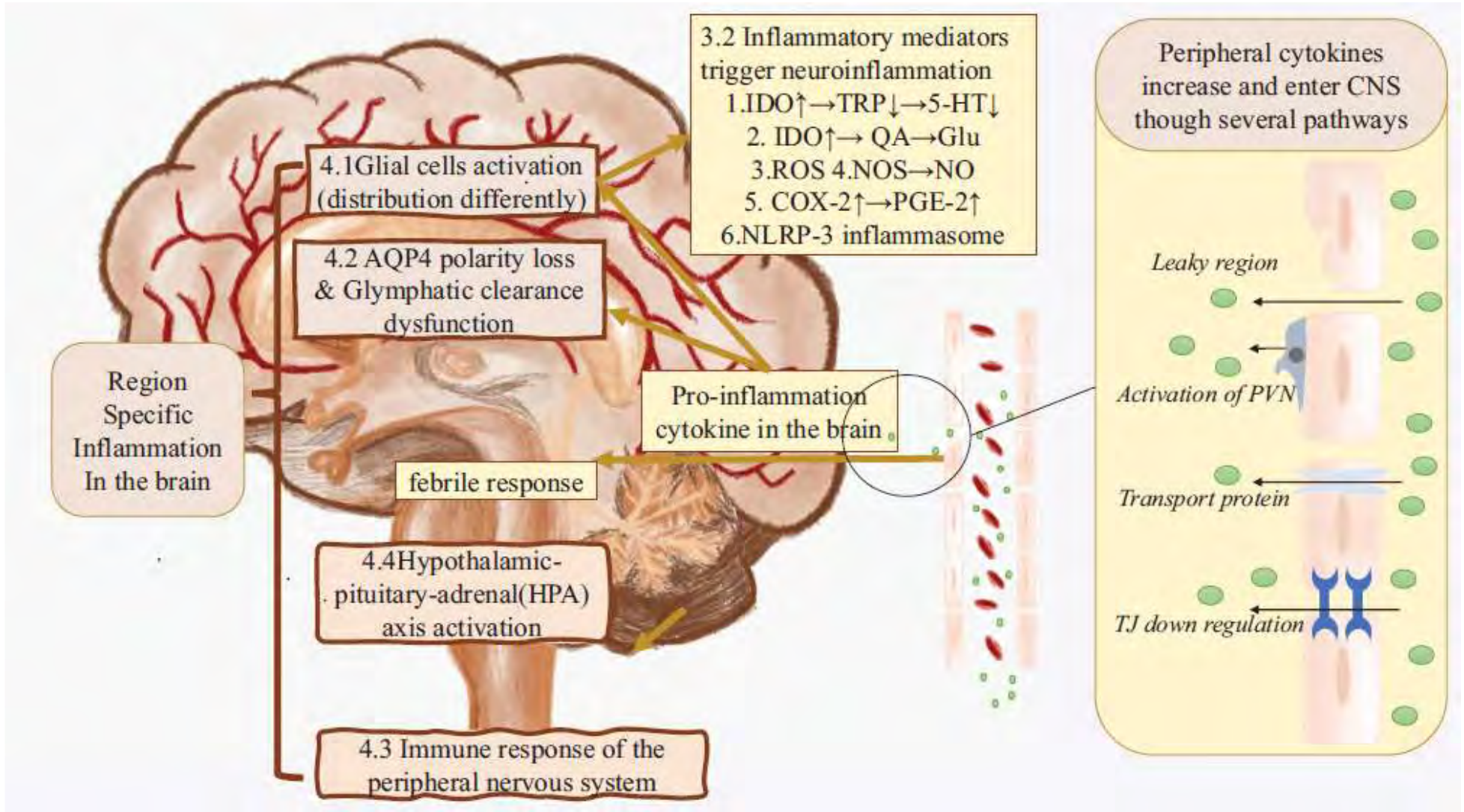






Louveau et al., Nature. 2015

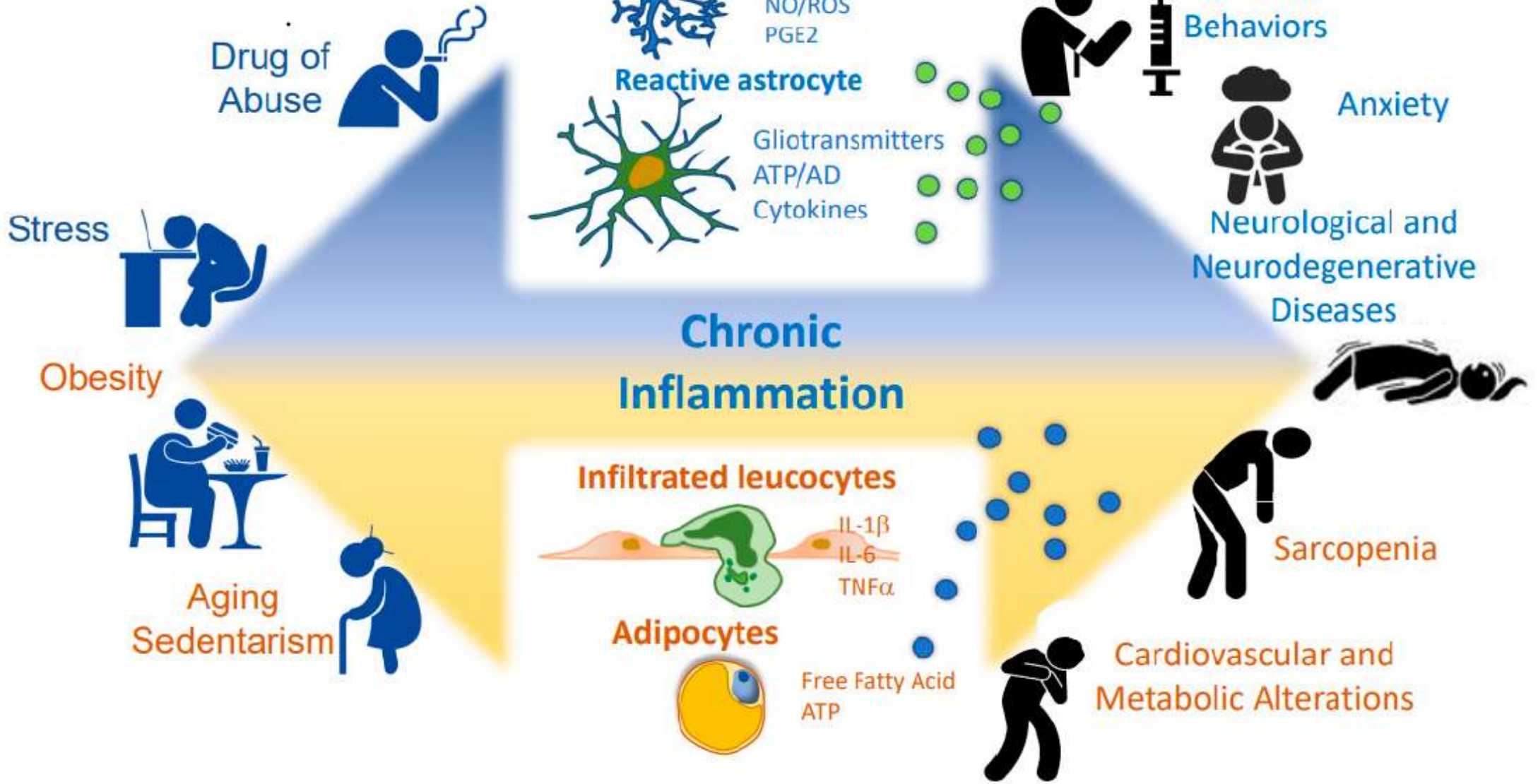
Peripheral and central inflammation



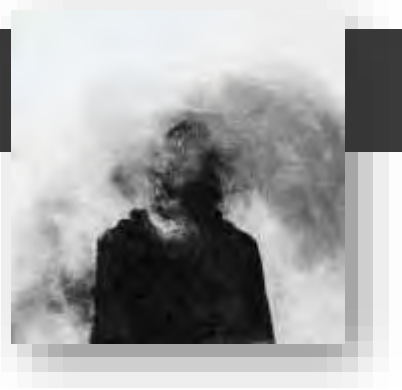
Sun Y, et al (2022) Front. Aging Neurosci

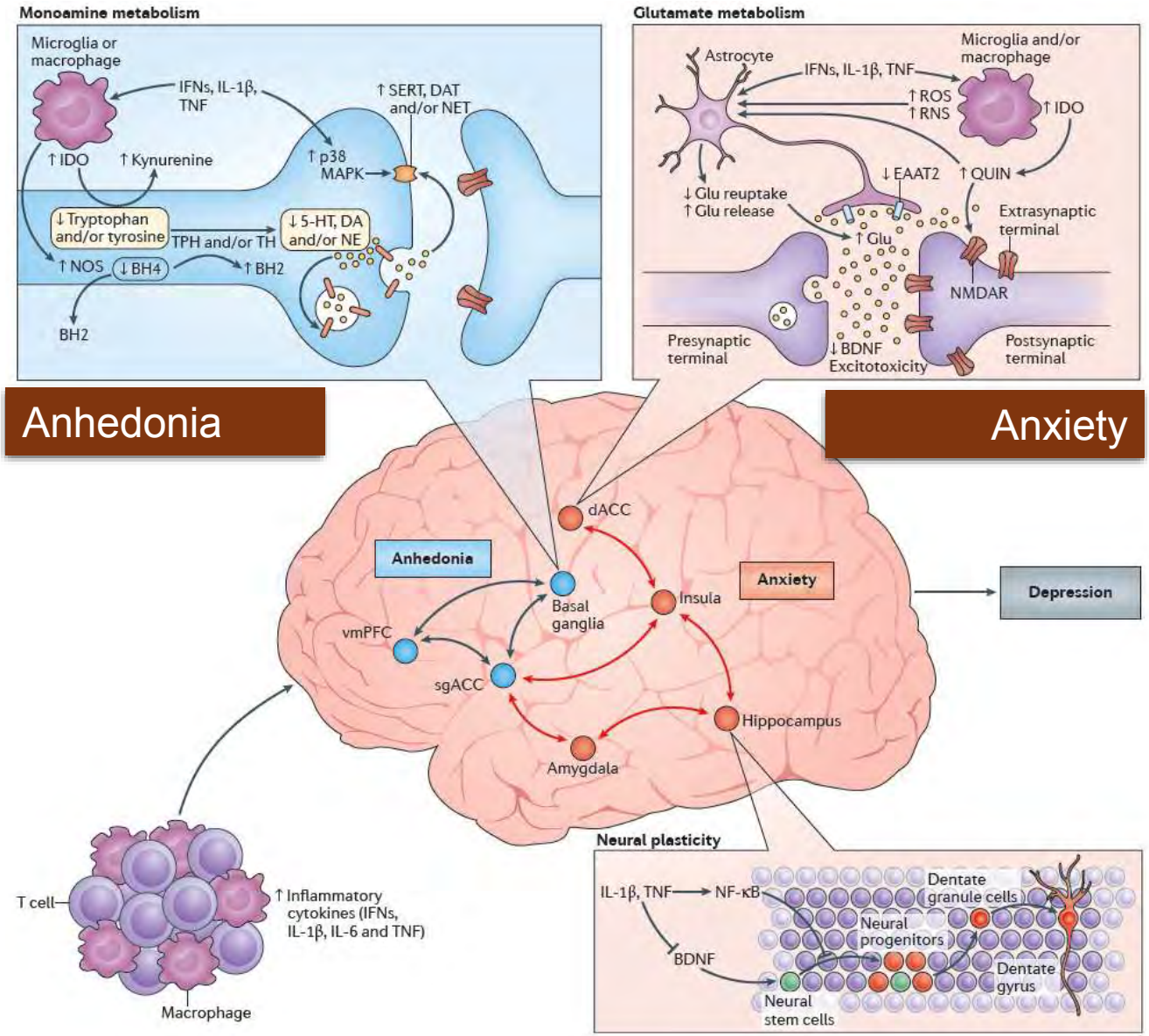
Inflammation From Peripheral Organs to the Brain: How Does Systemic Inflammation Cause Neuroinflammation?

Peripheral and central inflammation



Inflammation and neurotransmitters





Cytokine targets in the brain

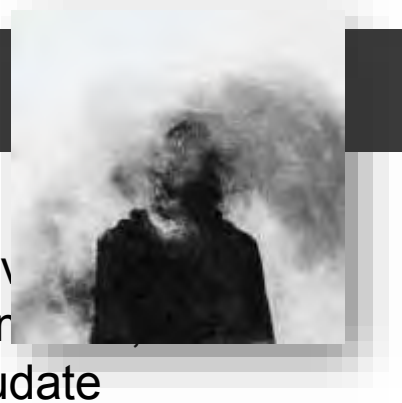
The inflammatory response → neurotransmitter systems → neurocircuits → behaviour (anhedonia, avoidance, alarm)

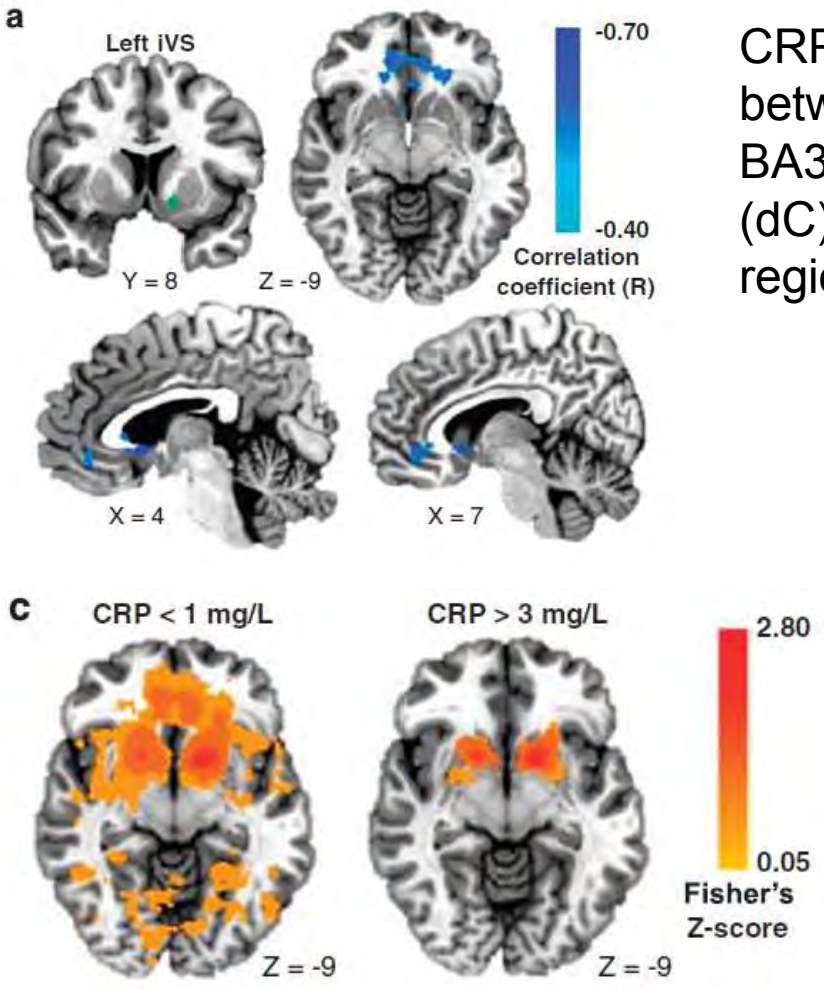
IFNs, IL-1β, TNF reduce the availability of **monoamines (5-HT, DA, NE)** by increasing transporters, reducing synthesis, decreasing precursors (IDO – QUIN - KIN).
Influence on NMDAR, BDNF and excitotoxicity.

Cytokine effects on neurotransmitter systems, especially DA, can inhibit several aspects of reward motivation and anhedonia in basal ganglia, vmPFC, sgACC and dACC -ativating circuits regulating anxiety, arousal, (amygdala, hippocampus, dACC and insula).

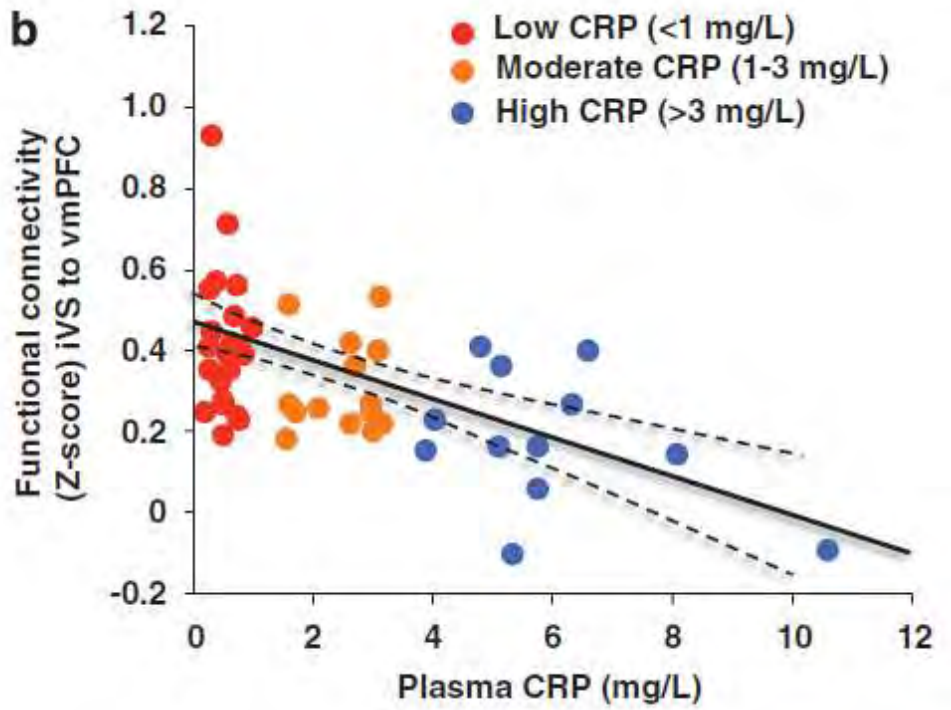
Miller and Raison Nat Rev Immunol 2016

Inflammation and neurotransmitters



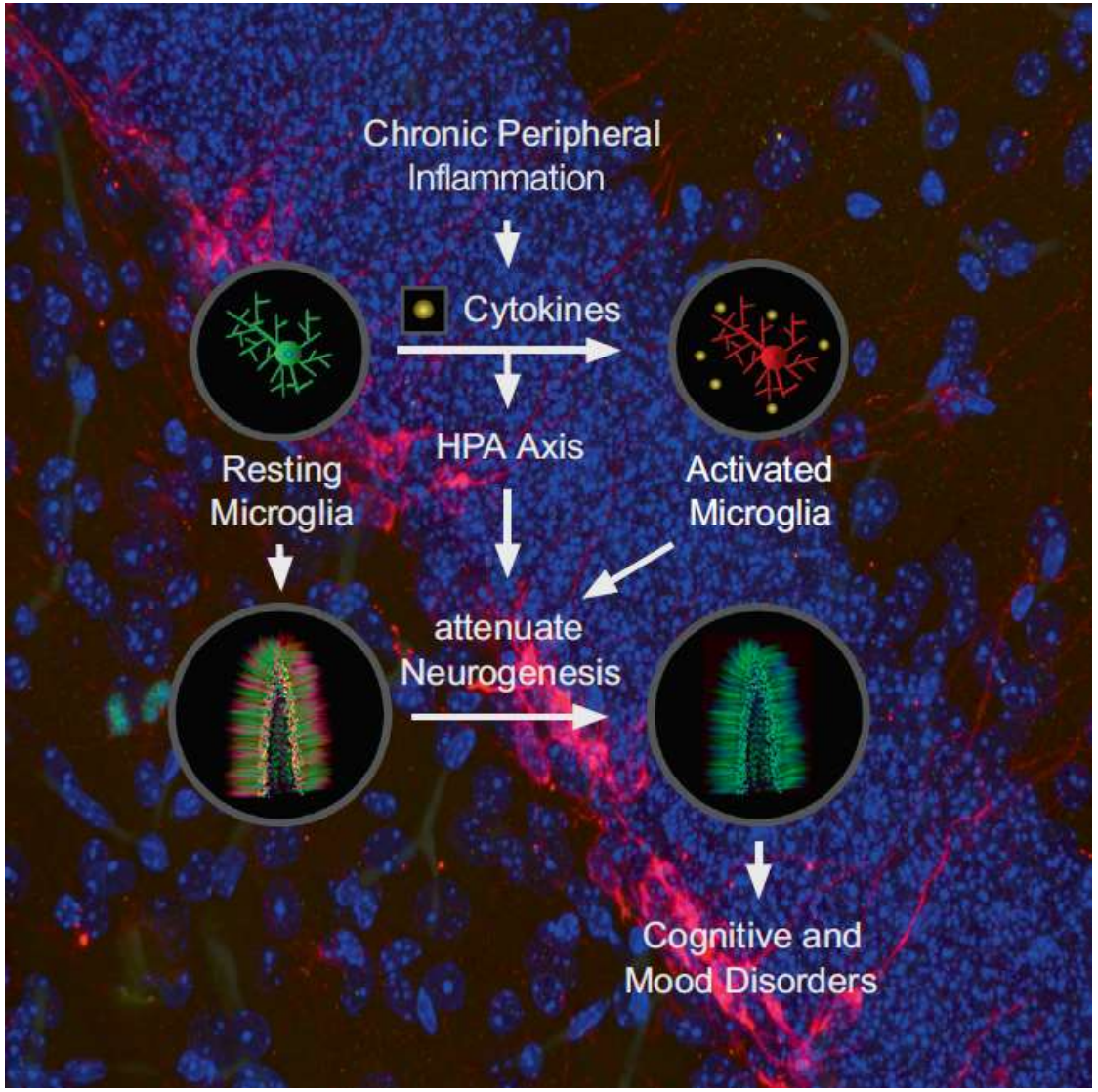


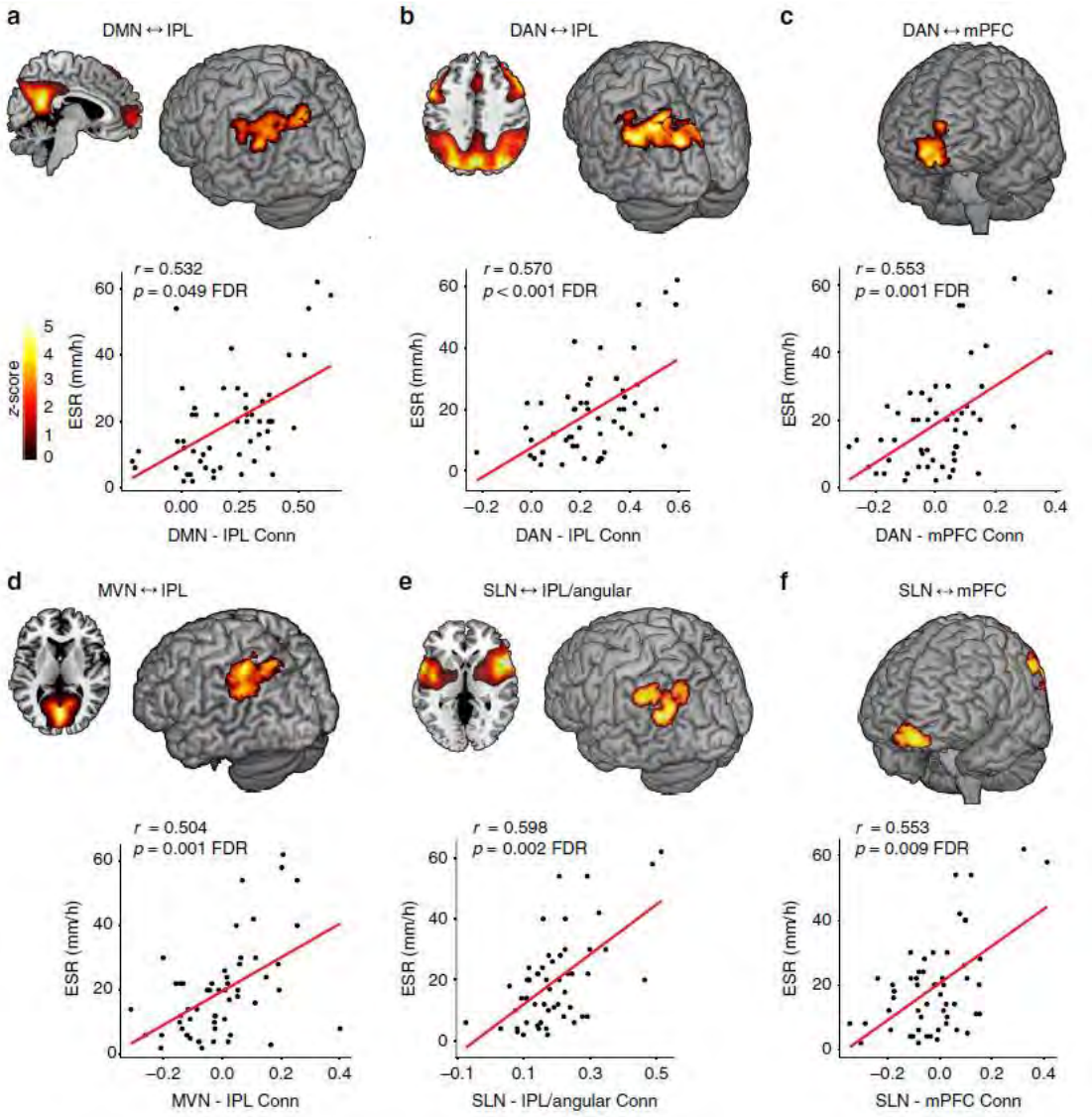
CRP negatively associated with functional connectiv
between ventral striatum (iVS) (green seed) and (vr
BA32), between putamen (vrP, dcP) and dorsal caudate (dC) subdivisions of the striatum and other cortical brain regions in depressed subjects



Felger et al., Molecular Psychiatry (2016)

Inflammation, neurotoxicity and disconnectivity

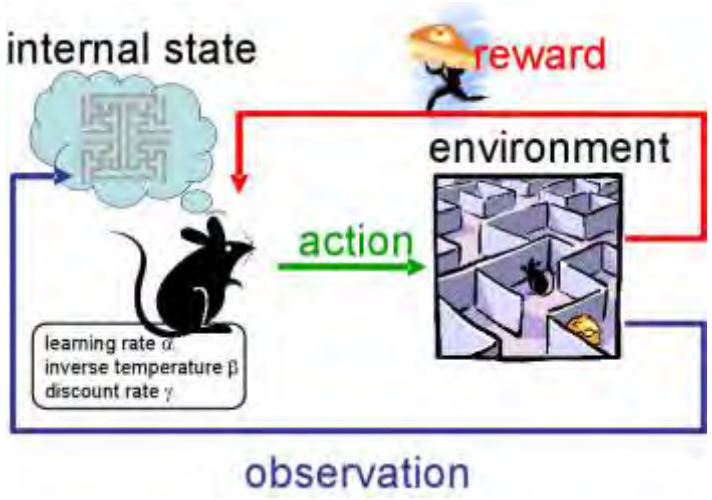


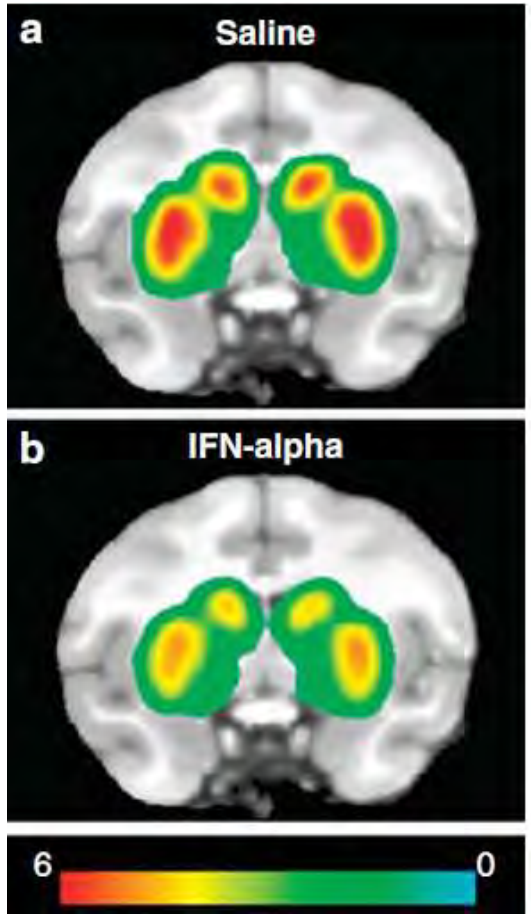


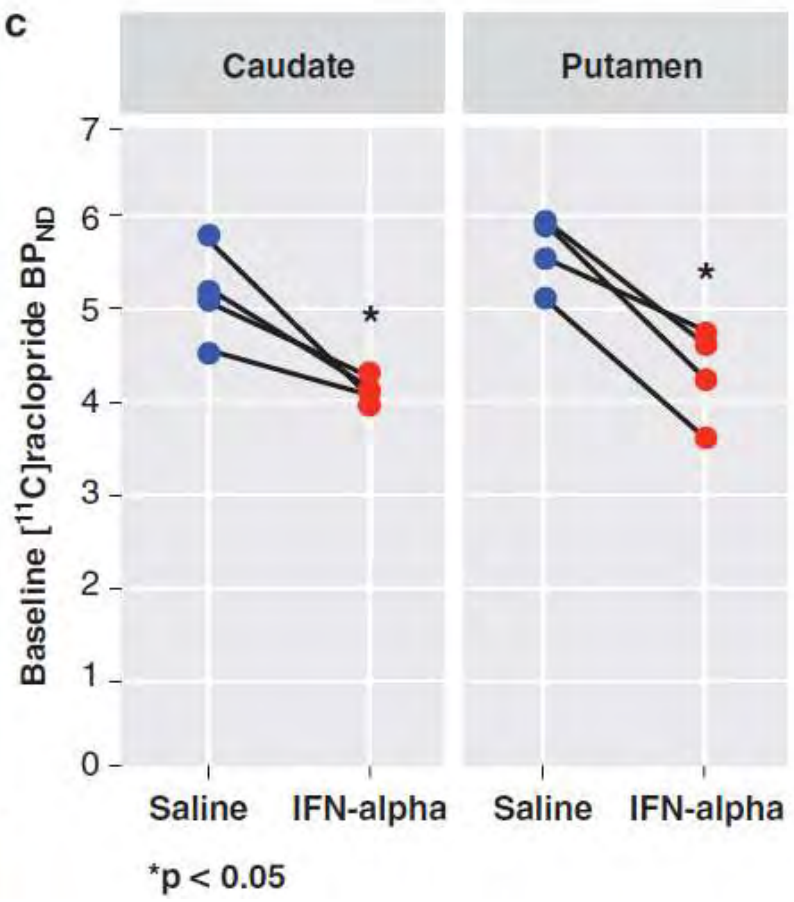
Chesnokova et al., Brain, Behavior, and Immunity 58 (2016); Schrepf et al., Nat Comm 2019

Neuroinflammation and dopamine

4 weeks of Interferon-α Decreases Dopamine 2 Receptor Binding and Striatal Dopamine Release in Association with Anhedonia-Like Behavior in Nonhuman Primates

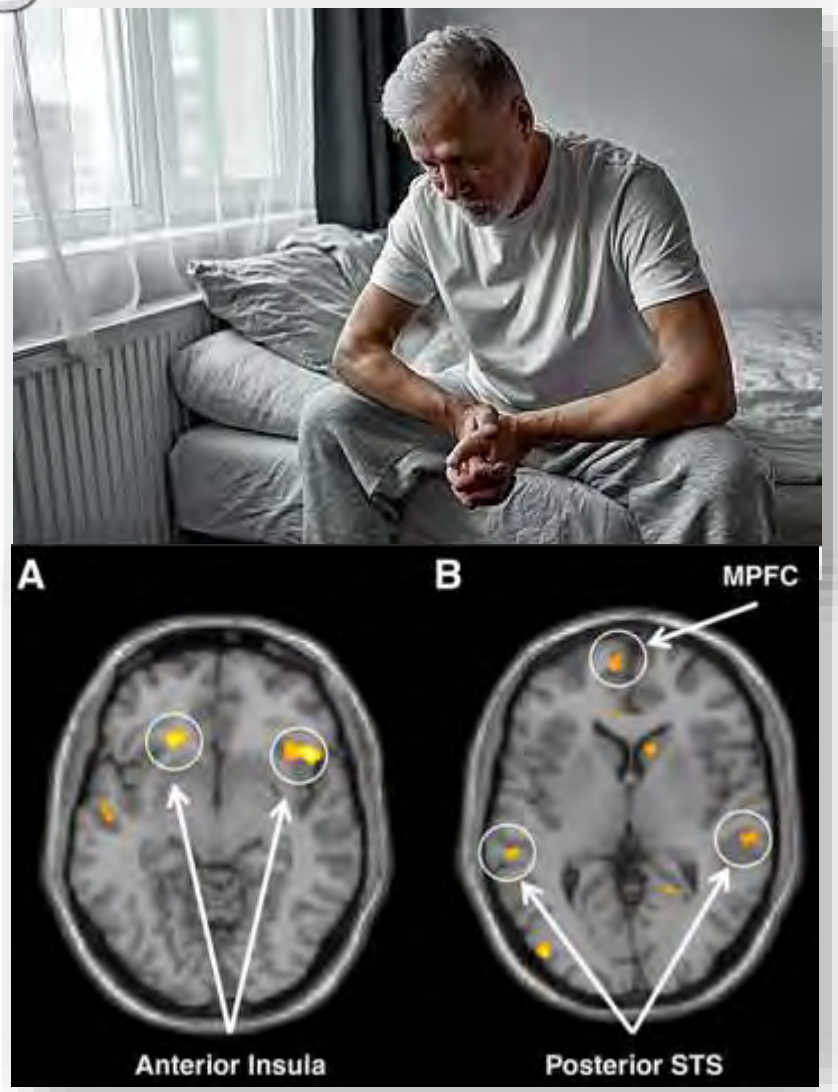






Felger et al., Neuropsychopharmacology (2013)

Sickness Behaviour

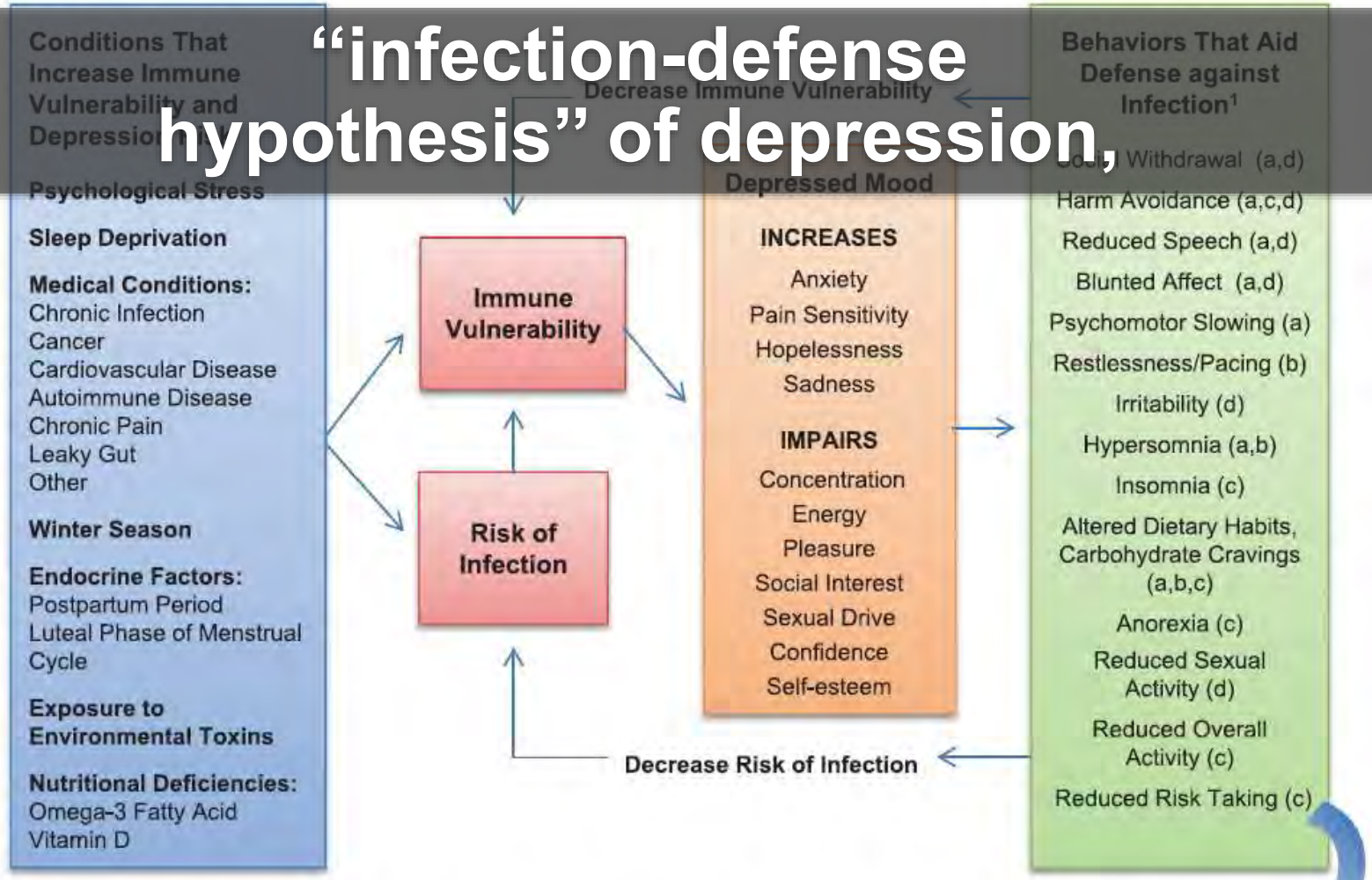


LPS → Proinflammatory Cytokines (IFN α)

- Fatigue
- Loss of drive and appetite
- Sleep disturbance
- Social withdrawal
- Decreased libido
- Depressed mood
- General malaise
- Aches and pains
- Cognitive impairment

Mondelli et al., Lancet Psychiatry 2017

"infection-defense hypothesis" of depression,



How Depression-Related Behaviors Decrease Risk of Infection and Immune Vulnerability:

a. Conserve or enhance metabolic resources for use by the immune system in fighting infection

b. Enhance immune function (e.g., increase NK cell activity and/or or antimicrobial action)

c. Reduce risk of further challenges to immune function (e.g., stress, physical injury, food-borne illness)

d. Discourage and/or avoid social contact to reduce risk of transmitting or contracting new infections

Brain, Behavior, and Immunity 31 (2013)

Inflammation and cognitive decline

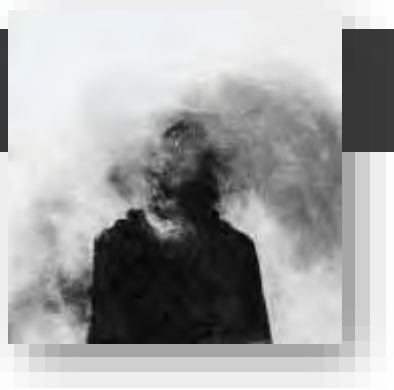
79 articles, 46 cross sectional AD or MCI vs controls, 33 longitudinal

cross-sectional studies
increased level of CRP [g 0.35, 95% CI (0.16, 0.55)]
IL-1b [0.94, 95% CI (0.04, 1.92)],
IL-6 [0.46, 95% CI (0.05, 0.88)],
TNF alpha [0.22, 95% CI (0.24, 0.68)],
sTNFR- 1 [0.74, 95% CI (0.46, 1.02)] in AD compared to controls. Similarly in MCI vs. control samples.

The data from longitudinal studies suggested that levels of IL-6 significantly increased the risk of cognitive decline [OR D 1.34, 95% CI (1.13, 1.56)]. However, intermediate levels of IL-6 had no significant effect on the final clinical endpoint [OR D 1.06, 95% CI (0.8, 1.32)].

Leonardo and Fregni; Front Aging Neuroscience, 2023

Inflammation and depression

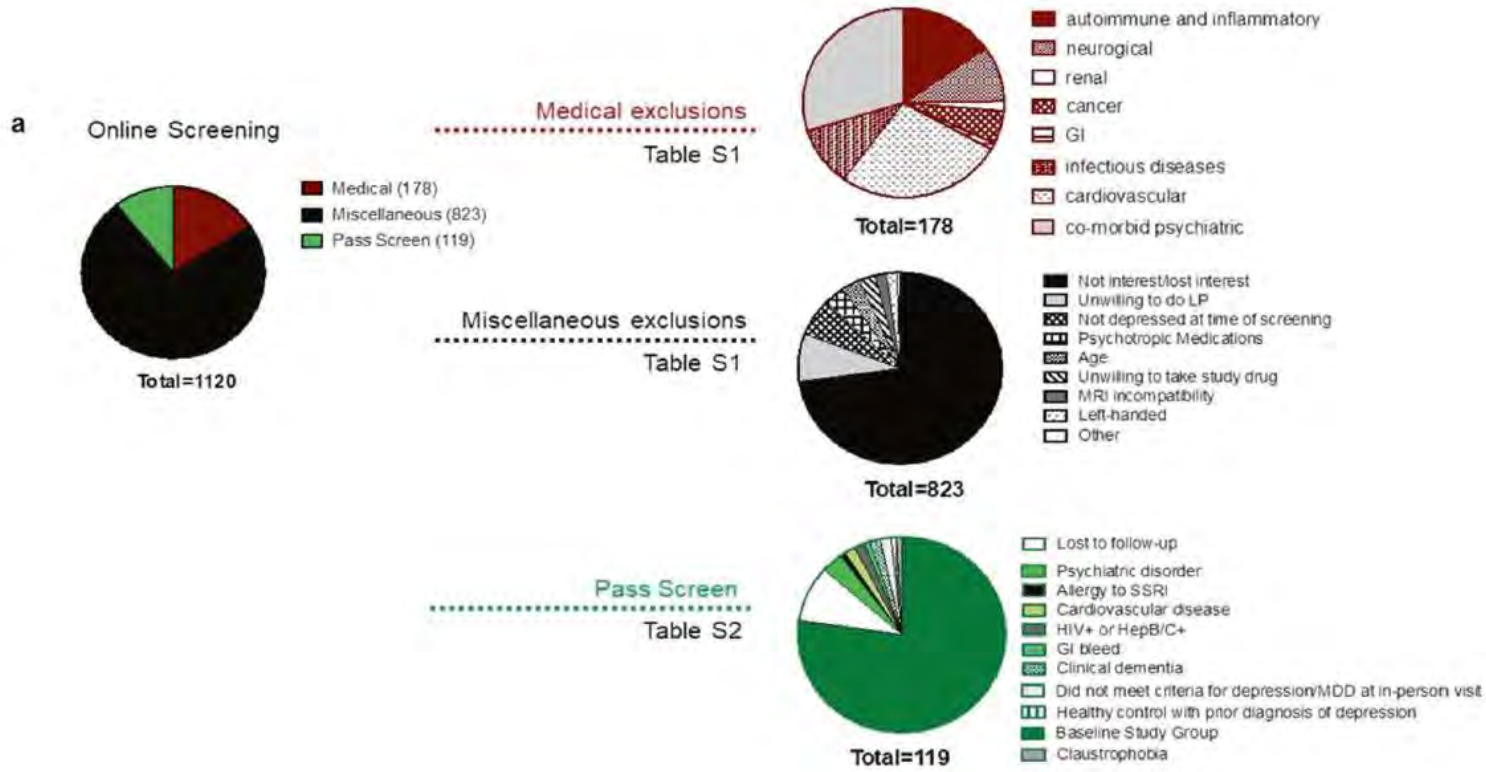


ARTICLE OPEN

Check for updates

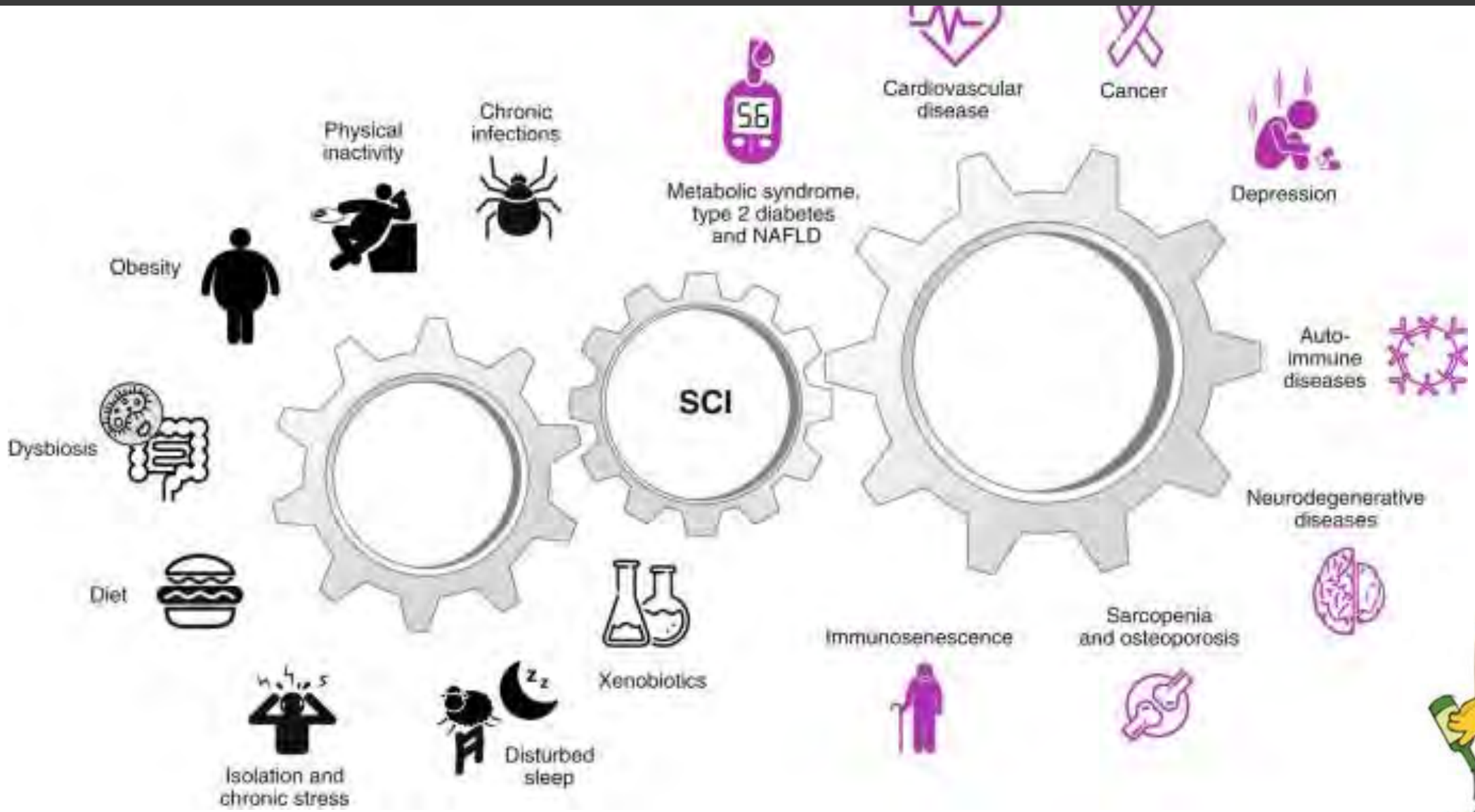
No increase in inflammation in late-life major depression screened to exclude physical illness

Eline T. Luning Prak[1,2], Thomas Brooks[3,4], Walid Makhoul[3], Joanne C. Beer[5], Ling Zhao[1,2], Tommaso Girelli[3], Carsten Skarke[4,6] and Yvette I. Sheline[3,7]✉



Transl Psychiatry, 2024

Lifestyle, inflammation, depression risk



Diet and inflammation

VITAMIN E: 9 studies in meta-analysis of vitamin E versus placebo. Depression, 354 participants, SMD –0.88 (95% CI: –1.54, –0.21; I2 = 87%). Anxiety: 306 participants, SMD of –0.86 (95% CI: –2.11, 0.40; I2 = 95%)

FLAVONOIDS: 36 clinical trials, 2788 participants; Depressive symptoms (mean diff = −1.65; 95% C.I., −2.54, −0.77).

Omega3- PUFAs: Individuals with depression exhibiting a pro-inflammatory phenotype receiving omega-3 polyunsaturated fatty acids experience improved motivation-related cognitive function

Crit Rev Food Sci Nutr 2023; Yan Bin Lee et al., Nutrients 2022; Giollabhui et al., Brain, Behavior, & Immunity - Health (2023)

Insomnia and inflammation

Treating insomnia improves depression and inflammation

23 studies. **The meta-analysis indicates moderate to large effect size (ES) improvement in depression** as measured with the Hamilton Depression Rating Scale (ES = −1.29, 95%CI [−2.11, −0.47]) and Beck Depression Inventory (ES = −0.68, 95%CI [−1.29, −0.06]).

Depress Anxiety. 2018;35:717–731; Irwin Nat Rev Immunol 2020

Inflammation + VD and treatment resistance

Increased inflammation (CRP, cytokines, N/L ratio) is **consistently associated with lower clinical response** to AD in depression or treatment resistant depression, especially if associated with vascular disease and WMH

Meta-analysis of 44 studies MDD responders had lower baseline IL-8 than non-responders (g = −0.28; 95%CI, −0.43 to −0.13).

Antidepressant treatment decreased IL6 and other pro-inflame cytokines

TNF-α (g = 0.60; 95%CI, 0.26–0.94) only in responders, responders showed significantly more decreased TNF-α levels compared with non-responders

Jha et al., 2017 PNEI; Breit et al., Journal of Psychiatric Research 159 (2023); Wang et al. Brain, Behavior, and Immunity 79 (2019)
Strawbridge et al., Eur Neuropsychophar 2015; Liu et al., Molecular Psychiatry (2020)

Anti-inflammatory drugs for LLMD

Systematic Review / Meta-analysis

Efficacy of anti-inflammatory treatment on major depressive disorder or depressive symptoms: meta-analysis of clinical trials

36 RCTs, whereof 13 investigated NSAIDs (N = 4214), 9 cytokine inhibitors (N = 3345), seven statins (N = 1576), 3 minocycline (N = 151), 2 pioglitazone (N = 77), and 2 glucocorticoids (N = 59).

Anti-inflammatory agents improved depressive symptoms compared to placebo as add-on in patients with MDD (SMD = 0.64; 95%-CI = 0.88, 0.40; I2 = 51%; N = 597) and as monotherapy (SMD = 0.41; 95%-CI = 0.60, 0.22; I2 = 93%, N = 8825). Antiinflammatory add-on improved response (RR = 1.76; 95%-CI = 1.44–2.16; I2 = 16%; N = 341) and remission (RR = 2.14; 95%-CI = 1.03–4.48; I2 = 57%; N = 270). We found a trend toward an increased risk for infections, and all studies showed high risk of bias.

Khohler-Forsberg Acta Psych Scand 2019

Anti-inflammatory drugs for LLMD

Review

Efficacy of infliximab in treatment-resistant depression: A systematic review and meta-analysis

Daniela V. Bavaresco[a], Maria Laura Rodrigues Uggioni[a], Sarah Dagostin Ferraz[a], Rudielly Moraes Machado Marques[a], Carla Sasso Simon[a], Valdemira Santina Dagostin[a], Antônio Jose Grande[b], Maria Inês da Rosa[a,*]

[a] Translational Biomedicine Laboratory, Graduate Program in Health Sciences, University of Southern Santa Catarina (UNESC), Criciúma, SC, Brazil
[b] Laboratory of Evidence in Health, Medicine and Health Sciences, University of State of Mato Grosso do Sul, Campo Grande, MS, Brazil

Infliximab (Antagonist of TNF alpha) for at least 4 weeks vs placebo add-on

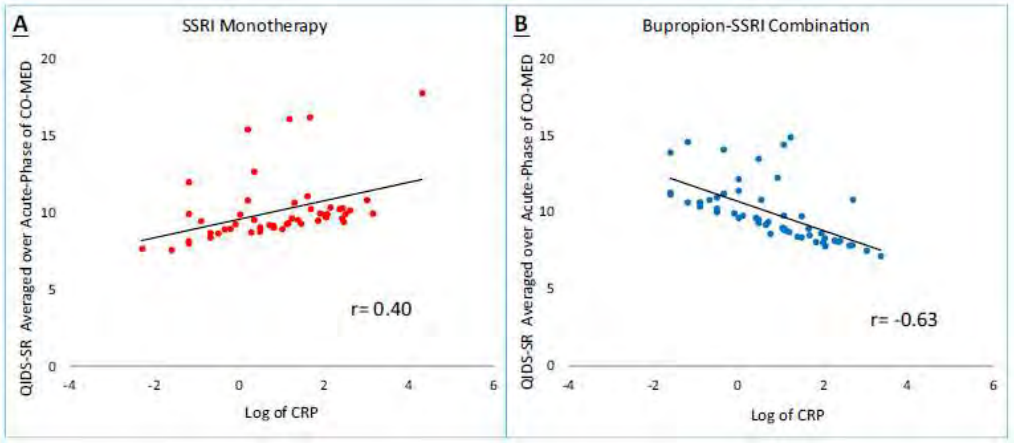
4 primary studies were included in the systematic review, with a total of 152 patients. The meta-analysis did not show a statistically significant effect of Infliximab as an adjuvant treatment for TRD.

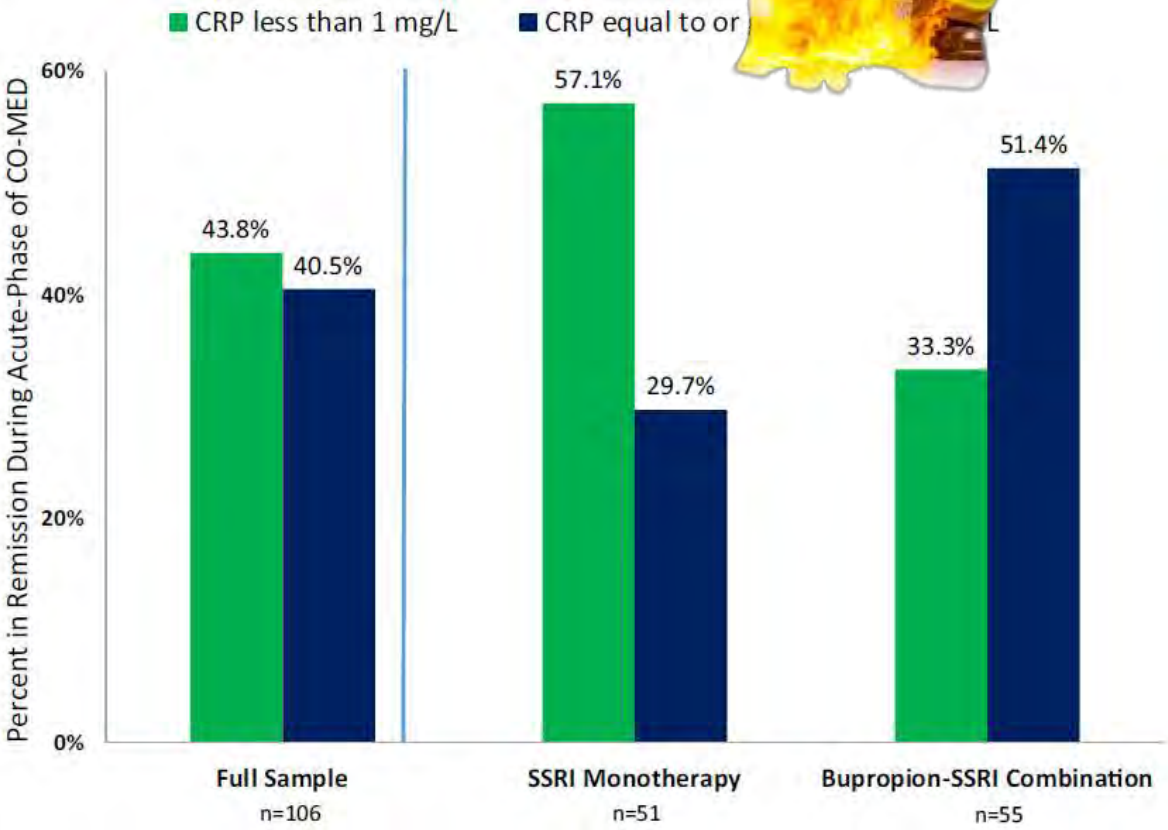
Pharmacology, Biochemistry and Behavior 188 (2020)

Precision anti-inflammatory for LLMD

Can C-reactive protein inform antidepressant medication selection in depressed outpatients? Findings from the CO-MED trial

Manish K. Jha[a], Abu Minhajuddin[b], Bharathi S. Gadad[a], Tracy Greer[a], Bruce Grannemann[a], Abigail Soyombo[a], Taryn L. Mayes[a], A. John Rush[c], Madhukar H. Trivedi[a,*]



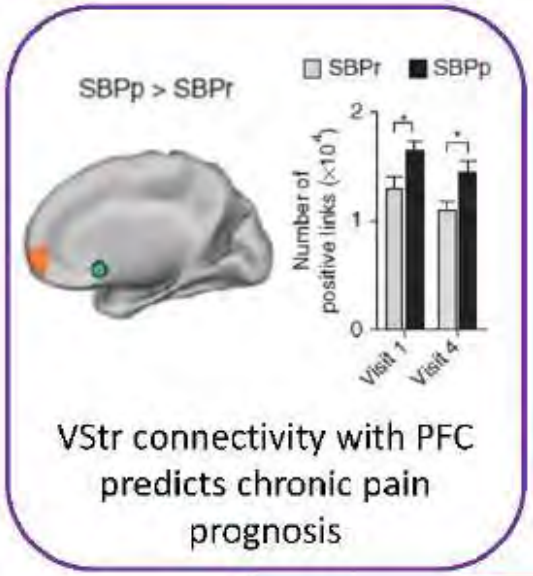


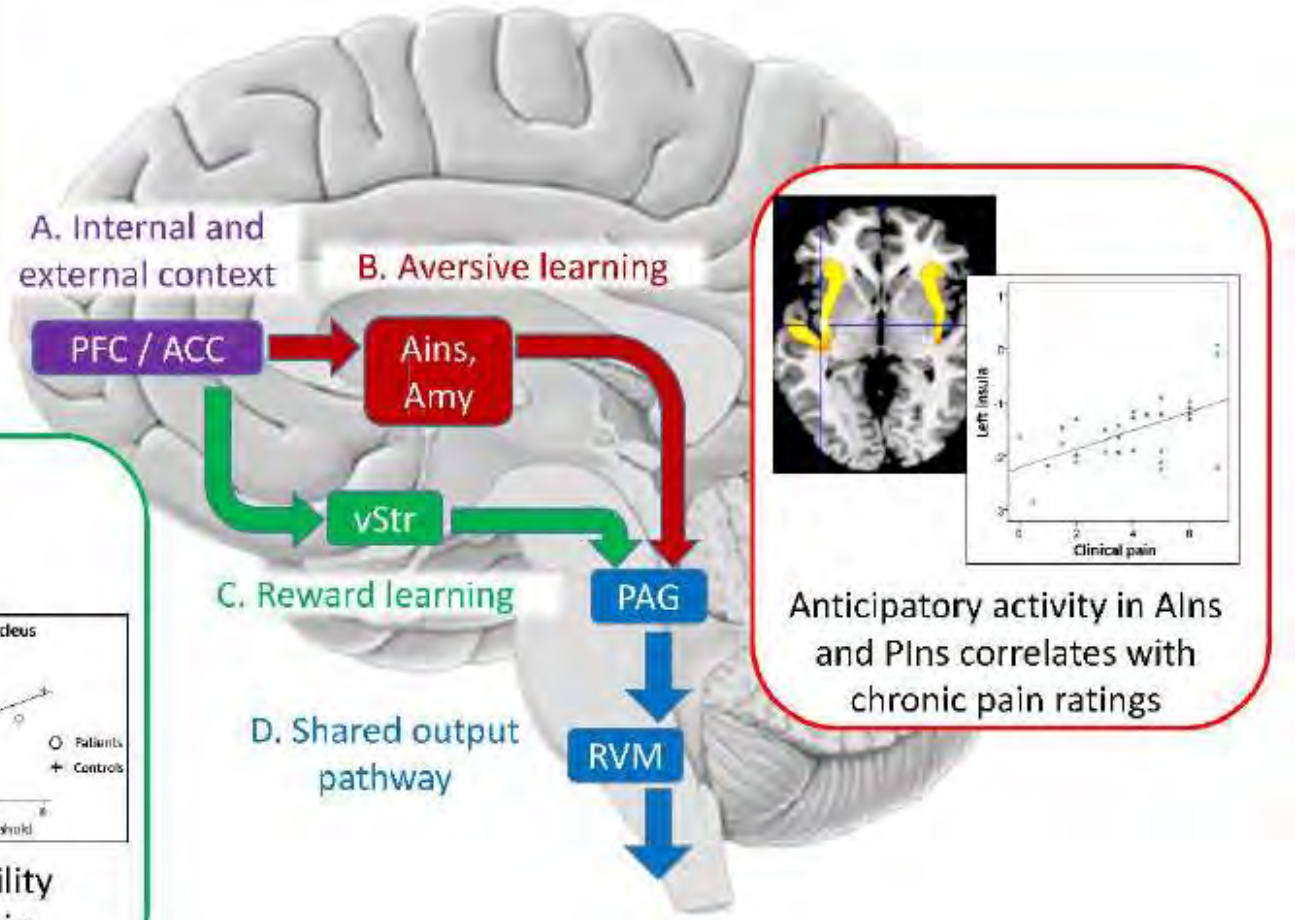
Psychoneuroendocrinology 78 (2017)

Sistemi omeostatici: i soliti ignoti

- Sistema endocannabinoide
- Sistema oppioide endogeno
- Sistema «endovanilloide»

The brain on pain



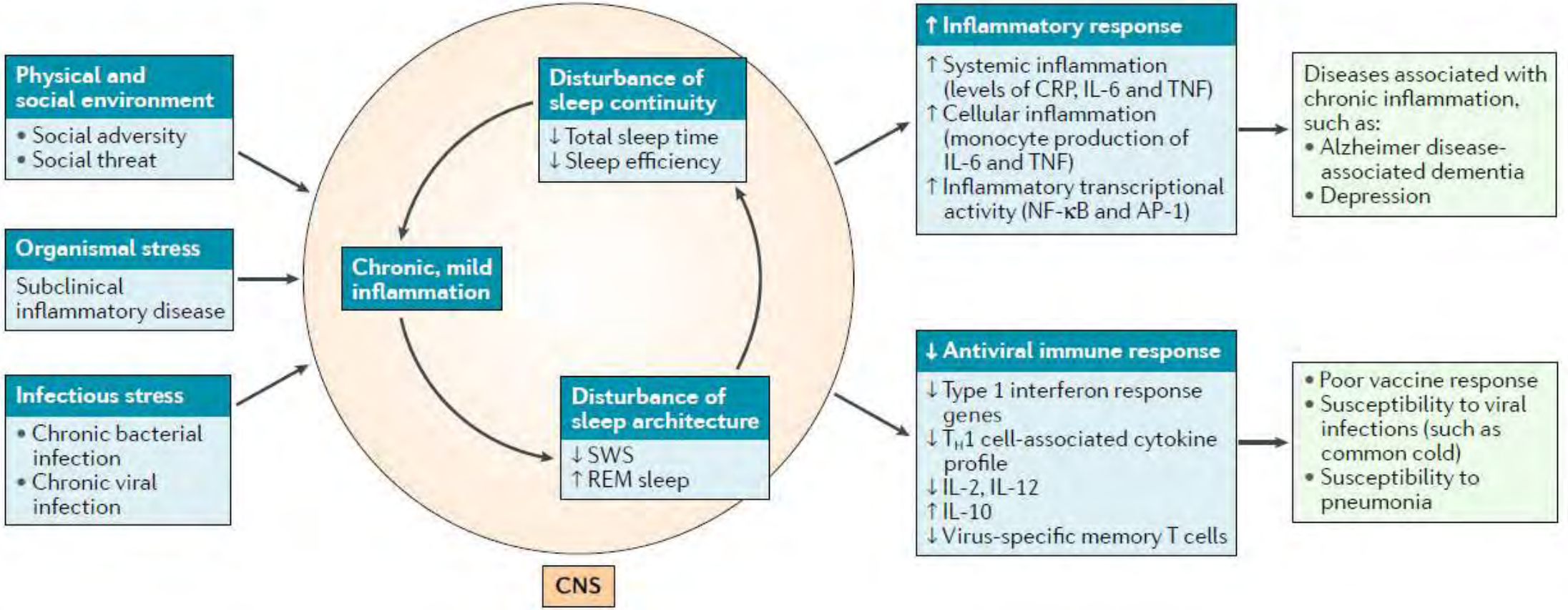


Roques et al., Nat Drug Discov 2012

Interplay of homeostatic systems

Sleep and inflammation: partners in sickness and in health

Michael R. Irwin



Irwin Nat Rev Immunol 2020

Modelli di depressione

PSYCHOLOGICAL INQUIRY
2020, VOL. 31, NO. 4, 271–288
https://doi.org/10.1080/1047840X.2020.1853461

Routledge
Taylor & Francis Group

TARGET ARTICLE

OPEN ACCESS

Lack of Theory Building and Testing Impedes Progress in The Factor and Network Literature

Eiko I. Fried

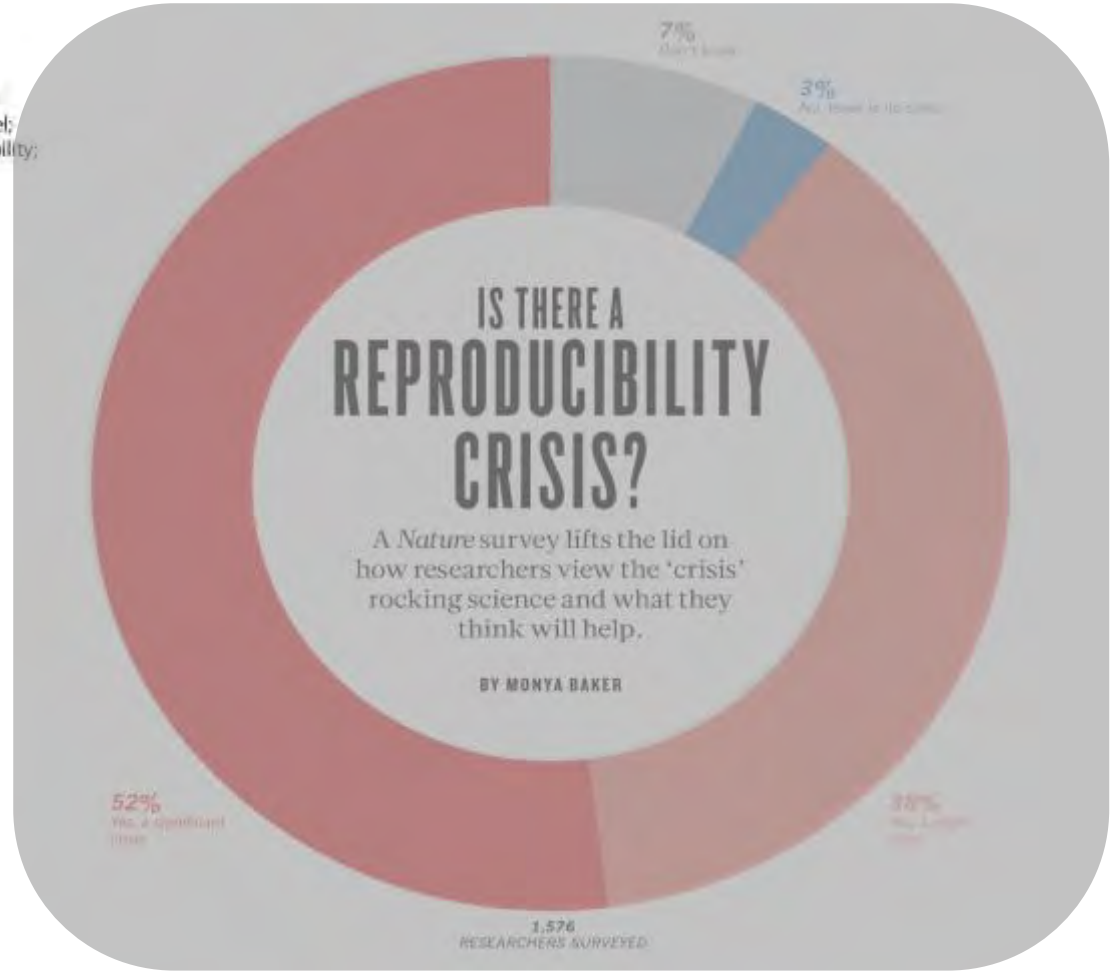
Department of Clinical Psychology, Leiden University, Leiden, Netherlands

ABSTRACT

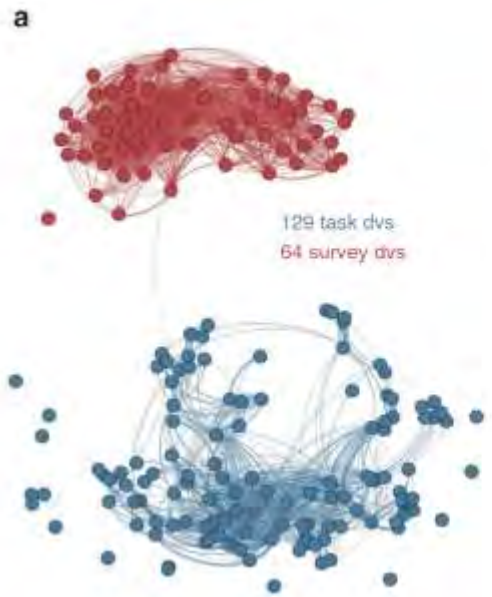
The applied social science literature using factor and network models continues to grow rapidly. Most work reads like an exercise in model fitting, and falls short of theory building and testing in three ways. First, statistical and theoretical models are conflated, leading to invalid inferences such as the existence of psychological constructs based on factor models, or recommendations for clinical interventions based on network models. I demonstrate this inferential gap in a simulation: excellent model fit does little to corroborate a theory, regardless of quality or quantity of data. Second, researchers fail to explicate theories about psychological constructs, but use implicit causal beliefs to guide inferences. These latent theories have led to problematic best practices. Third, explicated theories are often weak theories: imprecise descriptions vulnerable to hidden

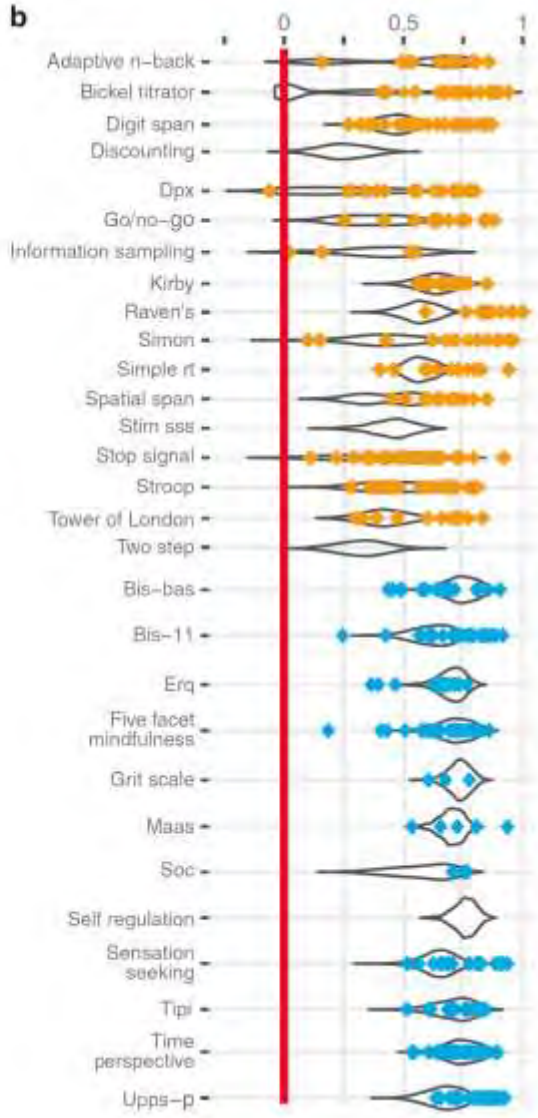
KEYWORDS

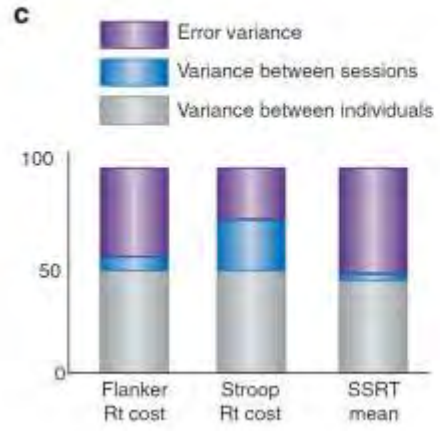
Factor model; formal theory; network model; open science; replicability; statistical equivalence; theory

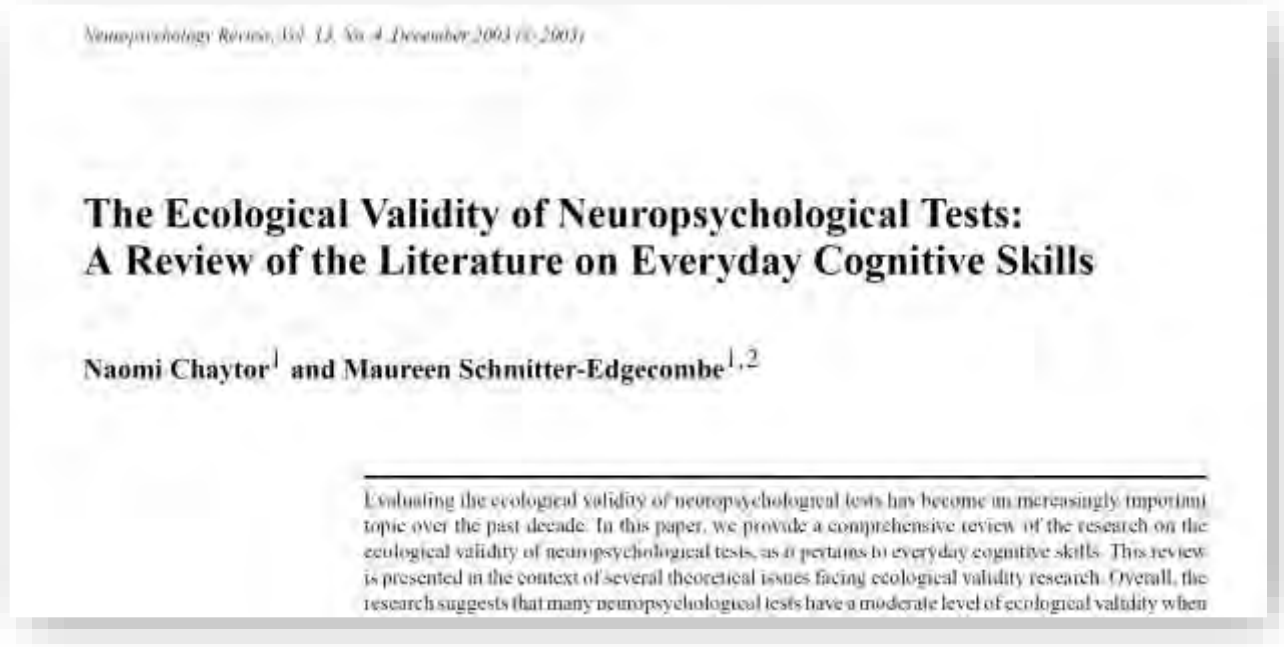


Measurement issues









Neuropsychology Review, Vol. 13, No. 4, December 2003 (© 2003)

The Ecological Validity of Neuropsychological Tests: A Review of the Literature on Everyday Cognitive Skills

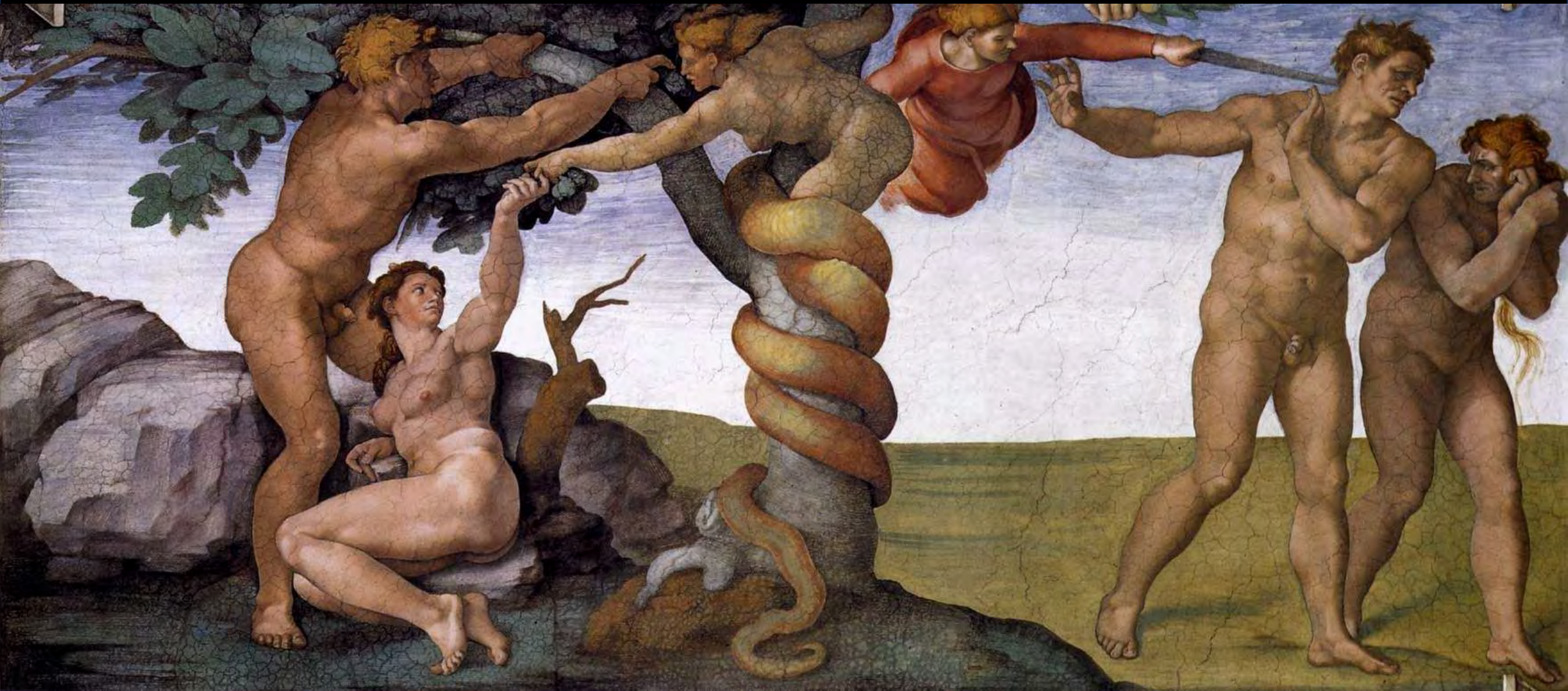
Naomi Chaytor[1] **and Maureen Schmitter-Edgecombe**[1,2]

Evaluating the ecological validity of neuropsychological tests has become an increasingly important topic over the past decade. In this paper, we provide a comprehensive review of the research on the ecological validity of neuropsychological tests, as it pertains to everyday cognitive skills. This review is presented in the context of several theoretical issues facing ecological validity research. Overall, the research suggests that many neuropsychological tests have a moderate level of ecological validity when

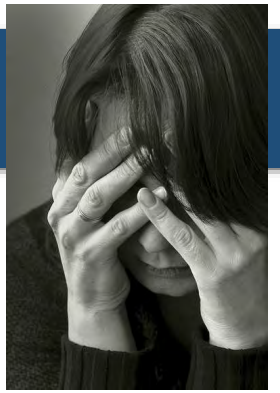
Modelli monodimensionali

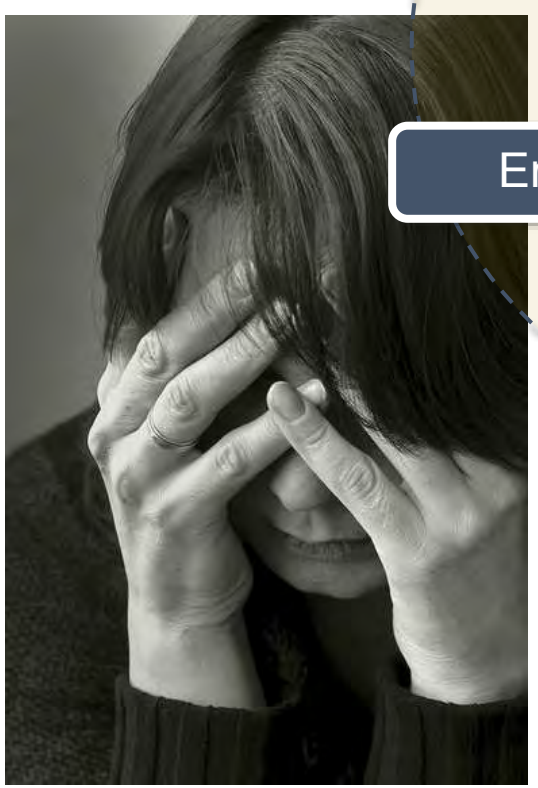
imbarazzo, fastidio, seccatura, incomodo,
bisogno, privazione, stento, carenza,
fatica, impiccio, difficoltà,
sofferenza, malessere
dis-agio, de-moralizzazione

Modelli multi-dimensionali



Dimensioni della LLMD





Emozionali

Tristezza
Ansia
Irritabilità
Anedonia
Mancanza di speranza
Senso di colpa

Cognitivi

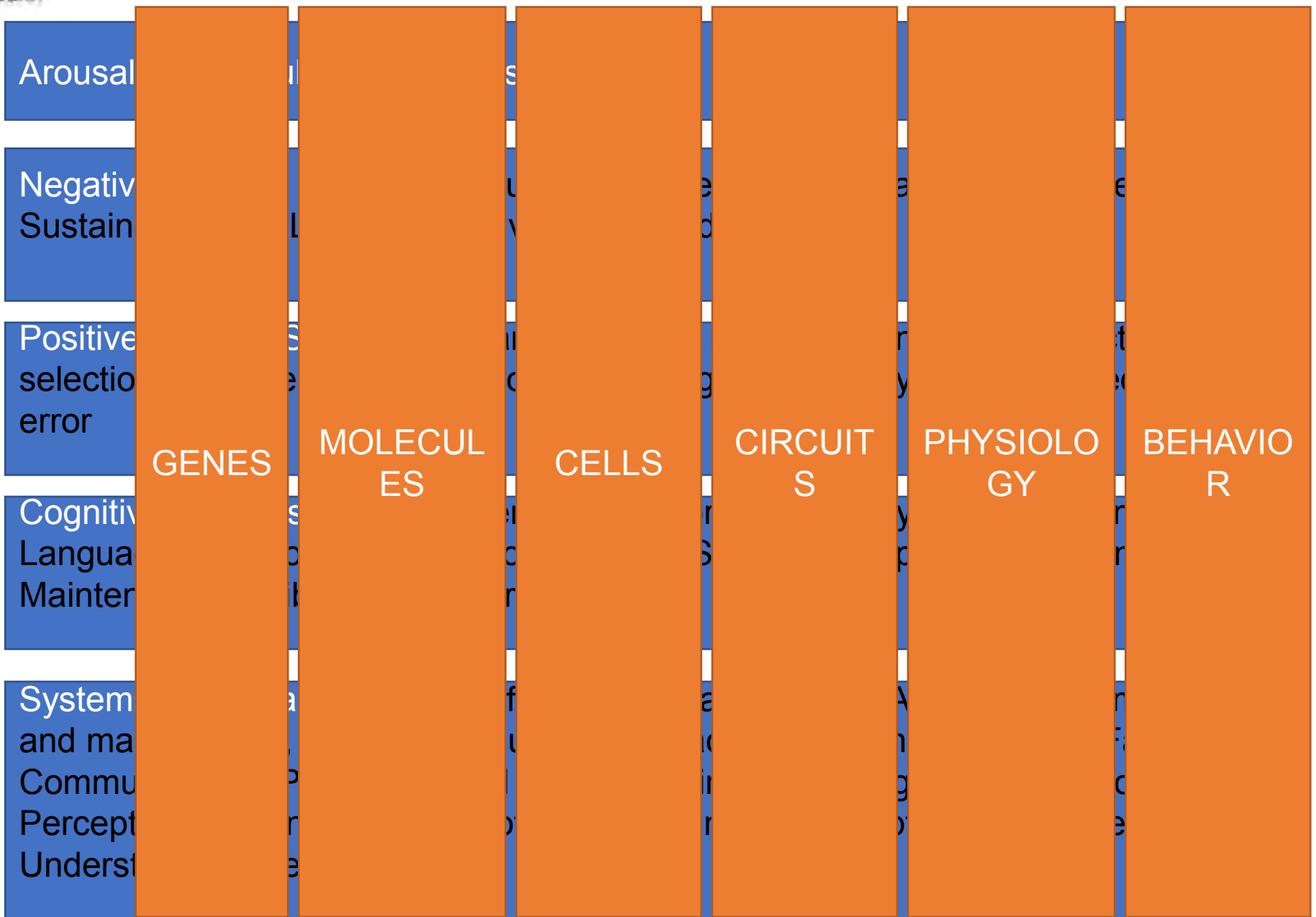
Attenzione e concentrazione
Memoria breve e lungo termine
Prendere decisioni
Pianificare
Organizzare
Trovare le parole
Rallentamento psicomotorio

Fisici e Neurovegetativi

Variazioni appetito
Variazioni sonno
Problemi sessuali
Mal di testa
Dolore al torace
Dolore somatico
Rallentamento motorio

RDOC criteria

National Institute of Mental Health



Fattori contestuali

Psychological Medicine

cambridge.org/psm

Context *v.* algorithm: evidence that a transdiagnostic framework of contextual clinical characterization is of more clinical value than categorical diagnosis

Original Article

Cite this article: van Os J *et al* (2021). Context *v.* algorithm: evidence that a transdiagnostic framework of contextual clinical characterization is of more clinical value than categorical diagnosis. *Psychological Medicine* 1–9. https://doi.org/10.1017/S0033291721003445

Received: 28 January 2021
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Accepted: 2 August 2021

Jim van Os[1,2,3], Lotta-Katrin Pries[2], Margreet ten Have[4], Ron de Graaf[4], Saskia van Dorsselaer[4], Maarten Bak[2,5], Gunter Kenis[1], Bochao D. Lin[6], Nicole Gunther[7], Jurjen J. Luykx[6,8,9], Bart P. F. Rutten[2] and Sinan Guloksuz[2,10]

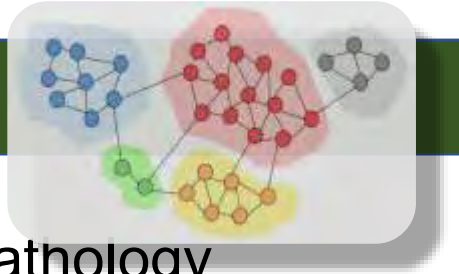
[1]Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Maastricht University Medical Centre, Maastricht, The Netherlands; [2]Department of Psychiatry, UMC Utrecht Brain Center, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands; [3]Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK; [4]Department of Epidemiology, Netherlands Institute of Mental Health and Addiction, Utrecht, The Netherlands; [5]FACT, Mondriaan

TRANSDIAGNOSTIC: symptoms are not specific to mental disorders, occurring in highly personal clusters

CONTEXTUAL: social, existential, somatic, and temporal factors

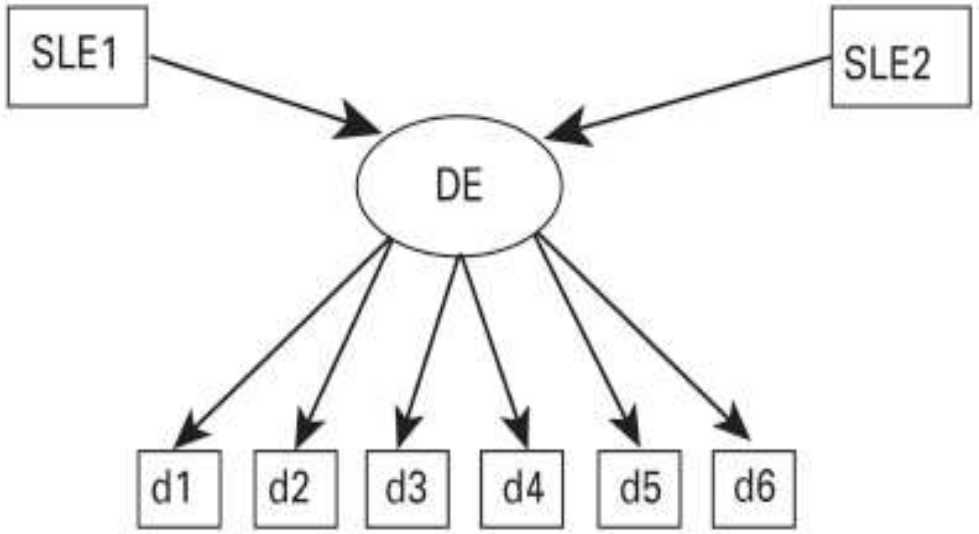
Modelli a network

Modelli a network

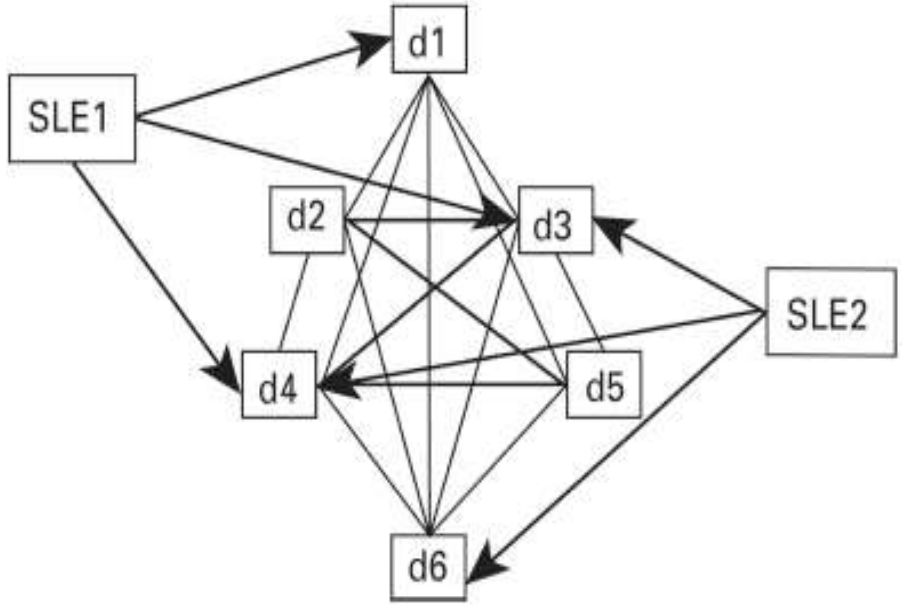


«Medicalized» (latent factor) model vs. network approach to psychopathology

- Common cause(s) → One or more pathogenetic mechanisms (lack of serotonin, HPA axis dysregulation, etc.) → symptoms of disease (disorder)



- Symptoms can cause each other
- Feedback/forward loops
- Divergent and convergent interactions based on biological, psychological, social mechanisms

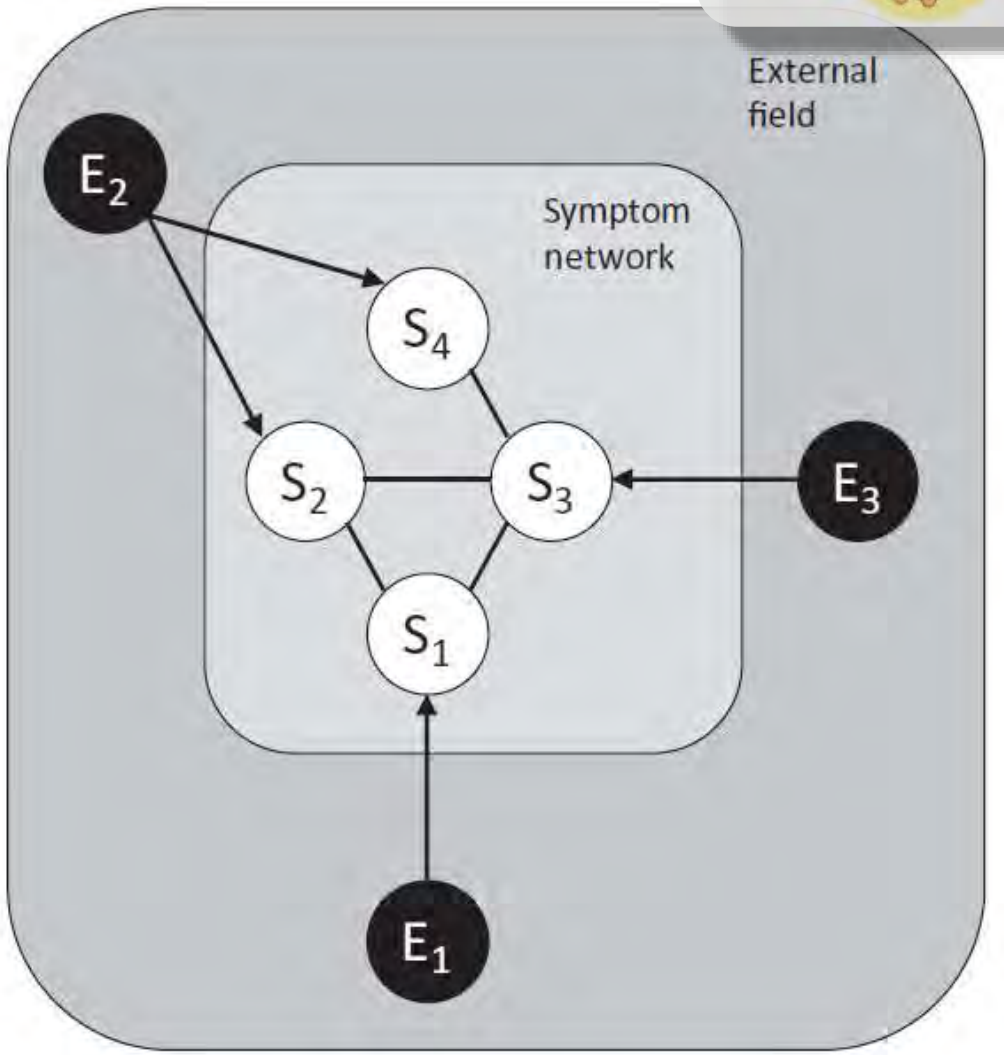


Network and «external field» variables

External field: conditions that **influence symptoms from outside the network** (e.g., adverse life events) by activating 1+ symptoms in the network (e.g., insomnia).

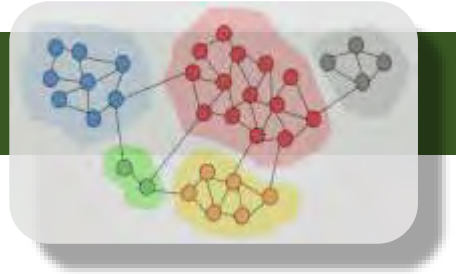
In turn, this may cause the symptom's neighbors (e.g., low mood, anxiety) to align their states

Outside of the psychopathology network but cot necessarily outside of the person (e.g. inflammation → fatigue)



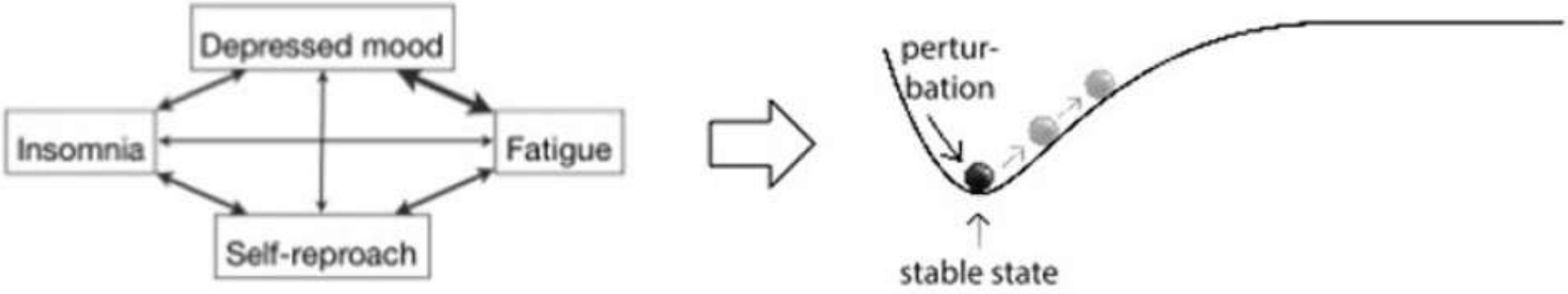
D. Borsboom, World Psychiatry, 2017

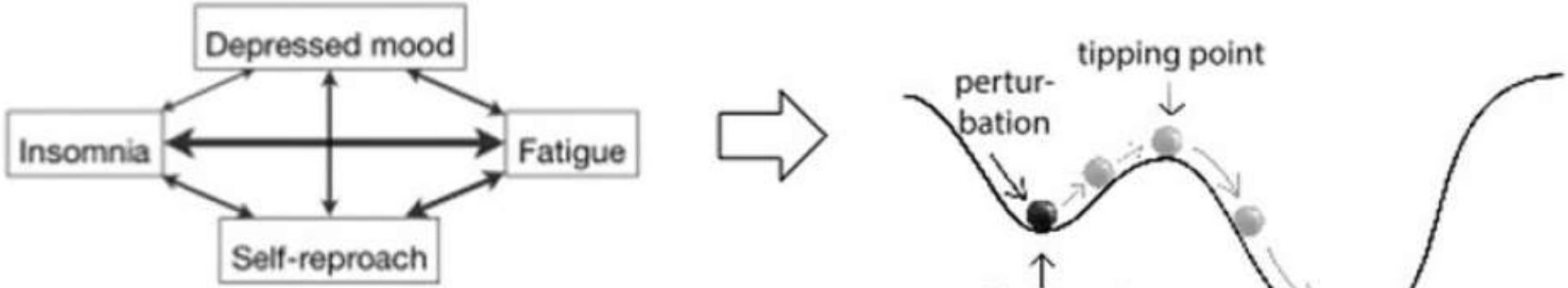
Stressors, hysteresis, network dynamics



Alice: network with low connectivity, 1 eq. point; high resilience
Bob: high connectivity, low resilience, 2 eq. points, low resilience

Alice





Bob

complexity, non-linearity, emergence

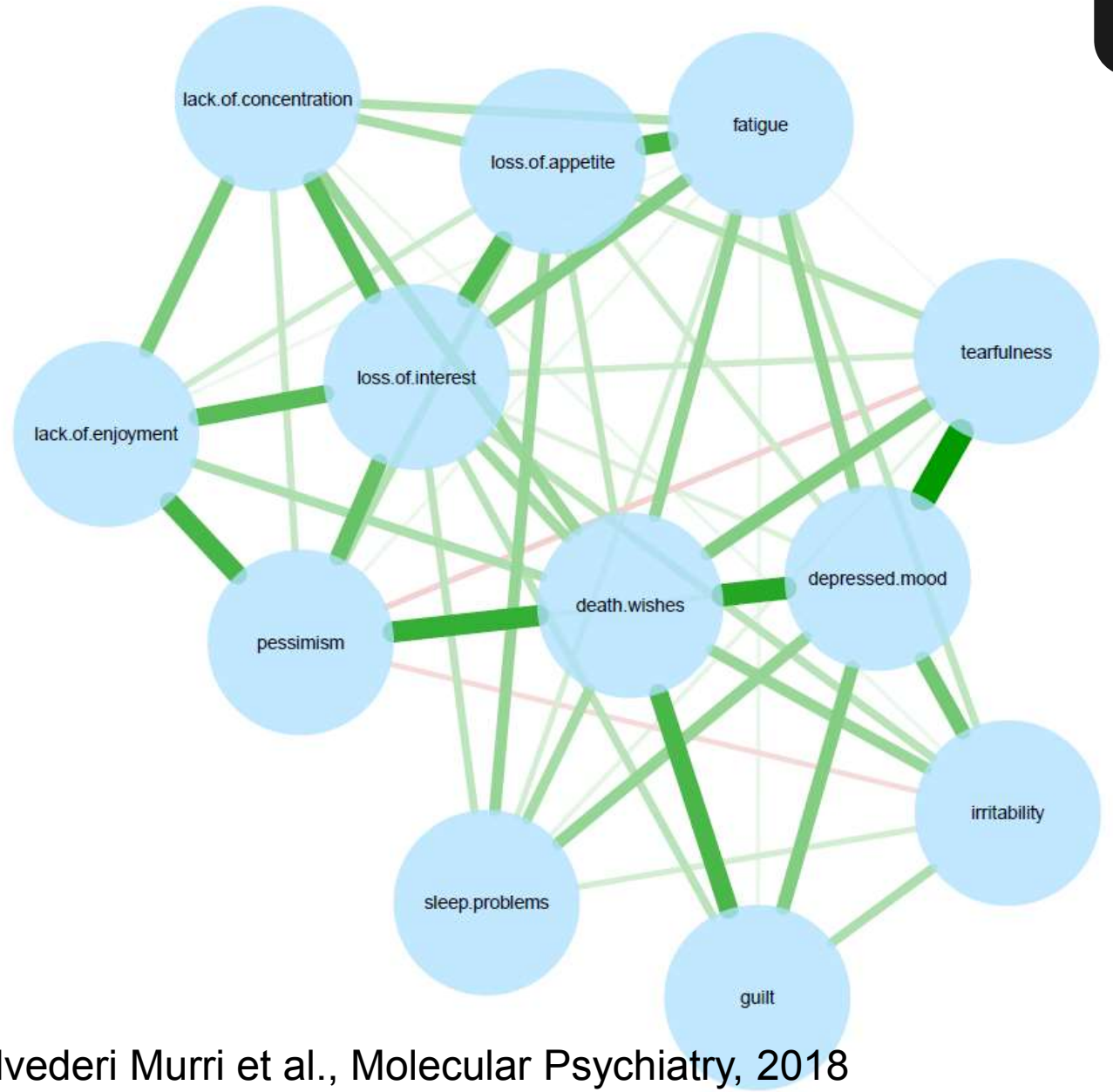
Borsboom et al., 2016

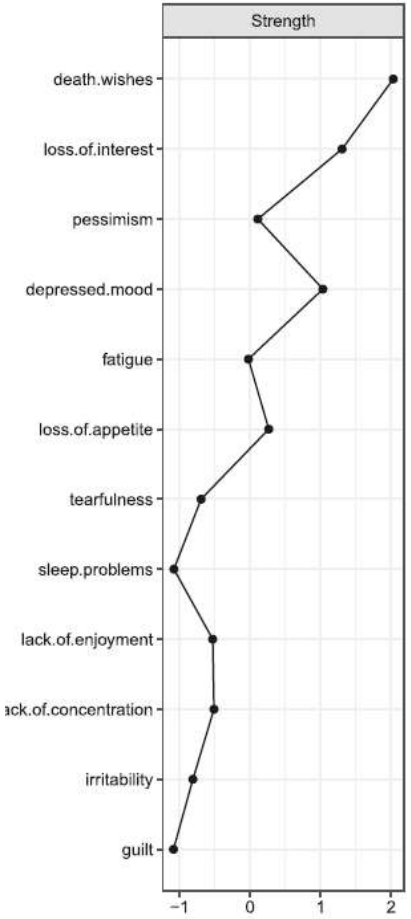
Depression in late life: central symptoms

8.557 participants aged 65+ from the general population (SHARE study, Europe)

Most central symptoms:

1. **Death wishes**
2. **Loss of interest**
3. **Depressed mood**
4. **Pessimism**





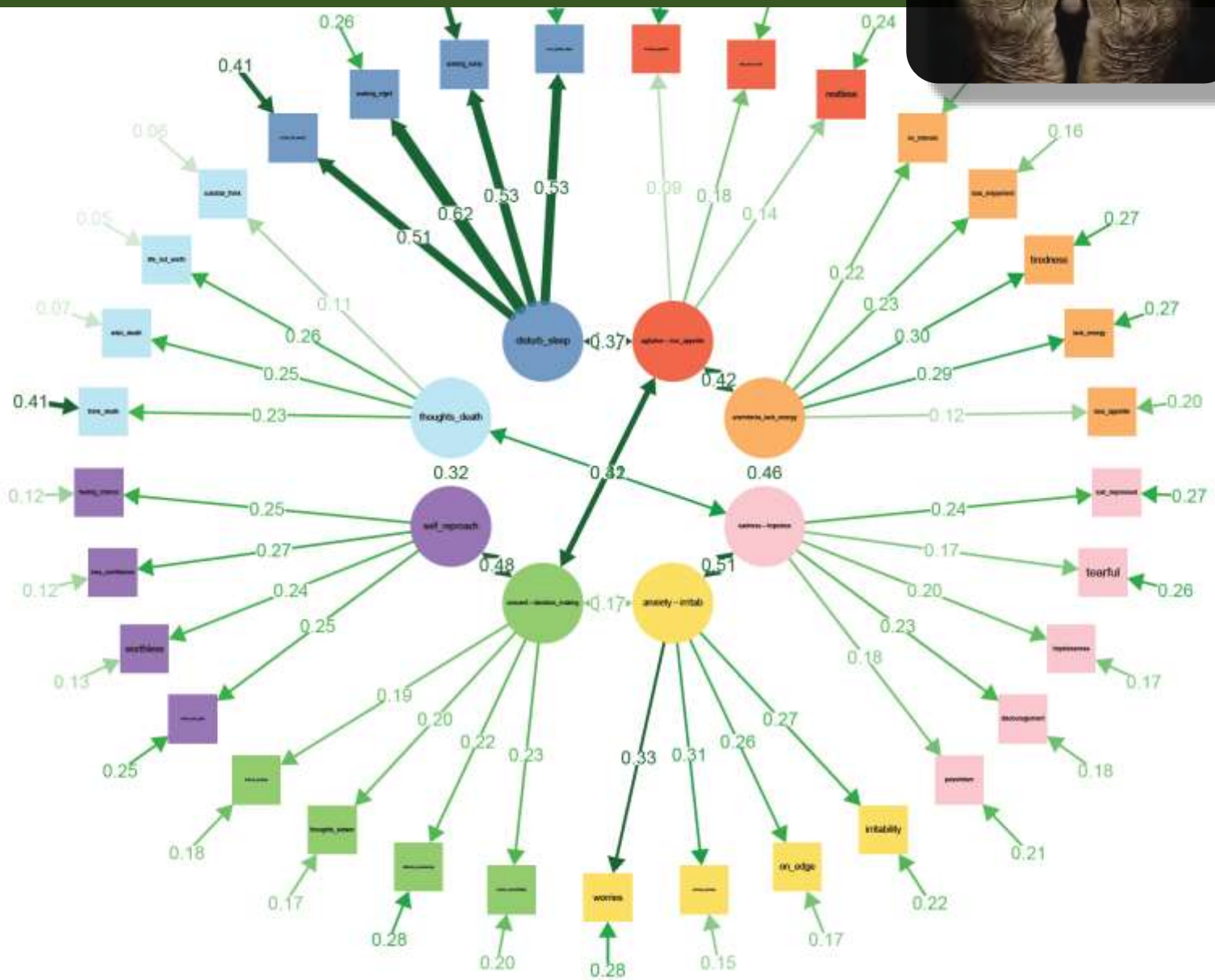
Belvederi Murri et al., Molecular Psychiatry, 2018

Depression in late life: symptom complexes

2623 participants aged 65+ from the general population (MENTDIS study, Europe): Latent Network Model

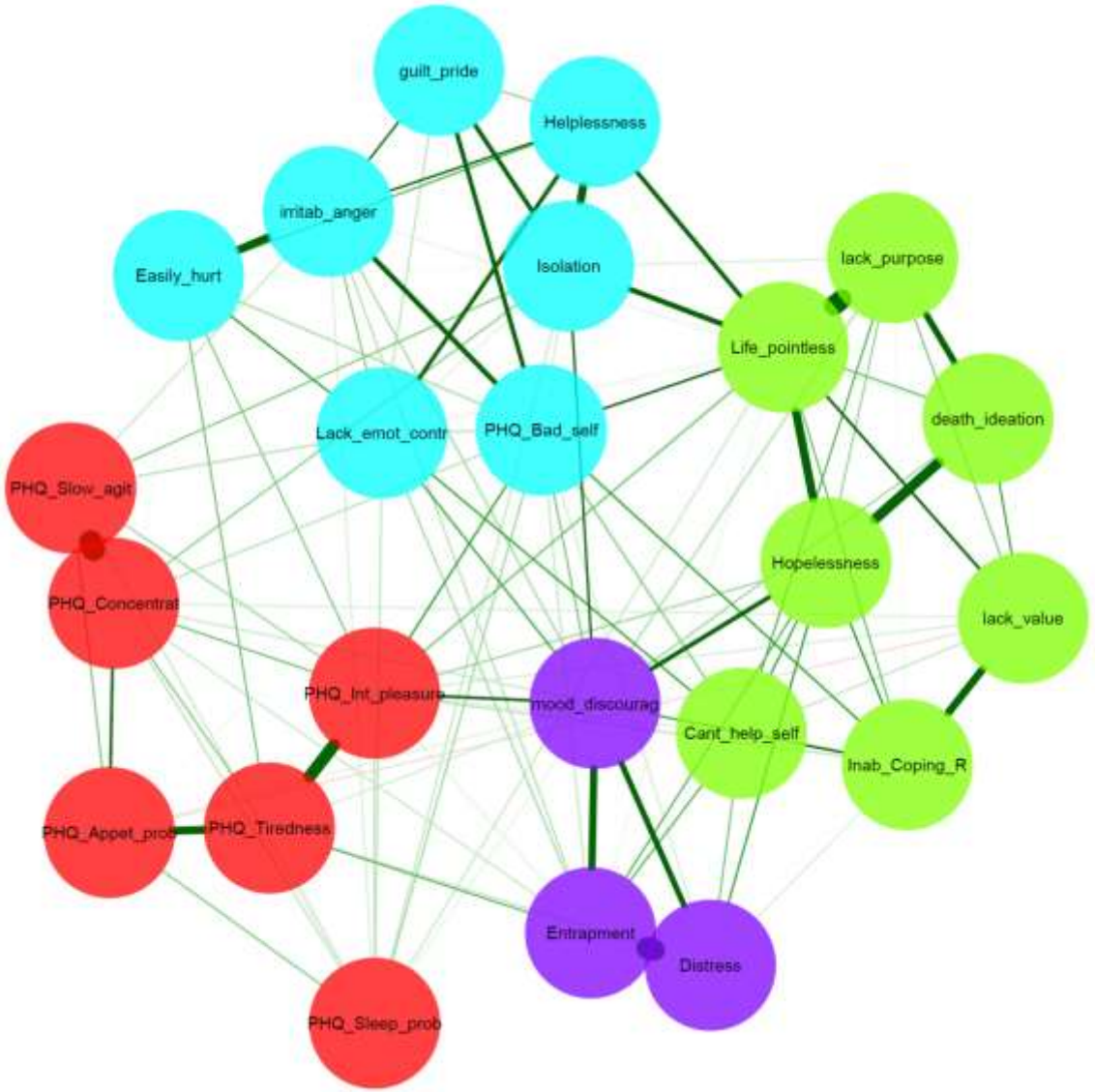
8 symptom complexes:

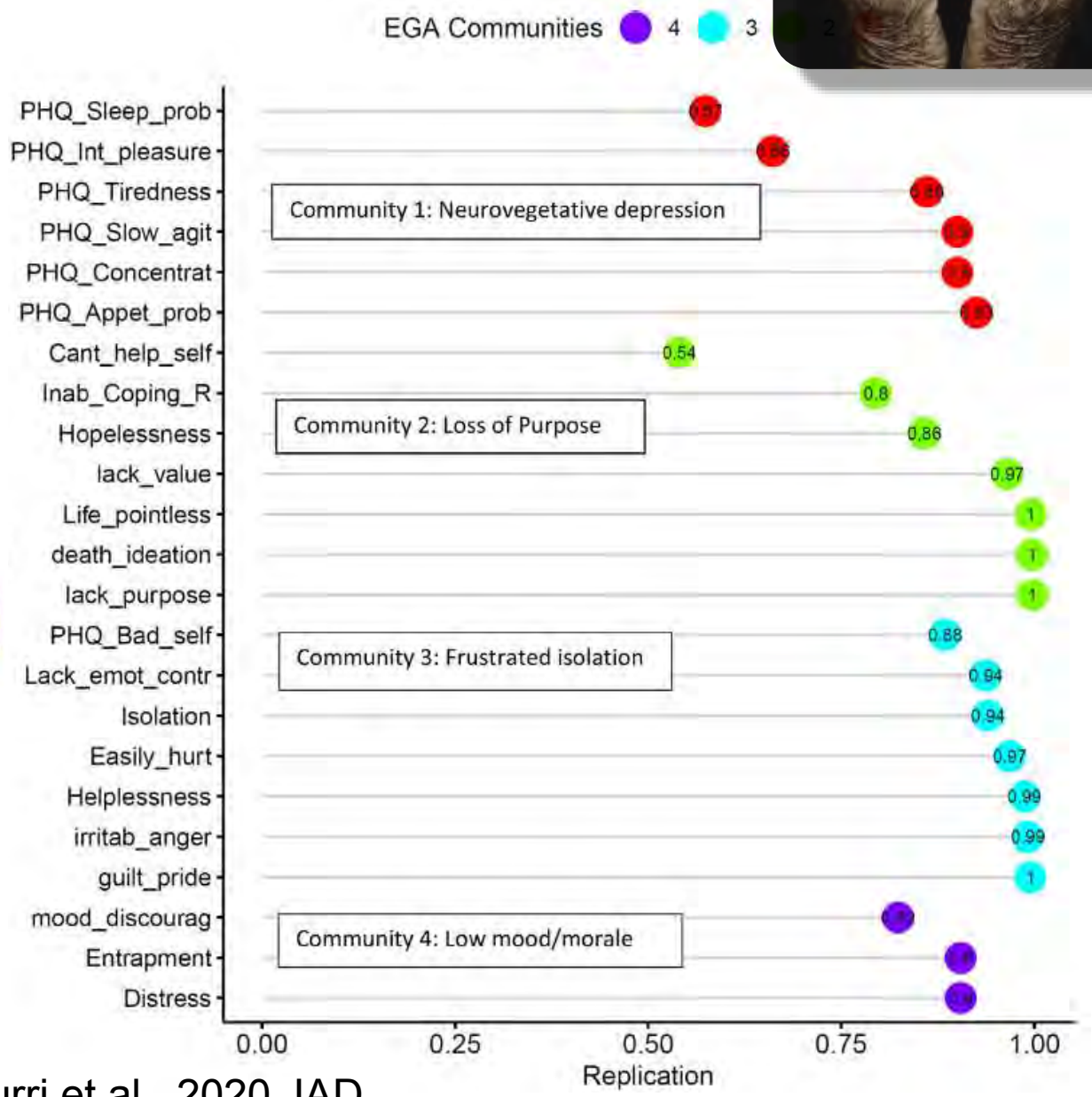
- sadness /hopelessness
- anhedonia/lack of energy
- anxiety/irritability
- self-reproach
- disturbed sleep
- agitation/increased appetite
- concentration/decision making
- thoughts of death



Belvederi Murri et al., Mol Psychiatry, 2021

Depression and demoralization in the hospital

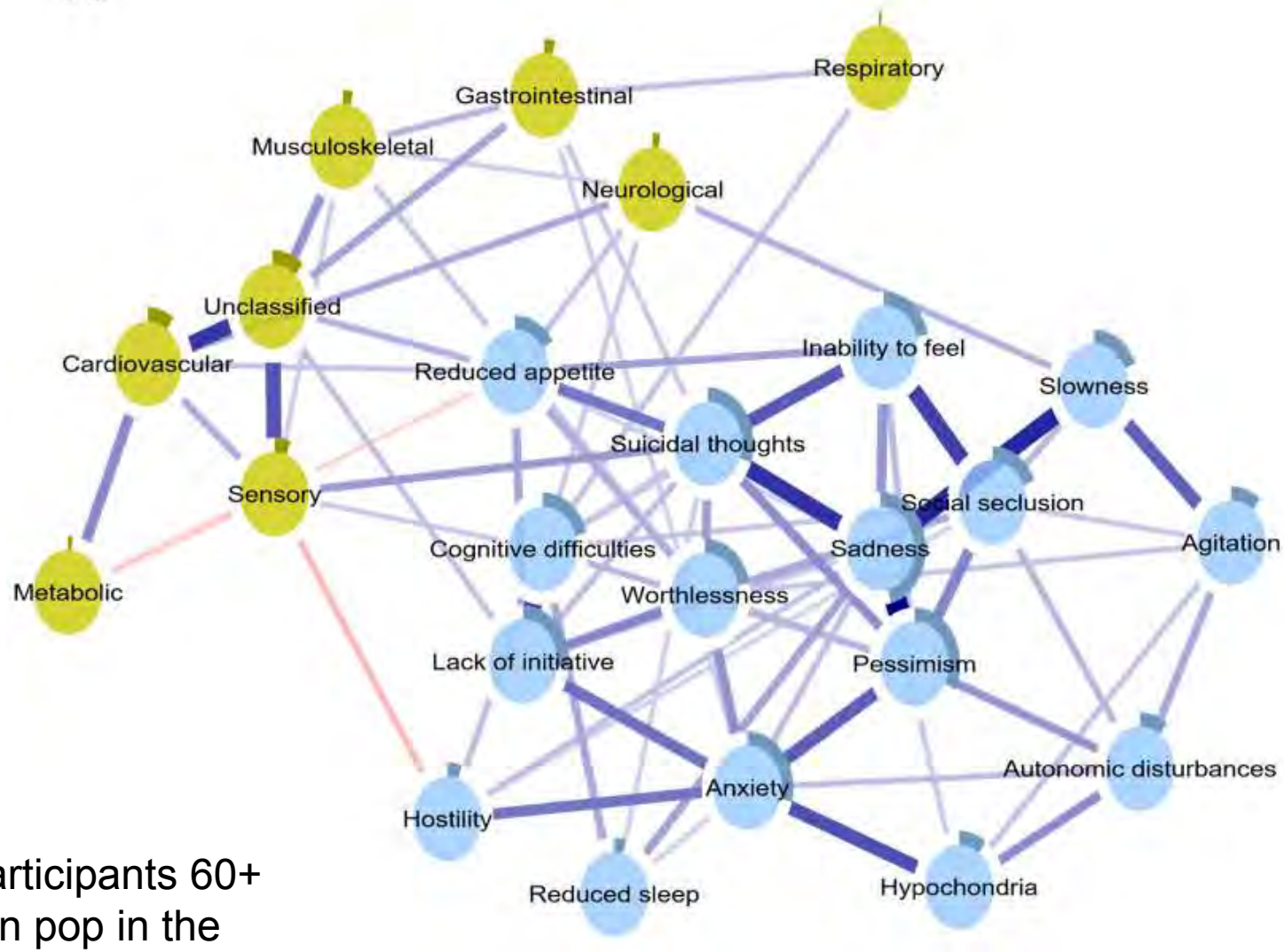




Belvederi Murri et al., 2020 JAD

Depression in multimorbidity: bridge symptoms

(A)



(B)

Somatic disease group	Bridging depressive symptom
Cardiovascular	Reduced appetite
	Inability to feel†
Neurological	Cognitive difficulty#
	Reduced appetite
	Slowness#
Gastrointestinal	Anxiety#
	Cognitive difficulty†
	Suicidal thoughts
Respiratory	Cognitive difficulty#
Sensory	Cognitive difficulty#
	Hostility
	Reduced sleep†
	Suicidal thoughts#
Metabolic	Reduced appetite
MSK	Worthlessness#
Unclassified	Lack of initiative
	Reduced appetite

2860 participants 60+ from gen pop in the SNACK study (Sweden)

Triolo, Belvederi Murri et al., Translational Psychiatry, 2021

Depression in cancer

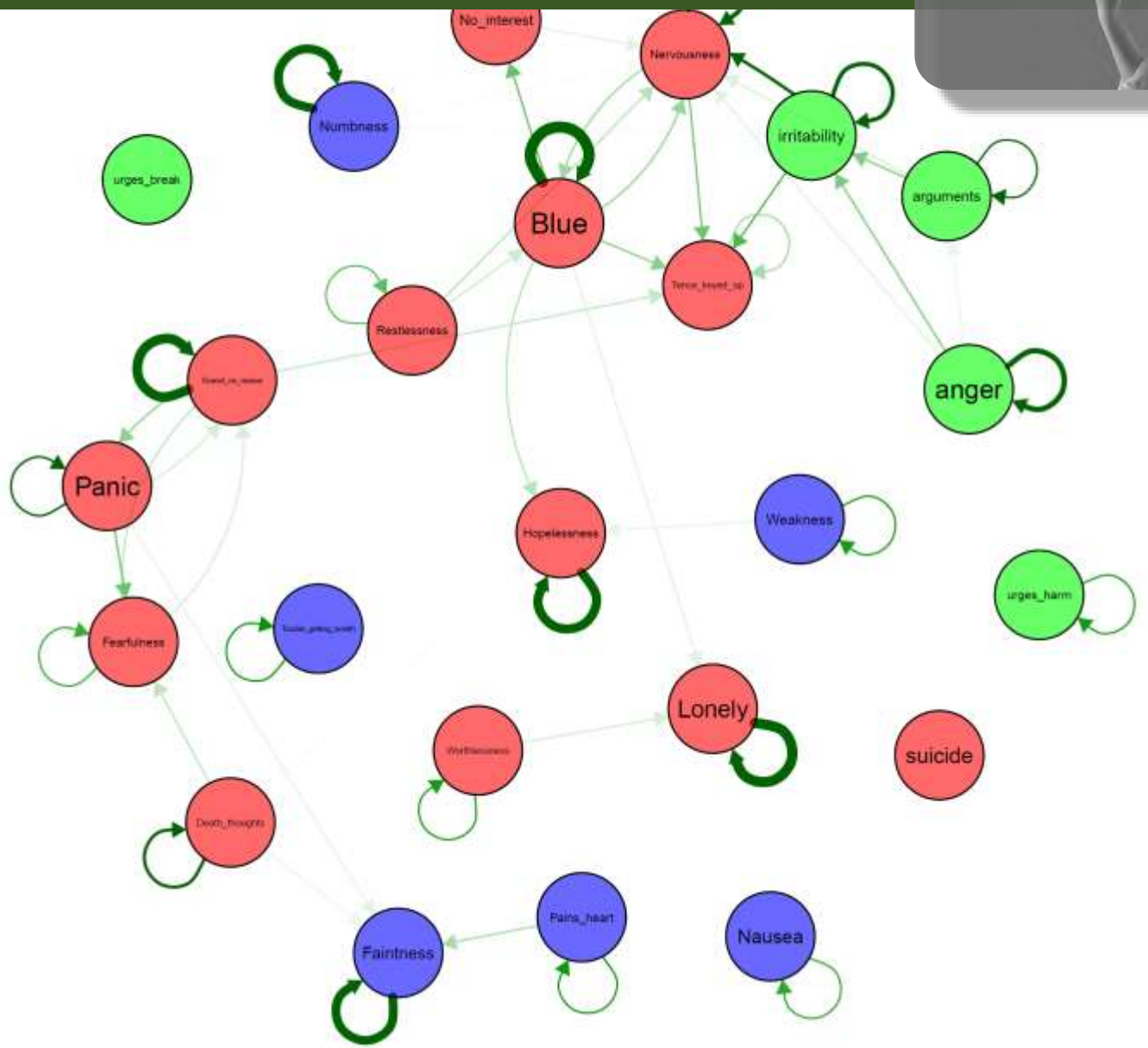
1100 participants from cancer units in the SIPO study (Italy)

3 communities: depression/anxiety, hostility, and somatic symptoms

Faintness, weakness, chest pain and dyspnoea connected with distress

Depressive sx and hostility connected with suicidal and death thoughts

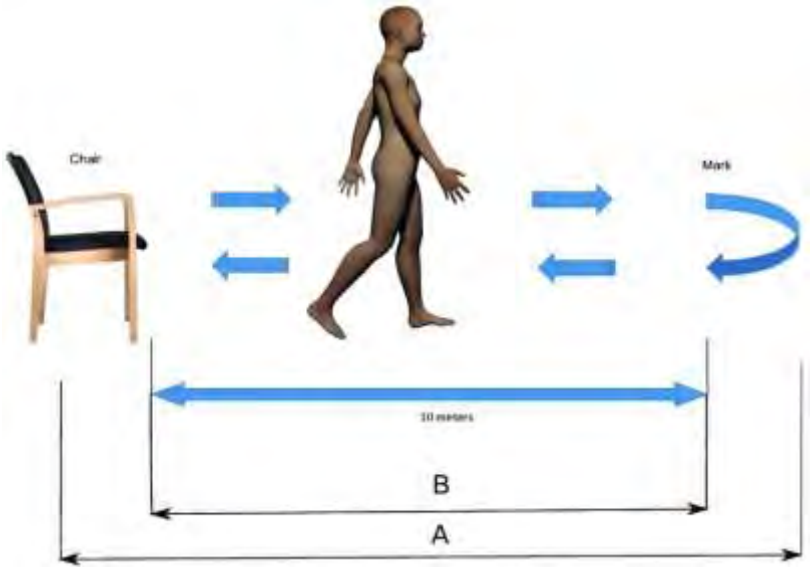
Sadness, irritability, nervousness, and tension cross-predicted each other over 3 months

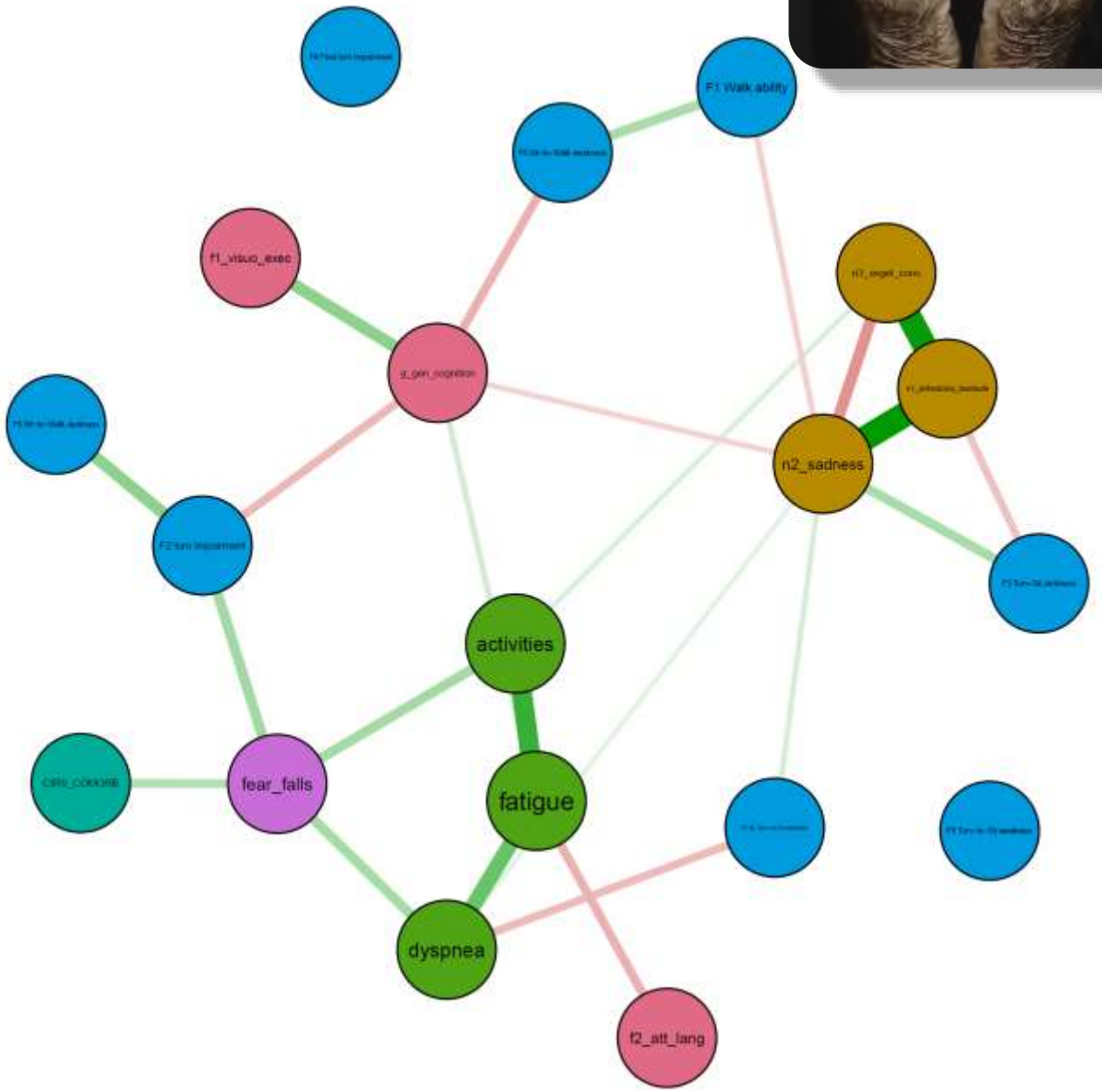


Belvederi Murri et al., J Psychosom Res, in review

Residual depressive symptoms

75 older adults with MDD after antidepressants. **Residual depression** associated with walking ability (accelerometer), dyspnea, cognitive abilities, fear of falling

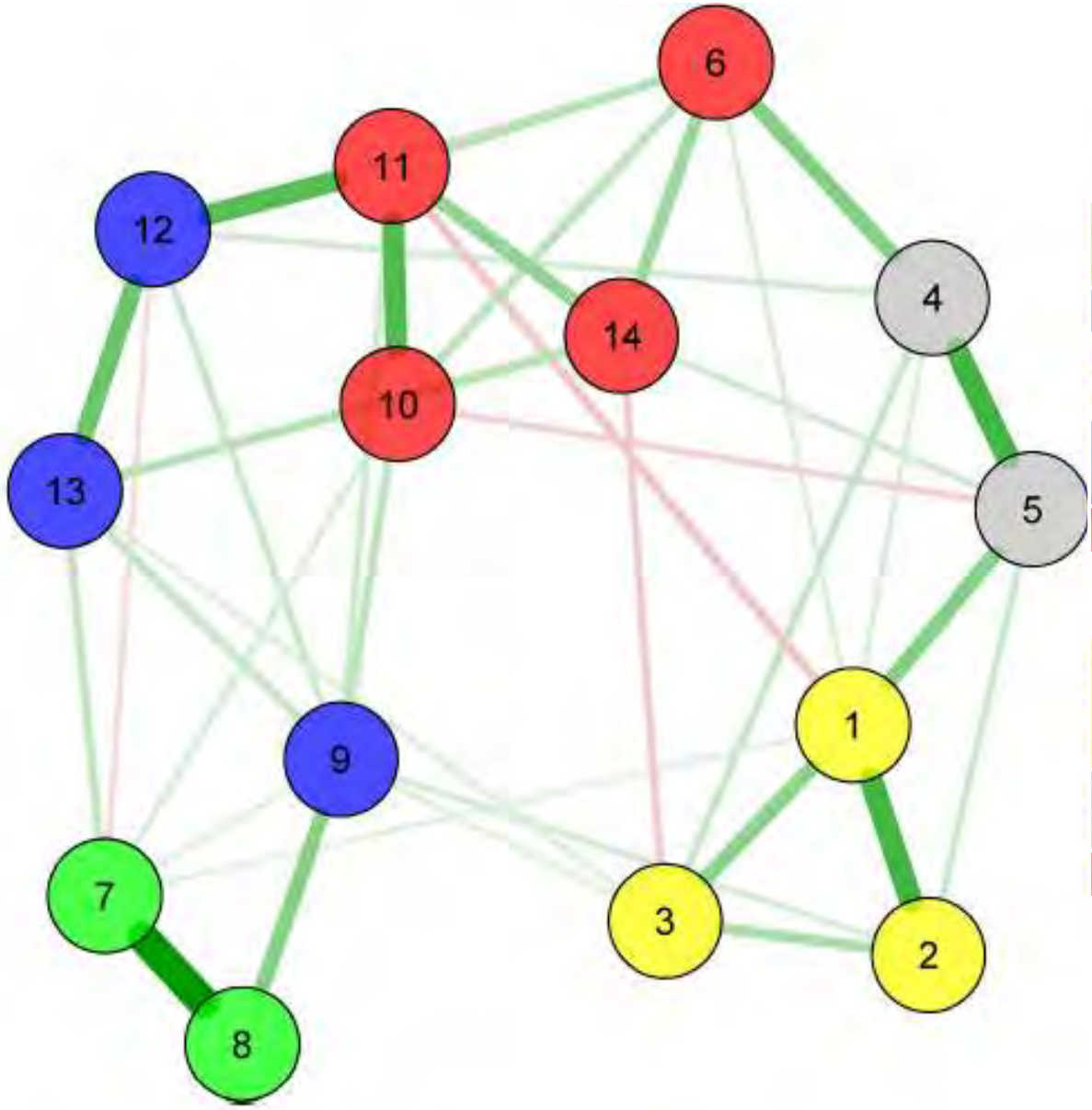




Depression in COPD

1587 participants with COPD in the COPDgene study (USA)

From COPD symptoms to anxiety and depression



CAT nodes

- 7: cough
- 8: phlegm
- 9: chest_tight
- 10: breathless
- 11: activity_limitation
- 12: not_confident_going_out
- 13: sleep_problem
- 14: low_energy

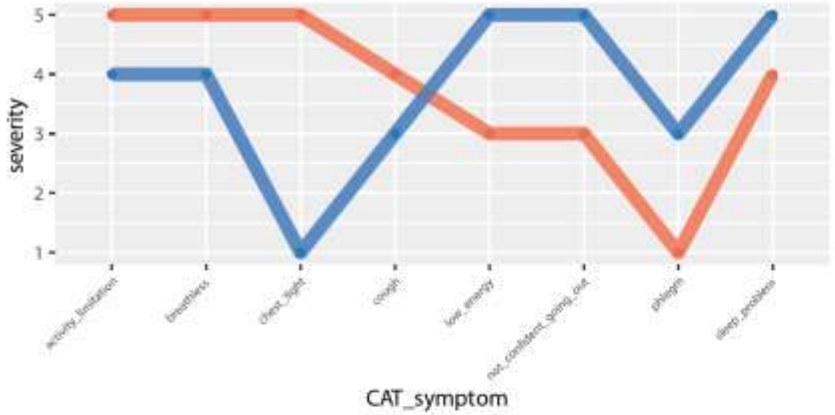
HADS-derived nodes

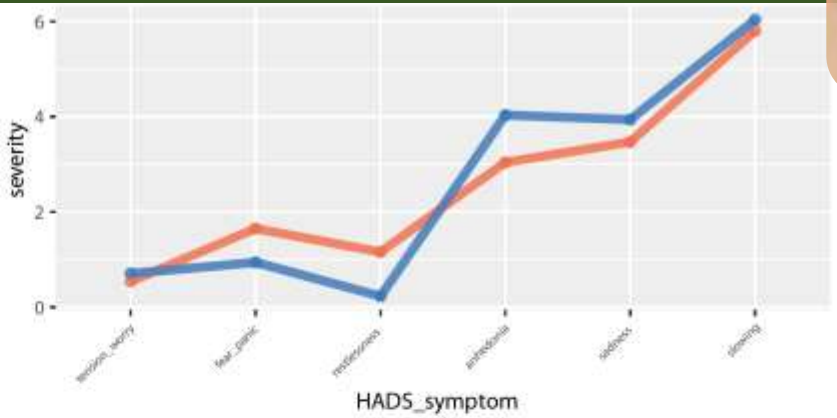
- 1: tension_worry
- 2: fear_panic
- 3: restlessness
- 4: anhedonia
- 5: sadness
- 6: slowing

Belvederi Murri – Yohannes et al., Respiratory Medicine, 2022

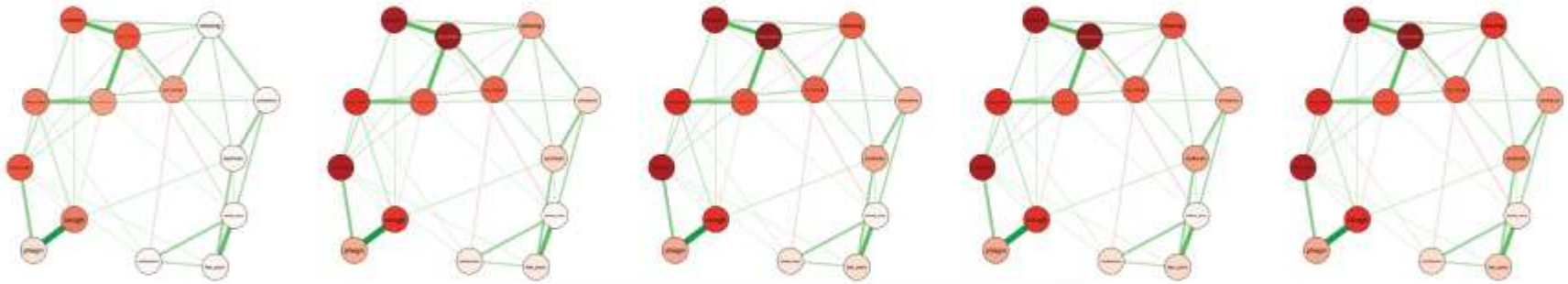
Depression in COPD: simulation

Symptom profile



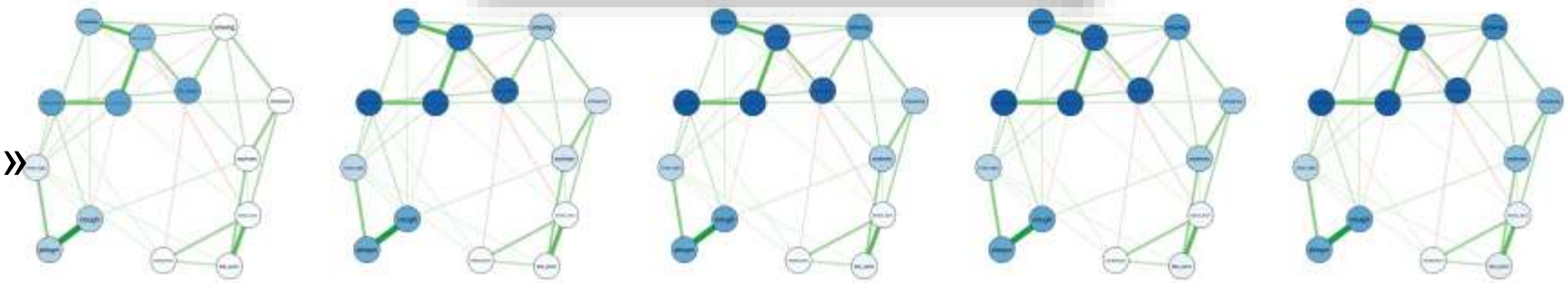


Patient A «dyspnea»



More severe panic

Patient B «weakness»



More severe anhedonia

Belvederi Murri – Yohannes et al., Respiratory Medicine, 2022

Identificazione precoce

Home | Make a Gift | Directions | Contact Us

Framingham Heart Study

A Project of the National Heart, Lung, and Blood Institute and Boston University

About | Participants | Our Investigators | Bibliography | For Researchers | Search

- Atrial Fibrillation
- Cardiovascular Disease
  - Cardiovascular Disease (10-year risk)
  - Cardiovascular Disease (30-year risk)
- Congestive Heart Failure
- Coronary Heart Disease
- Diabetes
- Hypertension
- Intermittent Claudication
- Stroke

Cardiovascular Disease (10-year risk)

(based on D'Agostino, Vasan, Pencina, Wolf, Cobain, Massaro, Kannel: 'A General Cardiovascular Risk Profile for Use in Primary Care: The Framingham Heart Study')

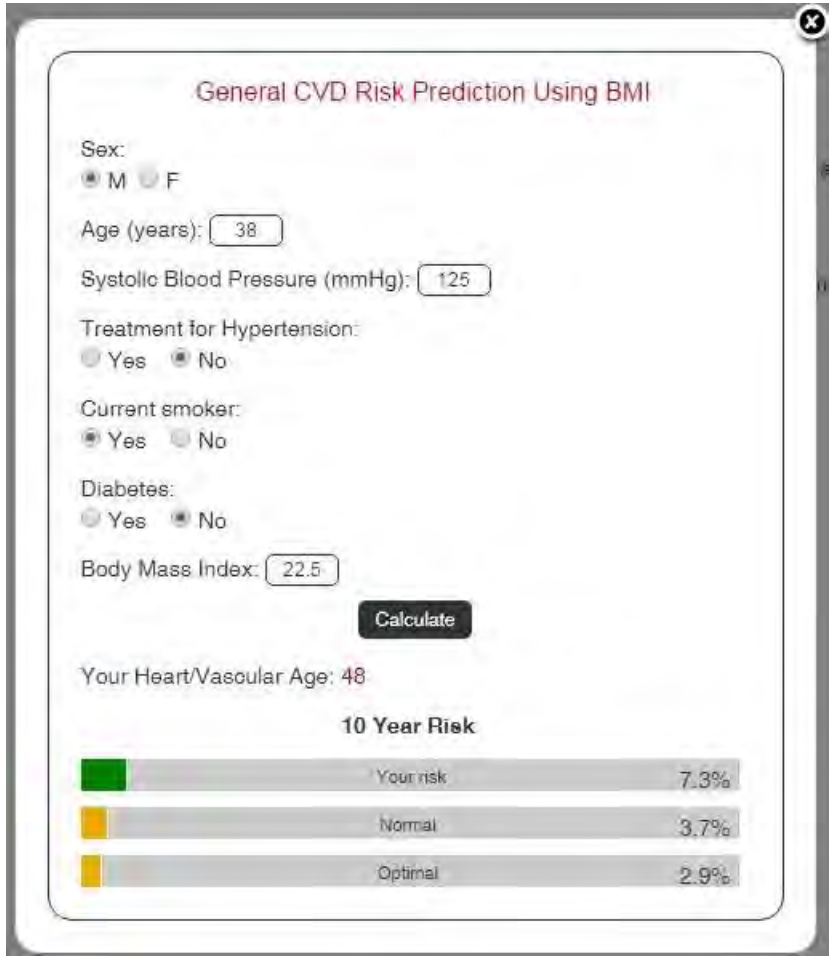
Outcome
CVD (coronary death, myocardial infarction, coronary insufficiency, angina, ischemic stroke, hemorrhagic stroke, transient ischemic attack, peripheral artery disease, heart failure)

Duration of follow-up
Maximum of 12 years, 10-year risk prediction

Population of interest
Individuals 30 to 74 years old and without CVD at the baseline examination

Predictors
- Age
- Diabetes
- Smoking
- Treated and untreated Systolic Blood Pressure
- Total cholesterol

Outcomes:
CVD (coronary death, myocardial infarction, coronary insufficiency, angina, ischemic stroke, hemorrhagic stroke, TIA, peripheral artery disease, heart failure)

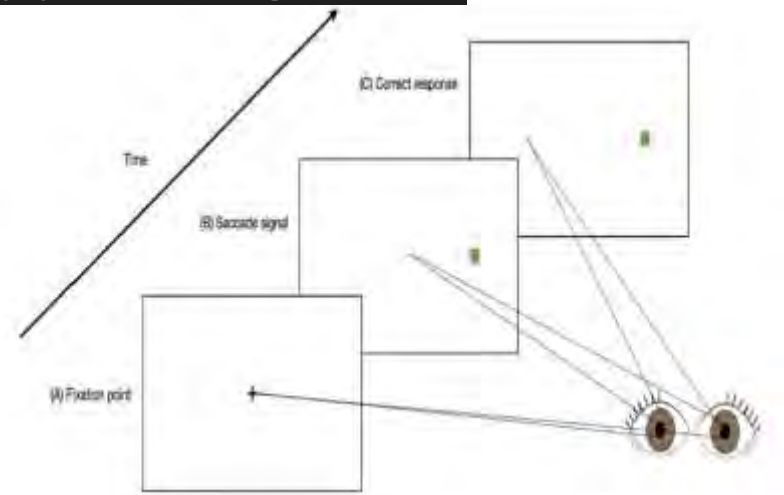


D'agostino et al., Circulation, 2008

https://www.framinghamheartstudy.org/risk-functions/cardiovascular-disease/10-year-risk.php#

Mental fatigue: detection

- Self-report -Experience sampling methods
- Attention Network Test (ANT) reaction times
- EEG Changes in occipital and frontal evident in theta and alpha brain waves
- HRV
- Fatigue from performing cognitive tasks, produced decreased alpha-frequency band (8–13 Hz) power in the middle occipital gyrus (object recognition), cuneus, and middle temporal gyrus (BA 19 and 39, language and semantic memory processing, visual perception, and multimodal sensory integration
- Antisaccade (inhibitory control)
- Cortisol scarcely associated



- Kunasegaran et al. PeerJ 2023

Table 1 Summary of self-reporting questionnaires used to detect mental fatigue.

Name of questionnaire	Description	Strengths	Weakness
Occupation fatigue exhaustion recovery (OFER) scale (*Winwood et al., 2005*)	15 items, classify and distinguish three subscales of mental fatigue (*i.e.*, chronic work-related fatigue traits, acute and end-of-shift states, and effective fatigue recovery between shifts).	Robust and embodies a gender bias and work-status free psychometric characteristic.	Only detects three domains of mental fatigue.
Visual analog scale to evaluate fatigue severity (VAS-F) (*Lee, Hicks & Nino-Murcia, 1991*)	18 items, l00-mm lines in the case of visual analogue lines between two extremes "not at all tired" to "extremely tired".	Uses semantic differential scale which gives a unique bipolar ordinal scale format that captures a person's feelings about a given item.	Frequent reluctance of individuals to use the highest and lowest extremes.
Fatigue assessment scale (FAS)	10-items, evaluates symptoms of chronic fatigue. Half the items measure physical fatigue and the other half measures mental fatigue. It is a unidimensional scale measuring fatigue independently from depression (*Michielsen, De Vries & Van Heck, 2003*).	It was found to be the most promising fatigue measure when compared to five other fatigue questionnaires (*De Vries, Michielsen & Van Heck, 2003*).	Four items appeared to be gender bias—women tended to score significantly higher than men (*De Vries et al., 2004*).
Multidimensional fatigue inventory (MFI) (*Smets et al., 1995*)	20 items, dimensions covered: General Fatigue, Physical Fatigue, Mental Fatigue, Reduced Motivation and Reduced Activity.	Good internal consistency (Cronbach's Alpha = 0.84).	Has not been validated with mentally fatigued individuals.
Fatigue severity inventory (FSI)	14 items, evaluates multiple aspects of fatigue such as perceived severity, frequency, and interference with daily functioning (*Donovan & Jacobsen, 2011*).	Validated with both female and male cancer patients with an age range of 18–24. It has an internal consistency of 0.94 (*Hann, Denniston & Baker, 2000*).	Does not correlate with mental fatigue in the MFI (*Lou et al., 2001*).

Predicting late life Depression 1: DRAT-up

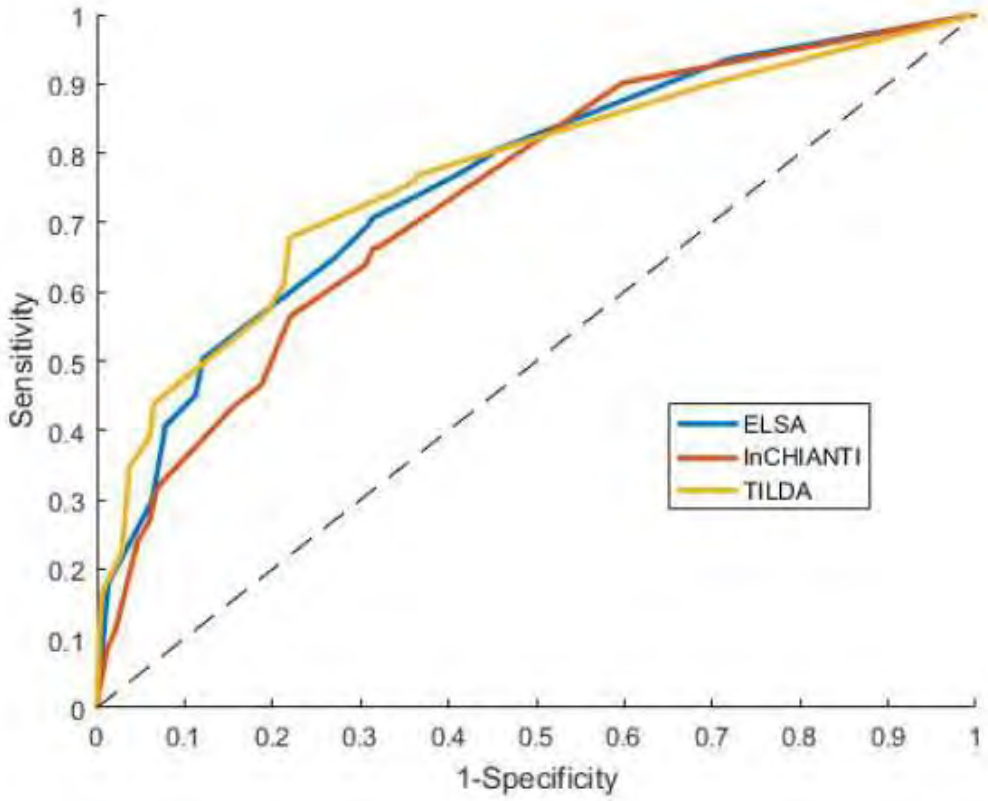
- Cole's 5 factors: **female gender, disability, current depression, sleep disorder, bereavement**
- Knowledge-based Risk Prediction Model based on probabilistic logic. Probability of depression conditional on the available information about risk factors exposure
- If data is missing: substitution with mean prevalence of RF from the population
- Tested on data from ELSA, InCHIANTI and TILDA, with 20206, 1359, and 3124 subjects respectively

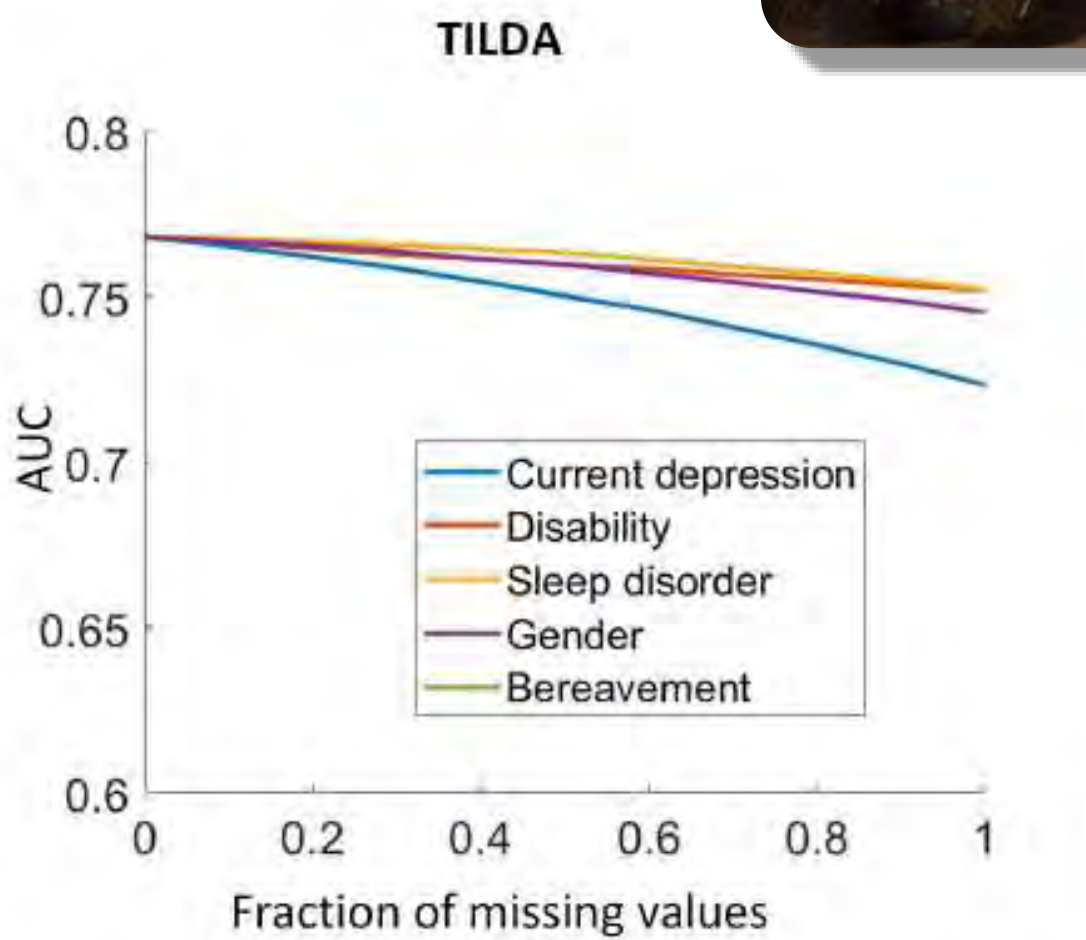
TABLE II
OPERATIONAL DEFINITIONS OF RISK FACTORS AND OUTCOME IN EACH DATASET

	ELSA	InCHIANTI	TILDA
Gender	Gender item	Gender item	Gender item
Disability	ADL or IADL >0	ADL or IADL >0	ADL or IADL >0
Sleep disorder	CES-D item 11 >0	"How would you rate your overall sleep quality during the last month?" score 3-4 (poor or very poor)	Rating "Most of the time" at any of the 3 items on: daytime sleepiness, difficulty falling asleep, early waking
Bereavement	Not used	Widow for 0-12 months	Not used
Current depression	Short version CES-D ≥4	CES-D ≥16	CES-D ≥16
Depression	Short version CES-D ≥4 after 2 years	CES-D ≥16 after 3 years	CES-D ≥16 after 2 years

Cattelani, Belvederi Murri et al., IEEE J Biomed Health Inform 2019

Predicting late life Depression 1: DRAT-up





Area Under the Curve (AUC) were 0.761, 0.736, and 0.768. Fairly robust to missing data

Cattelani, Belvederi Murri et al., IEEE J Biomed Health Inform 2019

Predicting late life Depression 2: Manto

Cognitive dysfunction

Executive function
Cognitive functions
Cognitive complaint
Awareness of dementia
“Fluid intelligence”

Social vulnerability

Ethnicity
Education (low/high)
Widowhood
Living arrangement
Residence (rural/urban)
“Neighborhood disorder”
Living alone
Accessibility of the home environment
Social contacts
Caregiving
Social activities
Intergenerational relationships
Poverty (not income, owning car/having food..)
Low income
Occupation
Leisure and religious activities

Predicting late life Depression 2: Manto

Poor physical health

Biological Parameters

Obesity

Weight loss

Metabolic syndrome

Vascular risk factors

Systolic BP

Antihypertensive use

Biological age (inflammatory, metabolic, cardiovascular, lung, liver, and kidney functioning)

Glucocorticoid receptor gene (NR3C1) methylation

Low vitamin D

Physical illnesses

Heart disease

Diabetes

Stroke

Hypertension

Heart failure

Myocardial infarction

Chronic Illnesses

TIA

Vascular disease (CHD or Stroke)

Asthma

Traumatic brain injury

Chronic disease burden / Multimorbidity

Physical symptoms

Pain

Sleep disorders

Fatigue

Shortness of Breath

Tinnitus

Functional limitations/disability /physical performance

Vision loss

Hearing loss

Eating problems

Oral health (non intact teeth)

Gait speed

Poor physical performance

Functional difficulties/limitations

Disability (ADL / IADL / self-rated)

Frailty (physical)

Predicting late life Depression 2: Manto

Healthcare and lifestyle

Healthcare use

5 or more physician visits in the past year

Physician visits

Hospitalizations

Trust in physician

Habits / lifestyle

Current smoking

Smoking

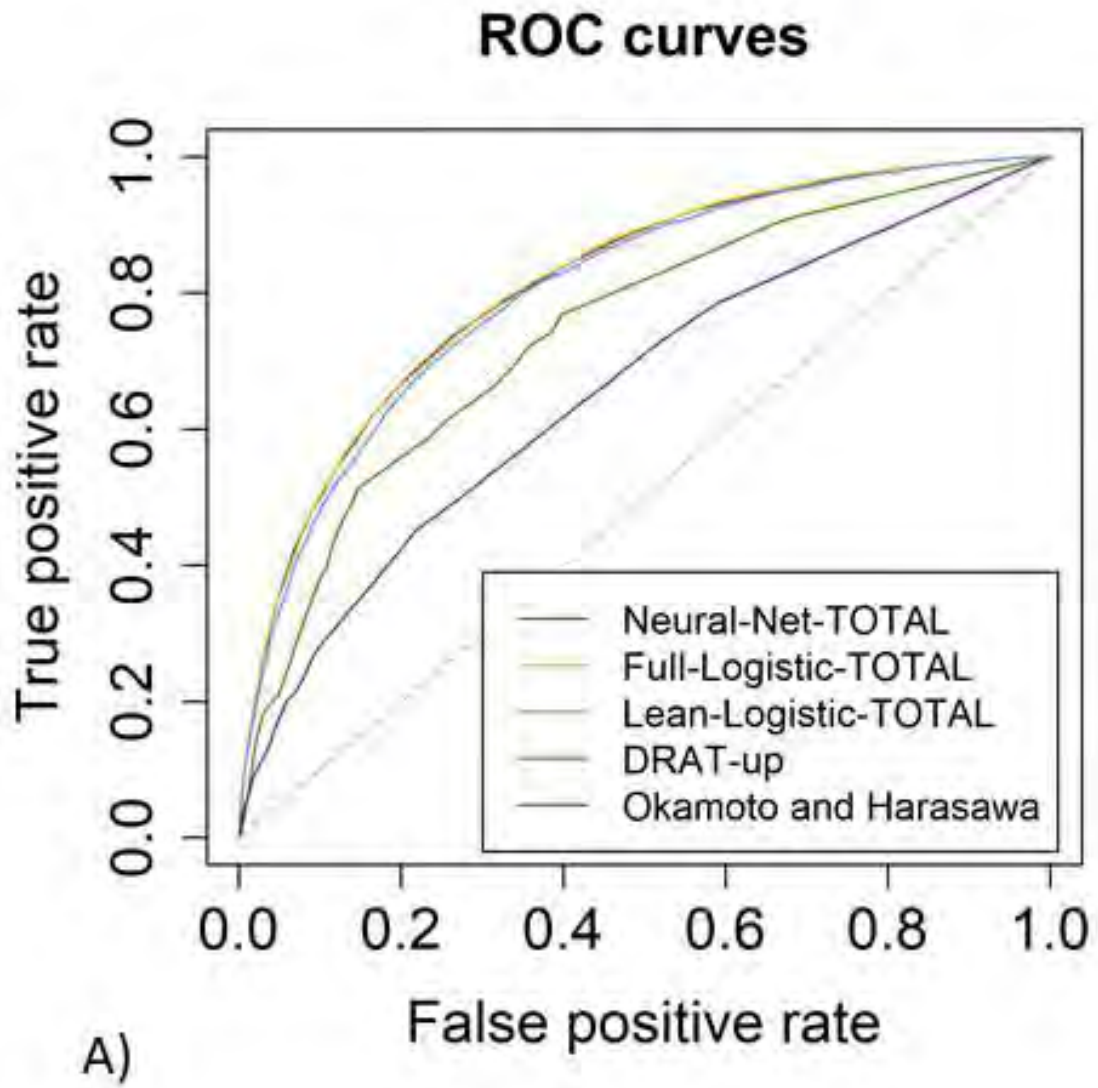
Diet

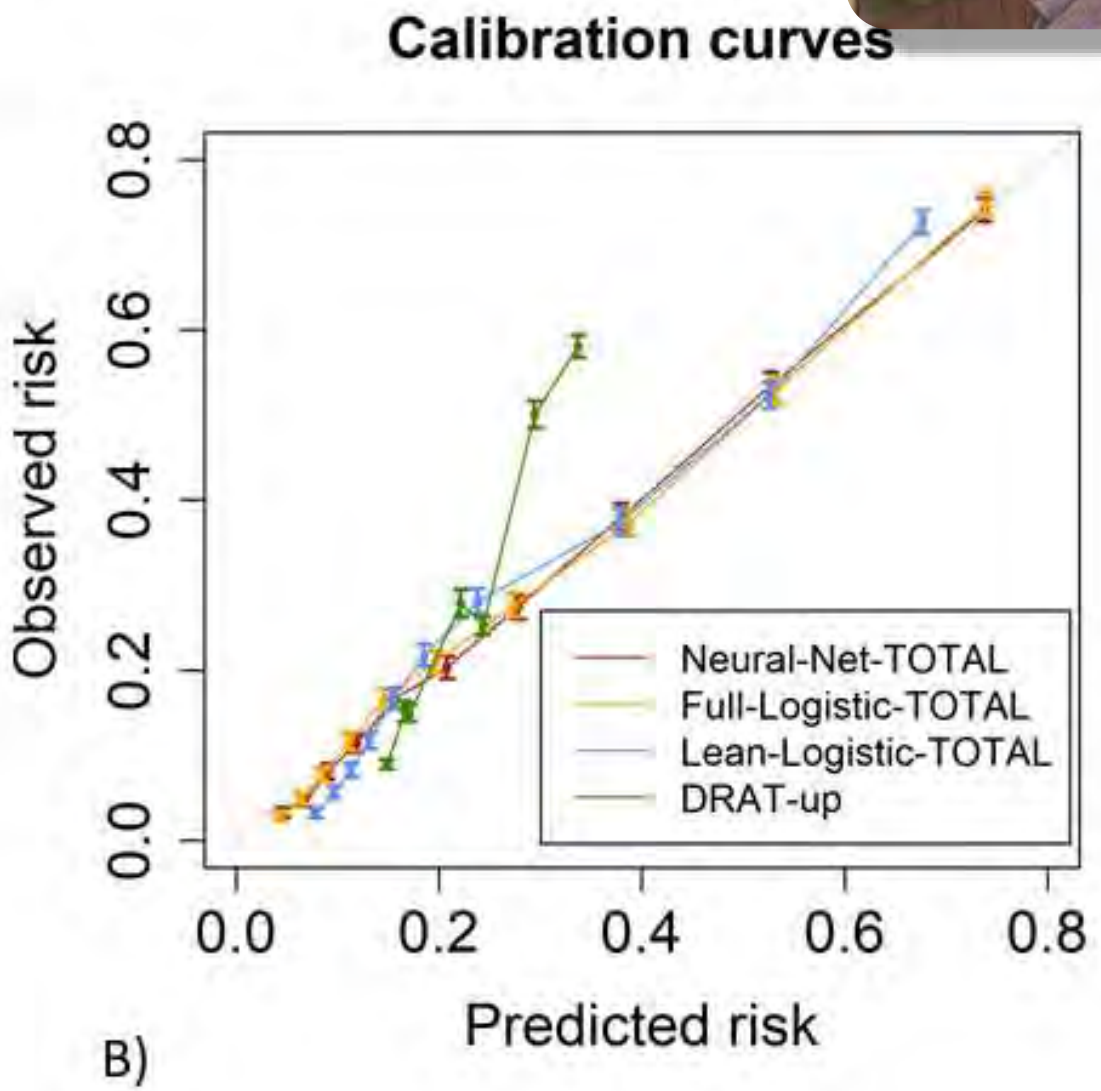
Alcohol use

Nutritional status

Physical inactivity

Predicting late life Depression 2: Manto





Belvederi Murri et al., Am J Ger Psychiatry, 2022

Predicting late life Depression 2: Manto

Sex, age, depressive symptoms, not reading books or newspapers, absence of activities in the previous year, loneliness, poor quality of life, negative views on aging, lack of vitality and optimism, difficulty in activities of daily living, dizziness, pain, and fatigue

Belvederi Murri et al., Am J Ger Psychiatry, 2022

Università degli Studi di Ferrara

manto.unife.it

Welcome

The Manto Depression Risk Calculator helps individuals and healthcare professionals to estimate a person's likelihood of being identified at high risk of developing depression in the next two years.
It is sufficient you answer **few questions about current symptoms of depression and other aspects of your life**, and you will receive an estimate of **your individual risk score**.

The risk assessment, using this calculator, should be performed for all **adults aged 55 and older** who **are not known to have dementia or severe cognitive impairments**.
Results can be reliably calculated even if the respondent is already depressed at the time of the risk assessment.

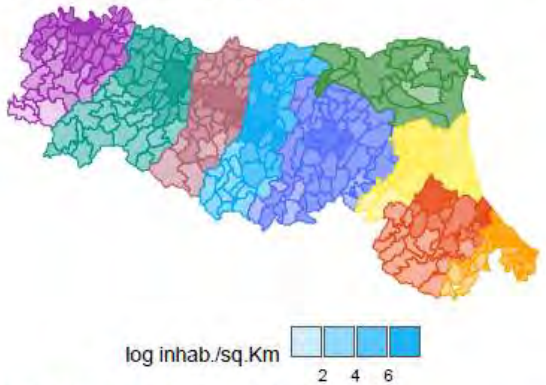
The data collected by the test is completely anonymous and cannot be traced back to your person nor will it be subject to disclosure.

Click below to get started.

Start now

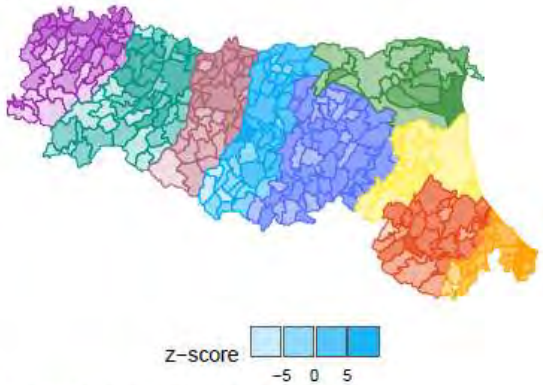
Regional Socio−economic Indices

Population density (log scale)



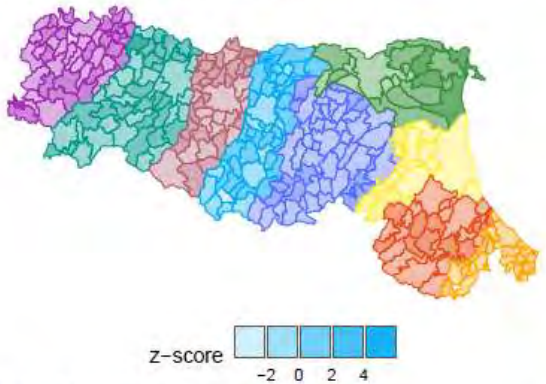
log inhab./sq.Km 2 4 6

Deprivation index



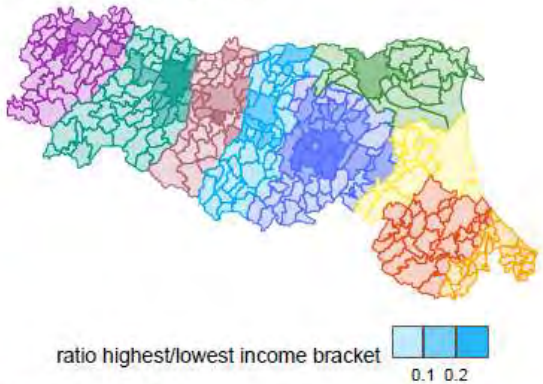
z−score −5 0 5

Educational deprivation index



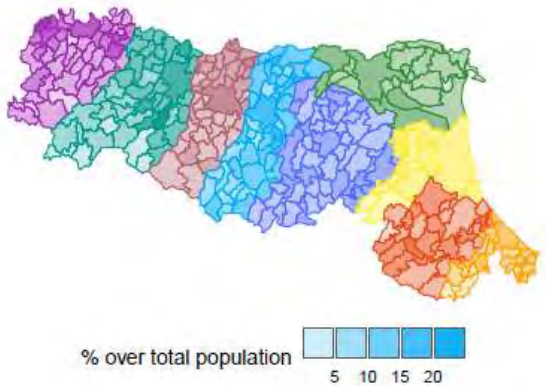
z−score −2 0 2 4

Economic inequality index



ratio highest/lowest income bracket 0.1 0.2

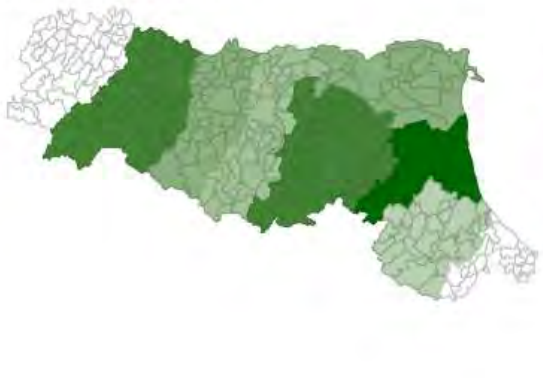
Percentage of migrants



% over total population 5 10 15 20

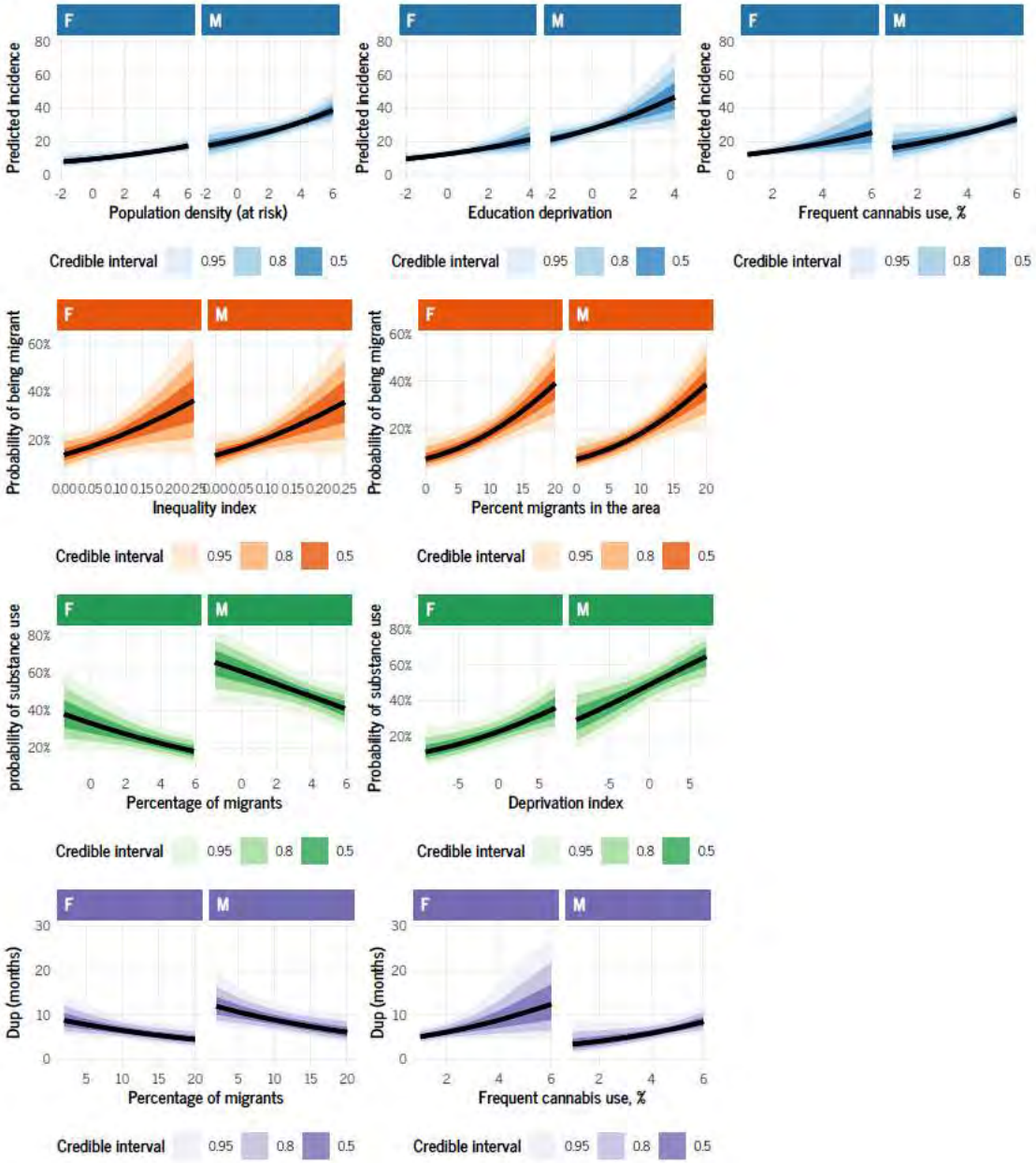
Frequent cannabis use

Province schoolers 15−19



% 4.0 3.5 3.0 2.5

Effects



The body in treatment

Esercizio fisico e depressione nell'adulto: Efficacia dopo aggiustamenti metodologici

-Moderate to large effect on depression compared to control (g=-0.68)

-Effect was small and not significant at follow-up (g=-0.22).

-Compared to no intervention yielded large and effect size(g=-1.24)

-Compared to usual care yielded moderate effect size (g=-0.48)

-Compared to psychological treatments or AD yielded small not significant effects (g=-0.22 and g=-0.08).

-**As an adjunct to antidepressant medication yielded a moderate effect (g=-0.50)**

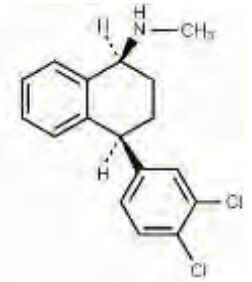
Kvam et al., JAD, 2016; Schuch et al., J Psychiatr Res. 2016

Esercizio fisico e depressione nell'adulto

- In several countries, physical activity is ALREADY recommended in clinical practice guidelines as an option for the treatment of subthreshold, mild, and moderate adult depression.

SEEDS

Anti-Depressant Sertraline (S)



•SSRI – low potential for drug interactions; hepatic metabolism.
•Good efficacy – first line treatment for LLMD.
•Starting dose 50mg – psychiatrist free to increase dose up to 200mg according to clinical response.

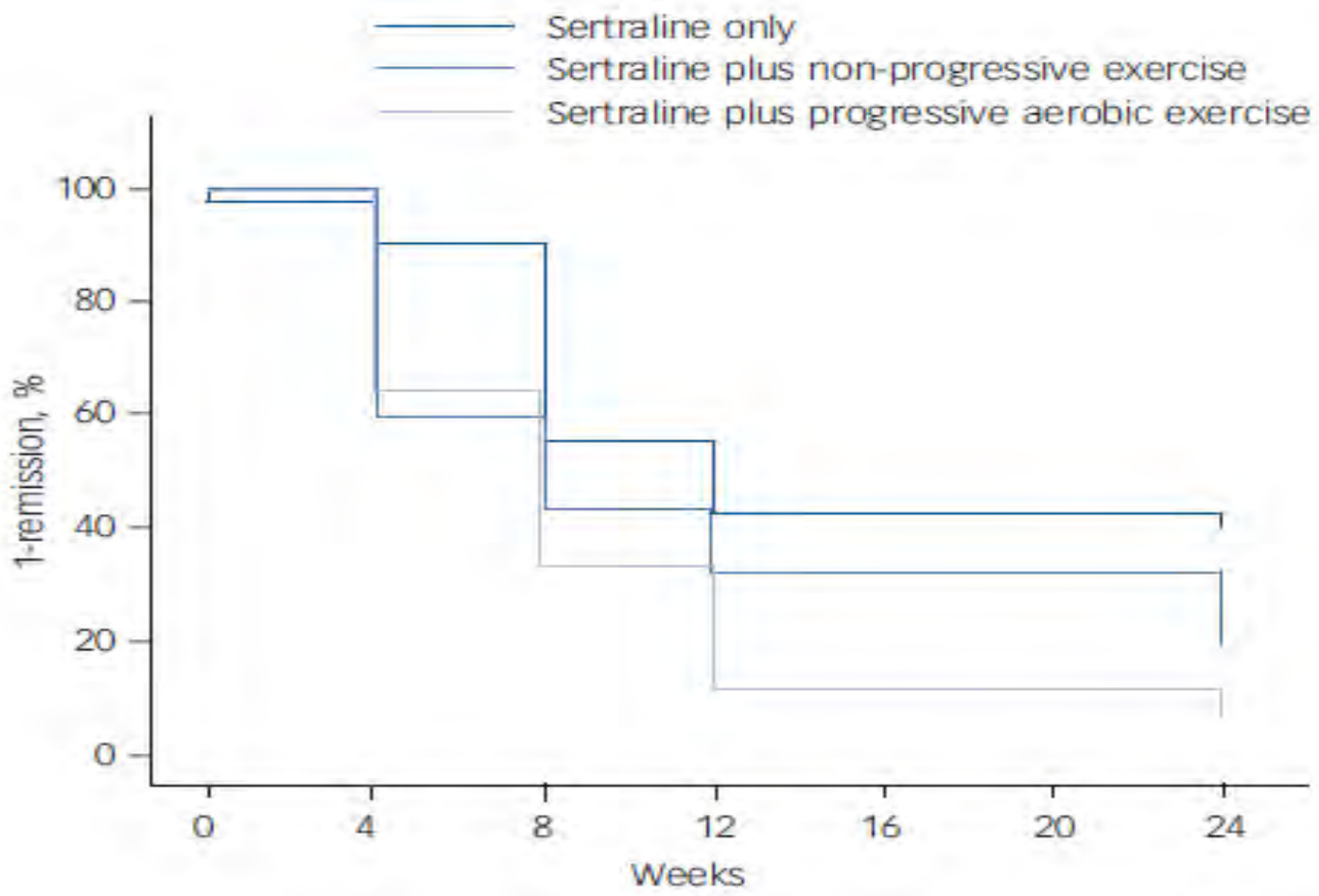
S+ Non-Progressive Exercise (S+NPE)

24 weeks, 3 times/week; 1 hour sessions; 4-6 participants with on-screen heart rate monitor; warm-up, walking, strengthening exercises, quiet calisthenics, mat work, stretching, instrumental and balance exercises.

S+ Progressive-Aerobic Exercise (S+PAE)

24 weeks, 3 times/week; 1 hour sessions, 4-6 participants with on-screen heart rate monitor; warm-up, exercise bike at target heart-rate range (60–70% of the peak heart rate, derived from peak VO_2 test and increasing along the 24 weeks).

SEEDS: risultati



Belvederi Murri et al.,2015

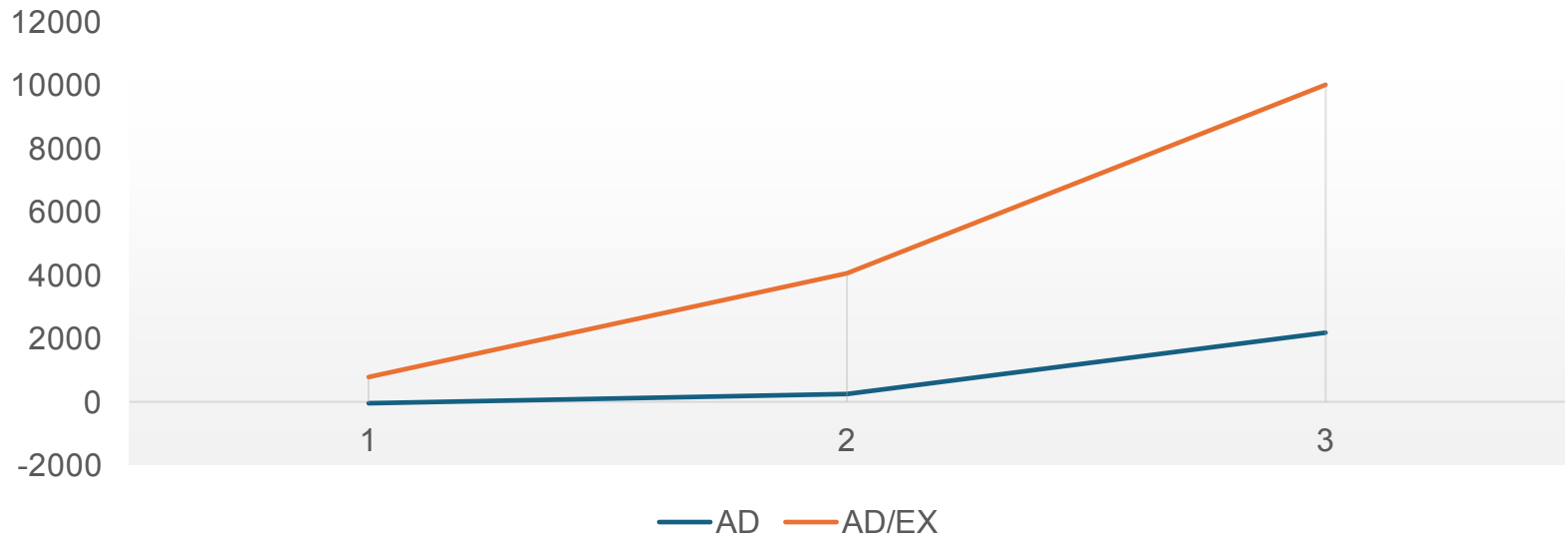
BJPsych The British Journal of Psychiatry
1–8. doi: 10.1192/bjp.bp.114.150516

THE AMERICAN JOURNAL OF
GERIATRIC PSYCHIATRY

Physical Exercise for Late-Life Depression: Effects on Heart Rate Variability

-**Significant improvements of HRV indices associated with sertraline**
- **Even greater improvements with sertraline + exercise**

Figure 1. Longitudinal changes of HF (vagal activity)



Toni, Belvederi Murri, Amore et al., Am J Ger Psych, 2016

General Hospital Psychiatry 49 (2017) A1–A5

Contents lists available at ScienceDirect

General Hospital Psychiatry

journal homepage: www.elsevier.com/locate/genhospsych

Editorial

Exercise as antidepressant treatment: Time for the transition from trials to clinic?

2. But how could exercise possibly change mood?

3. But there is no evidence!

4. But, even if there is evidence, it's methodologically weak!

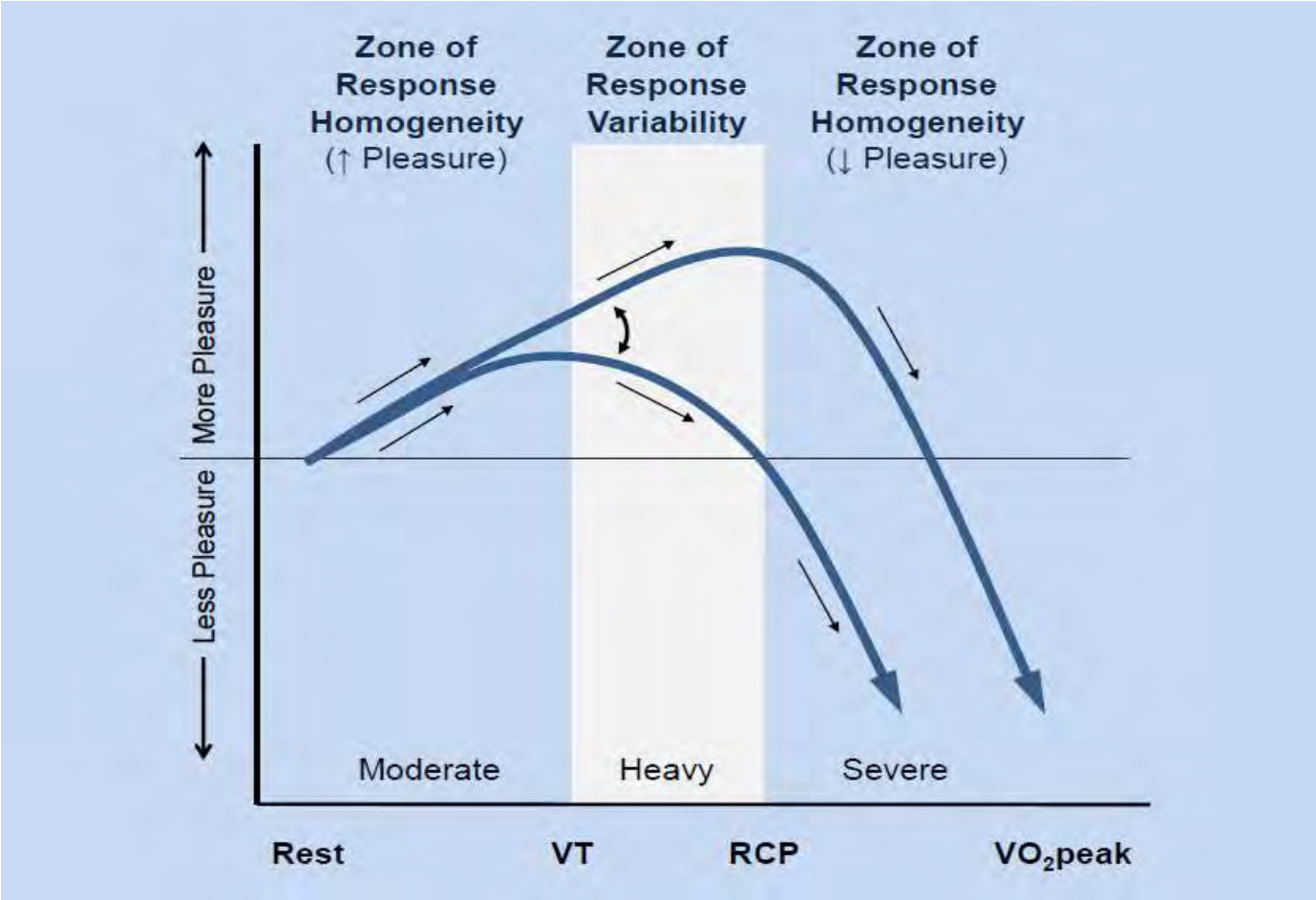
5. But patients won't do it!

Ekkekakis and Belvederi Murri; Gen Hosp Psych, 2017

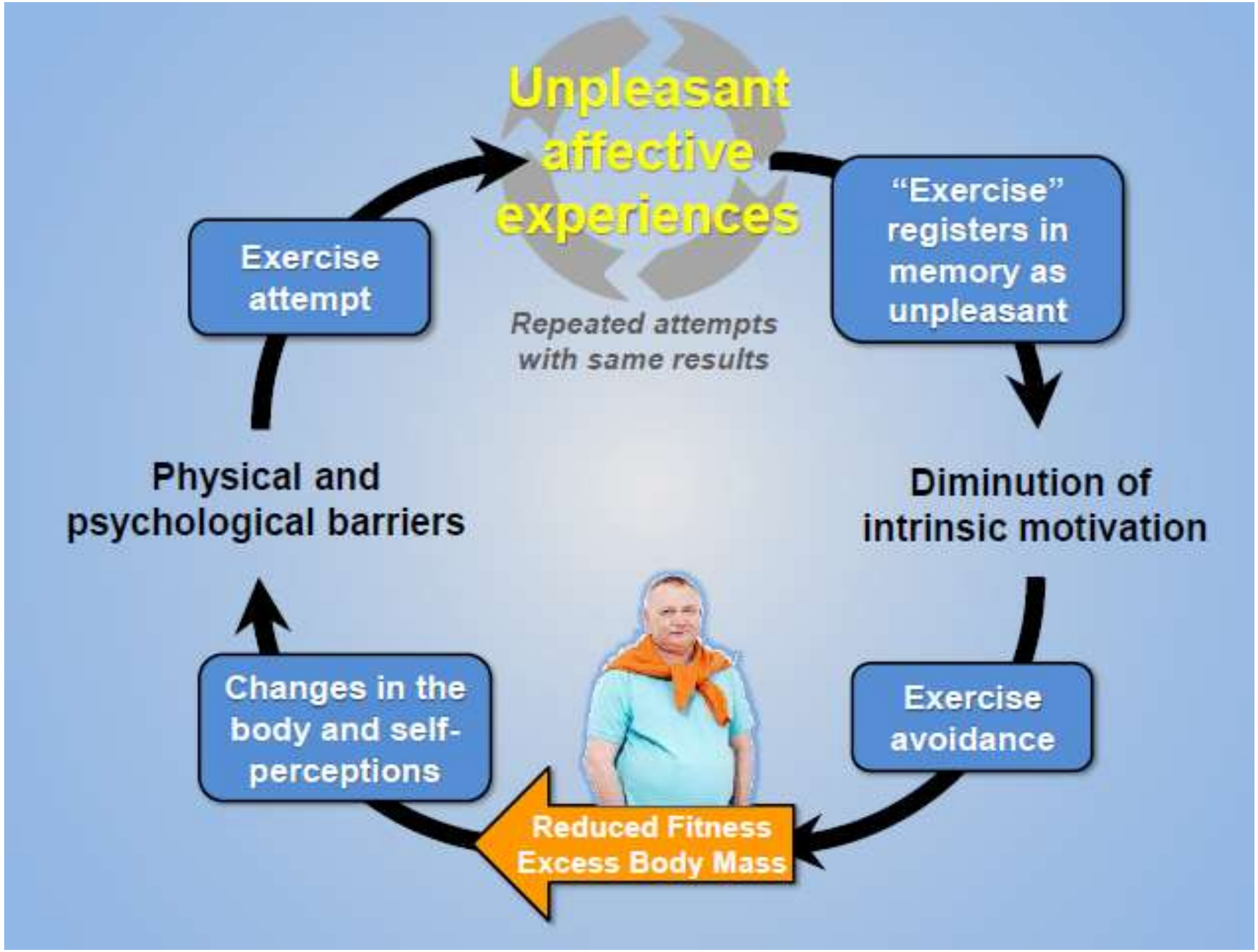
The Pleasure and Displeasure People Feel When they Exercise at Different Intensities

Decennial Update and Progress towards a Tripartite Rationale for Exercise Intensity Prescription

Panteleimon Ekkekakis,[1] *Gaynor Parfitt*[2] and *Steven J. Petruzzello*[3]

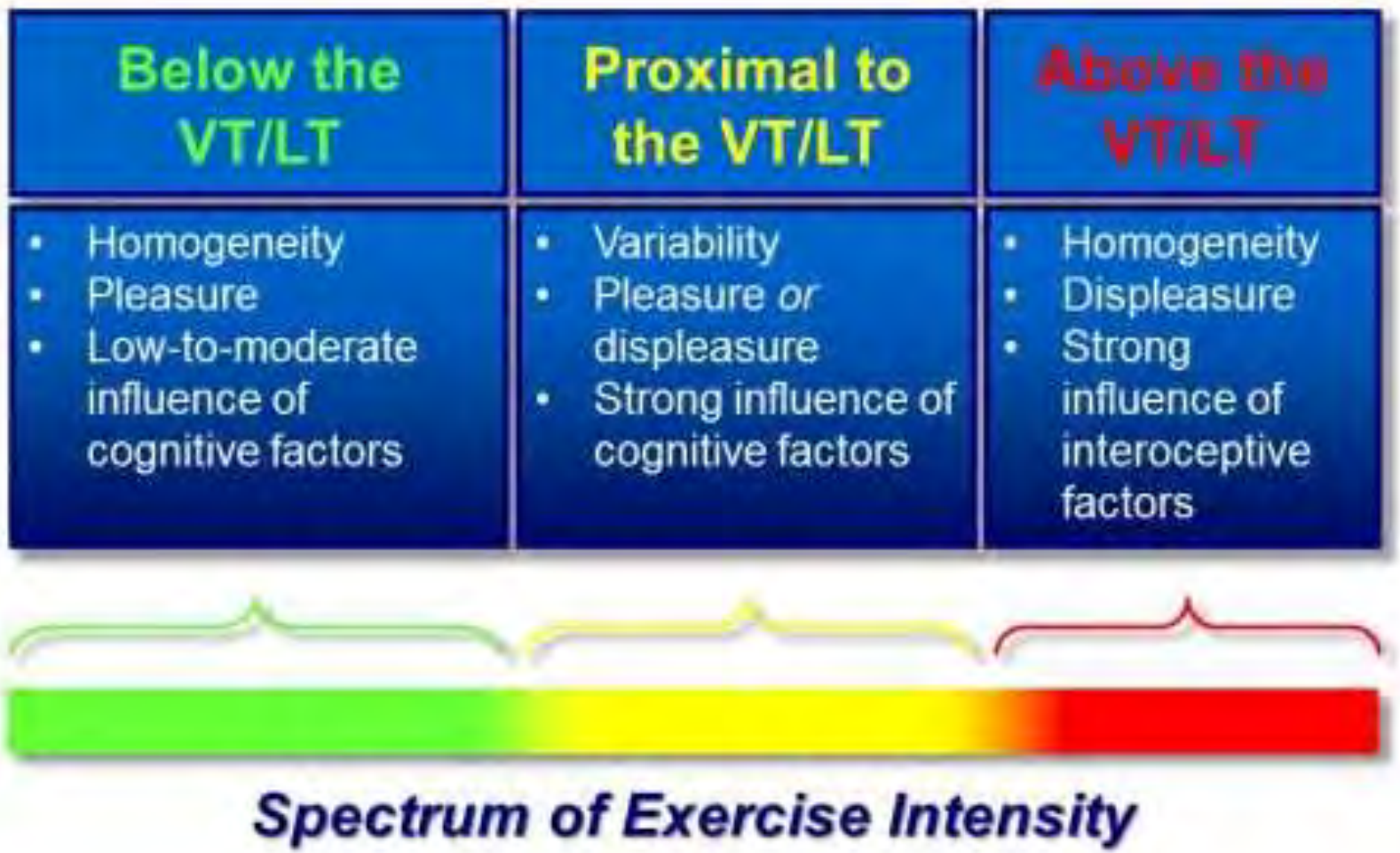


Sports Med 2011


Unpleasant affective experiences
"Exercise" registers in memory as unpleasant
Diminution of intrinsic motivation
Exercise avoidance
Reduced Fitness
Excess Body Mass
Changes in the body and self-perceptions
Physical and psychological barriers
Exercise attempt
Repeated attempts with same results

The Pleasure and Displeasure People Feel When they Exercise at Different Intensities

Decennial Update and Progress towards a Tripartite Rationale for Exercise Intensity Prescription



Sports Med 2011; 41 (8): 641-671

Ralf Brand[1] · Panteleimon Ekkekakis[2]
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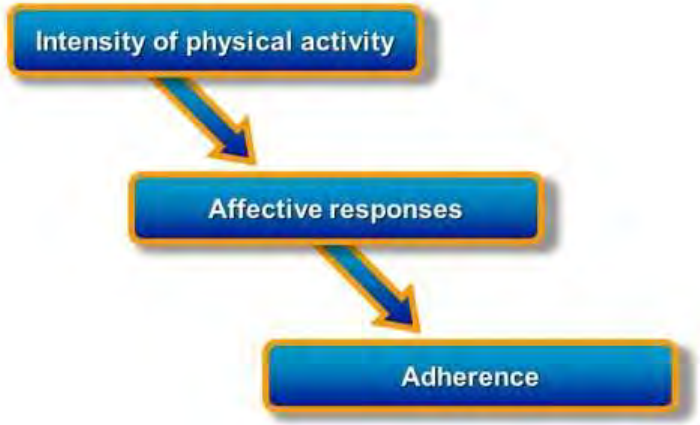
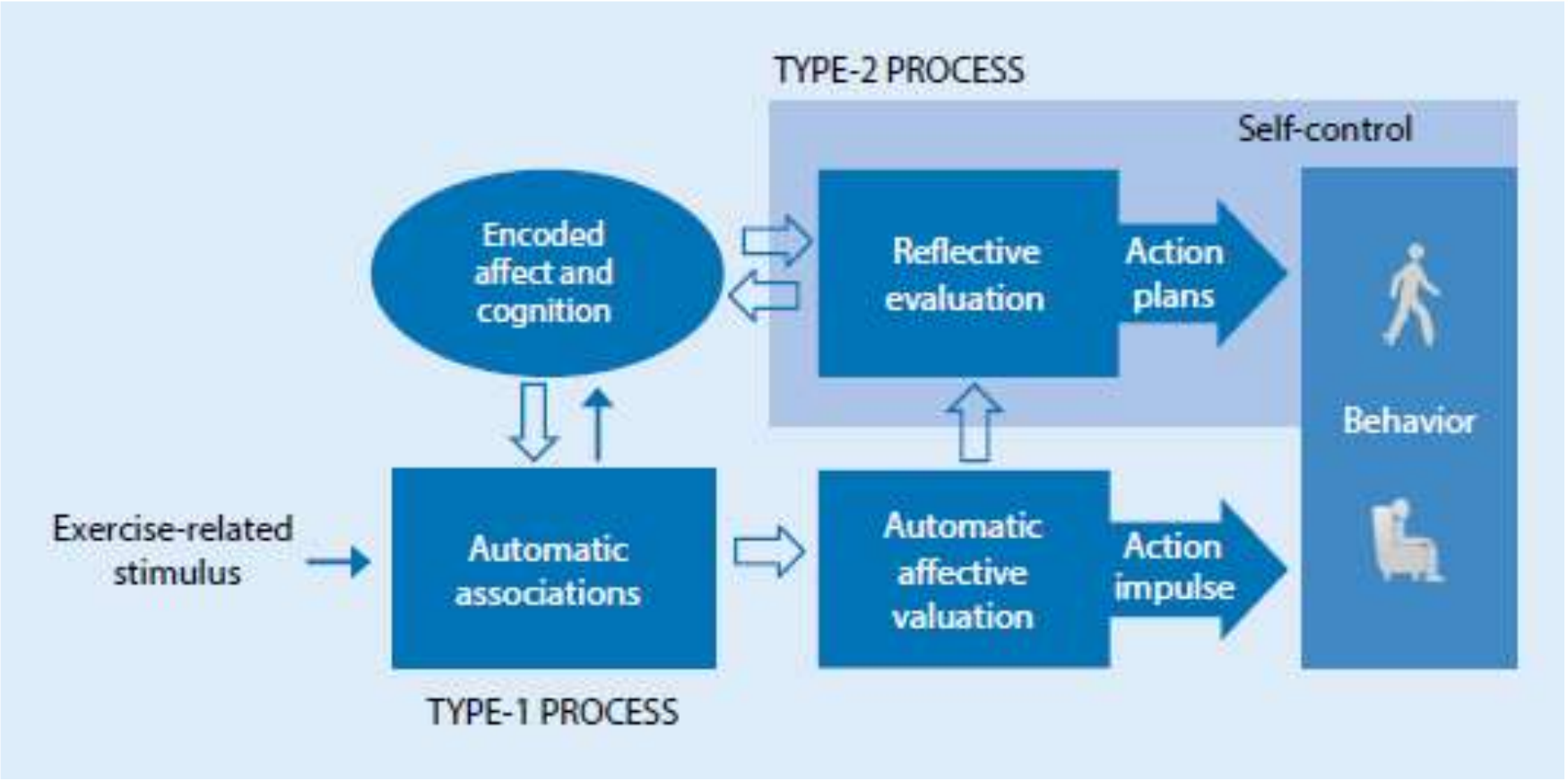
Affective–Reflective Theory of physical inactivity and exercise

Foundations and preliminary evidence





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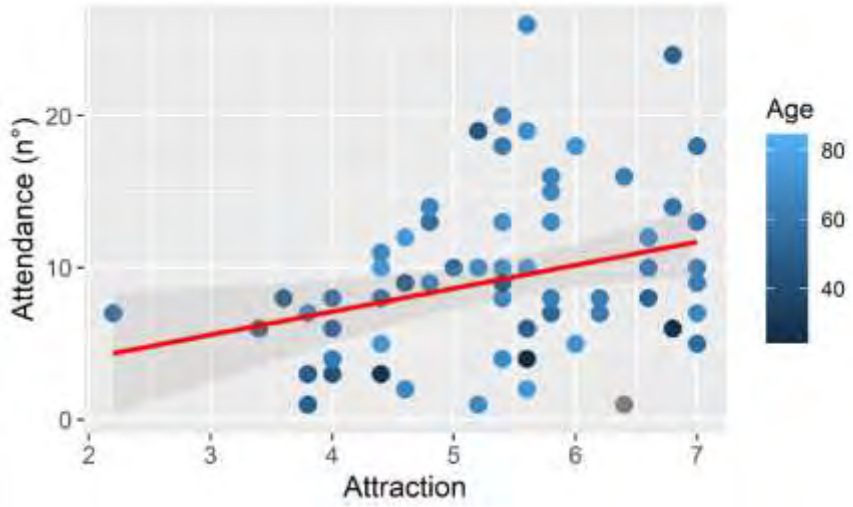
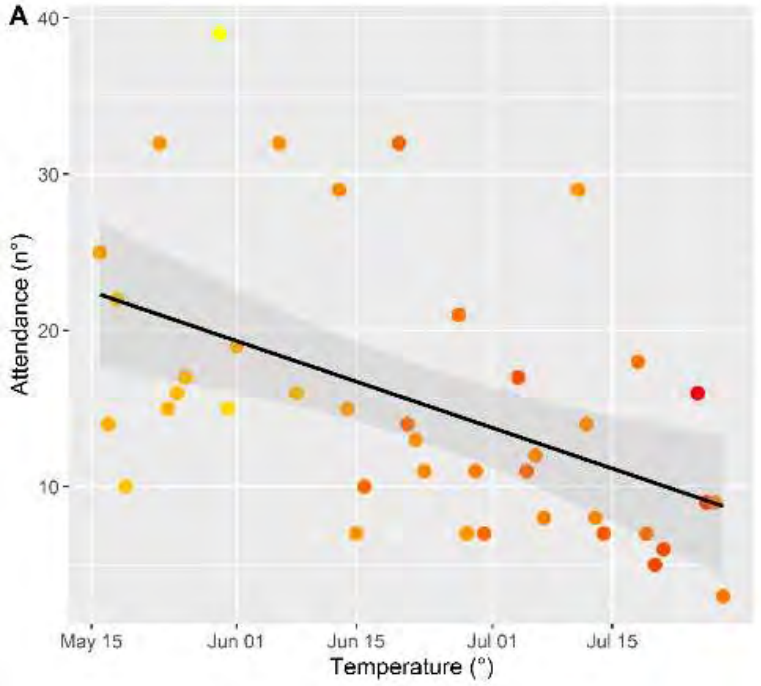
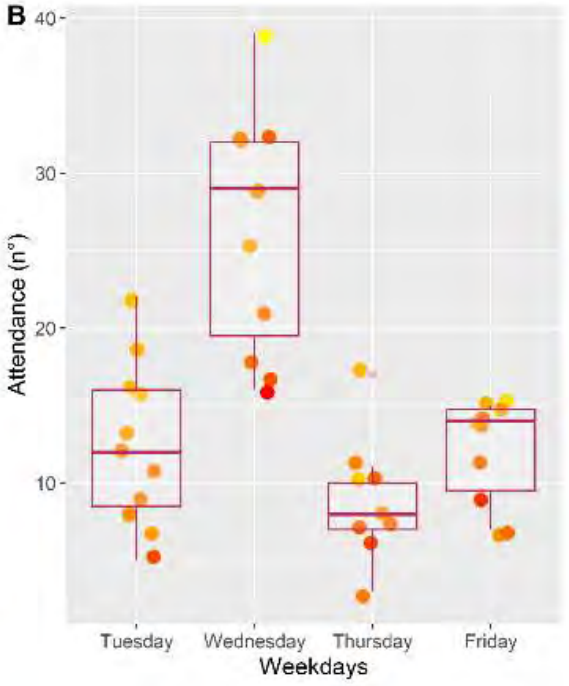
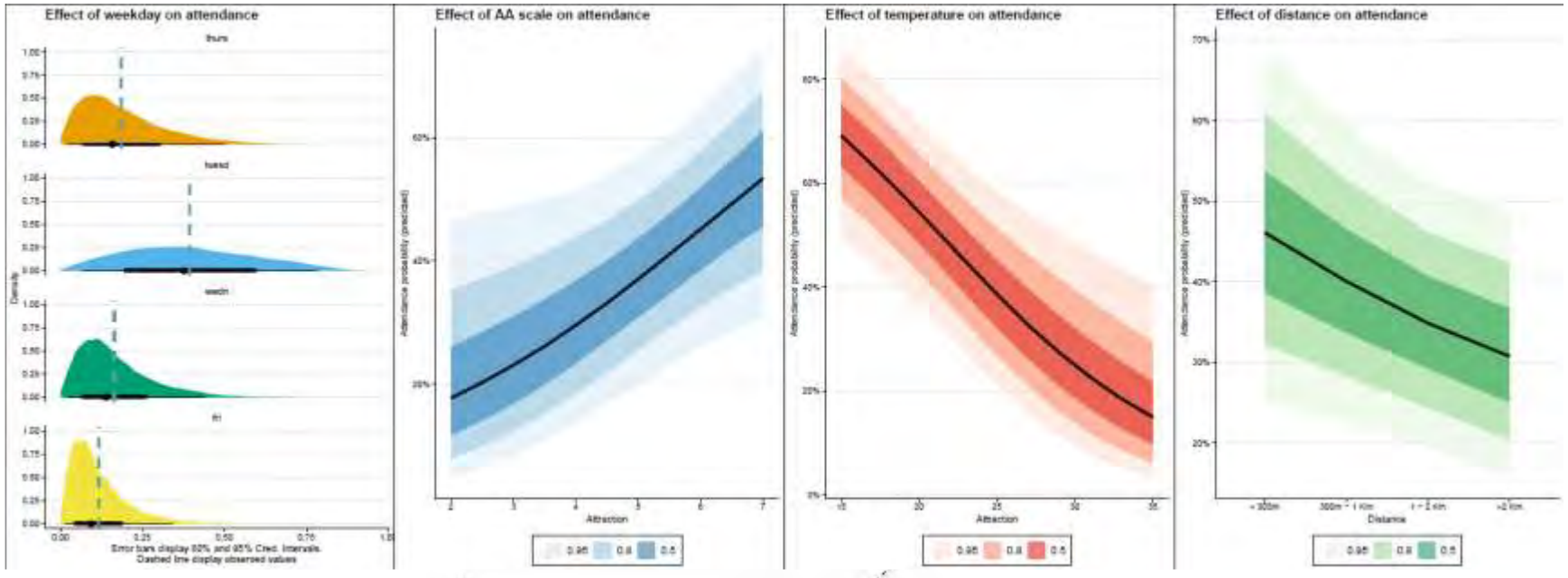
Esercizio fisico: predire la aderenza tp

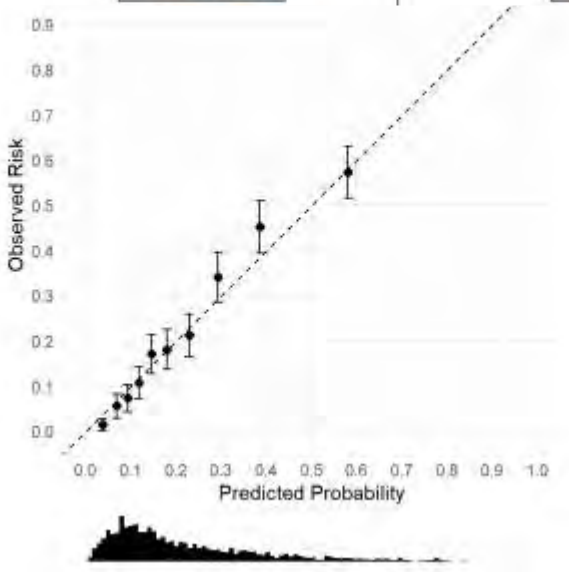


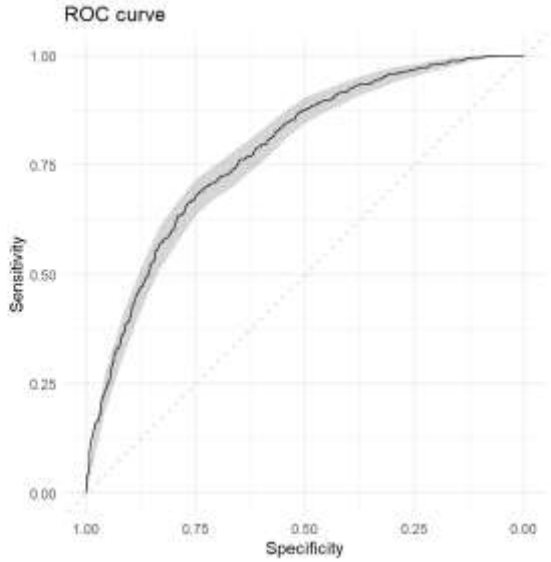




Esercizio fisico: predire la aderenza tp

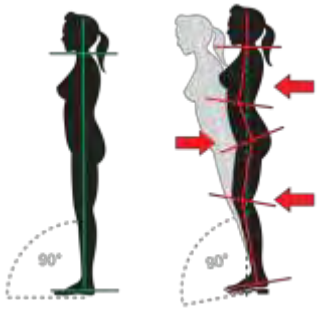






He.s.i.o.d. Study Intervention

Breathing/Postural Exercises Plus Antidepressant Drug (SSRI)



The intervention consisted of breathing and postural exercises, under trained staff supervision.

- Respiratory exercises: respiratory muscles training, forced expiration, thoracic expansion techniques, during the rhythmic recitation of hexameter poetry, which has known positive effects on cardio-respiratory synchronization.
- Postural exercises: upper and lower limb strengthening, motor coordination and education.
- The one-hour sessions were held weekly in groups of 5-10 subjects, for 24 weeks.

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