Depression: An Evolutionarily Conserved Mechanism To Terminate Protracted Separation Distress?

Reclaiming Our Most Costly Emotional Disorder from Reductionist Obfuscation and Ineffective & Unsafe Treatment

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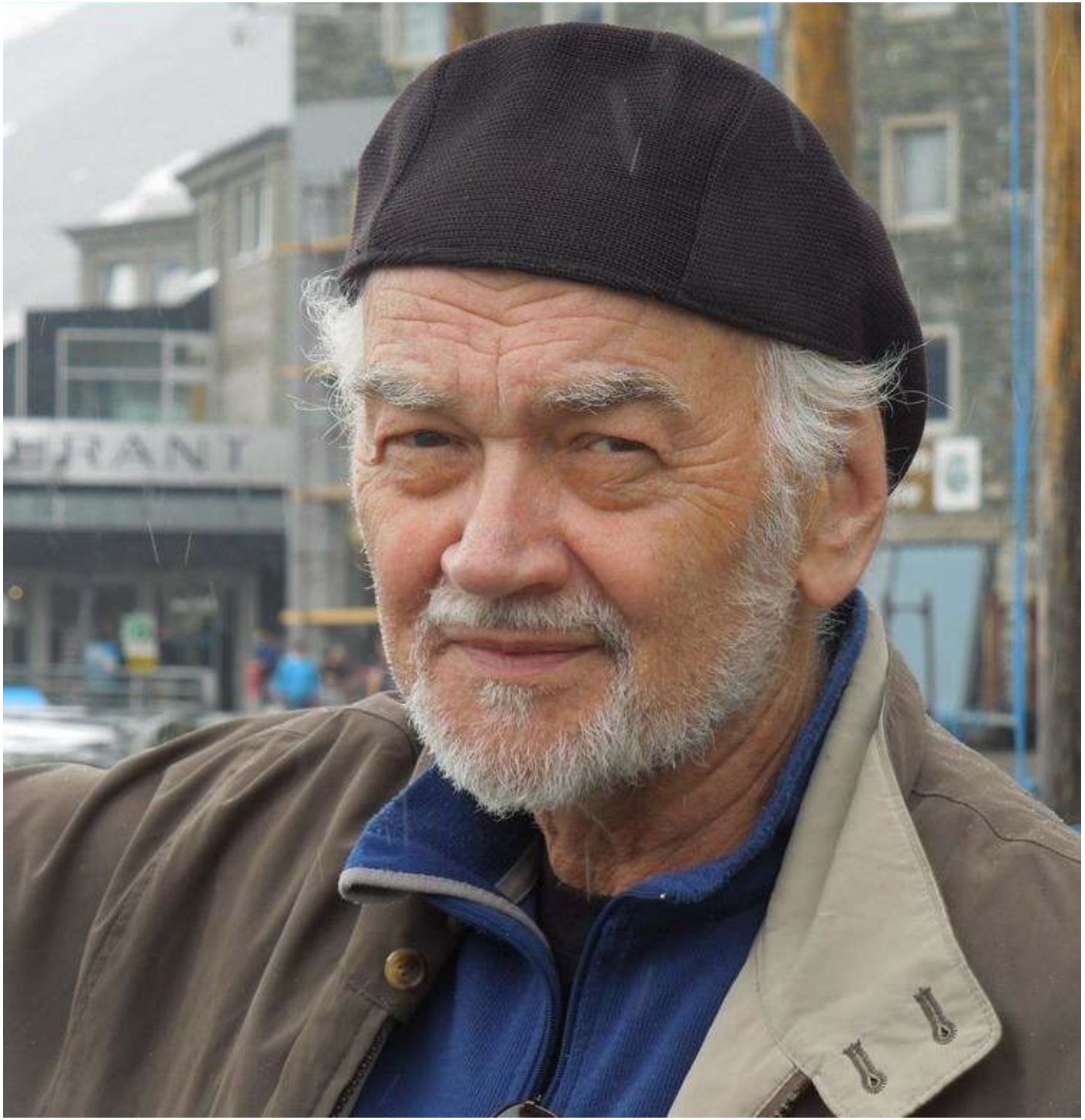
Jaak Panksepp
1943 to 2017

Genius, scholar, friend, co-author, mentor, a big softy, hard ass kind of guy!

Inspired multiple generations of scholars & scientists attempting to understand emotion, human behavior, and our deep continuity with the animal world.

Especially interested in ***social bonds and separation distress, empathy and play***.



Nature has placed mankind under the governance of two sovereign masters, pain and pleasure…they govern us in all we do, in all we say, in all we think: every effort we can make to throw off our subjection will serve but to demonstrate and confirm it.

Jeremy Bentham

The heart asks pleasure first
And then, excuse from pain -
And then, those little anodynes
That deaden suffering;
And then, to go to sleep;
And then, if it should be
The will of its Inquisitor,
The liberty to die.

Emily Dickenson

Depression is the most unpleasant thing I have ever experienced . . . It is that absence of being able to envisage that you will ever be cheerful again. The absence of hope. That very deadened feeling, which is so very different from feeling sad. Sad hurts but it's a healthy feeling. It's a necessary thing to feel. Depression is very different.

(J.K. Rowling, 2000, London Times)

We are here to awaken from the illusion of our separateness
– Naht Hahn

Original form of our hypothesis (Watt and Panksepp, 2009) – 3 core suppositions

- Depression is evolutionarily conserved – a basic vulnerability within social-affective endowment of mammalian brains, while disinhibition of conserved mechanism → depressive illness.
- Depression functions to adaptively shut down/delimit protracted separation distress, potentially harmful to infant mammals at least two ways (predation/metabolic conservation), thus protective in delimited form, helping to explain mammalian conservation.
- Depression, *like all other selected processes*, has no single biological 'lever' and instead is instantiated though a complex panoply of interactions but critically involves relationships between SEP DISTRESS and SEEKING ('brain reward' systems).
- Unfortunately, separation distress concepts are not widely penetrant within mainline psychiatry or psychology – more evidence for siloed knowledge?

The clinical problem space (formidable!)

- An ancient issue for human beings, classical descriptions of depression go back into antiquity (Hippocrates, Euripides, Galen)
- Far and away the most common psychiatric disturbance, and overall reason for any clinical contact, psych or medical.
- Probably still significantly under-diagnosed, true incidence is still poorly charted (? > 35-50% lifetime, if including milder forms (DD) > 65-90% lifetime). Increasing incidence in most surveys.
- *Single most expensive disorder faced by Western societies, second leading cause of disability*. Never had more antidepressants, or more prescriptions, and yet penetration unabated. Why?
- Given that depression increases many comorbidities (cardiac disease/stroke, immune dysfxn, diaobesity, cancer) & w/many psychiatric comorbidities (PTSD, addiction, anxiety disorders), true extent of human & economic costs > we can estimate.
- Many comorbidities beg critical questions! Becomes more evidence against dominant 'boxology' models of major diseases.

The scientific problem space

- Any reviewer faces huge conceptual/empirical problems, w/ sprawling, confusing, conflicted and fragmented literature.
- 10000+ reviews, 5000+ studies past 10 yrs – Herculean to review
- Ubiquity of depressive states argues that it cannot be written off as an 'illness' and begs basic question as to why selected.
- Adaptive basis of depression seems a paradoxical question (especially in view of suicide) but neglected.
- Popular media promotes notion of depression as illness caused by chemical imbalance (but this is non-explanation!)
- Dominant view has been that one can go from molecules to complex behavior, without considering neural systems (esp. conserved basic affective systems in mammalian brains).
- Some but not all bottom-up molecular views neglect depression's close connections to stress, pain, and emotional loss.

Scientific challenges (2)

- Despite reliance on animal models in drug development, assuming evolutionary continuity, psychiatry ignores issue of affective mammalian endowment (vs. embracing molecular reductionism).
- Limited number of prototype emotional systems: FEAR, RAGE, PLAY, LUST, SEP DISTRESS, maternal CARE (JP, 98), all perhaps evolutionary refinements of a basic SEEKING/basic motivational arousal system originally aimed at homeostasis.
- Much evidence suggests relationships between these prototype mammalian affective systems and depression.
- Child development work (Spitz, Bowlby, etc), and animal model work suggests depression might reflect evolutionarily selected mechanism to terminate protracted separation distress?
- Behavioral shutdown conserves precious metabolic energy in infant mammals & simultaneously reduces risk of predation.
- May be sibling process to two other highly conserved shutdown mechanisms: sickness behavior and hibernation.

Scientific challenges (3)

- Literature outlines dozens of neurobiological correlates and many potential candidate mechanisms:
  - Aminergic (generally ↓) and cholinergic (generally ↑) changes;
  - Alterations/overactivity in HPA axis (it's stuck??!);
  - Neuroendocrine changes with many neuropeptide alterations (CRF, SP, 3 opioids, oxytocin) w/ GC receptor resistance;
  - Cytokine and immune alterations;
  - Alterations in GABA and glutamate.
- A truly confusing panoply of neuromodulatory changes! Every system looked at shows some kind of alteration.
- Where is locus of control or 'center of gravity' for this 'chemical imbalance'? Attraction of single factor theories?
- Alterations in corticolimbic networks, & core nuclei (HYPO, cingulate, DL prefrontal cortex, HC, NAcc, AMYG). Default network appears 'stuck,'/hyperconnected, hypoconnectivity within emotional salience/frontoparietal networks?

Evolutionary Perspectives

- Early utility in relationship to separation distress provides mechanism recruited later in dominance conflicts.
- Keller and Nesse (2006/2000): subtypes of depression vis a vis adaptive challenge: social losses vs. dominance? (S. Blatt also)
- Selected to protect organisms by terminating behavior that would risk damage to organism (classically dominance conflict).
- Withdraw/retool/reset/re-engage more effectively later.
- Two case examples – adaptive/delimited vs. disinhibited/lethal.
- Presumably would be derived from antecedent/other shutdown mechanisms (sleep, sickness behavior, hibernation?)
- Mechanisms that kill several birds with one stone are likely to be selected. No selected mechanism/gene does only one thing
- Evolution takes what works and tweaks it to work even better in a new context, it doesn't have to reinvent wheel.

Depression and the social brain?
Depression and general health?

- The **'transmitter imbalance' hypothesis** of the 60's ↔ **'psycho-pharmacology revolution'** of the 70's.
- Despite lasting popularity of meme, no Axis I condition has been shown to be truly **caused** by a simple amine transmitter **deficiency**.
- Worrisome contrast between **scientific failure vs. staggering commercial success** of pharmaRxs based on this meme?
- Psychiatry proceeded with implicit assumption that **health of brain & health of body were separable domains**, and until recently, little attention to sleep, diet, exercise in Axis I Disorders in Psychiatry.
- Parallel assumption that healthy relationships had little biological impact.
- Growing evidence that **diet/MB & lifestyle causal variables** in Axis I disorders; stress, inflammation, and cellular phenotypes of aging look etiological, not simple neurochemical deficiencies.
- **Gene-environment mismatches** appear generative in many chronic diseases? A social brain genome operating in asocial or antisocial space?
- Many mainline psychiatric drugs may have very **serious long term health risks**, esp. neuroleptics, about which patients are often not warned. MITO issues, Ins resistance, diaobesity.

DSM-IV Criteria for Major Depressive Episode (little Δ in DSM-5)

A. Five (or more) symptoms have been present during the same 2-week period and represent a change; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

(Note: Do note include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.)

(1) ***Depressed mood*** most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful). **Note:** In children and adolescents, can be irritable mood. (Mood might be characterized by *sadness, emptiness, or hopelessness*).

(2) ***Markedly diminished interest or pleasure*** in all, or almost all, activities most of the day, NED – (subjective account or observation).

(3) Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. **Note:** In children, consider failure to make expected weight gains.

(4) ***Insomnia or hypersomnia*** nearly every day.

DSM-IV Criteria (DSM-5)

5. Psychomotor agitation or retardation nearly every day NED.
6. Fatigue or loss of energy NED.
7. Feelings of worthlessness or excessive or inappropriate guilt - may be delusional - not merely self-reproach or guilt about being sick, NED.
8. Diminished ability to think or concentrate, or indecisiveness, NED (subjective account or observed).
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms do not meet criteria for a Mixed Episode.

C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The symptoms are not due to direct physiological effects of a substance e.g., a drug of abuse, medication or a general medical condition e.g., hypothyroidism.

E. The symptoms are not better accounted for by Bereavement (longer time frame allowed beyond the previous arbitrary time frame of 2 month).

Issues Re: DSM-IV/V criteria

- Depressive alterations affect '**superordinate' cognitive & 'subordinate' homeostatic fxn**. Criteria cut across hierarchy of CNS functional domains (cognition, emotion, homeostasis).
- **"Depressed mood" as diagnostic criteria is circular.**
- What exactly **is** a depressed mood? **Loss of hopeful orientation?** Curiously, hopelessness has been removed from earlier DSM criteria, but now reinserted as a descriptor?
- **Hope is the willingness to struggle** (operationalized via forced swim test, a critical animal model).
- **Giving up of organism goals is fundamental dimension**, suggesting depression must affect motivational machinery.
- Criteria fail to make **careful distinction between sadness and depression** (a recurrent problem in several DSMs).
- Second core criteria: anhedonia/loss of interest: depression affects both **consumption** (↓ pleasure) & **pursuit** of rewards.
- **Bereavement exclusion** left vague. Hopelessness vs. sadness? But particularly crushing losses (young child, beloved spouse) show some depressive sxns, esp. feeling down & profoundly discouraged.

Social Bonds and Separation Distress

Mammalian System for Separation Distress forms underpinnings for many 'cognized' and commonplace negative emotions.

Social comfort and secure attachment appears protective against depression and many related disorders.

Separation distress concepts still not widely appreciated in mainstream psychiatry and mental health.

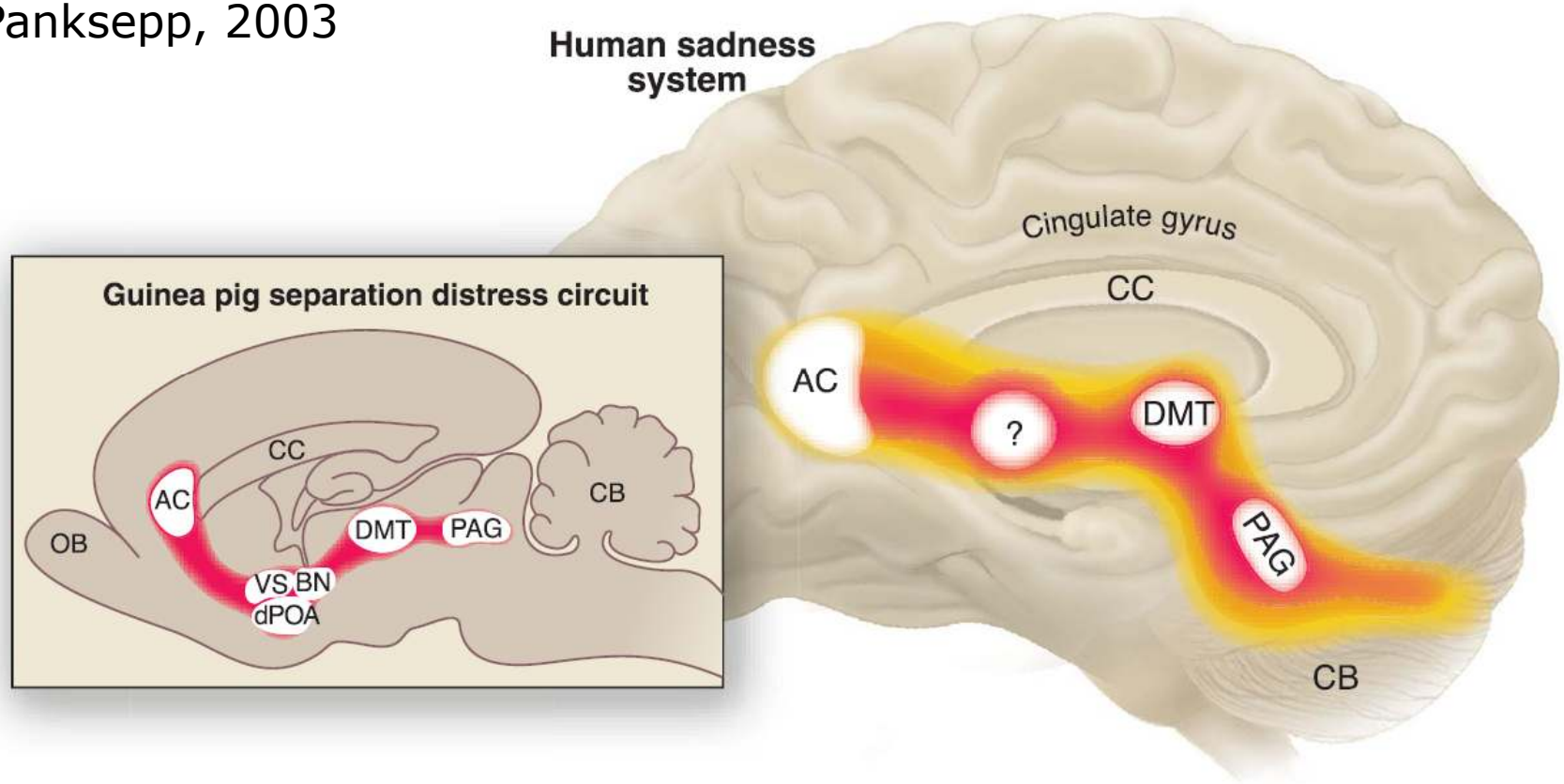
ACE intrinsically deepen feelings of aloneness & helplessness.

Within medicine, appreciation of the primacy of good attachment as health prerequisite is poor, outside of Pediatics.

Basic Emotional Systems	Key Brain Areas	Key Neuromodulators
Watt, 1998 – republished by J Panksepp many times over		
Appetitive Motivation **SEEKING**/ **(+)Expectancy** System	Nucleus Accumbens - VTA Mesolimbic and mesocortical outputs Lateral hypothalamus - **PAG**	**DA (+),** glutamate (+), opioids (+), **neurotensin** Many other neuropeptides.
RAGE/**Anger**	Medial amygdala to Bed Nucleus of Stria Terminalis (BNST). medial and perifornical hypothalamic to **PAG**	**Substance P (+),** ACh (+) , glutamate (+)
FEAR/**Anxiety**	Central & lateral amygdala to medial hypothalamus and dorsal **PAG**	Glutamate (+),**DBI, CRF, CCK, alpha-MSH, NPY**
LUST/**Sexuality**	Cortico-medial amygdala, Bed nucleus of stria terminalis (BNST) Preoptic hypothalamus, VMH, **PAG**	Steroids (+), **vasopressin,** & **oxytocin, LH-RH, CCK.**
CARE/ **Nurturance**	Anterior cingulate, BNST Preoptic Area, VTA, **PAG**	**oxytocin (+), prolactin (+)** dopamine (+), **opioids (+/-)**
PANIC/ **Separation Distress**	Anterior Cingulate, BNST & Preoptic Area Dorsomedial Thalamus, **PAG**	**opiods(-), oxytocin (-) prolactin (-) CRF (+)** glutamate (+)
PLAY/**Joy**	Dorso-medial diencephalon Parafascicular Area, **PAG**	**opioids (+/-),** glutamate (+) ACh (+), TRH?

Human and Rodent Separation Distress Systems

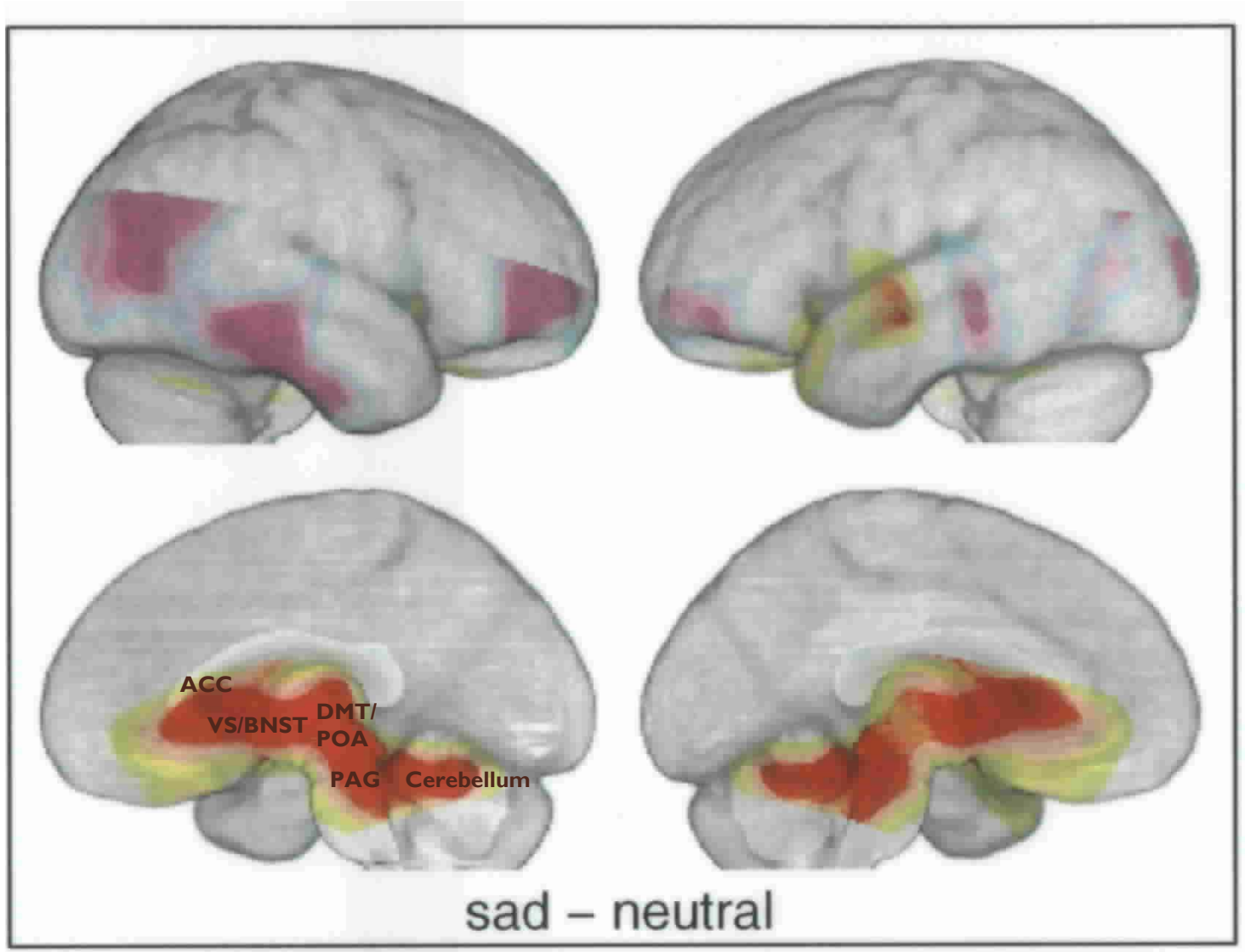
Panksepp, 2003



Protracted separation distress – potentially fatal, esp. in small creature that just lost its primary provider(s) of metabolic supplies. Lost animal shuts down, conserves energy, disconnects, staying where it is (vs. wandering around, crying & getting into trouble!)

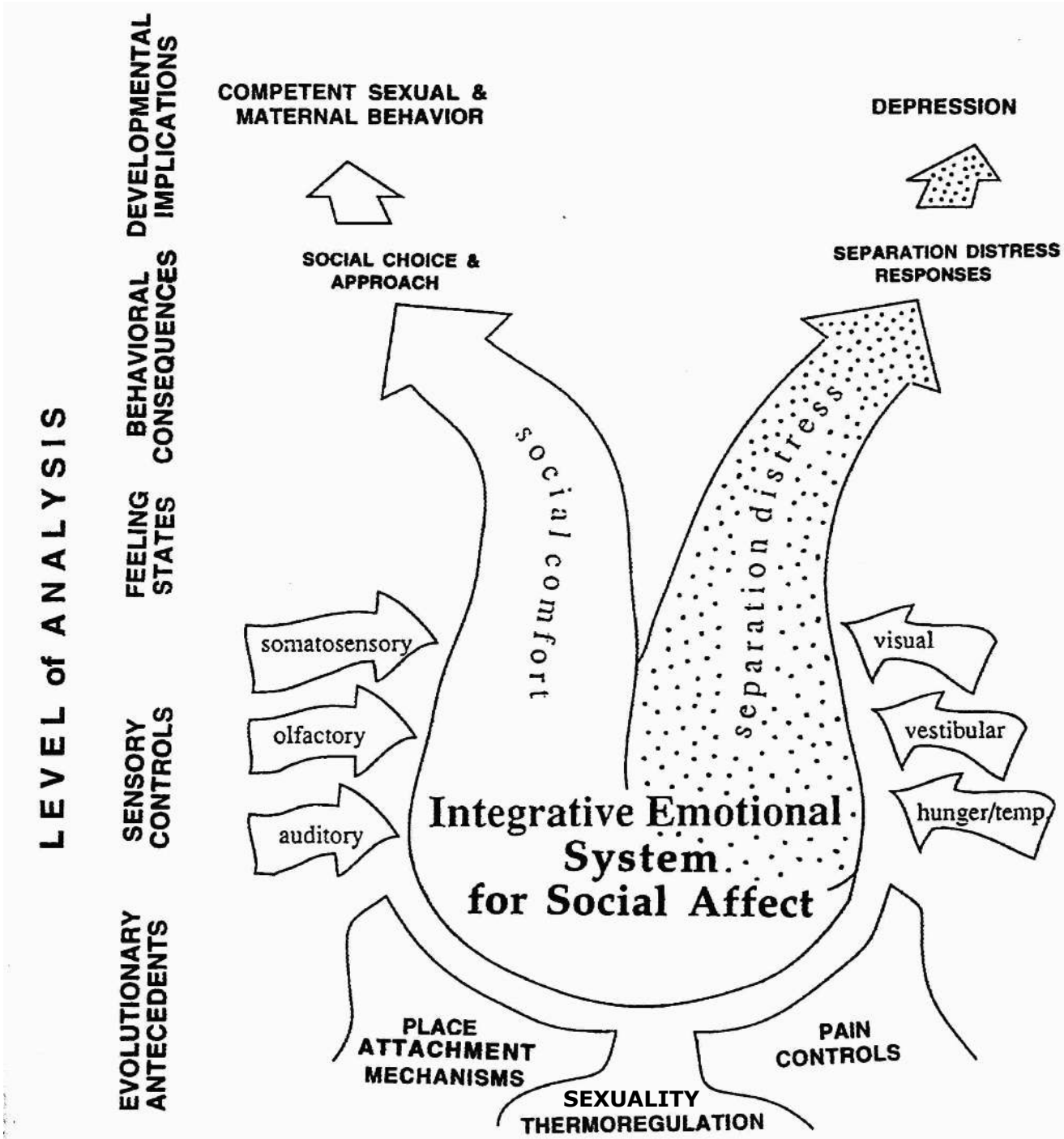
Most dramatic image of separation distress in humans

PET image unpublished (1999) @ Antonio Damasio's lab showing broad swath of cortical deactivation with intense limbic, basal forebrain, and upper brainstem activation.



The Separation Distress System

- Evolutionary underpinnings for feelings of sadness, aloneness, abandonment, rejection, desertion, & every flavor of social loss/defeat but also foundational for guilt, shame.
- Exquisitely painful, among deepest pains that mortal flesh is heir to. We will turn ourselves inside out to avoid separation distress and its many cognized derivatives.
- Alleviation of sep-distress among most positive comforts we can ever receive, promoting attachment and strong bonding.
- System mapped with separation distress calls in EBS in animals = Anterior cingulate/anterior thalamus, BNST/ventral septum, midline & DM thalamus, dorsal preoptic hypothalamic, dPAG.
- Opioids(-), oxytocin(-), prolactin(-) CRF(+), NPY(-) EndoCb(-)
- Association of sep-anxiety with ↑ amygdala volume, w/hyper-reactivity/functional coupling of amygdala to cortex (in viewing negative emotional faces) (Redlich et al, 2015)



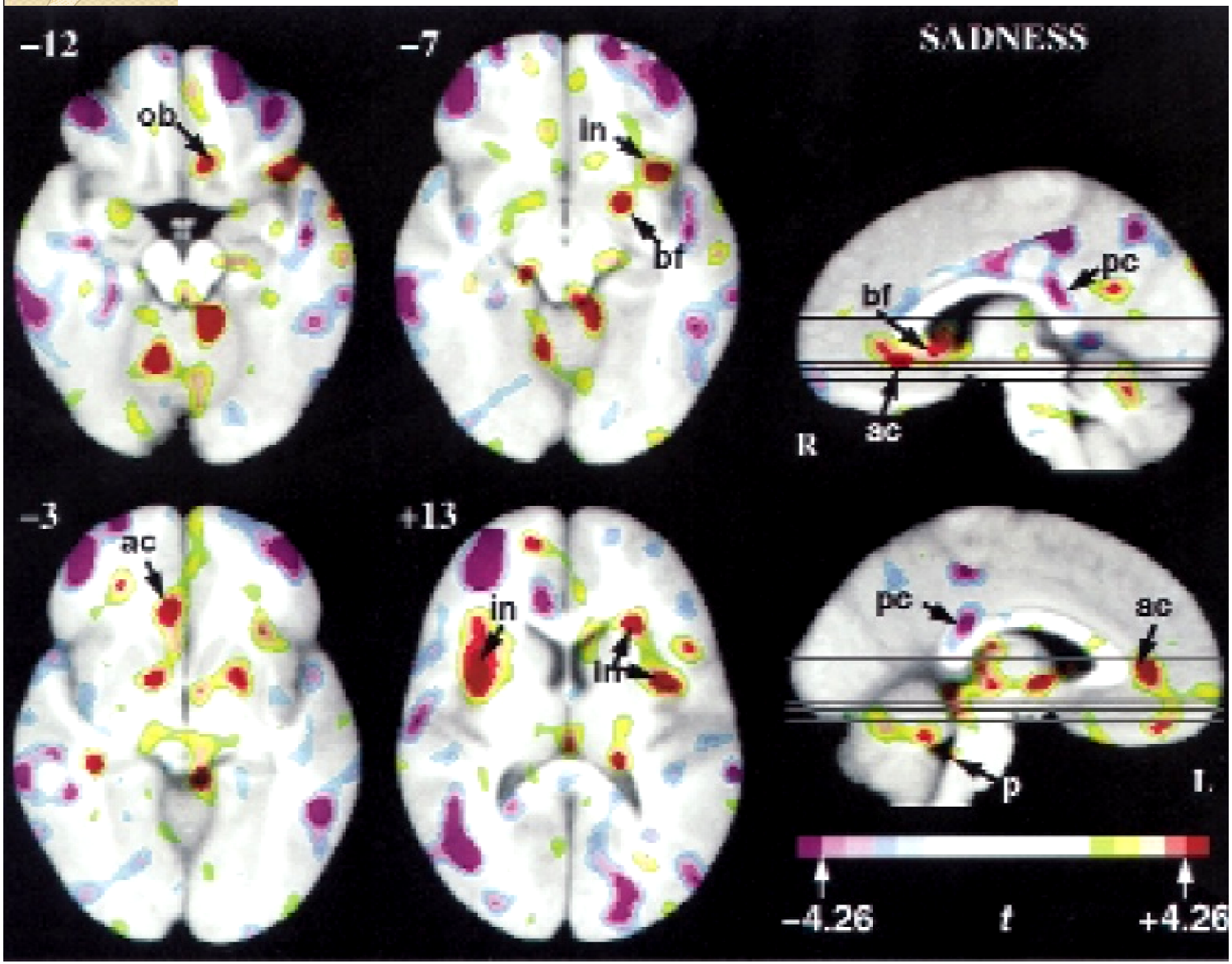
From J Panksepp, 1998, *Affective Neuroscience*, modified by DWatt

Figure 14.1. Schematic summary of the various influences and levels of analysis that are important in analyzing the potential nature of an integrative emotional system for social affect. (Adapted from Panksepp et al., 1997; see n. 3.)

Separation distress, stress & depression: key animal model findings

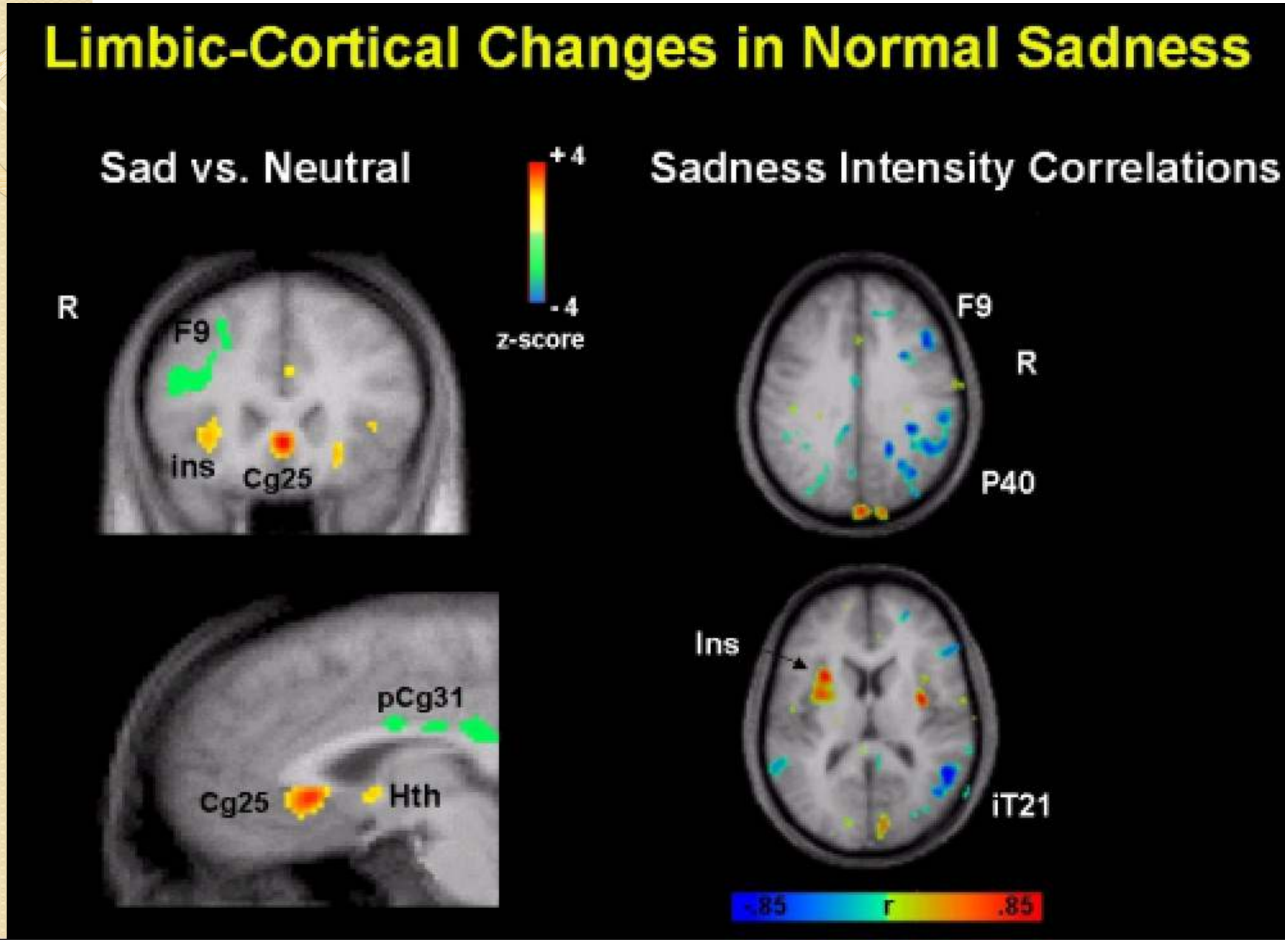
- CRF (intra-ventricularly) produces long-lasting separation distress cries in infant mammals. HPA & SepDistrs deeply tied.
- Separation distress: prototype stress for social brain, while ***social comfort/social play*** are biological opposites of stress.
- ***Increased handling*** (licking & grooming) by maternal animals → long-term epigenetic down-regulation of stress cascades, → ↑ emotional resilience (Meaney). Also mitigates effects of early separation stress (countering upregulated HPA axis)
- ***Grooming/massage*** promotes opioid/oxytocin release – does this drive long term changes in stress physiology?
- Animals subjected to early sep. distress show permanent up-regulation of stress axis (via epigenetic changes), ↓5-HTR, EstR, OxytR, ↓GABA, ↓ neuroplasticity, while ↑INFLAM/PI cytokines.
- These changes mitigated by EE, exercise, extra attention from dams, esp. licking & grooming, also by non-isolate housing.
- Long-term security in early attachment significantly reduces long-term risk of depression. Early loss/trauma increases risk.

Published image from Damasio et al – shows much more restricted 'hot spots'

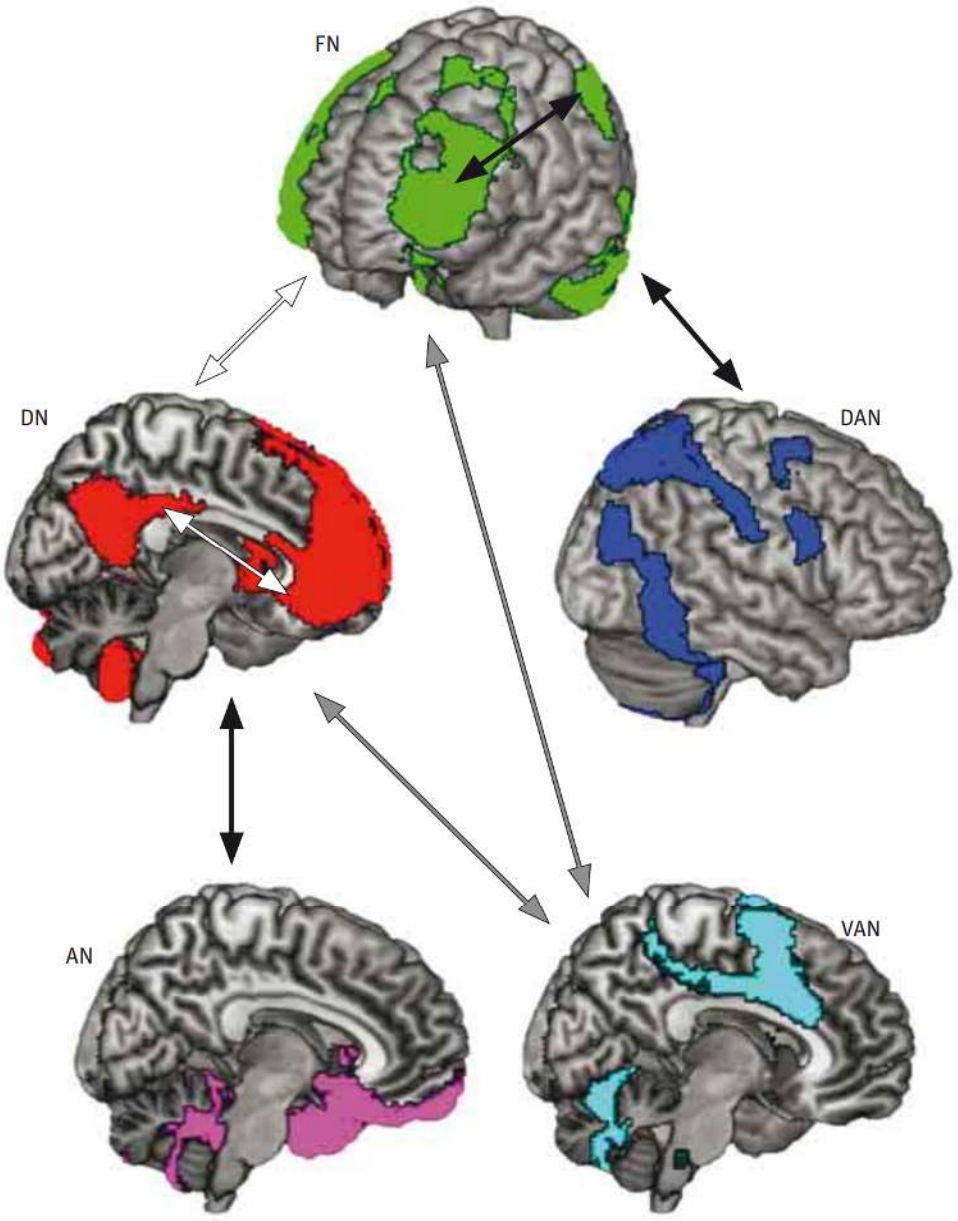


Note the bilateral, but asymmetric, activations of the insula (in) and the mixed activation–deactivation in cingulate cortex (activations anterior deactivations posterior).

Further Imaging of Sadness

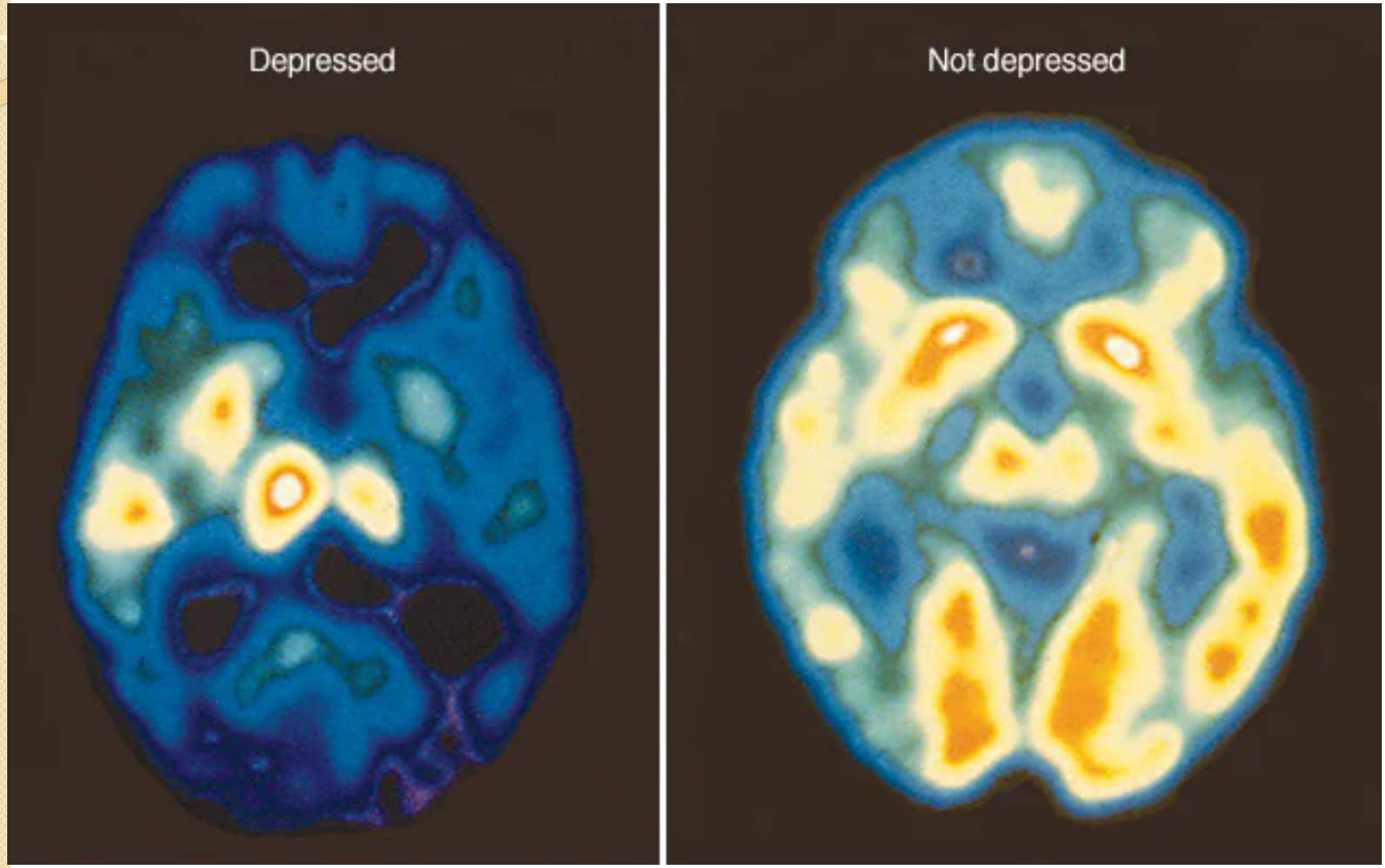


Depression - altered large scale cortical networks



Reduced connectivity among regions of frontoparietal network (FN) may underlie general deficits in cognitive control, whereas ↑↑ connectivity between the FN & default network (DN) & ↓↓ connectivity between the FN and dorsal attention network (DAN) may reflect biases toward ruminative thoughts at the cost of attending to the external world. Meanwhile, ↓↓ connectivity between the affective network (AN) and medial prefrontal cortex regions that mediate top-down regulation may reflect impaired ability to upregulate or downregulate emotions or arousal, whereas abnormal connectivity between the ventral attention network (VAN) and posterior regions may reflect altered or biased salience monitoring. LEGEND - Black arrows = hypoconnectivity in MDD; white arrows = hyperconnectivity in MDD; and gray arrows = abnormal (hypo-connectivity & hyperconnectivity)

Major Depression: mostly global hypo-metabolism (L>R in this case - Mayo Clinic)



Trauma, abuse, and depression: course correction on seductive mistakes

- In 90's (Nemeroff, Teicher, others), psychiatry began correcting distorting effects of neglect of environmental factors, esp. social relationships in mainstream psychiatry's depression modeling.
- Biomarkers of depression (ΔCRF/glucocorticoids/cytokines) now appreciated as biomarkers for childhood trauma/neglect.
- True incidence of neglect and abuse ('ACE') unknown – current epidemiology suggests 25-35% ***w/highly motivated underreporting***.
- ~40-50% of patients w/mood disorders report trauma, is negative prognostic factor (sxn severity/treatment refractory/comorbidity).
- 20% report multiple forms of maltreatment (neglect, P/S/V abuse)
- Between ~2-5 x risk factor in relationship to suicide attempts.
- In general, early trauma → ↑ classic pro-inflammatory cytokines (CRP, IL-6, IL-1β, TNF-α), down-regulates CRF inhibition via gluco-corticoid feedback, and reduces BDNF. <u>All classic findings in MD; closely mirroring findings in early separation in animal models!</u>

Neurotransmitter Perspectives

Includes classical monoamine, acetylcholine, amino acid transmitters, newer neuropeptidergic issues and their complex interactions (minimally charted!)

Discovery of rapidly acting glutamatergic class of drugs (e.g. Ketamine) has changed the pharmacology of depression more than any other discovery in the last 50 years, energizing more detailed probing of glutamate/GABA systems

Short form of a VERY long story on depression and neurotransmitters . . .

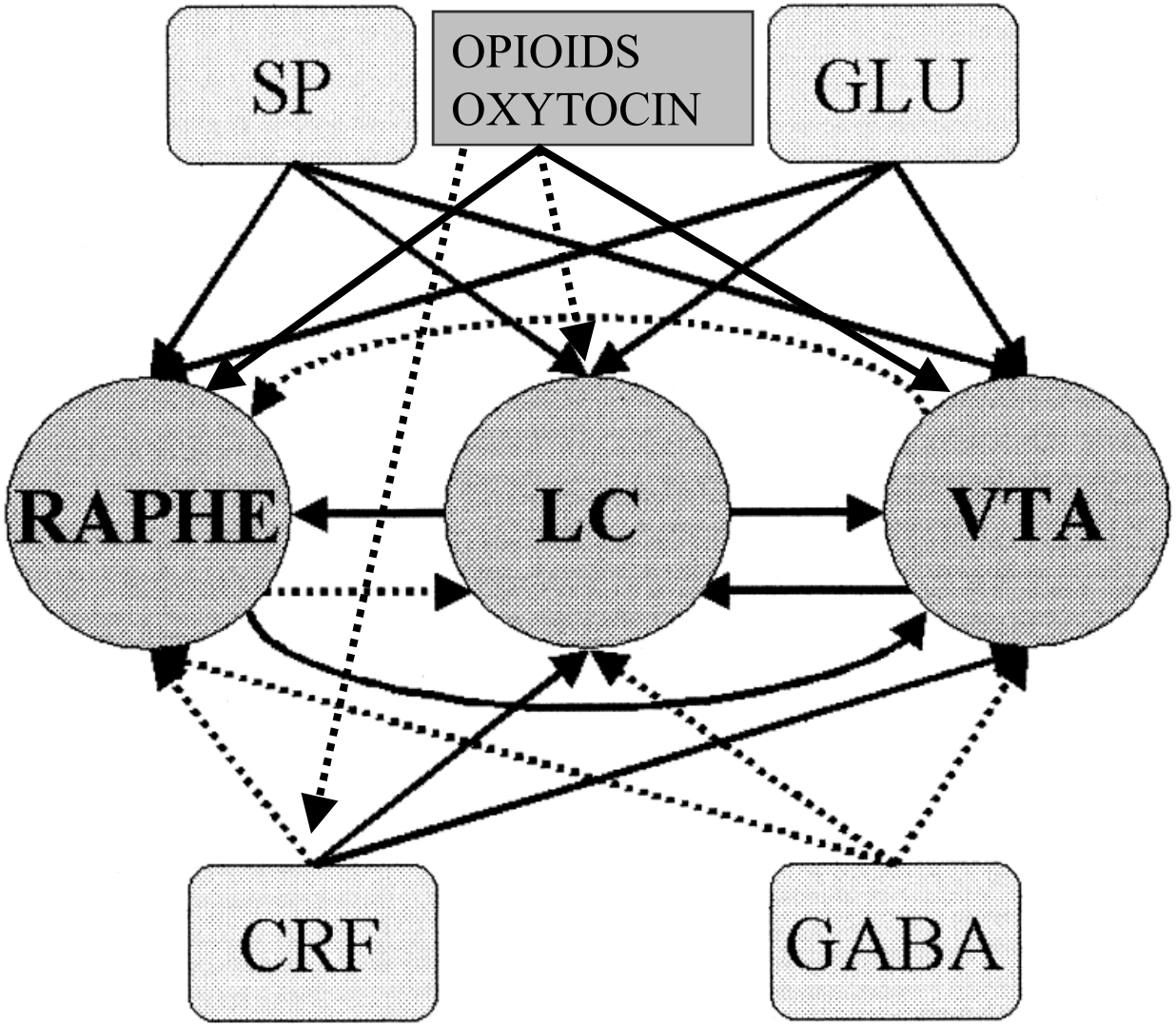
- Systems with most potent, direct and immediate effects on mood and affect are **NOT** NE & 5-HT! Rather many others!
- DA, CRF/glucocorticoids, cannabinoids, opioids, other NP (neuropeptides) which we cannot manipulate (BBB) & cytokines all have more potent and immediate effects on mood.
- Effects of NE/5-HT-RI drugs are well *downstream of direct synaptic boosting* (putative effects on neuroplasticity).
- Every transmitter system studied (aminergic, hormonal, peptidergic, immunologic) appears altered in depression.
- Putative locus of a chemical imbalance? Leading/trailing edges are unclear, but DA, kappa/mu opioids, CRF/stress axis, other NP, INFLAM & GLU/GABA signals all critical to affective state.
- Is this a *chemical imbalance* or a rotated and 'torqued' system?

Interactions Between Neuromodulatory Systems → Non-linear dynamics

Depression may reflect an 'attractor state' within interactive global state controls. Complexity means functional studies needed to map attractor states and dynamics.

Changes in one system might quickly recruit compensations in multiple other systems.

Solid lines = excitatory relationships, dashed = inhibitory relationship.



Depression underwritten by a complex recursion across multiple systems?

- While earlier notions assumed that INFLAM & HPA axis changes epiphenomenal to aminergic shifts, recent work reverses this.
- A general down-regulation of amine systems (DA, NE, 5-HT), but also ↓GABA, oxytocin & mu opioids? All due to INFLAM/HPA ?
- Upregulation of GLUT & Kappa opioids, while stress axis appears stuck on 'high', and not being normalized by negative feedback from cortisol, due to ↑pro-inflammatory cytokines.
- Increased k opioid signaling → ↓VTA DA (& motivation/reward-seeking), while stress axis upregulation/dysregulation promoting ↑ conscious dysphoria but also driving upregulated k opioid signals, while declining mu opioids and oxytocin (SEP DISTRESS) may contribute potently to the stress axis upregulation.
- *Entire system of neuromodulatory controls appears to pivot around an axis that we call 'depression', where the locus of control for this process looks quite diffuse and highly distributed, as neurochemical signaling systems reverberate w/ one another in complex ways.*

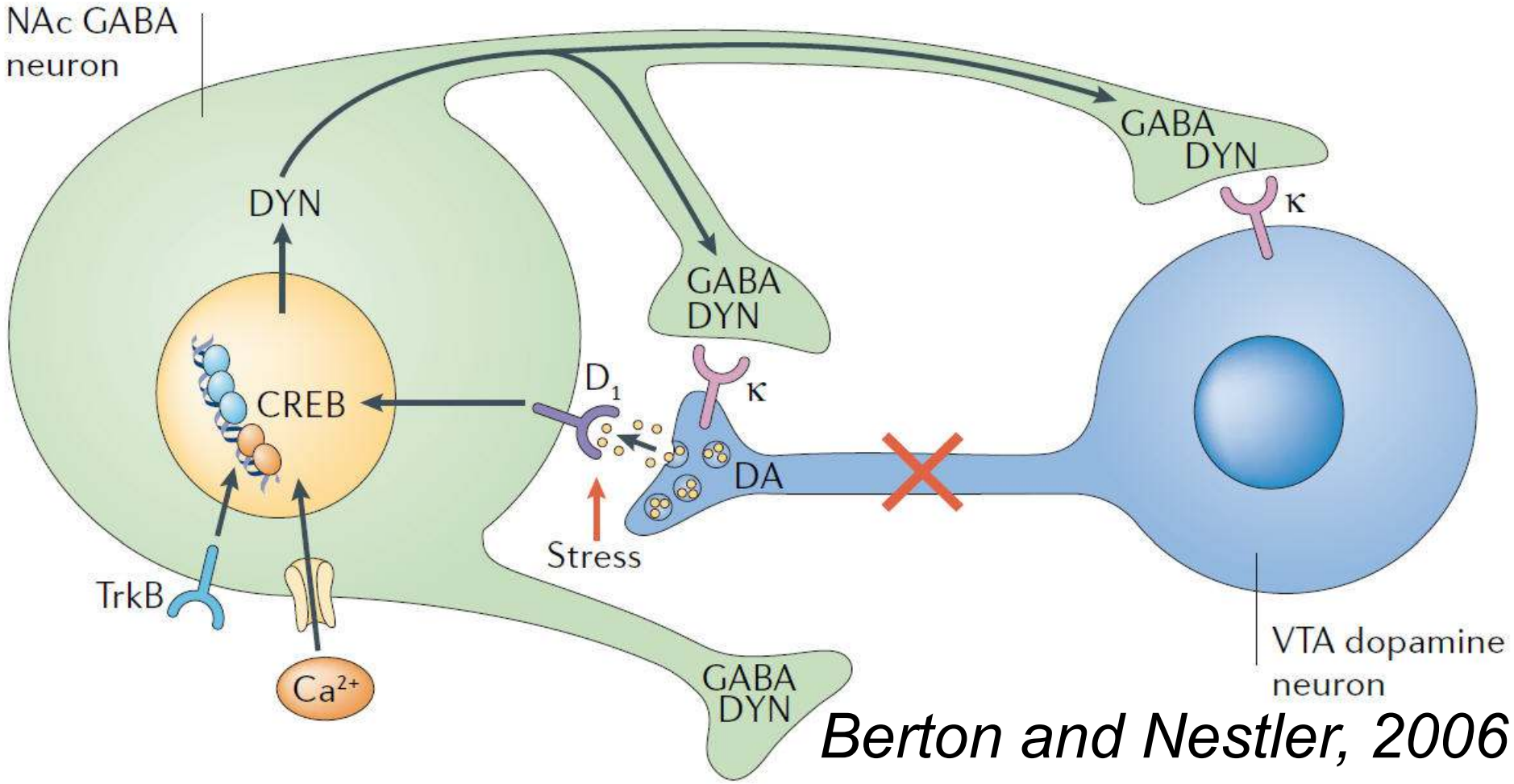
DEPRESSIVE FACTOR	DRIVEN BY	PRODUCING	BEHAVIORAL/SYMPTOMATIC CORRELATES/COMORBIDITIES
Increased CRF, often w/hypercortisolemia, ↑CCK & ↓ BDNF.	Multifactorial limbic signals to paraventricular nucleus leading to activation of HPA stress axis, w/failing negative feedback	Increased dynorphin, ↓↓5-HT, reduced BDNF, GCs→ HC atrophy ↑↑ MAO B from GCs → ↓VTA DA. ↑separation distress? ↓ ventral HC feedback on several brainstem systems?	Dysphoria, sleep & appetite loss. Declining motivation. Reduced short-term memory, other cognitive deficits?
Increased ACh (Acetylcholine)	Reduction of social and other rewards, opioid 'withdrawal', and any other social punishment.	Facilitation of separation distress circuitry and other negative emotions. Inhibition of VTA/DA. Effects on other core variables?	Negative affect and excess attention to negativistic perceptions and thoughts?
Decreased mu opioids and oxytocin	Separation distress, other stressors, including physical illness and pain	Disinhibition/release of stress cascades; decreased 5-HT & DA; overdriven NE? Increased cytokine generation?	Anhedonia and sadness, reduced positive affect and reduced sense of connection? Suicidality?
Increased dynorphin in accumbens & VTA	Stress cascades	Down regulation of VTA DA output, and mesolimbic DA system.	Anhedonia, dysphoria, loss of drive and motivation
Increased pro-INFLAM cytokines	Chronic stress, acute reduction of opioids/ other prosocial peptides? ↑NF-kB/AP-1 -permissive transcription factors	Promotion of stress cascades, increased HC stress/atrophy, ↓BDNF, ↓aminergic, ↑ glutamatergic tone.	Fatigue, malaise and appetitive losses. Increased cognitive disruption. Anhedonia?
Reduced serotonergic drive/tone	↑stress, corticosteroids, and cytokines, decreased mu opioids.	Decreased dopaminergic, opioidergic and oxytocinergic tone. ↑ NE tone. ↓ BDNF?	Poor affective regulation? Impulsivity. obsessive thought, suicidality.
Diminished catecholaminergic (DA & NE) tone	↑Stress & dynorphin → Negative VTA feedback, upregulated MAO-B. Cytokines ↓monoamine precursors, ↑reuptake → global amine deficit.	Reduced BDNF. Effects on other core variables?	Diminished psychic energy/motivation, Fatigue, sluggishness, dysphoria. Impaired coordination of cognitive and emotional information processing?
Genetic vulnerabilities 3 dozen+ loci. Most with weak loading, large overlap w/SCHIZ	Most are inherited, w/ occasional mutations. SERT, CRHR1, Val66Met-BDNF, FKBP5 polymorphisms, with additive effects.	Vulnerability vs. resilience to wide variety of stressors, contributing to wide variety of psychiatric disorders (MD, AD, OCD, PTSD, BPD, SCHIZ), GenexEnvironment interactions create multiple phenotypes.	Lack-of-resilience phenotype? Eventually, there will be precision psycho-pharmacology around these various genetic vulnerabilities ('personalized medicine').
Severe early environmental stressors - adverse childhood experiences, esp. neglect/abuse	Abuse & neglect (often trans-generational), severe empathy failures on part of caretakers, conflict atrocities, war, natural disasters.	↑ pro-INFLAM cytokines, glucocorticoid resistance, corticolimbic network changes, ↓ neurotrophin signal, methylation/other epigenetic changes in stress axis/BDNF/INFLAM genes.	At time of abuse/neglect, acute/intense negative affects: rage, fear, aloneness, helplessness. Status/post abuse, often a sense of humiliation, shame and self-loathing, often with PTSD symptoms. chronic ↓self-esteem w/chronic dysthymia
Recent acute stressors – loss of relationship, social defeat, illness, assault physical pain, financial reversal.	Social vicissitudes –human misfortune vs. 'uncanny' recapitulations of childhood trauma	Decreased mu opioids, ↑CRF/stress axis activation, ↑ IL-6, other proinflammatory cytokines.	Feeling acutely and severely stressed or even 'stressed out,' and preoccupied with troubles, poor sleep (onset/maintenance), and feeling helpless to mitigate situation. Dysthymia/mild or Prodromal depression?

Biogenic Amines

- Most antidepressants modulate amine systems (DA, NE, 5-HT).
- Most lay persons, media & some MDs believe story of depression begins and ends w/monoamines, but many questions remain.
- Simple amine deficiency hypotheses (Shieldkraut, 1967) fallen by the wayside (with good reason). Synaptic 5-HT/NE altered within hours.
- Reserpine (blocks catecholamine/indolamine pump) most powerful model for monoamine depletion, but is not universally depressogenic.
- Despite massive literature (piles & piles of correlations between depression and changes in amine systems), deciphering precisely what is going on in amine systems remains confusing.
- Older amine-centered conceptions about depression reflect a 'hedged' conception ("depression as a Spreading Adjustment Disorder of Monoaminergic Neurons" – a SADOMN?) (Harro & Oreland)
- Avoids previous oversimplifications, but so general as to lack value.
- Perhaps monoamine perspectives are a bit like looking for lost keys under the streetlight? Systems we can readily manipulate, vs. neuropeptide, immune and endocrine systems that are less accessible.
- Increasing attention to glutamate, immunologic, and neuroendocrine systems – of course all of these interactive with biogenic amines.

Dopaminergic Issues

- DA took back seat to NE/5-HT in early days of amine hypothesis – that has now reversed almost completely.
- Apathy (severest form is AKM) thought related to VTA hypofunction.
- Anhedonia & loss of motivation, psychomotor slowing all suggest obvious DA involvement (but perhaps two different pathways?).
- Lowered levels of HVA in CSF of depressed pts.
- Antidepressants increase affinity of D_2 agonists in limbic BG but not in neostriatum BG (↑receptors? ↑sensitivity?)
- DA antagonists make some pts depressed, amphetamine, Wellbutrin, other DA drugs can be effective antidepressants. ECT → ↑ DA tone (lowering of pro-DA drugs pre-ECT).
- Learned helplessness: decreased EBS NAcc. responding, (mesolimbic VTA system downregulated). Reversed by TCAs.
- Mesolimbic dopamine activity appears augmented by many antidepressants (even those with just NE or 5-HT effects).
- Recent work suggests VTA may shut down secondary to effects of dynorphin on accumbens feedback to VTA, but INFLAM signals also look critical to reduced motivation/apathy.

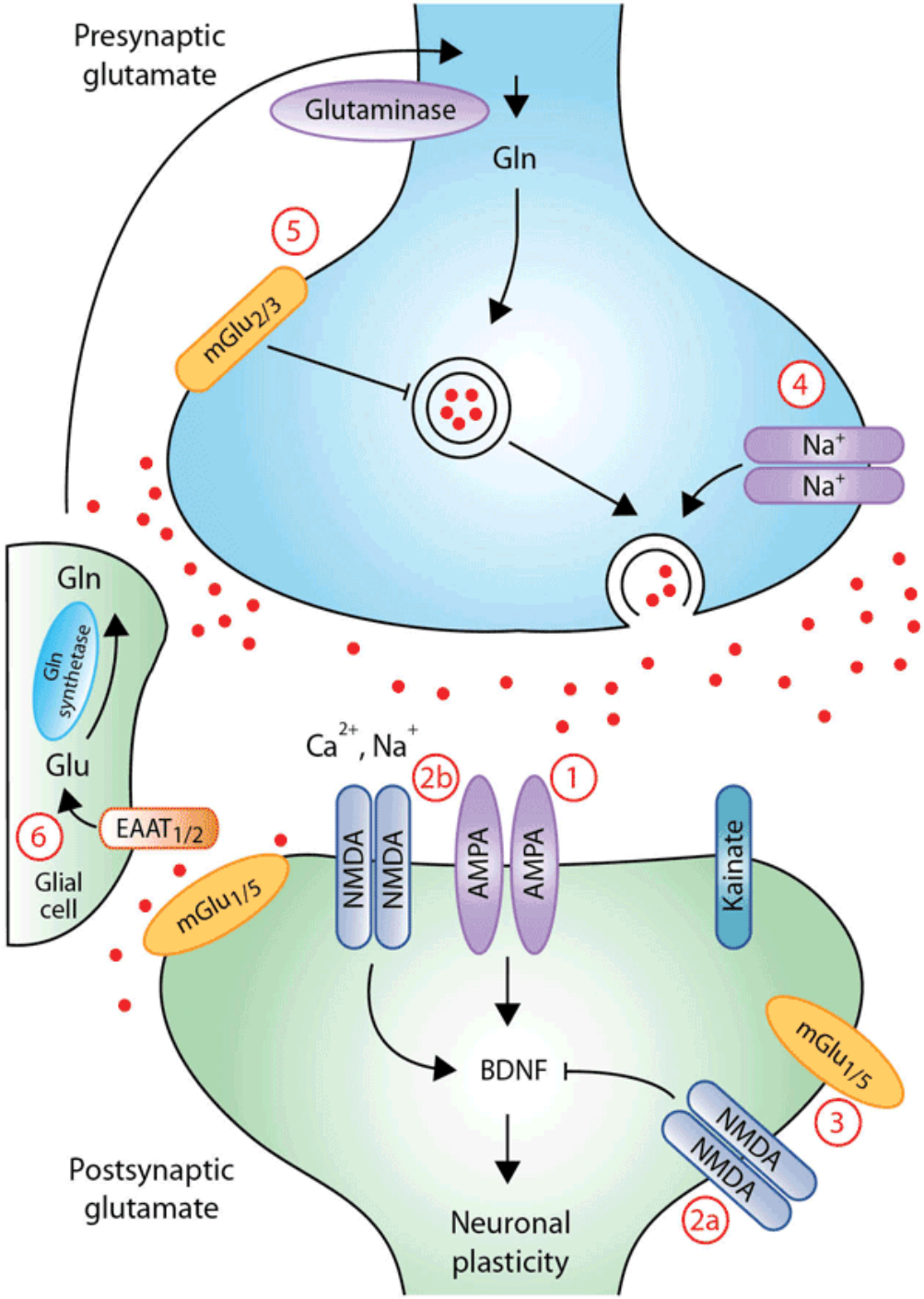


Berton and Nestler, 2006

Dynorphin in NAc in Depression: Activation of CREB (cAMP-responsive element binding protein) by CRF/TrkB mediates upregulation of dynorphin. CREB activated by D1 receptors (or TrkB-BDNF) promotes ↑ expression of dynorphin. Dynorphin → ↓ VTA projection system (↓ separation distress → anhedonia). This may drive transition to despair phase of separation distress . . .

Glutamate

- Most critical excitatory-to-excitatory transmitter, widely ramifying, network creating – involved in everything CNS does.
- Why/where is GLUT transmission elevated in depression, if it is?
- Unknown, but central to separation distress circuitry, appears to be concomitant to chronic stress cascade signals.
- Most studies of depressed patients have found lowered MRS glutamate levels in depression esp. in anterior brain regions, but serum levels of elevated GLUT and CSF glutamine in depressed pts.
- Although Ketamine created interest in NMDA antagonists, they have been all disappointing. Ketamine not effective via NMDA antagonism but through other effects (AMPA, opioids, cytokines)
- Glutamatergic neurons → primary excitatory input to LC, through both NMDA/aspartate receptors: ↑ LC output → in NE depletion?
- Injecting LC with a CRF antagonist abolishes stress induced ↑ glutamatergic activity (CRF ↔ GLU).

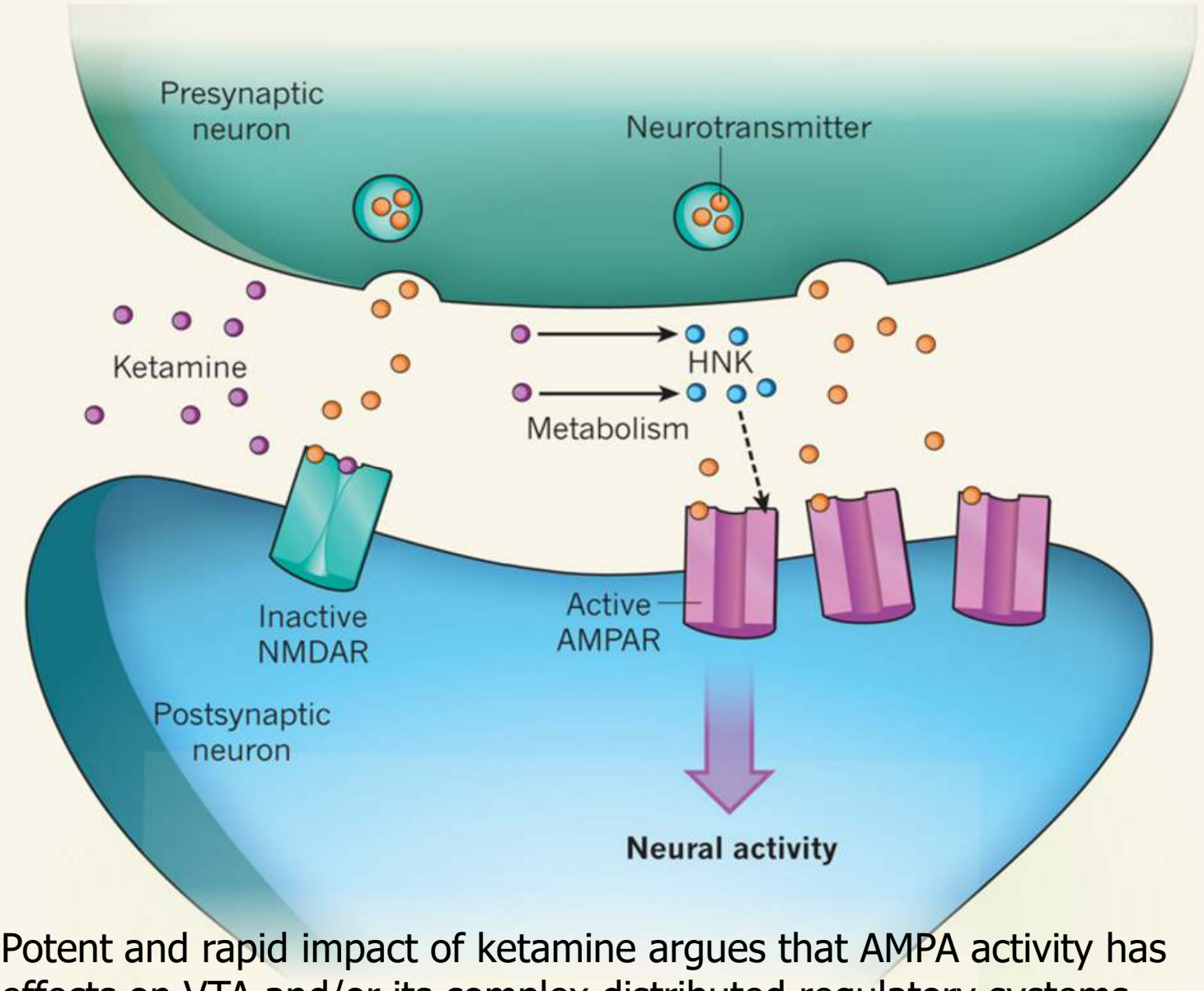


TRIPARTITE GLUTAMATE SYSTEM Within glutamatergic system lie several potential targets for antidepressants: **1) NMDA** antagonists (all failed!) but modulators of isglycine receptor more promising **(GLYX-13)**; **2) AMPA agonists, esp. Ketamine; 3) metabotropic GLU receptor** (mGLU), effecting mGLU +/- presynaptic GLUT release; **4) Na+ channel modulation** effecting glutamate release **5) ↑ GLUT uptake and transport** into glial cells.

LEGEND

Gln=glutamine, EAAT=excitatory amino acid transporters, BDNF=brain derived neurotrophic factor

Previous vs current views of ketamine



Potent and rapid impact of ketamine argues that AMPA activity has effects on VTA and/or its complex distributed regulatory systems

Recent work on Ketamine

- Highly effective w/ rapid onset (~1-2hrs), lasting ~ days to ~1wk.
- Thought to be an NMDA antagonist w/ effects on interneurons, but other NMDA antagonists (MK-801) not antidepressant.
- Animal model work (Zanos et al *Nature* 2016) ketamine metabolized into AMPA agonist 2R 6R HNK (hydroxy-nor-ketamine) generating therapeutic effects, while NMDA antagonism side effects (dissociation/hyperkinesis).
- In classic animal models (FST/LH), HNK is robustly antidepressant.
- HNK ~ 3 fold higher (after isodose ketamine) in brains of female vs. males animals, suggesting differential metabolism across genders (? basis).
- Confirms prior work showing positive correlations between antidepressant responses and plasma HNK levels, lower dose F vs M.
- NBQX, which reduces AMPA-R activity, prevented and even reversed antidepressant effects of both ketamine and HNK in mice.
- Why is AMPA agonist antidepressant?: ↑ BDNF, but Ketamine also has anti-INFLAM (↓TNF-α) & mu agonist effects. Val/Val carriers (rs6265) in BDNF gene show ↑ketamine response vs. Met carriers, suggesting Val66Met polymorphism in BDNF gene genetic biomarker for >ketamine responders.

Psychedelics – with & w/out psychotherapy – an AD drug revolution in the making?

- Several distinct chemical classes of psychedelic compounds (indolamines, phenylalkylamines, ergolines) but all show primary serotonergic properties (5HT-2a partial agonism).
- Co-administration of 5HT-2a antagonist abolishes drug effects, although some 5HT-2a agonists (lisuride) not psychedelic/AD.
- Striking effects on mean firing rate, ↑bursting, w/subsequent activation of the post-synaptic AMPA receptors, ↑BDNF.
- Marked changes in L5/6 pyramidal neurons, esp. PFC, w/diffuse effects on thalamocortical gating (Δ top-down & bottom-up).
- Disinhibits sensory information, esp. visual while dampening effect of priors/habits/system predictions. Disrupts PPI.
- Down-regulation of DMN – possible substrate for mystical experience/boundary dissolution? But is mystical experience required for Rx effect, or mediated by opioidergic activation?

GABA function

- Preclinical AM (parvalbumin) and clinical models suggest depression/vulnerability to it assoc. w/↓ GABA function.
- Not clear entirely why or how? Chronic stress?
- Plasma levels of GABA are low in depressed pts.
- GABA agonists effective in various animal models & w/modest antidepressant activity in humans.
- GABA is inhibitory input to LC (NE) & DR (5-HT), which isn't consistent with amine centered models.
- VTA receives basal forebrain and BG GABA feedback, which also inhibitory. Also not consistent!
- In view of evidence for both DA hypoactivity and GABA hypoactivity, DA and other amine effects likely not from GABA but from other systems.

Endogenous Opioid Systems in Depression

Opioids Centrally Involved in Pleasure/Pain in Mammalian Brains

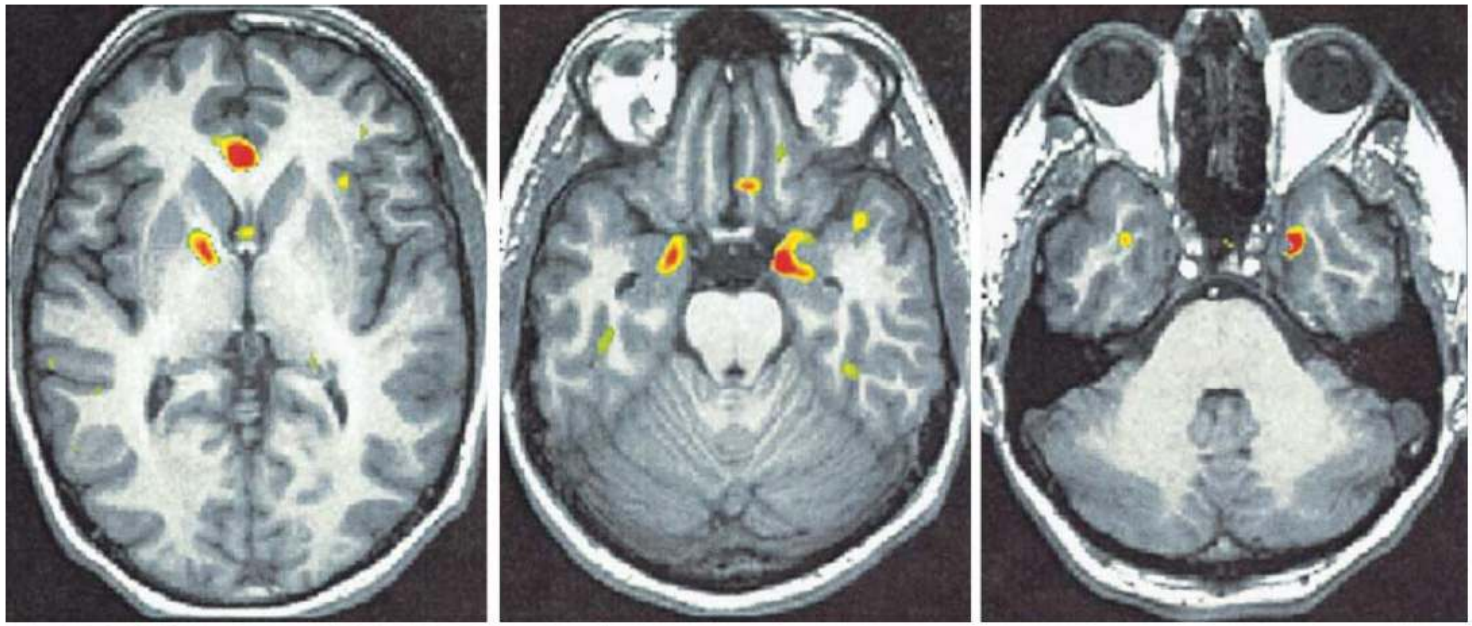
Suggesting Key Roles in Depression

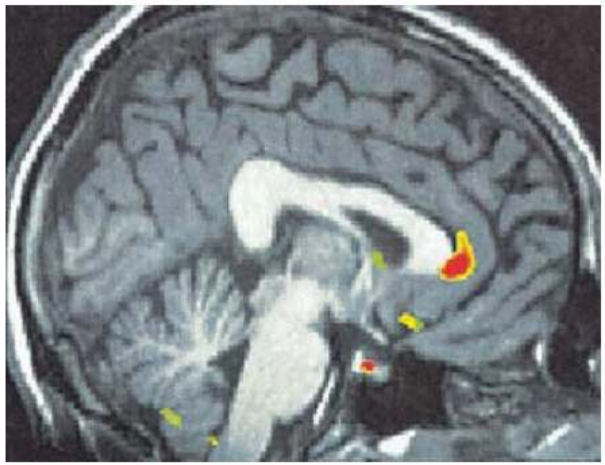
Both Mu and Kappa Opioids Critical

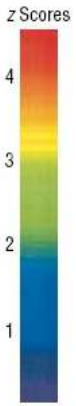
Opioid systems (Mu/delta/Kappa)

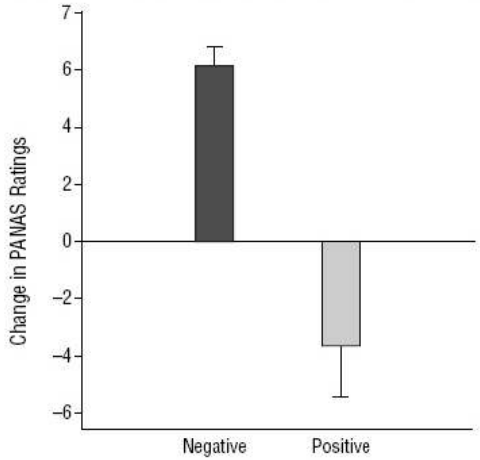
- Mu opioid system almost totally neglected in traditional otherwise excellent reviews (e.g. Nestler and Barton).
- Neglected in rush to nominate oxytocin as 'love hormone'
- Long-term evidence that opioid chemistries inform every aspect of pleasure/pain regulation in all mammals.
- Opioid theory of social attachment (Panksepp, 1971). Attachment - an adaptive form of addiction → survival!
- Mu opioids along with oxytocin and prolactin are most effective molecules in suppressing separation distress.
- Low opioid tone confirmed in sadness reactions in humans (Zubieta, 2003 – see next slides).
- Psychiatry is opioid-phobic at this point – opioidergic effects from compounds seen as negative chit.

Zubieta et al confirm reductions in mu opioid system in sadness



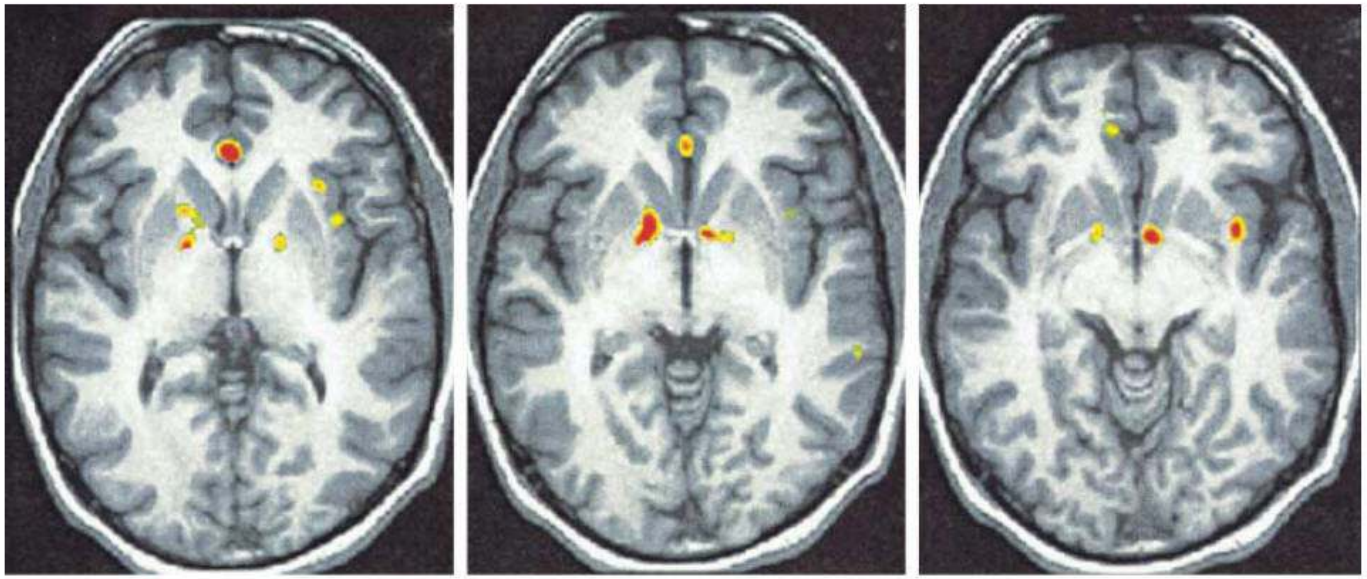


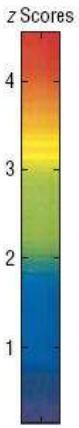


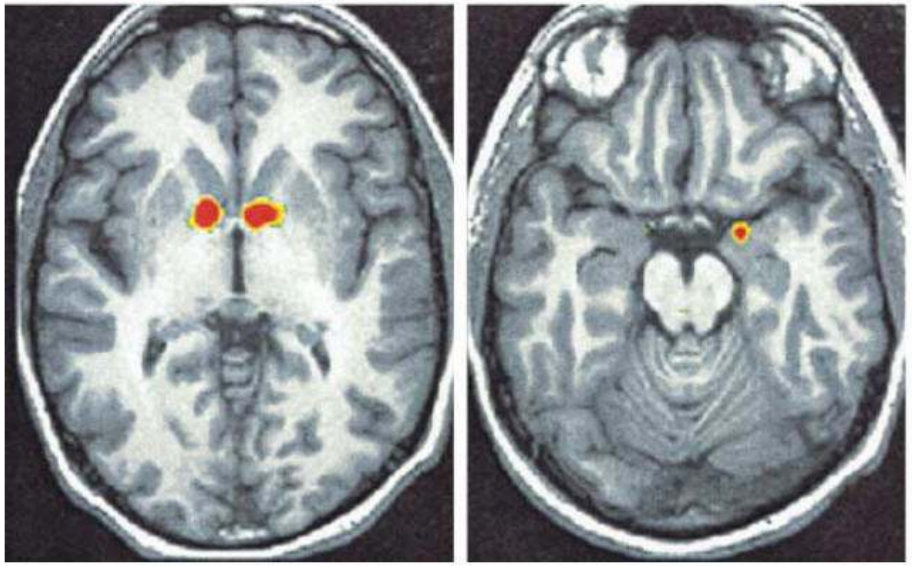


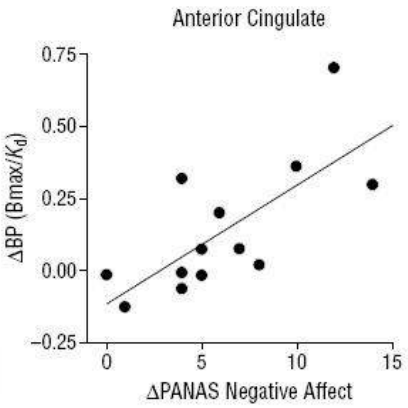
Z Scores reflect regions w/most change in mu opioid receptor binding (sadness compared to neutral condition). Changes in rostral ant. cingulate, amygdala, right ventral pallidum, left inferior temporal cortex (? hypothalamus)

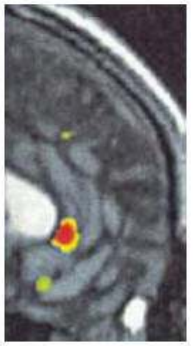
Zubieta et al Mu Opioid Changes











TOP ROW: Correlations btwn regions of reduced opioid activity & ↑ negative affect scores: rostral ant. cingulate, vtrl pallidum, L hypothalamus, left insular cortex and left amygdala.

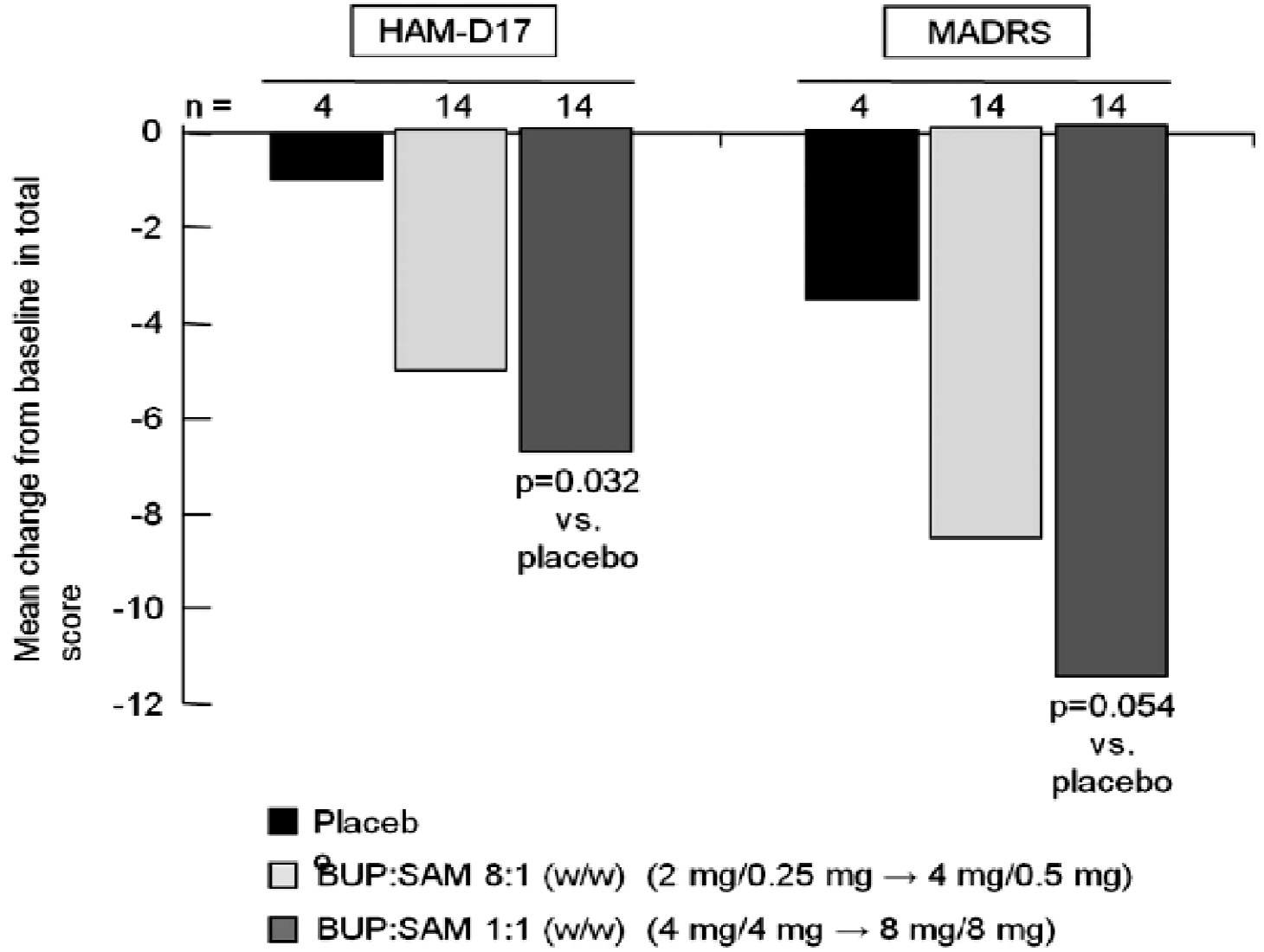
BOTTOM ROW: Correlations for reduction of positive affect: vtrl pallidum, left amygdala.

1st Treatment study on opioids & depression

- Bodkin et al. (1996): found buprenorphine (partial μ agonist, κ antagonist) effective in refractory depressions.
- 10 subjects w/treatment refractory unipolar nonpsychotic depression (open label study). Three subjects dropped out (nausea/malaise, not uncommon in opiate-naïve).
- Remaining seven completed four to six weeks of treatment w/ striking clinical improvement, often more rapid onset (1wk) than w/ traditional drugs.
- 4 of 7 (57%) showed full remission (Hamilton Rating Scale < or = 6). 2/7 (29%) moderately improved, 1/7 deteriorated.
- No follow-up study with proper double blinding until 2006!
- Our group tried for years to get permission to study in properly blinded trial against aminergic drugs, to no avail.
- Opioid-phobic perspectives have dominated biopharma for past 5 years – almost as distorting as denial of addiction potentials from opioids

2nd (blinded) study of buprenorphine

Ehrich et al., Neuropharmacology (2015) 1-8.



- J Neurosci. 2008 Jan 9;28(2):407-14.
- **The dysphoric component of stress is encoded by activation of the dynorphin kappa-opioid system.**
- Land BB, Bruchas MR, Lemos JC, Xu M, Melief EJ, Chavkin C.
- Dysphoric properties of chronic stress are encoded by opioid peptide dynorphin, acting on specific stress-related neuronal circuits.
- Using several forms of stress in mice, (FST/LH), both produced aversion, but blocked by a kappa-opioid receptor antagonist, and **absent in mice lacking dynorphin**.
- Injection of CRF produced place aversion, blocked by dynorphin gene deletion or kappa antagonism. CRF-induced place aversion blocked by a CRF_2 receptor antagonist but not by a CRF_1 receptor antagonist.
- **Results suggest that aversive effects of stress mediated by CRF_2 receptor stimulation of dynorphin release and KOR activation.**
- Using antibody directed at KOR, we found that **stress and CRF each caused dynorphin-dependent KOR activation in BL amygdala, NAcc, DR, and HC**.
- **Dynorphin is a key mediator of dysphoria and its effects, and suggests kappa-receptor antagonists as promising therapeutics**.
- (We already HAVE a kappa antagonist available, pigeon-holed as a drug for treating addiction only).

Kappa opioids and depression

- Kappa opioids: regulate neg. feedback on VTA.
- Application of kappa agonist Salvinorin A produces depressive phenotype in FST (forced swim test) and in electrical self-stimulation tests (tests central to current drug design methodology)we but also dissociation/derealization/depersonalization.
- Kappa antagonists prolong forced swim behavior, suggesting increasing resistance to depression.
- Messenger RNA for dynorphin increased in patch versus matrix compartments of BG in suicides.

Neuroendocrine Alterations in Depression

Many Aspects of Neuroendocrine Function Are Altered

Underlying Dynamics Still Poorly Understood

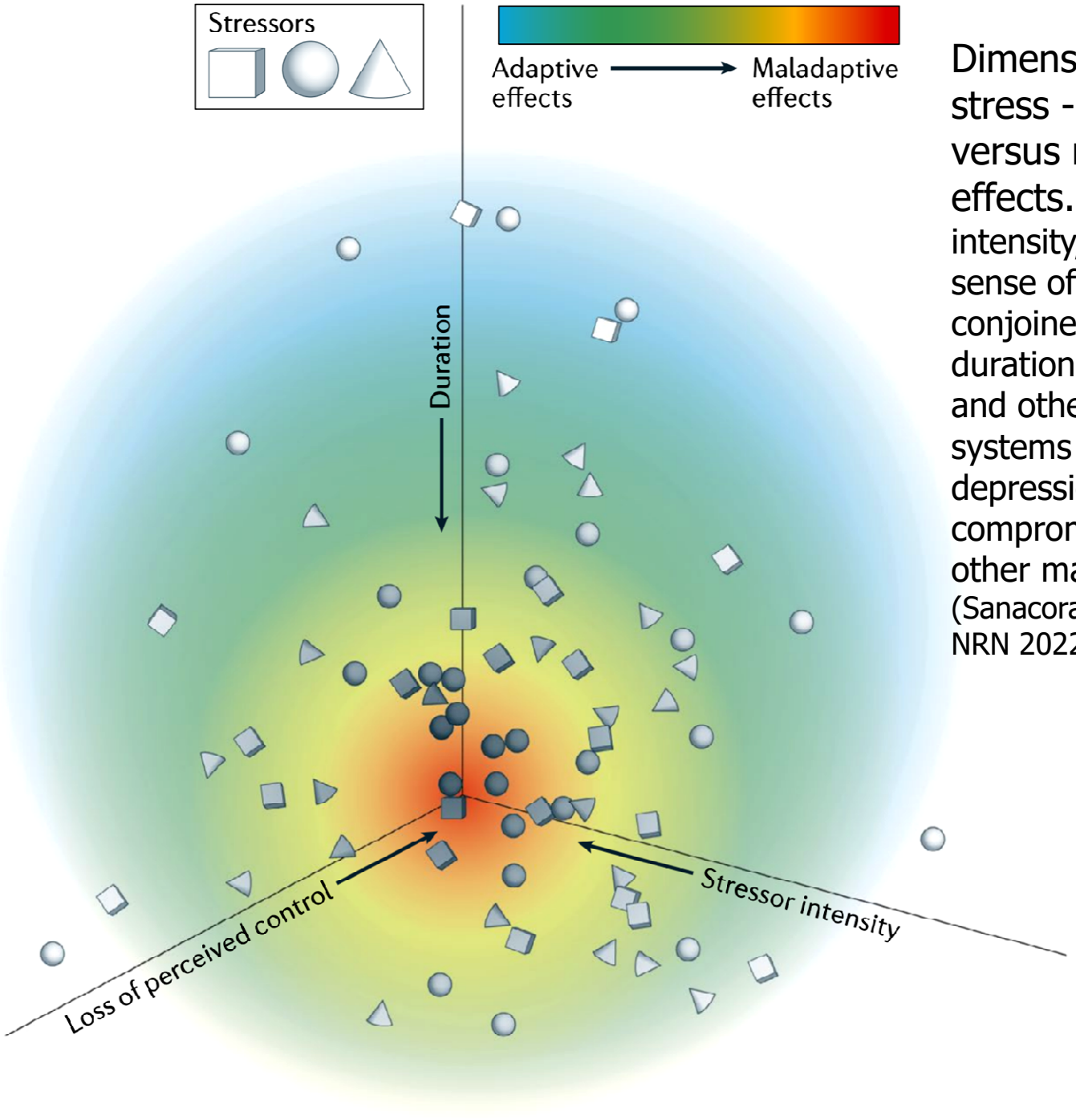
HPA Stress Axis Changes Best Studied

Neuroendocrine Alterations

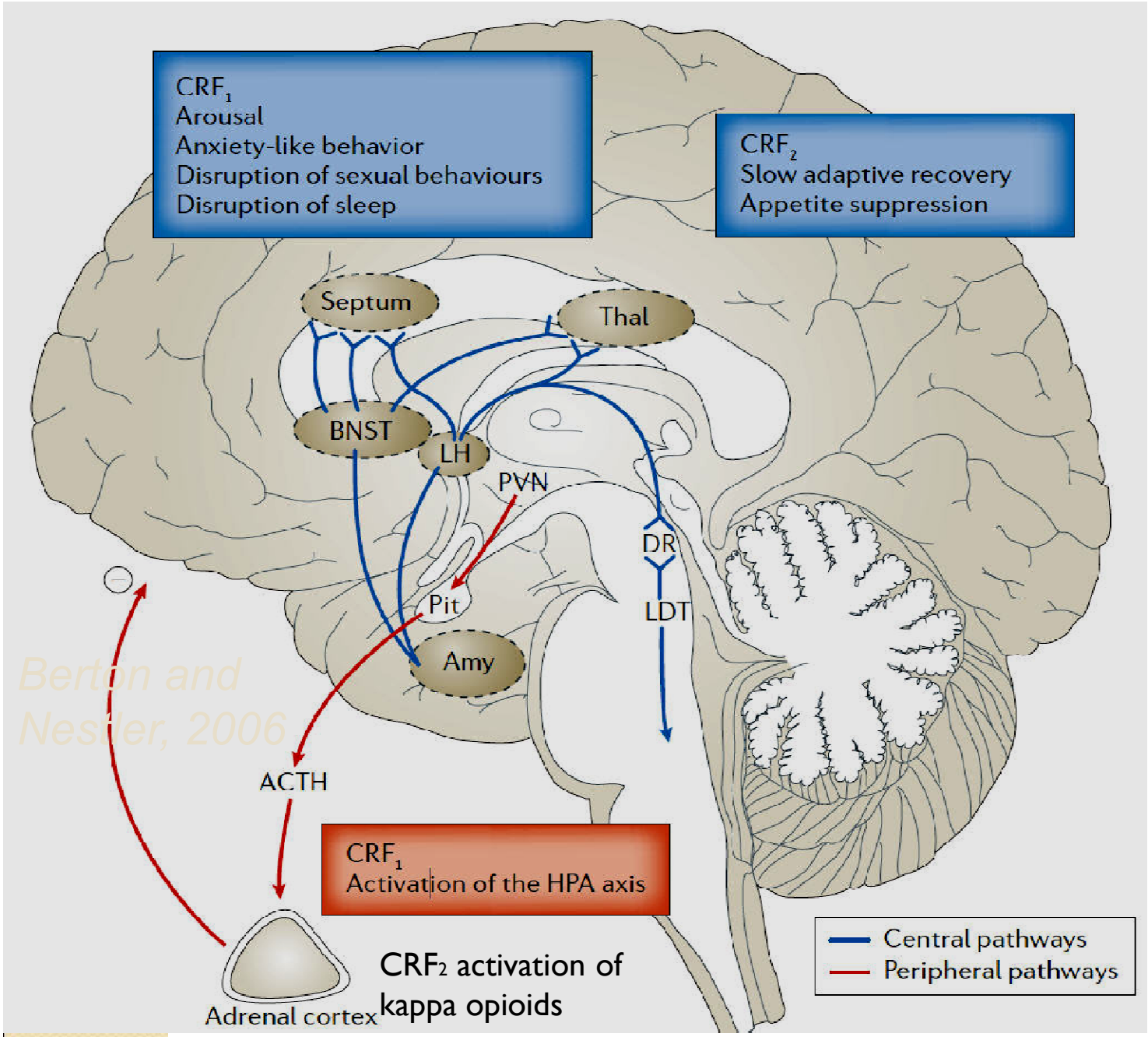
- Originally viewed as epiphenomenal. Complex and confusing!
- Disruption of thyroid, growth hormone function, ↓ secretion of melatonin, prolactin, FSH & luteinizing hormone. Mostly hypoactive.
- Pervasive effect of depression on deep regulatory mechanisms affecting the brain & body, consistent with a global shut-down.
- Alterations in HPA stress axis, stress axis 'revved up', w/ alterations in CRF/ACTH/cortisol loops and set points.
- Most early (pre-2010) results failed to control for effects of Adverse Childhood Exper, so impossible to know without replication/control.
- Glutamatergic disinhibition from ↑ corticosteroids . . .
- Stress axis issues best studied, but no satisfactory integration of all the data points.

HPA Axis: Not Epiphenomenal

- Findings of elevated cortisol (sustained ↑ HPA without negative feedback on system) esp. in evening/nighttime. Elevated cortisol atrophies HC, shrinks dendritic trees, drives cognitive decline.
- CRF in ventricles → anxious & depressive phenotype.
- Hypercortisolemia causes GM reductions in limbic structures, as seen in depression.
- Classic finding of non-suppression of cortisol after dexamethasone. Not invariant (psychotic/severe depressions).
- HPA normalization/dysregulation: predictor for remission/ relapse of symptoms in patients with MD.
- CRF_1 antagonists may ameliorate depression. Classic biogenic amine anti-depressants may lower CRF. GR antagonists (Mifepristone) may be effective in psychotic depression.
- MR antagonists (spironolactone) *interfere* w/ antidepressants.
- Early-life stress produces ↑ emotional and neuroendocrine reactivity & creates a vulnerable phenotype for depression, with life-long upregulation of CRF.

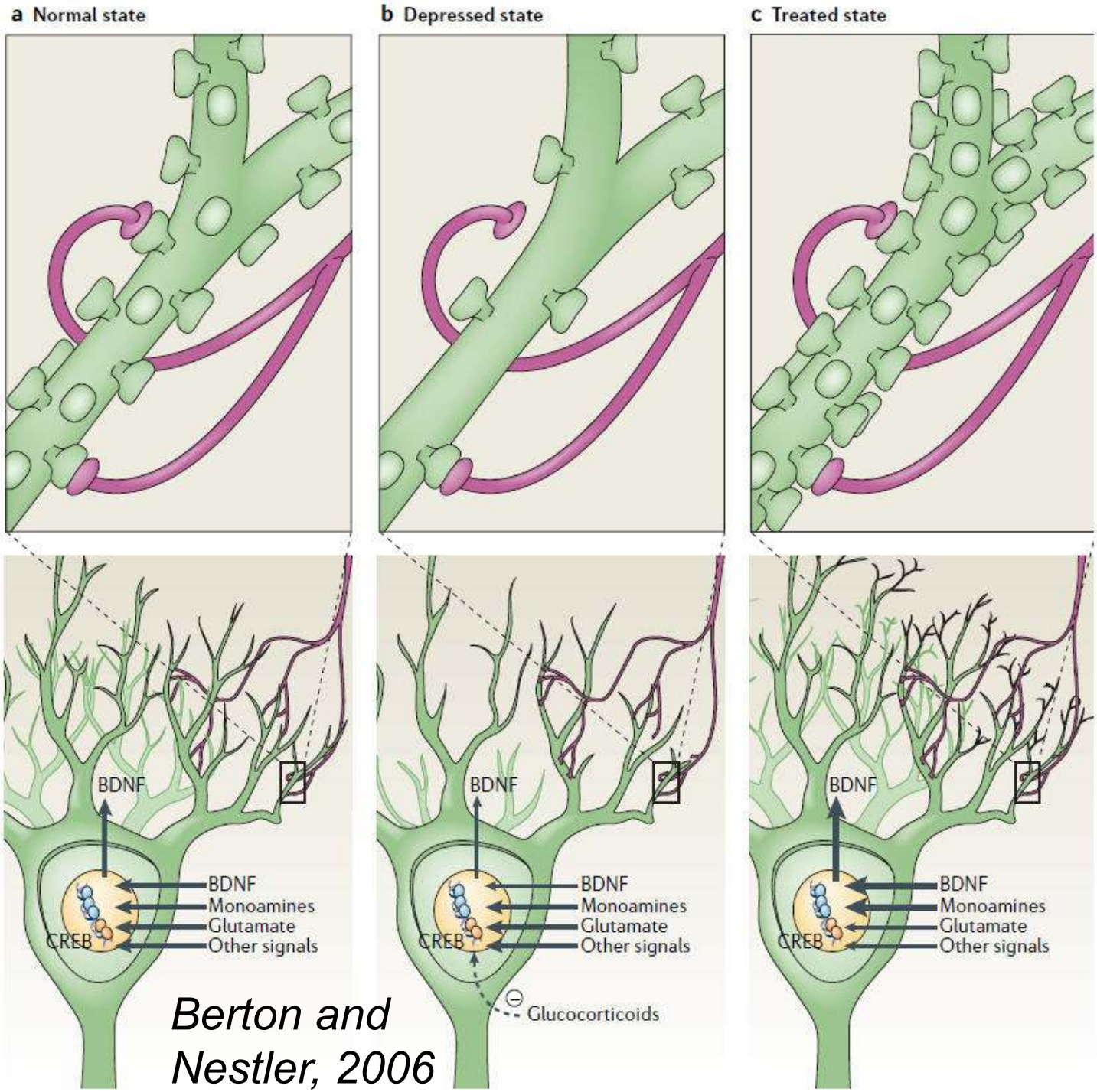


Dimensionality of stress - adaptive versus maladaptive effects. Punitive intensity, increasing sense of helplessness, conjoined w/chronic duration push CNS and other biological systems towards depression, immuno-compromise, and other maladaptions. (Sanacora, Yan & Popoli, NRN 2022)



Corticotropin-releasing factor system. CRF triggers release of ACTH from pituitary (CRF1 receptors). ACTH drives glucocorticoid production from adrenals. Increased glucocorticoid levels lowers hypothalamic CRF expression via negative feedback through HC/HYPO glucocorticoid receptors. Feedback control interfered with via ↑ cytokines (which disinhibits CRF) yielding positive feedback. Critical circadian oscillator is superimposed on this feedback.

Amy, amygdala; BNST, bed nucleus of stria terminalis; DR, dorsal raphe; HPA, hypothalamic–pituitary–adrenal; LDT, lat.dorsal tegmental nucleus; LH, lat. Hypothal.; Pit, pituitary;



Berton and Nestler, 2006

Neurotrophic mechanisms in depression drug action.

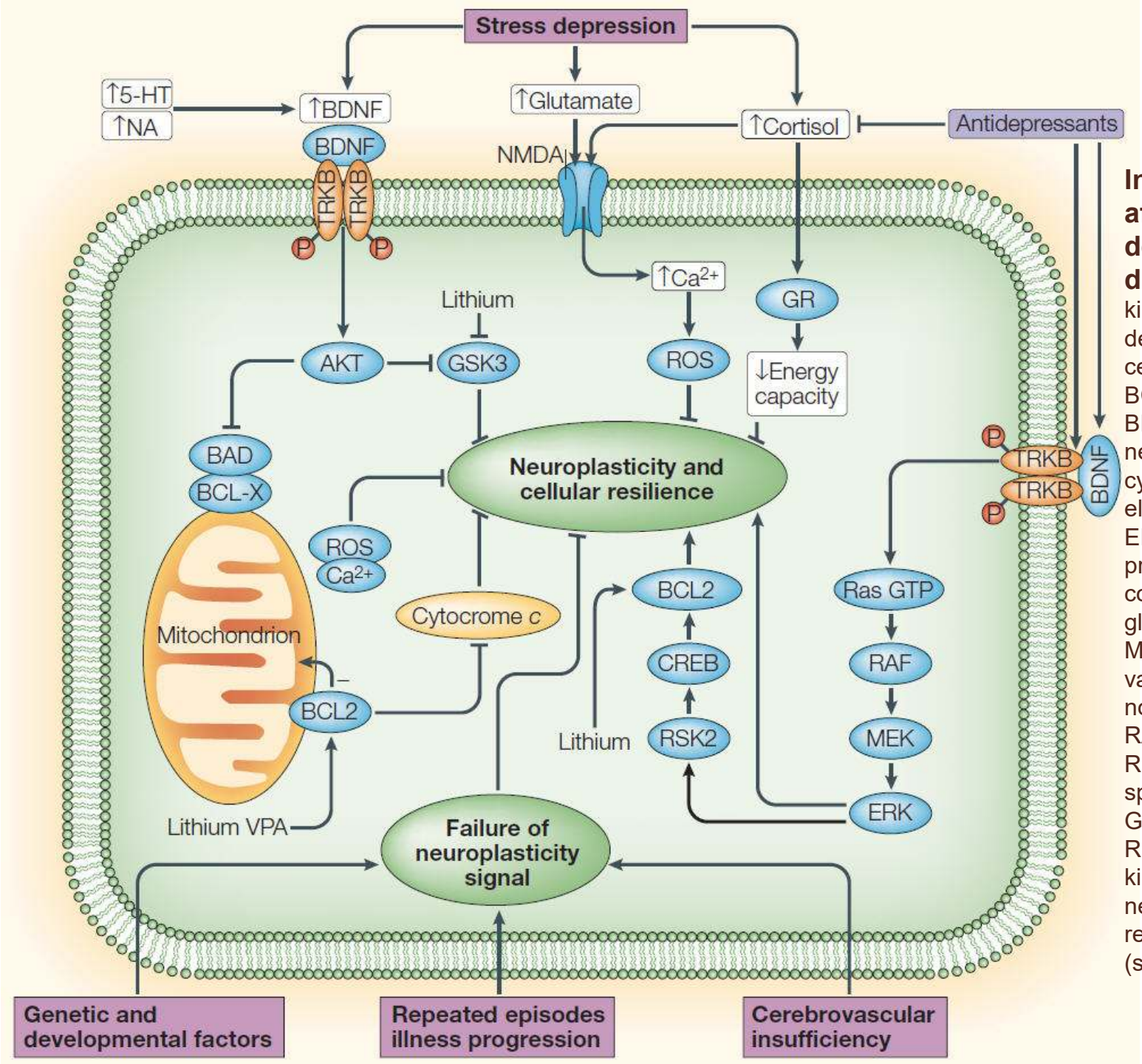
a | Normal hippocampal pyramidal neuron & regulation by BDNF.

b | Severe stress: ↓ dendritic arborization and↓ BDNF expression. Reduction in BDNF mediated by gluco-corticoids, ↓ transcription (through CREB) that controls BDNF expression.

c | Antidepressants: opposite effects to those in **b**: ↑arborization/BDNF expression of hippocampal neurons. Mediated by activation of CREB. Antidepressants reverse or prevent effects of stress on HC.

However, this has been recently debated in that some measures show increased apoptosis from SSRIs

Neuroplasticity Cascades in Depression



Intracellular pathways affected by anti-depressants & mood disorders AKT, protein kinase B; BAD, BLC-assoc. death promoter; BCL2, B-cell leukemia/ lymphoma 2; BCL-X, BCL2-like protein 1; BDNF, brain-derived neurotrophic factor; CREB, cyclic AMP responsive element binding protein; ERK, mitogen activated protein kinase 1; GR, gluco-corticoid receptor; GSK3, glycogen synthase kinase 3; MEK, ERK kinase; VPA, valproate; NA, noradrenaline; P, phosphate RAF, RAF proto-oncogene; ROS, reactive oxygen species; Ras GTP, Ras GTPase-activating protein; RSK2, ribosomal protein S6 kinase polypeptide 3; TRKB, neurotrophic tyrosine kinase receptor type B; 5-HT (serotonin).

Neuroinflammatory Perspectives on Depression

Evolution may have carved multiple variations on behavioral shutdown, adaptive and operative in different contexts:

Sickness behavior, depression, hibernation may all be mechanistically related, but these processes are poorly mapped in terms of basic relationships.

Social stress signals and inflammatory signals may be evolutionarily conjoined in basic ways, as our ancestors faced injury conjoined with social/predator stress.

Immune system is critically relevant in depression – surprising or not?

- Traditional view: *sickness behavior, depression, & hibernation* in separate 'bins'? Depression 'medicalized' as maladaptive while others adaptive.
- Evolutionary view: these all share a 'trunk-line' relationship as variations on ancient behavioral shutdown mechanism(s).
- Is circadian regulation perhaps the original trunk-line for these conserved shutdown mechanisms?
- Evidence base is still modest for this, remaining to be probed:
  - Sleep deprivation is pro-inflammatory (esp. innate vs. adaptive immunity)
  - Hibernation inhibited by anti-depressants, stimulants & characterized by increased GLUT signaling (shared with depression).
  - Circadian dysfunction of various types, even simple sleep deprivation, are underappreciated risk factors for depression.
  - Evolutionary argument: depression is in part a metabolic conservation? (infant mammals losing primary source of metabolic supply)?
  - Cytokines do affect behavior directly via variety of mechanisms/targets.
- The original 'circadian shutdown' (sleep) is in part inflammatory.
- How might microbiome-CNS-immune interfaces figure into depression (see last slide in this section).

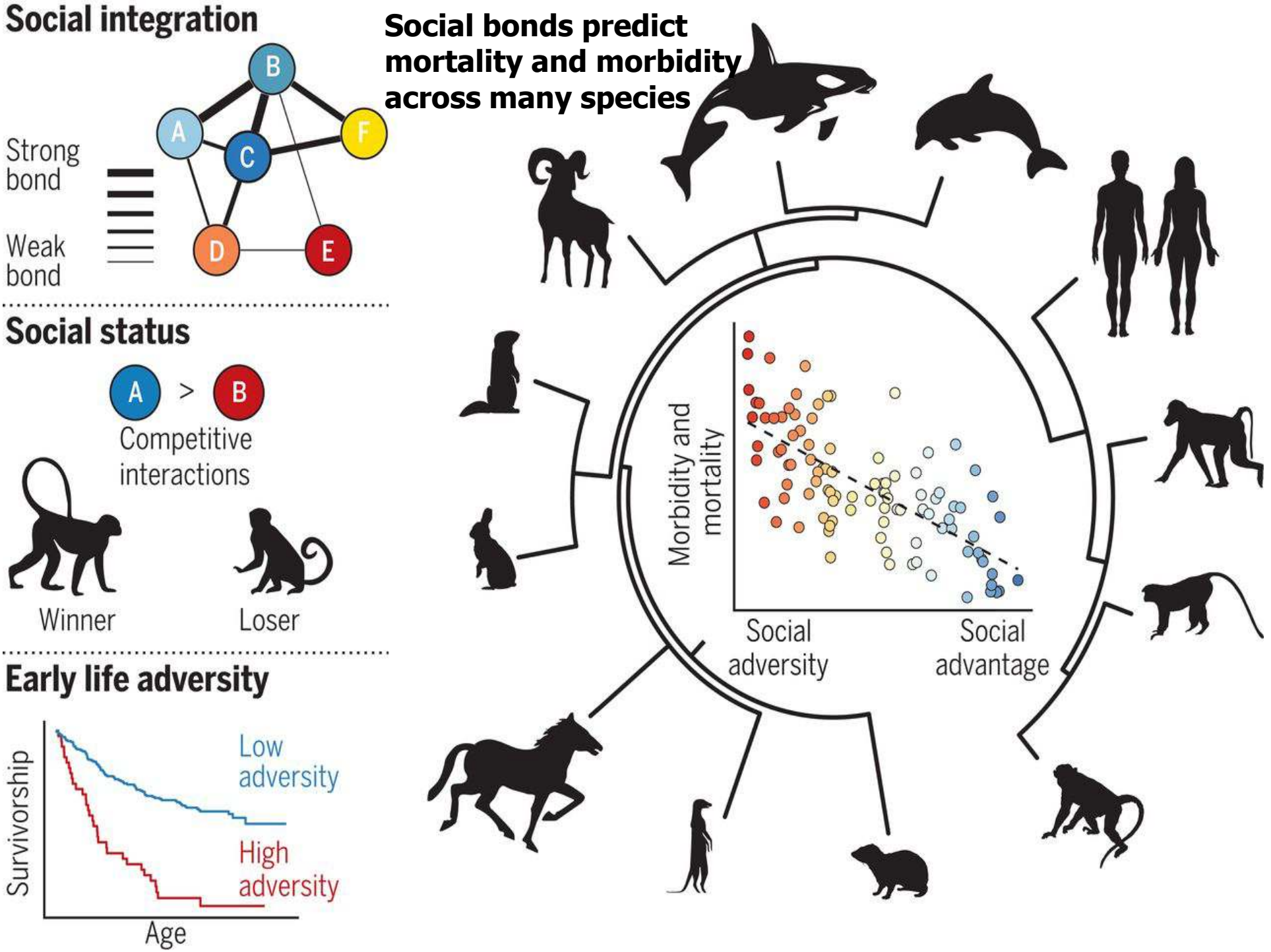
Overlapping. . . . but not synonymous

- Major Depression
  - Depressed mood w/loss of hopeful orientation/SI
  - Decreased interest
  - Anhedonia (↓ pleasure)
  - Loss of motivation – can be severe, admixed w/fatigue, esp. w/poor sleep
  - Agitation, psychomotor slowing
  - Loss of self-esteem often times w/ ↑ shame, guilt
  - Loss of appetite in more common phenotype
  - Decreased attention, WM, SOP, executive fxns/decision making
  - Mostly maladaptive (unless brief)
- Sickness behavior
  - Generalized malaise/'pan-algesia' w/dysphoria, but not despair or SI
  - Decreased interest
  - Anhedonia (↓ pleasure)
  - Fatigue – can be severe, with secondary effects on motivation?
  - Slowing/lethargy
  - Sleepiness, but with poor sleep?
  - No clear self-esteem issues
  - Loss of appetite
  - Cognitive fog, with similar phenotype to depression but can progress to delirium
  - Adaptive → immunocompetence but debilitating/depressing in LT.

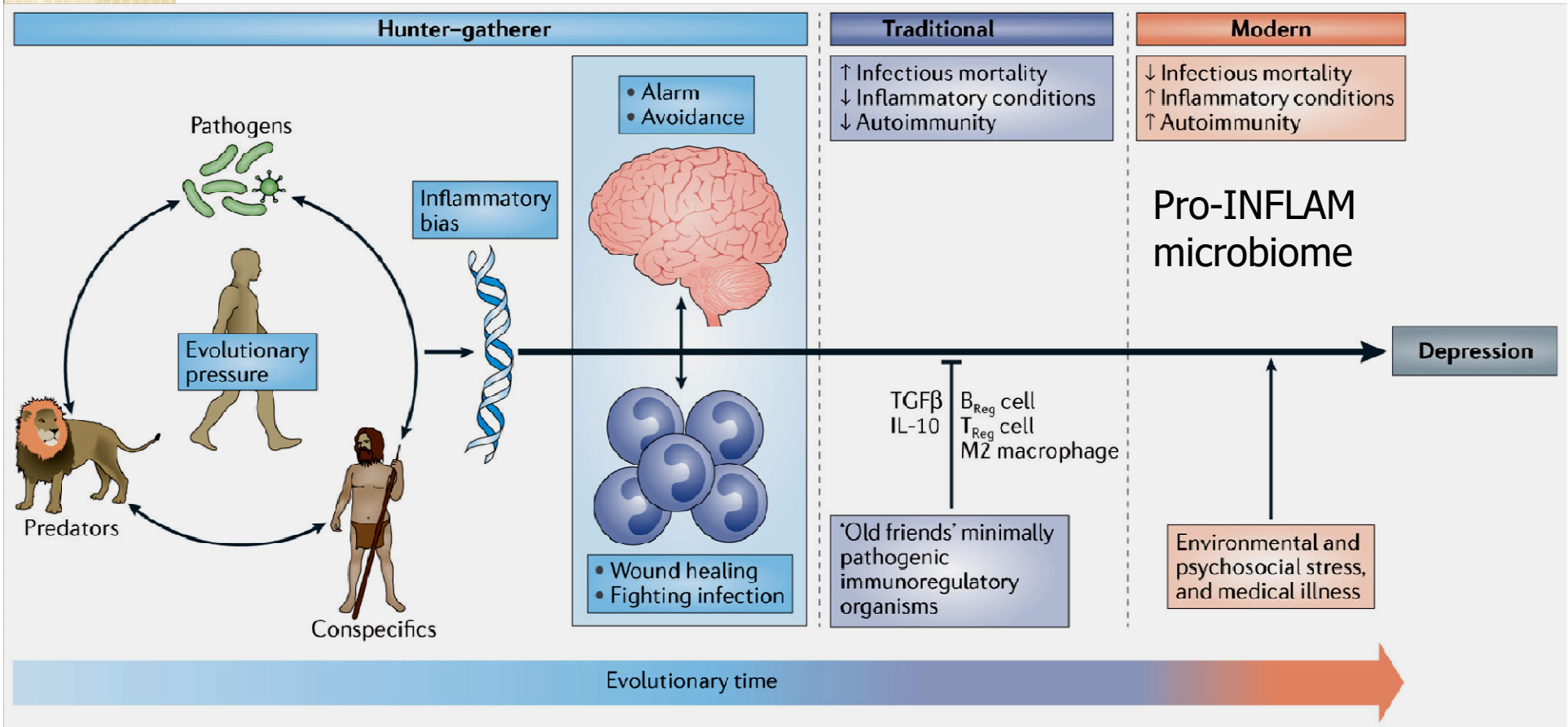
Is fatigue the most non-specific symptom of all? Widest differential diagnosis?

- One is tempted to assume that fatigue with its enormous commonality would be well mapped. . . . but still fundamentally mysterious!
- Has both normoadaptive/pathological variations. 'Normal' fatigue appears from acute exercise and/or sleep debt. Sleep/rest resolves normal fatigue.
- Associated w/ virtually every pro-inflammatory condition under the sun → fundamental relationship between ↑pro-inflammatory cytokines & fatigue. Differential effects of various pro-INFLAM cytokines not well mapped.
- Classic differential diagnosis includes metabolic, liver & kidney disease, infectious, endocrine, and psychiatric disorders especially depression, sleep disorders, nutritional problems, cancers and even just lack of activity and exercise. It is harder to specify major illnesses that <u>do not cause fatigue</u>.
- And yet despite this heterogeneity, evidence argues that all causes may index effects of pro-inflammatory signals/molecules on CNS reticular arousal systems, perhaps most especially the suprachiasmatic nucleus.
- ***Fatigue sits at intersection of circadian, inflammatory & MITO issues?***
- Ruling out its many reversible causes can yield chronic fatigue syndrome Dx.

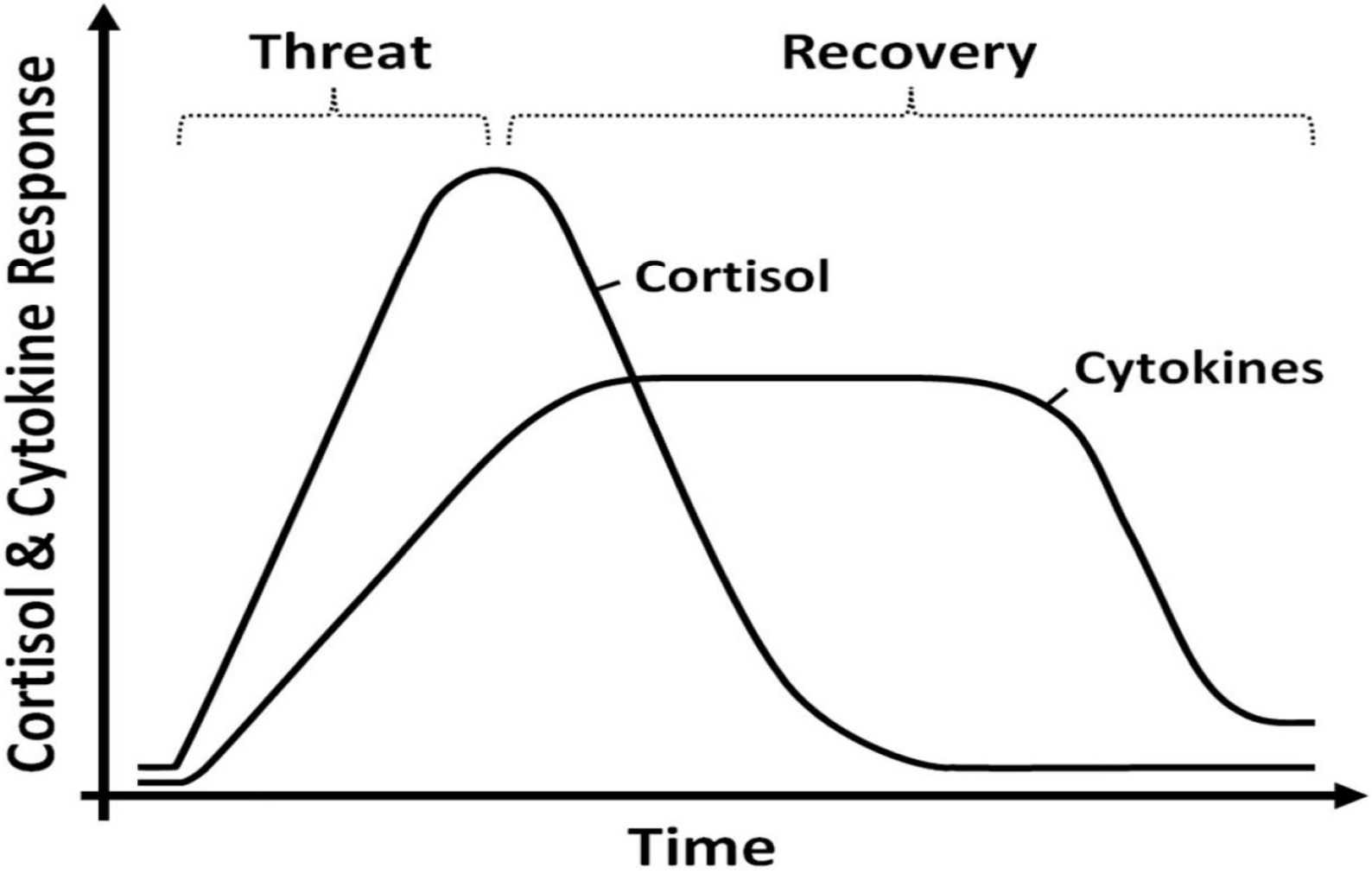
Social bonds predict mortality and morbidity across many species



Environmental changes from HG→ ↑INFLAM



Early evolutionary pressures from interactions w/pathogens, predators and conspecifics (rivals) resulted in inflammatory bias w/integrated suite of immunological & behavioral responses for fighting infection and healing wounds, while maintaining vigilance against attack. This inflammatory bias held in check during much of human evolution by ***regulatory T-cells, B cells, M2 macrophages, interleukin-10 (IL-10) transforming growth factor-β (TGFβ)***. In modern times, sanitized environments in developed societies rife w/ psychological challenges but lacking in infectious challenges (primary sources of morbidity and mortality across most of human evolution). In absence of traditional immunological checks & balances, psychological challenges of the modern world instigate ancestral immunological and behavioral repertoires promoting depression via INFLAM mechanisms.



Conjoining of stress and inflammatory activation:

Corticosteroid spike blunts any potential sickness behavior (fatigue/disinterest from cytokine activation), while allowing behavioral activation and mobilization of resources without major immunosuppression. Might optimize & prepare for situations involving both social conflict and potential injury. Trade-offs? (Slavich, 2018)

We are in an alien environment from the standpoint of our genome, w/global effects!

Original Evolutionary Environment

1) Intense aerobic exercise (2+ hrs/d)
2) 8-9+ hours sleep (see #1)
3) Calorie limitations (periodic CR)
4) High phytochemical/polyphenol diets
5) Omega-6/Omega-3 ratio 1:1 to 2:1)
6) High intake of fiber (~50-100 gm/d)
7) Low sugar/carbs, except fruits/veggies
8) Intake of K+ > Na+ (K+ > 3 gm/d)
9) Pro-alkaline diet
10) UVB → higher Vit D (40-80+).
11) NIR from sun → ↑melatonin/↓OS
12) Minimal to no glycated proteins
13) Intimate social groups/tribes
14) Early mortality: infection, starvation, predation, and violence/wars: life expectancy 35 to 45

Modern Technological Environment

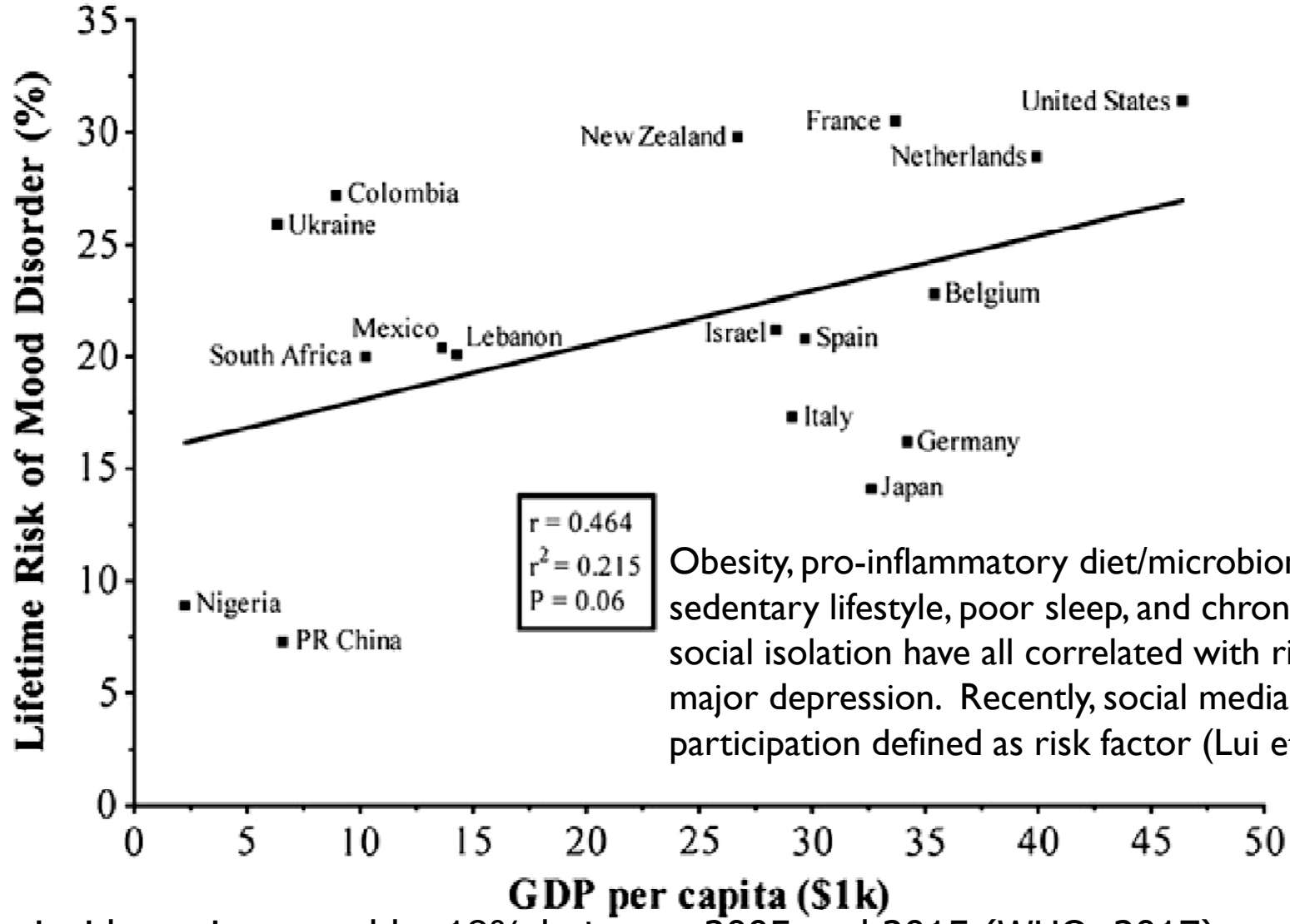
1) Minimal to no aerobic exercise
2) ≤7 hrs (see #1), many ≤6 hrs
3) Unlimited calories
4) Low phytochemical/polyphenol diets
5) Omega-6/Omega-3 ratio 12:1 - 20:1
6) Low intake of fiber (≤ 15 gm/d)
7) High sugar/carbs, <u>not</u> from fruits/veg
8) Intake of Na+ > K+ (Na+ > 3 gm/d)
9) Pro-acidic diet
10) Vit D deficiency/insufficiency (≤30)
11) No NIR from sun → ↓melatonin/↑OS
12) Lots of glycated protein (milk)
13) Social isolation is very common
14) Death from an advanced disease of aging with life expectancy 75 to 85

Exercise, polyphenols, adequate Vit D, sleep, social support/intimacy, low BMI, low homocysteine, high fiber, good omega 3/6 ratio, **all are anti-inflammatory**. Western lifestyles in toto are **hugely pro-inflammatory** relative to hunter-gatherer lifestyle. Immune system disinhibited by these changes, worsening in aging, with MITO health/function deteriorated.

Cultural aspects of attachment and social connection failure → ↑↑ depression?

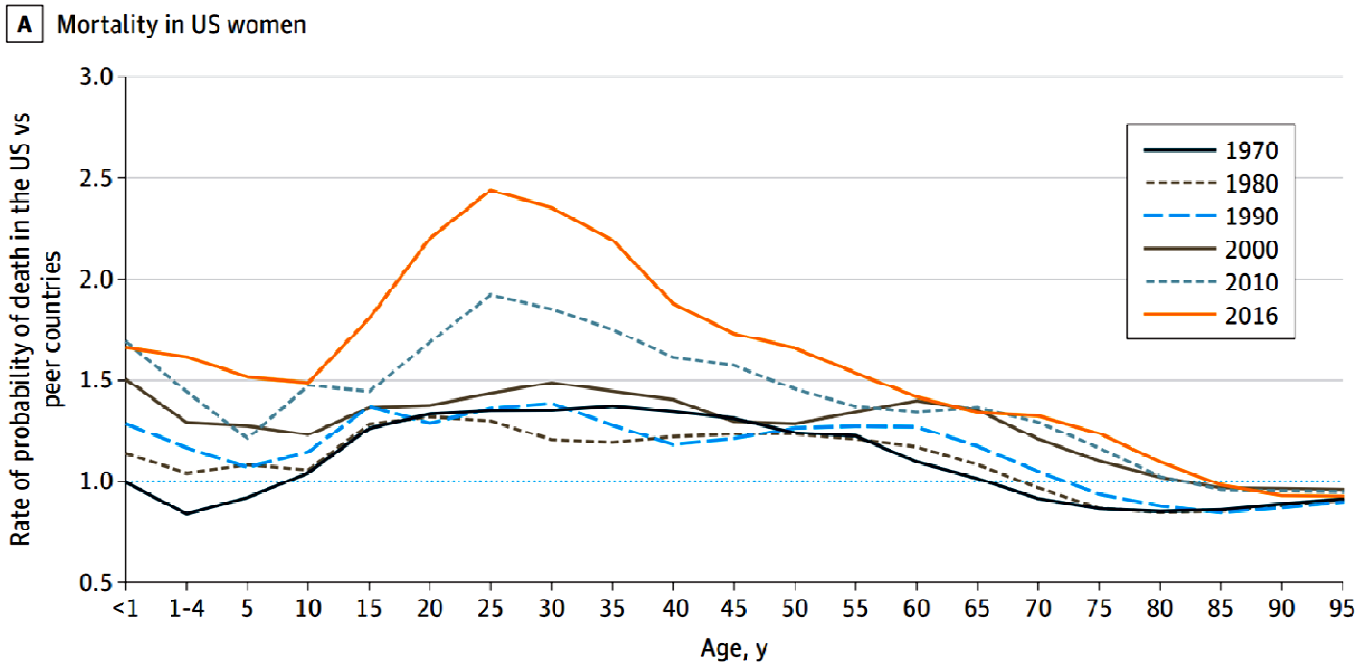
- Poorly studied and even actively ignored in our culture, but possibly to probably related to many factors:
  - Much of attachment/attachment failure is heavily ***trans-generational***.
  - ***High incidence*** of child abuse, neglect & other ACE? ~30-40% w/ACE?
  - ***Violence levels are high***, including violence against women, with ~¼+ of women having some form of domestic violence exposure (prob. more)
  - ***Substance abuse***, which is especially destructive in perinatal mothers.
  - Related to all of the above, a ***higher incidence of sociopathy***?
  - ***Culture glorifies materialism***, addictive pursuit of immense wealth.
  - Culture glorifies related problems of ***narcissism/rugged individualism***?
  - ***Appeal of fundamentalist doctrines*** as compensatory for poor attachment security and poor social support?
  - ***Increasing social media involvement*** which predicts stress, poor QOL.

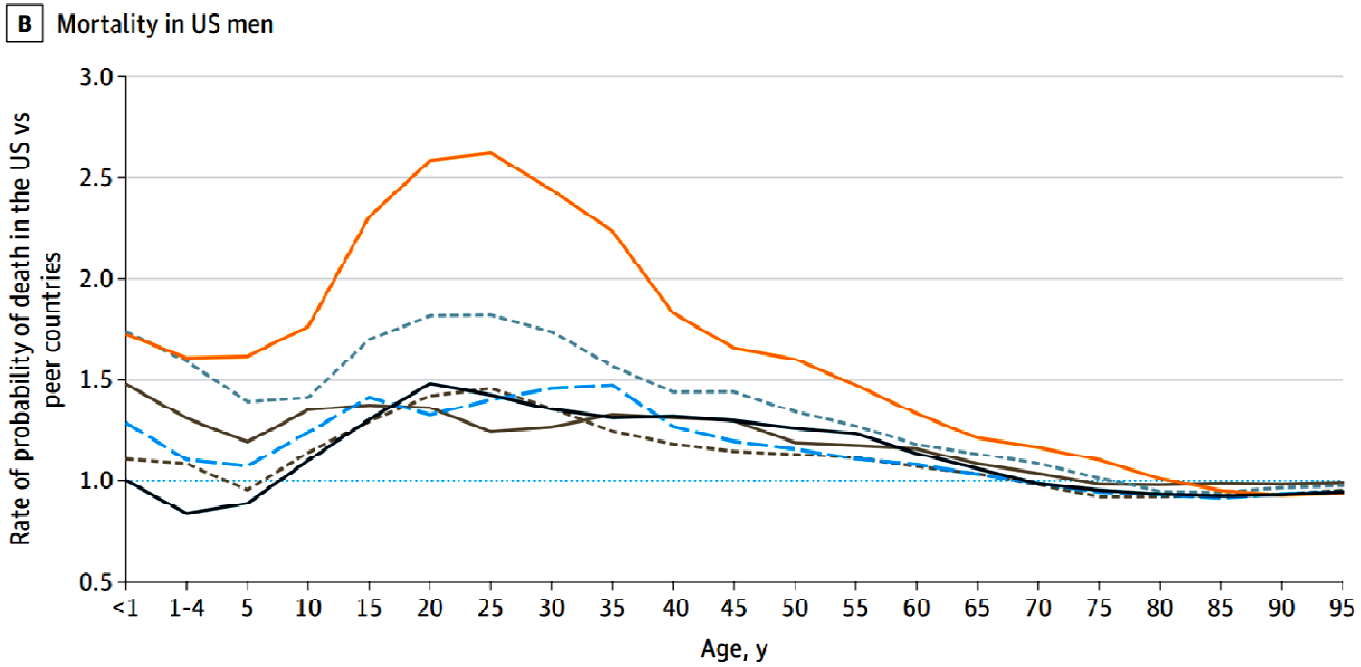
Is depression in part a disease of modern industrialized society? (Hidaka, 2012) If so, why?



Obesity, pro-inflammatory diet/microbiome, sedentary lifestyle, poor sleep, and chronic social isolation have all correlated with risk for major depression. Recently, social media participation defined as risk factor (Lui et al.

Its incidence increased by 18% between 2005 and 2015 (WHO, 2017)





From Sterling and Platt, 2022, JAMA

Probability of death in the US vs average probability of death in peer countries. A value greater than 1.0 indicates that individuals in the US experienced a higher probability of dying in that age group relative to th peer country average. The relative rise in US mortality has grown markedly since 2000. Reprinted wit permission from the National Academy of Sciences.[1]

Figure 2. Deaths of Despair Rise Steeply in the US vs Western Europe, Canada, Australia, and Japan

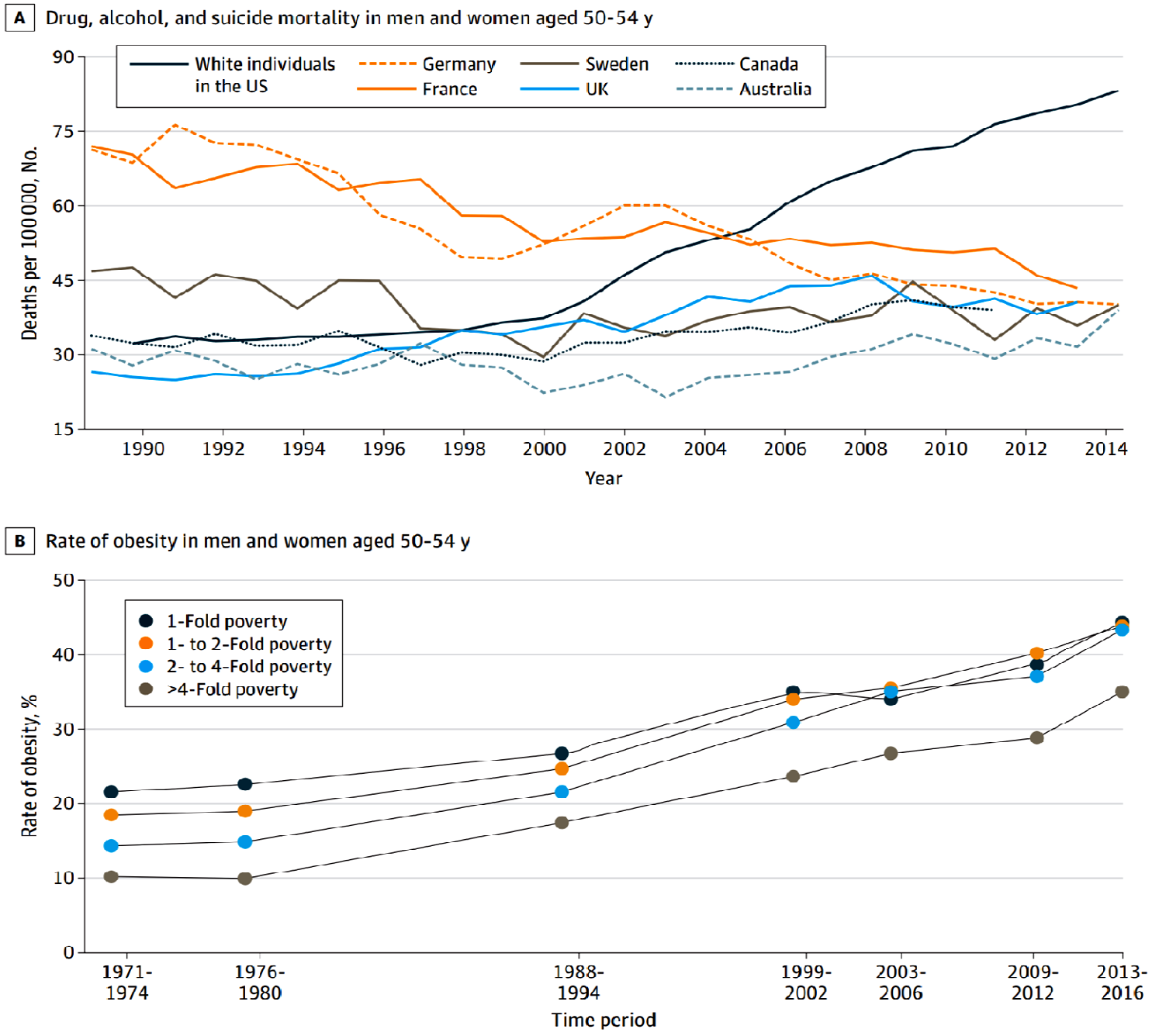
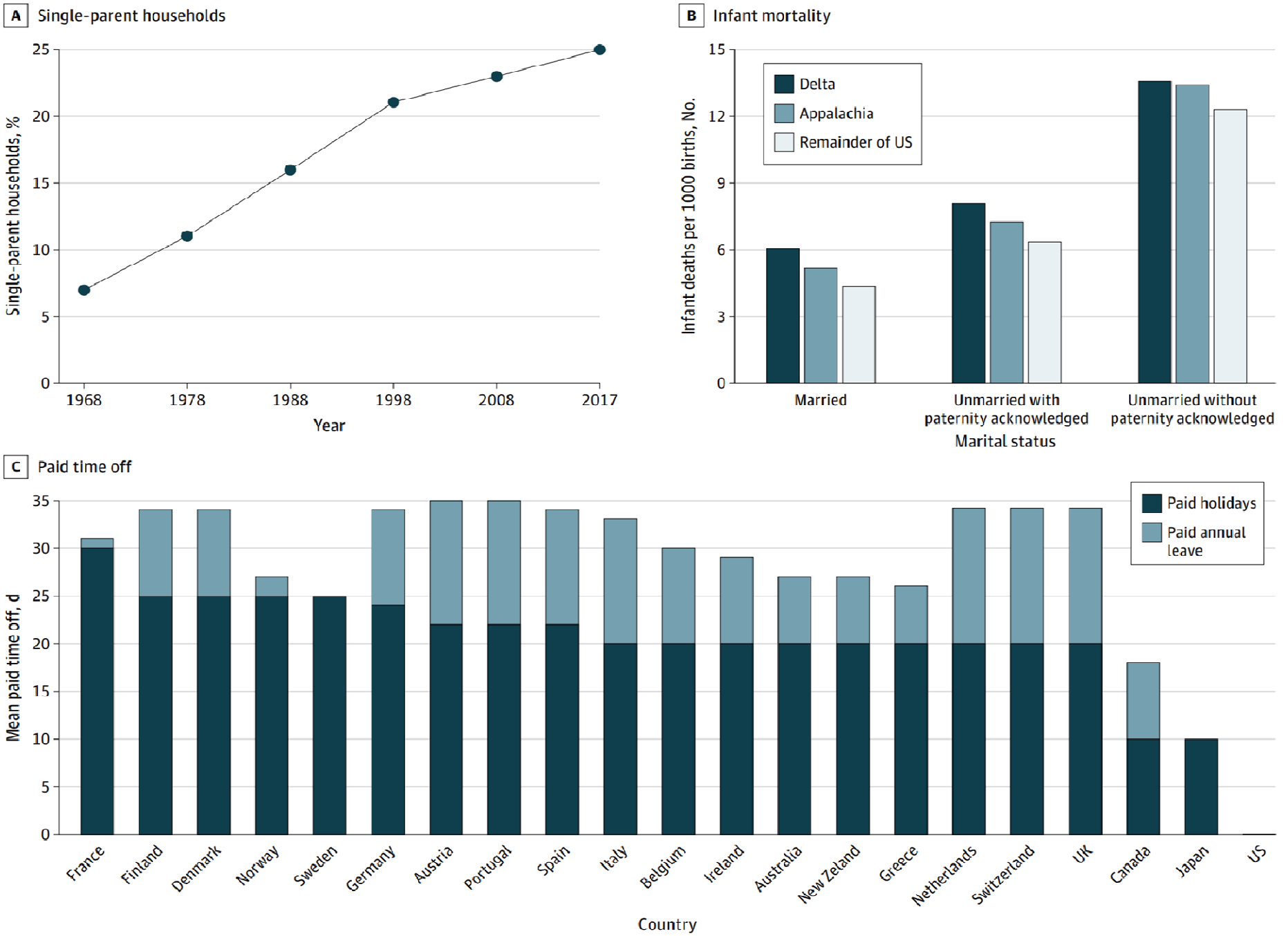
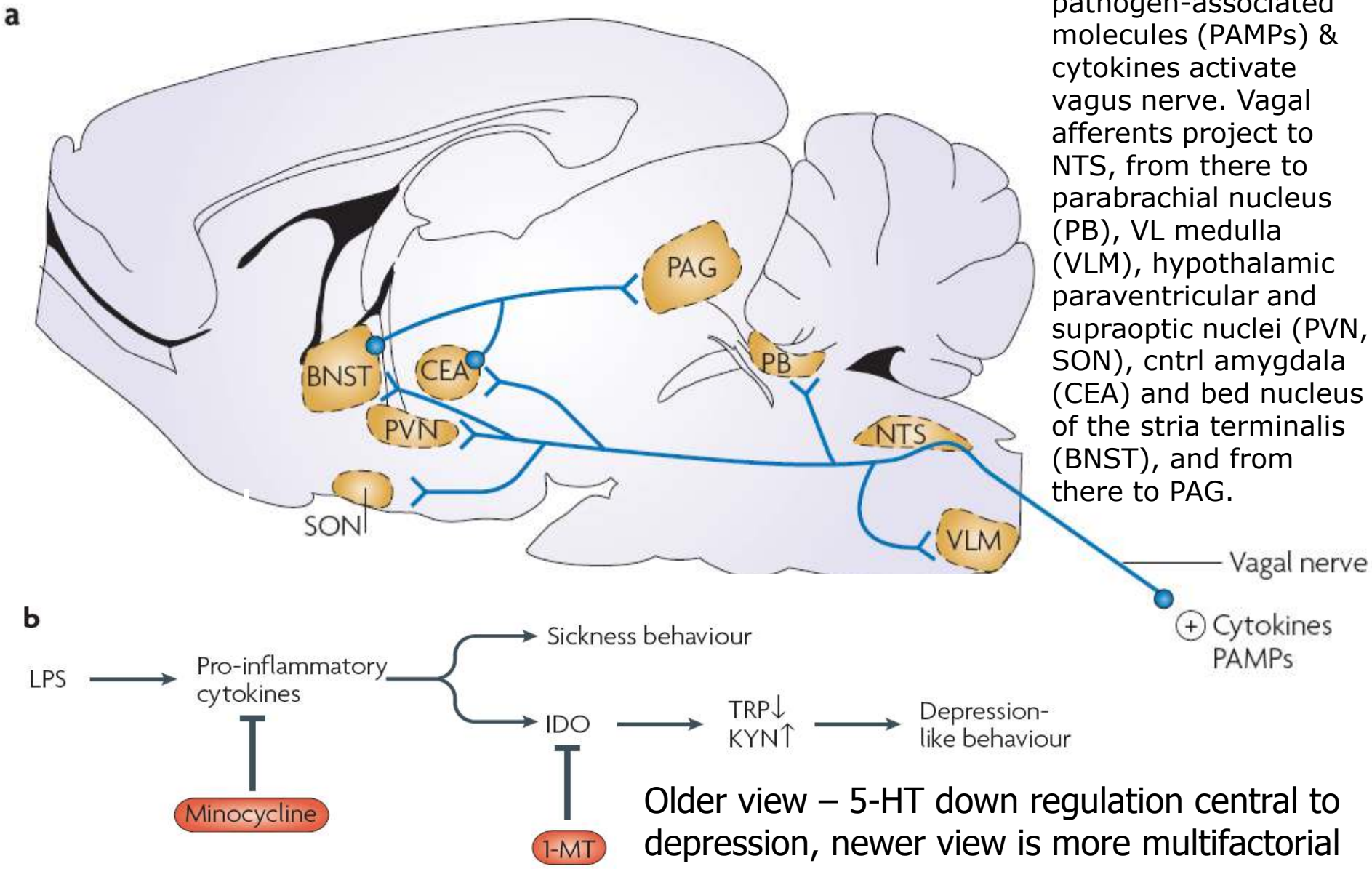


Figure 4. Changes in US Family Structure



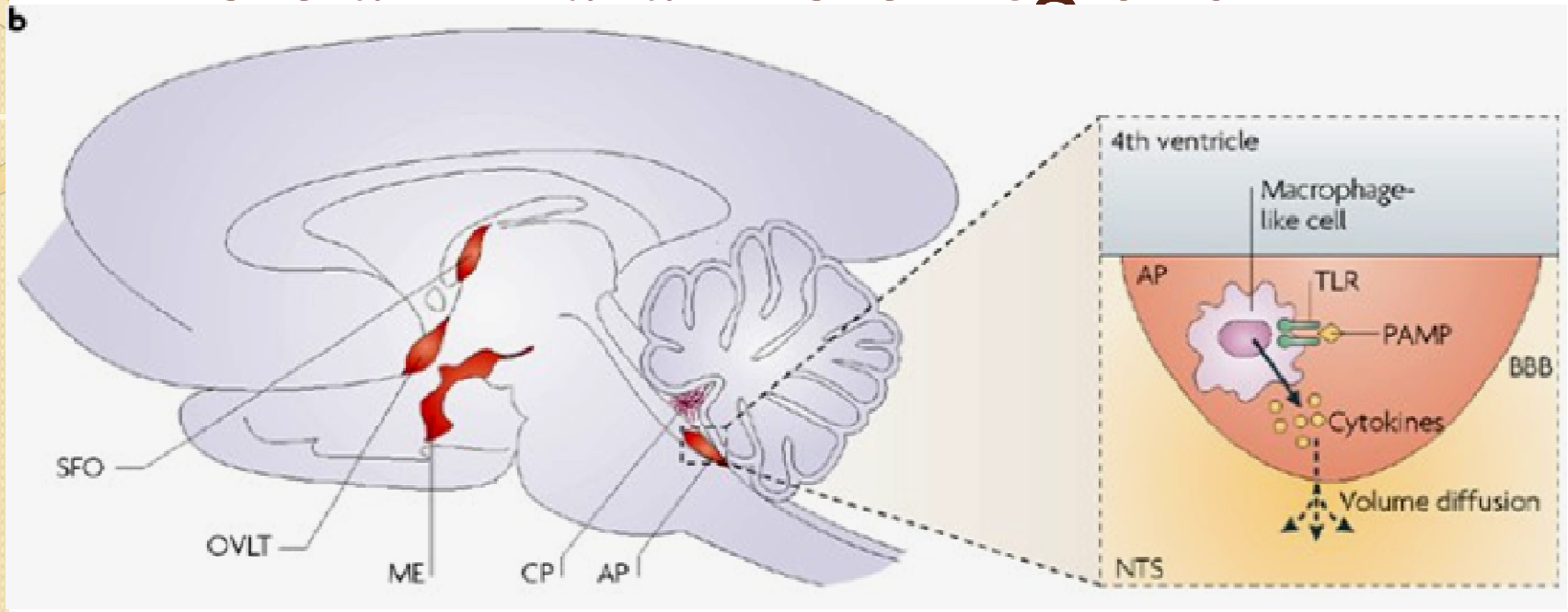
Classical View of Cytokine-Vagal-CNS Relations Delimited Immune-CNS Interaction

Peripherally produced pathogen-associated molecules (PAMPs) & cytokines activate vagus nerve. Vagal afferents project to NTS, from there to parabrachial nucleus (PB), VL medulla (VLM), hypothalamic paraventricular and supraoptic nuclei (PVN, SON), cntrl amygdala (CEA) and bed nucleus of the stria terminalis (BNST), and from there to PAG.



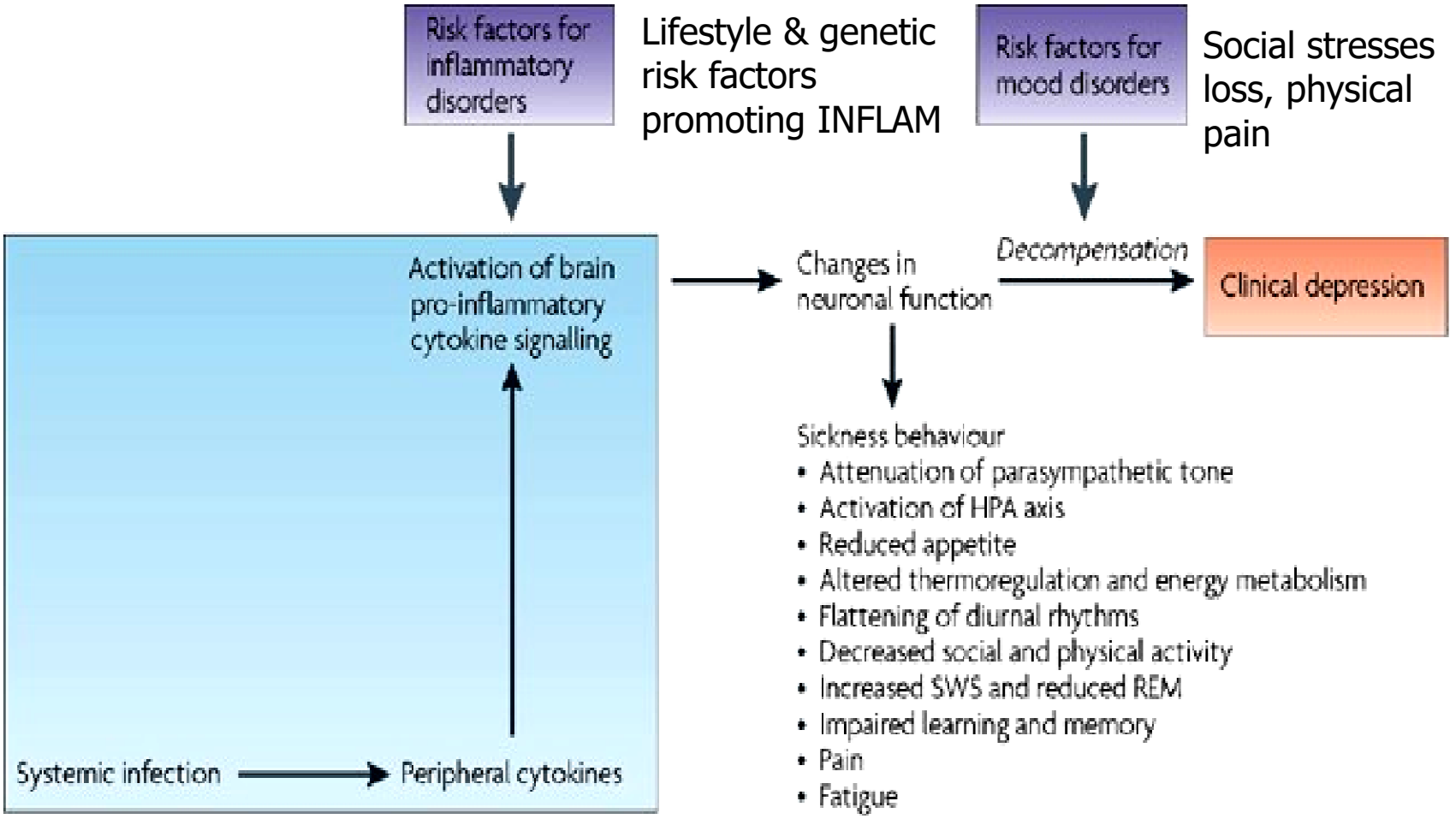
Older view – 5-HT down regulation central to depression, newer view is more multifactorial

Blood Brain Barrier Weaker in Key Limbic and Paralimbic Regions



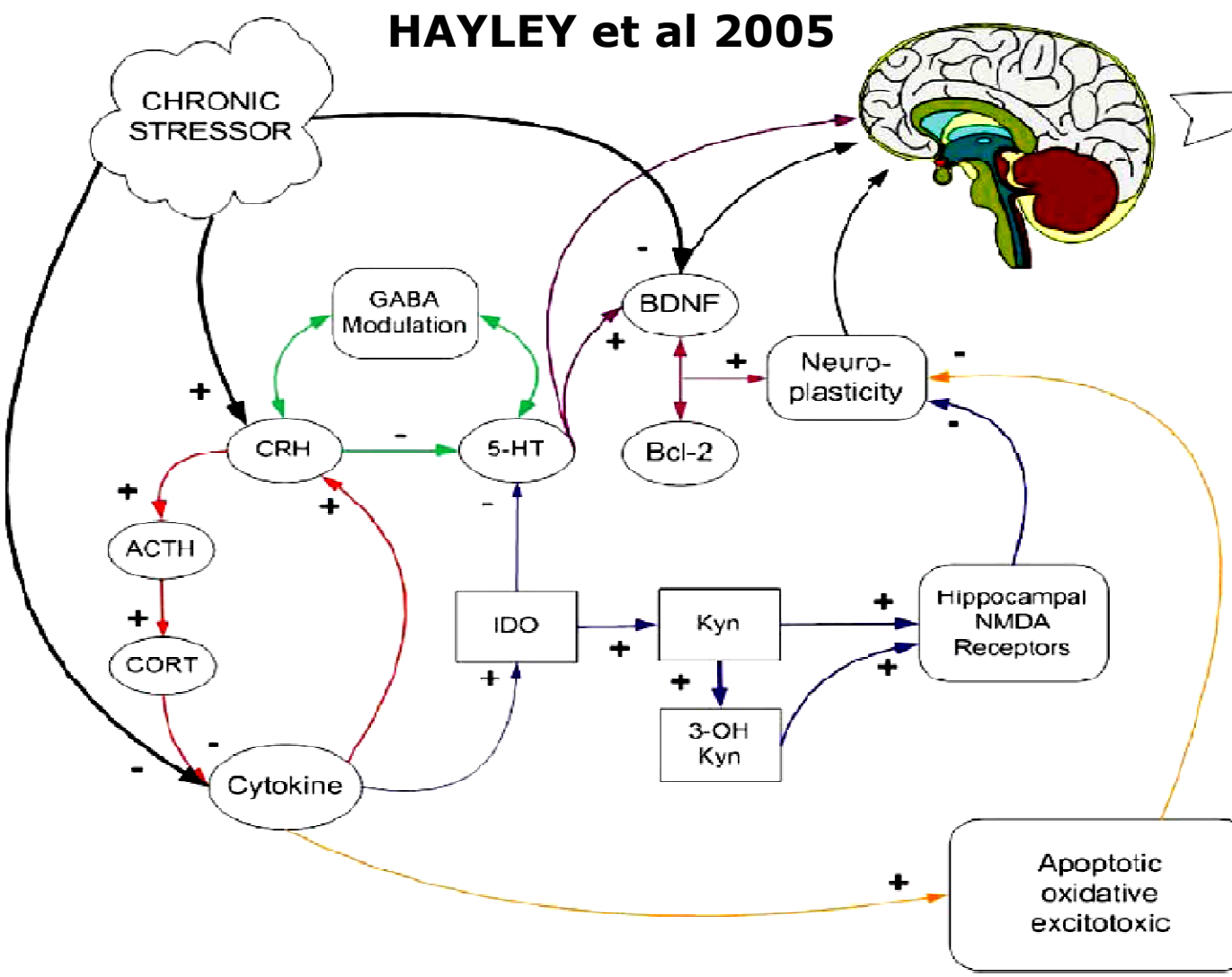
The **Classic Humoral Pathway** involves PAMPs gaining access to CNS at from the choroid plexus (CP) circumventricular organs, including median eminence (ME), organum vasculosum of the laminae terminalis (OVLT), area postrema (AP) and supraformical organ (SFO). In the circumventricular organs, PAMPs induce production & release of pro-inflammatory cytokines by microglia expressing Toll-like receptors (TLRs). As circumventricular organs lie outside the blood–brain barrier (BBB), these cytokines still need to reach the brain. They do so by several mechanisms (volume diffusion, various chaparones, induction of cytokine release by endothelial cells making up the BBB, and perhaps others currently unknown).

Pro-inflammatory states in periphery → CNS functional Δ → sickness behavior & depression



Nature Reviews | Neuroscience

Cytokine-CHF-Serotonin-BDNF Interactions in Depression



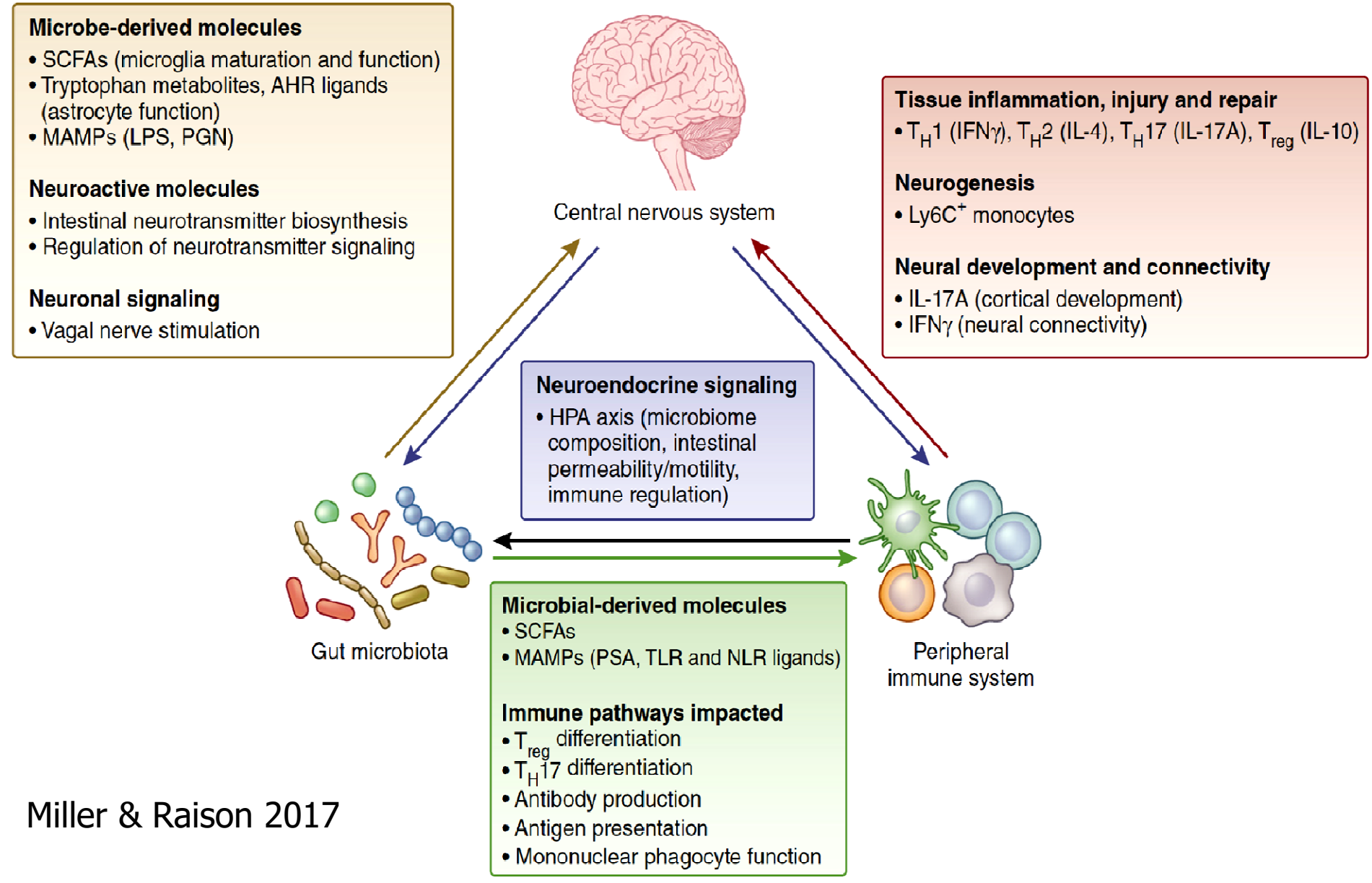
Stressors ↔ cytokines, ↑CRF, ↓BDNF (black lines). CRF modulates GABA & 5-HT (green); **Cytokines ↓ 5-HT, growth & anti-apoptotic factors (BDNF/BCL-2), ↓ plasticity & survival, ↑ depression** (purple lines); Cytokines → ↑HPA axis, promoting Δ consistent w/depression (red lines); Cytokines: decrease neuroplasticity via apoptotic, oxidative & excitotoxic processes (orange lines); Cytokines provoke IDO which impairs 5-HT, promoting NMDA toxicity (blue lines)

Cytokines and Depression

Proinflammatory cytokines (e.g., IL-1, TNF-α, IFNγ) play a large role in depression – evidence base:

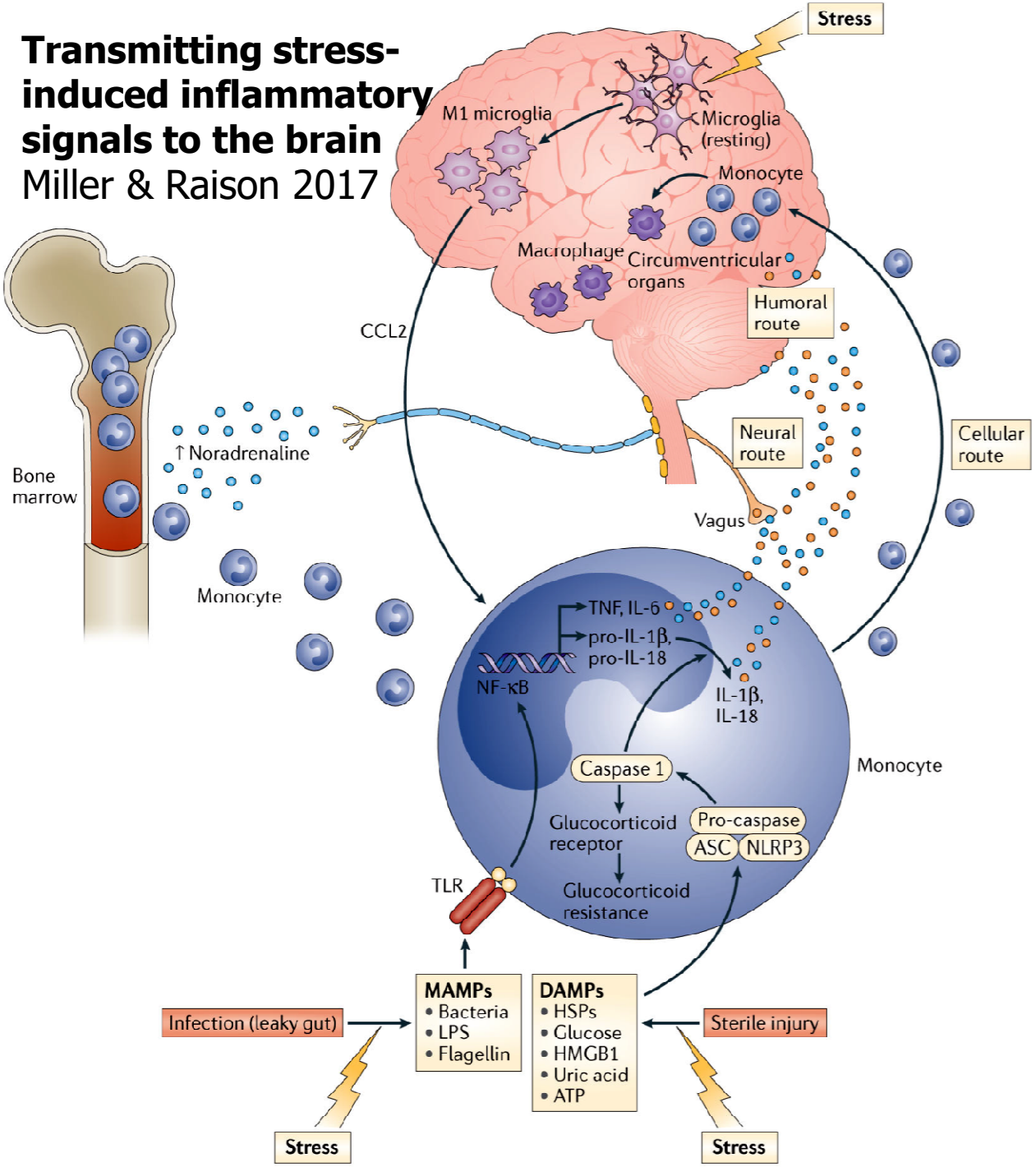
- Several illnesses characterized by chronic inflammation (e.g. RA, AD) accompanied by increased risk for MD.
- Administration of pro-inflammatory cytokines (in CA or hep. C Rx) significantly increases risk for MD.
- HPA axis dys-regulated: why cortisol negative feedback not effective to reduce CRF unclear until discovery of immune signals. Cytokines → HPA axis hyperactivity by ↓ negative feedback inhibition of corticosteroids on HPA axis → CRF 'overdrive'.
- Cytokines reduce 5-HT by ↓tryptophan through activation of enzyme indoleamine-2,3-dioxygenase (IDO).
- Cytokines increase neuroplasticity stress/neurotoxicity in HC promoting atrophic changes via ↑ kynurenine/NMDA.
- Cytokines don't cross BBB but are received by BBB cells, but lipid transport and BBB permeability also effected by stress signals.
- Interactions around GLUT and glial cell operators, disinhibition/ loss of glutamatergic regulation.

Immune ↔ CNS ↔ Microbiome



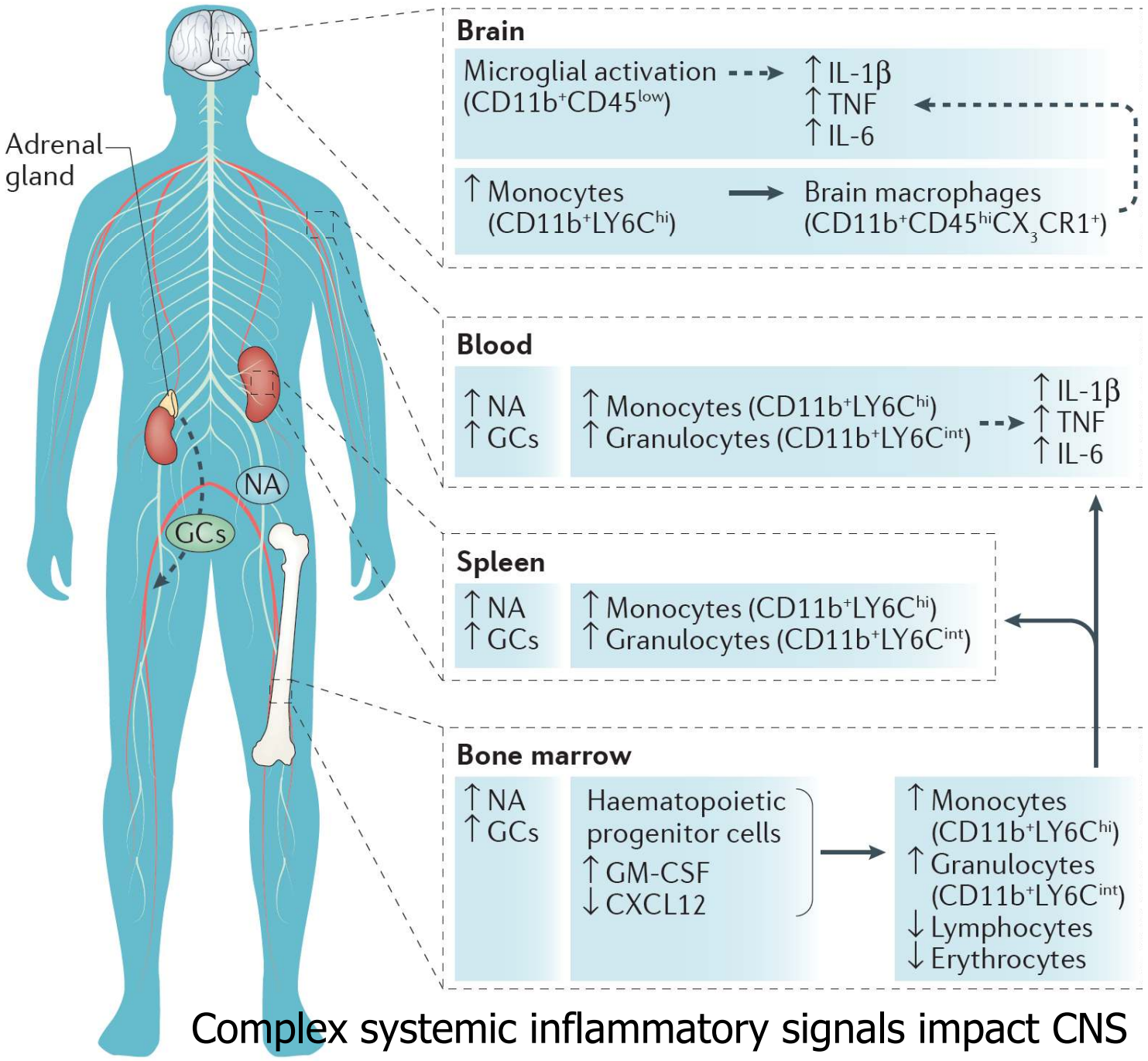
Miller & Raison 2017

Transmitting stress-induced inflammatory signals to the brain
Miller & Raison 2017

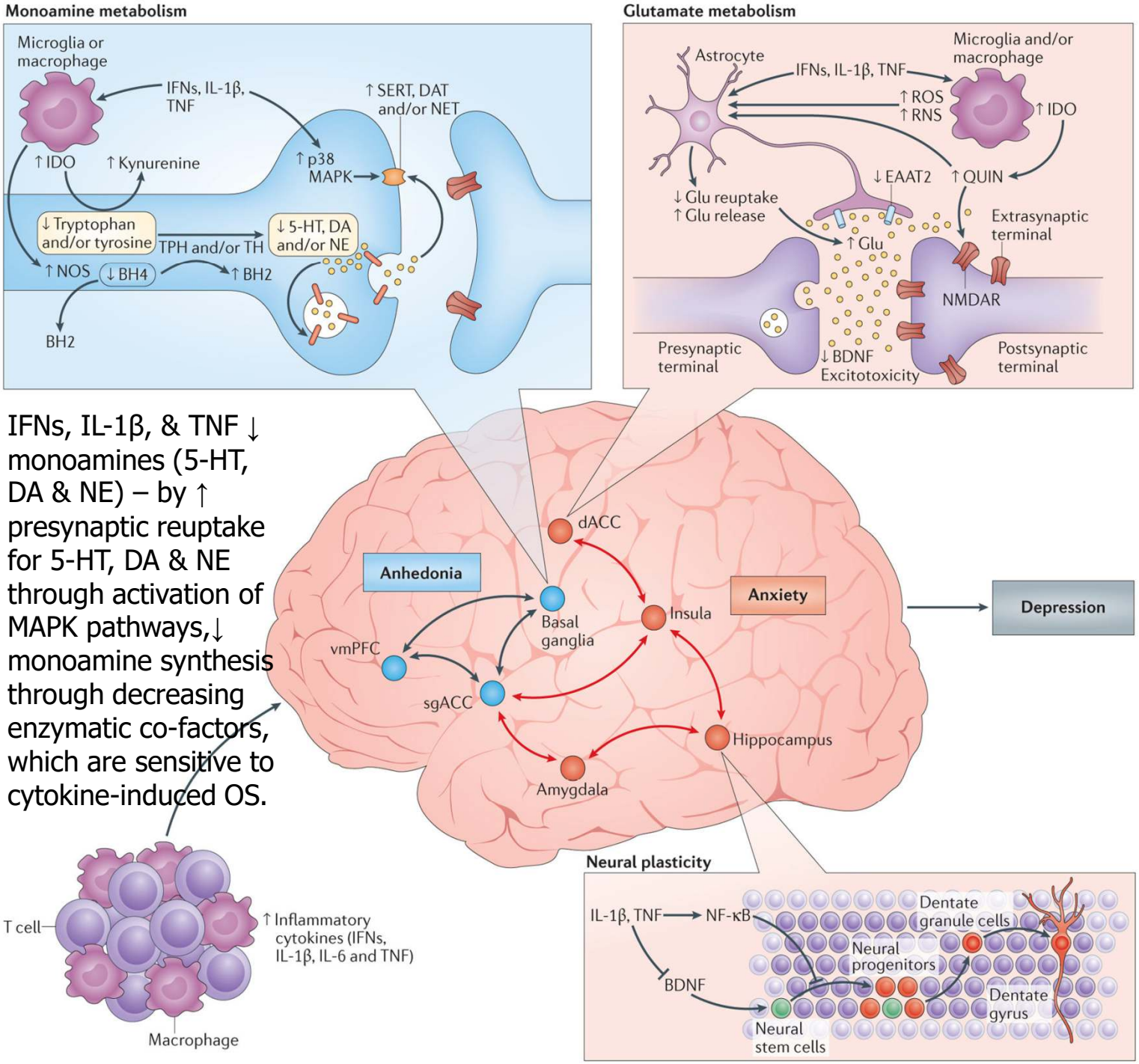


In stress, catacholamines (NE) released by SNS stimulate bone marrow → myeloid cells (monocytes) entering periphery, encountering stress-induced damage-associated molecular patterns (DAMPs), bacteria, bacterial products such as microbial-associated molecular patterns (MAMPs) leaked from GI system. These DAMPs/MAMPs activate inflammatory signaling pathways (NF-κB & NLRP3) in inflammasome. Stimulation of NLRP3 activates caspase 1→ production of IL-1β & IL-18 while also cleaving glucocorticoid receptors→ GCR resistance. Activation of NF-κB → TNF & IL-6, which along w/ IL-1β & IL-18 access CNS via humoral & neural routes. Stress → activation of microglia into pro-inflam phenotype, which release CC-chemokine ligand 2 (CCL2) that in turn attracts activated myeloid cells to the brain. Activated macrophages perpetuate central inflammatory responses. ASC, apoptosis-associated speck-like protein containing a CARD; HMGB1, high mobility group box 1; HSP, heat shock protein; LPS, lipopolysaccharide; TLR, Toll-like receptor.

Repeated stress exposure → activation of HPA axis→ adrenal release of g-corticoids. Sympathetic activation → ↑catecholamines into blood & localized ↑ noradrenaline NA into immune organs. These hormones and neuro-transmitters influence development, trafficking & activation state of both peripheral & central immune cells.



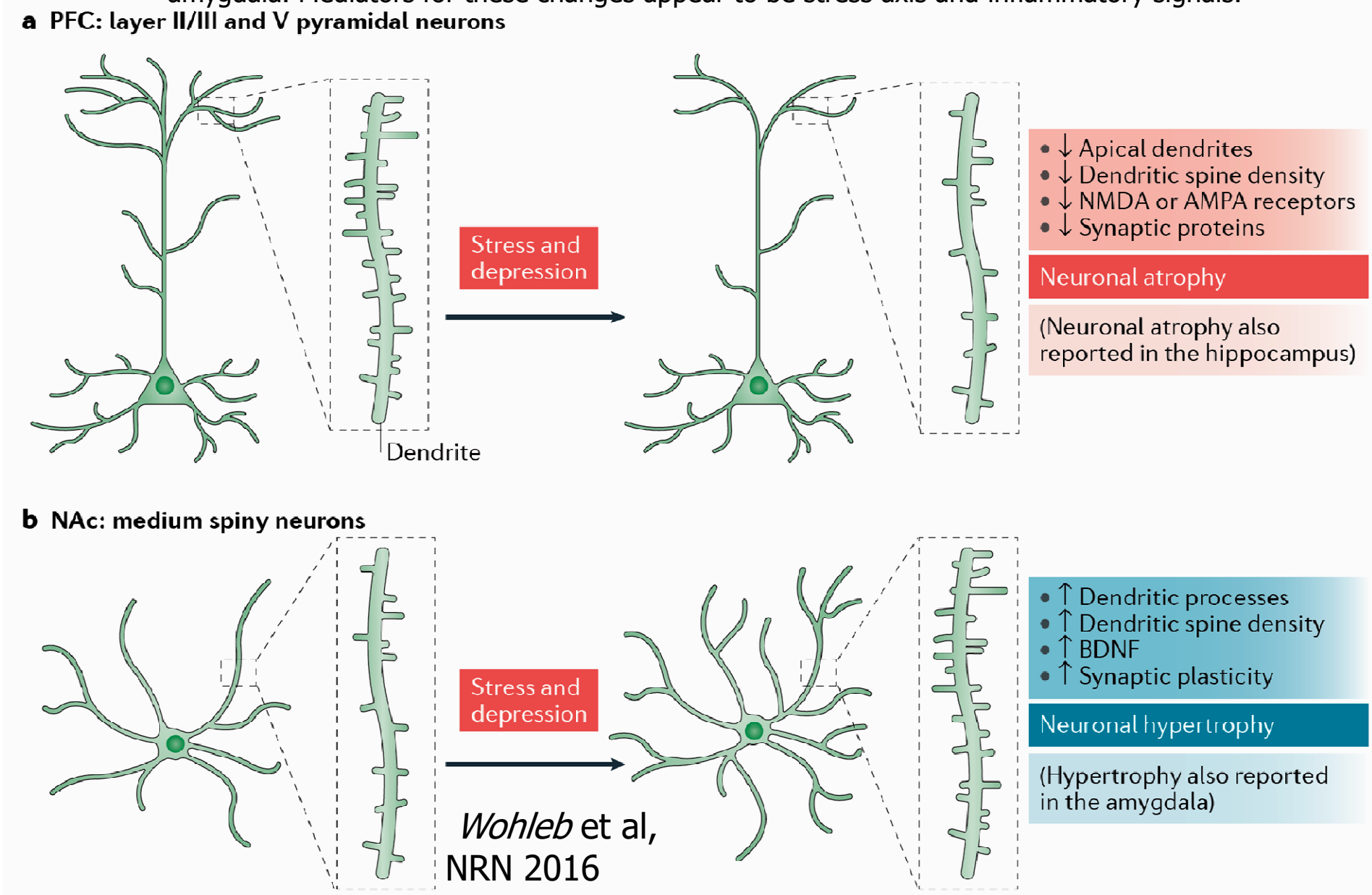
Complex systemic inflammatory signals impact CNS



Cytokines ↓ monoamine precursors by↑indoleamine 2,3-dioxygenase (IDO), breaking down tryptophan into kynurenine. Activated microglia convert kynurenine to quinolinic acid (QUIN), binding to NMDA receptors, with cytokine-induced ↓ astrocytic Glu reuptake & stimulation of astrocyte Glu release, in part by induction of ROS & RNS, can lead to excessive Glu. Excessive Glu, esp. when binding to extrasynaptic NMDARs, can in turn lead to decreased brain-derived neurotrophic factor (BDNF)/excitotoxicity.

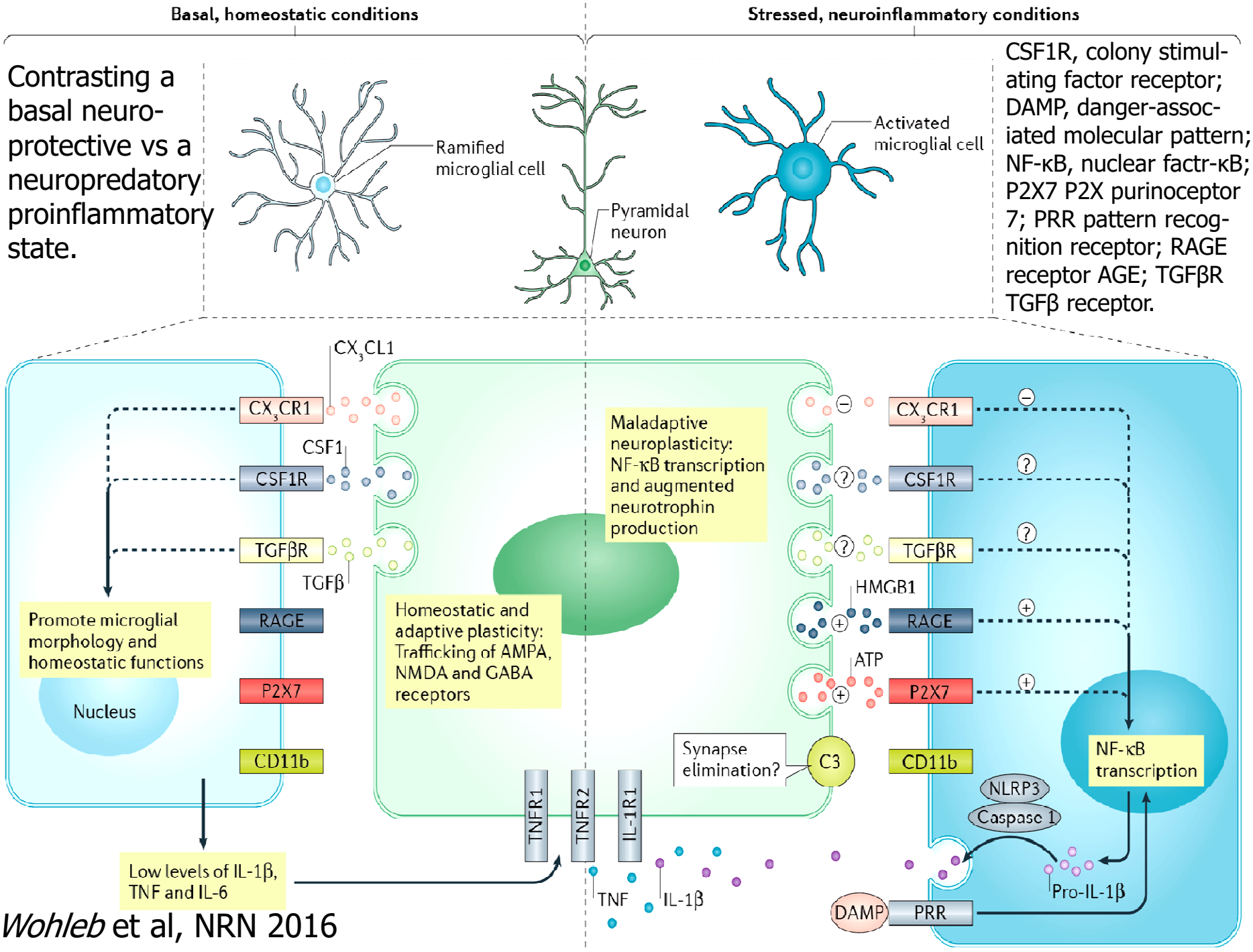
Inflammation →↓ BDNF in HC, affecting neuronal integrity, LTP neurogenesis, & dendritic sprouting, affecting learning & memory. Cytokine effects on neurotransmitter systems, especially DA, can inhibit aspects of reward motivation & anhedonia in corticostriatal circuits involving BG, vmPFC and subgenual/dorsal anterior cingulate cortex (sgACC and dACC), also activating circuits for anxiety, arousal, alarm/fear (amygdala, HC, dACC and insula).

a | Observed changes in GLUT pyramidal neurons in depression - similar dystrophic responses reported in HC. **b** | By contrast, depression-associated changes in GABAergic medium spiny neurons in NAc include ↑ dendritic complexity, associated w/ ↑ levels of BDNF. Comparable effects seen in amygdala. Mediators for these changes appear to be stress axis and inflammatory signals.



Wohleb et al, NRN 2016

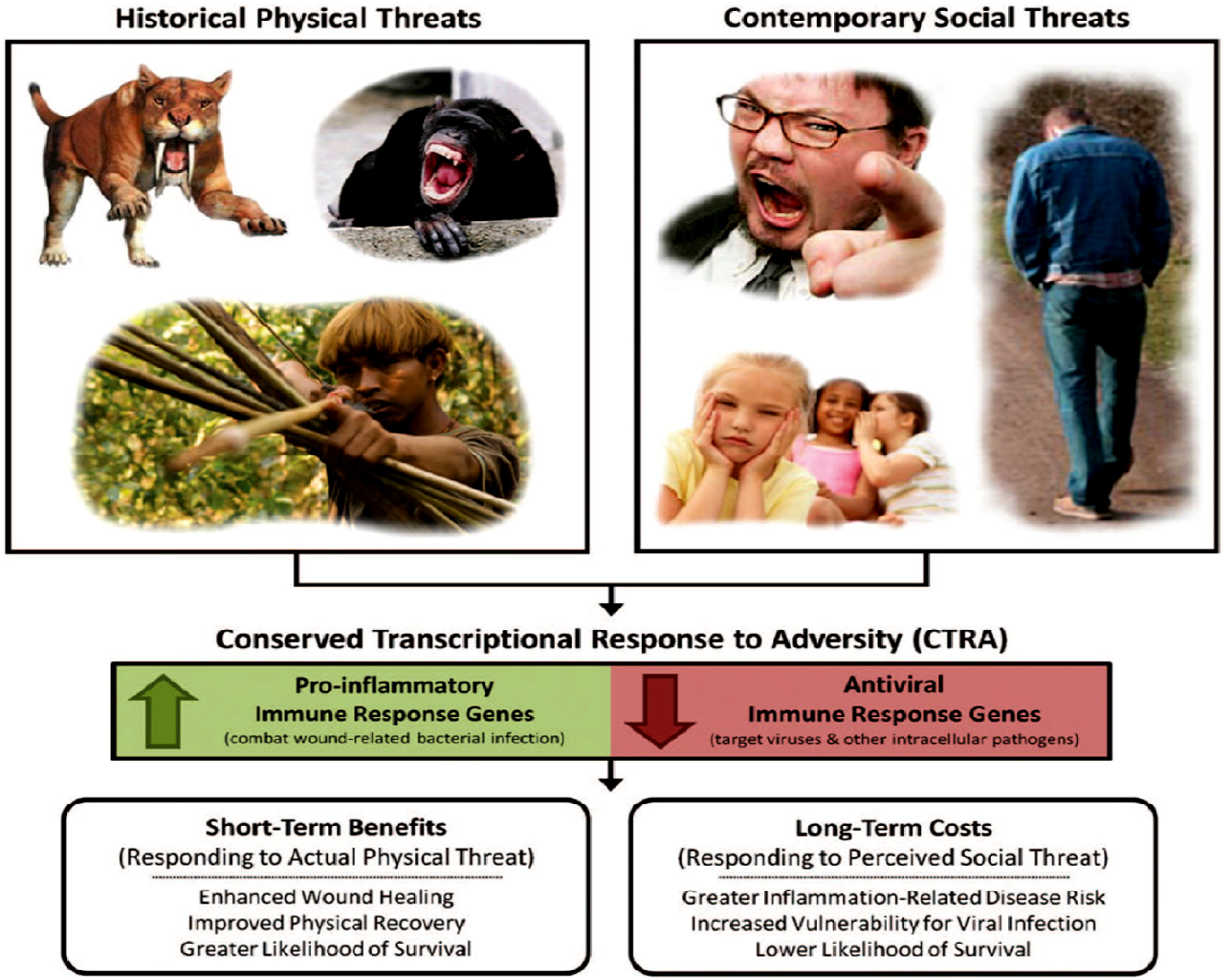
Contrasting a basal neuro-protective vs a neuropredatory proinflammatory state.



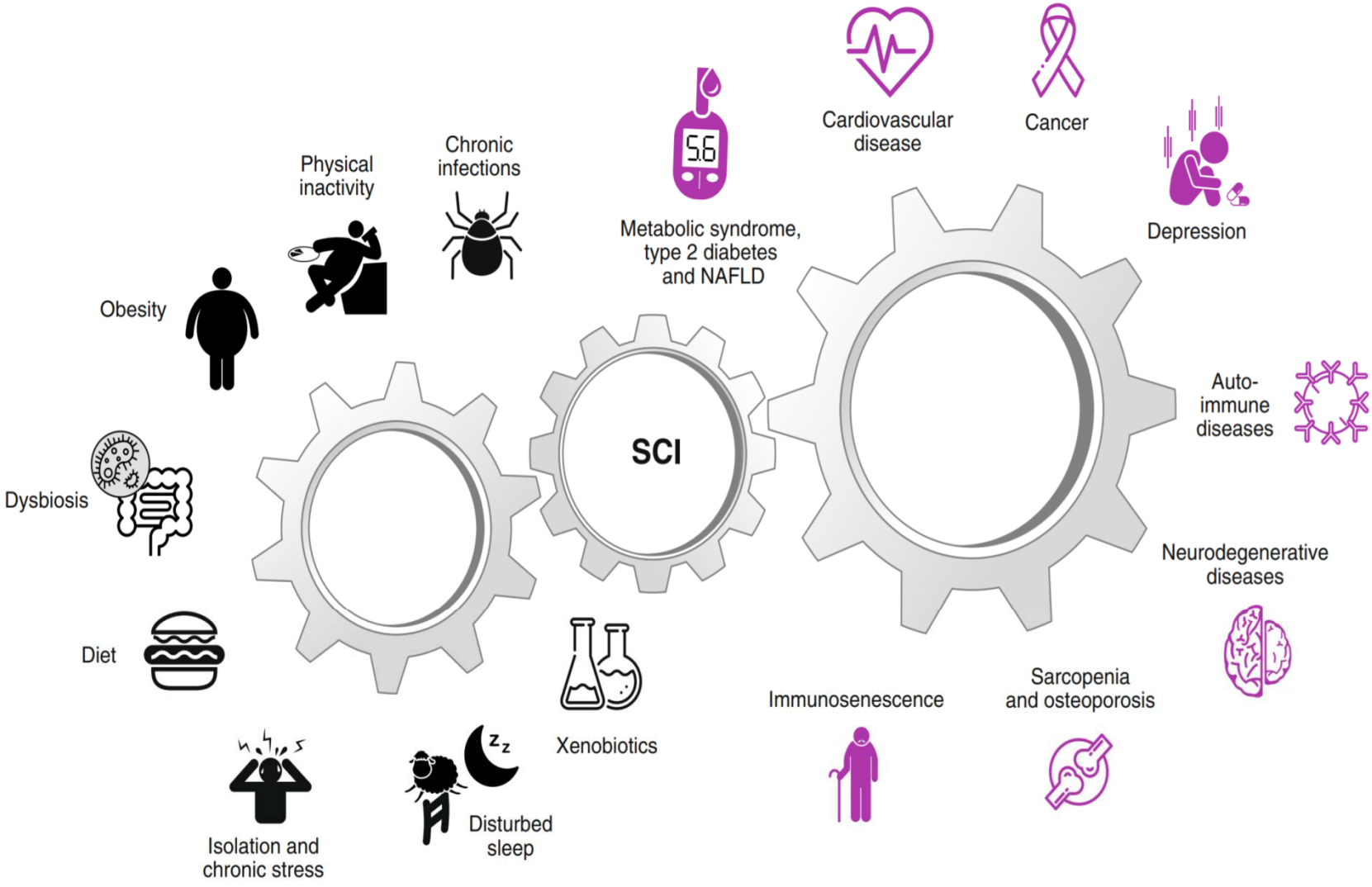
CSF1R, colony stimulating factor receptor; DAMP, danger-associated molecular pattern; NF-κB, nuclear factr-κB; P2X7 P2X purinoceptor 7; PRR pattern recognition receptor; RAGE receptor AGE; TGFβR TGFβ receptor.

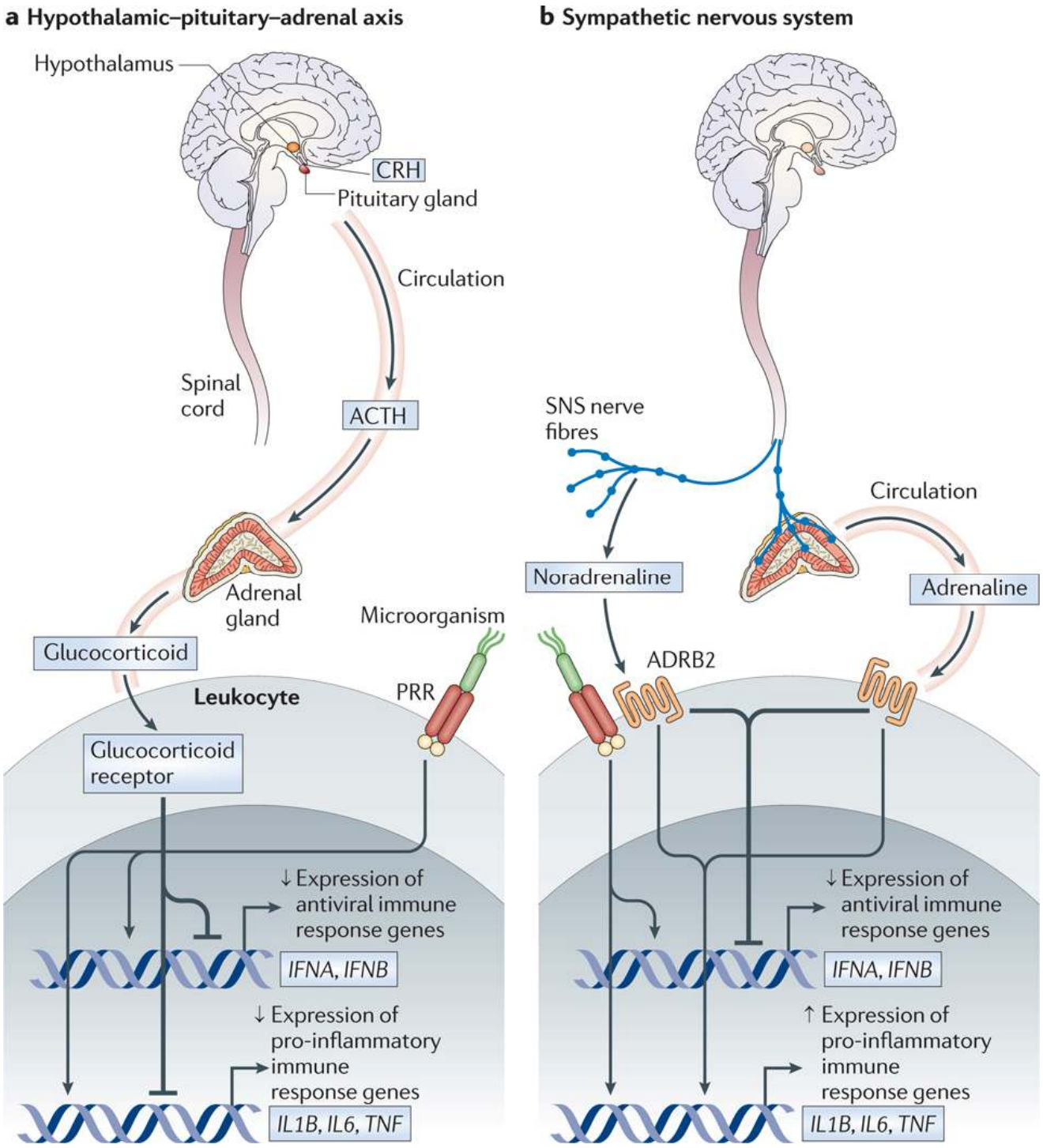
Wohleb et al, NRN 2016

Chronic social stress – ↑↑ inflammation, bacterial defense but ↓↓ antiviral defense



Downsides of chronic INFLAM may extend past depression to all its known comorbidities





CNS regulation of innate immune response gene programs: a | HPA axis distributes glucocorticoid hormones to regulate gene expression in virtually every cell. Hormone activation of GCr (in leukocytes) suppresses pro-inflammatory gene networks. Activation of cytokine receptors in hypothalamus triggers production of GC by HPA axis - body's primary systemic mechanism for negative feedback control of pro-inflammatory gene expression triggered by microbial pattern recognition receptors (PRRs).

b | During fight-or-flight responses/acute injury, nerve fibers from SNS release NE into lymphoid organs/other major organ systems (vasculature/perivascular tissues) and many peripheral tissues in which pro-inflammatory reactions occur. SNS also stimulates adrenals to release adrenaline into systemic circulation. Both of these neuromediators regulate vascular function and stimulate leukocyte adrenergic receptors. SNS-induced transcriptional alterations can modulate haematopoiesis, redeploy leukocytes between tissue and blood, and repress IRF-mediated antiviral immune response gene programs while enhancing many NF-κB pro-inflammatory programs.

ACTH, adrenocorticotropic hormone; ADRB2, β2-adrenergic receptor; CRH, corticotropin-releasing hormone; IL, interleukin; IRF, interferon regulatory factor; NF-κB, nuclear factor-κB; TNF, tumour necrosis factor.

Integrating many disparate neurobiological storylines in depression

Is there an alternative to serial primary factor theorizing about depression?

How to put the pieces together?

Biology & Psychology of Resilience: Inverse of Depressive Phenotype?

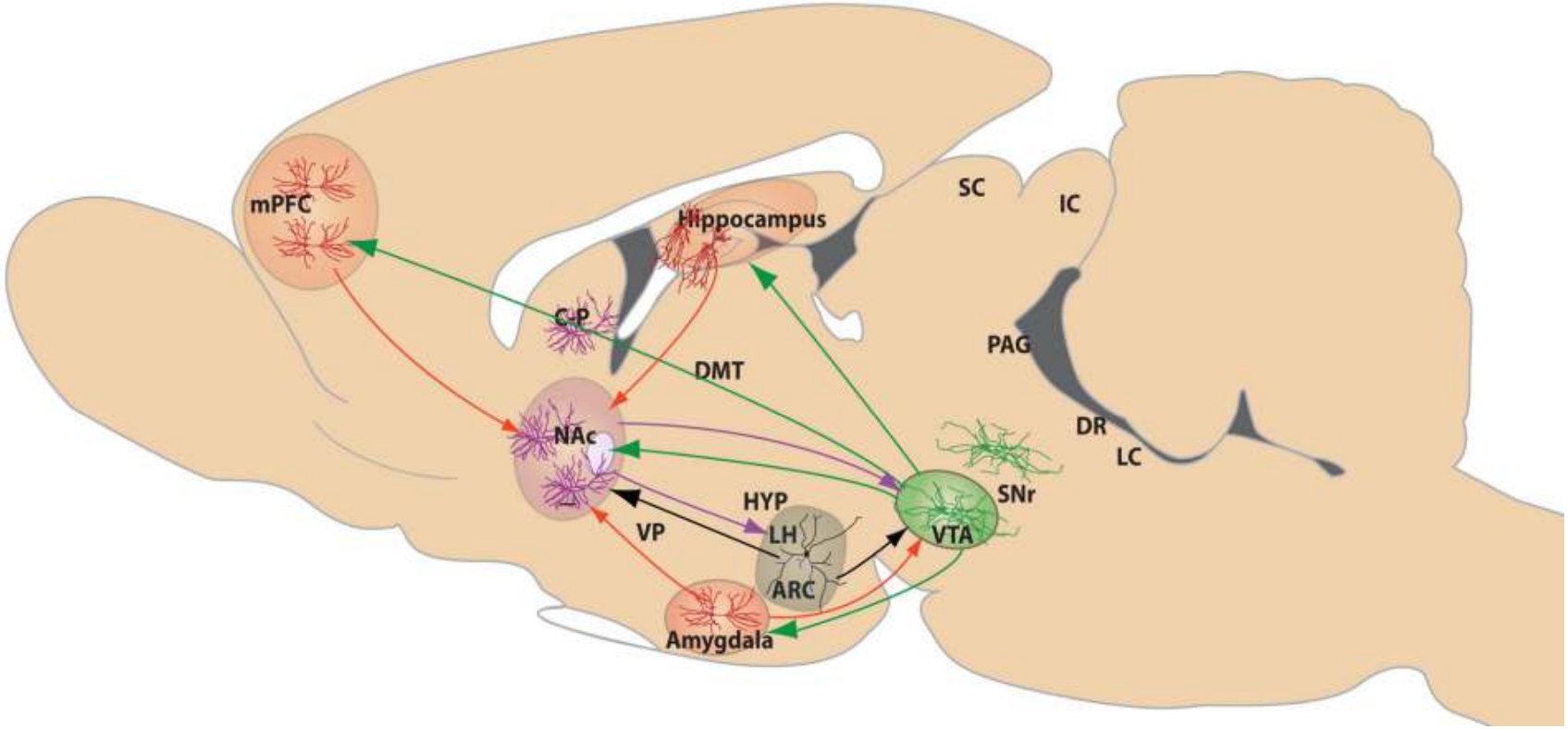
Genetic, Epigenetic and Environmental Factors Promoting Resilience

Psychosocial Factors in Resilience?

- Facing fears w/ active coping strategies (→planning & problem solving).
- Facilitated by stress 'inoculation' (exposure to tolerable stress) during development, may be linked to fear extinction mechanisms?
- Active or 'fight–flight' responses in animals have been linked to a more transient activation of the hypothalamus-pituitary-adrenal (HPA) axis.
- Optimism and positive emotions (play/other prosocial responses) → ↓ sympathetic arousal helps maintain SEEKING (mesolimbDA) activity.
- Cognitive reappraisal (reinterpreting meaning of negative stimuli) → potential reduction in negative affects/improved affective regulation.
- Social competence & openness to social support promotes resilience.
- A sense of purpose and strong internal frameworks of beliefs about right and wrong are more characteristic of resilient individuals.
- Spiritual beliefs and practices may also facilitate resilience in face of trauma, as extensions/stabilizers of pro-attachment responses.
- Suggests a group of coping skills and pro-social abilities in resilient individuals, allowing them to seek and receive support, behavioral strategies, etc., in face of moderate to severe stress.

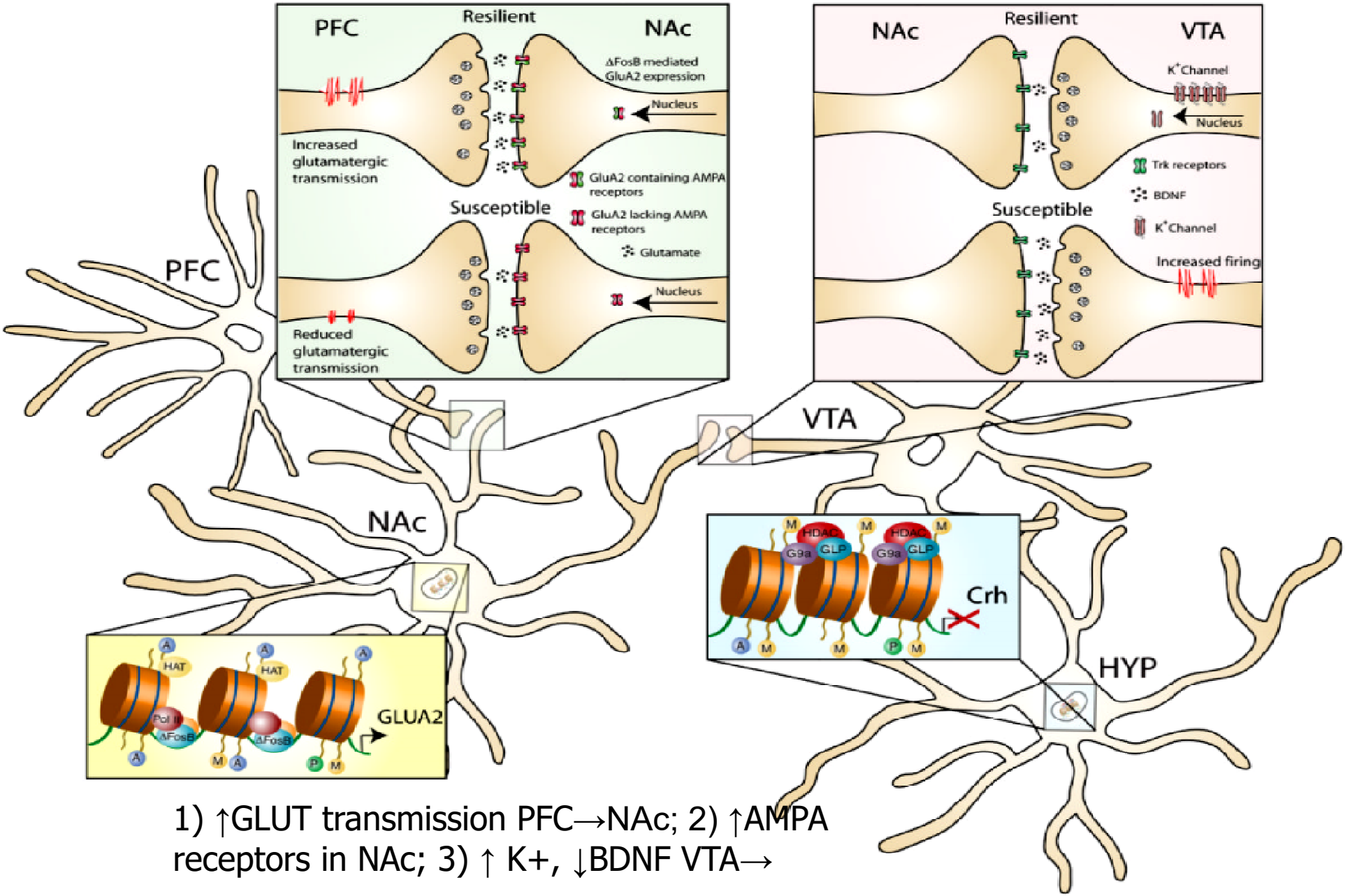
From Feder, Nestler and Charney, NRN

Affective Networks Central to Stress Responsivity and Resilience (Russo et al NRN)



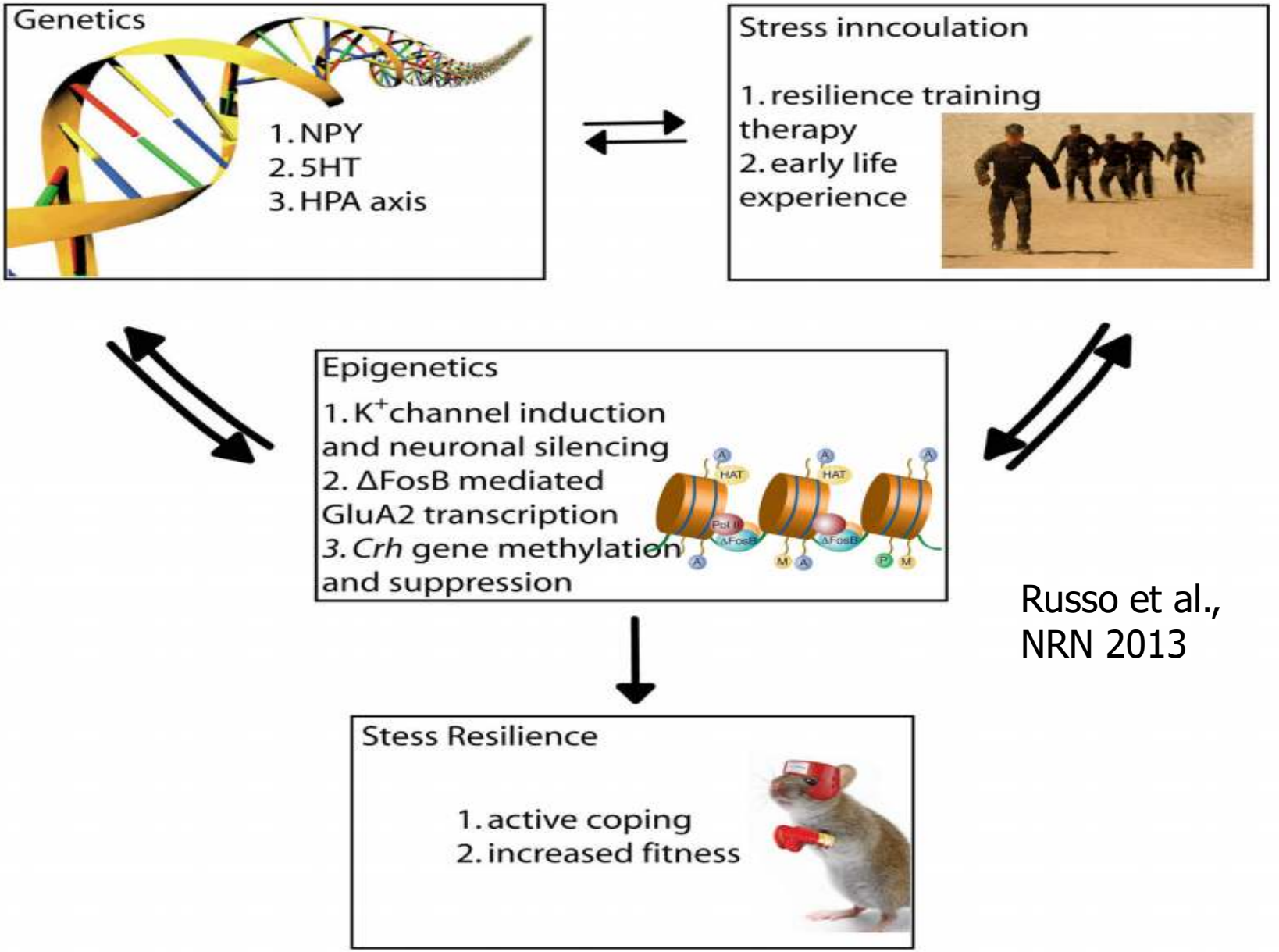
Red = Glutamatergic efferents. Purple = GABAergic efferents. Green = DA efferents. Black lines = Peptidergic efferents. Amygdala, PFC and HC glutamatergic neurons (red), GABAergic NAc medium spiny neurons (purple), hypothalamic peptidergic neurons (black), and VTA dopaminergic neurons (green) - neuronal cell types regulating stress responses and resilience. CP=caudate-putamen; DMT=dorsomedial thalamus; SC=superior colliculus; IC=inferior colliculus; VP=ventral pallidum; SNr=substantia nigra; PAG=periaqueductal gray; DR=dorsal raphe; LC=locus ceruleus.

Synaptic/molecular factors in resilience



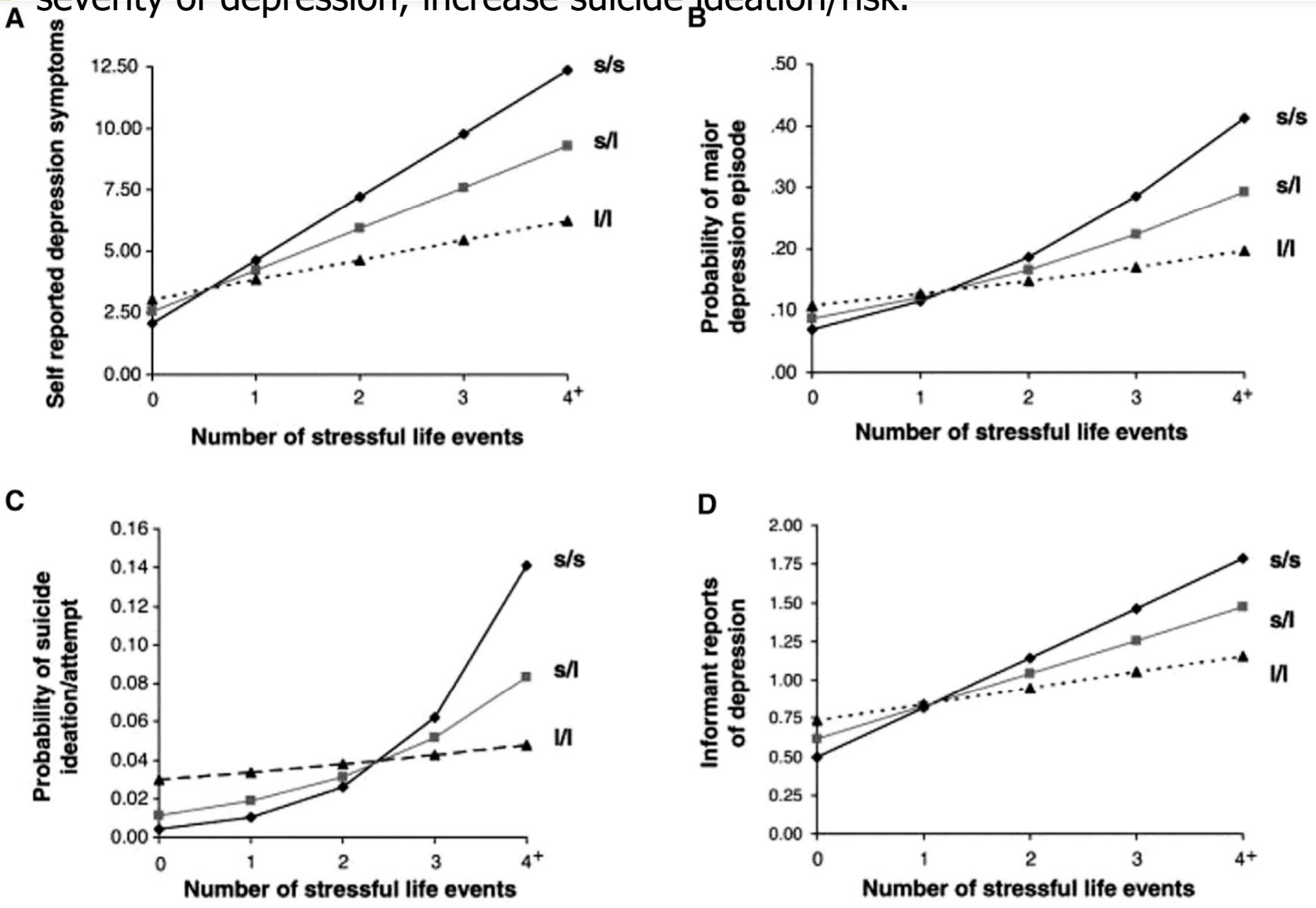
1) ↑GLUT transmission PFC→NAc; 2) ↑AMPA receptors in NAc; 3) ↑ K+, ↓BDNF VTA→

Gene-Environment Interactions?



Russo et al., NRN 2013

Gene environment interactions – Serotonin transporter allele interacts w/early life stressors (neglect & abuse), increase probability of and severity of depression, increase suicide ideation/risk.



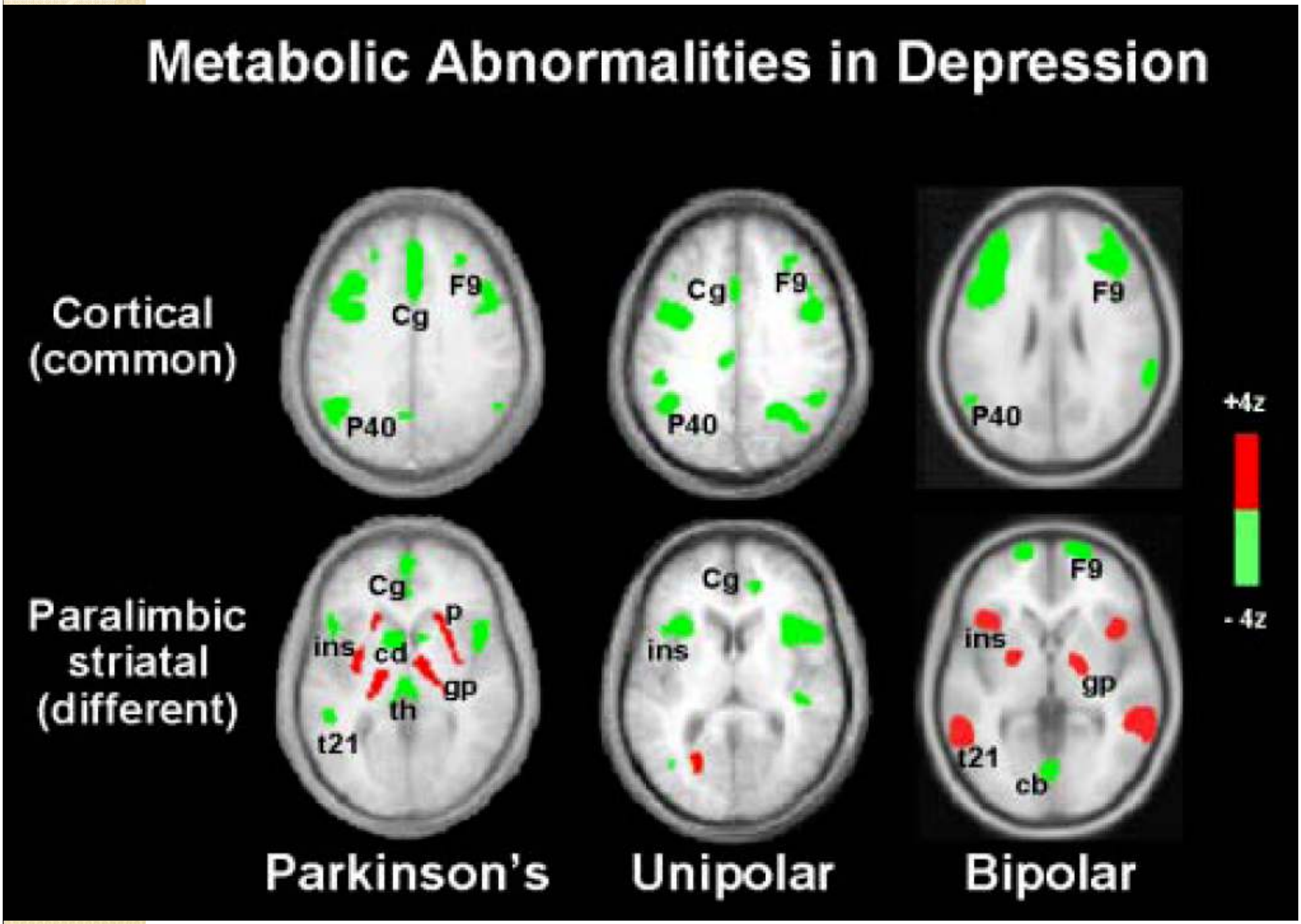
. Influence of Life Stress on Depression: Moderation by a Polymorphism in the 5-HTT Gene

Functional Imaging of Depression

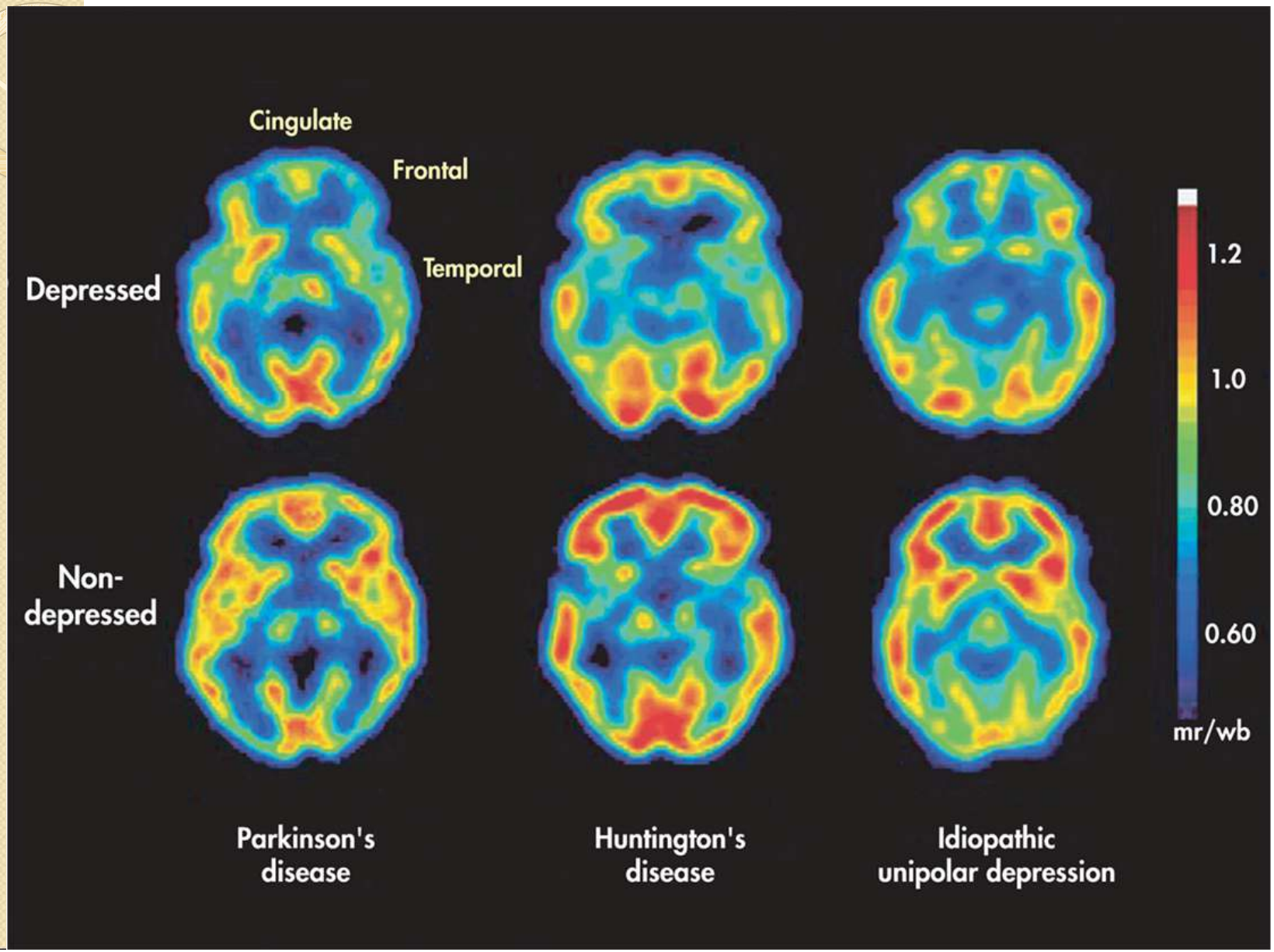
Frontal-Limbic Changes

DLPFC, HC, NAC, other limbic ROS

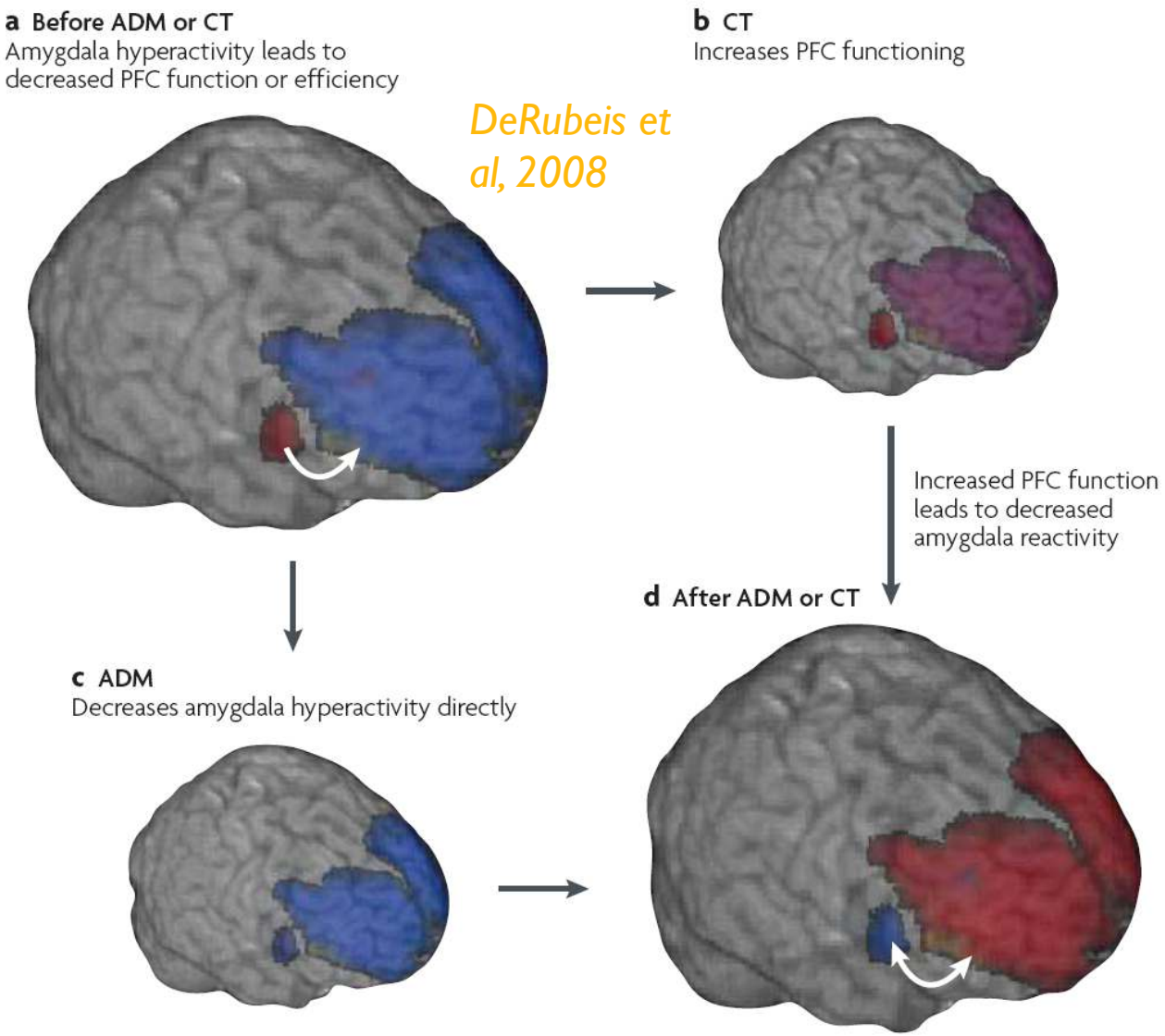
Metabolic Abnormalities in Depression



Functional Imaging of Depression shows hypofrontality across many groups



Changes To Amygdala-PFC Network Function Associated With Antidepressants and Cognitive Rx



a | During depression, Amyg. activity increased (red), prefrontal activity decreased (blue) relative to activity in healthy individuals.

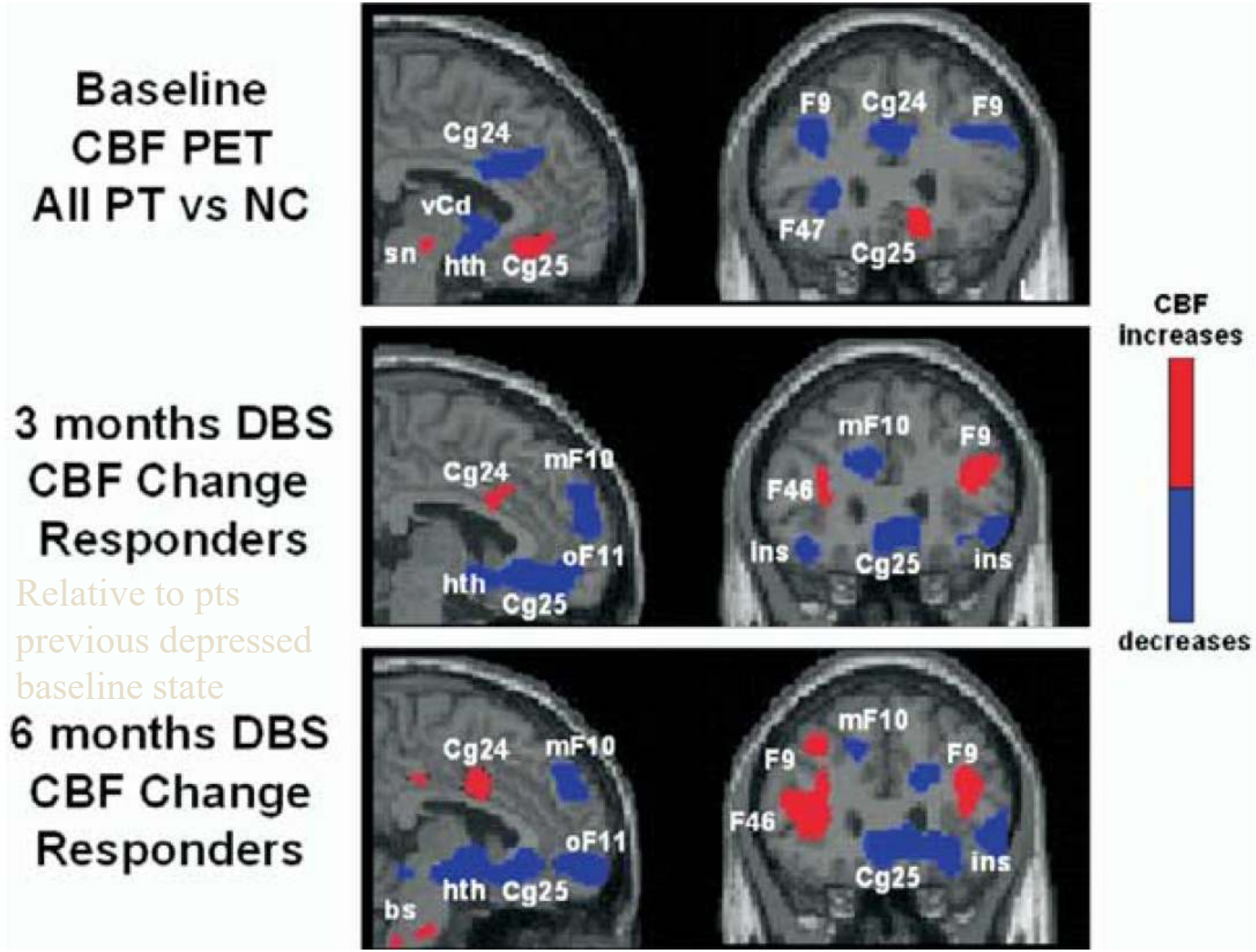
b | Cognitive therapy (CT) effectively exercises prefrontal cortex (PFC), yielding increased inhibitory function.

c | Antidepressant medication (ADM) targets amygdala function directly, decreasing its activity.

d | After ADM or CT, amygdala function decreased & prefrontal function is increased. Double-headed arrow between amygdala and PFC represents bidirectional homeostatic influences believed to operate in healthy individuals.

Mayberg's DBS findings in refractory severe depression

Hypo-activation F9 F47 DLPFC areas, dorsal cingulate. Hyperactivation of subcallosal cingulate, and midbrain areas. Extensive ↓ of hypothalamus, basal forebrain, subcallosal cingulate in refractory depression.



Big Picture View: What is the 'forest' if we have been mostly seeing the trees

- Attachment failure/loss, other forms of social loss, chronic pain are all prototype depressogenic stressors.
- Depression terminates protracted separation distress (protective in short run in infant mammals, not if protracted).
- Sickness behavior and depression: related and conserved forms of behavioral shutdown? Shared origins? If so, what is the trunk-line?
- Long history of 'single factor' theories in psychiatry. . . . many modulatory systems altered and with immune/endocrine shifts.
- Limitations of linear/single factor theories in the brain. Brain is massively parallel system. Circular (recursive) causality' concepts, w/many putative 'primary' factors being interactive.
- INFLAM synergizes with stress – INFLAM and neuroplasticity represent a functional bifurcation – can't do both at same time.
- Pro-inflammatory modern lifestyles, particularly combined with social isolation, may be promoting depression 'en masse'.
- Looking for single factor treatment for all types of depression likely to remain foolish. Think multiple modes of intervention at all levels of severity.

A DEPRESSIVE MATRIX?

DEPRESSIVE FACTOR	DRIVEN BY	PRODUCING	BEHAVIORAL & SYMPTOMATIC CORRELATES
Increased CRF, hypercortisolemia, choleocystokinin & reduced BDNF	Multifactorial limbic influences on paraventricular nucleus promoting activation of HPA stress axis	Increased dynorphin, decreased 5-HT, reduced neuroplasticity/ HC atrophy. Intensification of Separation Distress. Disrupted ventral HC feedback on core affective regions?	Dysphoria, sleep & appetite loss. Reduced short-term memory, and other cognitive deficits?
Increased Acetylcholine	Reduction of social and other rewards, opioid withdrawal, and any other social punishment.	Facilitation of separation distress circuitry and other negative emotions. ? effects on other core variables?	Negative affect and excess attention to negativistic perceptions and thoughts?
Decreased mu opioids and oxytocin	Separation distress, other stressors, including physical illness and pain	Disinhibition/release of stress cascades; decreased 5-HT & DA; overdriven NE. Promotion of cytokine generation?	Anhedonia and sadness, reduced positive affect and reduced sense of connection? Suicidality?
Increased dynorphin in accumbens/VTA	Stress cascades	Down regulation of VTA and mesolimbic DA system.	Anhedonia, dysphoria, loss of and motivation
Increased cytokines	Acute but probably not chronic stress, acute reduction of opioids?	Promotion of stress cascades, decreased serotonergic and increased glutamatergic tone. Impairment of HPA axis negative feeback	Fatigue, malaise and appetitive losses. Increased cognitive disruption. Anhedonia ?
Reduced serotonergic drive/vulnerability	Stress, increased corticosteroids, cytokines, decreased mu opioids.	Lowered dopaminergic and increased noradrenergic drive. Less functional segregation among brain systems.	Poor affective regulation? Impulsivity. Obsessive thought, suicidality.
Diminished catecholaminergic (DA & NE) tone	Constitutional vulnerability, stress and poor reward availability	Reduced "signal-to-noise" processing in all sensory-perceptual and motor/executive systems.	Fatigue, Diminished psychic "energy": appetitive sluggishness, dysphoria. Impaired coordination of cognitive and emotional information processing

Challenges for a view of depression as a shutdown of the social brain?

- Heterogeneity of depression: agitated vs. retarded, hypo vs. hyper -phagic and –somnic.
- How does original mechanism yield a more chronic depressive process than can become an illness?
- After several depressions, do induction mechanisms become disinhibited, removed from acute stressors?
- How? Epigenetically? Other routes?
- Resistance to depression? Resilience as flip side of depressive vulnerability?
- Evidence suggests that comforting/empathic interactions with parental figures or surrogates build in resilience and resistance to depression.

Treatment	Effectiveness	Neurobiological Effects
Tricyclics	Probably somewhat more effective than SSRIs but with major SE	Blocking reuptake of 5-HT and NE
MAO Inhibitors	Probably somewhat more effective than SSRIs but with major SE	Preventing breakdown of monoamines via MAO-A inhibition
SSRIs	Roughly 50% efficacy for any one drug, roughly 65% efficacy after using or trying several drugs.	Blocking reuptake of serotonin
SNRIs		Blocking reuptake of norepinephrine
Atypical Antidepressants	Variable. Sometimes used as adjunctive agents, with SSRIs/SNRIs.	Wellbutrin: NE/DA RI Tianeptine: ↑ uptake of 5-HT(!) Mirtazapine: (auto receptor) alpha-2 adrenergic (↑ NE/5-HT) and 5-HT2 blockade Nefazodone: 5-HT2 blockade?
Mixed 5-HT/NE RI	Probably somewhat more effective than 'pure' NE or 5-HT reuptake inhibitors	Norepinephrine and serotonin RI (reuptake inhibition)
Lithium	Regarded as adjunctive for monopolar, preventative for bipolar	Many molecular effects, but therapeutic mechanism is unknown.
Electroconvulsive Therapy	Highly effective 80-95%, single most effective therapy, although some patients remain refractory.	Unknown. Re-baselining of neuromodulatory systems? ↑ BDNF? ↑ monoamines/GABA ? ↑ Delta opioids? Hypothalamic effects?
Regional TMS	Although initial studies suggested effectiveness on par with ECT, a recent study did not support this.	Inhibition versus excitation of prefrontal cortical tissues, promoting left PFC and/or inhibiting right PFC.
Vagal Nerve Stimulation	Regarded as adjunctive to other therapies for refractory depression.	Unknown, but presumably ↑ parasympathetic nuclei in lower brainstem → effects on VL PAG & other limbic structures?
Psychotherapies	Variable. More effective in less severe depression and in depression associated with trauma	Empathic support → ↑ affective regulation, ↓ negative affects, ↑ pro-social responses? ↓ CHF/stress cascades? ↑ opioid/oxytocin?
Deep Brain Stimulation	Only one pilot study, but in severely ill and highly refractory population, 5/6 patients showed benefit.	Neurodynamic disruption of overactive subcallosal cingulate (area 25). Effects on multiple limbic and paralimbic regions?

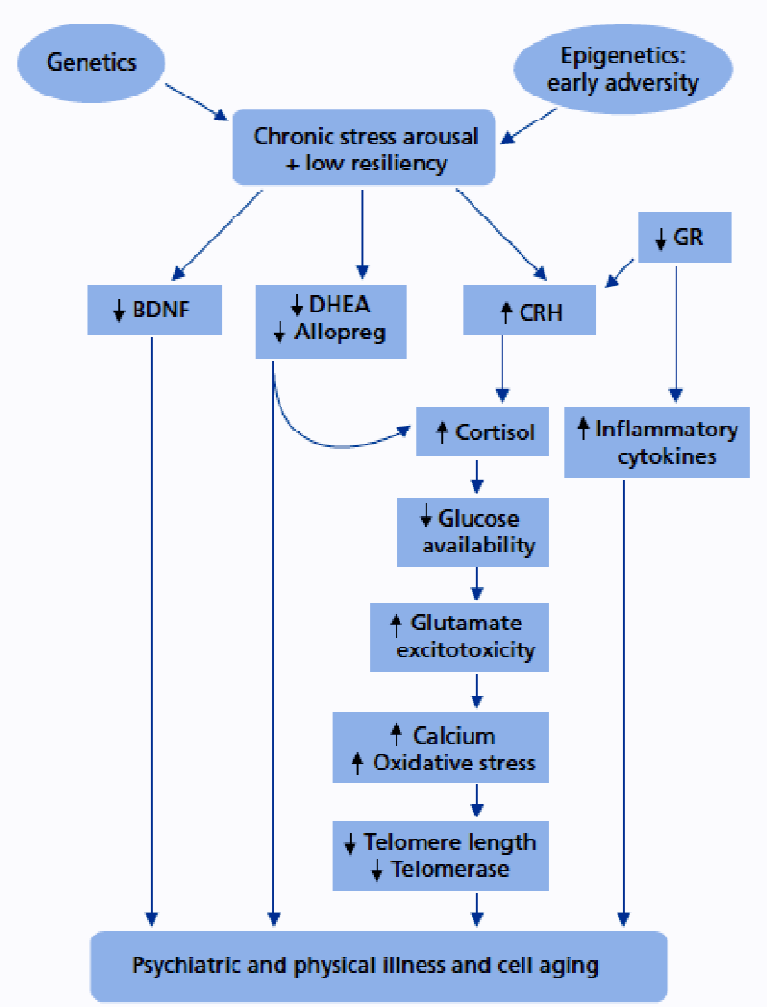
Pharmacology in the Pipeline?

- $CRF_{1/2}$ antagonists (CRF_1 toxicity issues)
- AMPA Agonists
- GR_2 antagonists (Mifepristone)
- Triple reuptake inhibitors
- Substance P antagonists
- Pure κ antagonists
- CB_1 cannabinoid receptor agonists (or antagonists?)
- Melatonin agonists
- Galanin antagonists (inhibits NE/5-HT)
- Histone deacetylase inhibitors (↑ plasticity) ?
- Blocking tissue plasminogen activator (TPA) - mediates CRF responsivity → ↓ CRF
- Pro-inflammatory cytokine blockers
- Neuropeptide Y agonists

Wide variety of targets BEGS the question – why single target Rx approach, esp. if depression reflects complex perturbations in many signaling systems?

Towards a unifying framework for chronic disease: mechanistic links to aging/diseases of aging

(Wolkowitz, Reus, and Mellon, 2011)



Potentially damaging mediators Increased	Potentially protective mediators Decreased
• Hyperactive LHPA axis and hypercortisolemia (with net hypercortisolism or hypocortisolism)	• Neurosteroids (eg, DHEA* and allopregnanolone)
• Synaptic glutamate and excitotoxicity	• Insulin sensitivity
• Intracytoplasmic calcium	• Intracellular glucose
• Free radicals with oxidative stress	• Antioxidants
• Inflammatory cytokines	• Anti-inflammatory/immuno-modulatory cytokines**
	• Neurotrophic factors (eg, BDNF)
	• Telomerase***

Elevated cortisol, w/ ↓ glucocorticoid receptor function (GC resistance) results in altered immune function and ↑ proinflammatory cytokines. Changes in glucocorticoid-mediated activity alters neurotransmitter fxn, neurotrophins, & other mediators. Dysregulation and sustained activation of HPA axis → depression. Dysregulation of HPA axis leads to intracellular glucose deficiency, GLUT hyperactivity, ↑cellular Ca+ concentrations, mitochondrial damage, free radial generation, & increased oxidative stress. This cascade, coupled w/a milieu of increased inflammatory cytokines, may lead to accelerated cellular aging (effects on telomere/ telomerase maintenance system). Juxtaposition of ↑damaging processes w/↓ protective/ restorative processes → ↑ cellular damage, apoptosis, physical disease. Stress and inflammation conjoined may accelerate aging phenotypes!

Implications of Psychological/ Affective View of Depression: Current Practice Issues

The excessive 'medicalization' of depression

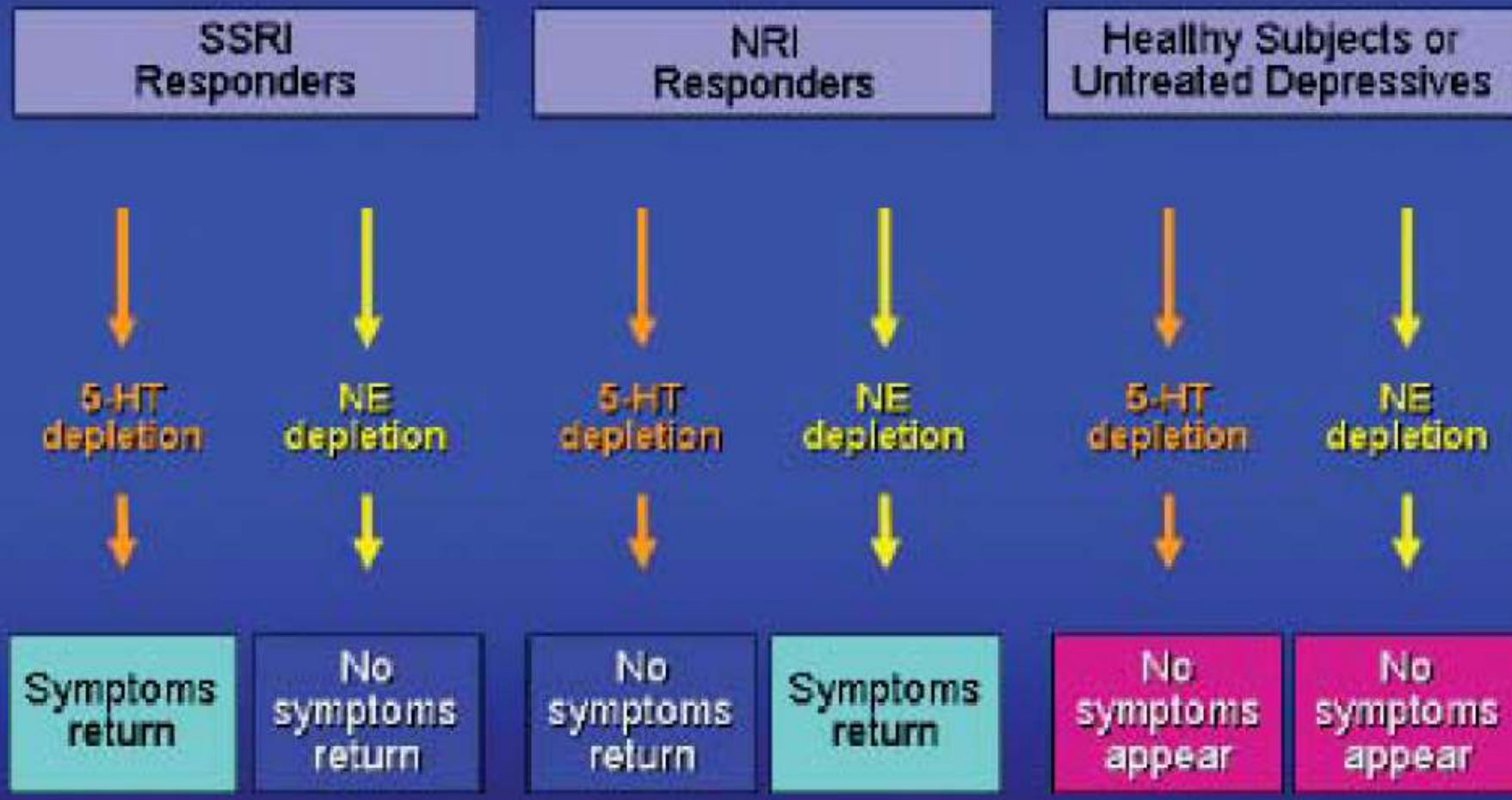
Evidence that mainline antidepressants not very effective

Shorting of psychotherapy in treatment paradigms

The corruption of empirical research

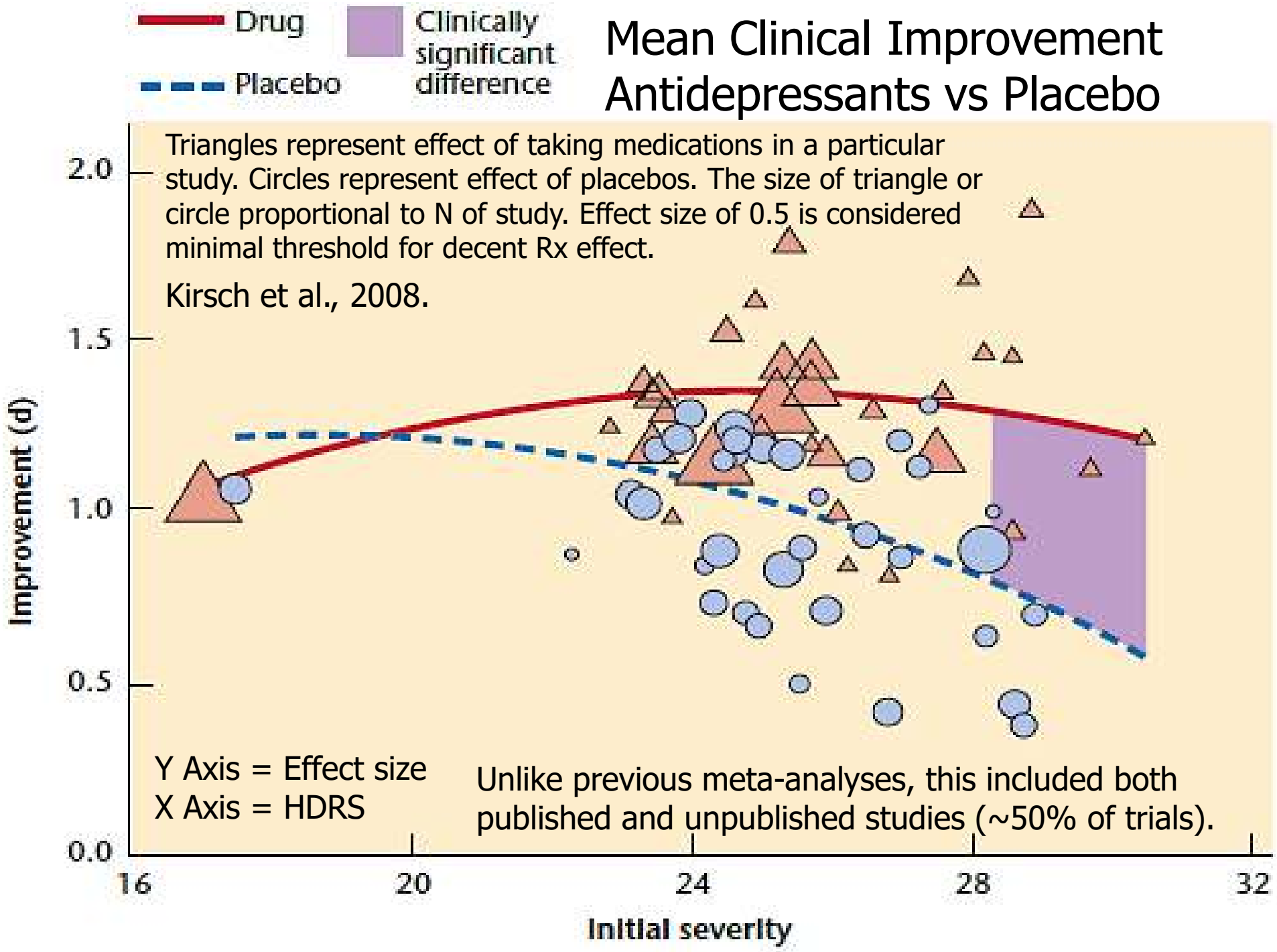
Conflicts of Interest

Neurotransmitter Depletion Studies

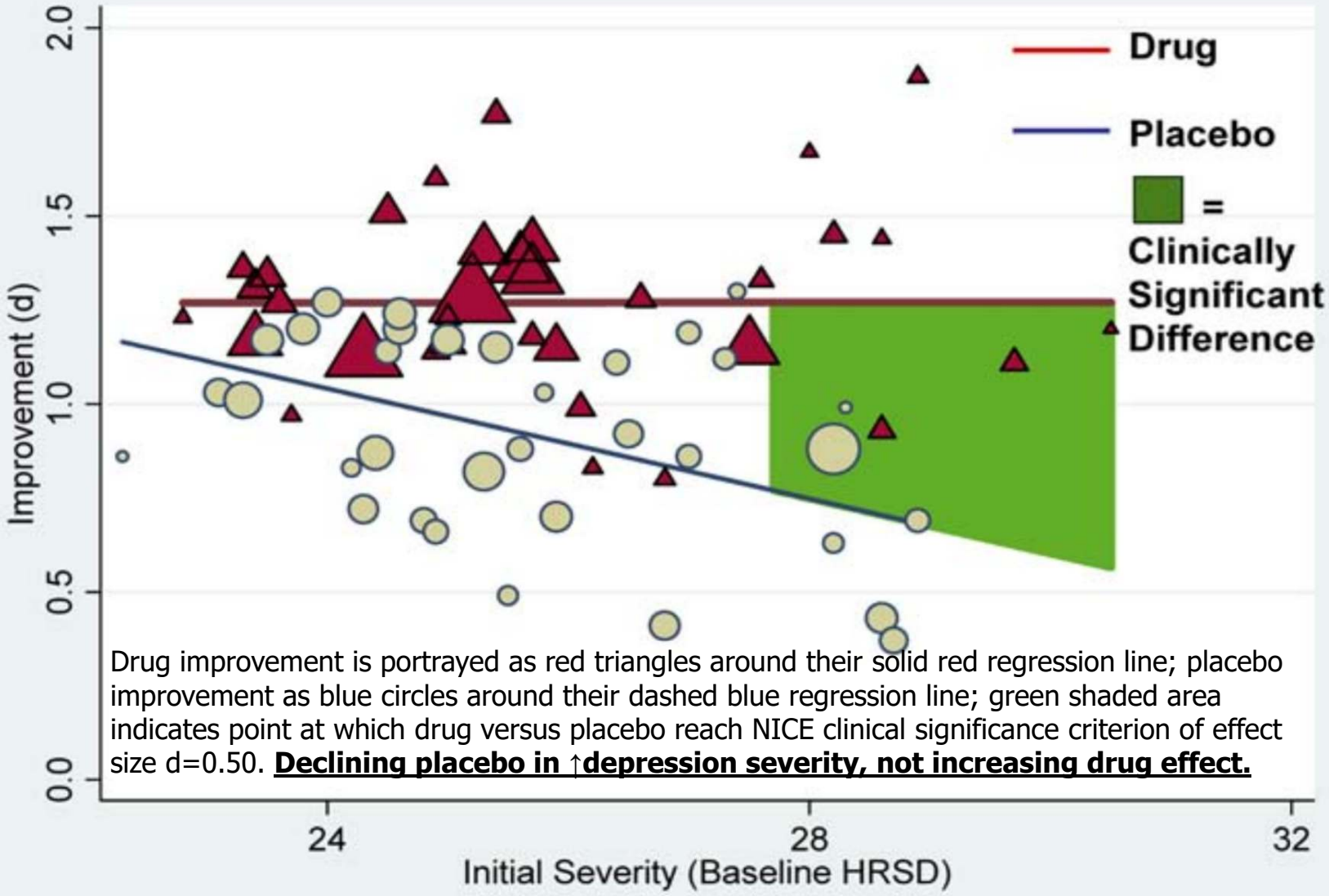


Depletion means depletion of dietary precursors. "Symptoms returning" means 30 to 40% of ex-patients become symptomatic. Reserpine ≤ 40% become depressed, even with high doses.

Mean Clinical Improvement Antidepressants vs Placebo

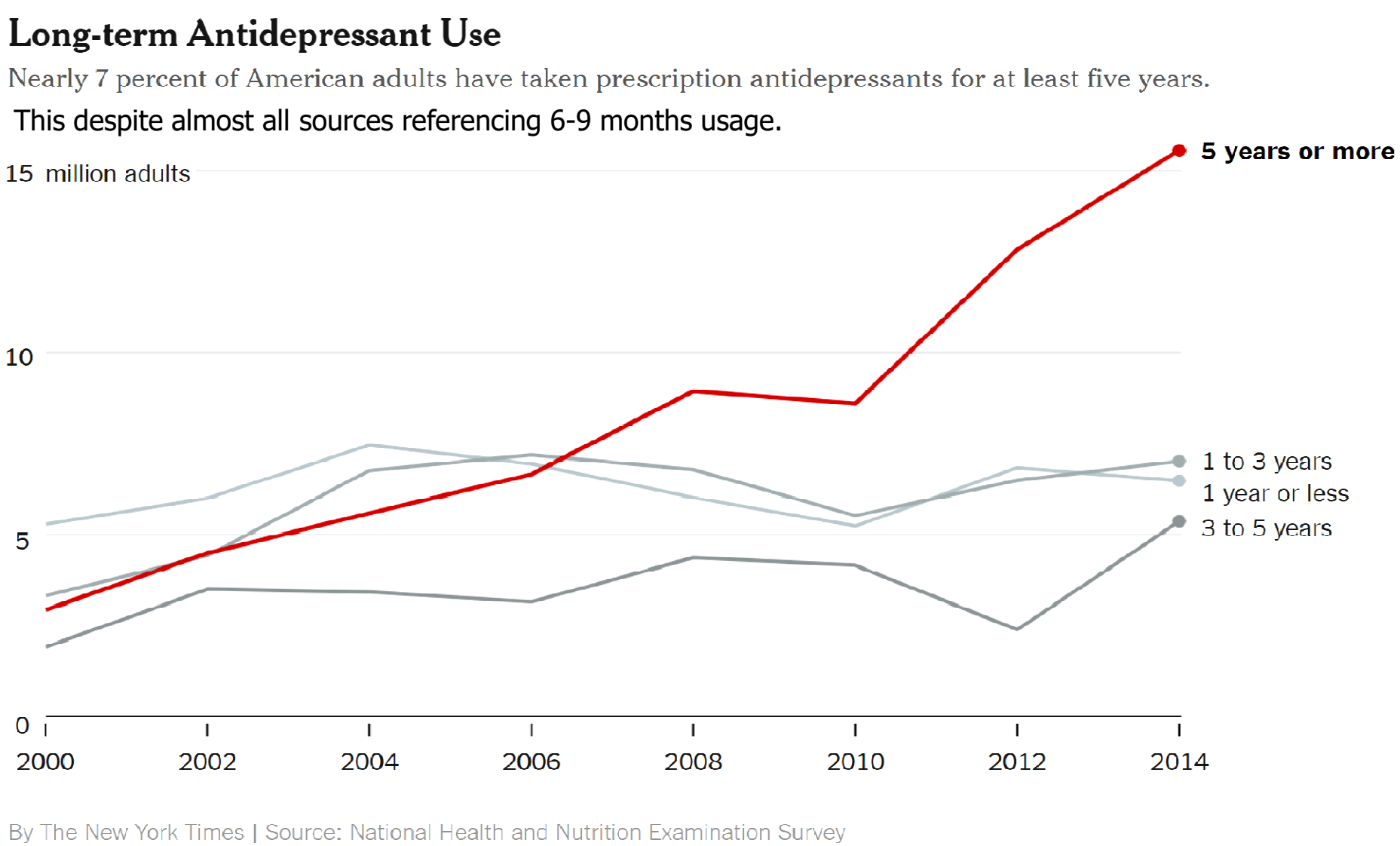


Comparison of drug versus placebo in more severe depressions

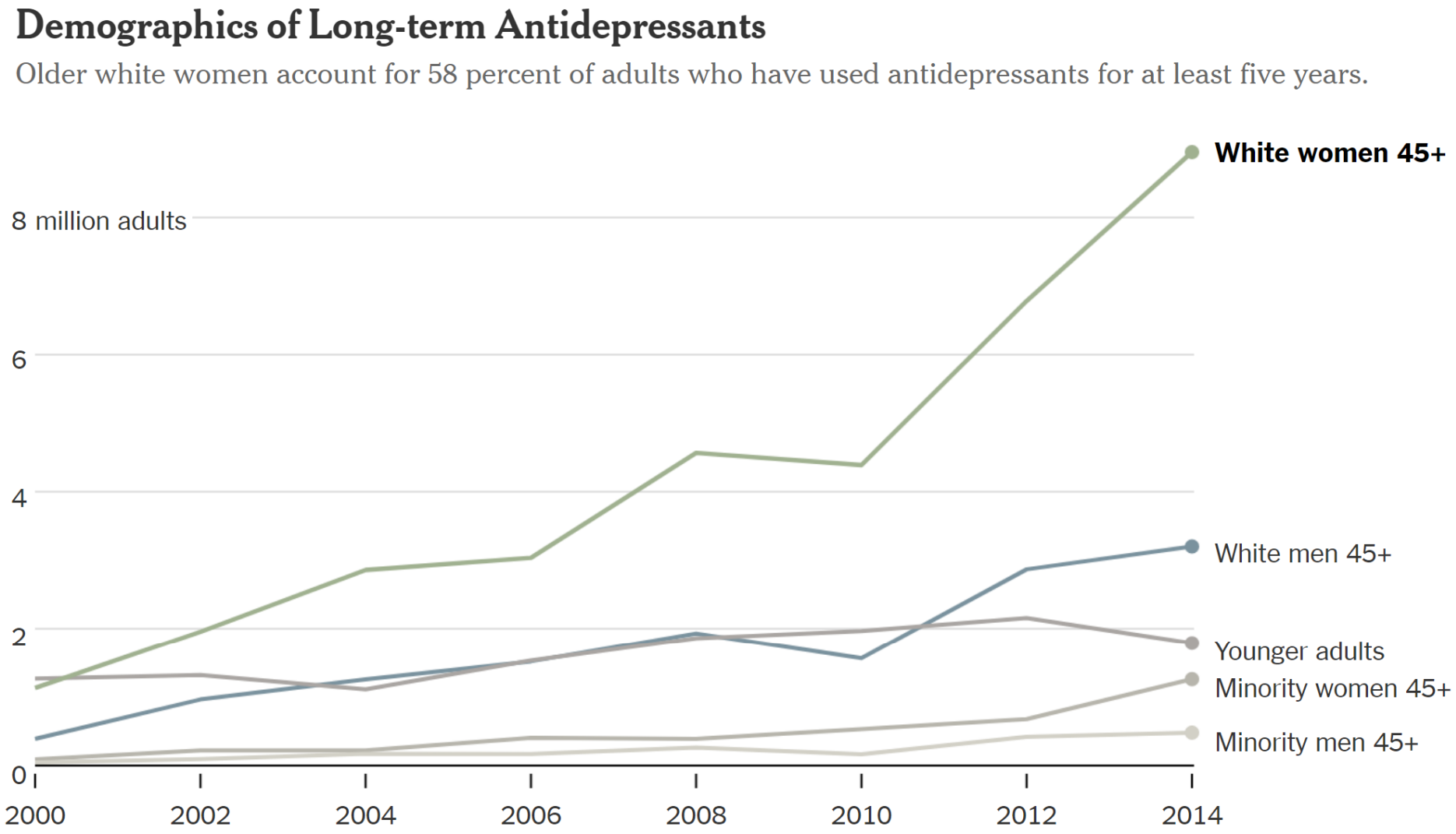


Drug improvement is portrayed as red triangles around their solid red regression line; placebo improvement as blue circles around their dashed blue regression line; green shaded area indicates point at which drug versus placebo reach NICE clinical significance criterion of effect size d=0.50. **Declining placebo in ↑depression severity, not increasing drug effect.**

Chronic use of antidepressants is exploding *without any data about risks/benefits!*



And is demographically skewed for uncertain reasons



How can Big Pharma get first line anti-depressants approved w/such modest efficacy?

- Kirsch (2014) combined both published & unpublished trials on mainline antidepressants: 43% showed statistically significant benefit, while 57% failed to show benefit or only equal to placebo.
- 94% of published studies showed benefit, but when unpublished studies added, 51% of total studies showed benefit over placebo.
- When placebo response was subtracted, 82% of antidepressant response was lost (18% of drug effect was not placebo).
- Average antidepressant effectiveness amounted to ~2 points on the Hamilton Depression Scale (17 items, scored 0 to 53).
- FDA requires **2 trials** showing statistically significant (not clinically significant!) separation of drug from placebo. ***However, FDA allows an indefinite number of trials to get the two successful ones!***
- Kirsch meta-analysis results (2008, 2014) have been replicated by Fountoulakis & Mçller (2011 → Calculations corrected - raising antidepressant effect to 2.5 points on HDRS, undercutting confidence in Kirsch statistics, but not generating materially different conclusions.
- In mild to moderate depression these drugs are simply not effective.
- In moderate to severe depression, drug effect size is greater, placebo reduced. But ketamine/psychedelic Rx, rTMS, ECT offer ↑ efficacy.

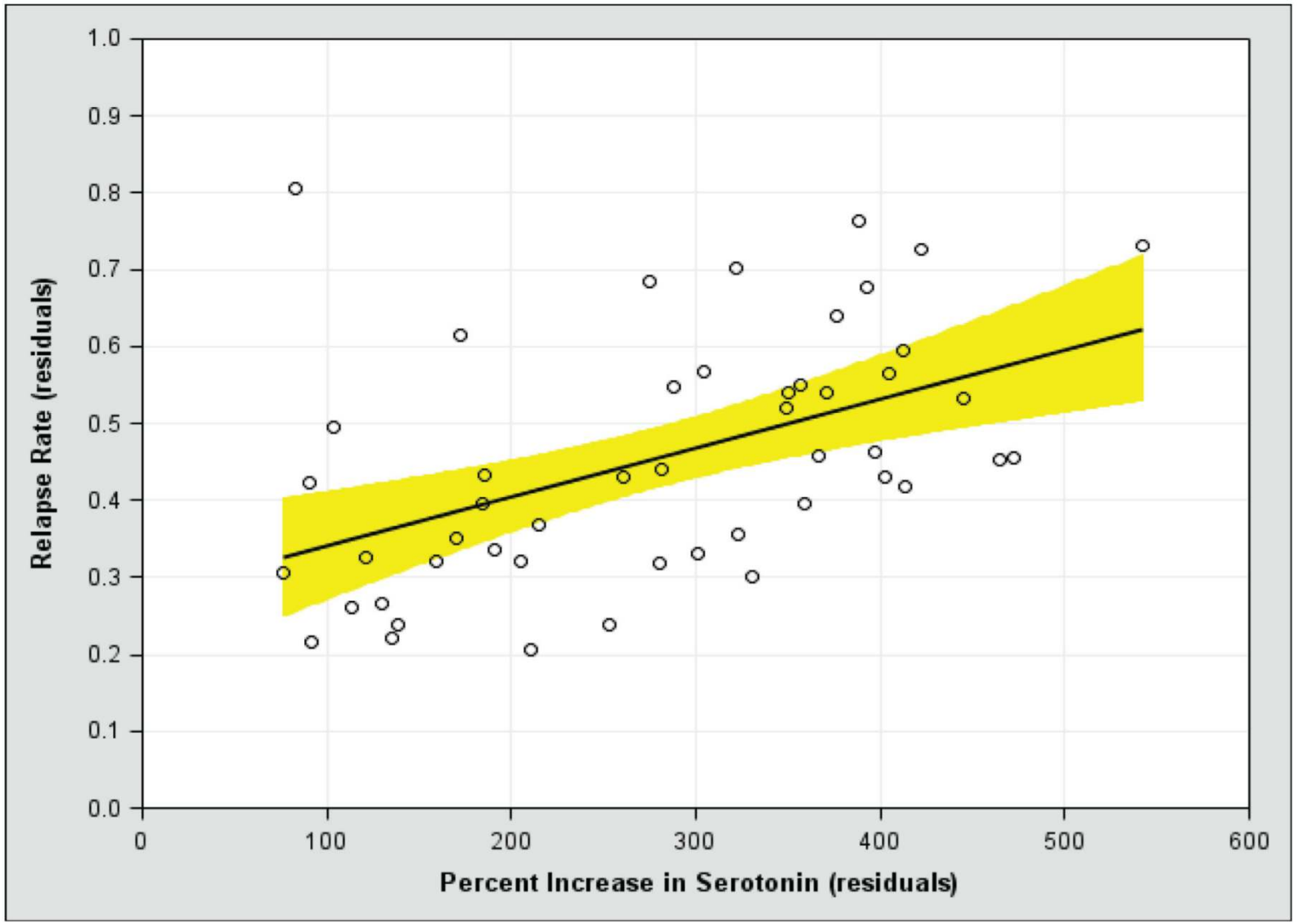
Known Harms ('side effects') of SSRIs, SNRIs, TCAs – 65+% users report SE

- Sexual dysfunction (65+%) – very problematic, leads to depressogenic shame, and disrupts intimacy (which is antidepressant).
- Insomnia – problematic again due to depressogenic impact esp. if ↓↓SWS.
- Long-term weight gain and subsequent exposure to risk of diaobesity.
- GI side effects particularly nausea, diarrhea, dyspepsia, other G.I. upset.
- Serotonin withdrawal syndrome, esp. with Paxil. Very long taper required.
- Disruption of coagulation, increased risk of hyponatremia.
- Increased autism risk in pregnancy exposure, over and above known teratogenic issues for some (Paxil).
- Still unclear whether ADD potentiate risk for suicide, or simply SI, but large meta analysis suggested increased risk in youngest patients, but not adults.
- Pro-apoptosis in vitro, assumption of pro-plasticity based on BrdU signal - ??
- Cognitive dysfunction, including particularly attention, WM, with increased risk for MVAs. Never properly reviewed prior to approval (!)
- Increased risk of death (elderly), again not reviewed PTA or tested in AM(!).

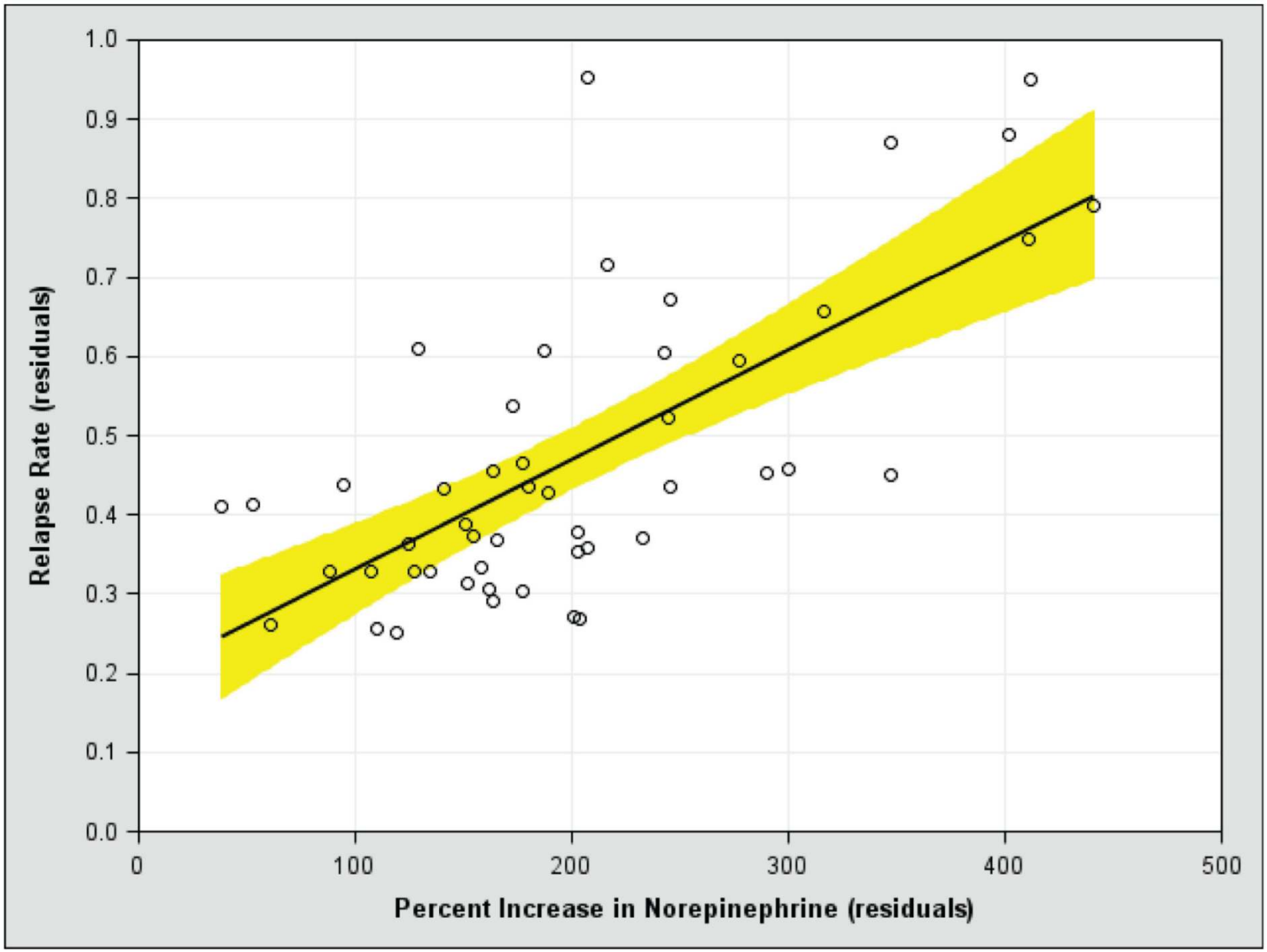
Far and away the biggest & most disturbing question – still unknown.

- By forcing a down regulation of serotonin and other amine systems (compensatory), do antidepressants actually increase risk of depressive relapse after discontinuation? **Never researched!**
- Does it cause mid-term or long-term serotonergic or other aminergic down-regulation, lasting longer than withdrawal period, or other perturbations in other neural signaling systems might increase vulnerability to depression? **Again, never researched!**
- It is astonishing that millions of patients are not told that these critical questions have never been researched. Also not informed that preliminary data shows ↑↑ risk for relapse after discontinuation.
- Despite the trials authorizing and proving efficacy over and above placebo were typically eight weeks, many patients take for years (!)
- Risk for relapse in drug-naïve major depression is ~ 21%, while it is 43.3% with SSRI, 47.7% w/SNRI, 55.2% w/TCA, 61.8% w/fluoxetine, and 75.1% w/MAOI, suggesting differential/additive aminergic effects.

SSRI/SNRI/ TCA may increase risk for relapse?

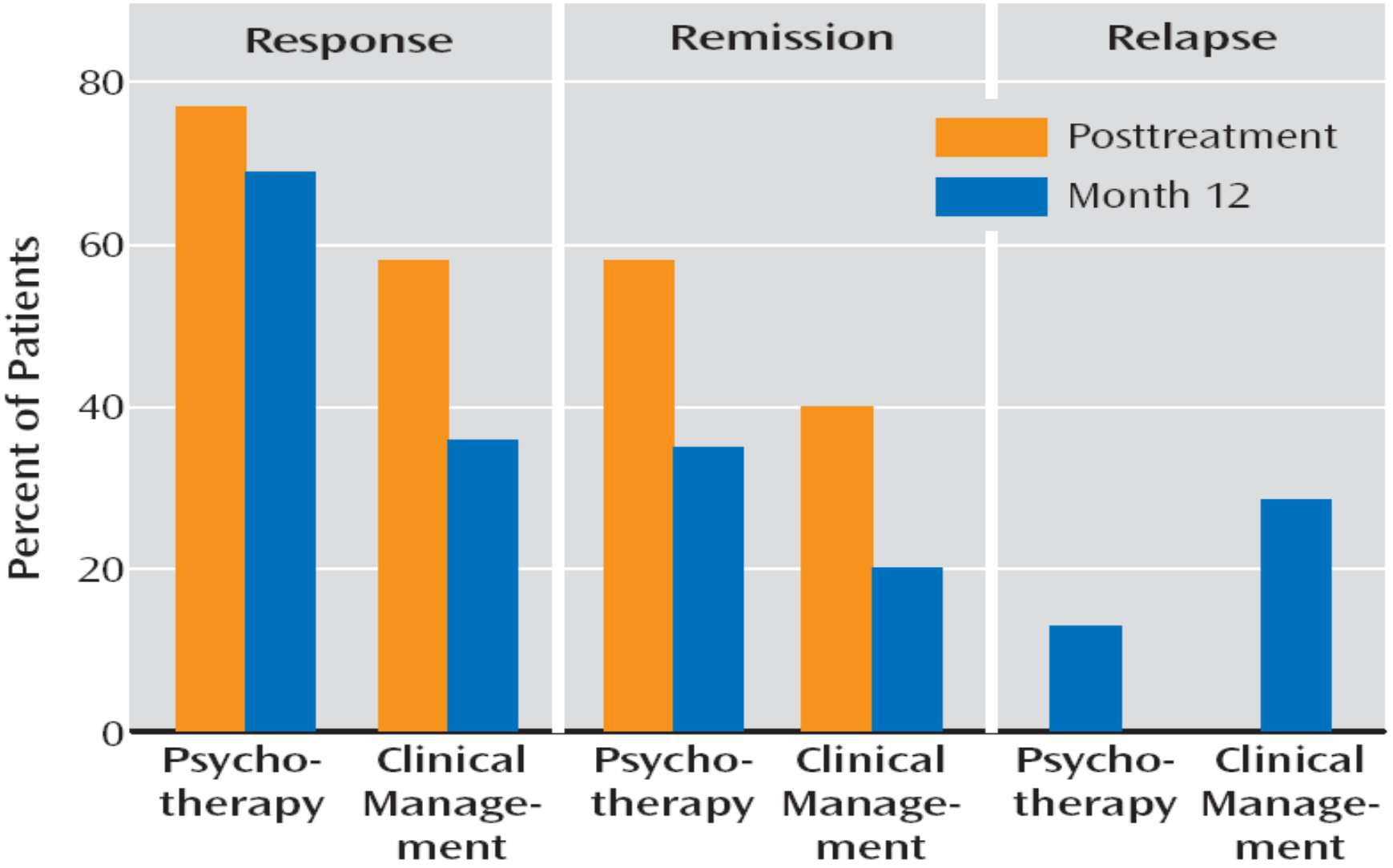


The risk of relapse after antidepressant discontinuation (y-axis) versus the perturbational effect of antidepressants on serotonin in rodent medial prefrontal cortex (x-axis), after controlling for covariates. A score of 100 on the x-axis means the antidepressant has no effect on serotonin.



The risk of relapse after antidepressant discontinuation (y-axis) versus the perturbational effect of antidepressants on norepinephrine in rodent medial prefrontal cortex (x-axis), after controlling for covariates. A score of 100 on the x-axis means the antidepressant has no effect on norepinephrine

Data underlining importance of psycho-therapy (STAR*D – very 'pharma friendly')



Implications of SEP DISTRESS hypothesis of depression for Tx of mild-moderate depression

- Careful, detailed elucidation of and attention to precipitating stressors, inc around 1st depressive episode. Recapitulations?
- Varieties of SEP DISTRESS – actual losses, but also ***shame, guilt***, esteem/social status losses & degree of isolation.
- Attention in Rx relationship to many flavors of above – feeling rejected, abandoned, distanced, unworthy, judged, or a burden. "The alliance is everything!" Importance of corrective experience.
- Mitigation of isolation and chronic pain, esp. given evidence that social and physical pain share overlapping neurology.
- Attention to sleep/sleep hygiene, diet and exercise. ***Massively neglected*** in traditional psychiatric approaches. But how could brain health be functionally uncoupled from general health?
- Catch 22 of overcoming exercise motivational deficit in depression? Group and social formats for exercise?
- Mitigation of pro-inflammatory Western diets – processed carbs, sugars, wheat, low fiber, low Omega-3, low polyphenol.
- High dose Omega-3, where EPA > DHA by 1.2-1.5 gms/day.
- Light therapies, attention to circadian regulation/dysfunction.

Distortion and Corruption of Psychopharmacology Research on Depression

At best, Big Pharma has exaggerated drug effect sizes

At worst, it has seriously corrupted scientific research

Can any drug study done with funding from Big Pharma be considered fully or easily scientifically interpretable?

Conflicts of interests: A pandemic in psychiatry?

Ioannidis (2008): Antidepressant effectiveness overstated/oversold

- Five of top 35 drugs anti-depressants – sales > $1 billion.

Drug (brand name)	Rank across all drugs	Sales (billions $)
Venlafaxine XR (Effexor XR)	6	2.25
Escitalopram (Lexapro)	10	2.10
Sertraline (Zoloft)	15	1.77
Bupropion XL (Wellbutrin XL)	16	1.67
Duloxetine (Cymbalta)	35	1.08

- Leading the 'medicalization' of depression: 4000+ trials.
- Many published (and controlled) trials: statistically significant effects – appears to be prototype evidence-based medicine.
- BUT . . . . two recent meta-analyses raise lots of questions.
- Review of 74 FDA trials (many not published) 1987-2004: 38/74 found statistically significant benefits. 36/74 negative, including 11/36 which were 'reprocessed' to suggest positive benefits, while 22/36 negative trials never published.
- Effect sizes were inflated between 11-69% (average ~32%).

Anti-depressant Effectiveness: A Myth Constructed by Big Pharma?

- FDA data, re-examined, show effect size of 0.31 on average- threshold for clinically important effectiveness is effect size of > 0.5 (= 3 points HDRS). Suggests relatively modest positive effect.
- No aminergic agent exceeded this threshold in FDA datasets.
- Meta-analysis *of published data only* would suggest 4 out of 12 antidepressants exceed effect size of 0.5. Not true!!
- Additional meta-analysis (PloS Medicine): asked a question never before posed: *is there a relationship between baseline severity of depression and difference in effectiveness between drug and placebo??*
- Regression analysis: drug-placebo differences generally small, but increased with increasing severity of depression.
- In pts w/ more severe depression (HDRS >28), placebo less effective (placebo mechanism is falling apart), therefore effect size of drug greater, but no evidence that drugs more effective per se.
- Many severely depressed pts excluded – hospitalized.

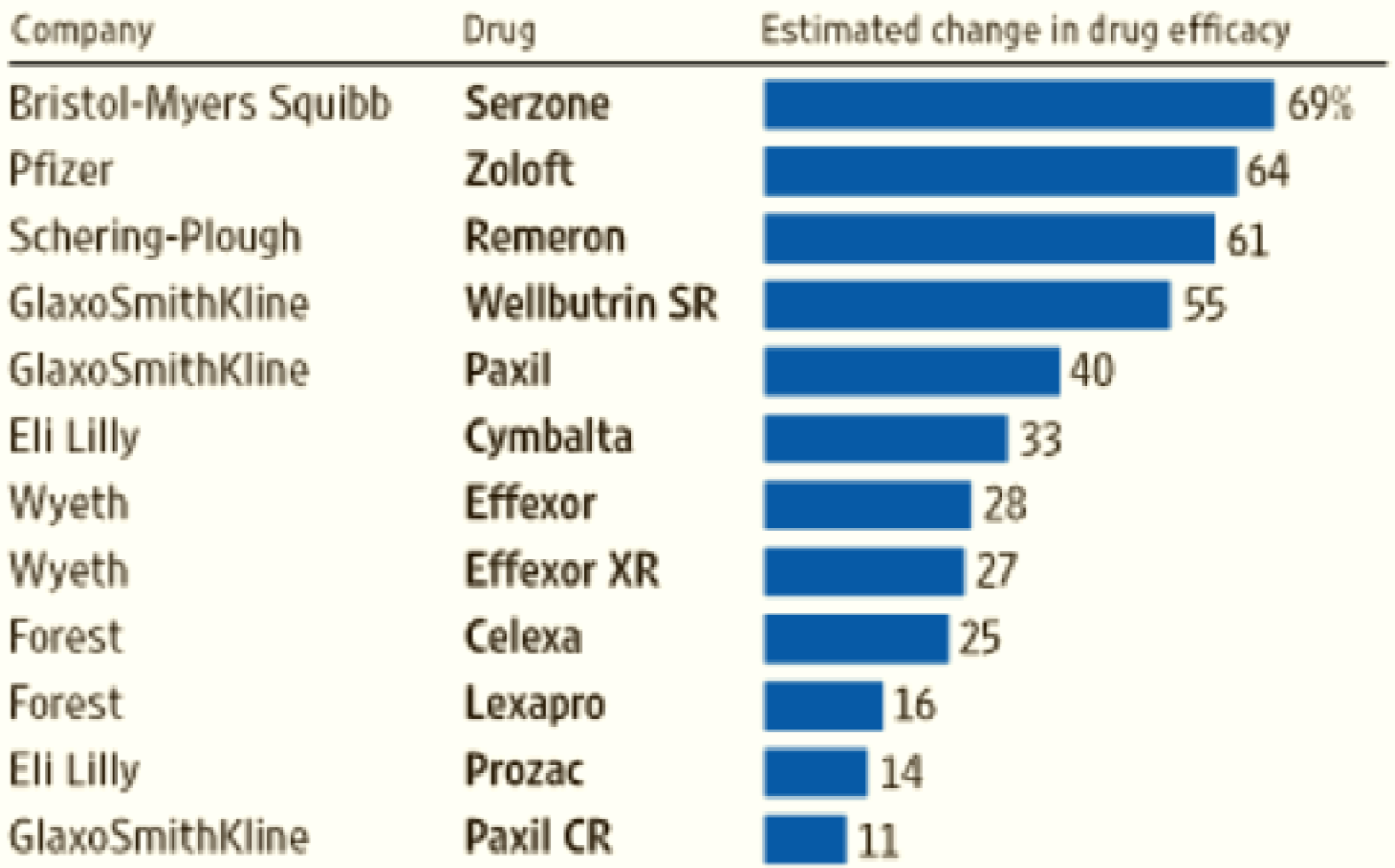
Antidepressant Drug Effects and Depression Severity: A Patient-Level Meta-analysis

Jay C. Fournier, MA; Robert J. DeRubeis, PhD; Steven D. Hollon, PhD; Sona Dimidjian, PhD; Jay D. Amsterdam, MD; Richard C. Shelton, MD; Jan Fawcett, MD ***JAMA.*** 2010;303(1):47-53.

- **Context:** Antidepressant medications represent the best established treatment for major depressive disorder, but there is little evidence that they have a specific pharmacological effect relative to pill placebo for patients with less severe depression.
- **Objective:** To estimate the relative benefit of medication vs placebo across a wide range of initial symptom severity in patients diagnosed with depression.
- **Data Sources:** PubMed, PsycINFO, & Cochrane Library databases searched from January 1980 through March 2009, along with other meta-analyses and reviews.
- **Study Selection:** Randomized placebo-controlled trials of antidepressants approved by the Food and Drug Administration in the treatment of major or minor depressive disorder were selected. Studies were included if authors provided original data, had adult outpatients, included a medication vs placebo comparison for at least 6 weeks, and did not exclude patients on via a placebo washout period, and used Hamilton Depression Rating Scale (HDRS). Data from 6 studies (718 patients) were included.
- **Data Extraction:** Individual patient-level data were obtained from study authors.
- **Results** Medication vs placebo differences varied substantially as a function of baseline severity. **Among patients with HDRS scores below 23, Cohen *d* effect sizes for the difference between medication and placebo were estimated to be less than 0.20** (a standard definition of a small effect). Estimates of the magnitude of the superiority of medication over placebo increased with increases in baseline depression severity and crossed the threshold defined by the National Institute for Clinical Excellence for a clinically significant difference at a baseline HDRS score of 25.
- **Conclusions:** The magnitude of benefit of antidepressant medication compared with placebo increases with severity of depression symptoms and may be minimal or nonexistent, on average, in patients with mild or moderate symptoms. For patients with very severe depression, the benefit of medications over placebo is substantial.

Under Wraps

Estimate of how much the impression of each drug's effectiveness was inflated by not publishing unfavorable studies



Company	Drug	Estimated change in drug efficacy
Bristol-Myers Squibb	Serzone	69%
Pfizer	Zoloft	64
Schering-Plough	Remeron	61
GlaxoSmithKline	Wellbutrin SR	55
GlaxoSmithKline	Paxil	40
Eli Lilly	Cymbalta	33
Wyeth	Effexor	28
Wyeth	Effexor XR	27
Forest	Celexa	25
Forest	Lexapro	16
Eli Lilly	Prozac	14
GlaxoSmithKline	Paxil CR	11

Source: New England Journal of Medicine

Cherry-picking methodologies in large scale drug trials?

- Use of placebo-lead in prior to actual study (excludes pts with good response to placebo/inflates treatment effect).
- Exclusion criteria (arbitrary and would inflate Tx effects):
  - Short episode duration
  - Mild severity of illness
  - Psychiatric co-morbidities
  - Long duration of illness
  - History of non-response to similar treatments
- Short follow up period (~ 6 wks, rarely 8 wks). No long term studies, despite fact that increasing # of patients take for yrs.
- Even with these manipulations, only ~ 50% trials reach SS.
- Little if any accounting for negative effects, or harms. No research on whether chronic SSRI downregulate 5-HT?
- Risk of suicide issue in children as example: suggests delays between improved motivation and improved mood.

Other Major Distorting Influences

- Marketing directly to patients/consumers.
- Promoting of chemical imbalance pseudo-biology in endless advertizing, parroted by physicians, as though this simplistic idea is actually the state of the art.
- Managed care requires psychotherapy preauthorized, while medicines require only a prescription.
- Unholy connections between researchers and Big Pharma creating severe conflicts of interest.
  - Gross distortions of research and gross misconduct
  - Joseph Biederman received $1.6 million from pharmaceutical companies, reporting only a tiny fraction of this; he claims that his research findings were never influenced by drug company money and financial perks. Despite these doubious claims, he spearheaded a 4000% increase in Dx of childhood bipolar disorder from 1994-2003. Has not been fully rolled back.

The court papers show Johnson & Johnson's Titusville, N.J.-based subsidiary Janssen Pharmaceutica:

- Budgeted $6.4 million to hold "educational summits" and sponsor advisory panels in part to counter negative media reports on the research, diagnosis and treatment of children with mental illness;
- Drafted research that Biederman was to present at a medical conference; asked him how to deal with unfavorable research results suggesting that a placebo worked as well as Risperdal;
- Discussed clinical trials for drugs as "growth opportunities" and tied trial proposals to sales potential.
- A 2002 annual report for the center stated that its research must satisfy three criteria: improve psychiatric care for children, have high standards and "**move forward the commercial goals of Johnson & Johnson**," according to court documents.
- "We strongly believe that the center's systematic scientific inquiry will enhance the clinical and research foundation of child psychiatry and lead to the safer, more appropriate and more widespread use of medications in children," the report stated. "Without such data, many clinicians question the wisdom of aggressively treating children with medications, especially those like neuroleptics, which expose children to potentially serious adverse events."

Treatment Algorithms for MD

- Don't just rely on psychopharmacology, even with serious depressions! For mild-mod depressions, **start with psychotherapy and lifestyle and sleep interventions**. Consider multiple modalities.
- SSRIs and similar drugs minimally effective in mild to mod depression.
- Affecting multiple systems probably on average more effective then single aminergic approaches. Stimulants underutilized in apathetic depressions, Buprenorphine underutilized, pigeon-holed for addiction.
- Psychotherapy, exploratory/supportive, with exploration of precipitating stressors, aimed at mitigation of helplessness, and likely critical in trauma-related depressions.
- REDUCE SOCIAL ISOLATION!!
- Exercise programs. Opioid, 5-HT, BDNF, anti-INFLAM effect.
- Evaluation of sleep, diet. Reduce pro-INFLAM diets, ↑ SW sleep.
- Meditation/relaxation therapies underutilized. Tai Chi, Yoga, etc.
- Vagal nerve stimulation, not very available, in anxious depressions.
- ECT, ketamine (AMPA agonist) for refractory depressions. rTMS may also be useful here, esp. for those frightened off from ECT.
- EBS for severe refractory depressions that fail to respond to ECT.