PsychoNeuroImmunology 101:
Practical Tips on How Immunology Can Serve Psychiatry in Improving Outcomes

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Disclosure

- The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration).
  - The off-label use of celecoxib, naproxen, ibuprofen, lovastatin, simvastatin, minocycline and aspirin, pioglitazone, etanercept, adalimumab, ustekinumab, and infliximab for the treatment of depression will be discussed.

- Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.
- This activity has been independently reviewed for balance.

Multiple Mind–Body Pathways Connection

Why PNI Matters to Psychiatrists

Sadness

- ❑ **Distinct symptoms?**
- ❑ **Are these seemingly distinct symptoms connected?**
- ❑ **Which specialty should deal with such a patient?**

Pain

Reduced Functionality

PNI Explains How Mind and Body are One

A Highly Connected Unitary System

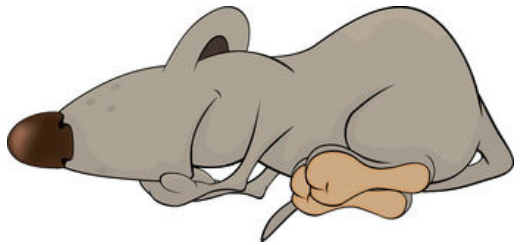
- Pain
- Stiffness
- Disease activity
- Insomnia
- Fatigue
- Cognitive dysfunction
- Anxiety
- Depression
- Weight gain
- Etc.

What is PNI and Why It Matters in Psychiatry?

History of Psycho-Neuro-Immunology (PNI)

Where It All Began (1975):
*The Birth of PNI (**P**sycho**N**euro**I**mmunology)*

Rats were conditioned to associate saccharin-laced water (CS) with the drug cyclophosphamide (US), an immunosuppressant drug, which induced nausea.



After conditioning the rats, simply giving them the saccharin-laced water led to death of some rats due to a compromised immune system.

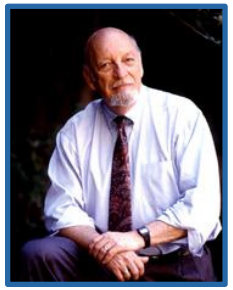
CS = conditioned stimulus; US = unconditioned stimulus.

Ader R, et al. *Psychosom Med*. 1975;37(4):333-340.

What Does This Mean? *Immunity is as Responsive to Emotions as it is to Antigens*

"Physical" factors can induce abnormal immune response

"Emotional" factors can induce abnormal immune response



The immune system is connected to Emotions, Thoughts, Beliefs, etc. and can be modified in both positive and negative ways—this is the basis of PNI.

Ader R, et al. *Psychosom Med*. 1975;37(4):333-340.

Robert Ader, PhD

- Professor Emeritus of Psychiatry at the University of Rochester Medical Center for 50 years
- Coined the term Psychoneuroimmunology —human mind can affect the ability of the immune system to fight disease
- Launched *Brain, Behavior and Immunity*
- Founder – Psychoneuroimmunology Research Society
- Proposed theory more than 30 years ago
- Met with much skepticism and scorn

www.urmc.rochester.edu/news/story/3370/robert-ader-founder-of-psychoneuroimmunology-dies.aspx. Accessed May 14, 2018.

Definition of PNI

"**Psychoneuoroimmunology** is a convergence of disciplines—namely the **behavioral** sciences, the **neurosciences**, **endocrinology**, and **immunology**—intended to achieve a more complete understanding of the way the **interaction among these systems** serve homeostatic ends and **influence health and disease**."

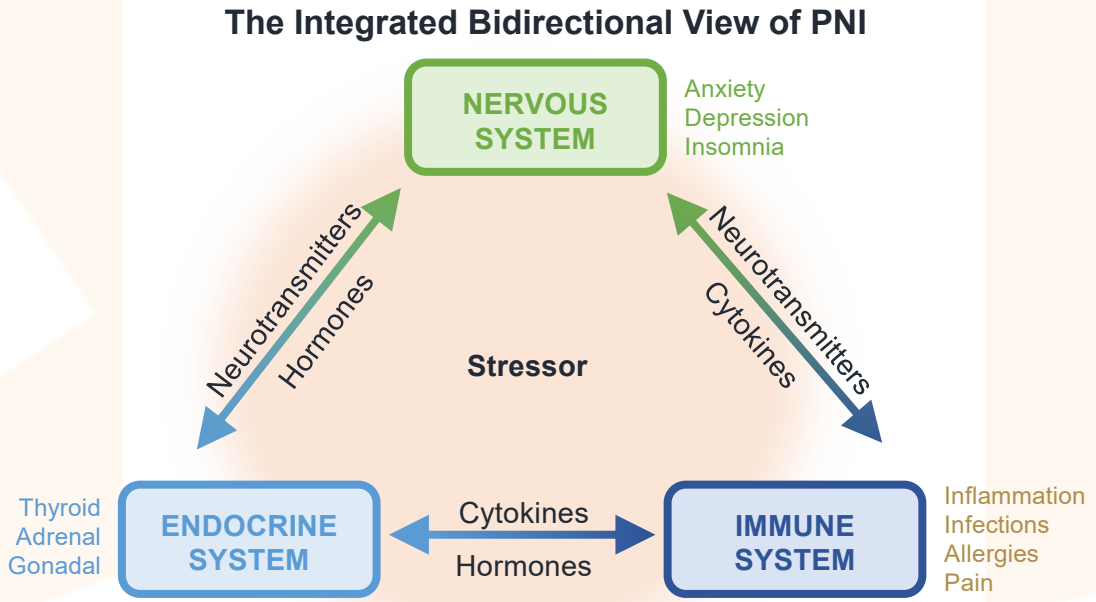
~ Robert Ader

Ader R (Ed). *Psychoneuroimmunology*. Fourth Edition. London, United Kingdom: Elsevier; 2007.

PNI Explains Brain–Body Link

"**PNI is a convergence of disciplines**—namely the behavioral sciences, the neurosciences, endocrinology, and immunology—intended to achieve a more complete understanding of the way the interaction among these systems serve homeostatic ends and influence health and disease."

—Robert Ader



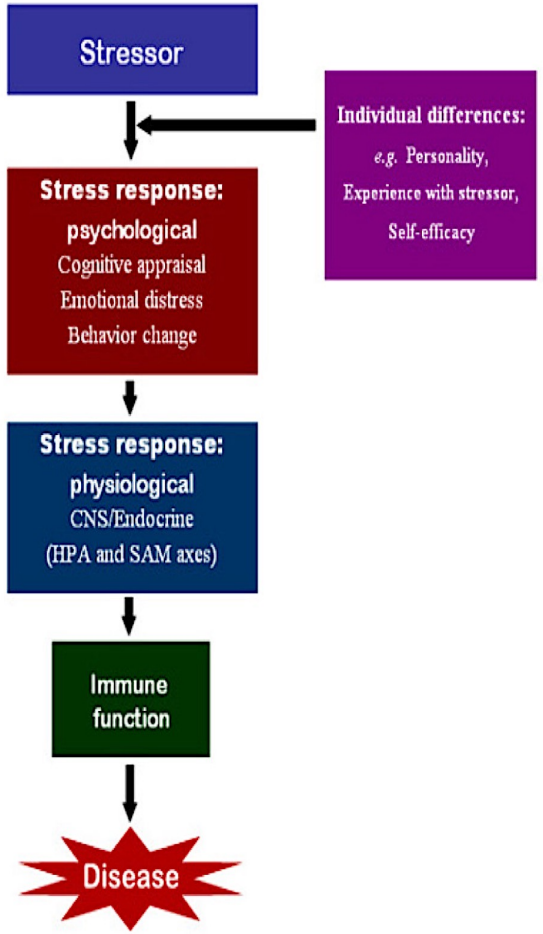
Mission statement. Psychoneuroimmunology Research Society. www.pnirs.org/society/index.cfm. Accessed May 14, 2018. Ader R (Ed). *Psychoneuroimmunology*. Fourth Edition. London, United Kingdom: Elsevier; 2007. Ader R, et al. *Psychosom Med*. 1975;37(4):333-340. Miller AH, et al. *Biol Psychiatry*. 2009;65(9):732-741.

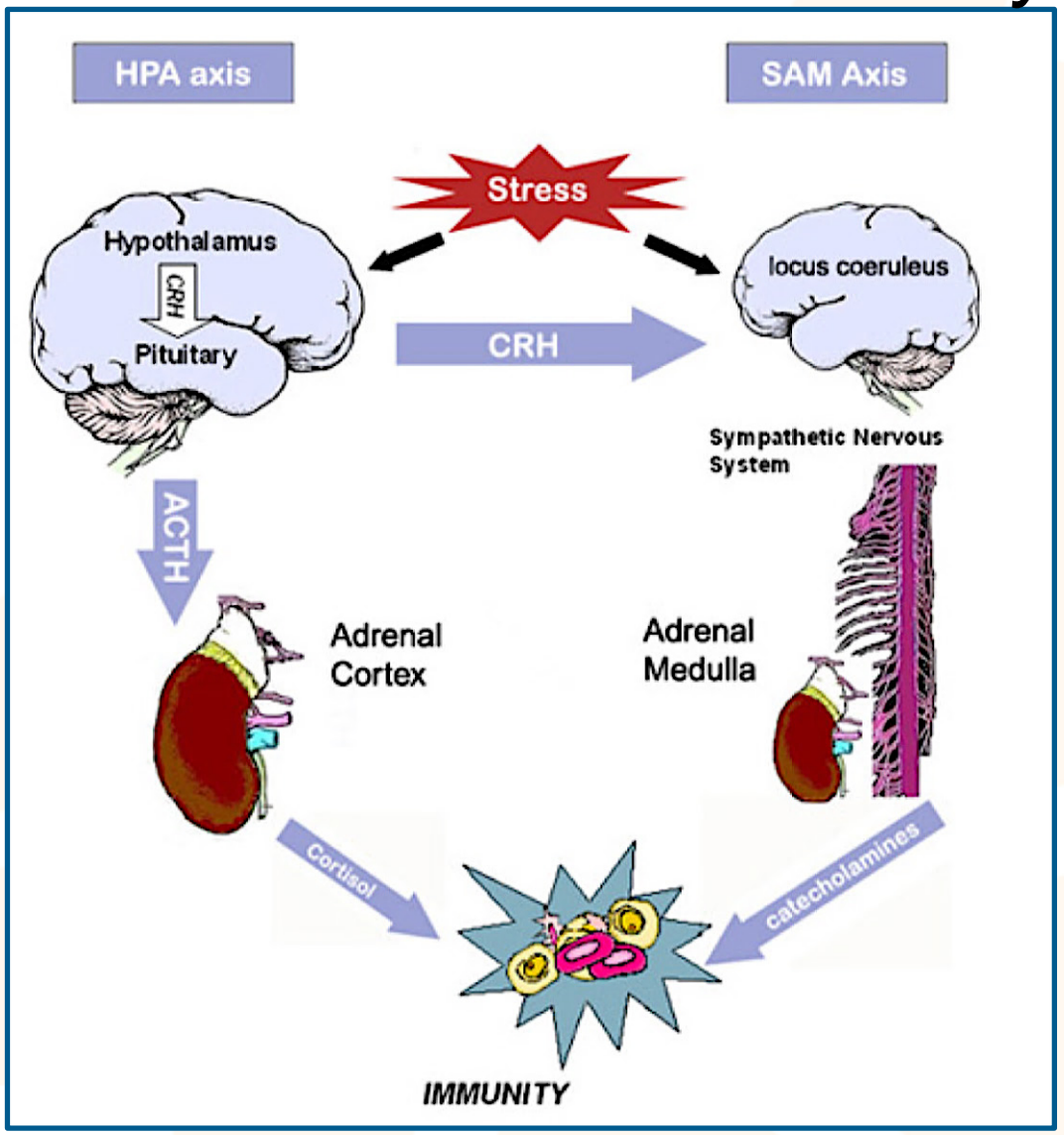
PNI Connects the Following “Unconnected” Specialties

https://pnirs.org/. Accessed May 14, 2018.

An "Old" *(and Incorrect)* View of the PNI System:

Unidirectional Conversation from HPA and ANS to Immune System

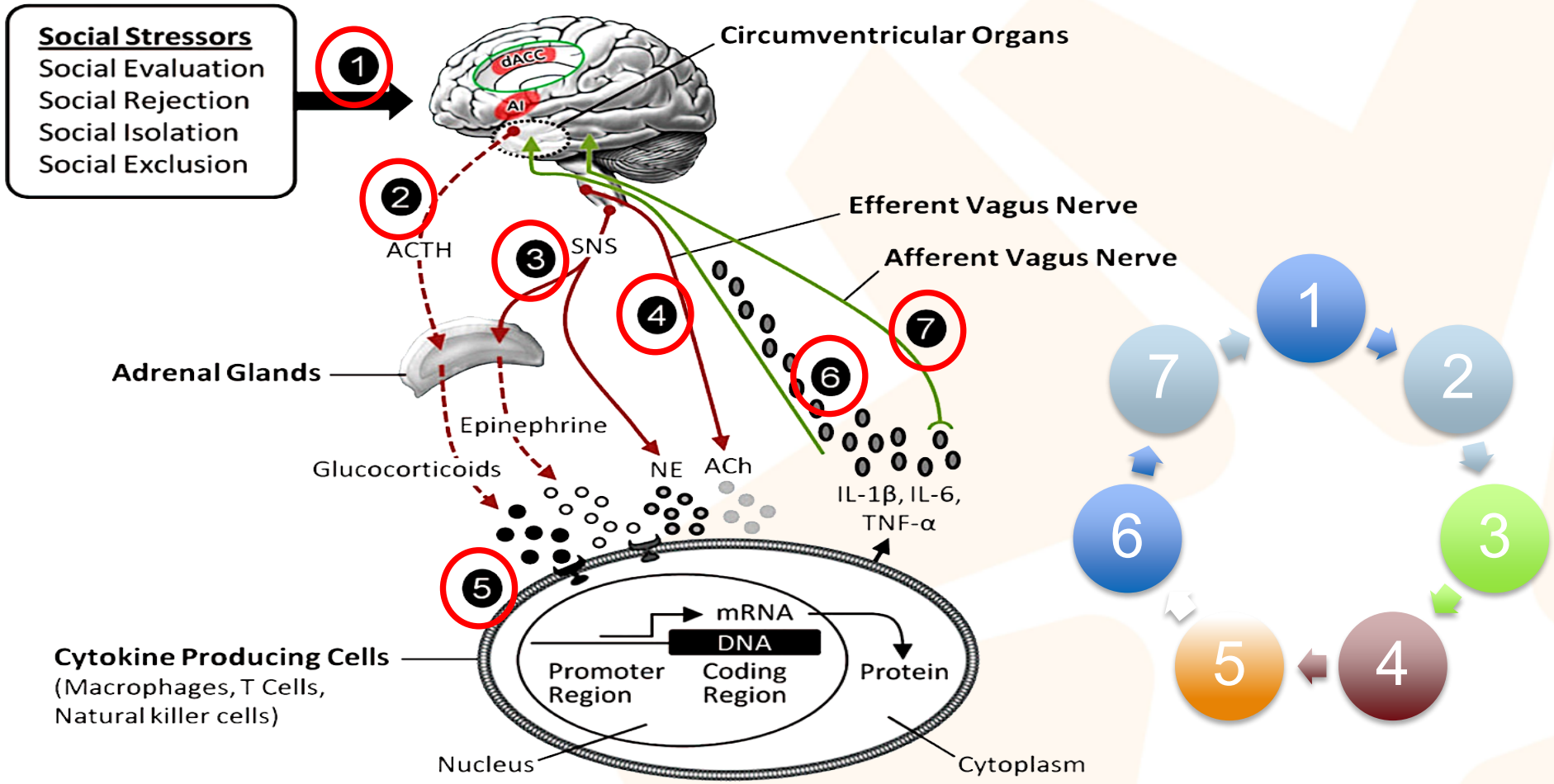




HPA = hypothalamic–pituitary–adrenal; ANS = autonomic nervous system; CNS = central nervous system; SAM = sympathetic–adrenalmedullary; CRH = corticotropin releasing hormone; ACTH = adrenocorticotropin hormone.

Thornton LM, et al. *Cellscience*. 2006;2(4):66-91.

Multiple Mind–Body Pathways Connect Stress to Inflammation—*Importance of PNI*

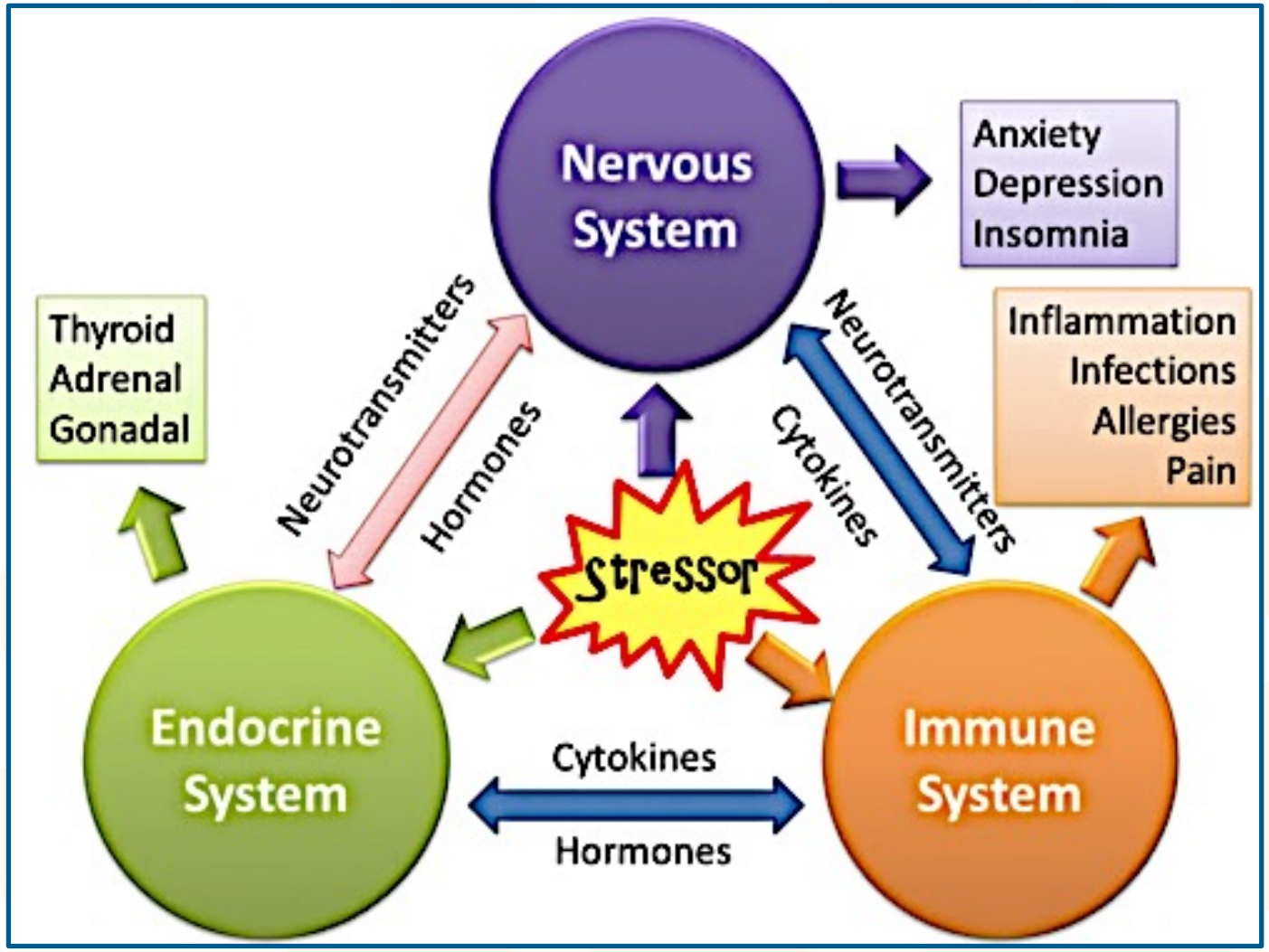


AI = anterior insula; dACC = dorsal anterior cingulate cortex; SNS = sympathetic nervous system; NE = norepinephrine; ACh = acetylcholine; IL = interleukin; TNF = tumor necrosis factor.

Slavich GM, et al. *Psychol Bull*. 2014;140(3):774-815.

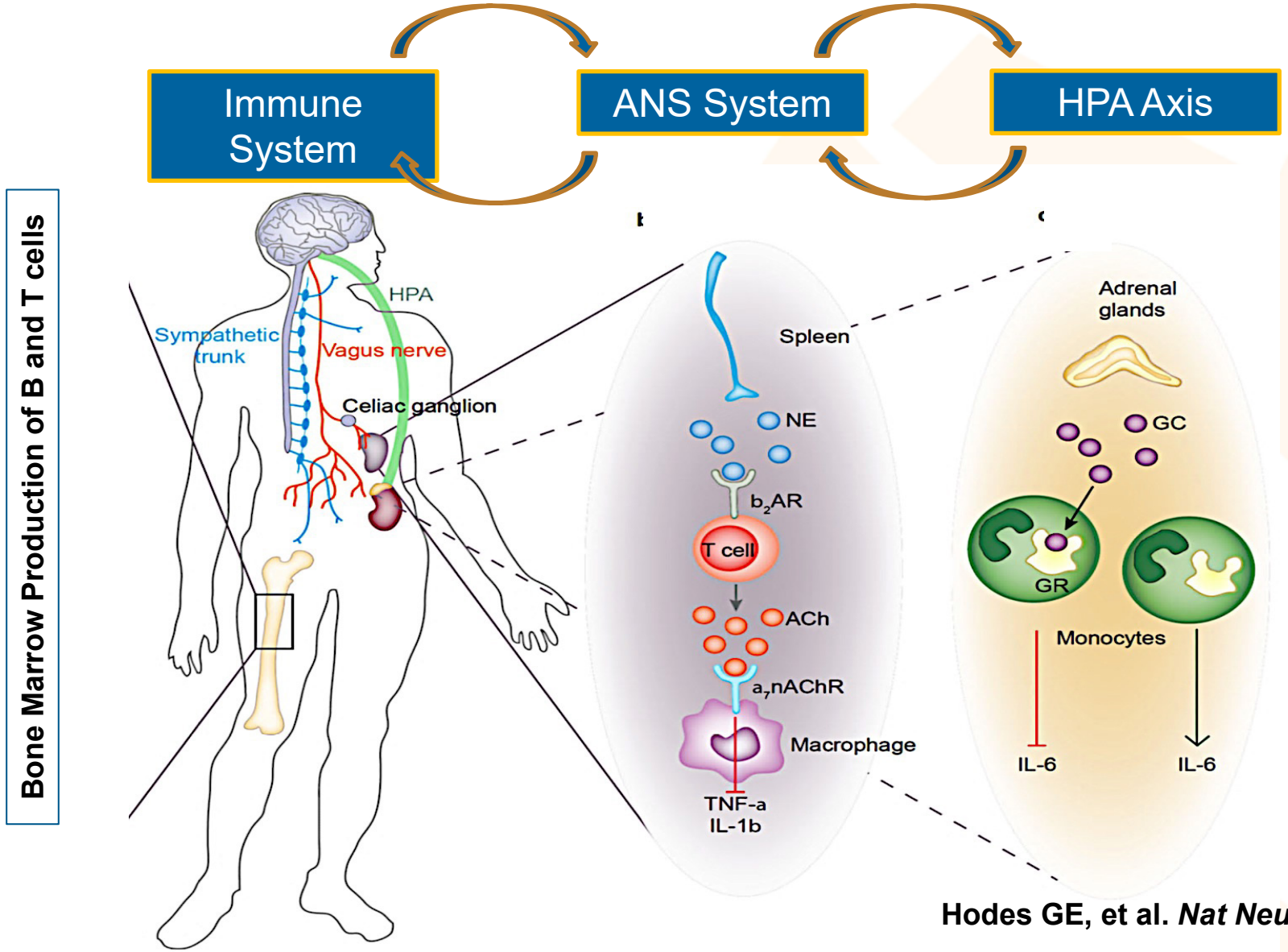
Note: There are 3 "Currencies" Used for Transactions in the PNI

1. **Neurotransmitters**
   a) Norepinephrine
   b) Epinephrine
   c) Serotonin, etc.
2. **Hormones**
   a) Cortisol
   b) Thyroid
   c) Melatonin, etc.
3. **Cytokines**
   a) IL-6
   b) IL-1β
   c) TNF-α, etc.



Miller AH, et al. *Biol Psychiatry*. 2009;65(9):732-741.

The PNI "Triad" in Health and Illness

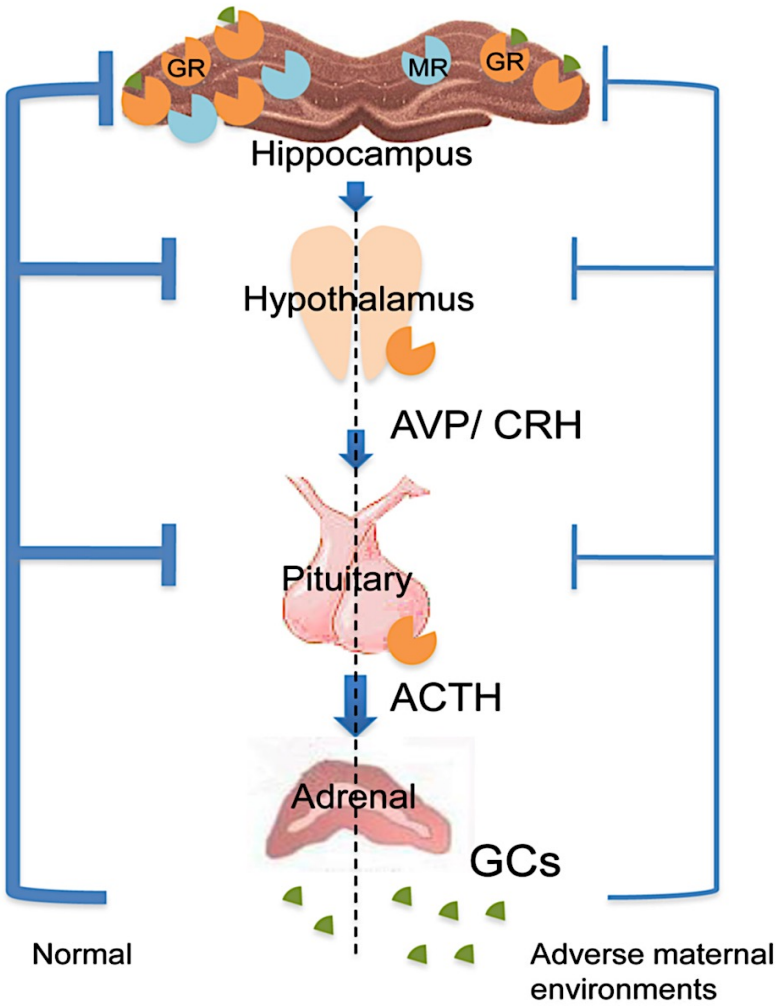


Hodes GE, et al. *Nat Neurosci*. 2015;18(10):1386-1393.

Chapter 2

What Sets Up the PNI System to Function Abnormally
&
The Consequences of Abnormal PNI Functioning

HHPA Axis and Maternal/Childhood Adversity



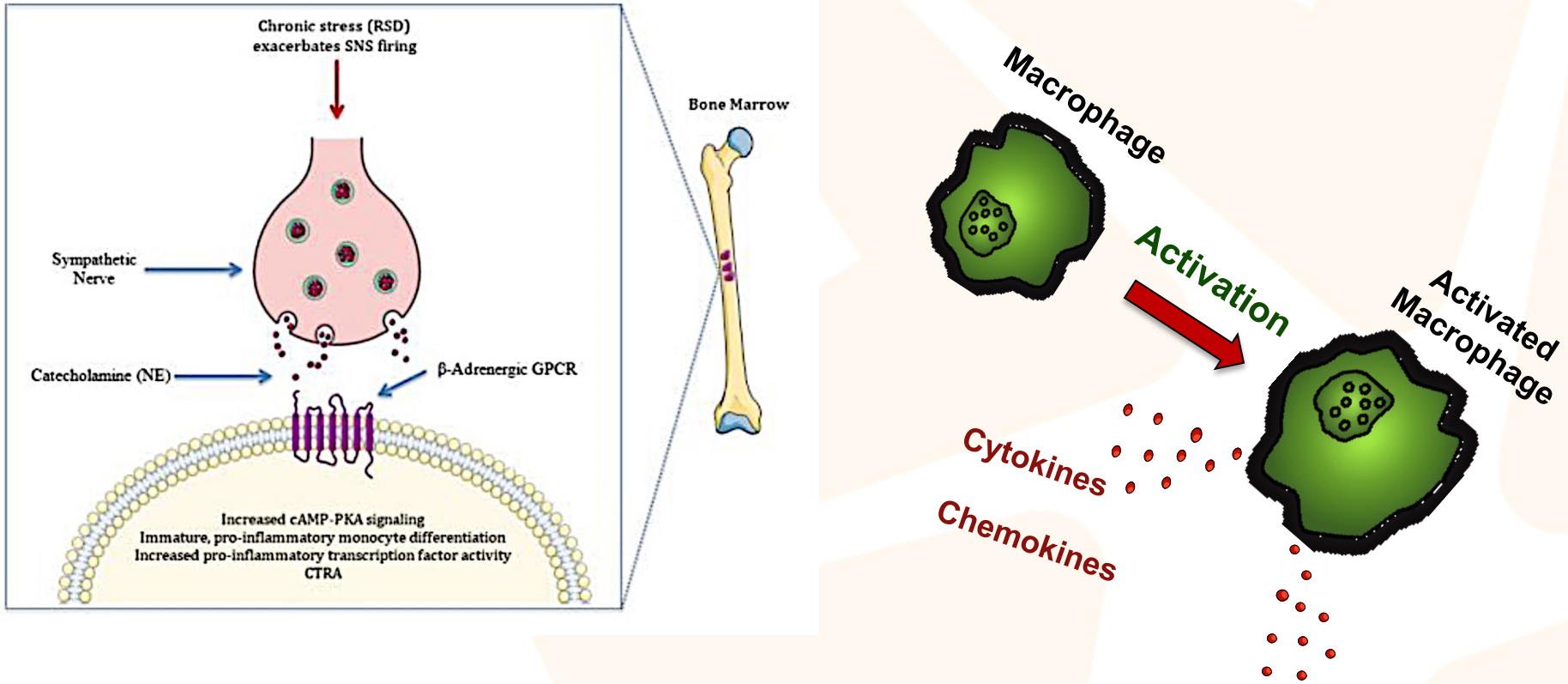
Adverse maternal environments can result in attenuated negative feedback regulation of HPA activity through decreased expression of GR in the hippocampus.

HHPA = hippocampal–hypothalamic–pituitary–adrenal; GR = glucocorticoid receptor; MR = mineralocorticoid receptor; AVP = arginine vasopressin; GC = glucocorticoid.

Xiong F, et al. *Front Neuroendocrinol*. 2013;34(1):27-46.

Social Stressors via the SNS Provoke Inflammation

Chronic stressors (such as repeated social disruption) exacerbate the activity of the sympathetic branch of the ANS.

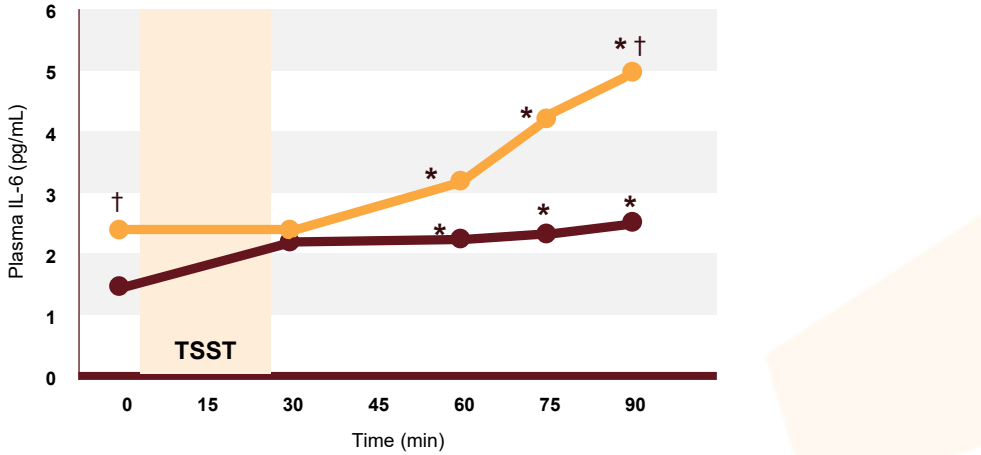


RSD = repeated social disruption; GPCR = G-protein coupled receptor; cAMP = cyclic adenosine monophosphate; PKA = protein kinase A; CTRA = conserved transcriptional response to adversity.

Friedler B, et al. *Acta Neuropathol*. 2015;129(4):493-509.

Psychosocial Stress Can Induce Inflammatory Response in Major Depression

Plasma IL-6 Levels before and after a Psychosocial Stressor Challenge (TSST)
N=28



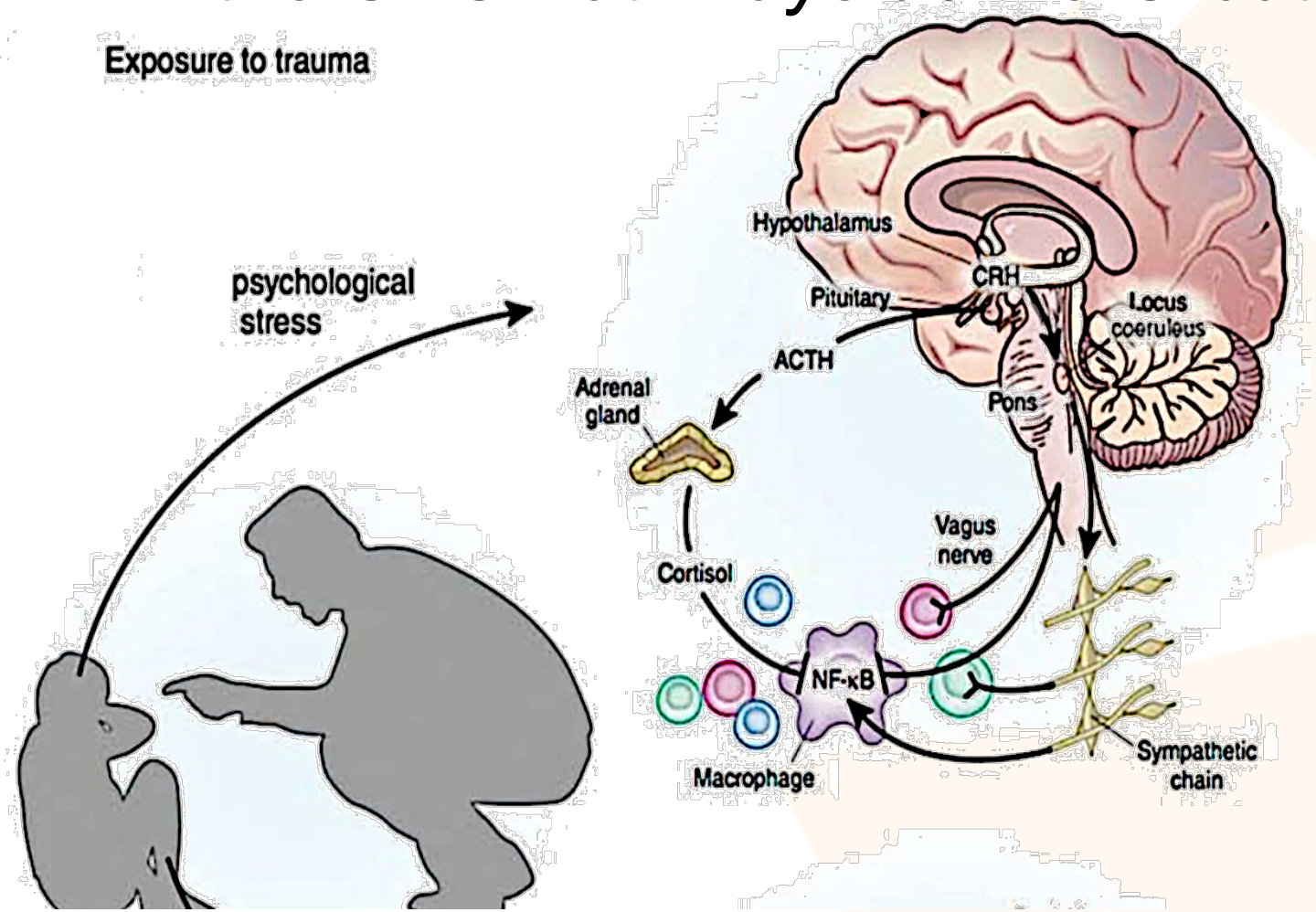
Participants with major depression had **significantly higher IL-6 levels** at baseline and 90 minutes after the stressor, as well as a greater IL-6 response to the stressor

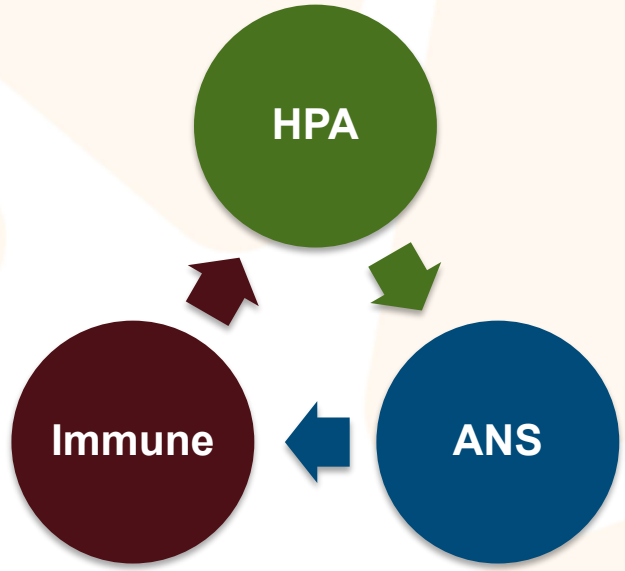
Participants with major depression had **increased early-life stress**‡

****P*<.05 vs baseline; †*P*<.05 between groups; ‡On Childhood Trauma Questionnaire. TSST = Trier Social Stress Test.**
Pace TW, et al. *Am J Psychiatry*. 2006;163(9):1630-1633.

Psycho-Neuro-Immunology:

The Immune System is Fully Integrated with the HPA Axis and the SNS Pathways as the Great Connectors



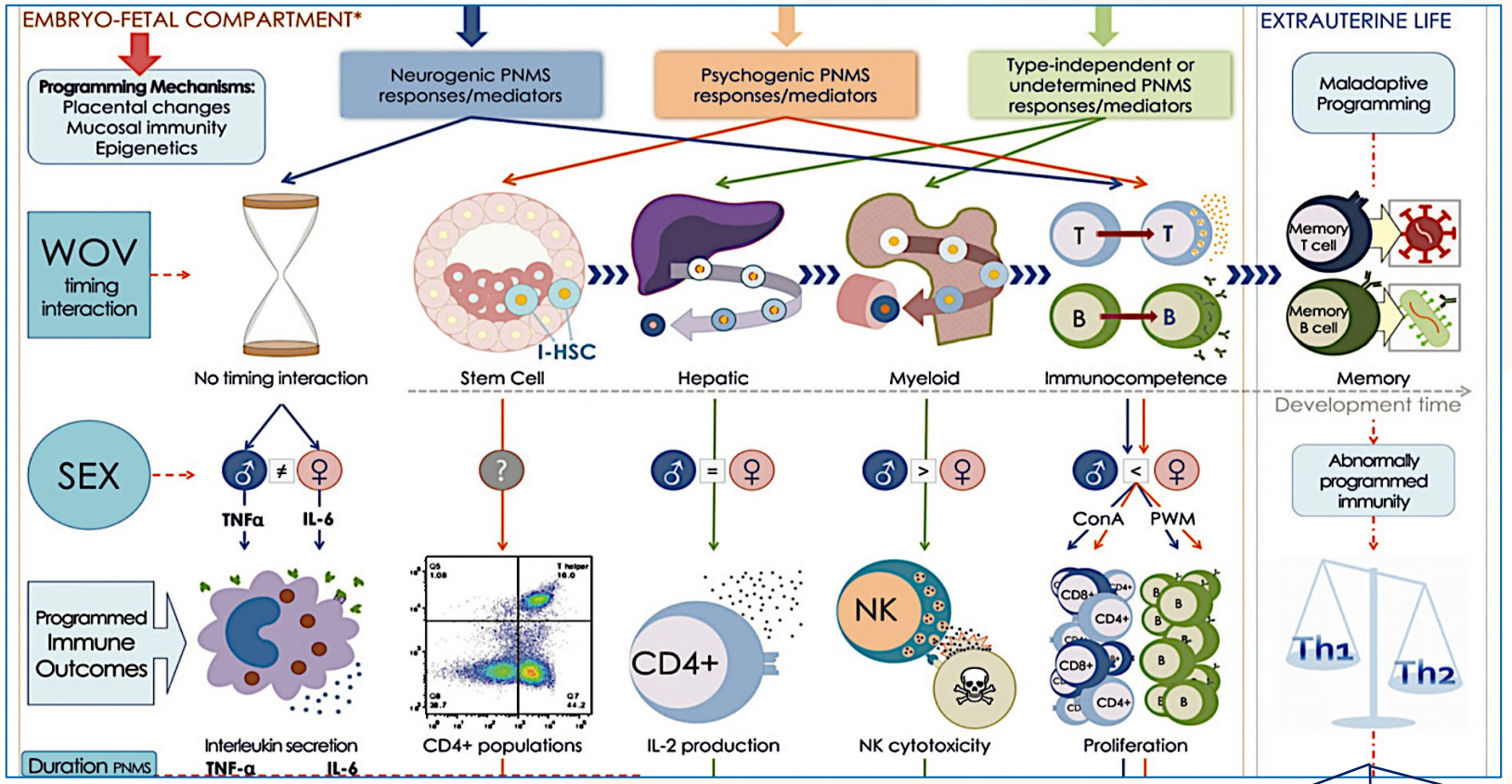


NF = nuclear factor.

Miller AH, et al. *Biol Psychiatry*. 2009;65(9):732-741.

Stress, No Matter When It Occurs, Can Reprogram the Immune System

Intra-uterine and Extra-uterine Stress and Its Impact on Immune System and Inflammatory Disorders



WOV = windows of vulnerability.

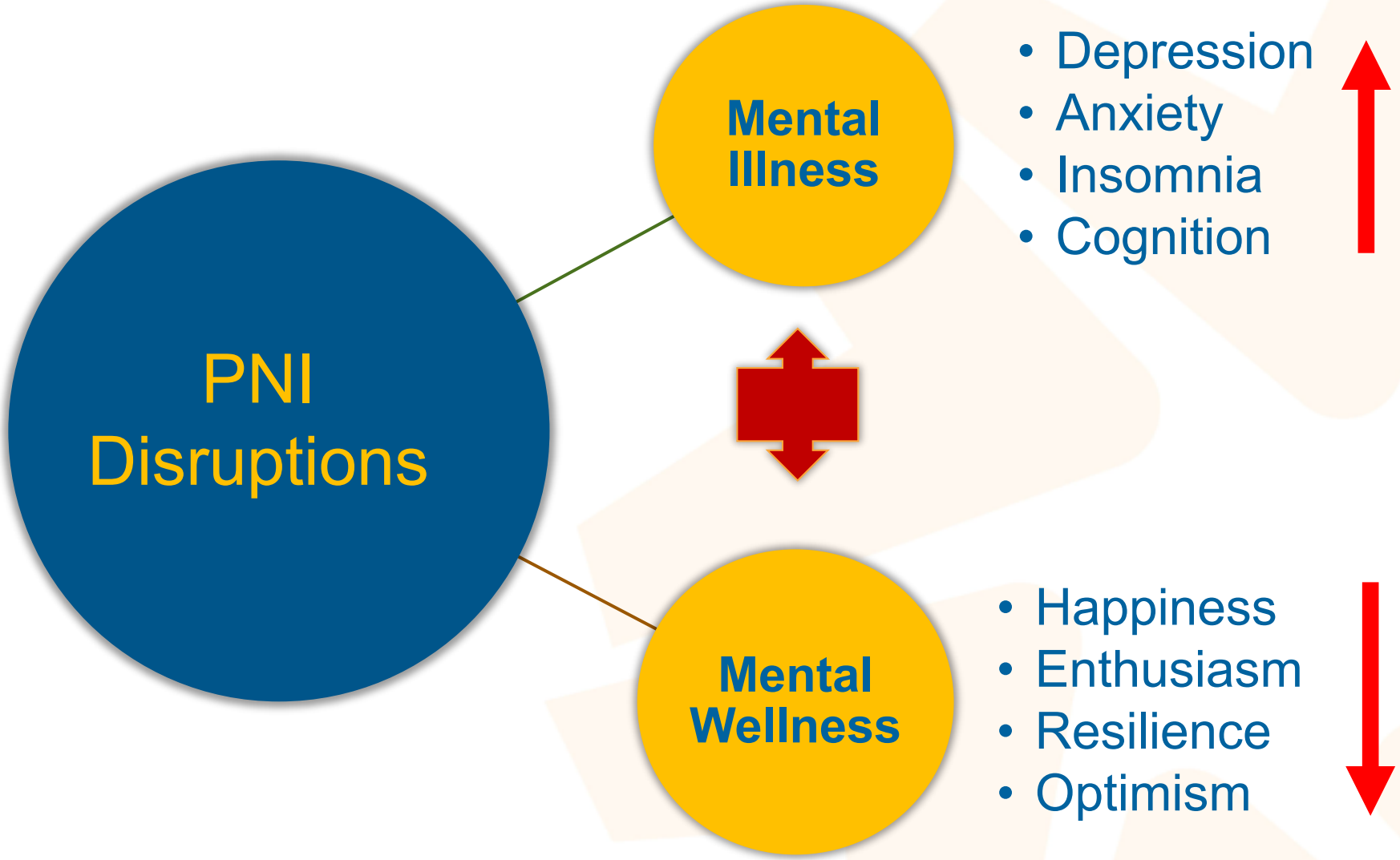
Veru F, et al. *Stress*. 2014;17(2):133-148.

Asthma

Allergies

Inflammatory Disorders

And Finally, PNI Disruptions Create a Bidirectional Negative Impact on Mood



Chapter 3

PNI Primer

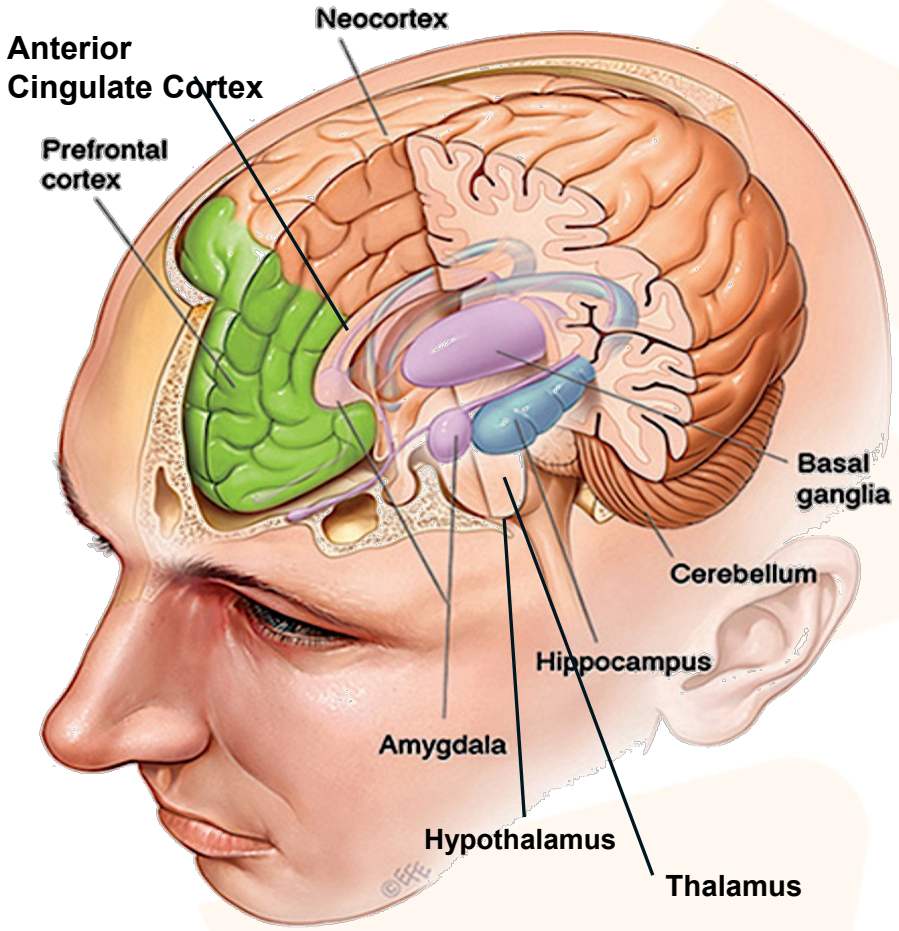
- Limbic System
- HPA Axis
- ANS
- Neuro-Immune System

Primer:
The Limbic System

CNS Organs Involved with:

1. Thought Processing
2. Emotion Processing

The Prefrontal Cortex and Limbic System:
An Introduction



Entire neuronal circuitry controlling emotional behavior and motivational drives

Szczepanski SM, et al. *Neuron*. 2014;83(5):1002-1018. Roxo MR, et al. *ScientificWorldJournal*. 2011;11:2428-2441.

Limbic System and Its PNI Modulating Tasks

Prefrontal Cortex

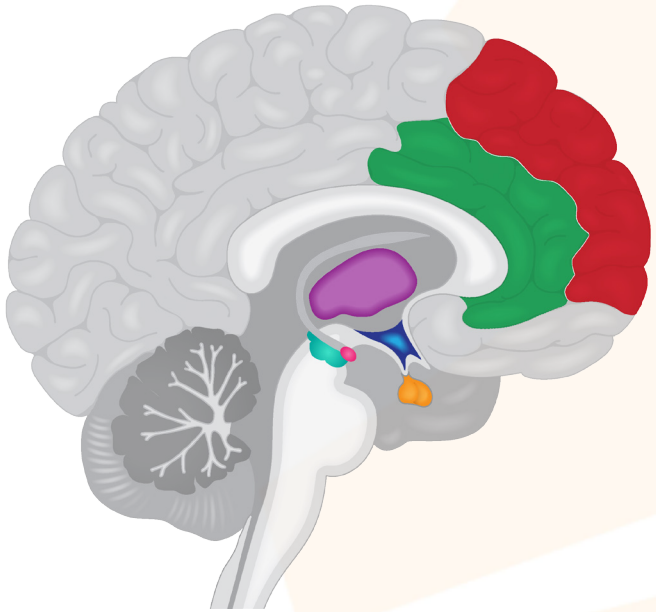
- Attention
- Abstract thinking
- Executive functions

Anterior Cingulate Cortex

- ANS and endocrine response
- Management of social behavior
- Emotional response to pain

Amygdala

- Anger/aggression regulation
- Anxiety regulation
- Fear regulation



Hypothalamus

- Sleep regulation
- Endocrine, ANS, and immune systems connection
- Appetite regulation
- Temperature regulation

Thalamus

- Relay of sensory and motor signals
- Alertness regulation

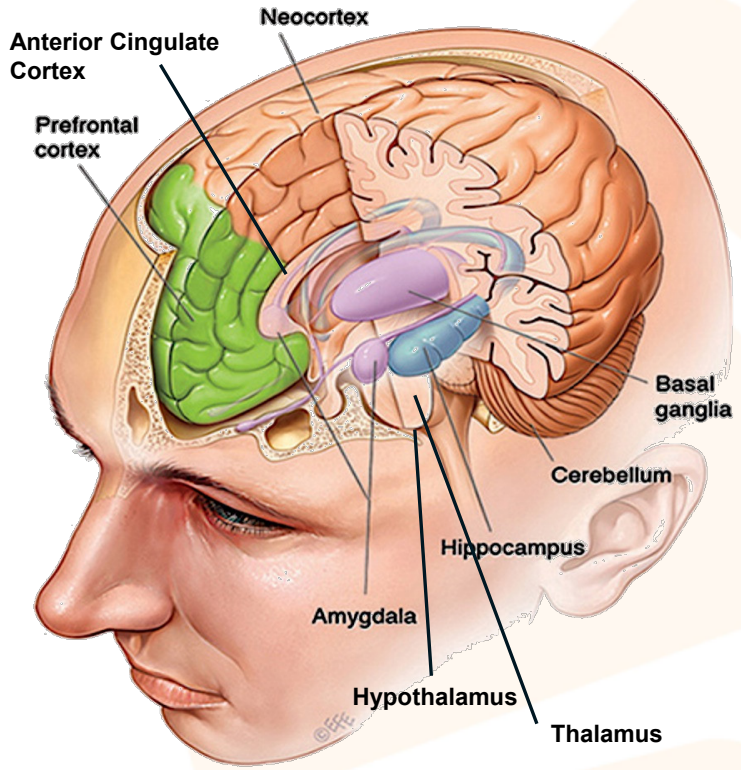
Hippocampus

- Memory
- Mood
- Learning

Siddiqui SV, et al. *Indian J Psychiatry*. 2008;50(3):202-208. Szczepanski SM, et al. *Neuron*. 2014;83(5):1002-1018. Roxo MR, et al. *ScientificWorldJournal*. 2011;11:2428-2441. Zhu LJ, et al. *PLoS One*. 2014;9(5):e97689. Cai D, et al. *Ann N Y Acad Sci*. 2011;1243:E1-E39.

Practical Clinical Implications:

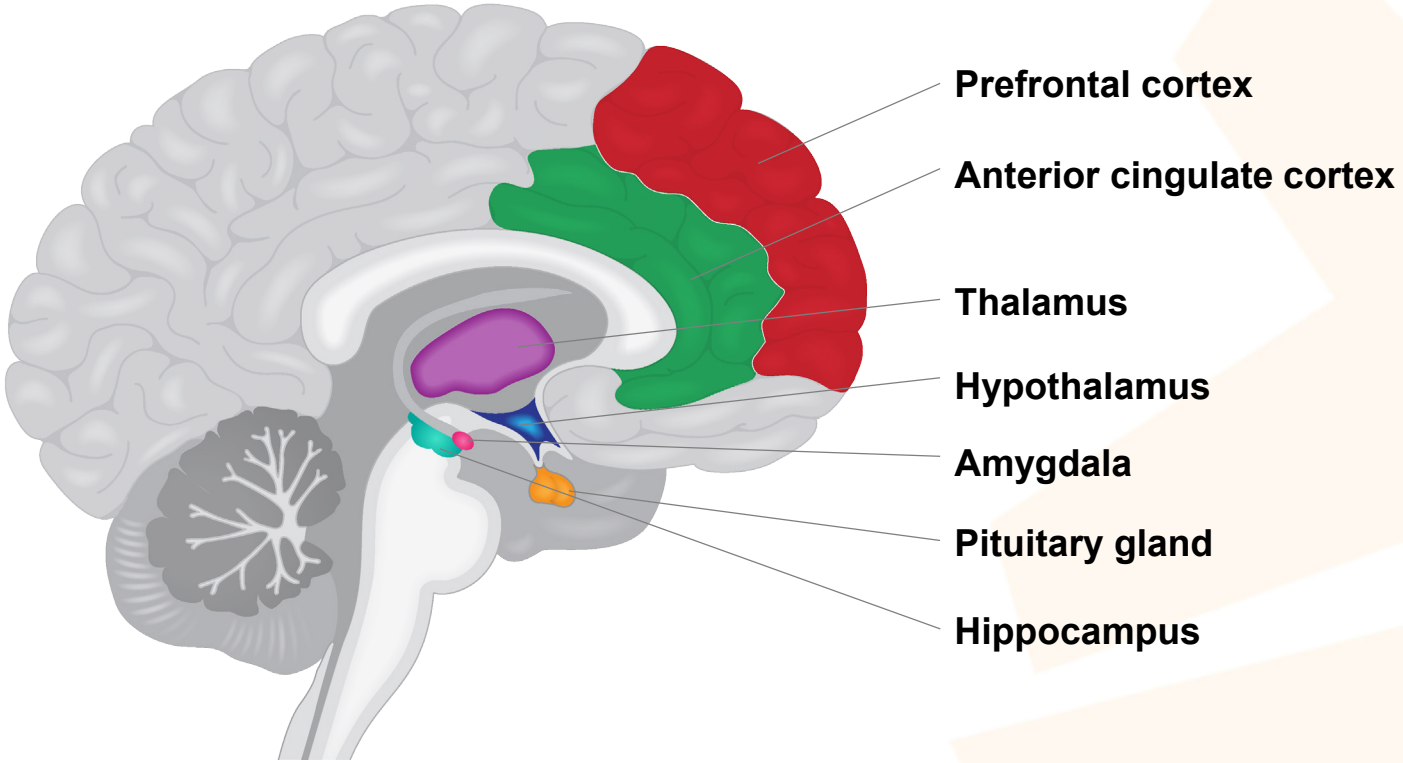
The Prefrontal Cortex, Limbic System, and Psychiatry



Limbic System Centric Interventions Can Negatively/Positively Impact:

1. Inflammation 2. Mood 3. Sleep 4. Pain 5. Coping

In Summary, the PFC and Limbic System are Prominent Players in the PNI System



AND

PNI Disruptions can Negatively Impact EACH of these Regions' Functioning Adversely

Siddiqui SV, et al. *Indian J Psychiatry*. 2008;50(3):202-208. Szczepanski SM, et al. *Neuron*. 2014;83(5):1002-1018. Roxo MR, et al. *ScientificWorldJournal*. 2011;11:2428-2441. Zhu LJ, et al. *PLoS One*. 2014;9(5):e97689. Cai D, et al. *Ann N Y Acad Sci*. 2011;1243:E1-E39. Rovó Z, et al. *J Neurosci*. 2012;32(49):17894-17908. Vertes RP, et al. *Neurosci Biobehav Rev*. 2015;54:89-107.

Primer:
The HPA Axis

The HPA Axis:
Let's Meet the Major Players

Hypothalamus

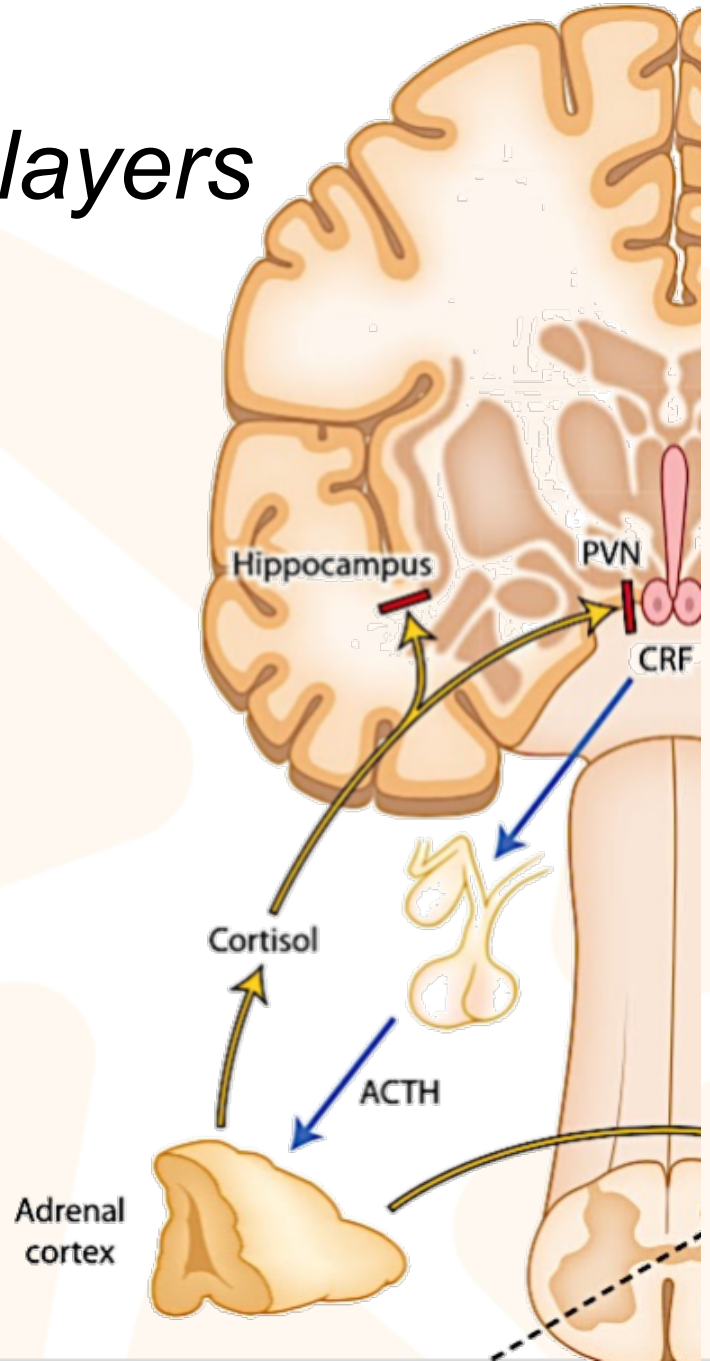
↓ **CRF**

Pituitary

↓ **ACTH**

Adrenal

Cortisol



PVN = paraventricular nucleus of hypothalamus; CRF = corticotropin-releasing factor.

Jain R, et al. *Curr Diab Rep*. 2011;11(4):275-284.

The HPA Axis is "So Yesterday"

Today's Emerging Paradigm is "HHPA Axis"

Hippocampus

↓

Hypothalamus

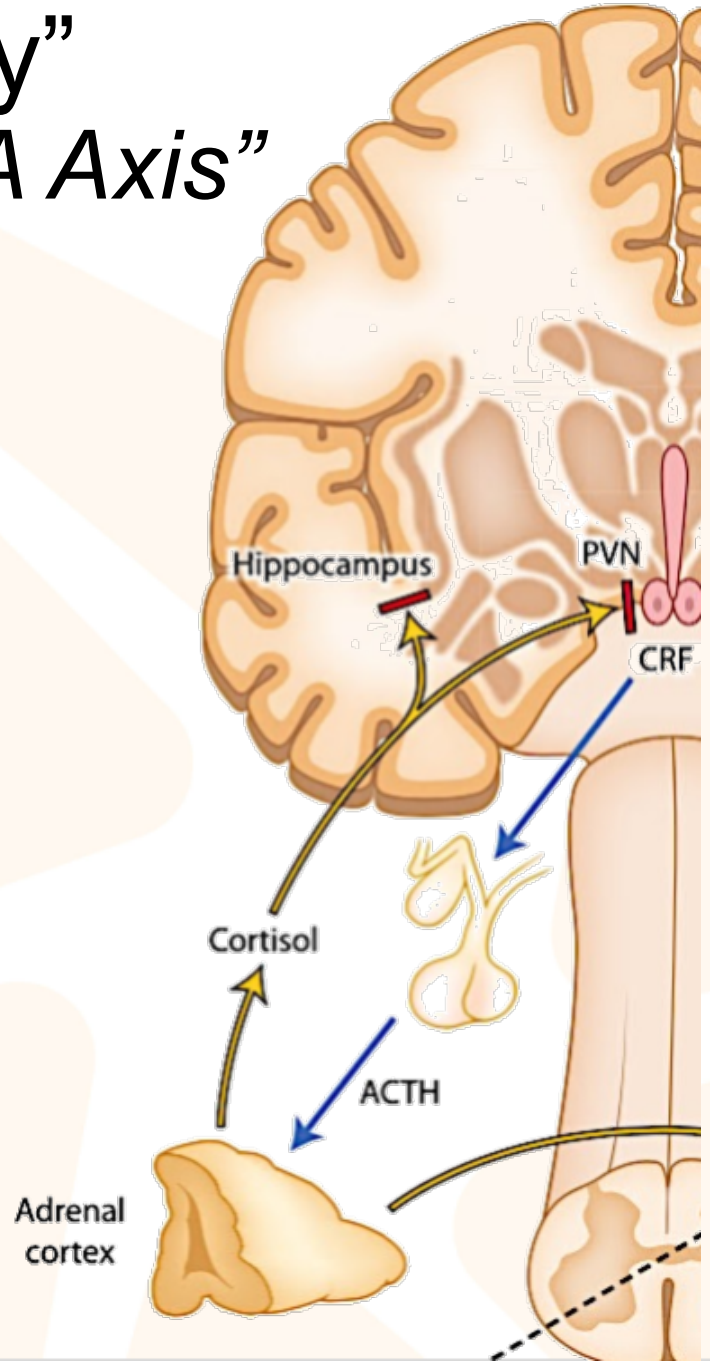
↓ **CRF**

Pituitary

↓ **ACTH**

Adrenal

Cortisol



Jain R, et al. *Curr Diab Rep*. 2011;11(4):275-284.

And the Implications of This Emergent View "HHPA Axis" are…

Hippocampus

↓

Hypothalamus

↓ CRF

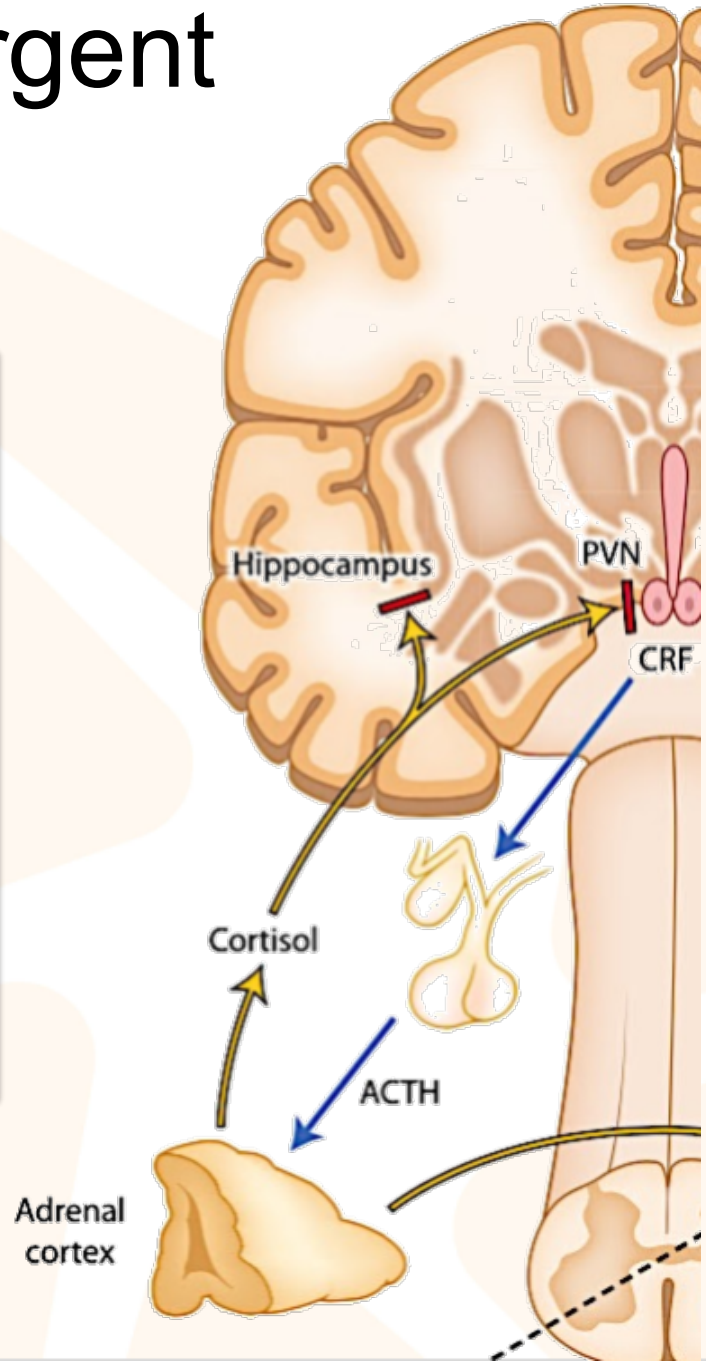
Pituitary

↓ ACTH

Adrenal

Cortisol

The HPA Axis will Respond to Thoughts/Beliefs, Memories (Positive and Negative), which are all stored in the Hippocampus



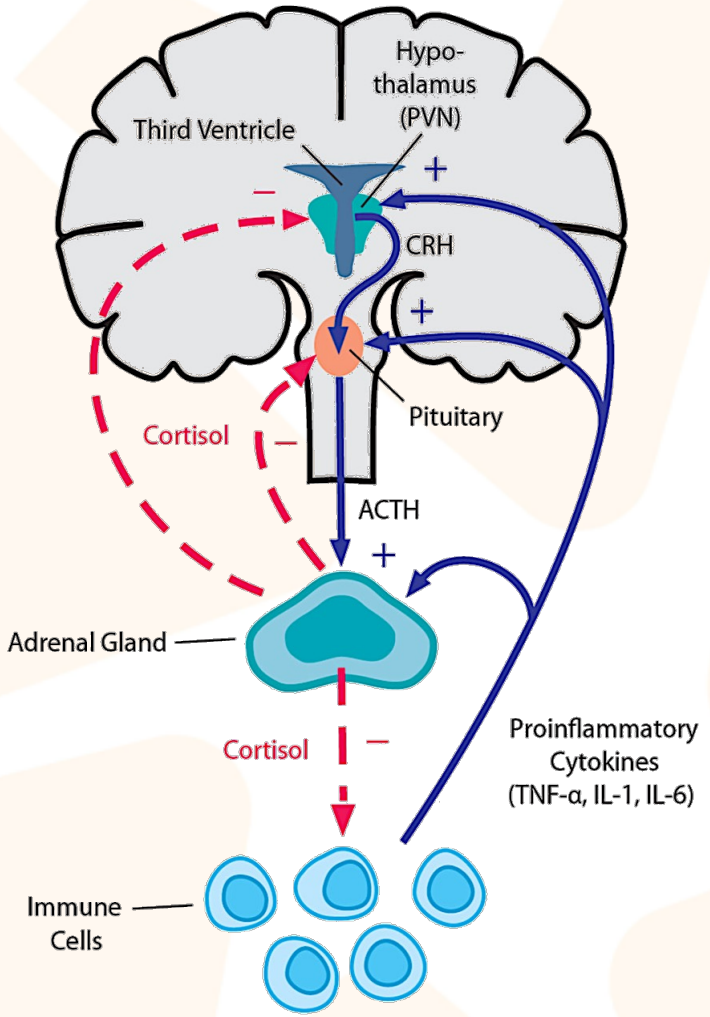
Jain R, et al. *Curr Diab Rep*. 2011;11(4):275-284.

HPA and Immune System in Healthy Homeostasis

- There is Bidirectional communication between the immune system and the HPA axis

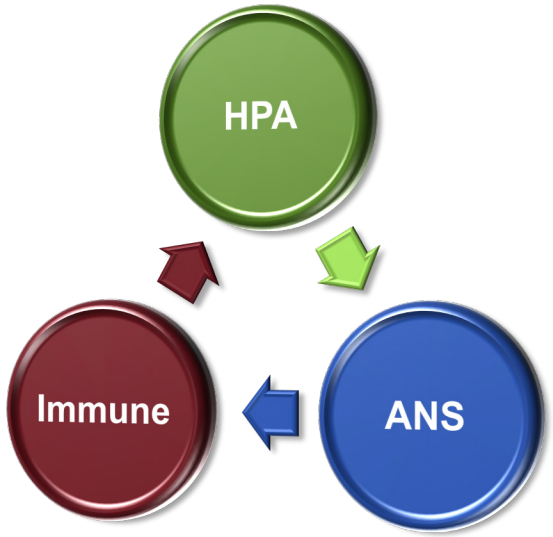
- Proinflammatory cytokines, such as TNF, IL-1, and IL-6, stimulate cortisol release by acting at all 3 levels of the HPA axis (solid blue lines)

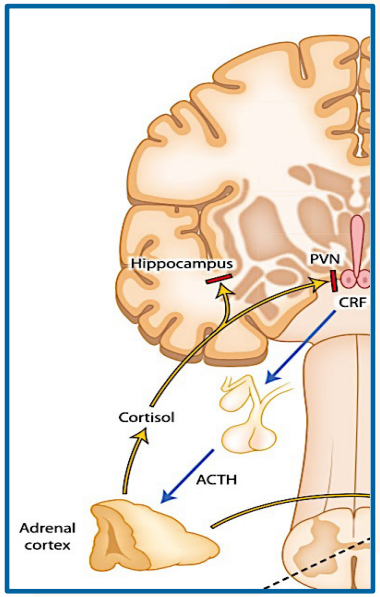
- In turn, glucocorticoids negatively feedback on the immune system to suppress the further synthesis and release of proinflammatory cytokines (dashed red line)

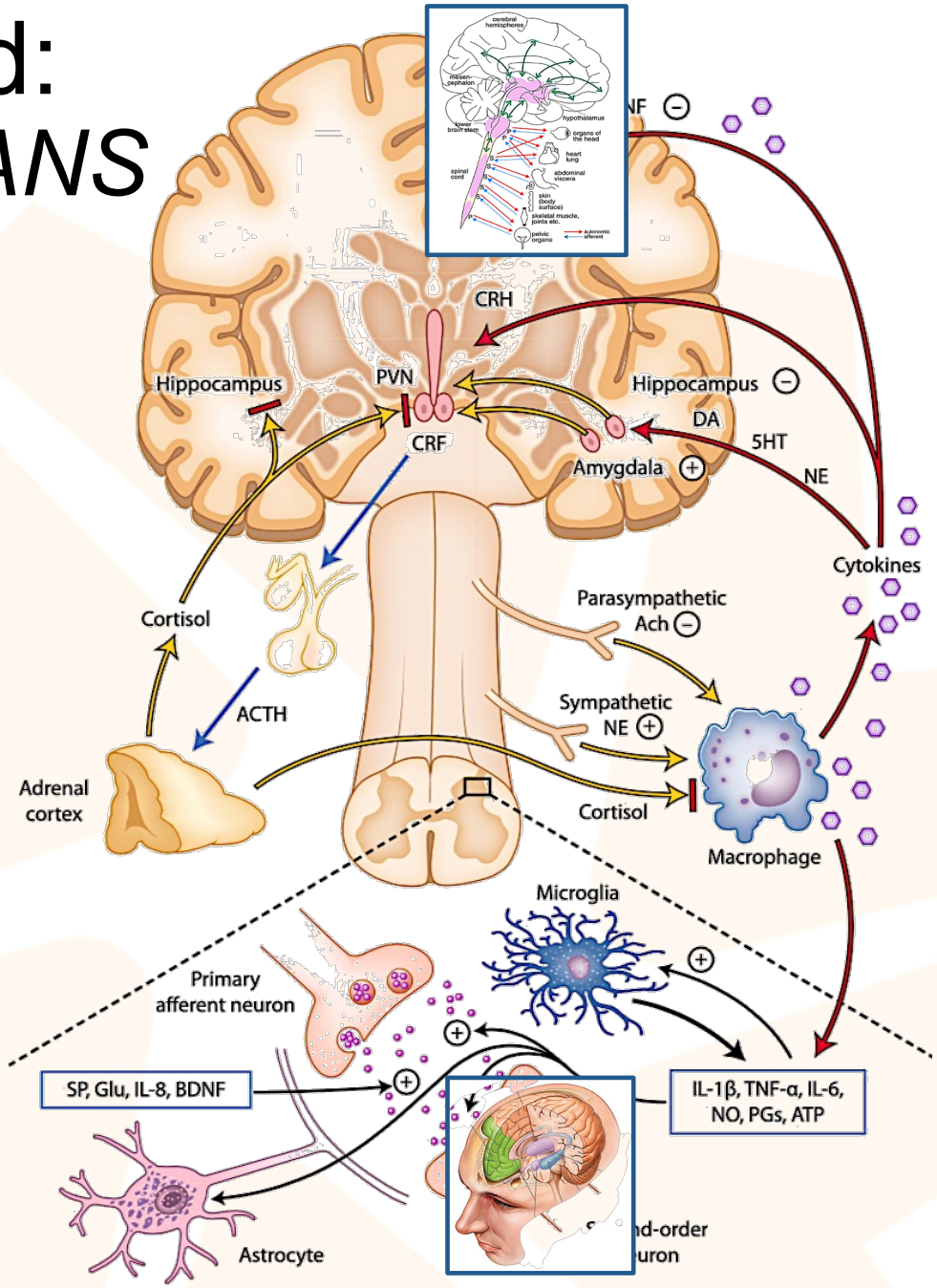


Silverman MN, et al. *Ann N Y Acad Sci*. 2012;1261:55-63.

No Man or Woman is an Island:
HPA Axis is Well Connected to the ANS and the Immune System

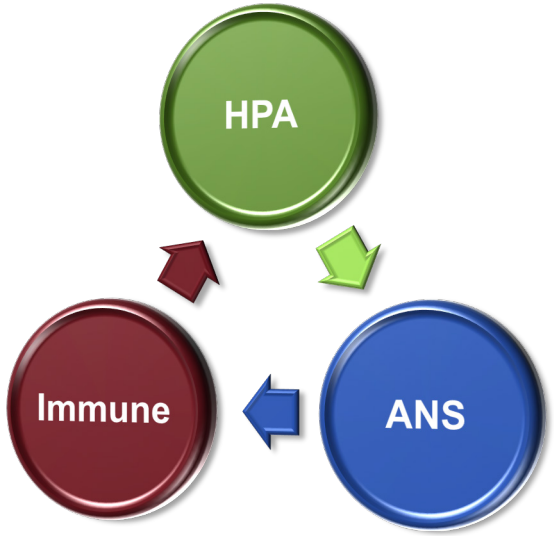


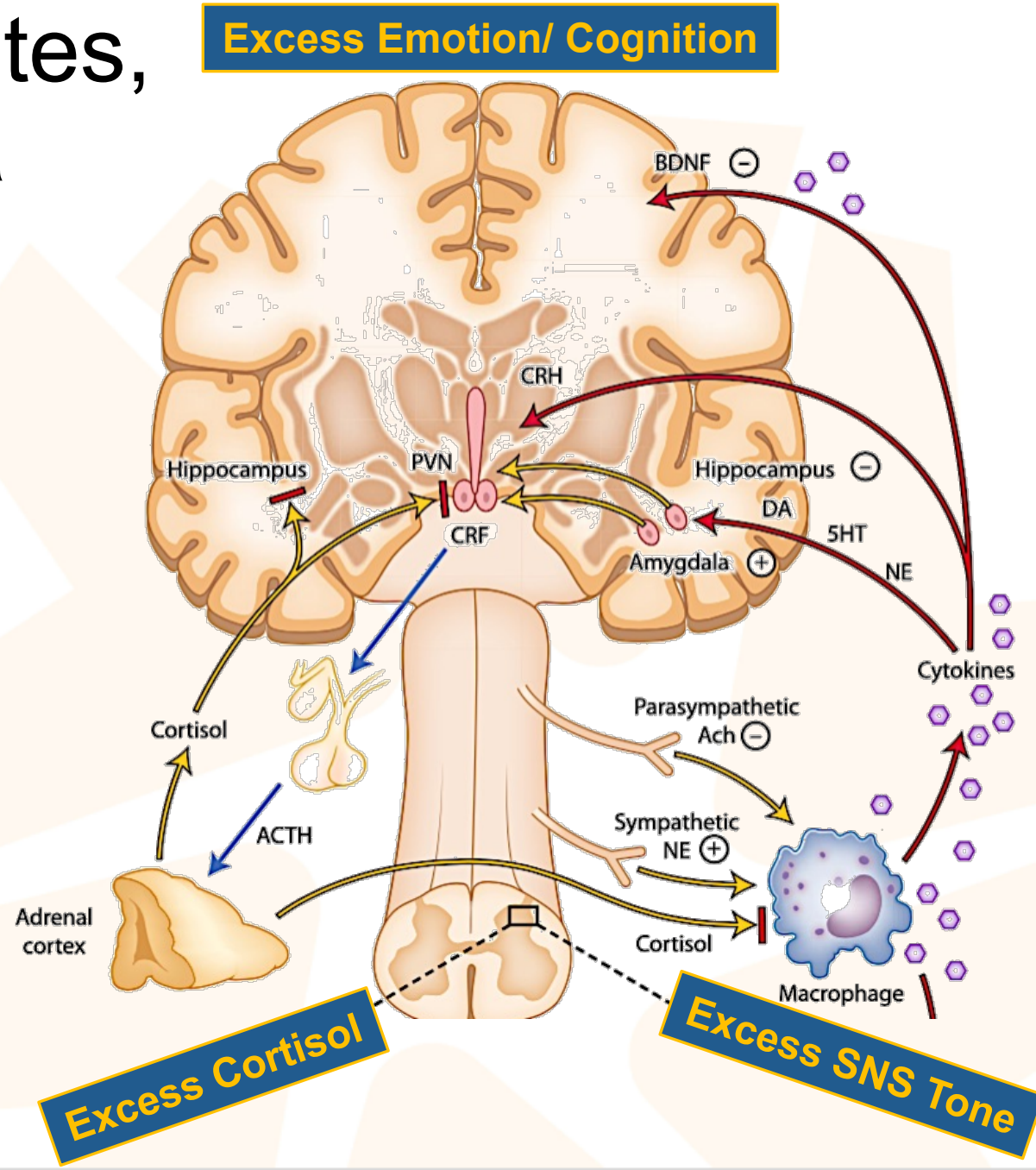




Jain R, et al. *Curr Diab Rep*. 2011;11(4):275-284.

HOWEVER, In Disease States, Any of the 3 Can Start a Negative Loop



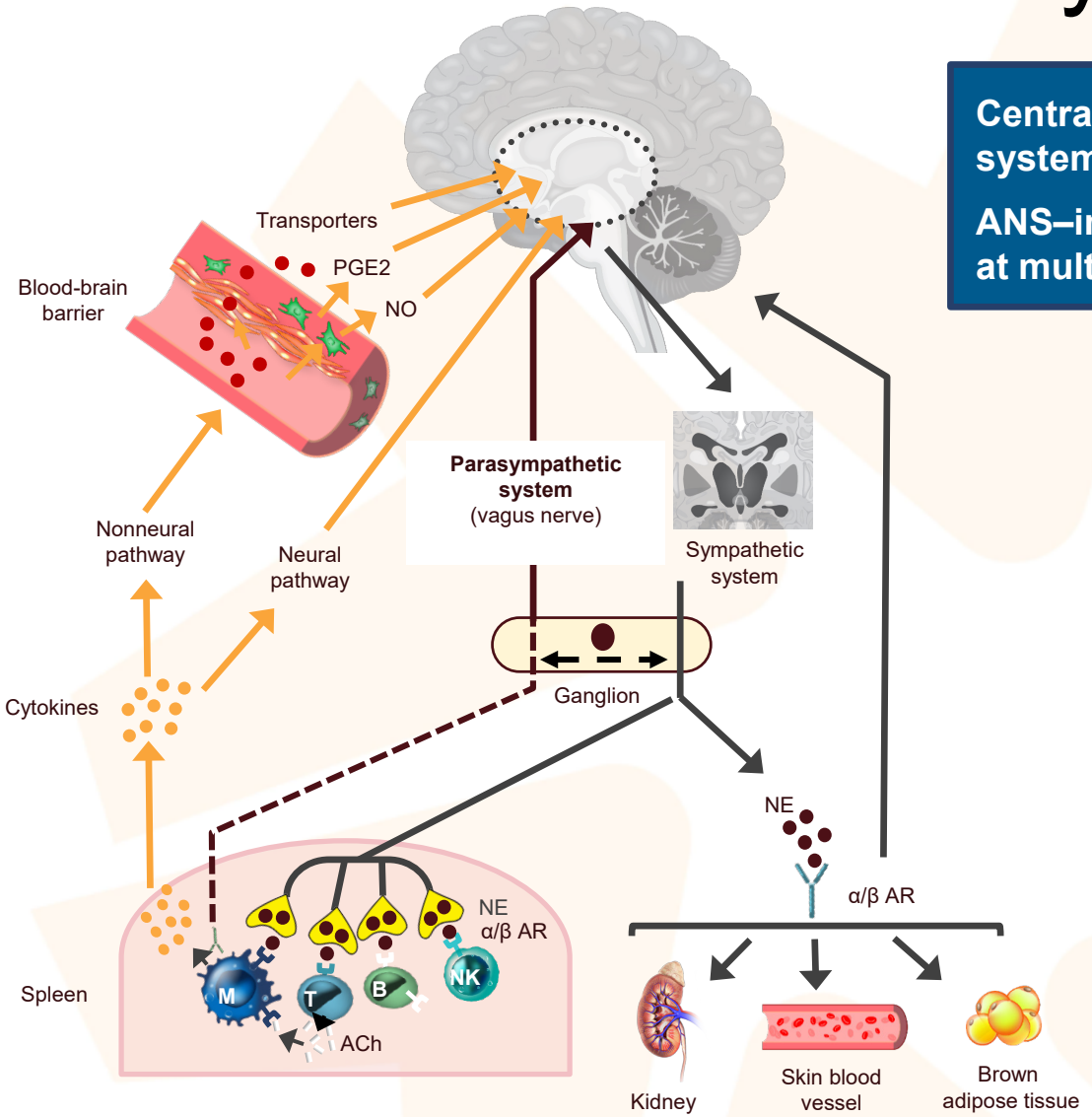


Jain R, et al. *Curr Diab Rep*. 2011;11(4):275-284.

Primer:
The ANS

- Sympathetic System
- Parasympathetic System

Sympathetic and Parasympathetic Arms of the ANS Exert Opposing Effects on the Immune System



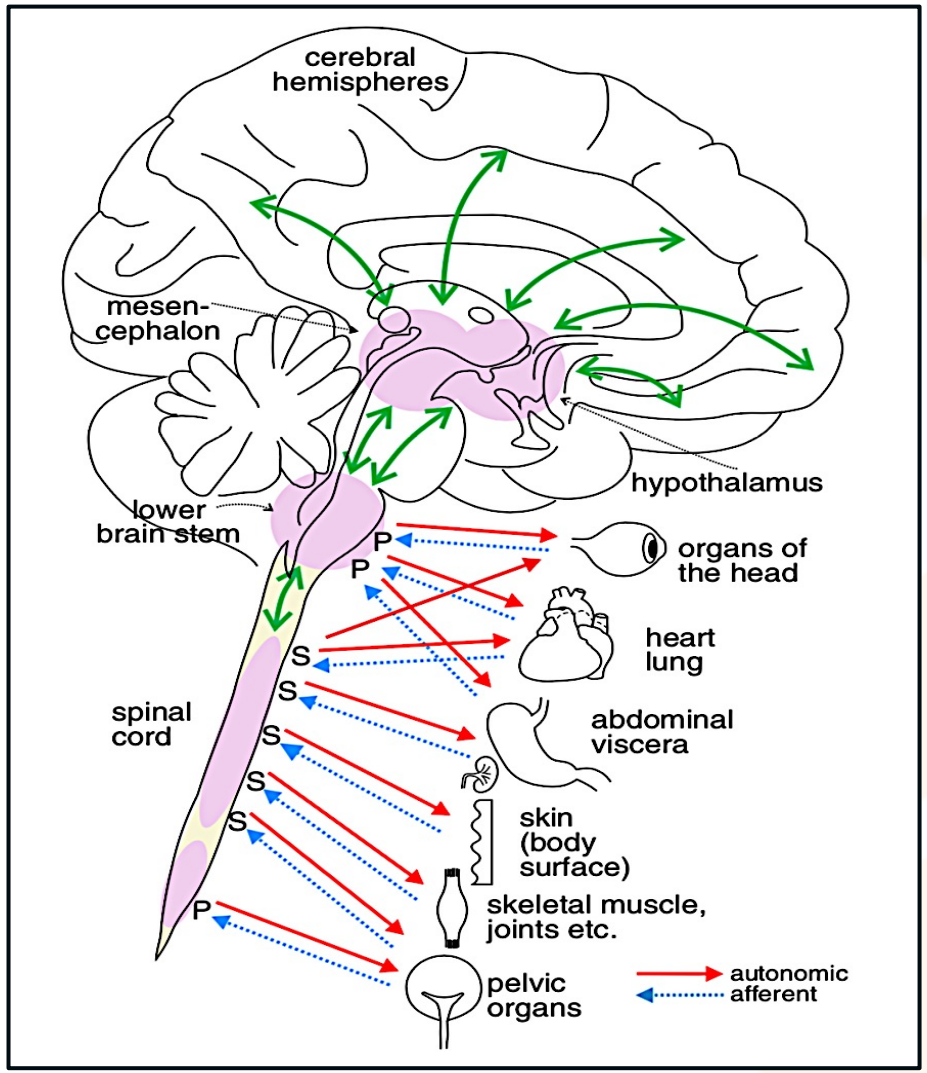
Central HPA–sympathetic system coupling

ANS–immune interactions at multiple CNS sites

AR = adrenergic receptor; B = B cell; M = macrophage; NO = nitric oxide; PGE2 = prostaglandin E2; T = memory T cell.

Kenney MJ, et al. *Compr Physiol*. 2014;4(3):1177-1200.

Sympathetic and Parasympathetic Systems:
Forever Intertwined and Exist in an Uneasy Embrace



Reciprocal communication between the brain and body tissues by efferent autonomic pathways and afferent pathways. The global autonomic centers in the spinal cord, lower and upper brain stem, and hypothalamus are shaded in violet. These centers consist of the neural circuits that are the bases of the homeostatic autonomic regulation and their coordination with the neuroendocrine, the somatomotor, and the sensory systems that establish behavior. The brain sends efferent commands to the peripheral target tissues through the peripheral autonomic pathways. The afferent pathways consist of groups of afferent neurons with unmyelinated or small diameter myelinated fibers. These afferent neurons monitor the mechanical, thermal, chemical and metabolic states of the body tissues.

P = parasympathetic; S = sympathetic.

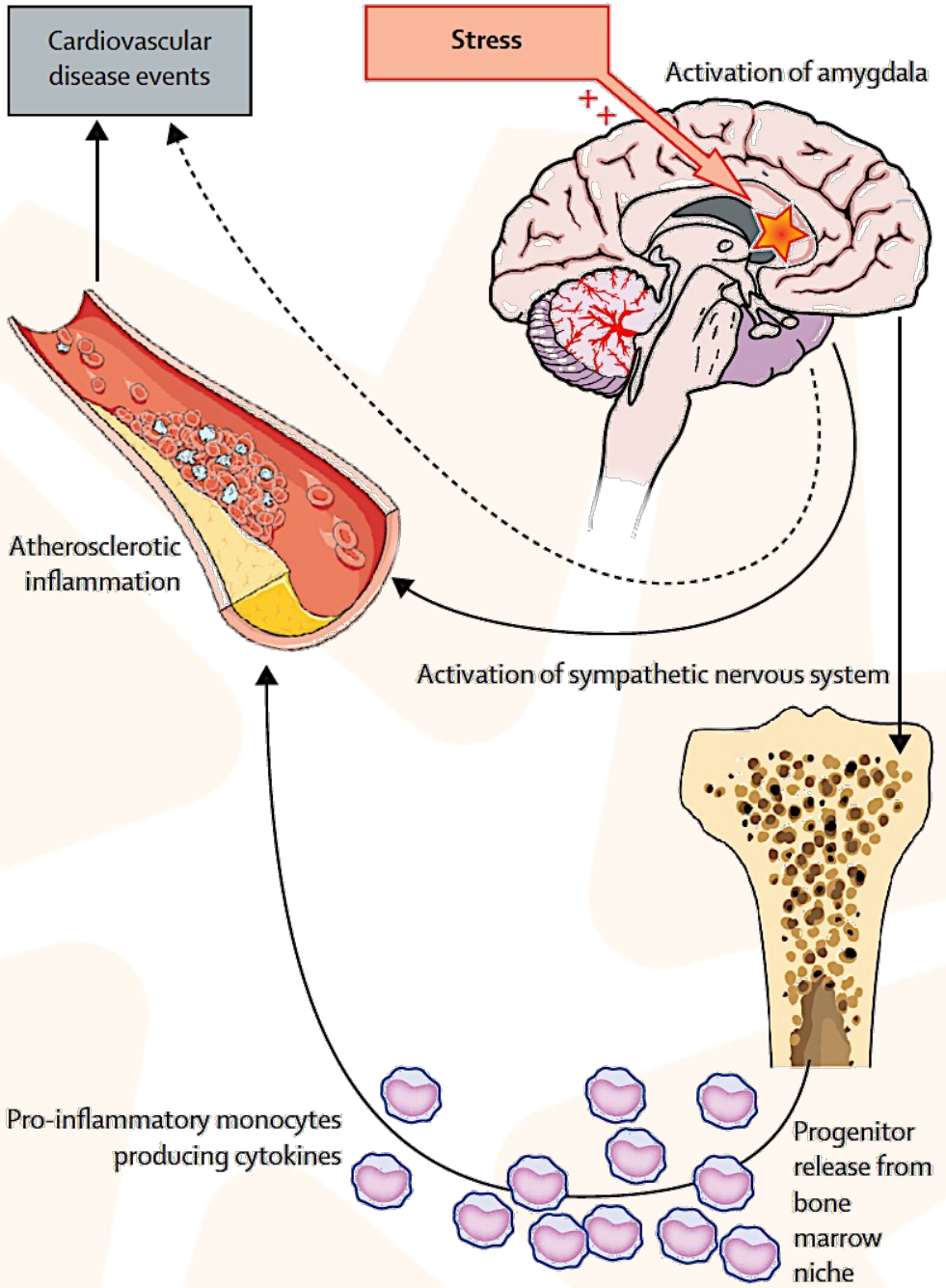
Jänig W. *Auton Neurosci*. 2014;182:4-14.

SNS, When Stressed, Can "Invade" Far-flung Places in the Body

Amygdala activity was associated with increased bone-marrow activity (r=.47; *P*<.0001)

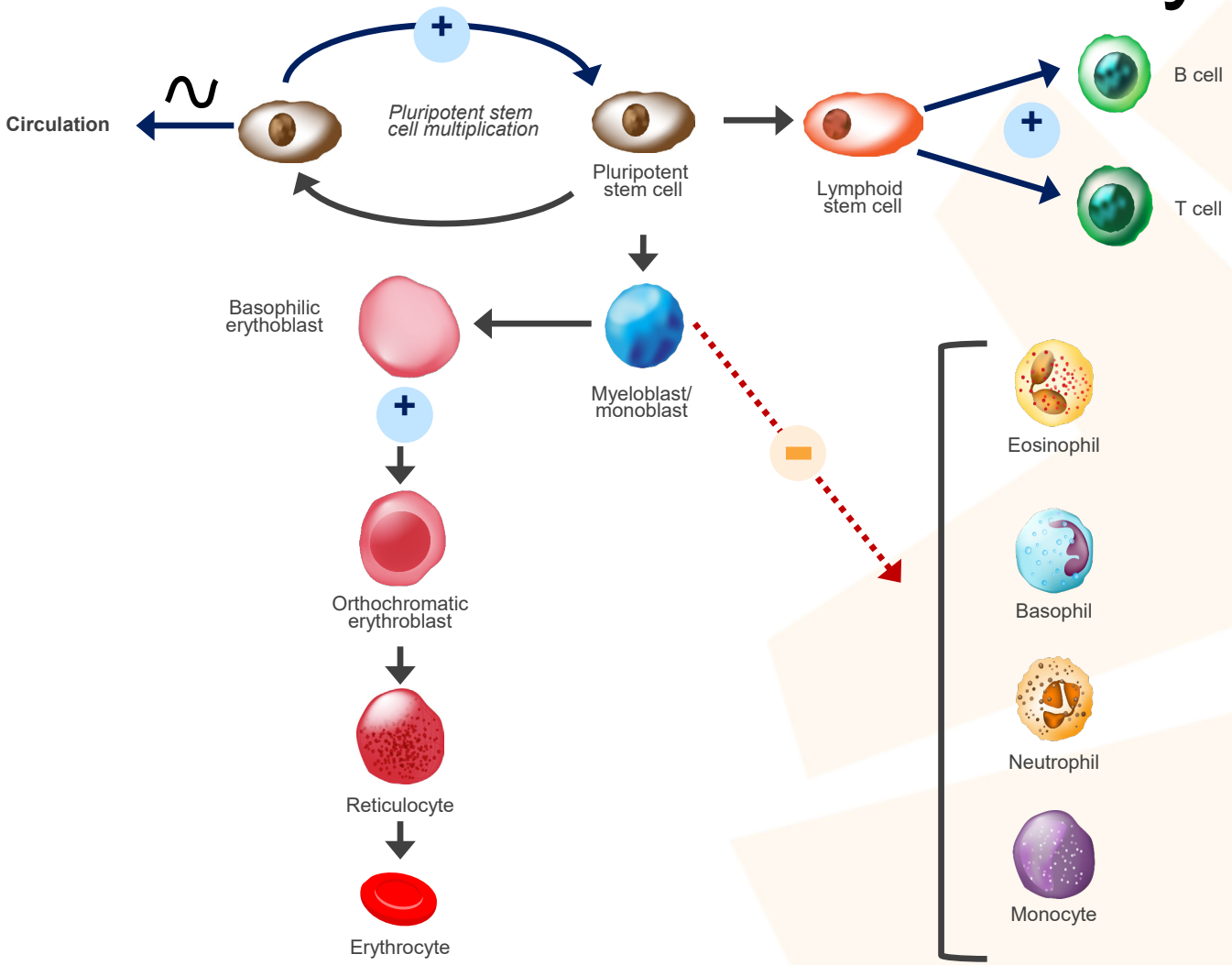
Amygdala hyperactivity increased arterial inflammation (r=.49; *P*<.0001)

Amygdala hyperactivity increased risk of cardiovascular disease events (standardized hazard ratio 1.59. *P*<.0001)



Tawakol A, et al. *Lancet*. 2017;389(10071):834-845.

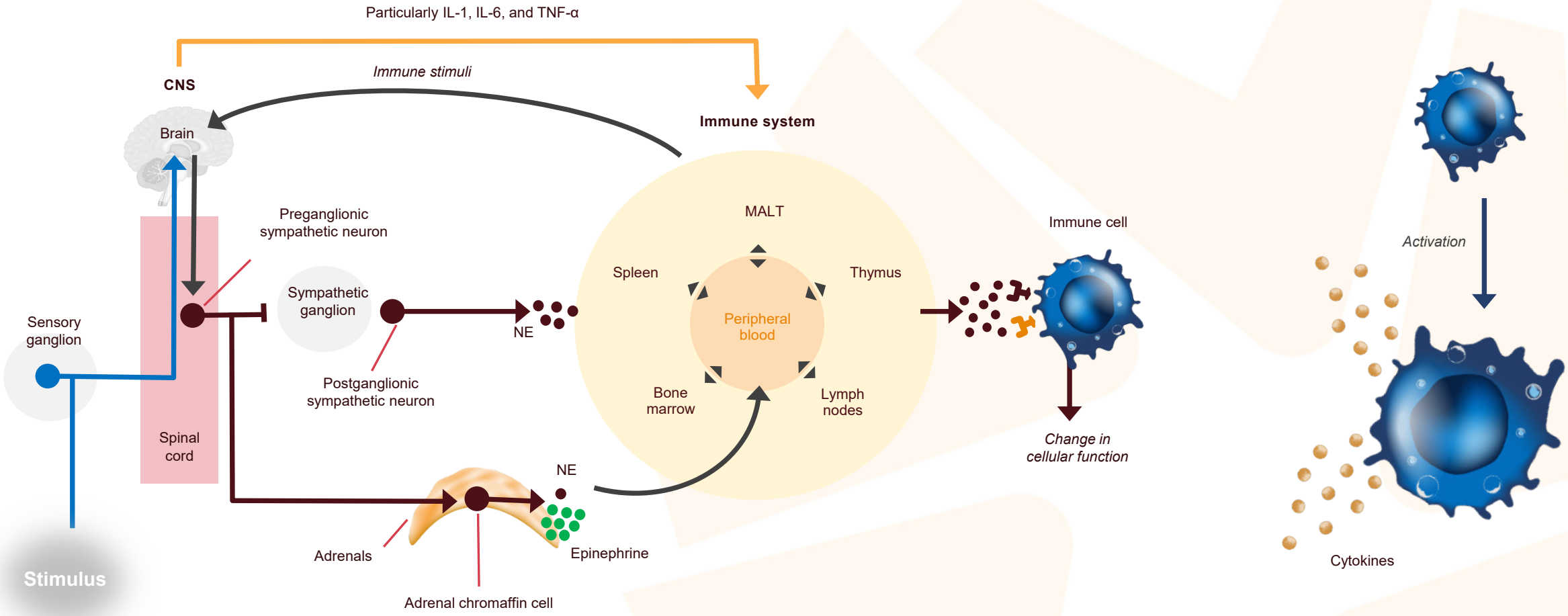
SNS Modulates Nearly Every Cell Line of the Immune System



Catecholamines, such as norepinephrine and epinephrine, impact immune cell proliferation

Bellinger DL, et al. *Auton Neurosci*. 2014;182:15-41.

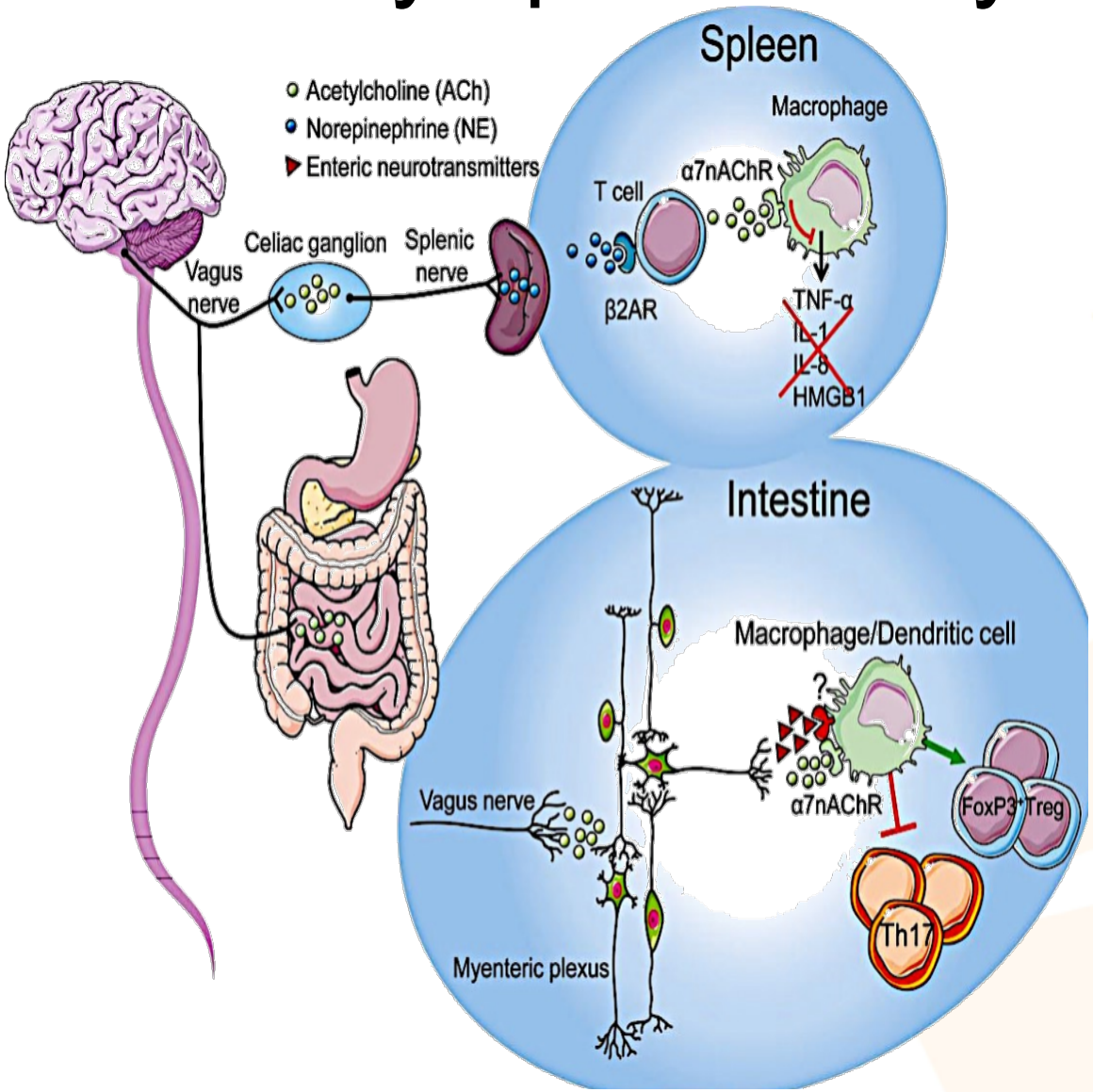
How the SNS Connects the CNS and Immune System



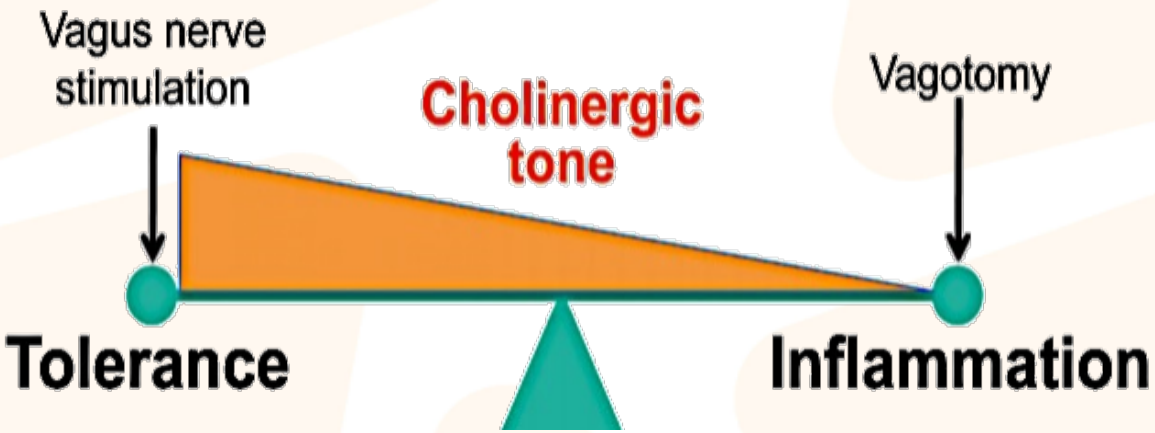
MALT = mucosa-associated lymphoid tissue.

Bellinger DL, et al. *Auton Neurosci*. 2014;182:15-41.

Parasympathetic System and Acetylcholine



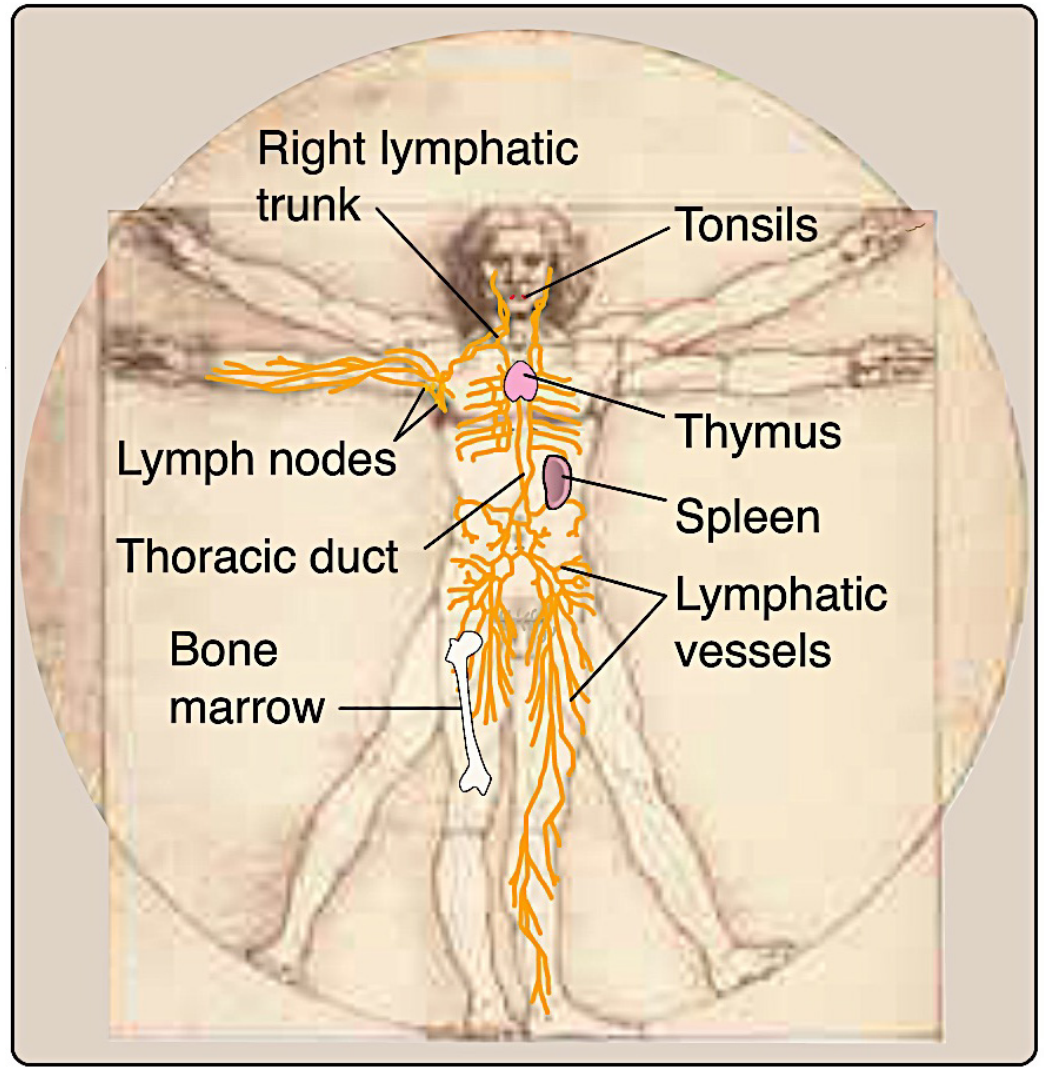
- Parasympathetic nerves supply every major organ system associated with inflammation
- The influence of the parasympathetic nerves extends to inflammatory cells which all express muscarinic receptors
- Muscarinic receptor signaling also stimulates proliferation and apoptosis of different inflammatory cells which potentially changes the overall inflammatory response



Scott GD, et al. *Chem Immunol Allergy*. 2012;98:48-69. Matteoli G, et al. *Gut*. 2013;62(8):1214-1222.

Primer:
Psycho-Immunology

The Major Players in the Immune System



Major “Macro” Members of the Immune System

- Bone Marrow
- Thymus
- Spleen
- Lymph Nodes
- Tonsils

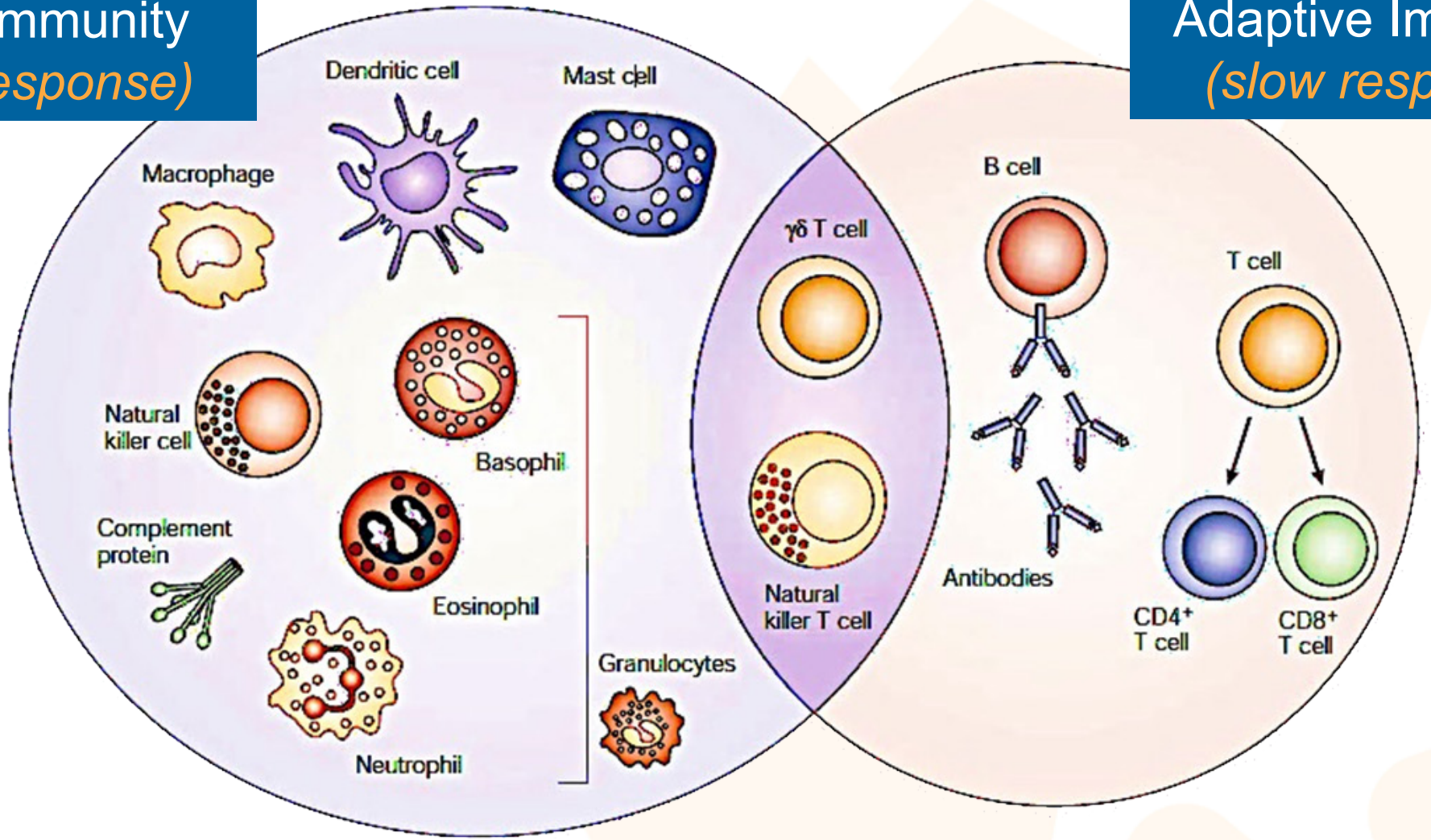
Immune System travels on 2 major highways:

- The Cardiovascular System
- The Lymphatic Circulatory System

Innate and Adaptive Immunity

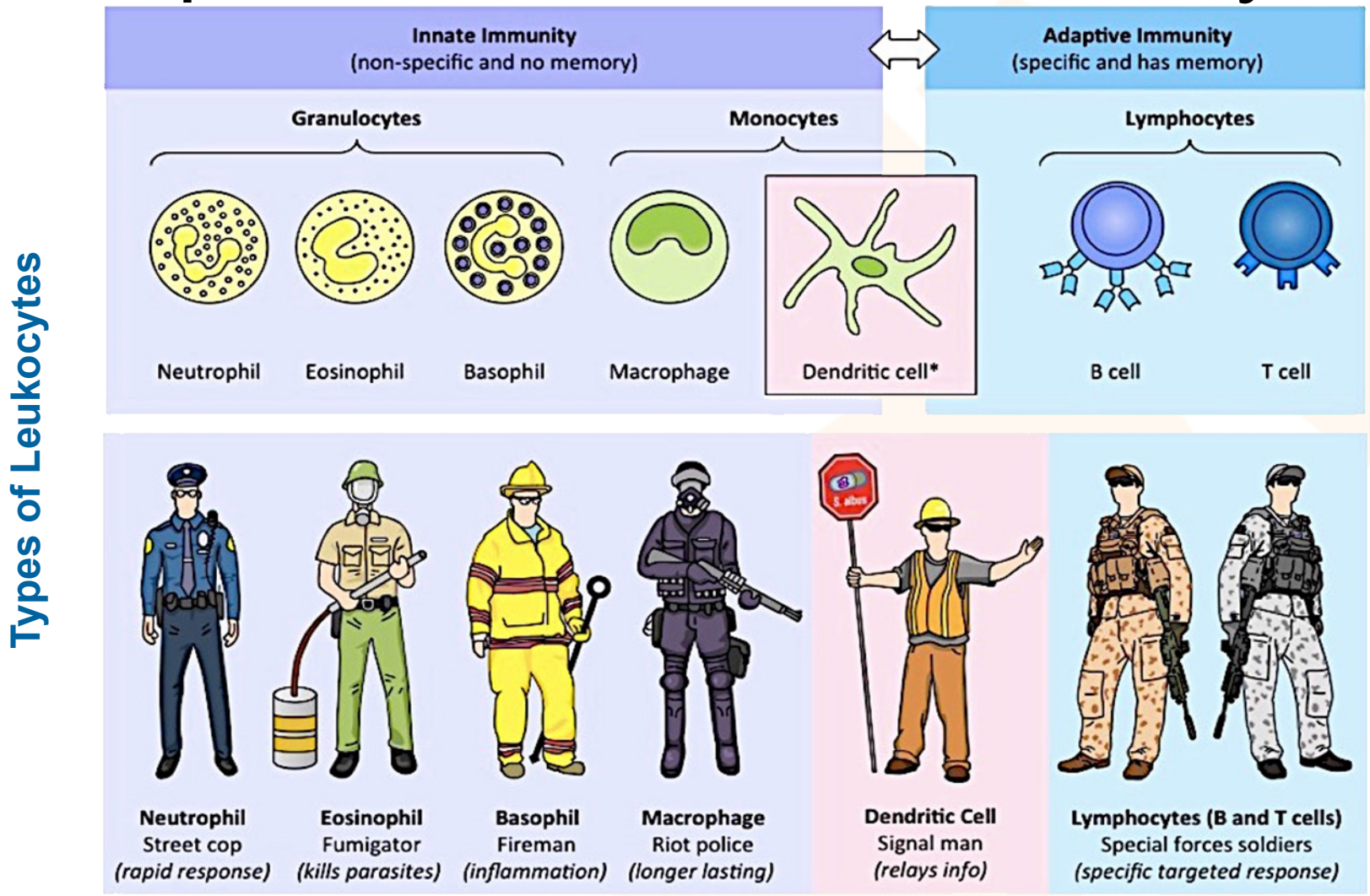
Innate Immunity
(rapid response)

Adaptive Immunity
(slow response)



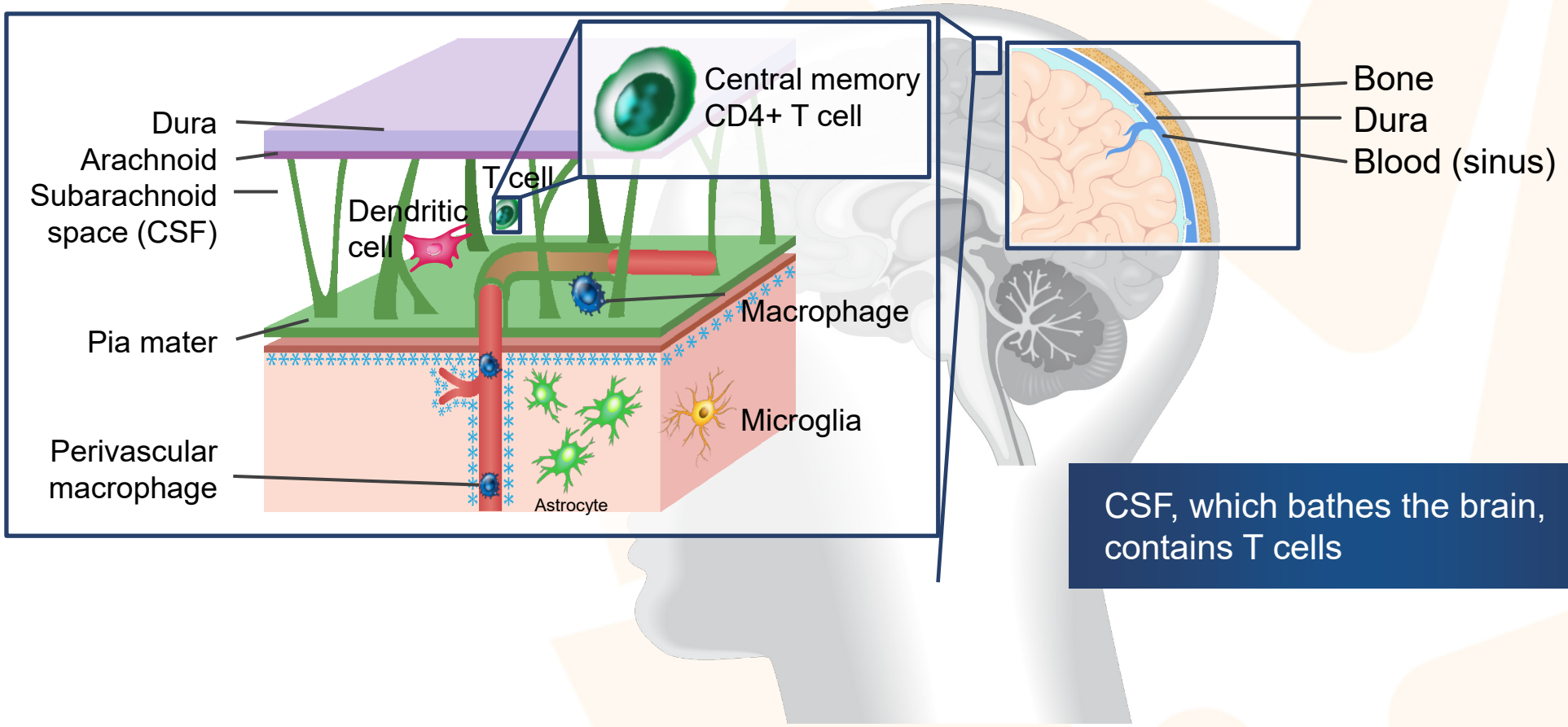
Dranoff G. *Nat Rev Cancer*. 2004;4(1):11-22.

Better Understanding of the Various Troops of the Neuro-Immune System



http://ib.bioninja.com.au/standard-level/topic-6-human-physiology/63-defence-against-infectio/types-of-leukocytes.html. Accessed May 14, 2018.

Immune Presence in the Brain is Far More Extensive Than Previously Known



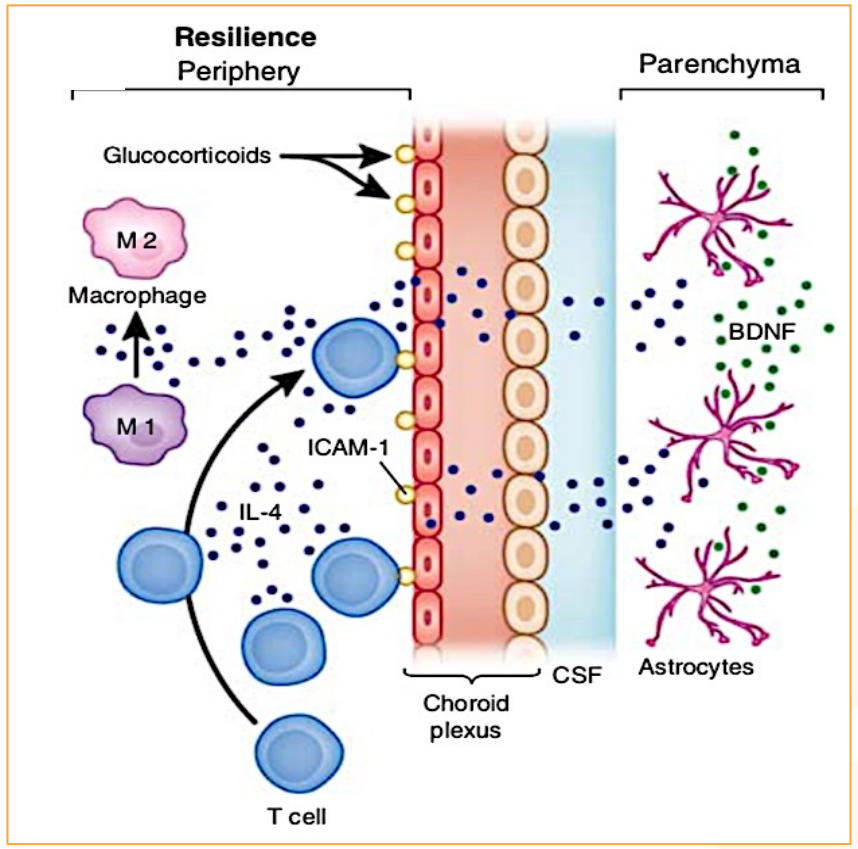
CSF, which bathes the brain, contains T cells

CSF = cerebrospinal fluid.

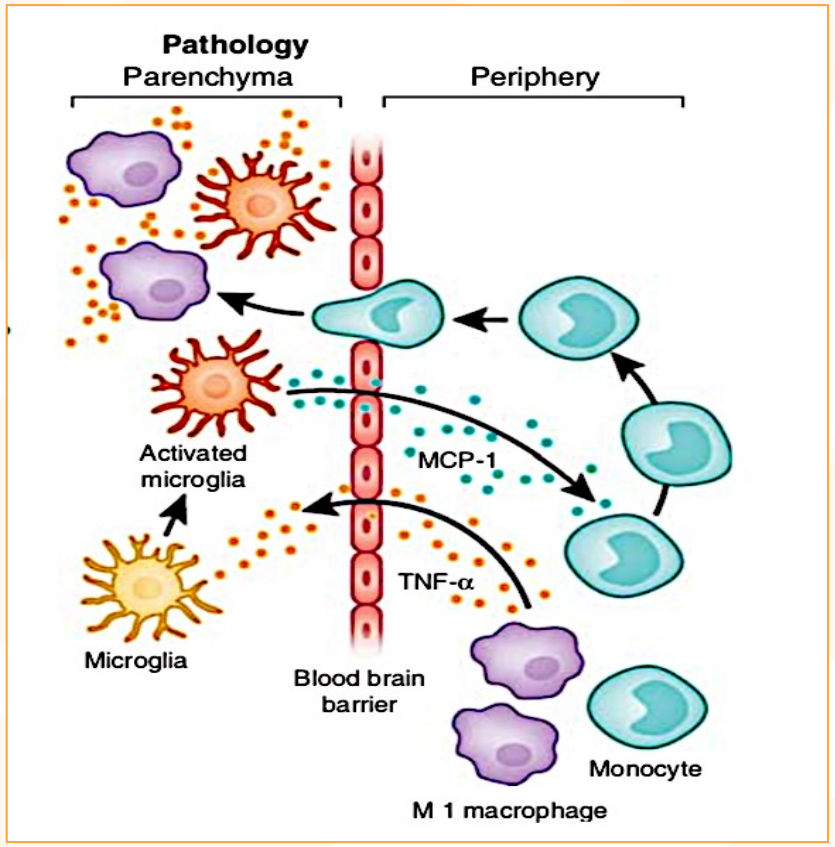
Prinz M, et al. *Nat Neurosci*. 2017;20(2):136-144.

How “Peripheral” (body) Inflammation Causes “Central” (brain) Inflammation

In Health



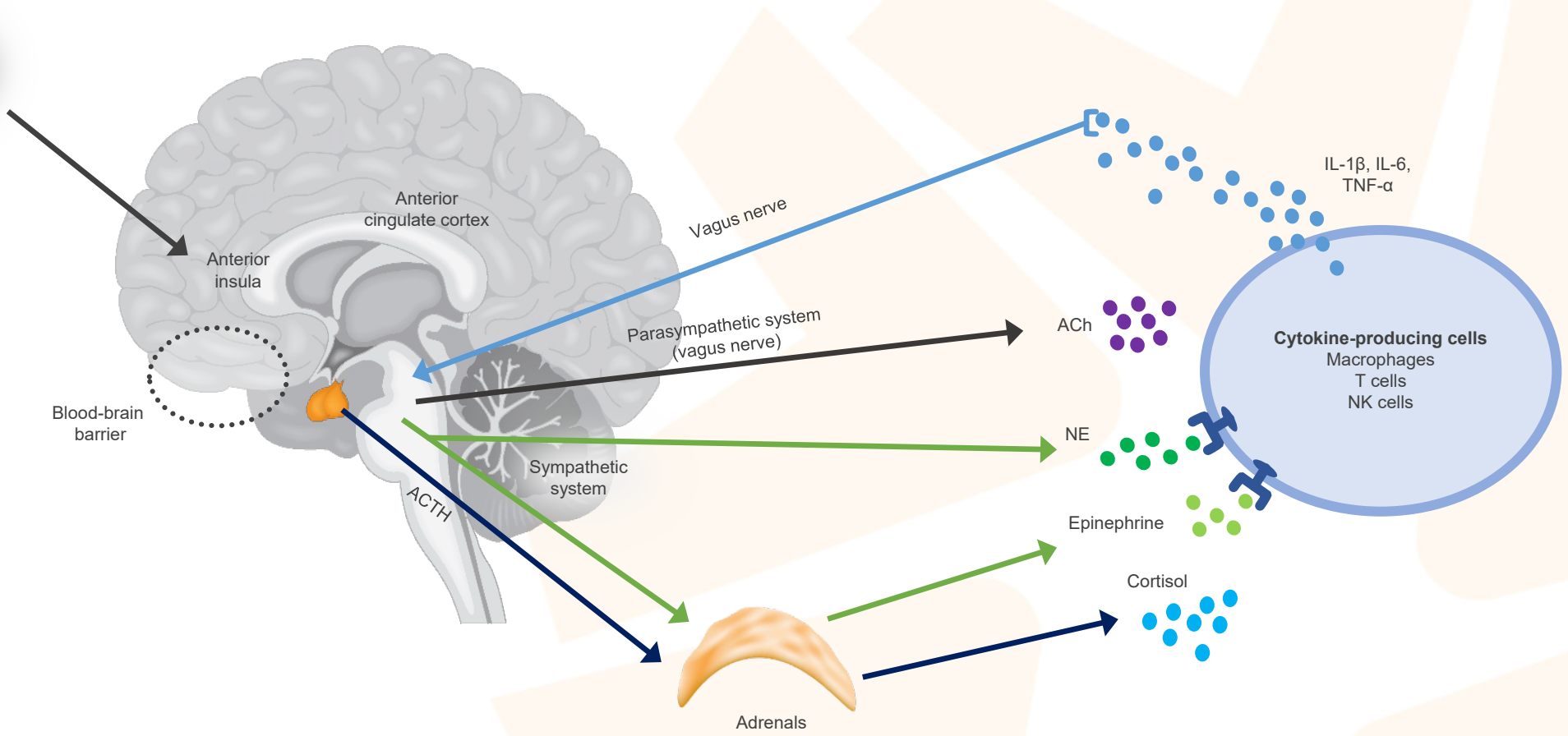
In Sickness



ICAM = intercellular adhesion molecule; BDNF = brain-derived neurotrophic factor; MCP = monocyte chemoattractant protein.

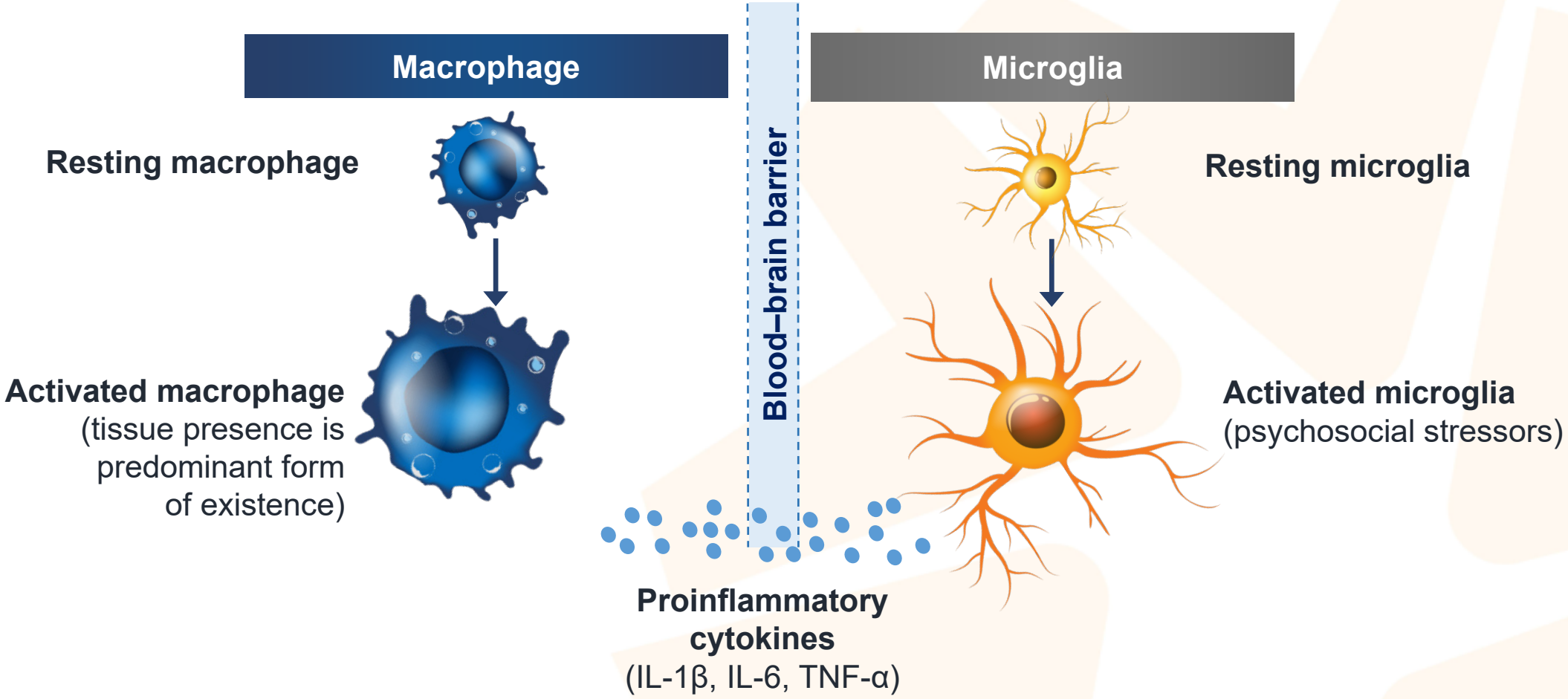
Haroon E, et al. *Neuropsychopharmacology*. 2012;37(1):137-162.

Multiple Brain–Body Pathways Connect Stress to Inflammation



Slavich GM, et al. *Psychol Bull*. 2014;140(3):774-815.

Macrophage–Microglia Interaction



Haroon E, et al. *Neuropsychopharmacology*. 2012;37(1):137-162. Raison CL, et al. *Trends Immunol*. 2006;27(1):24-31.

Why are Cytokines So Important in the PNI World?

Which Best Describes the Relationship between Increased Cytokine Levels and Depression?

1. **Increased Cytokine levels Cause Depression?**

2. **Depression causes Increased Cytokine levels?**

Answer is:
Yes and Yes

YES – Increased Cytokine Levels Cause Depression

YES – Depression Causes Increased Cytokine Levels

Jeon SW, et al. *World J Psychiatry*. 2016;6(3):283-293.

Here are 3 Reasons Why Cytokines are Important

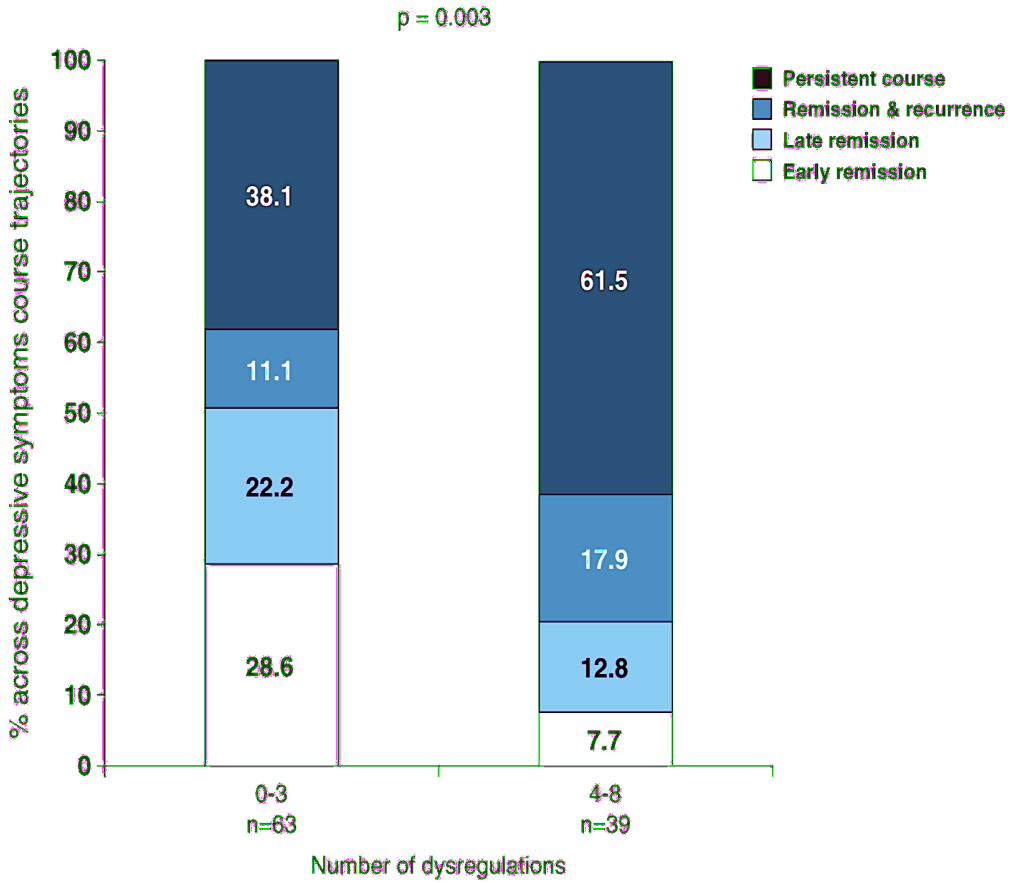
* Because Cytokines have easy access to CNS – primarily Astrocytes and Microglia
* Because Astrocytes and Microglia respond to peripheral cytokines and themselves produce cytokines
* Because Cytokines are Profound Precipitators of Neuropsychiatric Disorders (depression, delirium)

Chapter 4

Clinical Interventions Formulated Based on PNI Principles

Why Psychiatry Should Care about Inflammation and PNI Disturbances: *Chronicity and Lower Response Rates*

Course trajectories for recently started antidepressant users according to the number of inflammatory and metabolic dysregulations



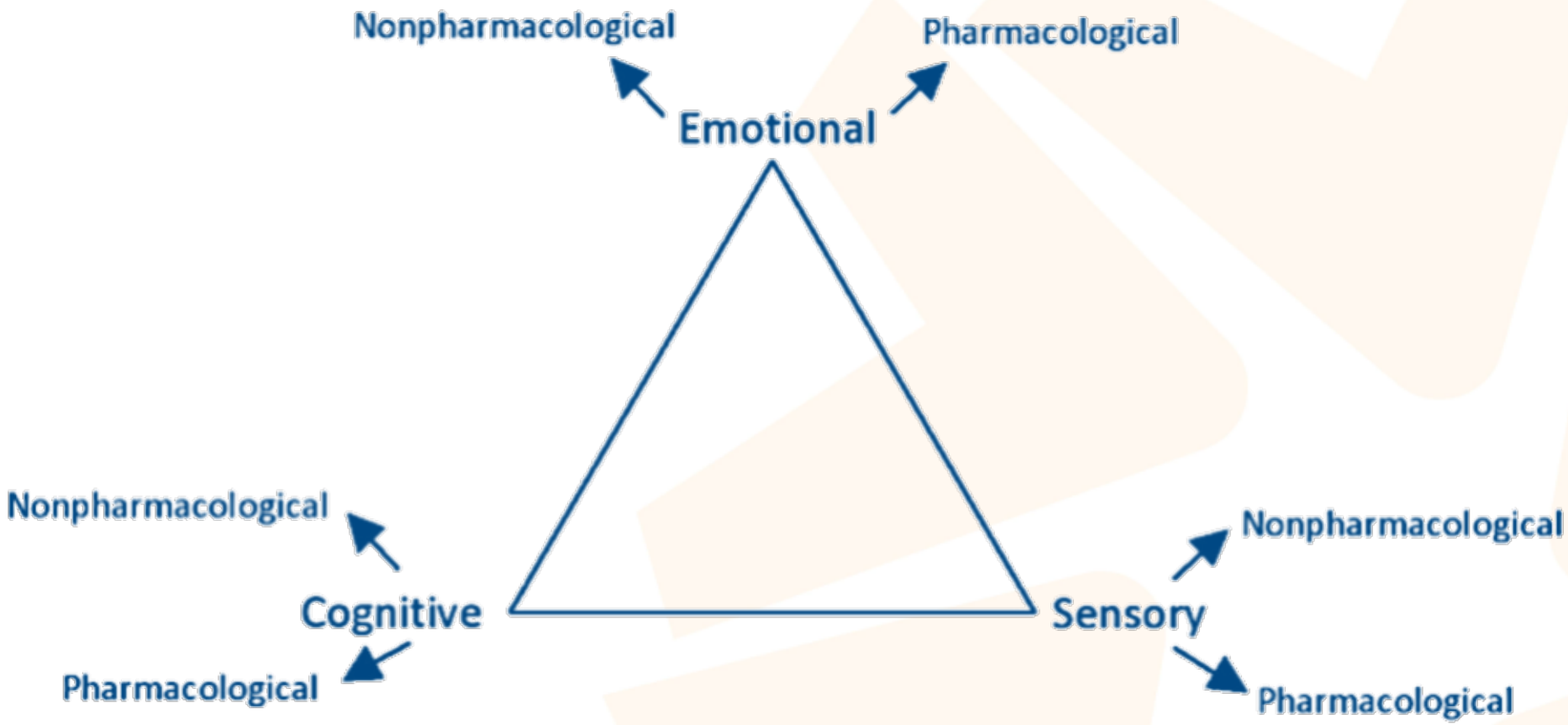
Inflammatory (CRP, IL-6, TNF-α) and metabolic (waist circumference, triglycerides, high-density lipoprotein [HDL] cholesterol, blood pressure, fasting glucose) factors were measured at baseline

Having ≥ 4 dysregulations lead to **6.85 INCREASED odds** of chronic depression

CRP = C-reactive protein.

Vogelzangs N, et al. *Neuropsychopharmacology*. 2014;39(7):1624-1634.

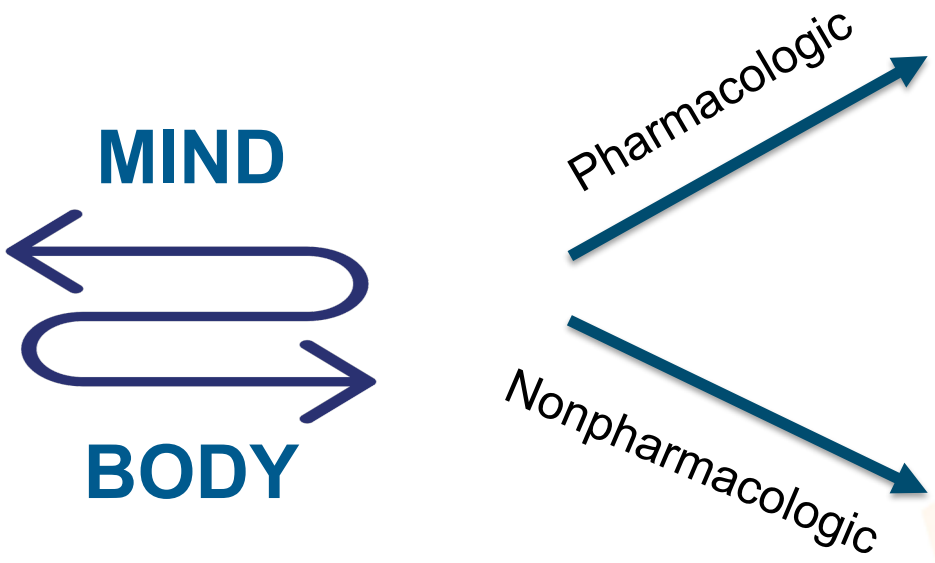
Therapeutic Options Available Through the SEC Model (Based on PNI Principles)



SEC = sensory, emotional, cognitive.

Jain R, et al. *South African Journal of Diabetes*. 2016;9(3):7-11.

Targeting with PNI as a Treatment Framework



Immunologic targets
Cytokines (eg, TNF-α, IL-1, IL-6)
Cytokine-signaling pathways (eg, COX, p38 MAPK, NF-κB)
Chemokines
T cells (eg, T regs, Th17, T effs)
Neurotransmitter targets
IDO and its metabolites (eg, KYN, QUIN, KA)
Tetrahydrobiopterin (BH4)
Neuroendocrine targets
Glucocorticoid receptor
Protein kinase-A
Autonomic nervous system targets
Parasympathetic outflow pathways (eg, vagal nerve stimulator, α7nAChR)
Non-pharmacologic targets
Adiposity
Diet (eg, *n*-3 PUFAs, Mediterranean diet)
Exercise
CAM (eg, meditation, Tai Chi, yoga)

Haroon E, et al. *Neuropsychopharmacology*. 2012;37(1):137-162.

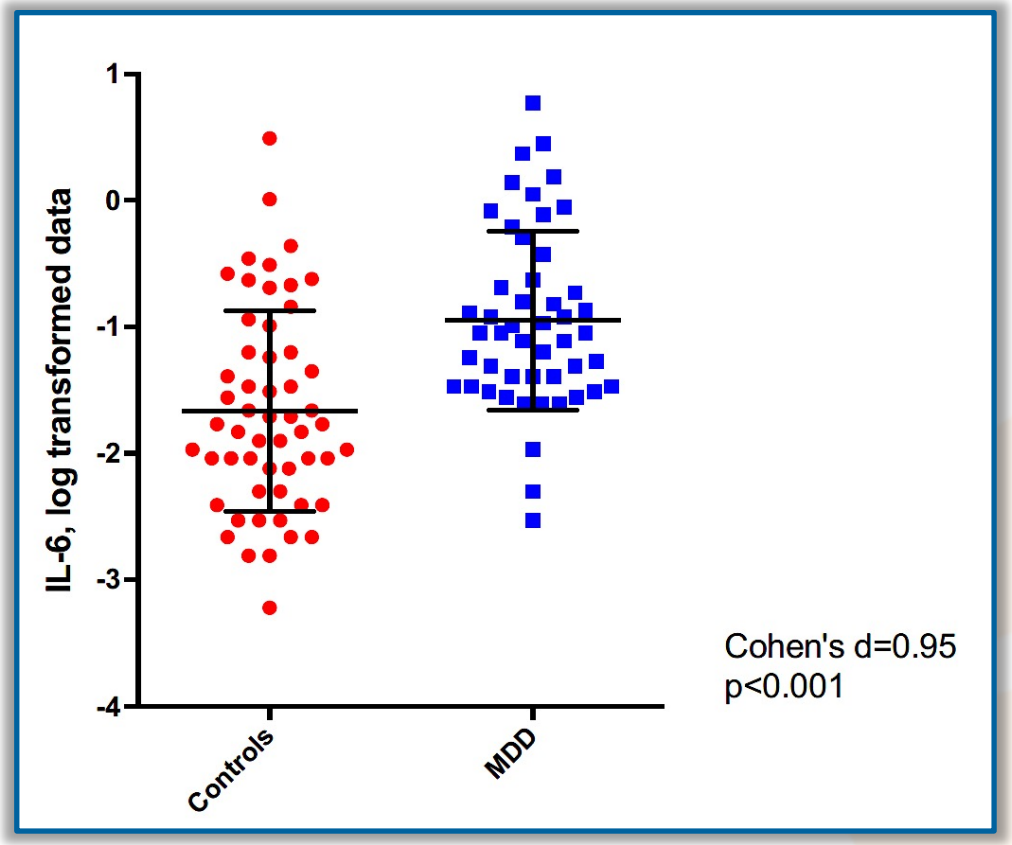
It Appears There are 2 Key Fundamental Laws We Clinicians Must Follow

In order to minimize the impact of immune – brain – metabolic changes, we must:

1. Seek to drive psychiatric illnesses to Remission
2. Seek to introduce Mental Wellness Concepts into the care of patients

Why Optimal Treatment Response is So Critical:
Impact on the PNI System

50 unmedicated MDD participants
and 55 healthy controls



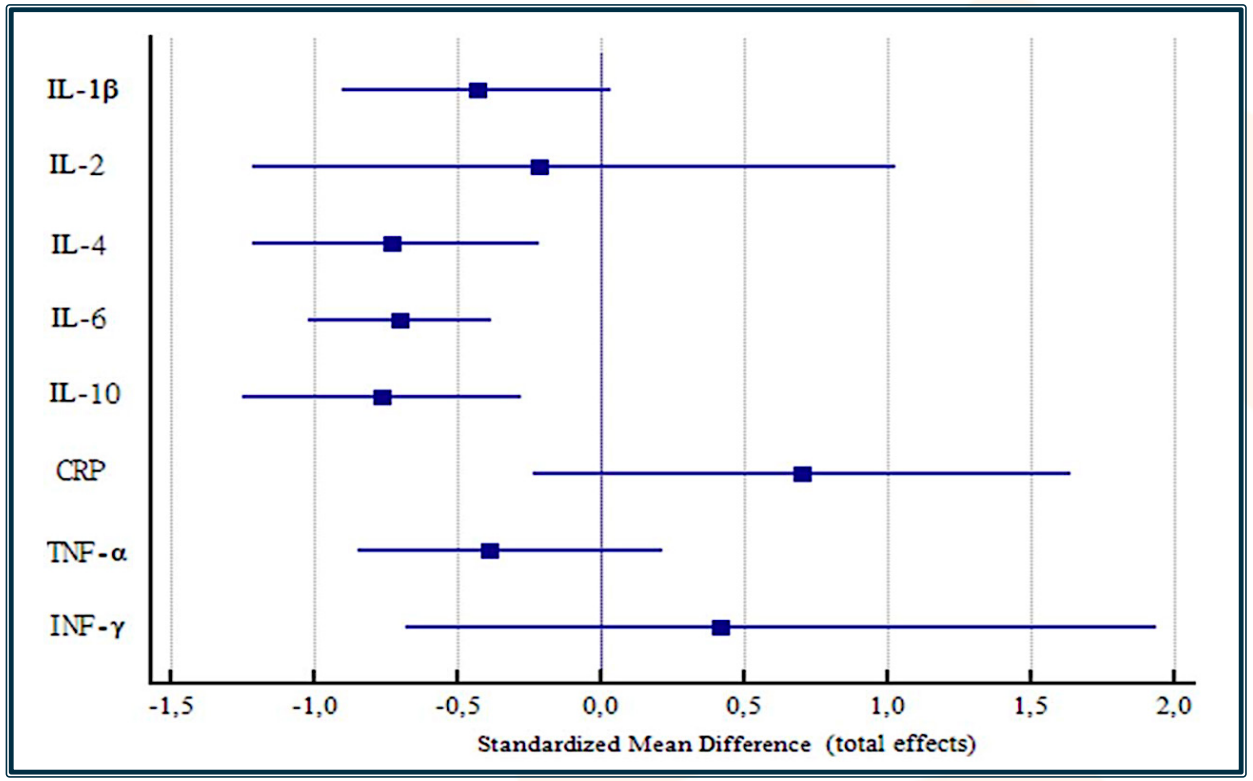
A subgroup of 22 MDD participants underwent open-label SSRI antidepressant treatment for 8 weeks

- **Responders** showed a significant **decrease** in IL-6 levels over the course of treatment (t=2.81, *P*=.019)
- **Non-responders** showed a nominal, but not statistically significant **increase** in IL-6 (t=1.76, *P*=.130)

MDD = major depressive disorder; SSRI = selective serotonin reuptake inhibitor.

Lindqvist D, et al. *Psychoneuroendocrinology*. 2017;76:197-205.

Do Our Current, "Standard" Antidepressants Impact Inflammation? *Answer*: Yes and No



Meta-analysis of 32 studies with 1137 participants treated with "classic" antidepressants

*YES – **significant decreases of IL-4, IL-6, and IL-10 in MDD participants after antidepressant treatment**

*NO – **no significant effect of antidepressant medication on IL-2, TNF-α, IFN-γ, and CRP**

Więdłocha M, et al. *Prog Neuropsychopharmacol Biol Psychiatry*. 2018;80(Pt C):217-226.

Antidepressants Do Have an Anti-inflammatory Signal

Author	Type of patients	Antidepressant(s)	Duration	Cytokines assessed	Outcome
Brunoni et al. [2014]	103 unipolar depressive patients	Sertraline (SSRI)	6 weeks	IL-2, IL-4, IL-6, IL-10, IL-17, INF-γ, TNF-α	↓IL-2, ↓IL-4,↓IL-6, ↓IL-10,↓IL-17,↓ IFN-γ
Basterzi et al. [2005]	23 MDD and 23 controls	Not specified (SSRI)	6 weeks	IL-6	↓IL-6
Eller et al. [2008]	100 MDD and 45 controls	Escitalopram (SSRI)	12 weeks	sIL-2R, IL-8, TNF-α	↓sIL-2R
Eller et al. [2009]	28 MDD and 45 controls	Escitalopram + bupropion (SSRI + atypical AD)	6 weeks	sIL-2R, IL-8, TNF-α	↑IL-8
Hernandez et al. [2008]	31 MDD and 22 controls	Fluoxetine, paroxetine, sertraline (SSRI)	52 weeks	IFN-γ, IL-1β, IL-2, IL-4, IL-10, IL-13	↑IFN-γ, ↑IL-1β, ↓IL-2, ↓IL-4, ↓IL-10, ↓IL-13
Lanquillon et al. [2000]	24 MDD and 15 controls	Amitriptyline (TCA)	6 weeks	IL-6, TNF-α	↓IL-6, ↓TNF-α
Piletz et al. [2009]	22 MDD and 17 controls	Venlafaxine (SNRI)	8 weeks	IL-1β, TNF-α	No significant change
Sluzewska et al. [1995]	22 MDD and 11 controls	Fluoxetine (SSRI)	8 weeks	IL-6	↓IL-6
Taraz et al. [2013]	50 MDD patients	Sertraline (SSRI)	12 weeks	IL-6, TNF-α, IL-10	↓IL-6, ↓TNF-α, ↑IL-10
Tousoulis et al. [2009]	250 with HF (154 with MDD)	Not specified (SSRI and SNRI/TCA)	6 months	IL-6, TNF-α	SNRI/TCA: ↓TNF-α
Tuglu et al. [2003]	26 MDD and 17 controls	Sertraline, fluoxetine, citalopram, fluvoxamine, paroxetine (SSRI)	6 weeks	TNF-α	↓TNF-α
Vogelzangs et al. [2012]	1132 current depression; 789 remitted depression; 494 controls	Not specified (SSRI, TCA and SNRI)	8 years	IL-6, TNF-α	SSRI: ↓IL-6
Yoshimura et al. [2009]	51 MDD and 30 controls	Paroxetine, sertraline, fluvoxamine (SSRI); milnacipran (SNRI)	8 weeks	IL-6, TNF-α	↓IL-6

Kopschina Feltes P, et al. *J Psychopharmacol*. 2017;31(9):1149-1165.

NSAIDs – Anti-Inflammatory Medication Treatment of Depression: *Preliminary Data Promising*

Study	Patient Population (Placebo Group/ Intervention Group-1/ Intervention Group-2)					Diagnosis	Treatment (N)	Treatment Effect
	N (Female)	Mean Age, Yrs (SD)	Mean Depressive Episodes (SD)	Duration Current Episode (SD)	Comorbidity			
NSAIDs Add-on treatment								
Müller, 2006	20 (12)/ 20 (8)	44.3 (13.5)/ 44.5 (11.6)	2.4 (1.2)/ 2.5 (2.3)	18.7 wks (20.8)/ 17.0 wks (21.7)	None	$HAMD_{17}$ 15-38	6 weeks NARI + placebo (20) vs. NARI + celecoxib 400mg (20)	Celecoxib superior
Akhondzadeh, 2009	20 (12)/ 20 (13)	34.2 (4.96)/ 34.65 (6.76)	3.52 (0.84)/ 3.40 (0.70)	n.a.	None	$HAMD_{17}$ ≥18	6 weeks SSRI + placebo (20) vs. SSRI + celecoxib 400mg (20)	Celecoxib superior
Hashemian, 2011	20 (20)/ 20 (20)	36.20 (12.79)/ 34.78 (7.39)	First-episode patients	Antidepressant naive	None	$HAMD_{17}$ 18-36	8 weeks SSRI + placebo (20) vs. SSRI + celecoxib 200mg (20)	Celecoxib superior
Abbasi, 2012	20 (6)/ 20 (7)	34.2 (6.9)/ 35.1 (8.0)	3.6 (0.9)/ 3.7 (0.8)	2.7 months (1.0)/ 2.4 months (0.9)	None	$HAMD_{17}$ ≥18	6 weeks SSRI + placebo (20) vs. SSRI + celecoxib 400mg (20)	Celecoxib superior. IL-6 predicted response
Monotherapy								
Fields, 2012	1,083 (488)/ 726 (342)/ 719 (330)	74.4/ 74.5/ 74.5	Only depressive symptoms	Not relevant	Family history of dementia	GDS	12 months placebo (1,038) vs. celecoxib 400 mg (726) vs. naproxen 440 mg (719) daily	No difference
Iyengar, 2013	297 (199)/ 593 (409)/ 607 (413)	61/ 61/ 61	Only depressive symptoms	Not relevant	Active osteoarthritis	PHQ-9	6 weeks placebo (297) vs. ibuprofen 2,400 mg or naproxen 1,000 mg (593) vs. celecoxib 200 mg (607)	Celecoxib, naproxen and ibuprofen superior to placebo

NSAID = nonsteroidal anti-inflammatory drug.

Kohler O, et al. *Curr Neuropharmacol*. 2016;14(7):732-742.

Other Anti-Inflammatory Medication Treatment of Depression: *Preliminary Data*

Study	Patient Population (Placebo Group/ Intervention Group-1/ Intervention Group-2)					Diagnosis	Treatment (N)	Treatment Effect
	N (Female)	Mean Age, Yrs (SD)	Mean Depressive Episodes (SD)	Duration Cur-rent Episode	Comorbidity			
Statins – add-on treatment								
Ghanizadeh 2013	34 (21)/ 34 (22)	32.5 (10.2)/ 31.7 (9.3)	n.a.	n.a.	None	$HAMD_{17}$ ≥18	6 weeks SSRI + placebo (34) vs. SSRI + lovastatin 30 mg (34)	Lovastatin superior
Gougol, 2015	22 (16)/ 22 (13)	34.2 (10.8)/ 36.4 (8.1)	n.a.	n.a.	None	$HAMD_{17}$ ≥22	6 weeks SSRI + placebo (22) vs. SSRI + simvastatin 20 mg (22)	Simvastatin superior
Minocycline – add-on treatment								
Miyaoka, 2012	25 (12)	46.9 (10.2)	n.a.	58.6 wks (46.8)	None	$HAMD_{21}$ ≥25	Open-label, not placebo-controlled: 6 weeks SSRI + 150 mg minocycline	Minocycline showed safe antidepressant effects
Pioglitazone Add-on treatment								
Sepanjnia, 2012	20 (15)/ 20 (14)	32.7 (5.4)/ 31.4 (5.4)	3.5 (0.8)/ 3.6 (0.8)	n.a.	None	$HAMD_{17}$ ≥22	6 weeks SSRI + placebo (20) vs. SSRI + pioglitazone 30 mg (20)	Pioglitazone superior
Monotherapy								
Kashani, 2013	20 (20)/ 20 (20)	20.3 (4.6)/ 21.2 (3.3)	Only depressive symptoms	Not relevant	PCOS, obesity (BMI≥27)	$HAMD_{17}$ ≤19	6 weeks metformin 1,500 mg (25) vs. pioglitazone 30 mg (25)	Pioglitazone superior to metformin

Kohler O, et al. *Curr Neuropharmacol*. 2016;14(7):732-742.

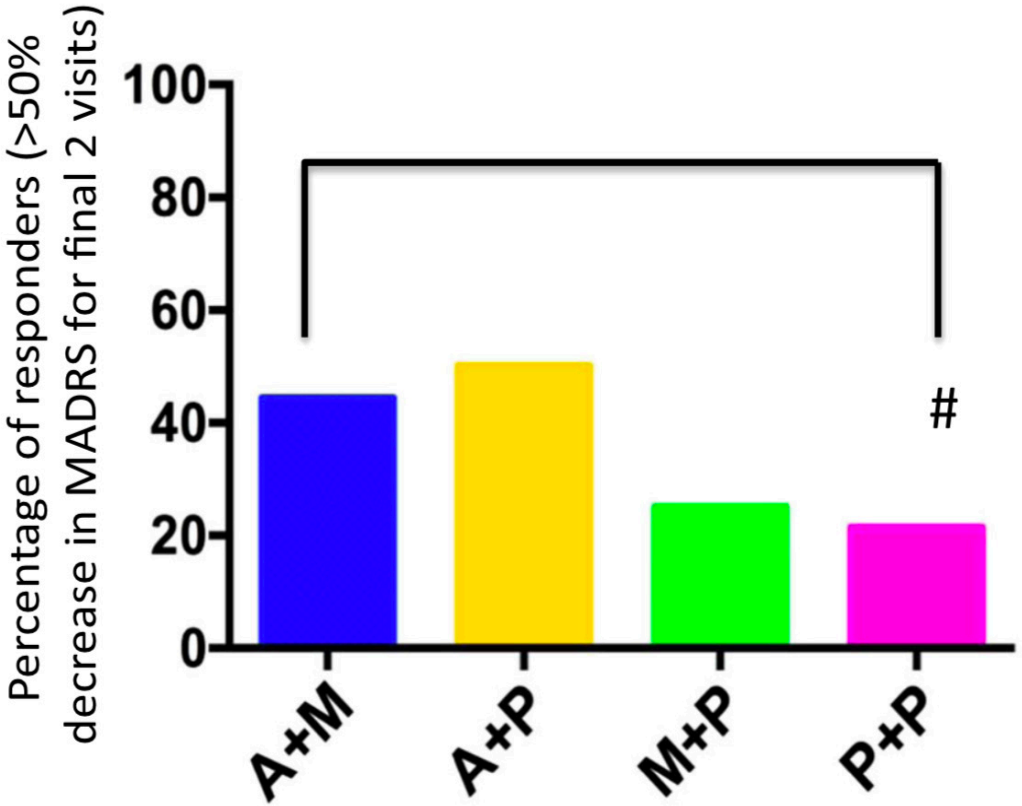
Cytokine Inhibitors – Anti-Inflammatory Medication Treatment of Depression: *Promising Early Evidence*

Study	Patient Population (Placebo Group/ Intervention Group-1/ Intervention Group-2)					Diagnosis	Treatment (N)	Treatment Effect
	N (Female)	Mean Age, Yrs (SD)	Mean Depressive Episodes (SD)	Duration Current Episode (SD)	Comorbidity			
Cytokine-inhibitors - monotherapy								
Tyring, 2006	307 (93)/ 311 (108)	45.6 (12.1)/ 45.8 (12.8)	Only depressive symptoms	Not relevant	Stable psoriasis	$HAMD_{17}$ BDI	12 weeks placebo (309 vs. etanercept 50 mg (311) injections twice weekly	Etanercept superior
Menter, 2010	52 (18)/ 44 (13)	43.3 (13.1)/ 45.6 (11.7)	Only depressive symptoms	Not relevant	Psoriasis	ZDS	12 weeks placebo (52) vs. adalimumab 40 mg (44) injections every other week	Adalimumab superior
Langley, 2010	410 (127)/ 820 (263)	47.0 (12.5)/ 46.0 (12.1)	Only depressive symptoms	Not relevant	Psoriasis	HADS-D	24 weeks placebo (410 vs. ustekinumab 45 mg (409) vs. ustekinumab 90 mg (411)	Ustekinumab superior
Raison, 2013	30 (20)/ 30 (20)	44.3 (9.4)/ 42.5 (8.2)	8.7 (24.8)/ 7.8 (24.8)		None	$HAMD_{17}$	12 weeks three infusions placebo (30) vs. infliximab 5mg/kg (30	Infliximab superior if CRP>5 mg/L

Kohler O, et al. *Curr Neuropharmacol*. 2016;14(7):732-742.

Bipolar Depression and PNI Based Interventions:
Minocycline + Aspirin

99 depressed outpatients with BD were enrolled in a 6-week, double-blind, placebo-controlled trial, and randomized to 1 of 4 groups: active minocycline (100 mg bid) + active aspirin (81 mg bid) (M + A); active minocycline + placebo aspirin (M + P); placebo-minocycline + active aspirin (A + P); and placebo-minocycline + placebo aspirin (P + P).

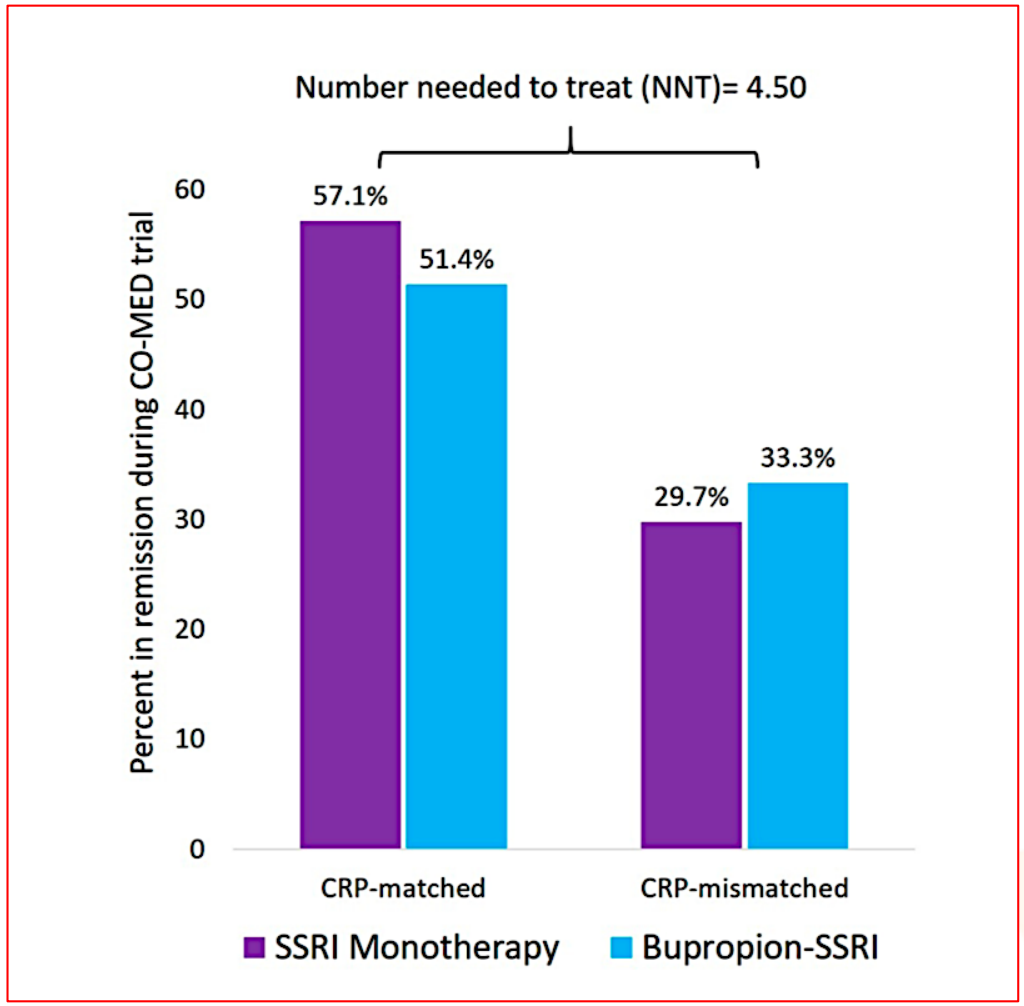


- There was a significant 3-way interaction between aspirin, minocycline, and IL-6, indicating that response to minocycline was significantly greater in participants in the M + P group with higher IL-6 concentrations
- Participants in the M + P group who responded to treatment had significantly greater decreases in IL-6 levels between baseline and visit 7 vs non-responders

Minocycline + Aspirin group showed a greater response rate than the P + P group (*P* [one-tailed]=.034, OR = 2.93, NNT = 4.7).

#*P*<.05 (one-tailed test). BD = bipolar disorder; MADRS = Montgomery-Åsberg Depression Rating Scale; NNT = number needed to treat.
Savitz JB, et al. *Transl Psychiatry*. 2018;8(1):27.

Psychopharmacology and PNI: *Can This Emerging Information Help Us Improve Outcomes in Psychiatry?*



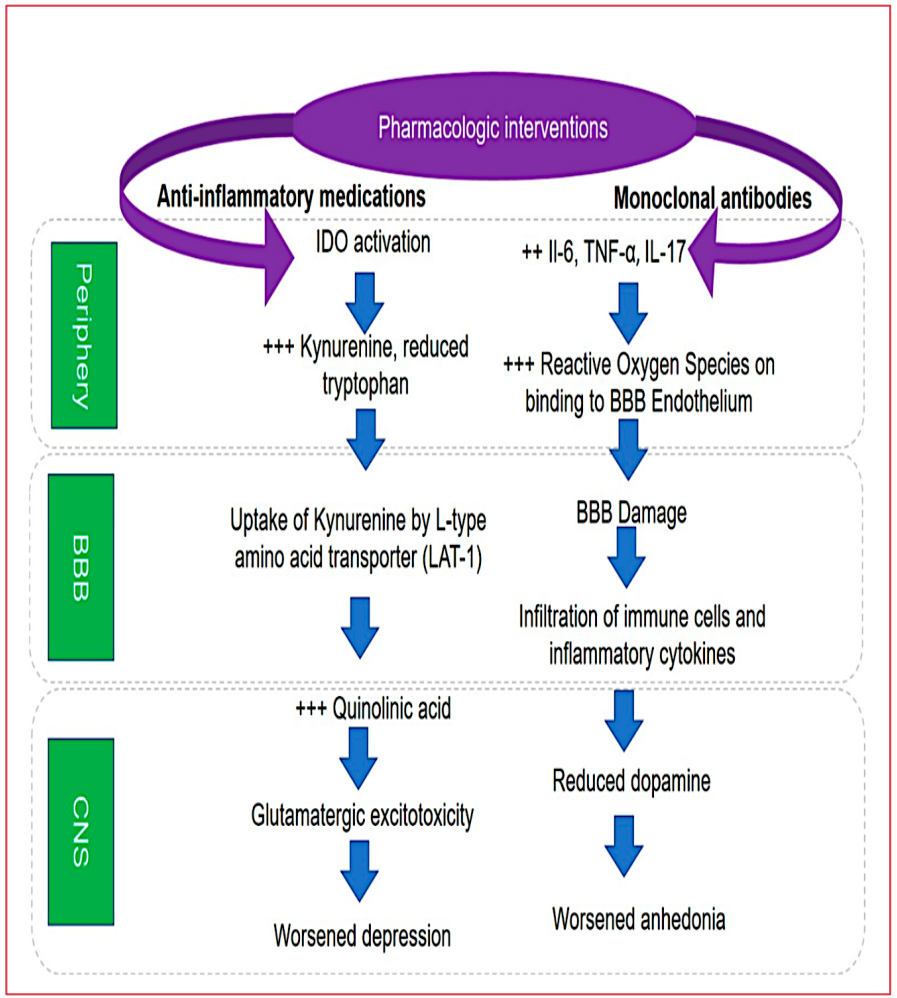
- **CRP matched treatment assignment refers to participants who received escitalopram only and had CRP < 1 mg/L, whereas those with CRP > 1 mg/L received bupropion-SSRI combination**
- **CRP mismatched is when above rule does not apply to sample**

Remission Rates:

- **CRP mismatched remission rate = 30.9%**
- **CRP matched remission rate = 53.1%**

Jha MK, et al. *Int J Mol Sci*. 2018;19(1).

Future Directions: *Psychopharmacology and PNI*



2 distinct pharmacologic interventions with the potential to reduce depressive symptom symptom severity. In the first pathway, activation of IDO results in severity.

In the first pathway, activation of IDO results in increased levels of kynurenine, converted to quinolinic acid by microglial cells.

This results in glutamatergic excitotoxicity and depressive symptoms cells.

Blockade by a pharmacologic agent can disrupt this cascade and reduce depressive symptoms and mitigate CNS effects of peripheral inflammation.

In the second pathway, similarly, anti-cytokine treatments may be effective in depressed patients with elevated levels of cytokines.

Treatments may be effective in depressed patients with elevated levels of inflammatory cytokines (IL-6, IL-17, and TNF-α) which result in BBB dysfunction.

IDO = indoleamine oxygenase; BBB = blood–brain barrier.

Jha MK, et al. *Int J Mol Sci*. 2018;19(1).

Nonpharmacologic PNI-Based Interventions to Improve Outcomes

There are Many *"2 for the Price of 1"* PNI Informed Interventions Available to Clinicians

We have identified 5 such interventions. This is based on strength of scientific evidence and our clinical experience.

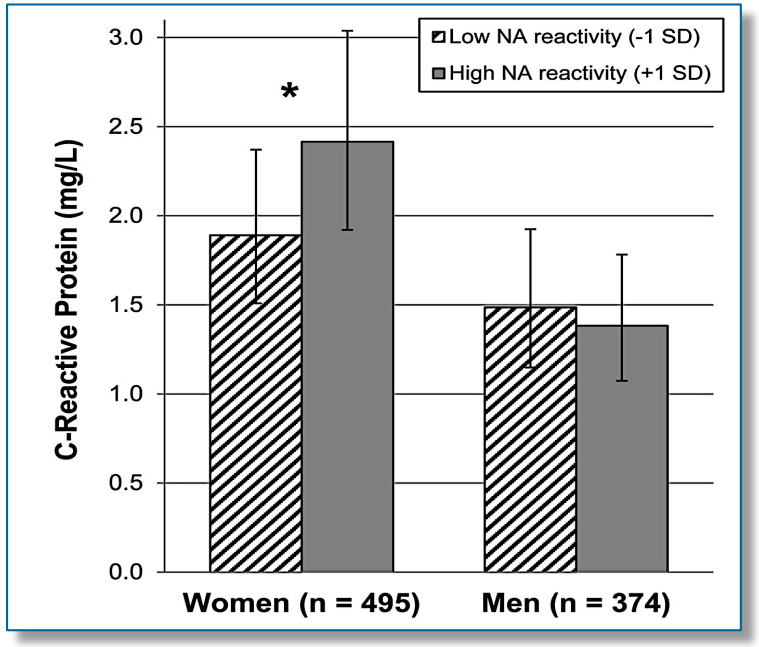
- **Exercise**
- **Mindfulness**
- **Optimized Sleep**
- **Optimized Nutrition**
- **Optimized Socialization**

Jain S, et al. Presented at: 29th Annual US Psychiatric and Mental Health Congress; October 2016; San Antonio, Texas.

Question: Do Either Negative Affect or Positive Affect Impact Inflammation?

A cross-sectional sample of 872 adults from the National Study of Daily Experiences (sub-study of Midlife in the United States II) reported daily stressors and affect

Answer: Both Negative Affect and Positive Affect Matter in Terms of Inflammatory Markers



Women who experienced greater NA had greater CRP levels (*P*=.03)

In other words, the presence of NA is inflammatory.

AND

People who experienced greater decreases in PA on days when stressors occurred (ie, PA reactivity) had elevated IL-6 (*P*=.01)

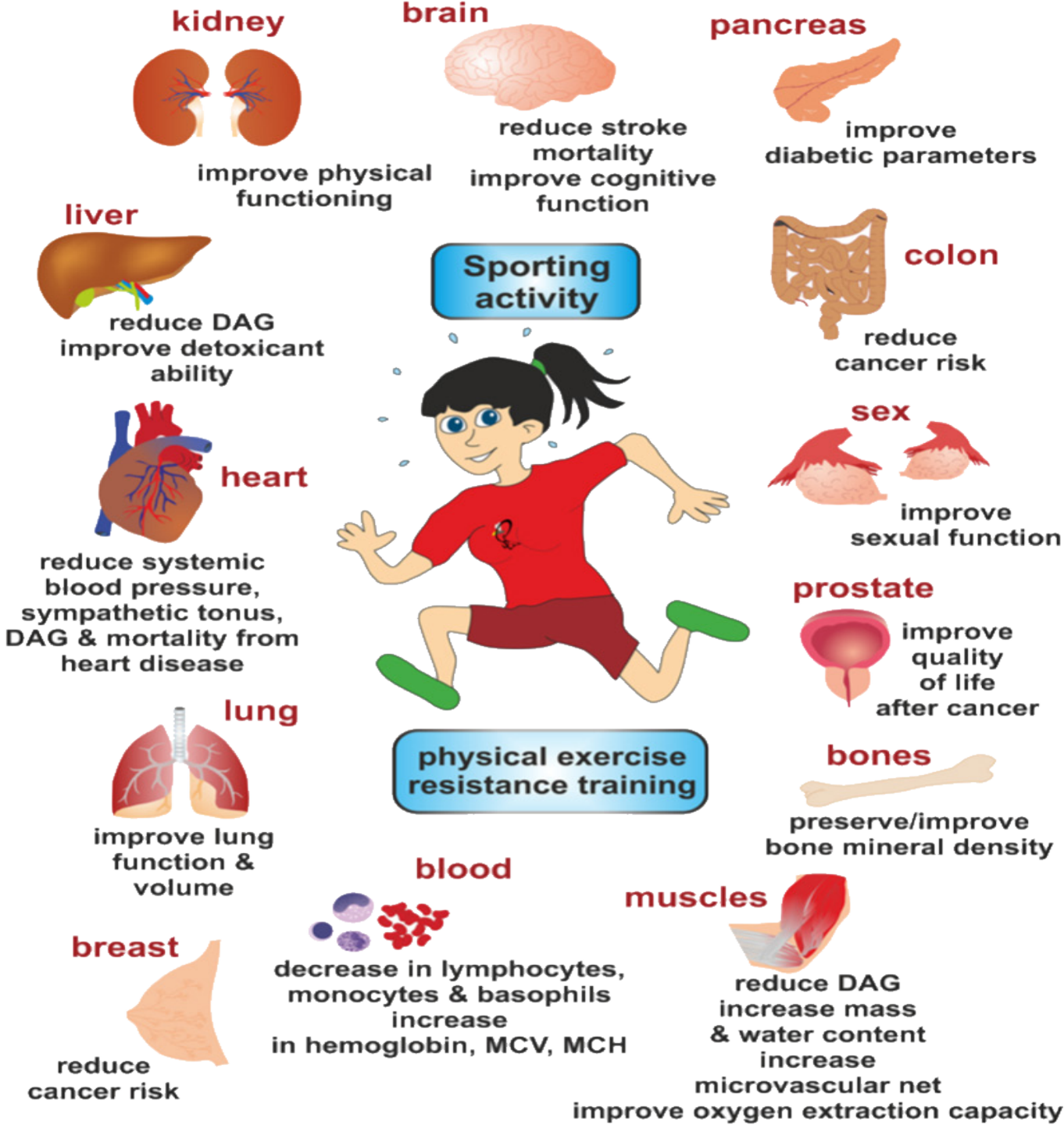
In other words, the loss of PA is inflammatory.

NA = negative affect; PA = positive affect.

Sin NL, et al. *Health Psychol*. 2015;34(12):1154-1165.

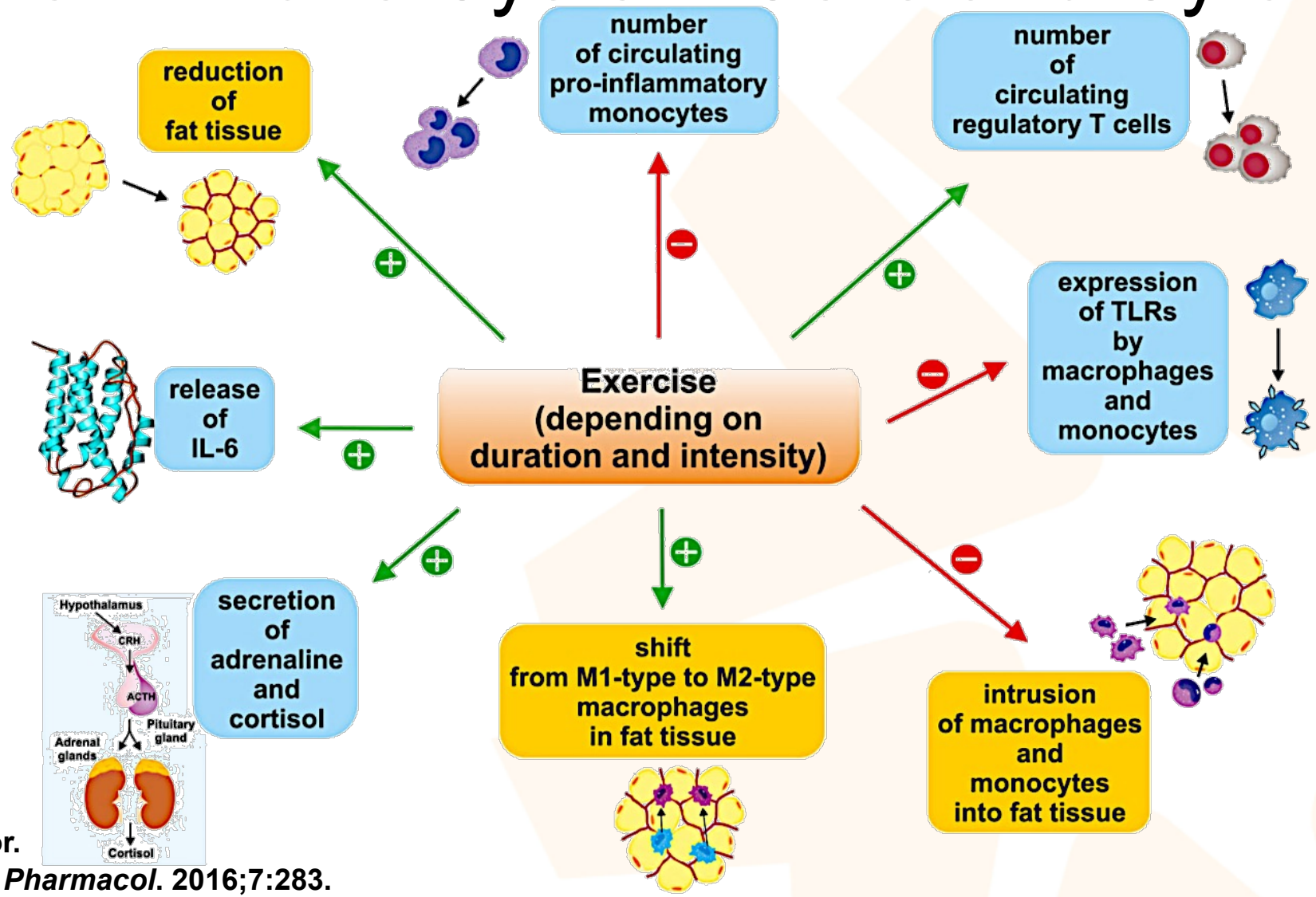
EXERCISE
and Its Connection to the PNI System

Exercise:
Its Direct and Indirect Effects on the Human Being



Schon HT, et al. *Front Pharmacol*. 2016;7:283.

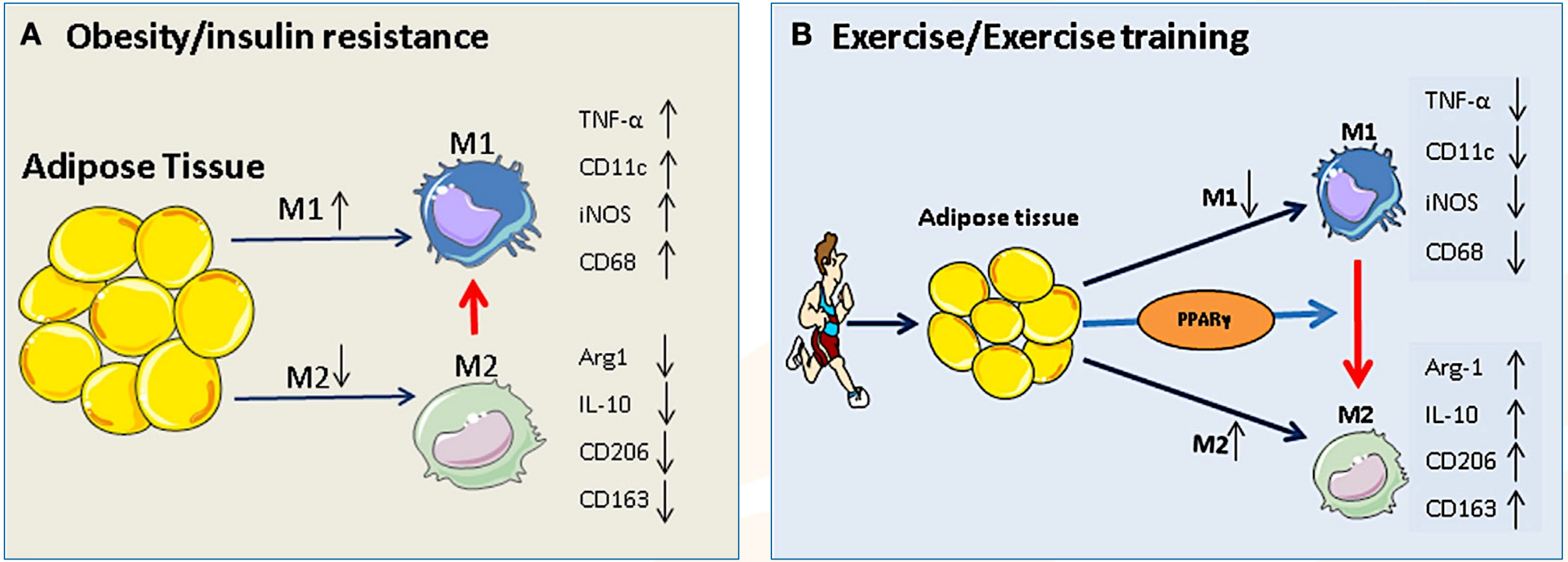
Physical Exercise Exerts a Host of Complex Effects on the Immune System Cells and Cytokines



TLR = toll-like receptor.

Schon HT, et al. *Front Pharmacol*. 2016;7:283.

How Exercise Exerts Its Immune Modulatory Effects

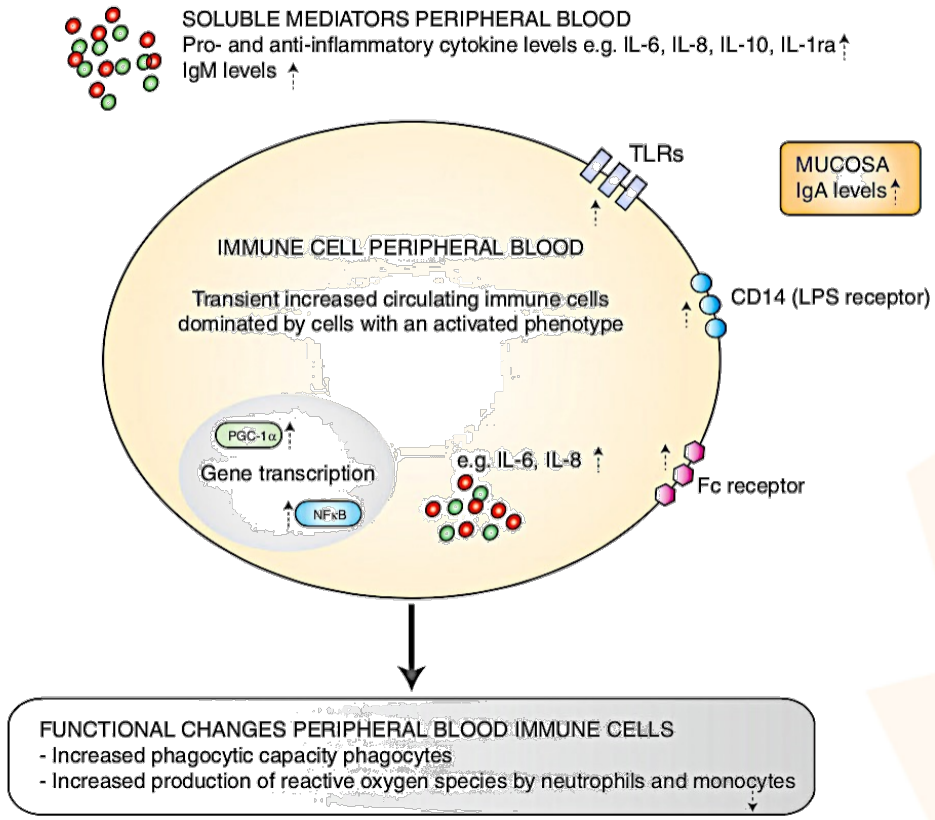


Goh J, et al. *Front Endocrinol*. 2016;7:65.

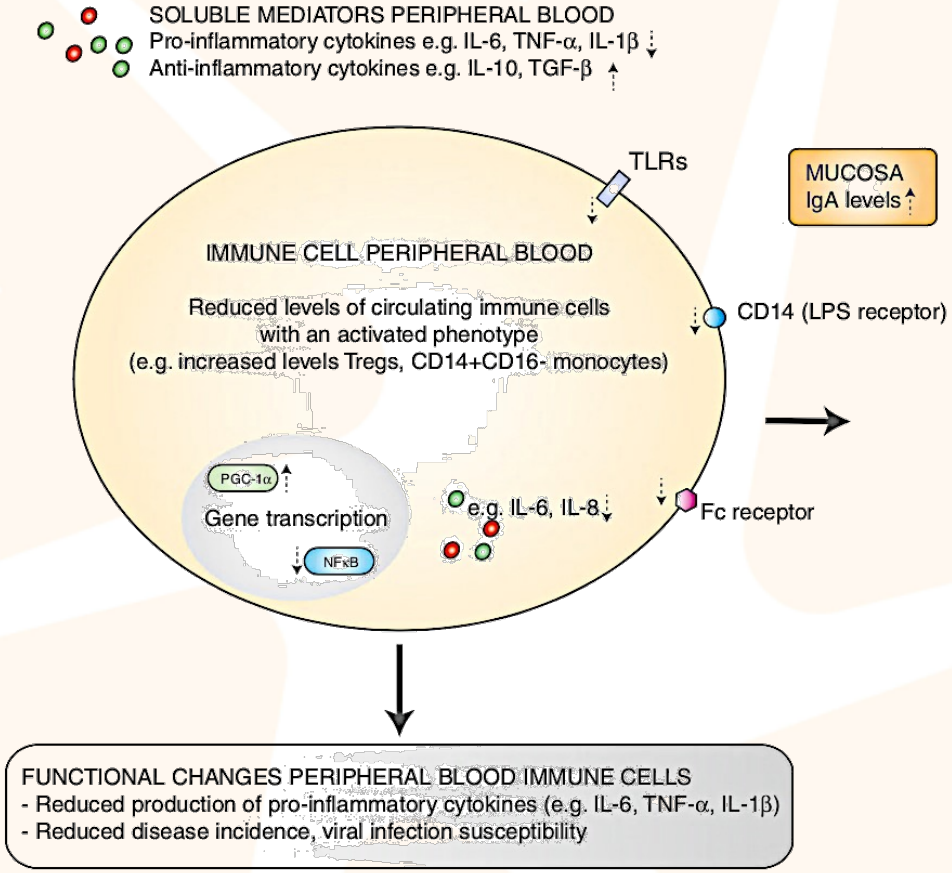
More is More: *Long-Term Exercise Further Positively Impacts Immune Functioning*

Short-Term Changes

Single exercise session: Immune activation and improved immune effector functions



Long-Term Changes



van de Weert-van Leeuwen PB, et al. *Respir Res*. 2013;14:32.

A Key Point about Exercise

All the mechanisms that contribute to the anti-inflammatory effects of exercise training are independent of its effects on weight loss.

You T, et al. *Sports Med*. 2013;43(4):243-256.

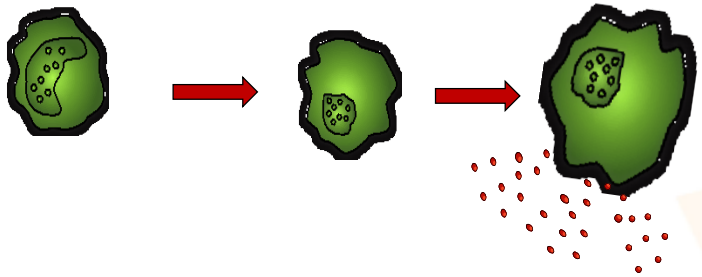
MINDFULNESS
and Its Connection to the PNI System

49 patients with breast cancer and 10 with prostate cancer enrolled in an 8-week mindfulness-based stress reduction program that incorporated relaxation, meditation, gentle yoga, and daily home practice. Assessments through 12-months post-initiation of Mindfulness practice.

Mindfulness Significantly Impacts Both Lymphocyte Functioning AND Cytokine Production

Immune cell subtypes and cytokine expression for participants with all four assessments ($n = 40$)

	Time 1		Time 2		Time 3		Time 4	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Lymphocytes								
Total lymph (% WBC)	28.45	9.46	29.86	7.27	29.99	7.37	29.35	7.95
CD3 (% lymph)	70.22	9.10	69.90	7.56	66.85	12.72	67.76	8.51
CD4 (% lymph)	45.77	10.56	44.74	10.49	44.52	9.97	45.46	10.95
CD8 (% lymph)	26.00	7.34	25.70	7.14	24.25	7.33	24.13	8.26
CD19 (% lymph)	12.56	6.27	12.82	6.58	13.80	6.59	13.98	6.92
CD56 (% lymph)	9.34	4.34	9.87	4.48	10.21	5.81	8.45	4.78
Cytokines (% of T-cells)								
IFN-γ	27.58	17.35	27.52	14.51	11.31	9.00	10.75	8.72
TNF	42.08	24.47	44.40	22.84	20.37	16.35	15.17	12.32
IL-4	3.17	2.82	3.16	2.76	0.99	1.48	0.27	0.34
IL-10	2.60	1.87	3.09	2.38	2.82	4.18	2.34	3.10



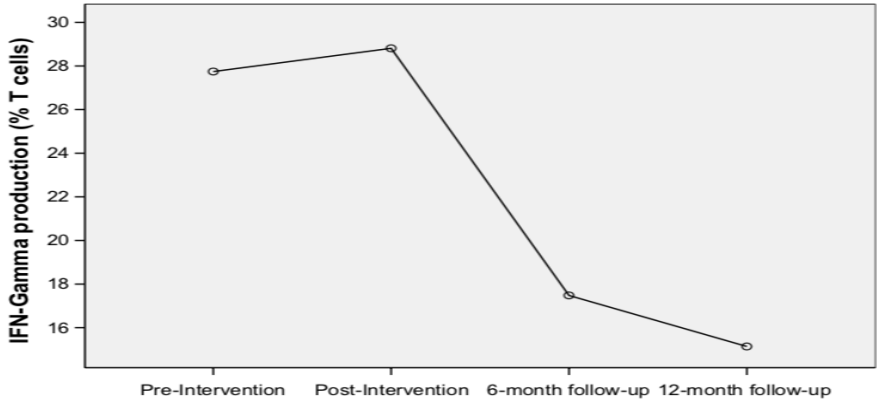


Fig. 4. Mean IFN-λ T-cell production across time.

Carlson LE, et al. *Brain Behav Immun*. 2007;21(8):1038-1049.

Long-Term Mindfulness Practice Reduces Subjective Stress AND Modulates HPA Axis Tone

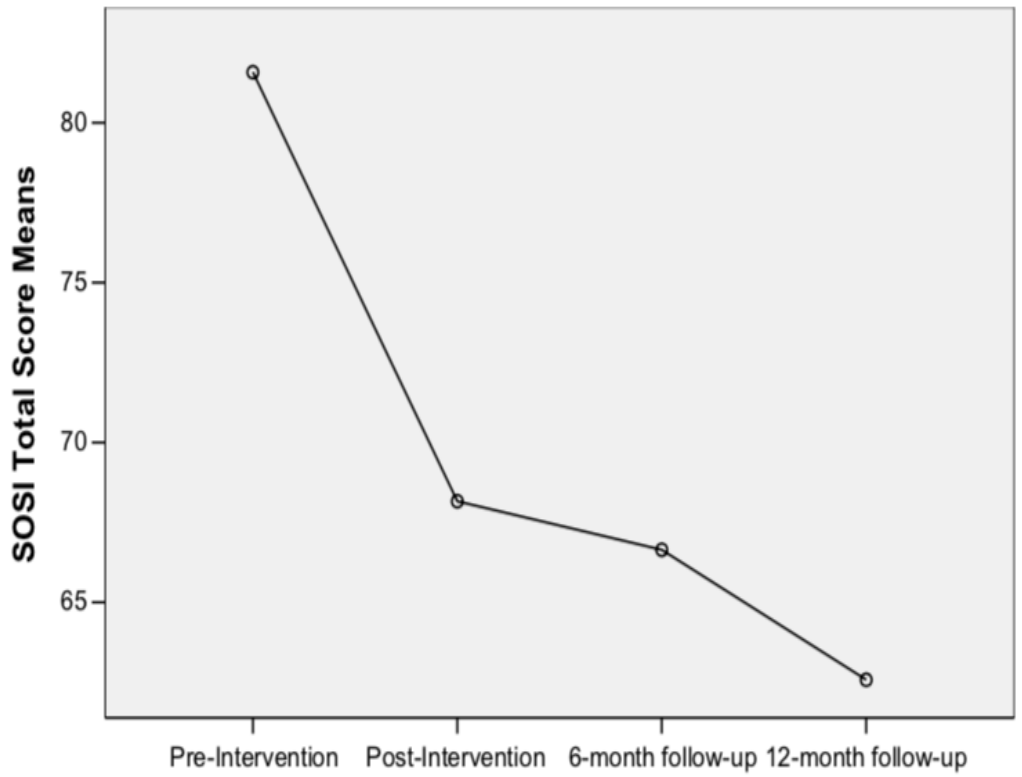


Fig. 2. Symptoms of stress inventory scores.

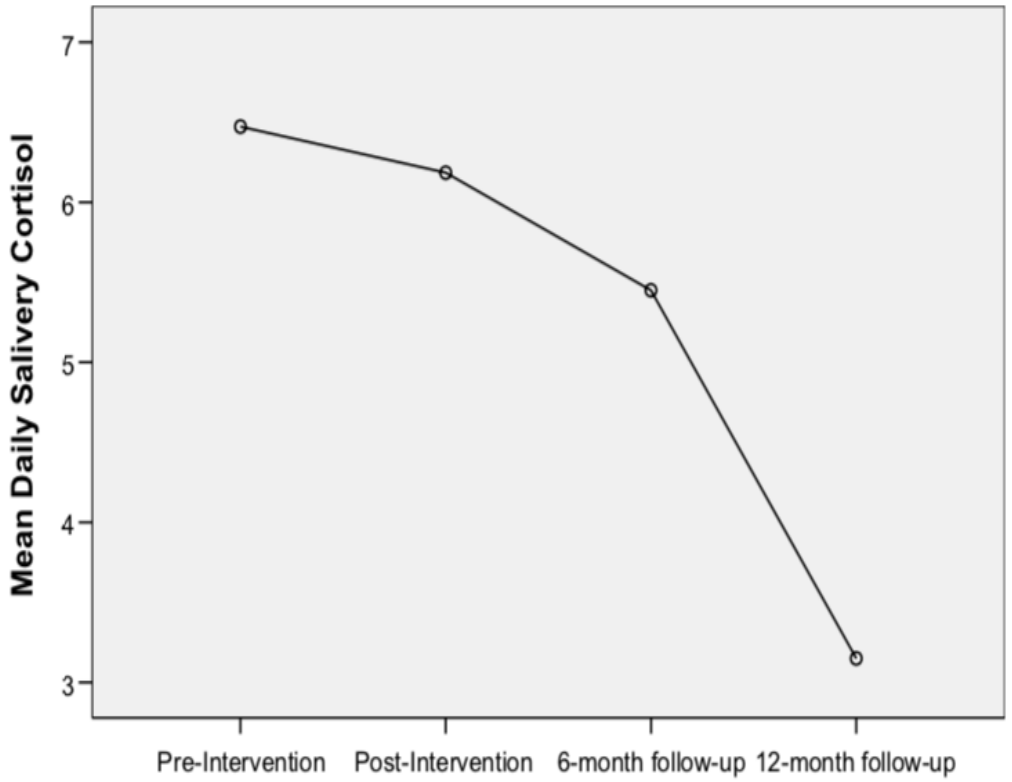
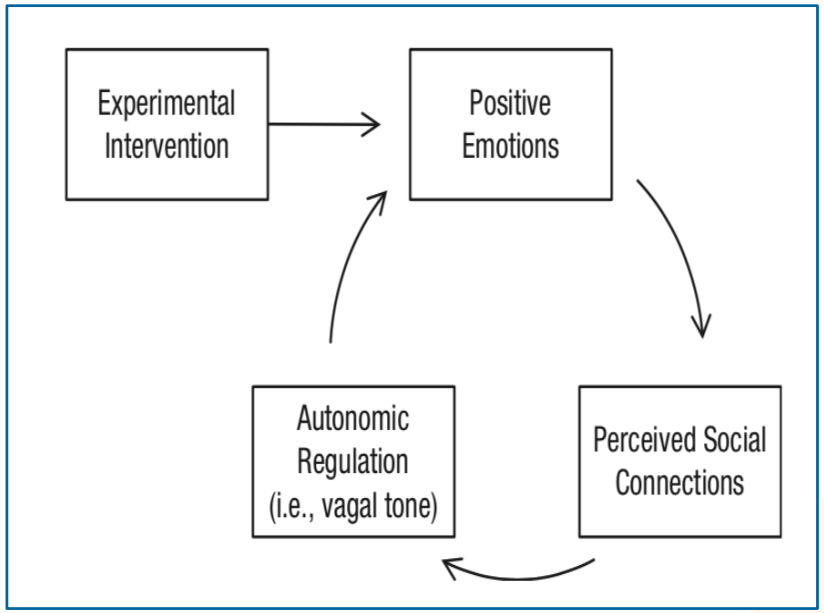
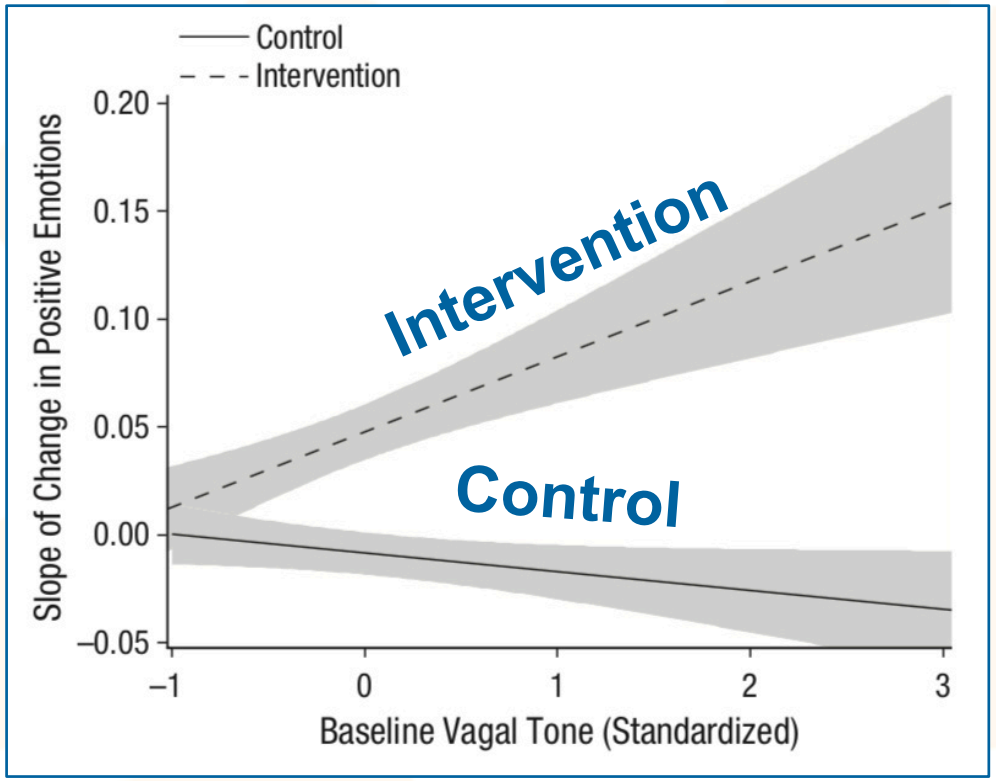


Fig. 3. Mean daily salivary cortisol values across time.

Carlson LE, et al. *Brain Behav Immun*. 2007;21(8):1038-1049.

"Upward Spiral": *Interventional Study Shows Positive Emotions Change Vagal Tone*





Vagal tone was assessed using spectral frequency analysis of heart rate data to obtain high-frequency heart rate variability

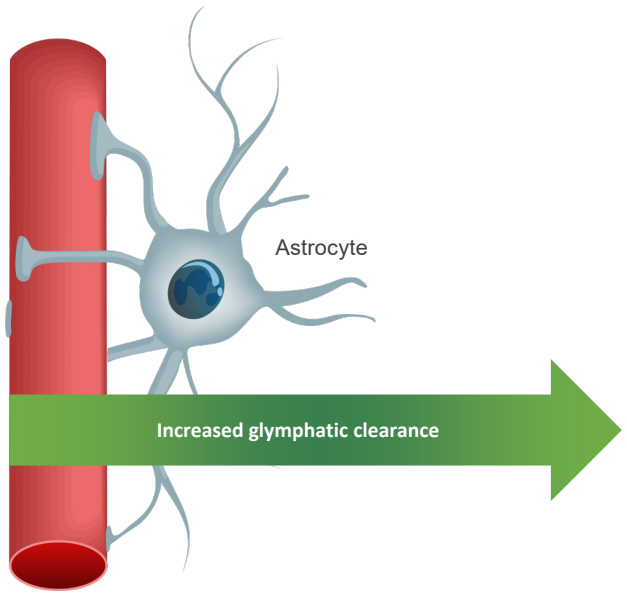
Kok BE, et al. *Psychol Sci*. 2013;24(7):1123-1132.

SLEEP
and Its Connection to the PNI System

Why Care about Sleep?
Sleep and Its PNI Implications

Normal Sleep

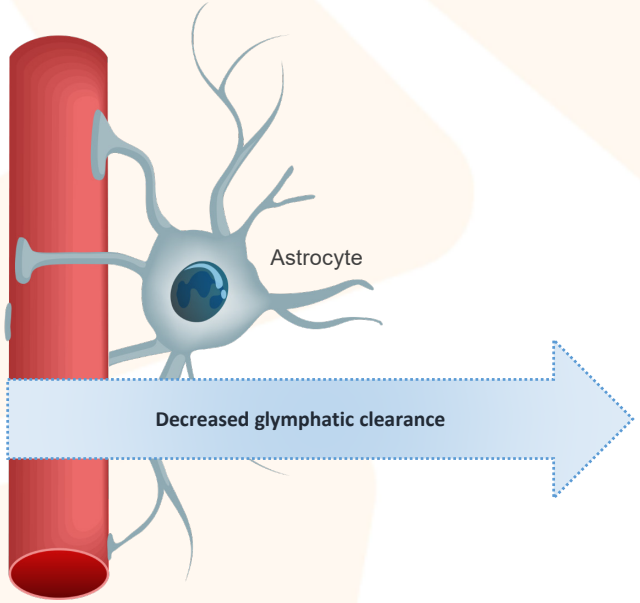
Increased intracellular ATP → Enhanced cellular repair mechanisms → **Decreased** inflammatory response → Enhanced cell survival



Enhanced tau clearance

Sleep Deprivation

Decreased intracellular ATP → Inhibited cellular repair mechanisms → Increased inflammatory response → **Decreased** cell survival



Oxidative stress
Endoplasmic reticular stress
Waste accumulation

→ Tau accumulation

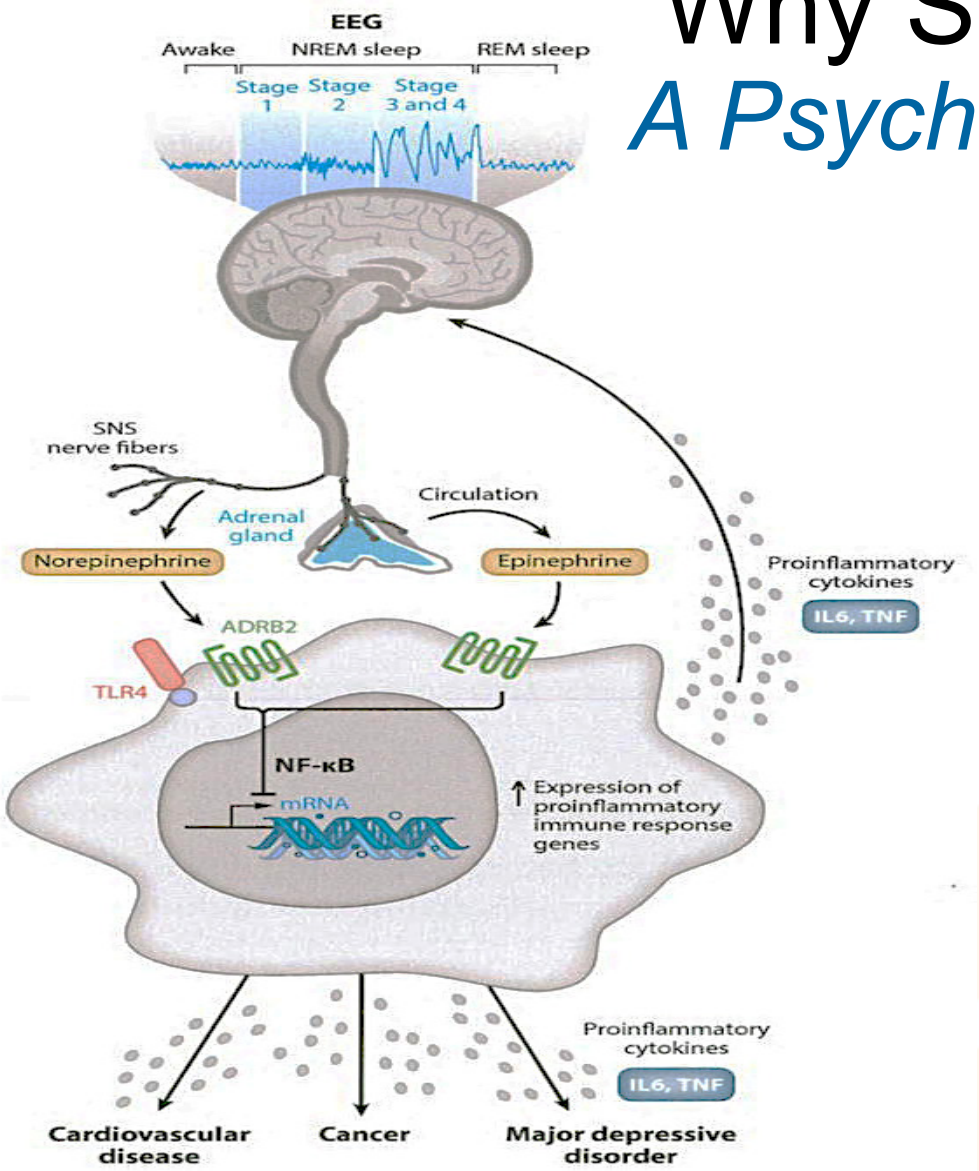
↓

Tauopathy

ATP = adenosine triphosphate.

Lucke-Wold BP, et al. *Neurosci Biobehav Rev*. 2015;55:68-77.

Why Sleep is Important for Health:
A Psychoneuroimmunology Perspective



Insomnia Activates:

- HPA System
- ANS System
- Inflammatory System

All 3! Insomnia is truly a PNI Modulator

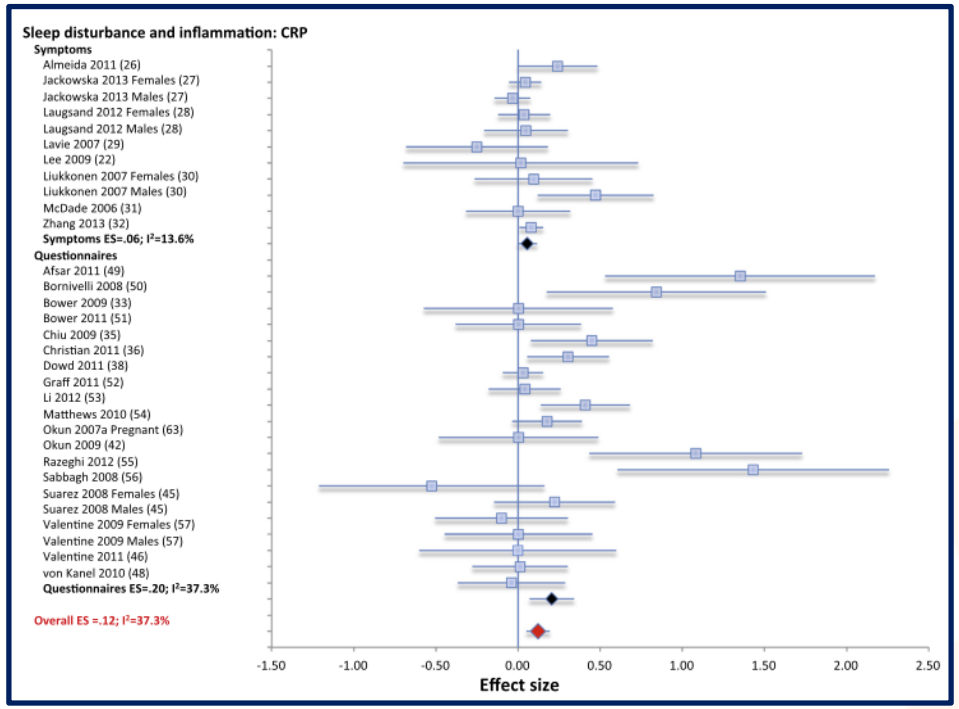
- Following a night of sleep loss, or during a period of sleep disturbance, nerve fibers from the SNS release the neurotransmitter NE into primary and secondary lymphoid organs and stimulate the adrenal gland to release stored epinephrine into systemic circulation.
- Both neuromediators stimulate leukocyte adrenergic receptors (eg, ADRB2) and activate NF-κB-mediated inflammatory programs. Intrinsic circuits detect microbes via pattern recognition receptors (PRRs) such as the TLR4 and stimulate inflammatory gene expression via transcription factors such as NF-κB. The production of proinflammatory cytokines IL-6 and TNF-α occurs. Bidirectional links between the brain and periphery allow the brain to regulate inflammatory activity, and inflammatory activity in turn can influence neural processes in the brain and alter sleep. When this dynamic is induced by sustained sleep disturbance, a feed-forward dysregulation of sleep can occur, which may also confer increased risk for inflammation-related disorders such as cardiovascular disease, cancer, and major depressive disorder.

Irwin MR. *Annu Rev Psychol*. 2015;66:143-172.

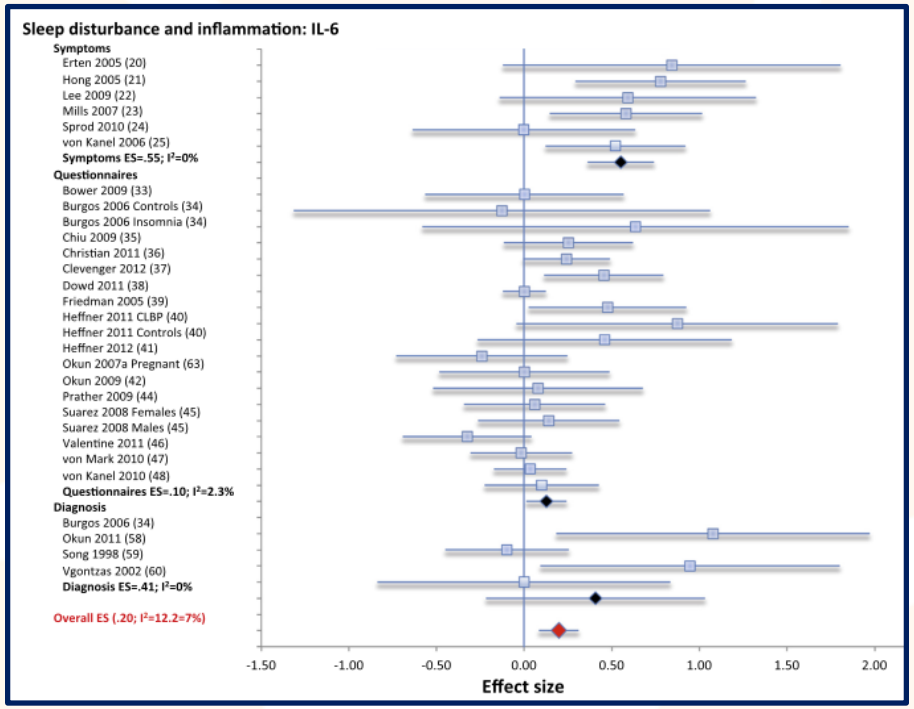
Sleep Disturbance and Systemic Inflammation

- **Systematic search of 72 primary research articles that characterized sleep disturbance and assessed inflammation by levels of circulating markers**
- **Sleep disturbance: Self-reported symptoms and questionnaires**

Sleep Disruption – CRP



Sleep Disruption – IL-6

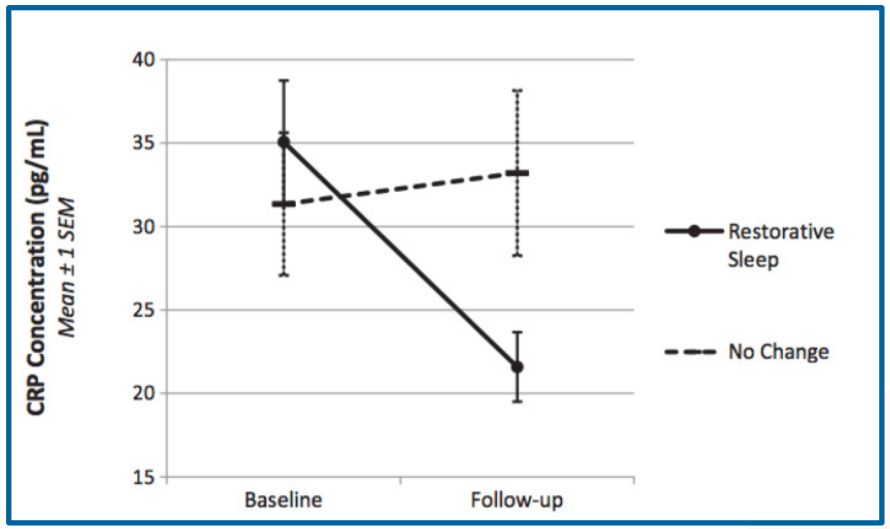


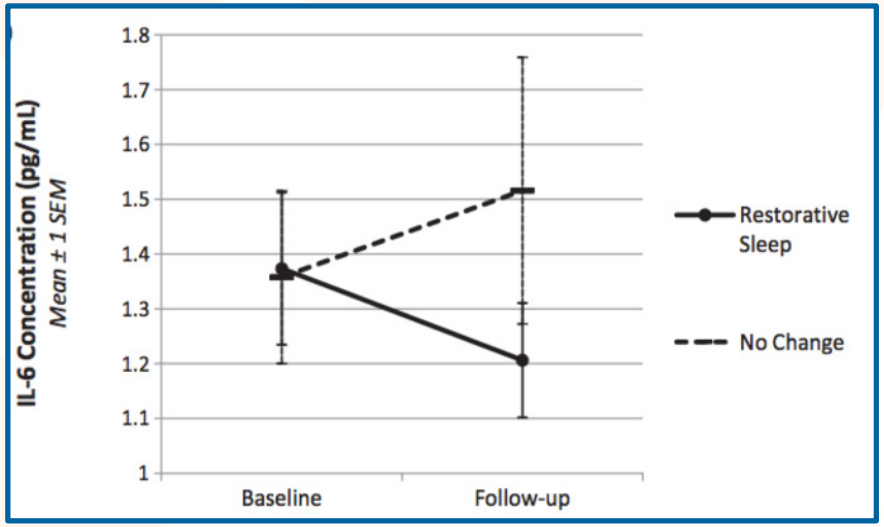
Sleep disturbance is associated with increases in markers of systemic inflammation

Irwin MR, et al. *Biol Psychiatry*. 2016;80(1):40-52.

Restorative Sleep Results in Lower Inflammation

- **Observational study of US military personnel (N=66) who presented for evaluation of sleep disturbance**
- **Examined the relationship between reported sleep changes and concentrations of IL-6 and CRP in peripheral blood**



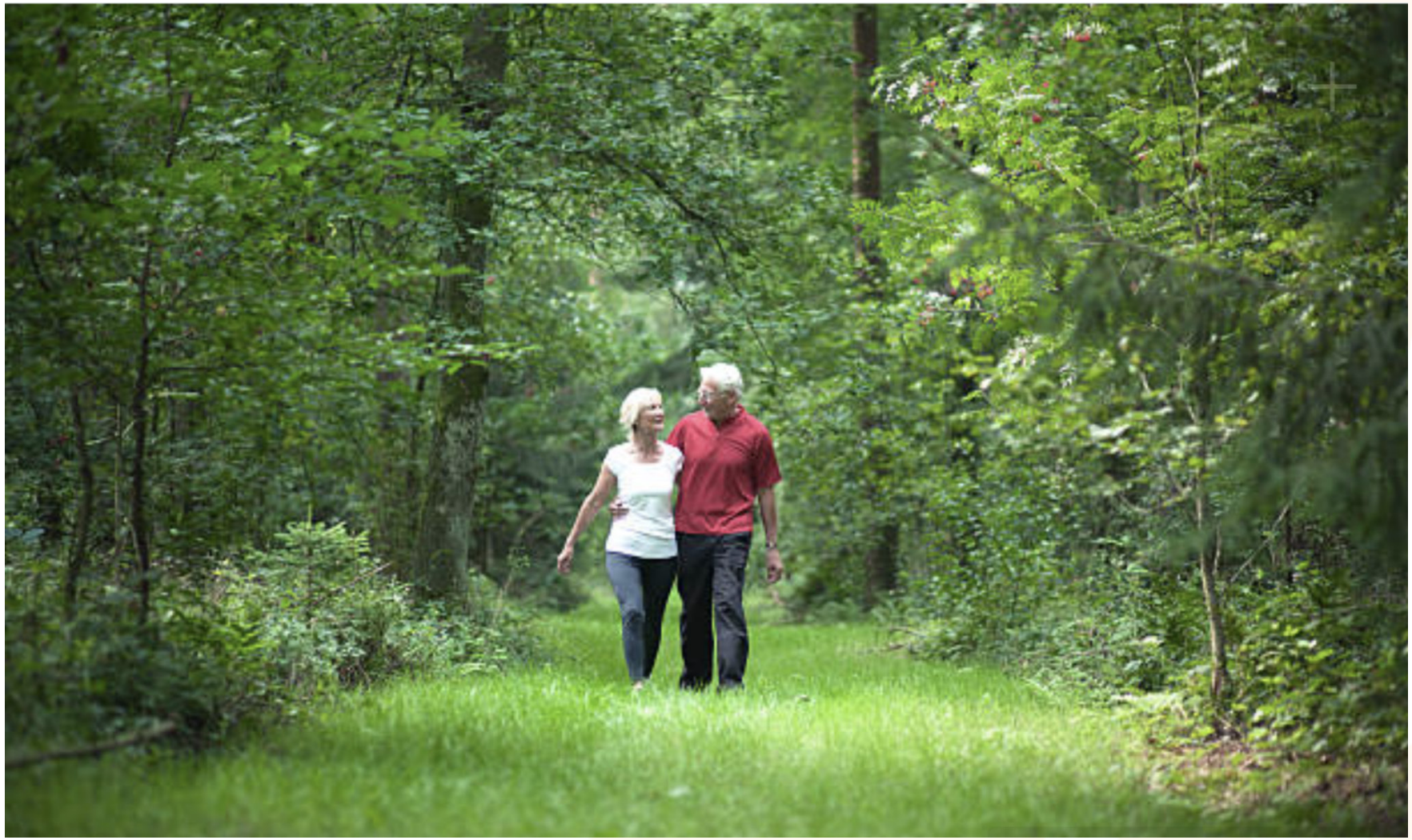


Change in inflammation markers (CRP and IL-6 concentrations) between baseline and follow-up for the restorative-sleep (n=34) and no-change (n=32) groups

The restorative-sleep group had significant reductions in CRP concentration and depression symptoms, as well as reduced fatigue and improvements in emotional well-being, social functioning, and physical functioning at follow-up.

Heinzelmann M, et al. *Sleep Med*. 2014;15(12):1565-1570.

Detect Anything Here that is Anti-Inflammatory??

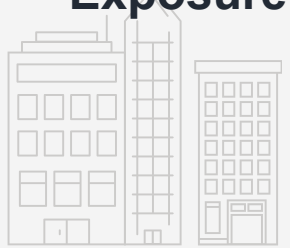


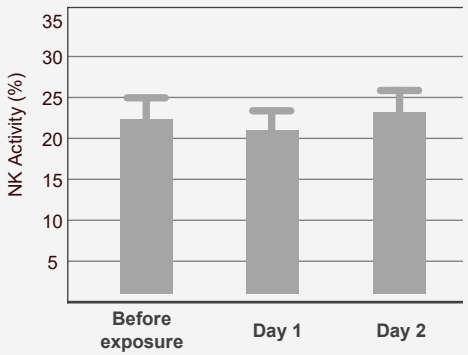
Detect Anything Here that is Anti-Inflammatory??

Change in Psychosocial Environment Can Positively Effect Immune Functioning

Effects of Forest Bathing Trip on NK (natural killer cells – a type of macrophage) Cell Activity

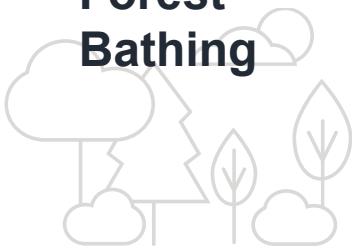
Urban Exposure

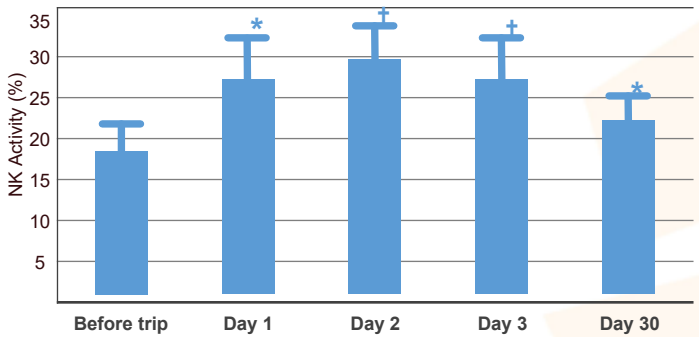




No change in NK cell activity for urban exposure

Forest Bathing





Forest bathing **increased NK cell activity, which lasted for 30 days** after the trip

Data are presented as the mean ± SE. **P*<.05 vs before trip; †*P*<.01 vs before trip.
NK = natural killer; SE = standard error.
Li Q. *Environ Health Prev Med*. 2010;15(1):9-17.

In Summation: *Nonpharmacologic Techniques, If Used Wisely, Positively Impact the PNI System*

Exercise	Exercise **30 minutes daily**; aim for at least **moderate** intensity
Sleep	Implement **sleep hygiene** practices daily
Nutrition	**Log** your daily meals/snacks/beverages/alcohol daily
Mindfulness	Practice mindfulness for at least **8 minutes daily**
Social Connectedness	**Call** a friend or family member daily

Jain S, et al. Presented at: 29th Annual US Psychiatric and Mental Health Congress; October 2016; San Antonio, Texas.

In Conclusion:

- We are compelled to believe that there is a tight bond between members of the PNI System and Mental Health
- These can adversely affect both short- and long-term mind–body outcomes for our patients
- Wise pharmacologic and nonpharmacologic treatment options are available to address these issues holistically
- Interventions should be designed with patient acceptability and acceptance in mind