PNI Europe
By Dr. Leo Pruimboom

Klinische PNI
Einführung

PNI Europe

2020 - 2042

Tag 1

09.00 - 09.45

Erwartungen

Pas auf: jede 30 Minuten, 2 Minuten Bewegung

Ihre Erwartungen auf Post Its

1. Was erwarten Sie inhaltlich von diesem Weiterbildung?
2. Und in Bezug auf Lernstrategien?
3. Was erwarten Sie von den Lehrern/Coaches?
4. Was erwarten Sie von sich selbst?

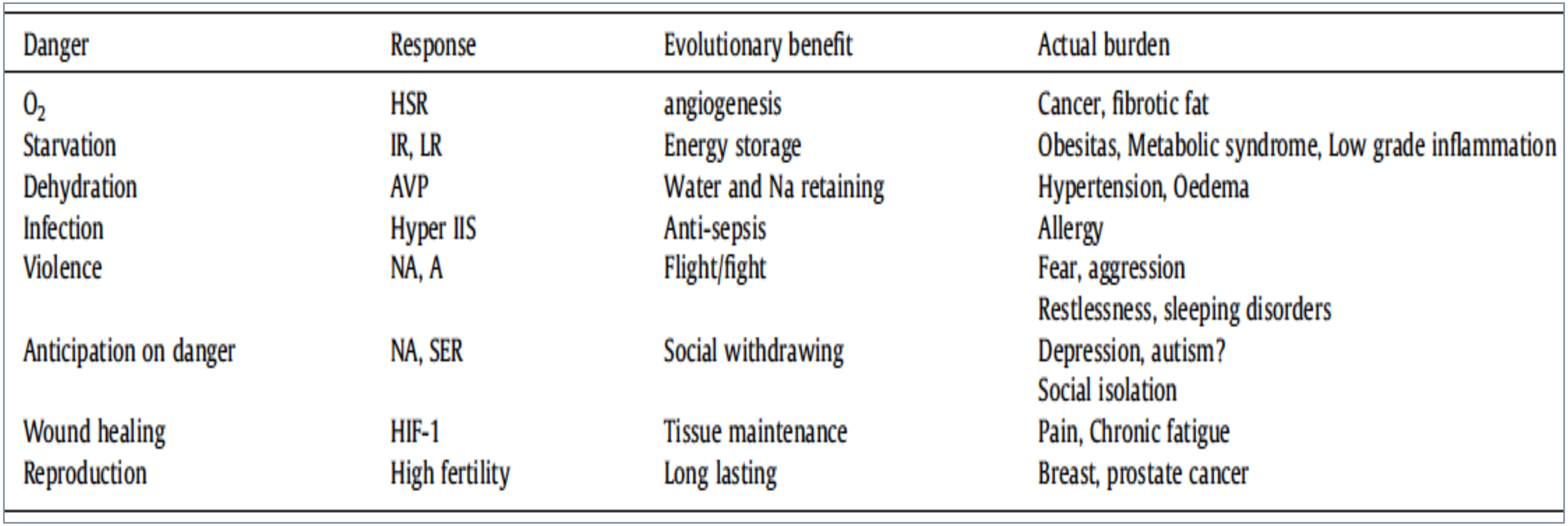
Tag 1

09.45 - 10.00

Warum sind Sie hier?

Proximal versus Ultiem

1. Ich will wissen, wie es funktioniert.
2. Ich will wissen, warum es so funktioniert, wie es funktioniert.
3. Ich will meinen Patienten besser helfen.
4. Ich will mir selbst helfen.
5. Ich bin nur neugierig.
6. Ich will den wissenschaftlichen Hintergrund von allem wissen.
7. Weil meine Eltern überlebten und sich fortpflanzten.

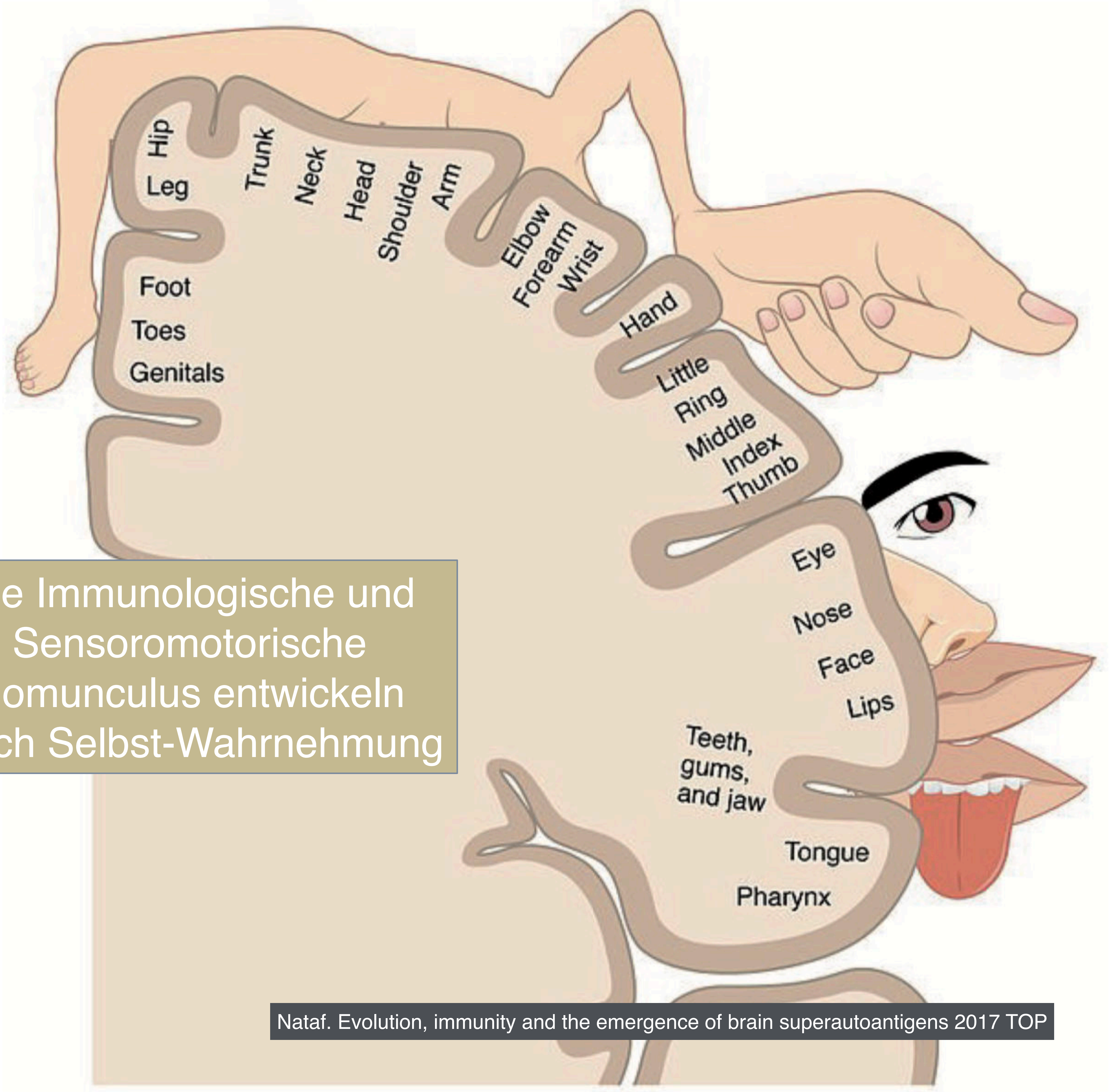


Danger	Response	Evolutionary benefit	Actual burden
O_2	HSR	angiogenesis	Cancer, fibrotic fat
Starvation	IR, LR	Energy storage	Obesitas, Metabolic syndrome, Low grade inflammation
Dehydration	AVP	Water and Na retaining	Hypertension, Oedema
Infection	Hyper IIS	Anti-sepsis	Allergy
Violence	NA, A	Flight/fight	Fear, aggression
			Restlessness, sleeping disorders
Anticipation on danger	NA, SER	Social withdrawing	Depression, autism?
			Social isolation
Wound healing	HIF-1	Tissue maintenance	Pain, Chronic fatigue
Reproduction	High fertility	Long lasting	Breast, prostate cancer

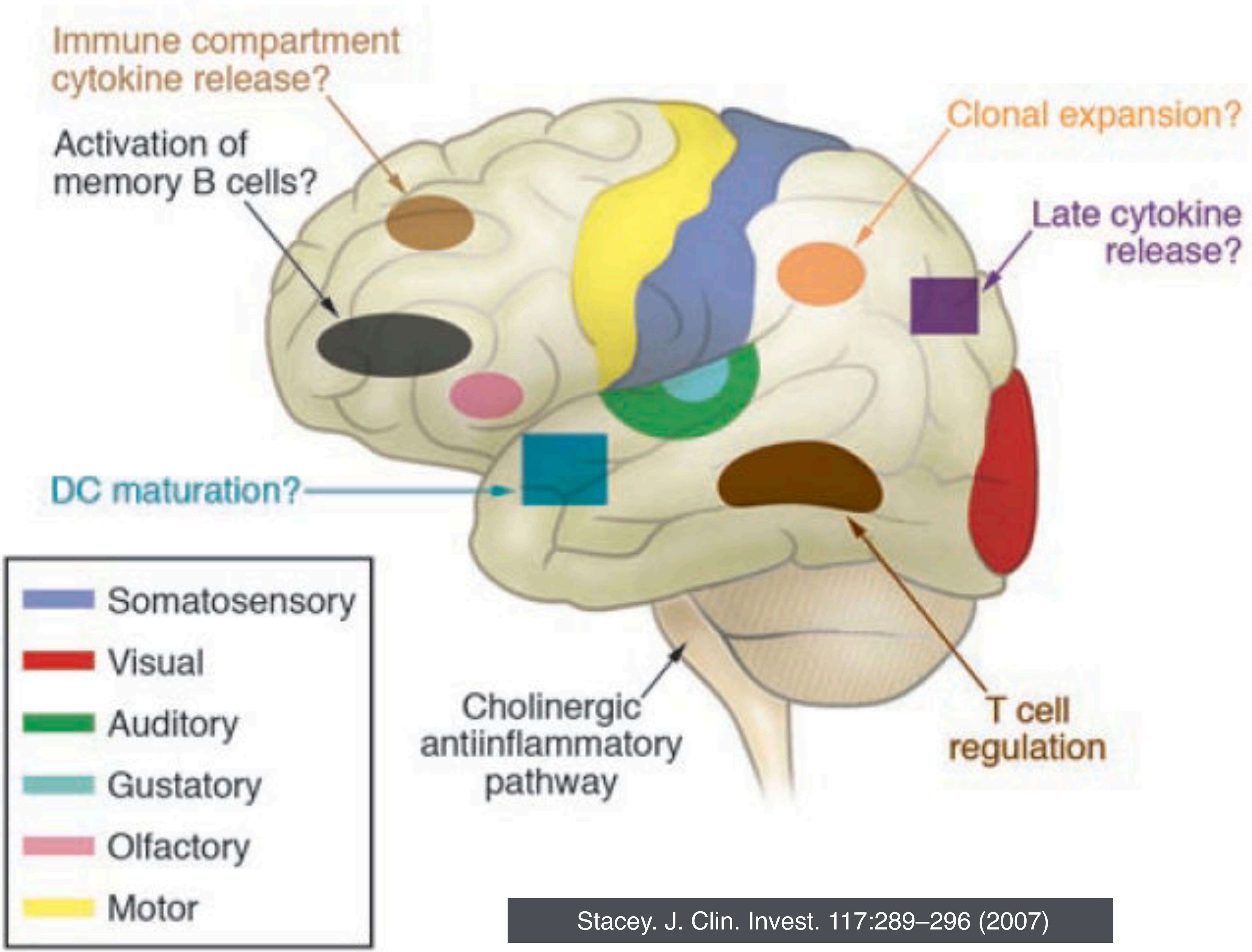
Wir haben diese Herausforderungen überlebt und dafür sind wir geschaffen.

Nettle D, et al. Behavioral Ecology 2013
Pruimboom L. Med Hypothesis 2011

Die Immunologische und Sensoromotorische Homunculus entwickeln durch Selbst-Wahrnehmung

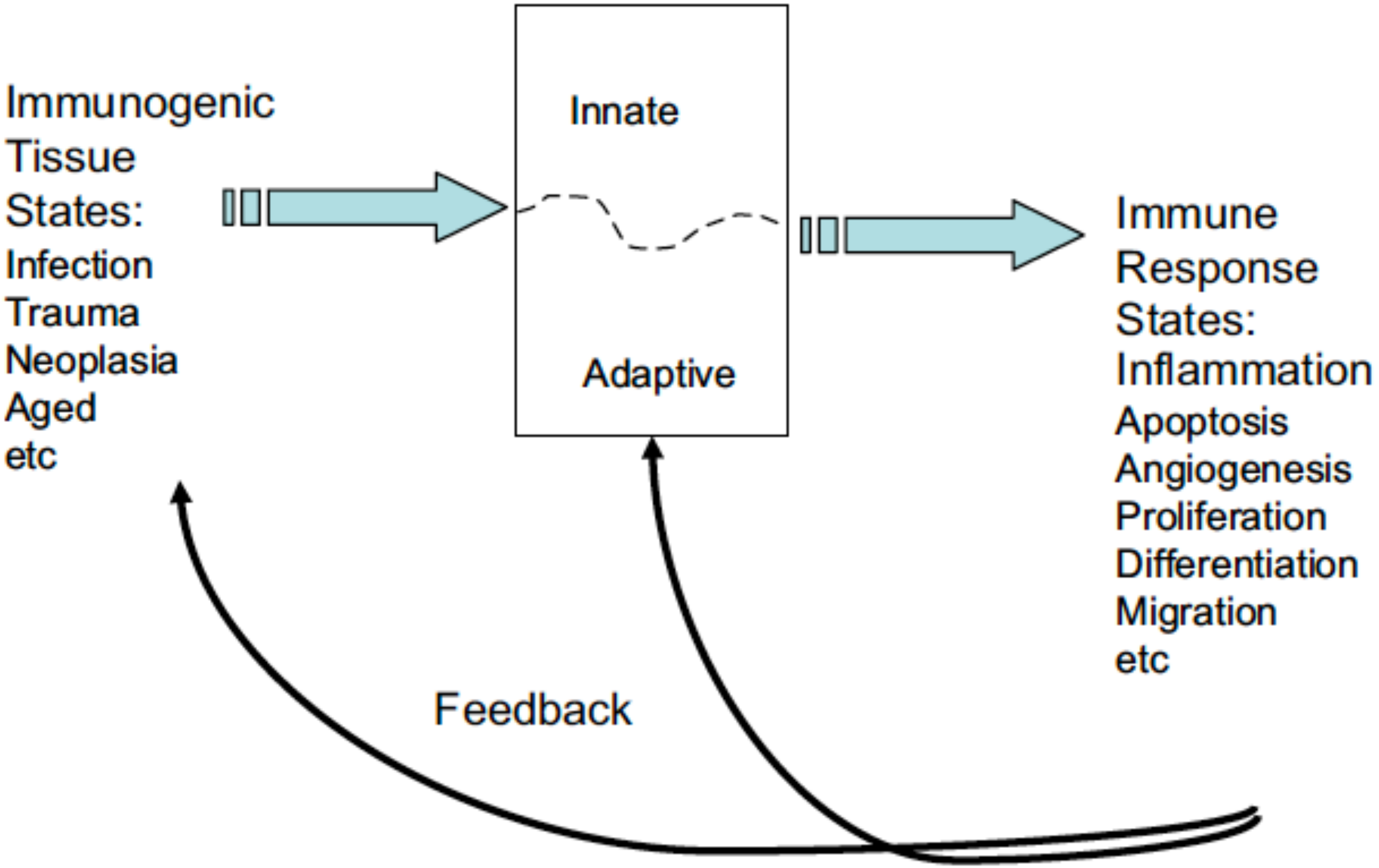

Hip
Leg
Trunk
Neck
Head
Shoulder
Arm
Elbow
Forearm
Wrist
Hand
Little
Ring
Middle
Index
Thumb
Foot
Toes
Genitals
Eye
Nose
Face
Lips
Teeth, gums, and jaw
Tongue
Pharynx

Nataf. Evolution, immunity and the emergence of brain superautoantigens 2017 TOP


Immune compartment cytokine release?
Activation of memory B cells?
Clonal expansion?
Late cytokine release?
DC maturation?
Cholinergic antiinflammatory pathway
T cell regulation
🟦 Somatosensory
🟥 Visual
🟩 Auditory
🟦 Gustatory
🟪 Olfactory
🟨 Motor

Stacey. J. Clin. Invest. 117:289–296 (2007)

Immune Computation



Immune system

Immunogenic
Tissue
States:
Infection
Trauma
Neoplasia
Aged
etc

Innate

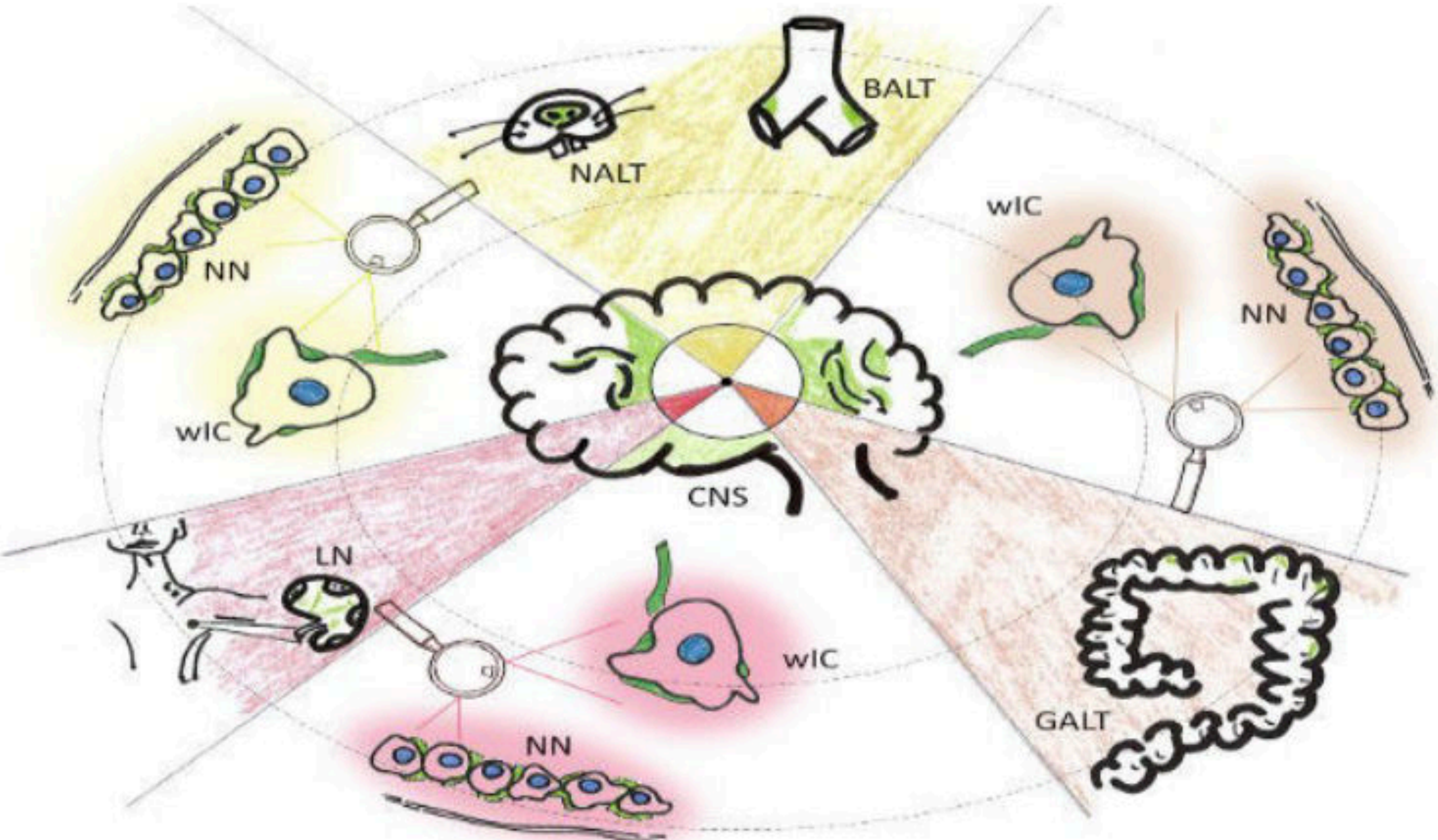
Adaptive

Immune
Response
States:
Inflammation
Apoptosis
Angiogenesis
Proliferation
Differentiation
Migration
etc

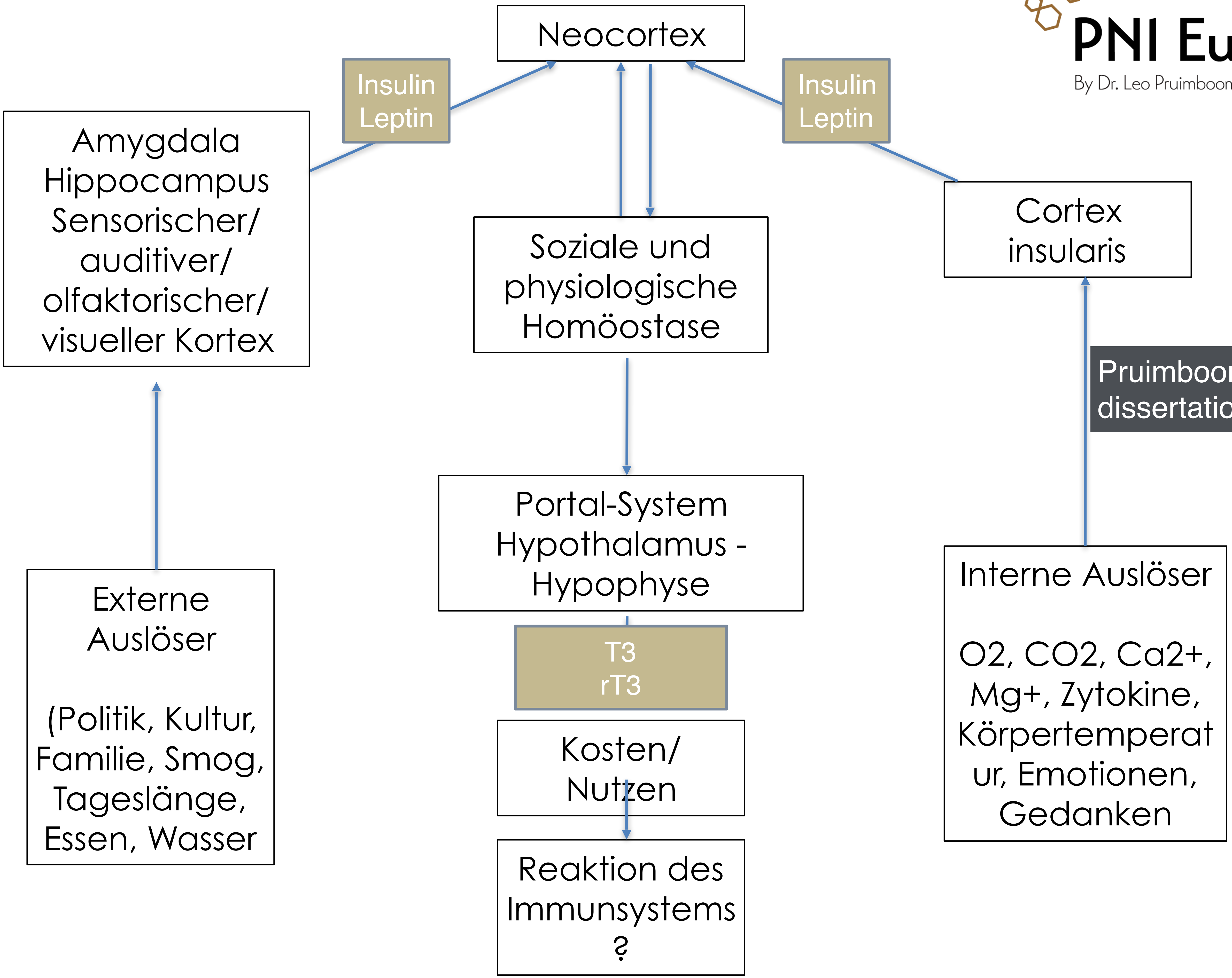
Feedback

I.R. Cohen / Journal of Autoimmunity 29 (2007) 246e249

Wüfling. The Emerging Role of Neuro-Immune Synapses and the Immunological Homunculu in the Context 2019



Schematic illustration of our recent findings of neural structures in secondary lymphoid organs put in context with the concepts of NI-synapse and immunological homunculus. Neural structures are colored green in all drawings as we suppose them to build up one coherent sensory system. The circle in the brain with three colored parts should represent the immunological homunculus, which gets topographically mapped information from different secondary lymphoid organs. Looking at the cellular level, in all lymphoid organs, single immune cells could be found densely surrounded by neural structures (wIC), probably forming neuro-immune synapses. Likewise in all lymphoid organs a high density of neurites always in gate areas could be observed as the neural nexus phenomenon (NN). The two dashed circles represent two different innervation locations of wIC and NN (see text). LN (red): lymph nodes, GALT (brown): gut associated lymphatic tissue, BALT (yellow): bronchus associated lymphatic tissue, NALT (yellow): nasopharynx associated lymphatic tissue, CNS: central nervous system, NN: neural nexus, wIC: neurally hard-wired immune cell.



Neocortex

Insulin
Leptin

Insulin
Leptin

Amygdala
Hippocampus
Sensorischer/
auditiver/
olfaktorischer/
visueller Kortex

Soziale und
physiologische
Homöostase

Cortex
insularis

Pruimboom. PhD
dissertation. 2017

Portal-System
Hypothalamus -
Hypophyse

T3
rT3

Kosten/
Nutzen

Reaktion des
Immunsystems
?

Externe
Auslöser

(Politik, Kultur,
Familie, Smog,
Tageslänge,
Essen, Wasser

Interne Auslöser

O2, CO2, Ca2+,
Mg+, Zytokine,
Körpertemperatur, Emotionen,
Gedanken

Dr. L. Pruimboom. 2017

The (non)permissive governor ©

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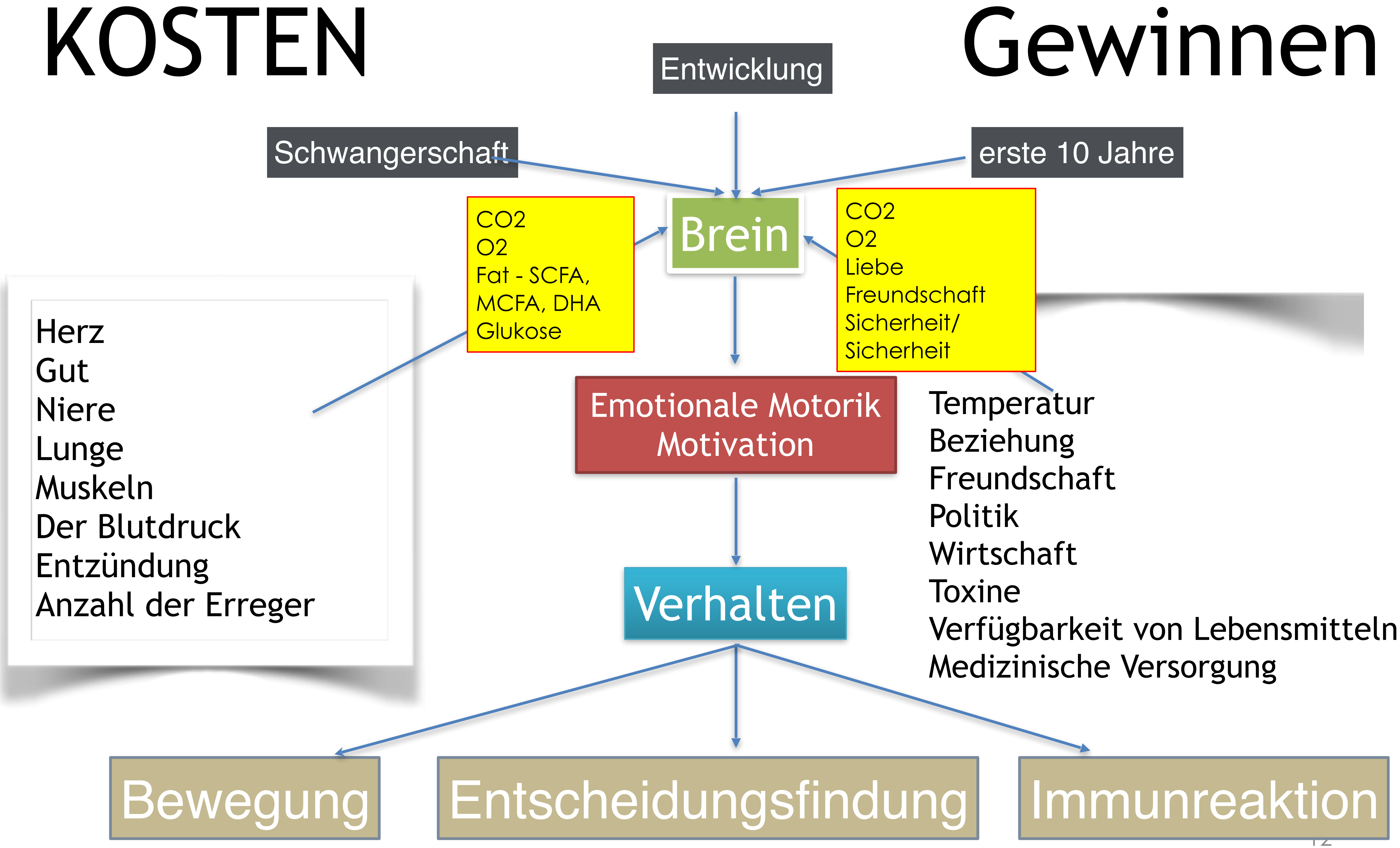


KOSTEN

Gewinnen

Entwicklung

Schwangerschaft

erste 10 Jahre

Brein

CO2
O2
Fat - SCFA,
MCFA, DHA
Glukose

CO2
O2
Liebe
Freundschaft
Sicherheit/
Sicherheit

Herz
Gut
Niere
Lunge
Muskeln
Der Blutdruck
Entzündung
Anzahl der Erreger

Emotionale Motorik
Motivation

Temperatur
Beziehung
Freundschaft
Politik
Wirtschaft
Toxine
Verfügbarkeit von Lebensmitteln
Medizinische Versorgung

Verhalten

Bewegung

Entscheidungsfindung

Immunreaktion

Tag 1

10.30 - 11.00

Welche Auswirkungen hat die Gesellschaft auf das Gehirn und das Immunsystem und umgekehrt?

Aktives Lernen

Tag 1

11.00 - 11.15

Die Kaffeepause

Tag 1

11.15 - 11.20

https://www.youtube.com/watch?v=Ym9Ub6cIa0M

Tag 1

11.20 - 12.00

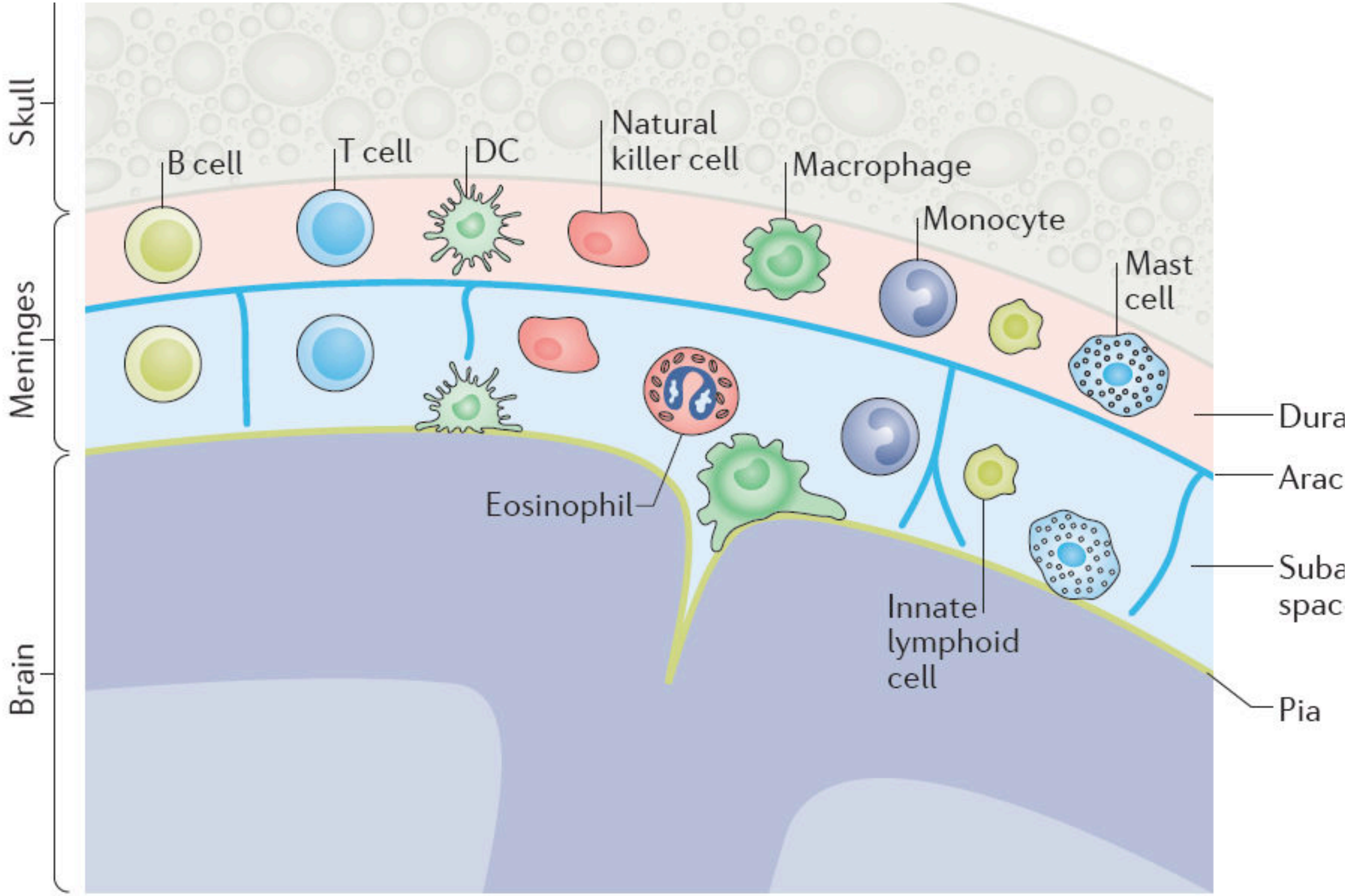
Das Immunsystem, das Gehirn und die Gesellschaft

Die neun Immunkomponenten

1. Barrieren = entzündungshemmender Teil des angeborenen IS = humoral
2. Pro-entzündliche AIS = Leukozyten
3. Antigen-präsentierende Zellen
4. Th1, T-Lymphozyten mit zytotoxischer Aktivität
5. Th2, B-Lymphozyten humoral
6. Th3, Treg = Immuntoleranz
7. Th17, T-Lymphozyten mit zytotoxischer Aktivität
8. Komplementär System (APP)
9. Die Verhaltens-IS

Pruimboom L. The Selfish Immune System. 2017

Alle Immunzellen sind in den Meningen vorhanden


Skull
Meninges
Brain
B cell
T cell
DC
Natural killer cell
Macrophage
Monocyte
Mast cell
Eosinophil
Innate lymphoid cell
Dura
Arac
Suba spac
Pia

Filiano. Kipnis. NATURE REVIEWS I **NEUROSCIENCE** VOLUME 18 I JUNE 2017 I

Immunreaktion im Winter und Sommer, Fieber, Süßigkeiten, Gewichtsverlust und Fe-Aufnahme

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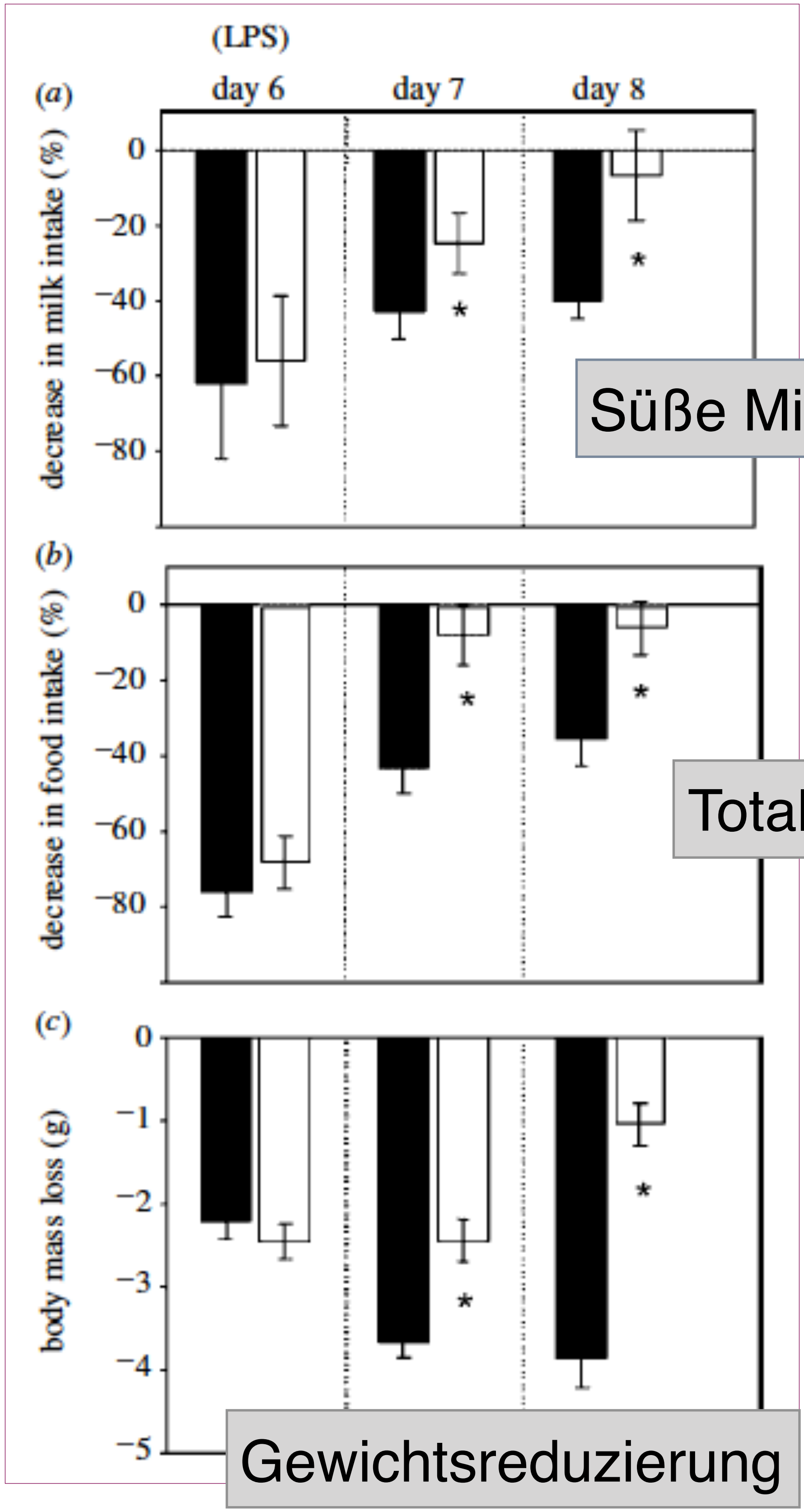
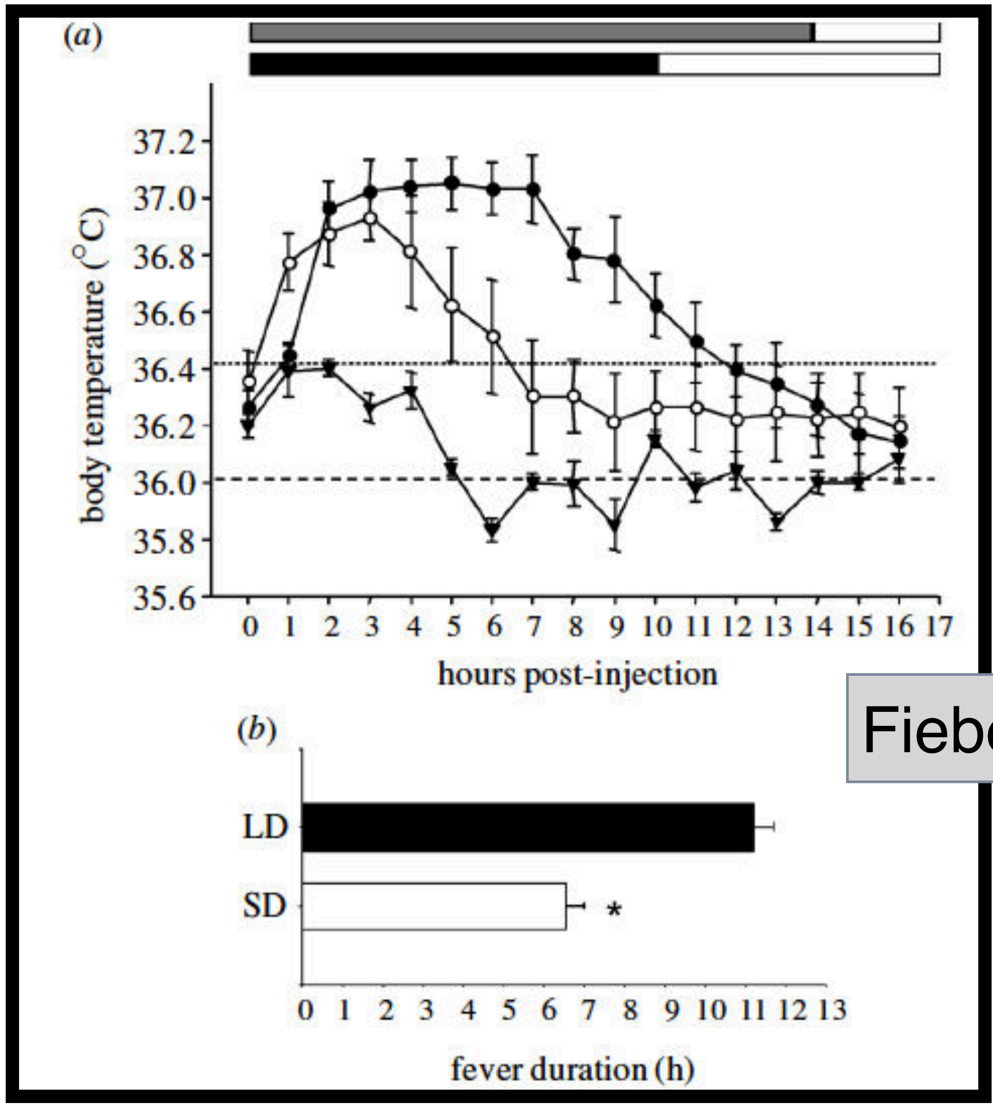


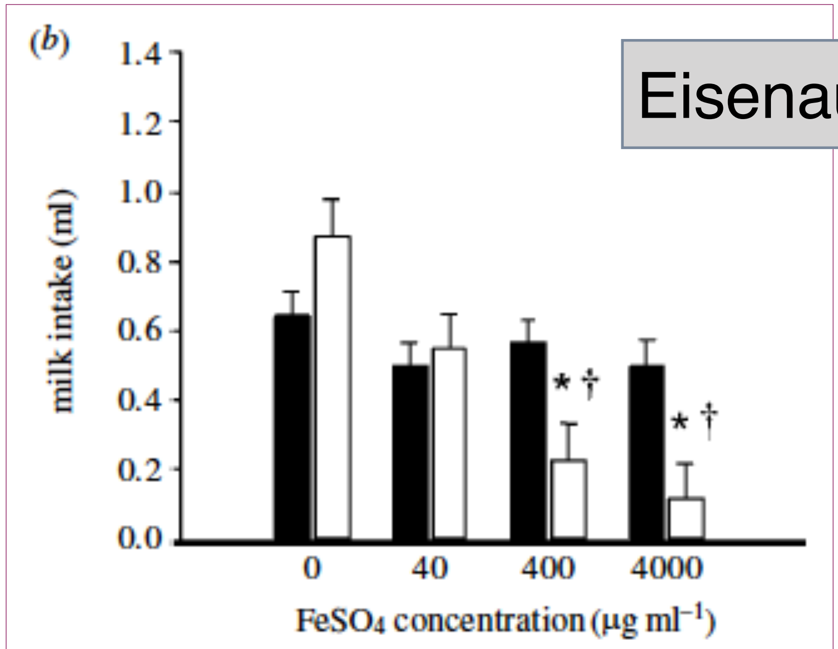
Süße Milch

Total

Gewichtsreduzierung

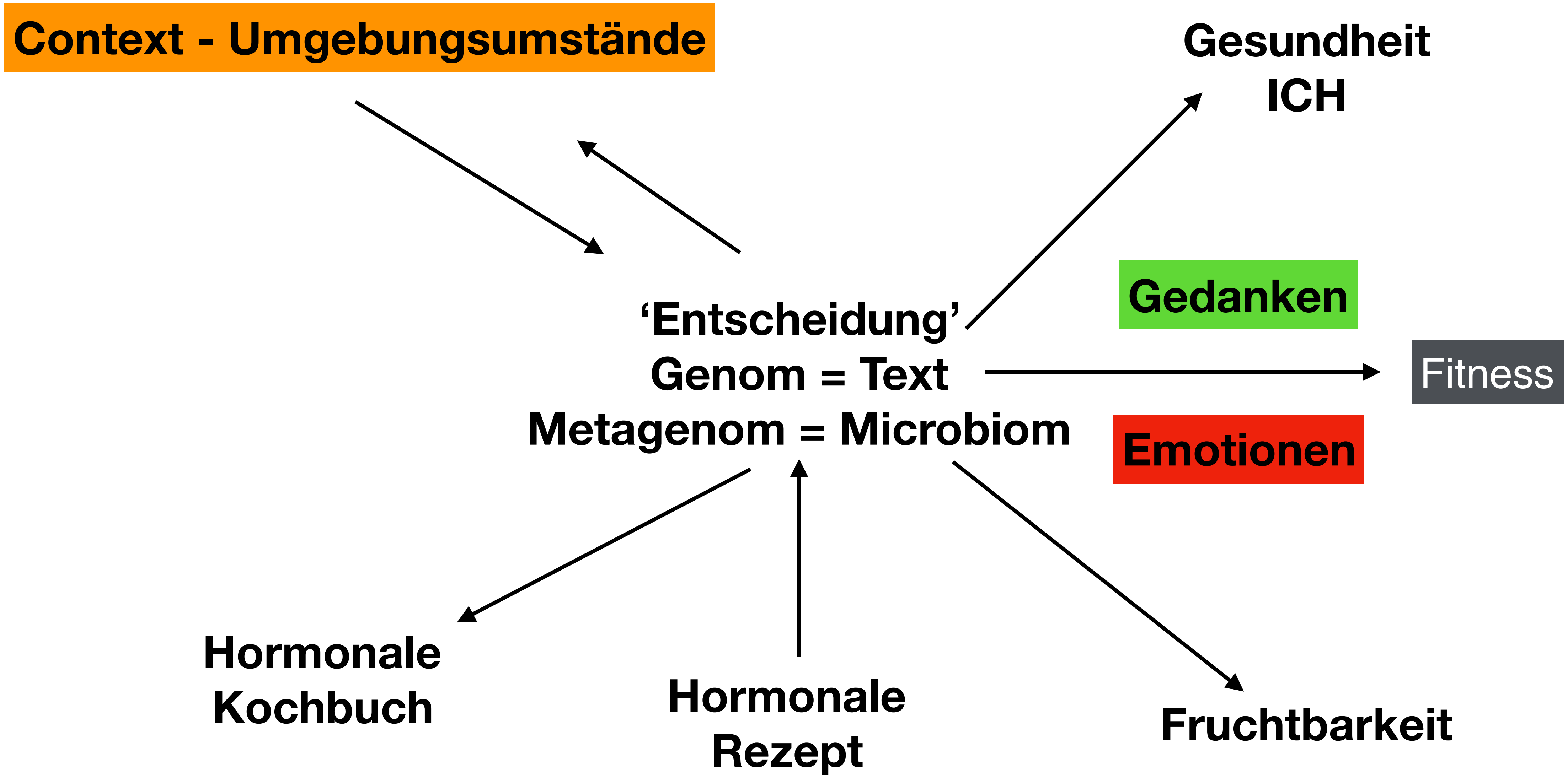


Fieber



Eisenaufnahme

Proc. R. Soc. Lond. B (2002) 269, 447±454



Context - Umgebungsumstände

Gesundheit
ICH

‘Entscheidung’
Genom = Text
Metagenom = Microbiom

Gedanken

Fitness

Emotionen

Hormonale
Kochbuch

Hormonale
Rezept

Fruchtbarkeit

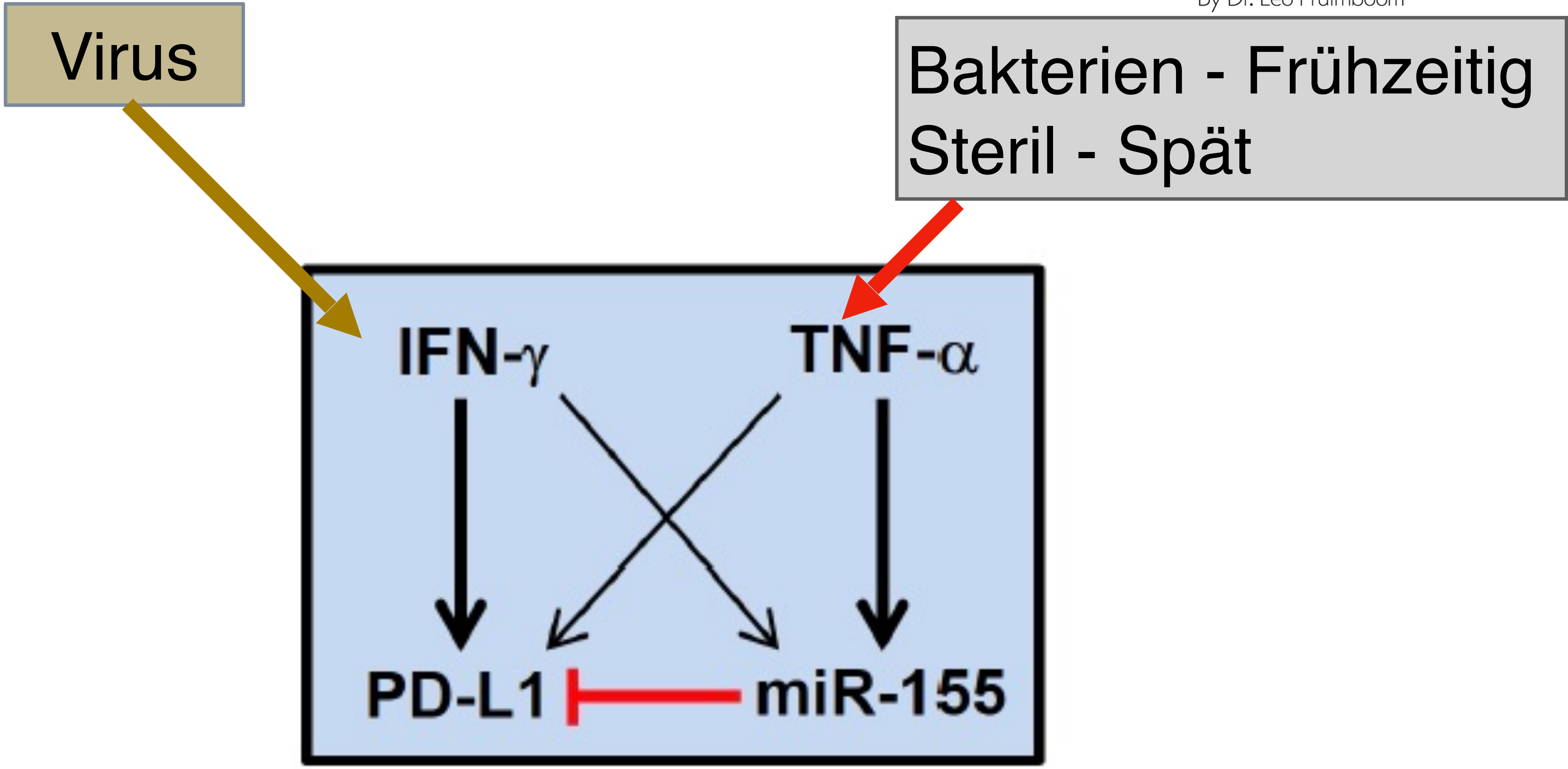
Einsam in der Welt

CORONA Virus
Krank

‘Entscheidung’
Th2 - AIS
Pro-Inflammatorisch

Kortisol Resistent
Estradiol

Weniger
Fruchtbarkeit

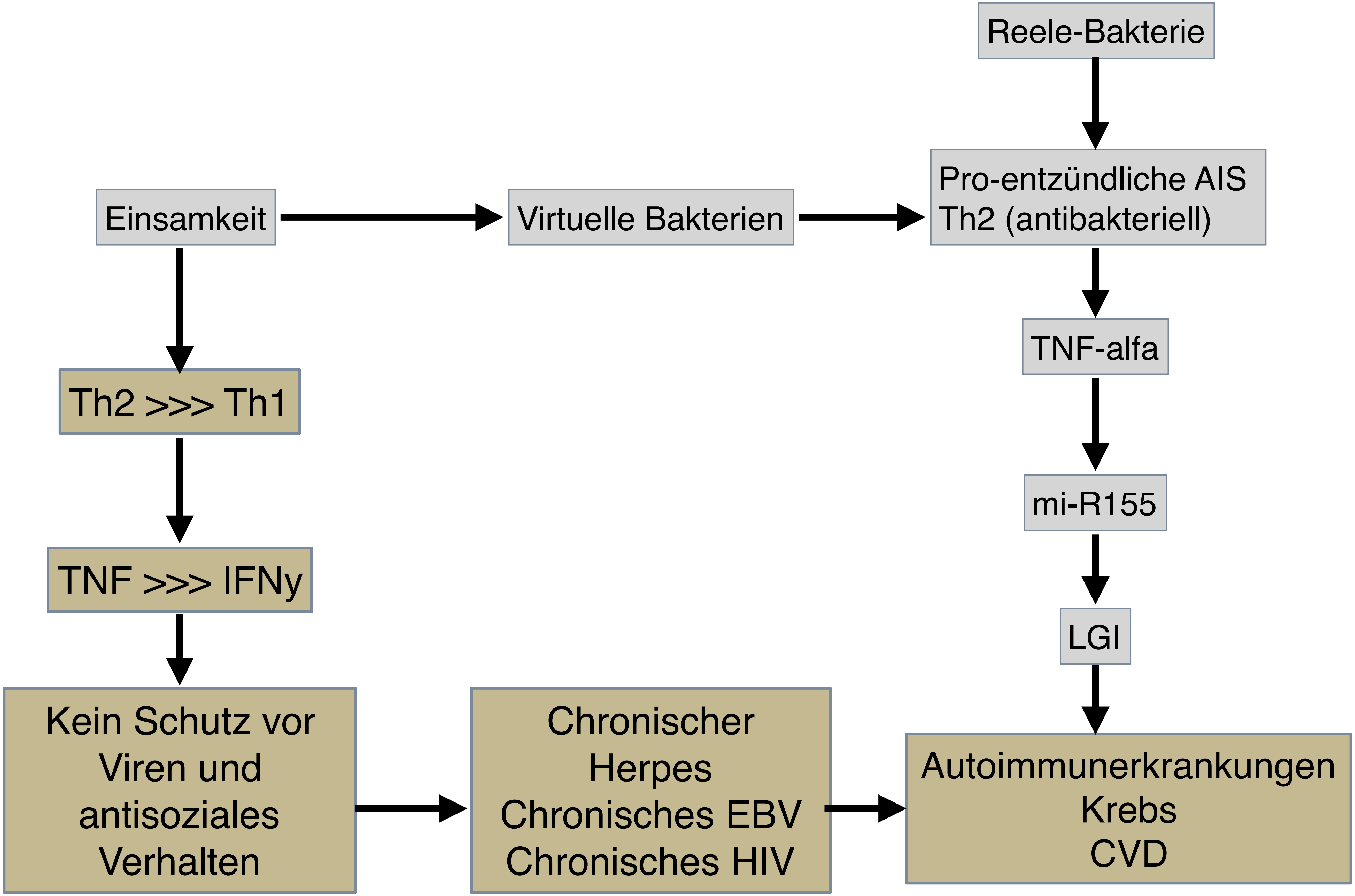


Virus

Bakterien - Frühzeitig
Steril - Spät

Curcumin, Resveratrol, Isoflavone, -Epigallocatechin-3-Gallat (EGCG), Lycopin, 3,3′ - Diindolylmethan (DIM) und Indol-3-Carbinol (I3C) hemmen miR-155

Ali. Drug, Healthcare and Patient Safety 2013:5 79–99
Lee. YBC. 2017



Reele-Bakterie

Einsamkeit

Virtuelle Bakterien

Pro-entzündliche AIS
Th2 (antibakteriell)

Th2 >>> Th1

TNF-alfa

mi-R155

TNF >>> IFNy

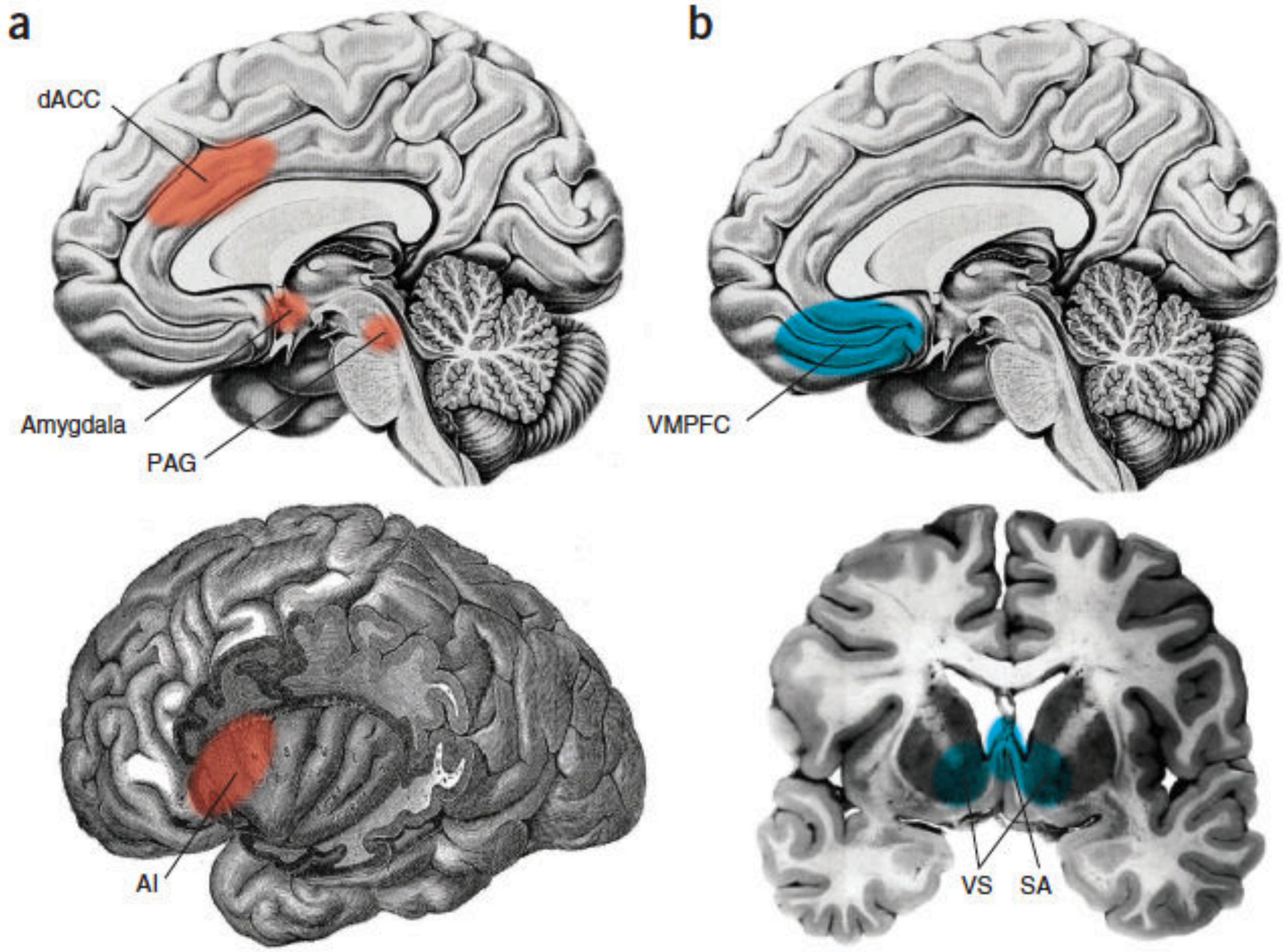
LGI

Kein Schutz vor Viren und antisoziales Verhalten

Chronischer Herpes
Chronisches EBV
Chronisches HIV

Autoimmunerkrankungen
Krebs
CVD

Die Neurologie der sozialen Verbindung und Einsamkeit


a
b
dACC
Amygdala
PAG
VMPFC
AI
VS
SA

Eisenberger.
nature
neuroscience
VOLUME 15 |
NUMBER 5 | MAY
2012

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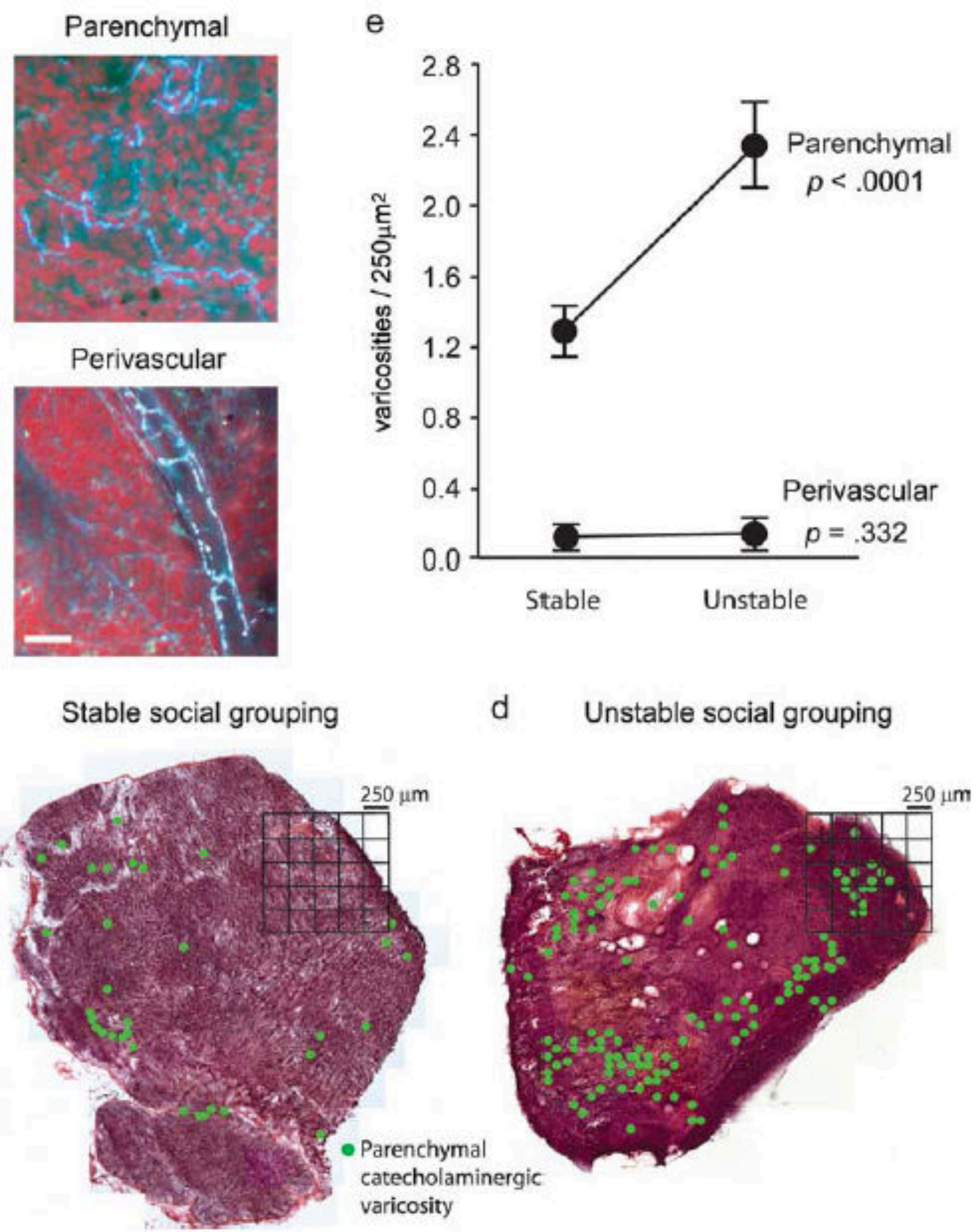

Chronische soziale Instabilität

Erhöhte Innervation der Lymphknoten durch noradrenerge Nerven und Entzündungsempfindlichkeit = evolutionär korrekt, führt aber nun zur Erkrankung.

Sloan. The Journal of Neuroscience, August 15, 2007 • 27(33):8857– 8865

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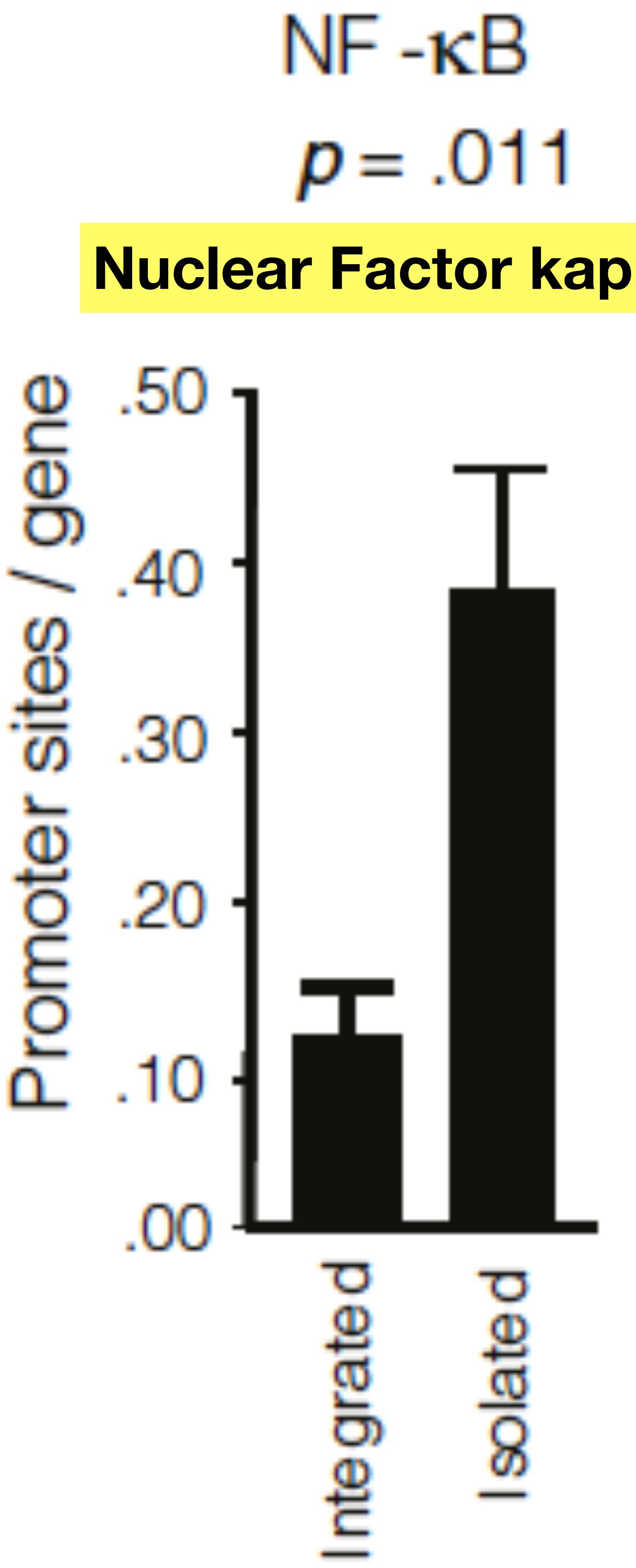
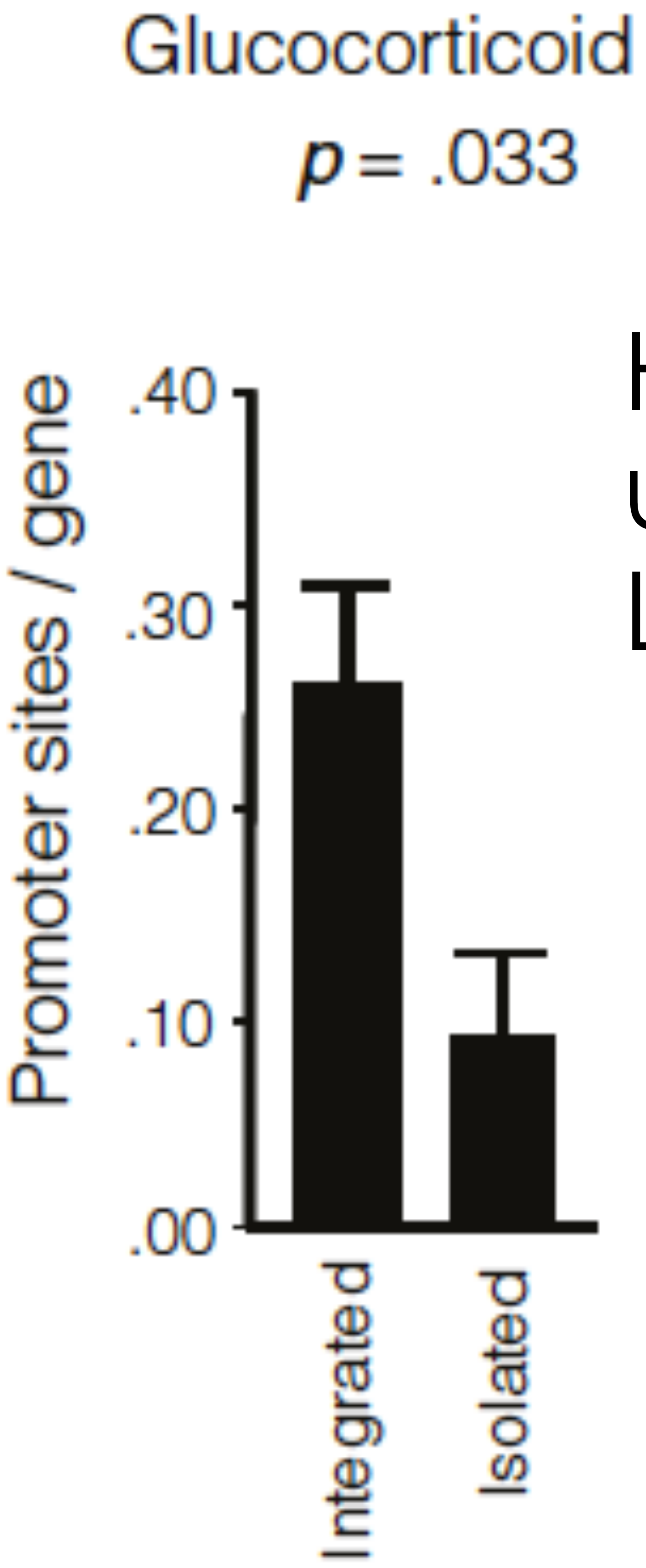
Entzündung

Cortisol Wirkung

Nuclear Factor kappa B





HPA-Achse wird unempfindlich bei Langzeitisolierung

Cole. Genome Biology 2007, 8:R189

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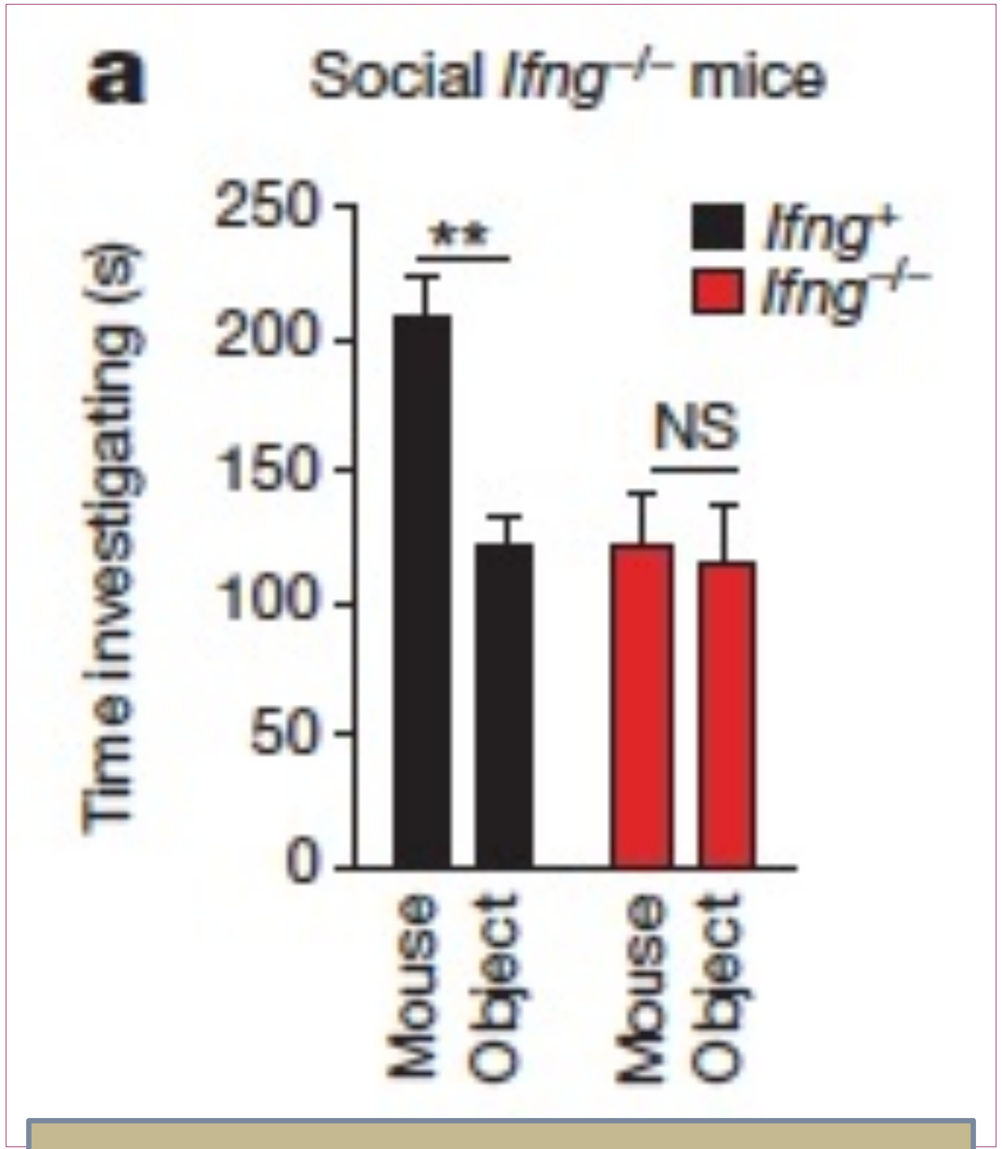
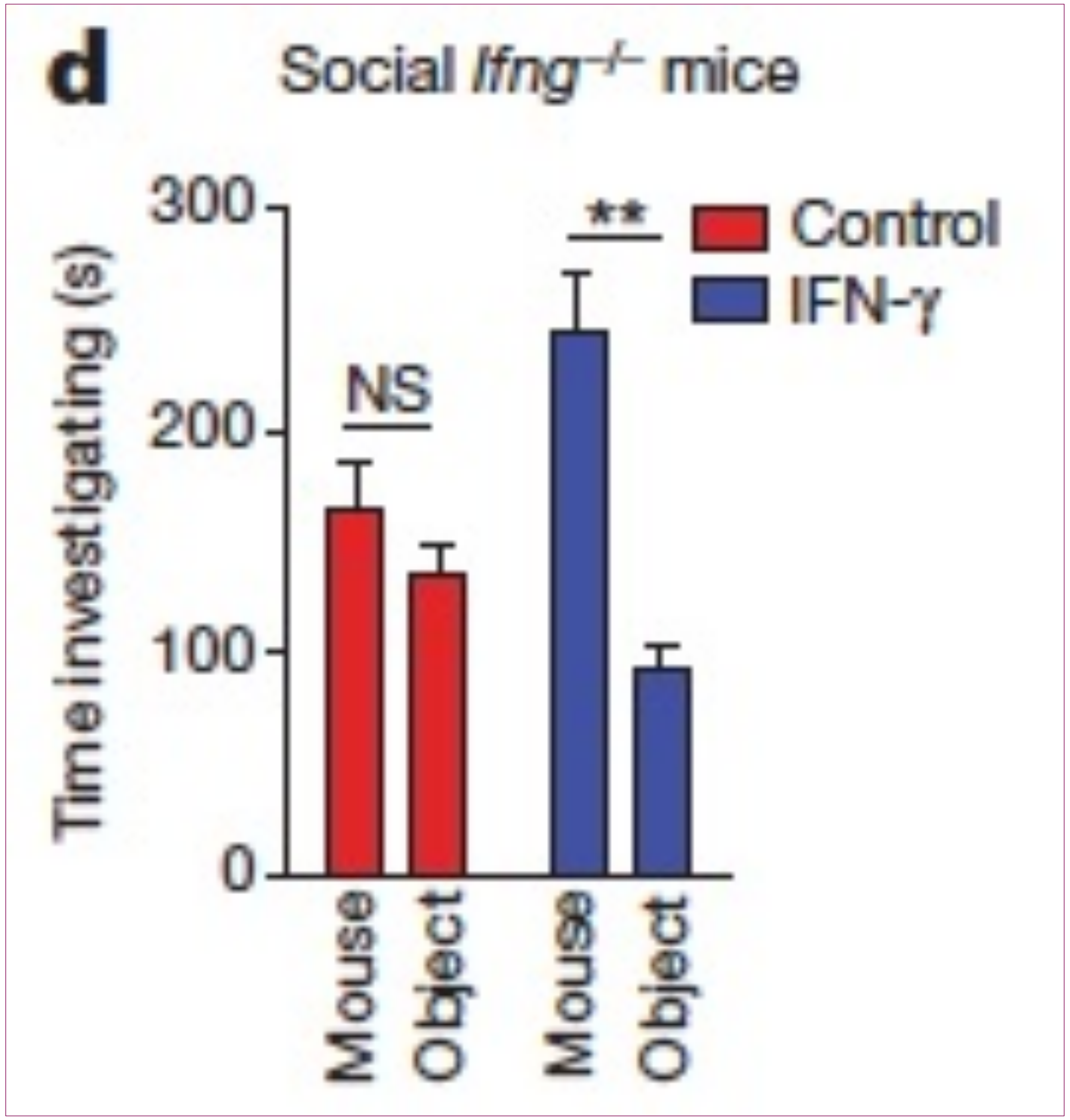
Unexpected role of interferon-γ in regulating neuronal connectivity and social behaviour

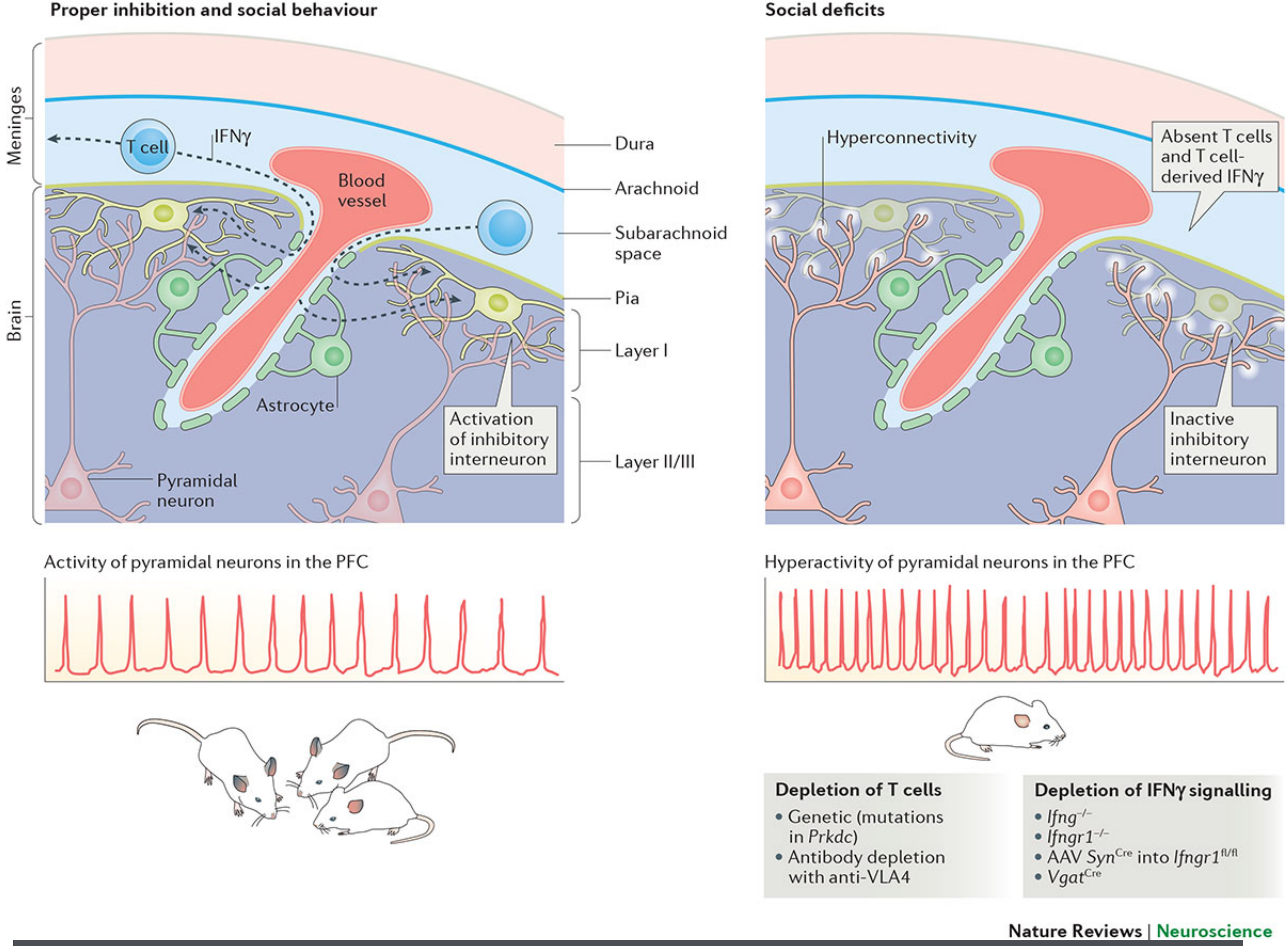


Mäuse, die kein Interferon produzieren können = weniger soziale Kontakte



Der soziale Kontakt erholt sich nach der Injektion mit T-Lymphozyten, die INFy

Filiano Nature 2016


Proper inhibition and social behaviour
Meninges
Brain
T cell
IFNγ
Blood vessel
Dura
Arachnoid
Subarachnoid space
Pia
Layer I
Layer II/III
Astrocyte
Activation of inhibitory interneuron
Pyramidal neuron
Activity of pyramidal neurons in the PFC
Social deficits
Hyperconnectivity
Absent T cells and T cell-derived IFNγ
Inactive inhibitory interneuron
Hyperactivity of pyramidal neurons in the PFC

Depletion of T cells

- Genetic (mutations in *Prkdc*)
- Antibody depletion with anti-VLA4

Depletion of IFNγ signalling

- *Ifng*$^{-/-}$
- *Ifngr1*$^{-/-}$
- AAV *Syn*$^{\mathrm{Cre}}$ into *Ifngr1*$^{\mathrm{fl/fl}}$
- *Vgat*$^{\mathrm{Cre}}$

Nature Reviews | Neuroscience

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Soziale Umgebung

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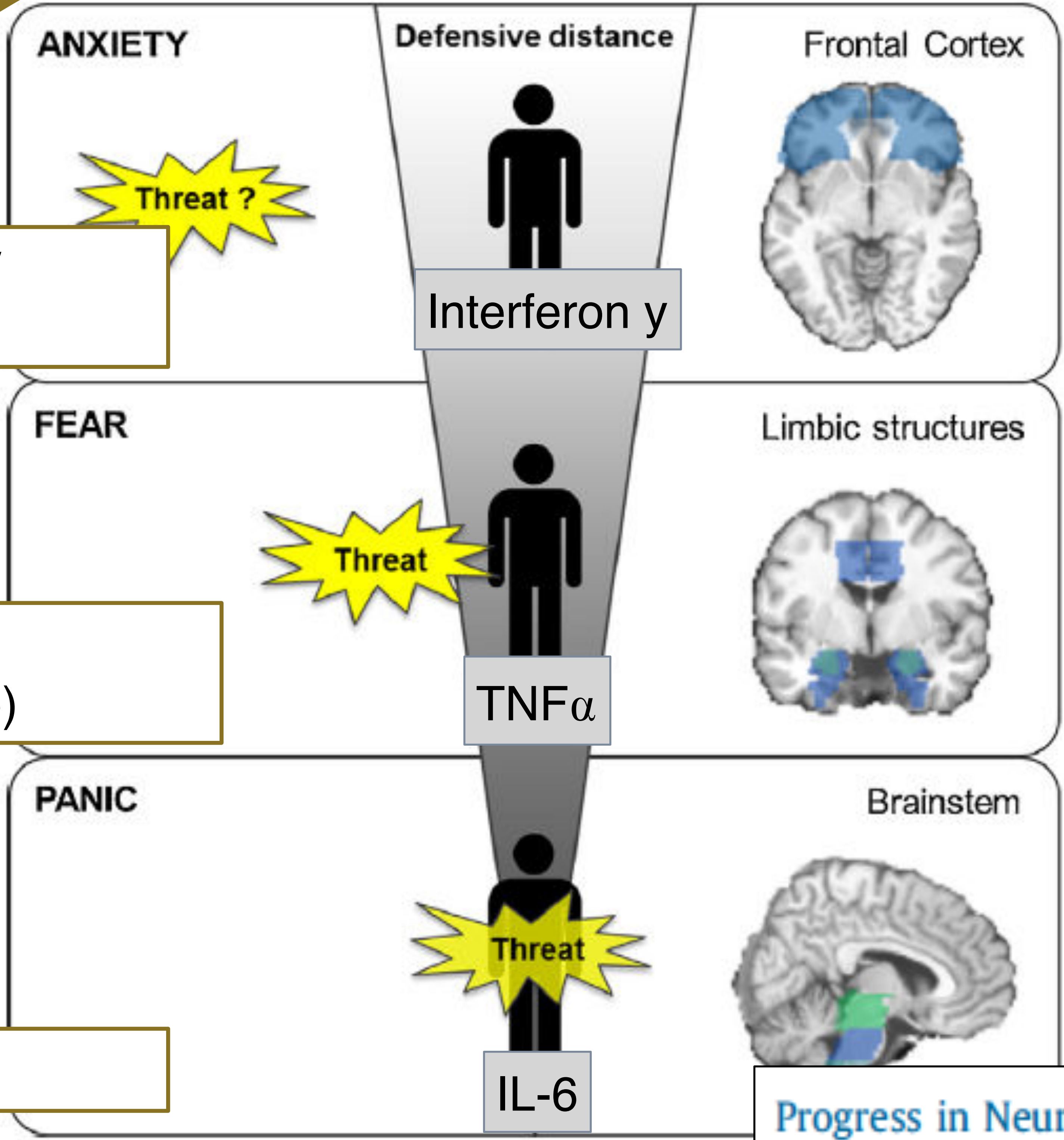
Interferon y


ANXIETY
Defensive distance
Frontal Cortex
Threat ?
FEAR
Limbic structures
Threat
PANIC
Brainstem
Threat

Interferon y

TNFα

IL-6

Therapie erkennen/ bewerten)

Reframing-/ Motivationstherapie)

Hormetische Reize

Angst, Furcht, Panik = linearer Zusammenhang

Progress in Neurobiology 129 (2015) 58–78

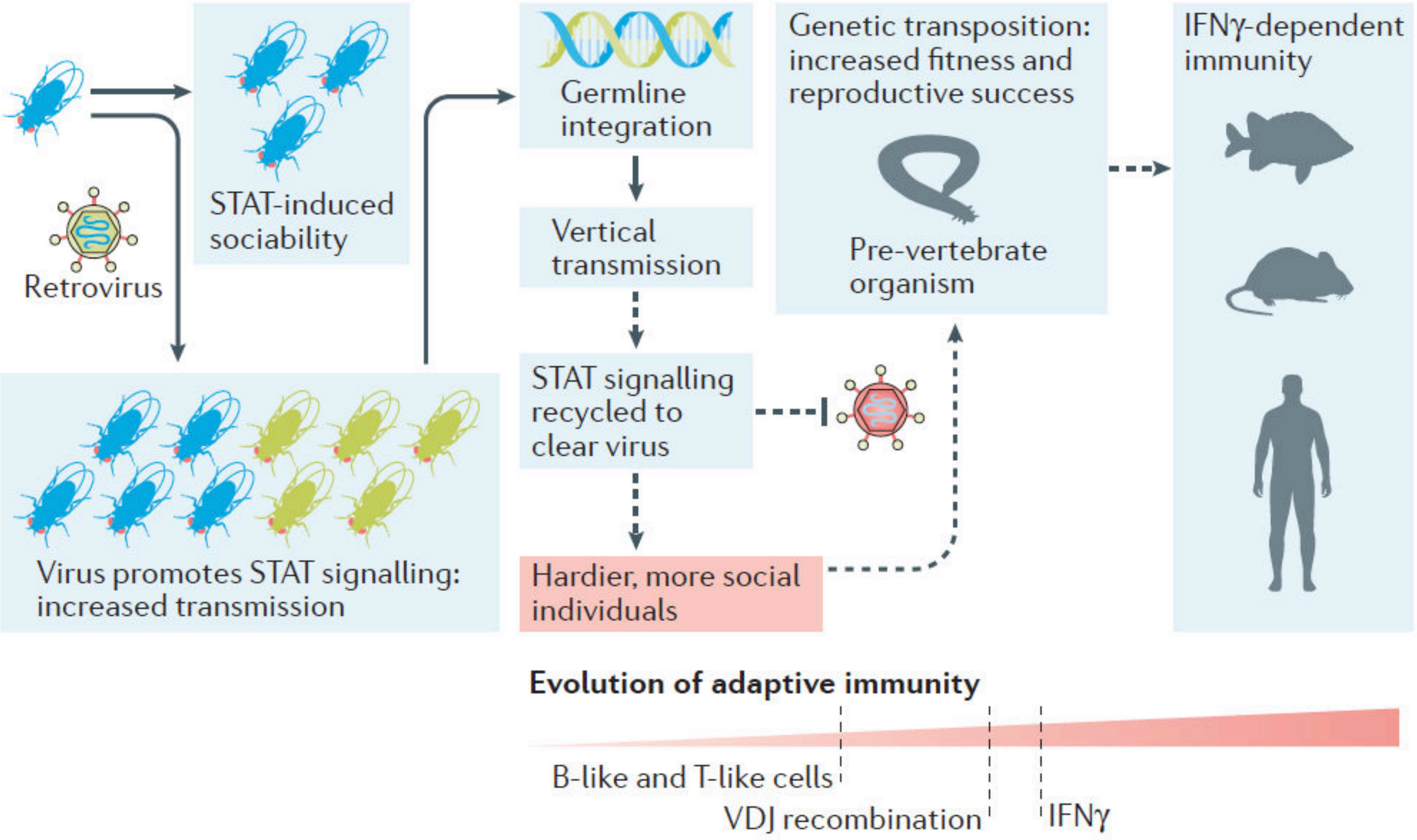
Erläuterung = Total logisch

Soziale Kontakte erfordern zwei grundlegende Funktionen

Schutz vor Viren (T-Zelle - IFN-y)
Soziale Kompetenz = Lärmentfernung = GABA-Zunahme über IFN-y in den Frontallappen

Übereinstimmend zeigen wir, dass hemmende Neuronen auf IFN-γ reagieren und die GABAergen Ströme (γ-Aminobuttersäure) in den Projektionsneuronen erhöhen, was darauf hindeutet, dass IFN-γ eine molekulare Verbindung zwischen der meningealen Immunität und den für das Sozialverhalten rekrutierten neuronalen Schaltkreisen ist.

Filiano Nature 2016


Retrovirus
STAT-induced sociability
Virus promotes STAT signalling: increased transmission
Germline integration
Vertical transmission
STAT signalling recycled to clear virus
Hardier, more social individuals
Genetic transposition: increased fitness and reproductive success
Pre-vertebrate organism
IFNγ-dependent immunity
Evolution of adaptive immunity
B-like and T-like cells
VDJ recombination
IFNγ

Filiano. Kipnis. NATURE REVIEWS I **NEUROSCIENCE** VOLUME 18 I JUNE 2017 I

Bacteriophagen
“Anti-virale macroschimmels”
“Anti-microschimmels”

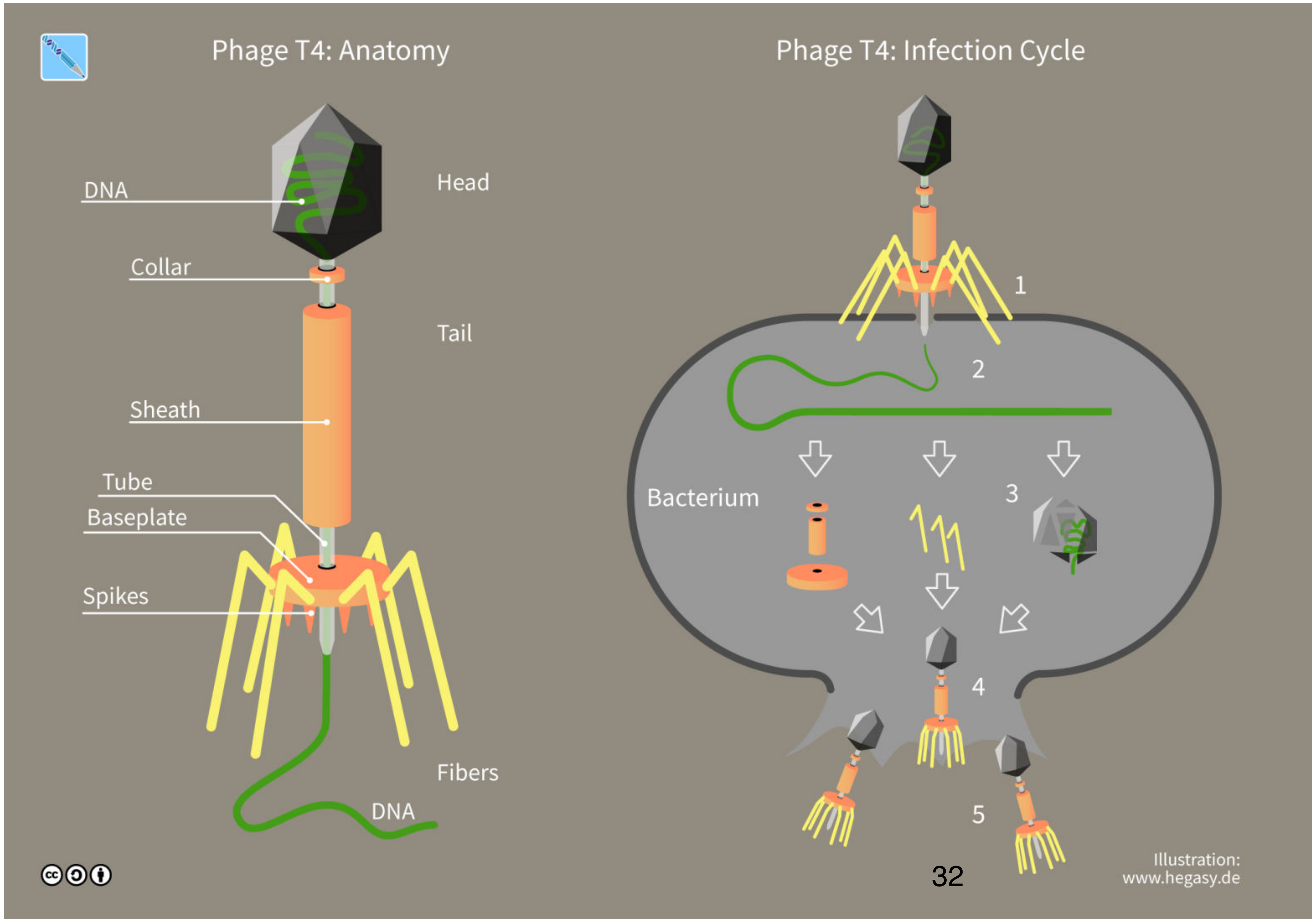
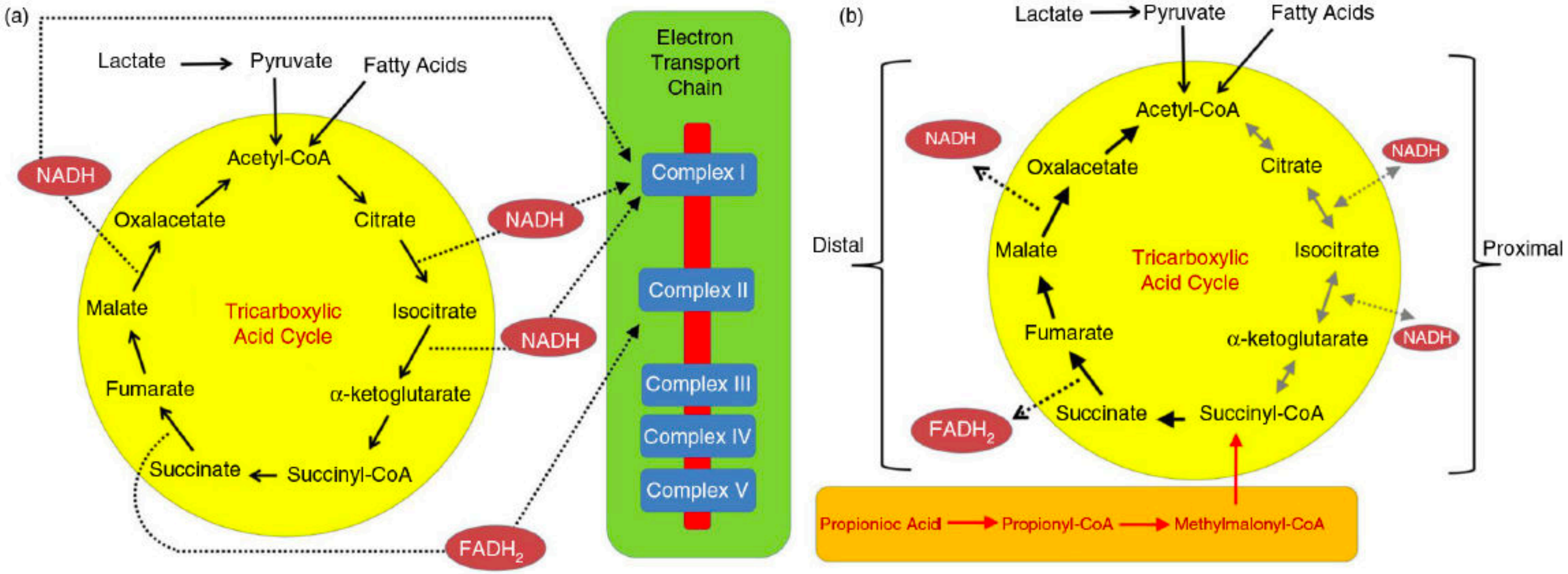

Phage T4: Anatomy
DNA
Head
Collar
Tail
Sheath
Tube
Baseplate
Spikes
Fibers
DNA
Phage T4: Infection Cycle
1
2
Bacterium
3
4
5

Illustration:
www.hegasy.de

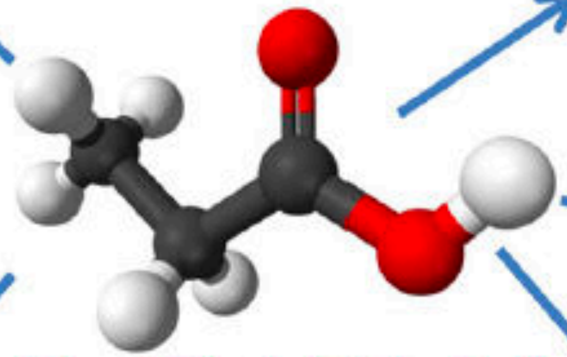
Autistische Kinder haben eine Flora, die mehr Propioinsäure produziert. Infolgedessen werden mitochondriale Schäden und Hyperaktivität im frontalen Kortex


(a)
Lactate
Pyruvate
Fatty Acids
Acetyl-CoA
Citrate
Isocitrate
α-ketoglutarate
Succinyl-CoA
Succinate
Fumarate
Malate
Oxalacetate
Tricarboxylic Acid Cycle
NADH
NADH
NADH
$FADH_2$
Electron Transport Chain
Complex I
Complex II
Complex III
Complex IV
Complex V
(b)
Lactate
Pyruvate
Fatty Acids
Acetyl-CoA
Citrate
Isocitrate
α-ketoglutarate
Succinyl-CoA
Succinate
Fumarate
Malate
Oxalacetate
Tricarboxylic Acid Cycle
NADH
NADH
NADH
$FADH_2$
Distal
Proximal
Propionoc Acid
Propionyl-CoA
Methylmalonyl-CoA

Propionsäure hemmt das erste Teil der Krebszyklus

McFabe. Microbial Ecology in Health & Disease 2015, 26: 28177

Gute und schlechte Gärung - Propionsäure als Gift



Short Chain Fatty Acid
Bacterial Fermentation
Products

Passive/active uptake to gut and CNS
(monocarboxylate transporters
(fatty acids, ketones)

Fatty Acid G coupled protein receptor activation
Neurotransmitter synthesis (catecholamine, 5HT) and release
Increased intracellular calcium

Gut motility and inflammation
Malabsorption
Tight/Gap Junction impairment barrier dysfunction
(immune and enteric nervous system effects)

Neuroinflammation/neurodevelopment
Cortical dysplasia

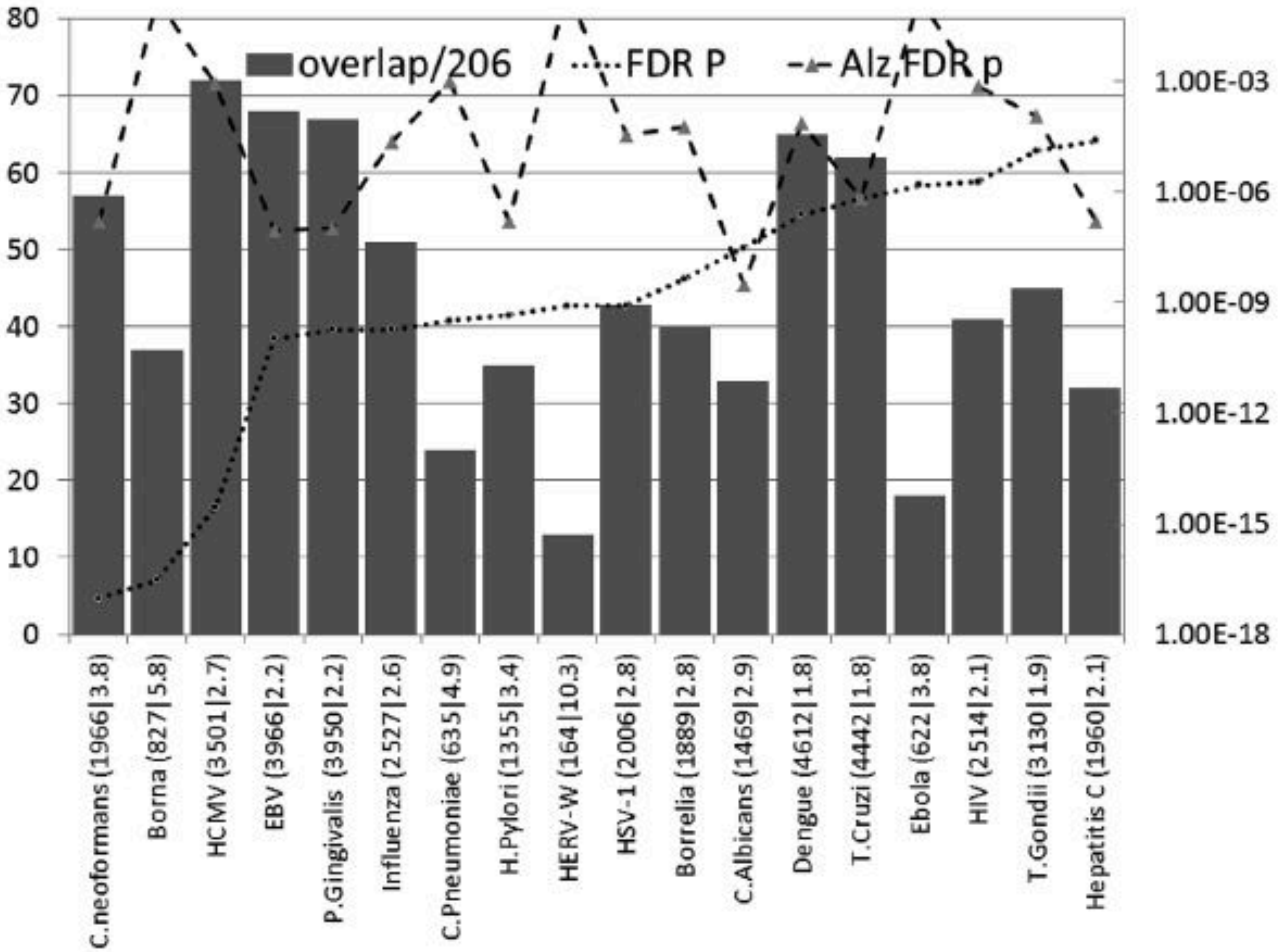
Gap Junction closure
Electrotonic coupling,
Neuronal Migration
Impaired synaptic pruning

Altered gene expression
(Histone deacetylase inhibition)
CREB activation (memory)
Epigenetic effects
(More pronounced at critical neurodevelopmental Windows)

Autism-like behavior
Repetitive, Antisocial, Object fixation,
Anxiety-like behavior, Perseveration
Seizure disorder, Dystonia, Tics,
Sensory processing

Mitochondria
Altered TCA cycle
Phospholipid alterations
Oxidative stress
Reduced glutathione,
Carnitine deficiency

McFabe. Microbial Ecology in Health & Disease 2015, 26: 28177

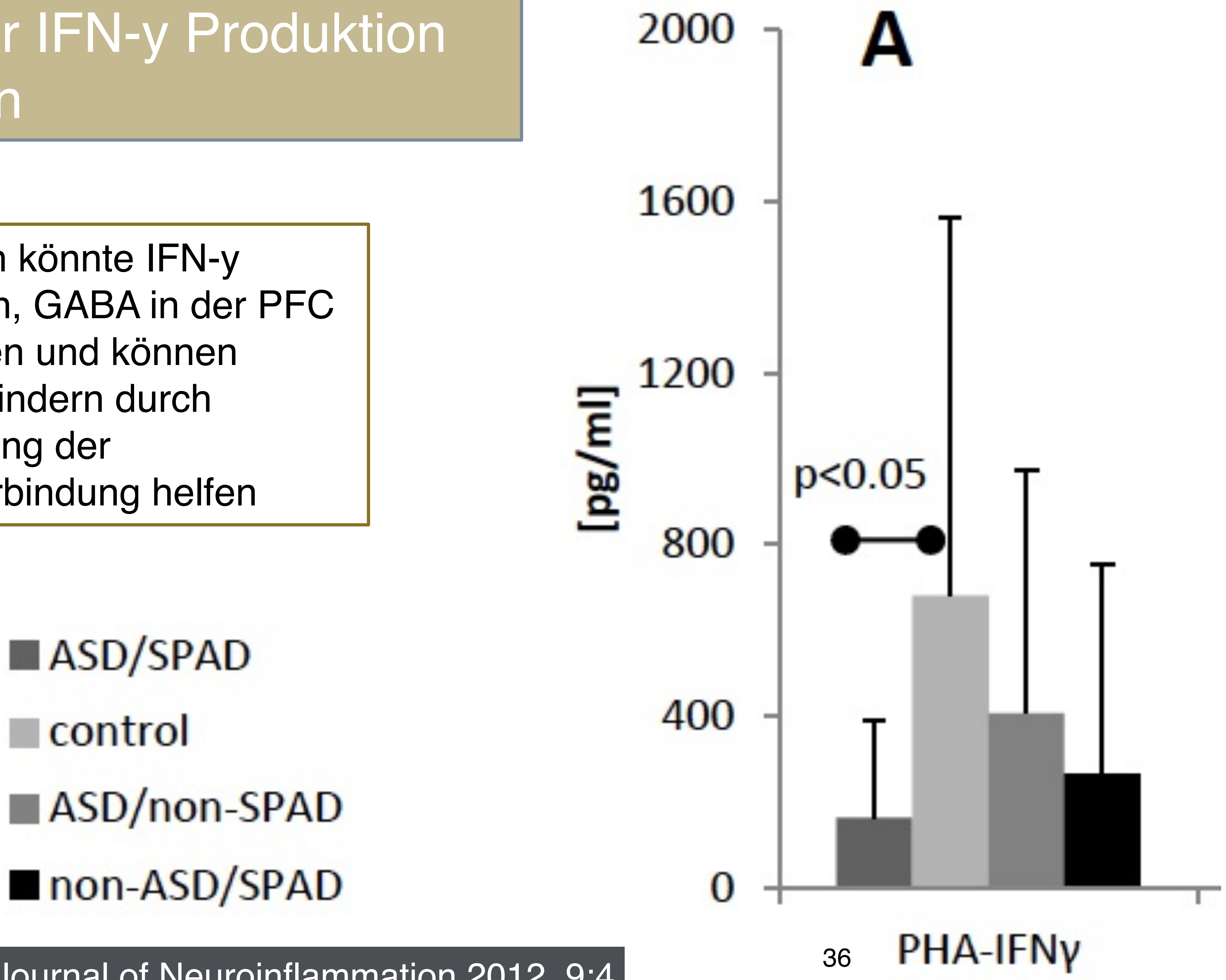


Kinder mit Autismus haben ein klares Problem mit dem Th1-Schutz

Carter. Autism genes and the leukocyte transcriptome in autistic toddlers relate to pathogen interactomes, infection and the immune system. A role for excess neurotrophic sAPPα and reduced antimicrobial Aβ. Neurochemistry International 126 (2019) 36–58

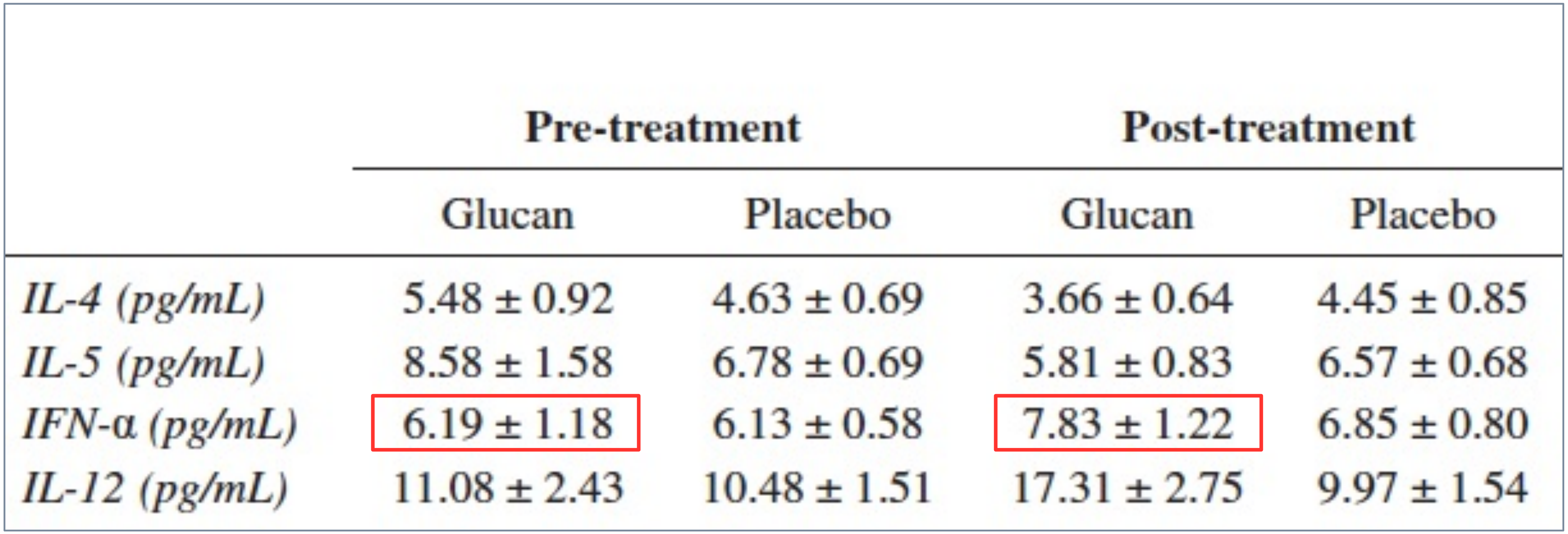
Kinder mit Autismus haben verringerte Sozialkompetenz die mit der IFN-y Produktion korrelieren

B-Glucan könnte IFN-y aktivieren, GABA in der PFC induzieren und können diesen Kindern durch Beruhigung der Hyperverbindung helfen



Jyonouchi et al. Journal of Neuroinflammation 2012, 9:4

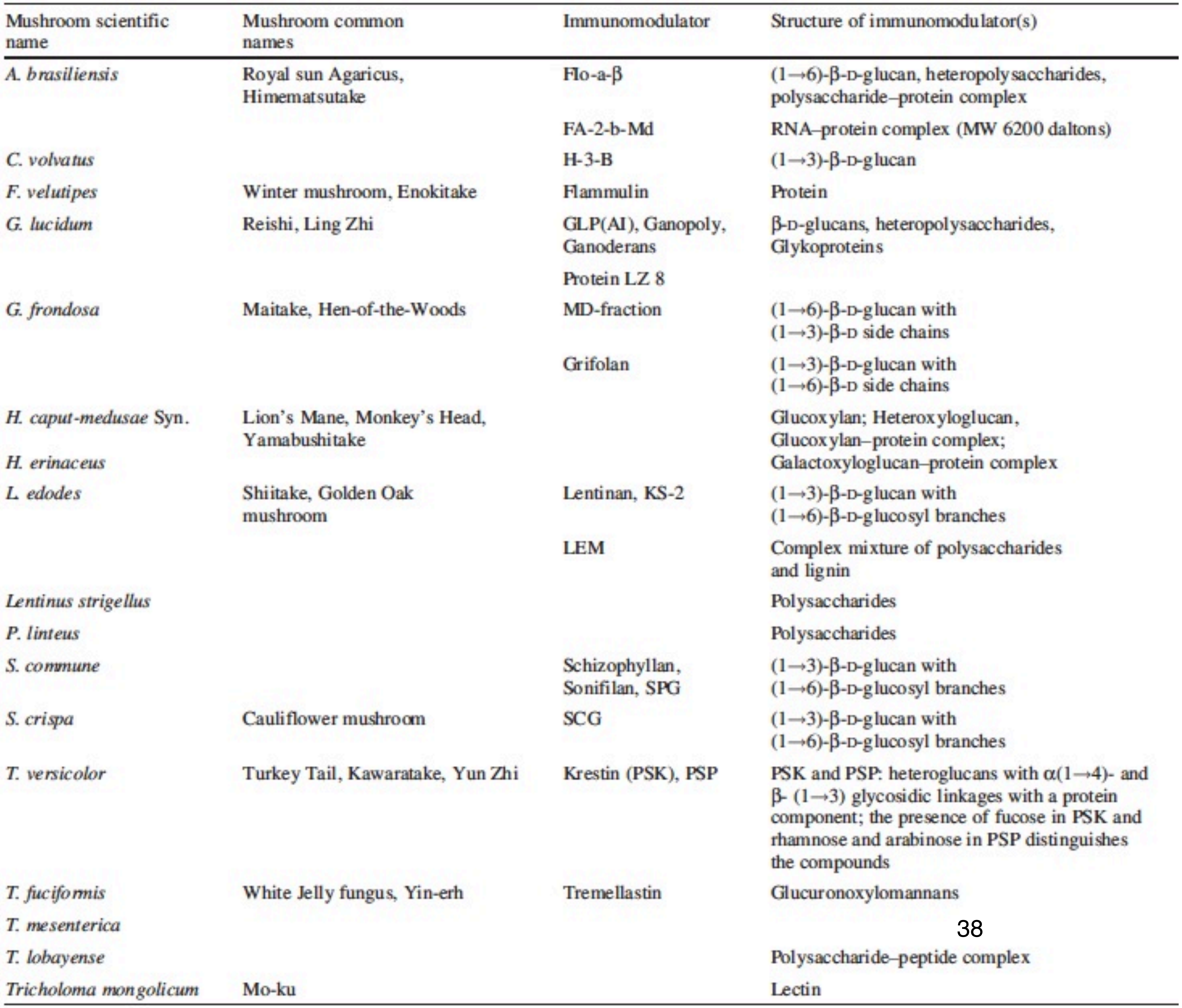
Beta-Glucan ist der Wirkstoff und verantwortlich für die Produktion von IFN-Y.



	Pre-treatment		Post-treatment	
	Glucan	Placebo	Glucan	Placebo
IL-4 (pg/mL)	5.48 ± 0.92	4.63 ± 0.69	3.66 ± 0.64	4.45 ± 0.85
IL-5 (pg/mL)	8.58 ± 1.58	6.78 ± 0.69	5.81 ± 0.83	6.57 ± 0.68
IFN-α (pg/mL)	6.19 ± 1.18	6.13 ± 0.58	7.83 ± 1.22	6.85 ± 0.80
IL-12 (pg/mL)	11.08 ± 2.43	10.48 ± 1.51	17.31 ± 2.75	9.97 ± 1.54

Kyrmaz. Eur. Cytokine Netw., Vol. 16 n° 2, June 2005, 128-34

Lindequist. eCAM 2005;2(3)285–299



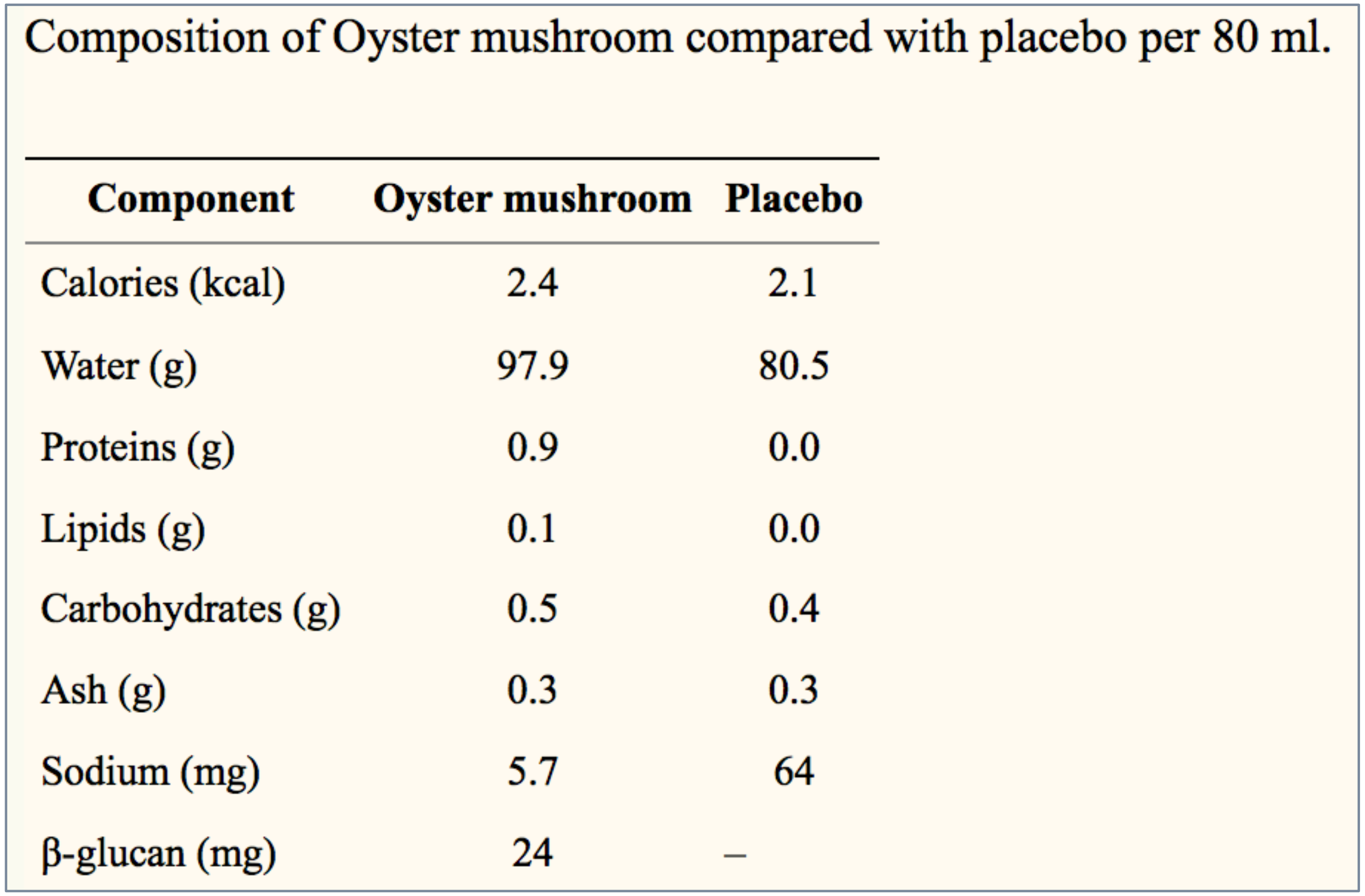
Mushroom scientific name	Mushroom common names	Immunomodulator	Structure of immunomodulator(s)
A. brasiliensis	Royal sun Agaricus, Himematsutake	Flo-a-β	(1→6)-β-D-glucan, heteropolysaccharides, polysaccharide–protein complex
		FA-2-b-Md	RNA–protein complex (MW 6200 daltons)
C. volvatus		H-3-B	(1→3)-β-D-glucan
F. velutipes	Winter mushroom, Enokitake	Flammulin	Protein
G. lucidum	Reishi, Ling Zhi	GLP(AI), Ganopoly, Ganoderans	β-D-glucans, heteropolysaccharides, Glykoproteins
		Protein LZ 8	
G. frondosa	Maitake, Hen-of-the-Woods	MD-fraction	(1→6)-β-D-glucan with (1→3)-β-D side chains
		Grifolan	(1→3)-β-D-glucan with (1→6)-β-D side chains
H. caput-medusae Syn. *H. erinaceus*	Lion's Mane, Monkey's Head, Yamabushitake		Glucoxylan; Heteroxyloglucan, Glucoxylan–protein complex; Galactoxyloglucan–protein complex
L. edodes	Shiitake, Golden Oak mushroom	Lentinan, KS-2	(1→3)-β-D-glucan with (1→6)-β-D-glucosyl branches
		LEM	Complex mixture of polysaccharides and lignin
Lentinus strigellus			Polysaccharides
P. linteus			Polysaccharides
S. commune		Schizophyllan, Sonifilan, SPG	(1→3)-β-D-glucan with (1→6)-β-D-glucosyl branches
S. crispa	Cauliflower mushroom	SCG	(1→3)-β-D-glucan with (1→6)-β-D-glucosyl branches
T. versicolor	Turkey Tail, Kawaratake, Yun Zhi	Krestin (PSK), PSP	PSK and PSP: heteroglucans with α(1→4)- and β- (1→3) glycosidic linkages with a protein component; the presence of fucose in PSK and rhamnose and arabinose in PSP distinguishes the compounds
T. fuciformis	White Jelly fungus, Yin-erh	Tremellastin	Glucuronoxylomannans
T. mesenterica			
T. lobayense			Polysaccharide–peptide complex
Tricholoma mongolicum	Mo-ku		Lectin

J Tradit Complement Med. 2016 Oct; 6(4): 424–430.
Published online 2015 Dec 29. doi: 10.1016/j.jtcme.2015.11.004
PMCID: PMC5067930
PMID: 27774430

Enhancement of the Th1-phenotype immune system by the intake of Oyster mushroom (Tamogitake) extract in a double-blind, placebo-controlled study

80 mg

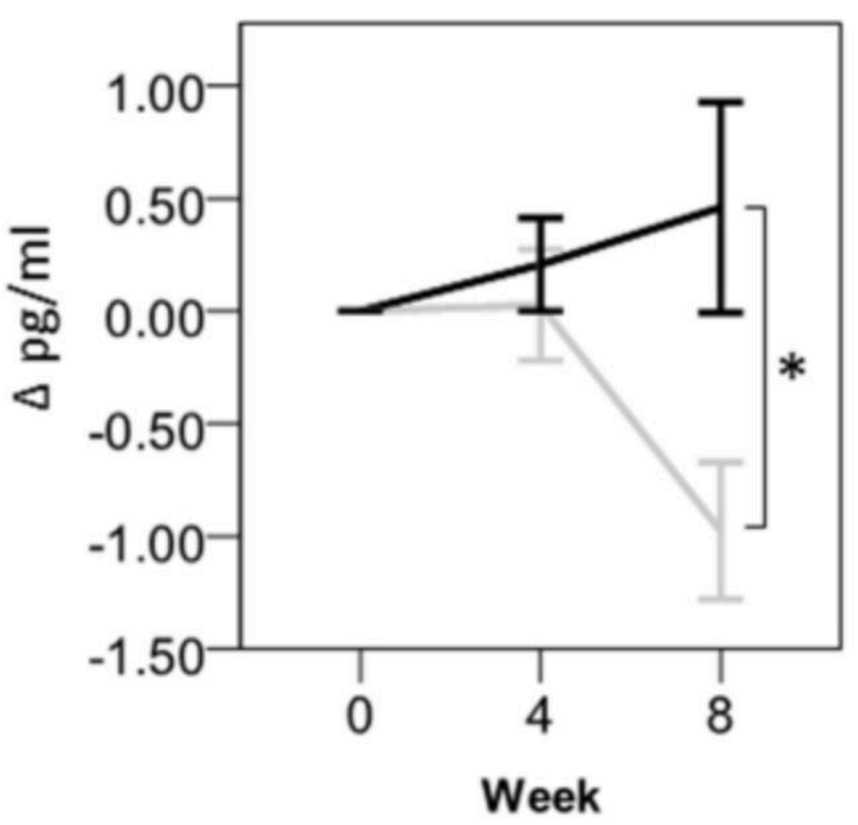
Aiko Tanaka, Mie Nishimura, Yuji Sato, Hiroki Sato, and Jun Nishihira*



Composition of Oyster mushroom compared with placebo per 80 ml.

Component	Oyster mushroom	Placebo
Calories (kcal)	2.4	2.1
Water (g)	97.9	80.5
Proteins (g)	0.9	0.0
Lipids (g)	0.1	0.0
Carbohydrates (g)	0.5	0.4
Ash (g)	0.3	0.3
Sodium (mg)	5.7	64
β-glucan (mg)	24	–

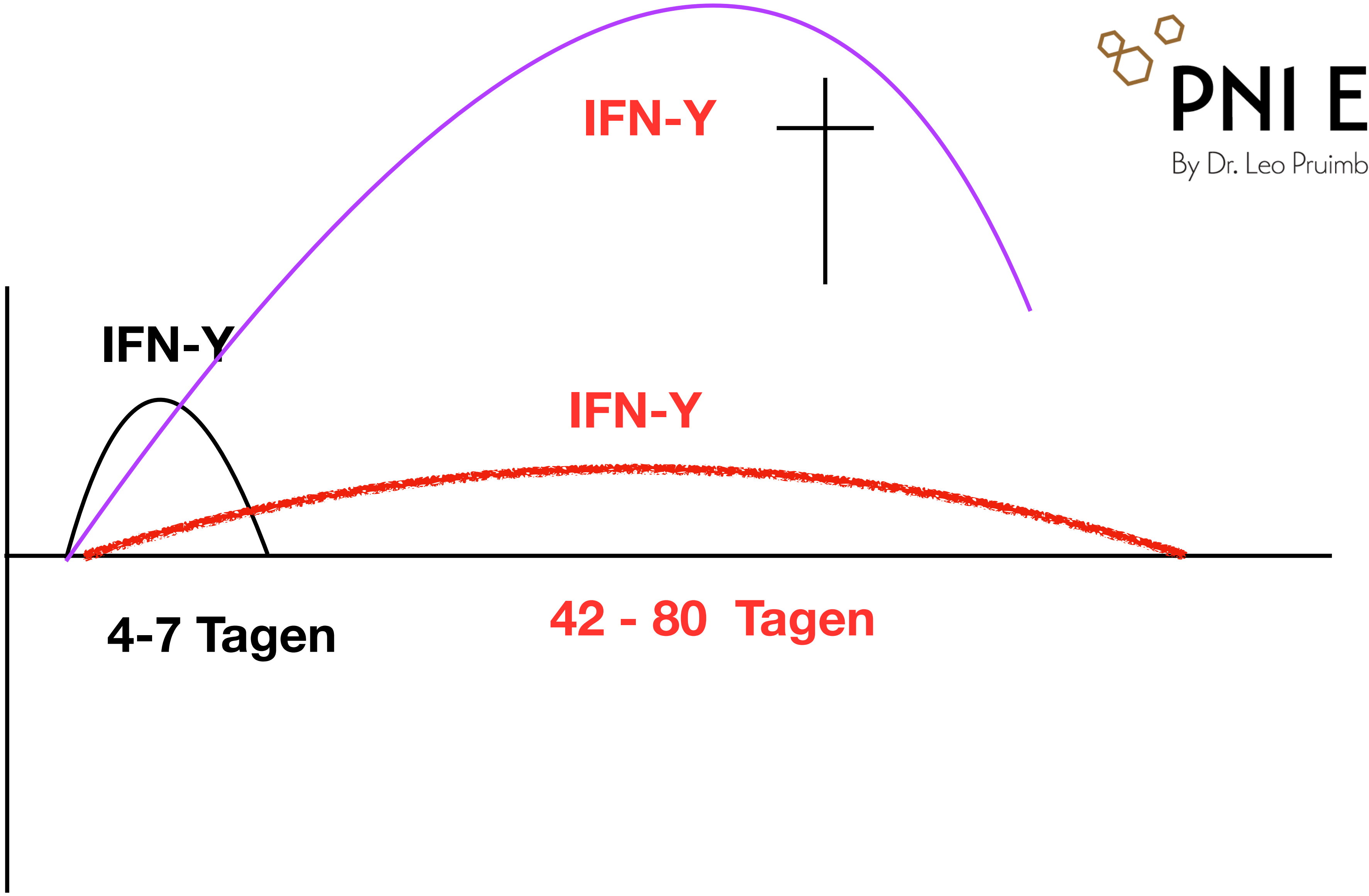
(a) Changes in the plasma level of IFN-γ



Cordyceps sinensis
Maitake
Shiitake
Austernpilz

Grifola frondosa (maitake) extract, gestandaardiseerd op minimaal 25% polysachariden	80 mg
Lentinula edodes (shiitake) mycelia extract, bevat lentinan	100 mg
Cordyceps sinensis (Chinese rupsenzwam) mycelium, gestandaardiseerd op minimaal 6% cordycepszuren	150 mg
Pleurotus ostreatus (gewone oesterzwam)	120 mg

Lindequist. eCAM 2005;2(3)285–299

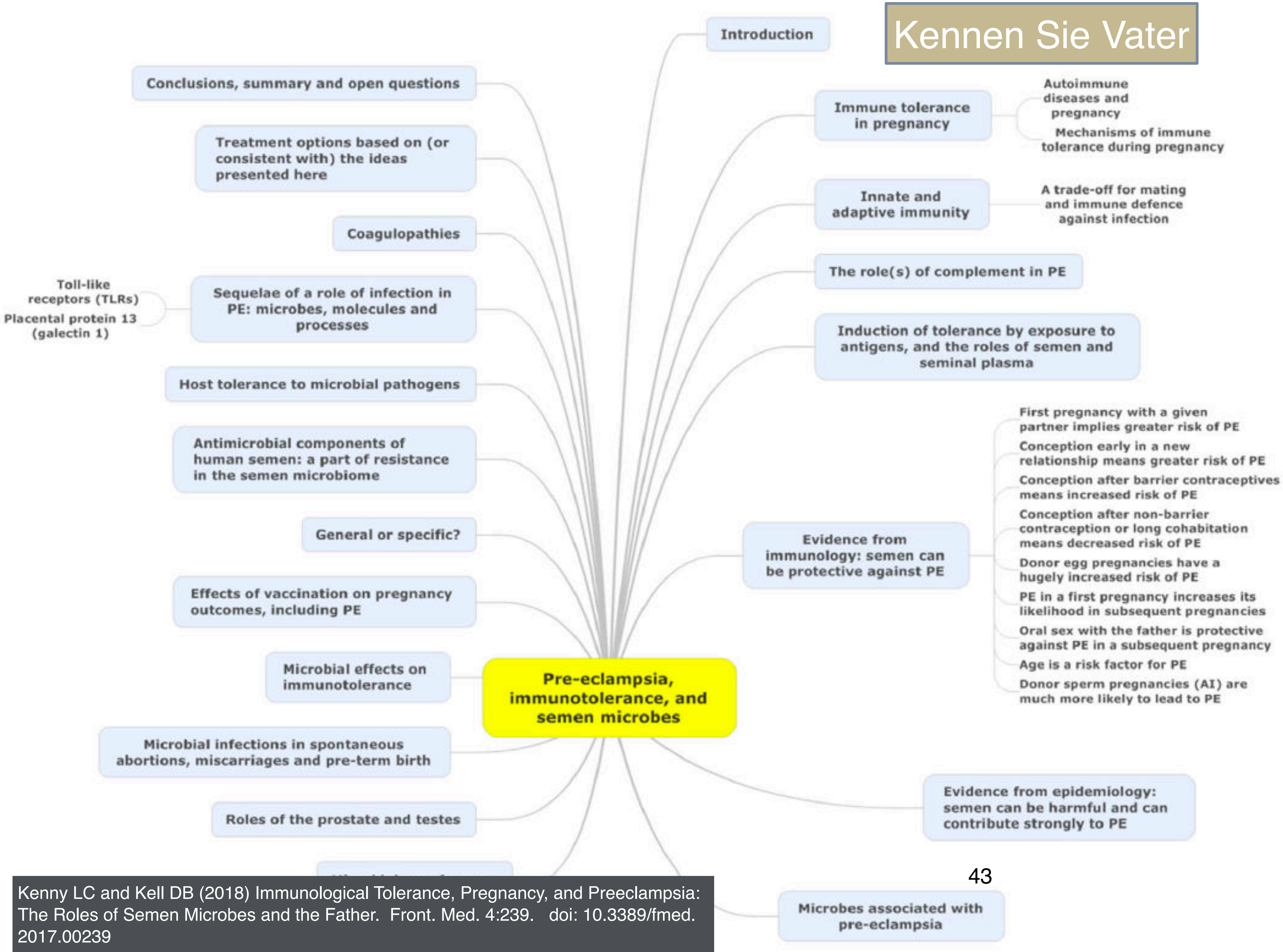

IFN-Y
IFN-Y
IFN-Y
4-7 Tagen
42 - 80 Tagen

Tag 1

Immunsystem und sexuelle Aktivität
Aktives Lernen
Das Text-Kontext-Modell

PNI Europe

Kennen Sie Vater



Pre-eclampsia, immunotolerance, and semen microbes

- Introduction
- Immune tolerance in pregnancy
  - Autoimmune diseases and pregnancy
  - Mechanisms of immune tolerance during pregnancy
- Innate and adaptive immunity
  - A trade-off for mating and immune defence against infection
- The role(s) of complement in PE
- Induction of tolerance by exposure to antigens, and the roles of semen and seminal plasma
- Evidence from immunology: semen can be protective against PE
  - First pregnancy with a given partner implies greater risk of PE
  - Conception early in a new relationship means greater risk of PE
  - Conception after barrier contraceptives means increased risk of PE
  - Conception after non-barrier contraception or long cohabitation means decreased risk of PE
  - Donor egg pregnancies have a hugely increased risk of PE
  - PE in a first pregnancy increases its likelihood in subsequent pregnancies
  - Oral sex with the father is protective against PE in a subsequent pregnancy
  - Age is a risk factor for PE
  - Donor sperm pregnancies (AI) are much more likely to lead to PE
- Evidence from epidemiology: semen can be harmful and can contribute strongly to PE
- Microbes associated with pre-eclampsia
- Roles of the prostate and testes
- Microbial infections in spontaneous abortions, miscarriages and pre-term birth
- Microbial effects on immunotolerance
- Effects of vaccination on pregnancy outcomes, including PE
- General or specific?
- Antimicrobial components of human semen: a part of resistance in the semen microbiome
- Host tolerance to microbial pathogens
- Sequelae of a role of infection in PE: microbes, molecules and processes
  - Toll-like receptors (TLRs)
  - Placental protein 13 (galectin 1)
- Coagulopathies
- Treatment options based on (or consistent with) the ideas presented here
- Conclusions, summary and open questions

Kenny LC and Kell DB (2018) Immunological Tolerance, Pregnancy, and Preeclampsia: The Roles of Semen Microbes and the Father. Front. Med. 4:239. doi: 10.3389/fmed.2017.00239

PNI Europe
By Dr. Leo Pruimboom

Freiwillige Sex	**2%**	**85%**
Stressvolle Sex	**8%**	**5%**

F/M : 100/107 = Testosteron = Immun-Suppressiv = Infektion Empfindlichkeit

Vater > 30 Jahr = female > 1%

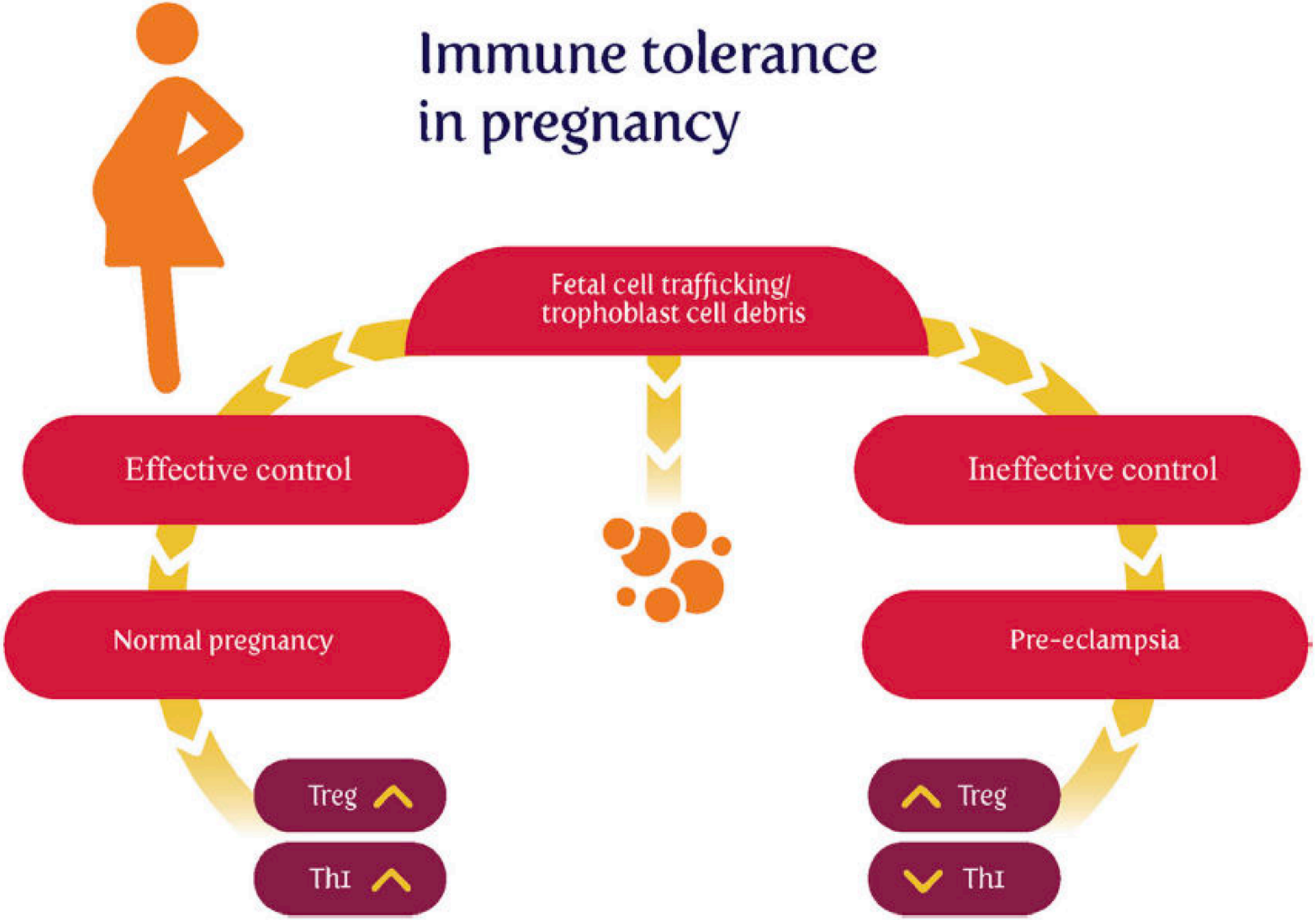
Totschlag: Biologische Eltern:Pflege-Eltern = 1:120

Down Syndrome = trisomie 21 Chromosom = Lebenswürdig = 50% BMR = 850 Kcal/Tag
Trisomie 17 = Nicht geboren

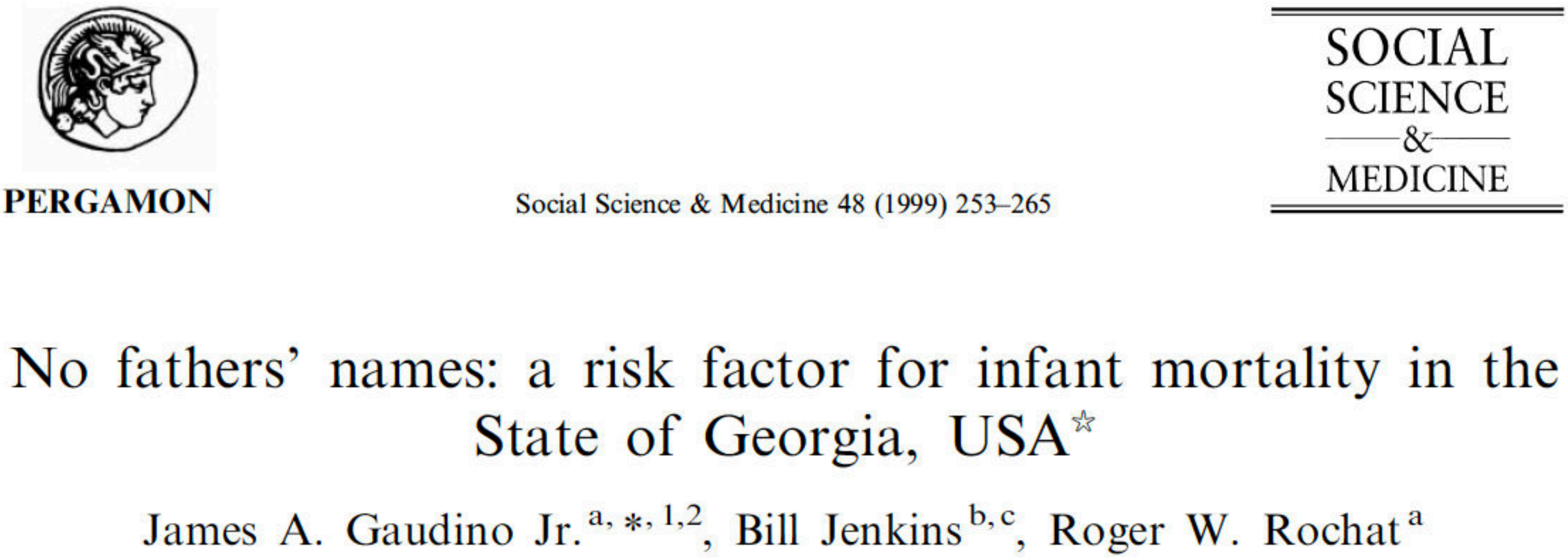
14 Jahr	**1/872**
25 Jahr	**1/1175**
49 Jahr	**1/11**
55 Jahr	**1/10**

Frau Orgasmus		Mann Orgasmus	
Stress	**Entspannt**	**Stress**	**Entspannt**
Vaginale	**Clitoris**	**Glande**	**Penis**
Parasympatikus	**Sympatikus**	**Sympatikus**	**Parasympatikus**
Testosteron	**Estriadol**	**Estriadol**	**Testosteron**

Kennen Sie Vater


Immune tolerance in pregnancy
Fetal cell trafficking/ trophoblast cell debris
Effective control
Ineffective control
Normal pregnancy
Pre-eclampsia
Treg ↑
Th1 ↑
↑ Treg
↓ Th1

Kenny LC and Kell DB (2018) Immunological Tolerance, Pregnancy, and Preeclampsia: The Roles of Semen Microbes and the Father. Front. Med. 4:239. doi: 10.3389/fmed.2017.00239



PERGAMON

Social Science & Medicine 48 (1999) 253–265

SOCIAL
SCIENCE
&
MEDICINE

No fathers' names: a risk factor for infant mortality in the State of Georgia, USA☆

James A. Gaudino Jr.[a,*,1,2], Bill Jenkins[b,c], Roger W. Rochat[a]

Wir fanden heraus, dass das Fehlen des Nachnamens des Vaters ein einzigartiger, unabhängiger Risikofaktor für die Säuglingssterblichkeit ist, der als Risikomarker nützlicher erscheint als ein unverheirateter Status. Solche Befunde legen nahe, dass neben dem Familienstand auch Faktoren, die mit der Anwesenheit männlicher Partner zusammenhängen, die Überlebenschancen der Babys beeinflussen.

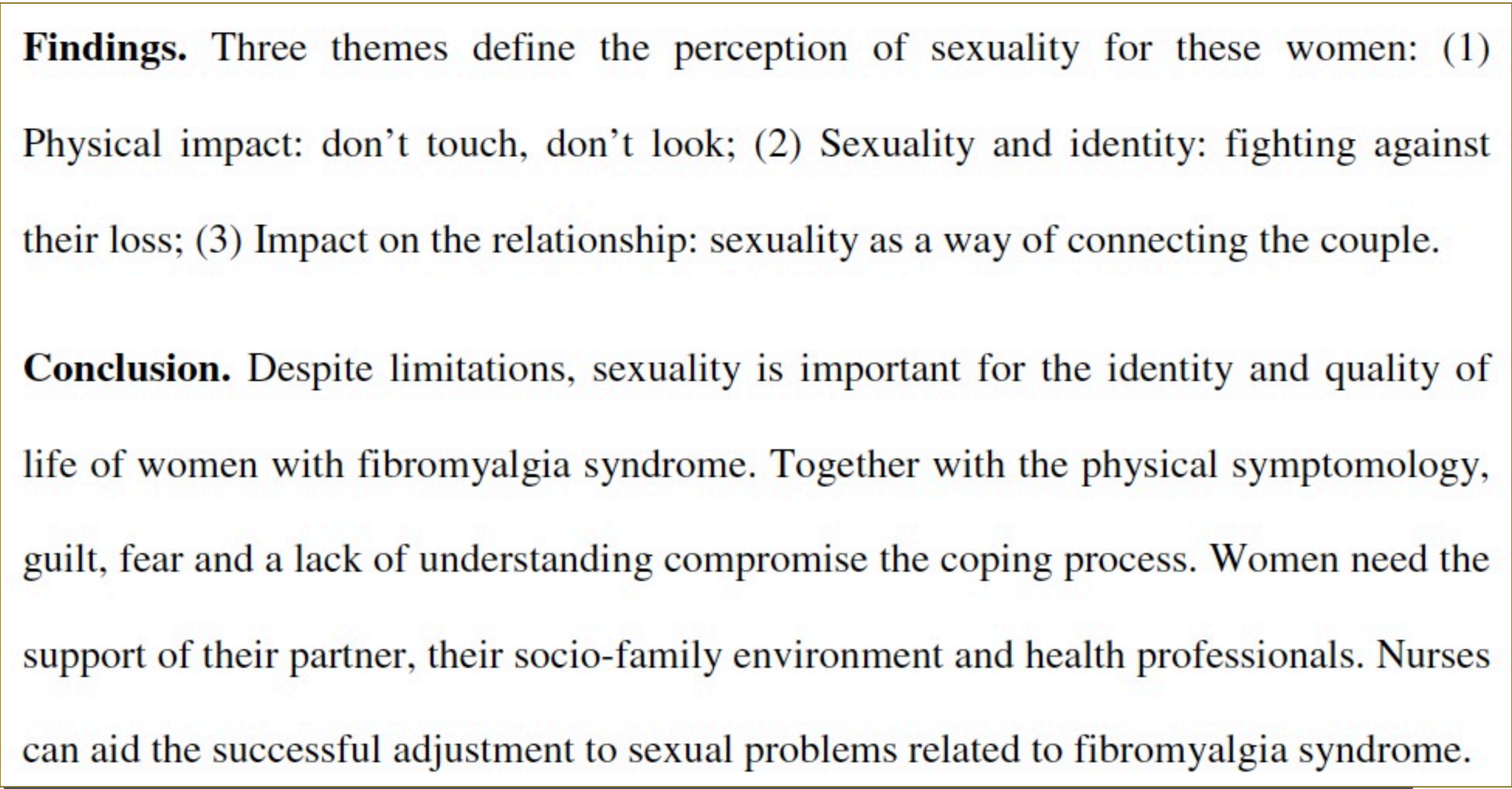
Seksuele component

Fragen zur sexuellen Komponente
Jede Veränderung ist essentiell = HPG-Achse = die wichtigste Achse des Hypothalamus. Wenn du dich nicht reproduzieren kannst, gehörst du nicht mehr dazu.

In dem Moment, in dem diese Komponente eine Rolle spielt, schalten Sie sofort auf die Abgabe des Fragebogens zu sexuellen Störungen um.

Dies ist oft ein Tabu; aber von großer Bedeutung (schauen Sie sich nur Menschen mit Fibromyalgie an, von denen viele sexuell oder körperlich missbraucht wurden, bevor sie krank wurden).

FMS und der sexuale Komponente

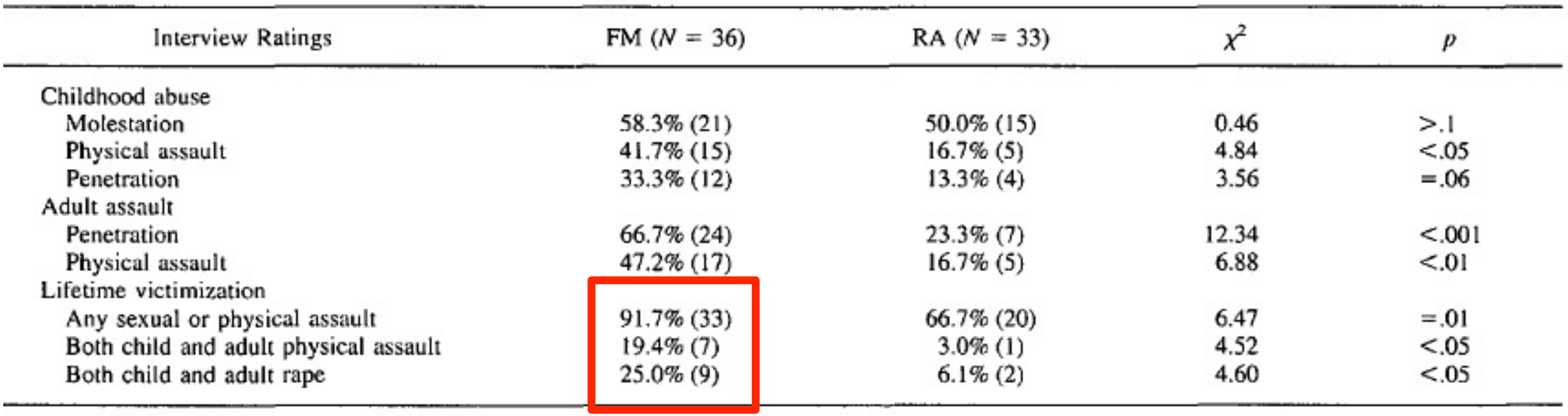


Findings. Three themes define the perception of sexuality for these women: (1) Physical impact: don't touch, don't look; (2) Sexuality and identity: fighting against their loss; (3) Impact on the relationship: sexuality as a way of connecting the couple.

Conclusion. Despite limitations, sexuality is important for the identity and quality of life of women with fibromyalgia syndrome. Together with the physical symptomology, guilt, fear and a lack of understanding compromise the coping process. Women need the support of their partner, their socio-family environment and health professionals. Nurses can aid the successful adjustment to sexual problems related to fibromyalgia syndrome.

MATARIN JIMENEZ T.M., FERNANDEZ-SOLA C., HERNANDEZ-PADILLA J.M., CORREA CASADO M., ANTEQUERA RAYNAL L.H. & GRANEROMOLINA J. (2017) Perceptions about the sexuality of women with fibromyalgia
syndrome: a phenomenological study. Journal of Advanced Nursing 73(7), 1646– 1656.

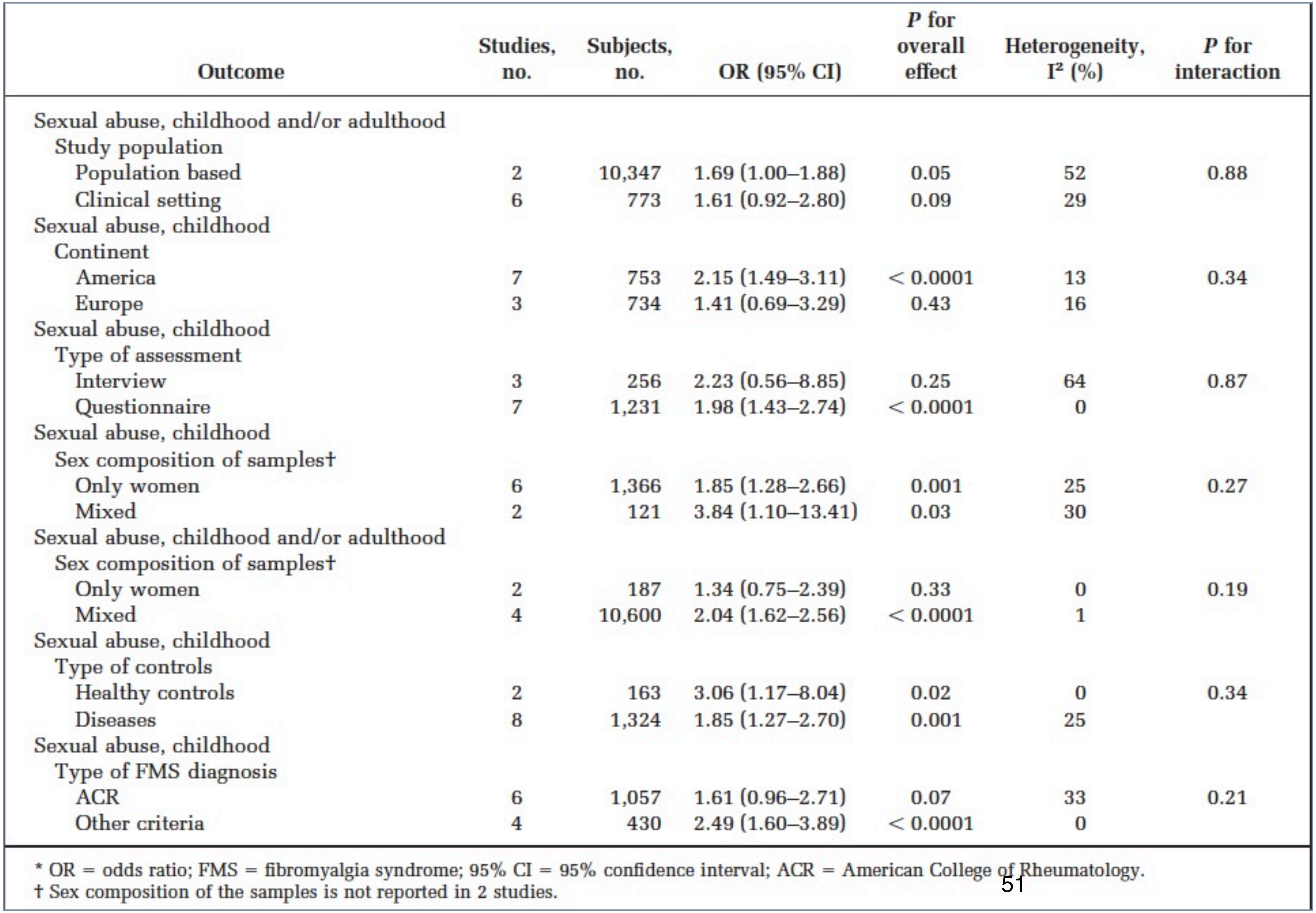
Sexueller und körperlicher Missbrauch bei Menschen mit Rheuma und FMS



Interview Ratings	FM (N = 36)	RA (N = 33)	χ^2	p
Childhood abuse				
Molestation	58.3% (21)	50.0% (15)	0.46	>.1
Physical assault	41.7% (15)	16.7% (5)	4.84	<.05
Penetration	33.3% (12)	13.3% (4)	3.56	=.06
Adult assault				
Penetration	66.7% (24)	23.3% (7)	12.34	<.001
Physical assault	47.2% (17)	16.7% (5)	6.88	<.01
Lifetime victimization				
Any sexual or physical assault	91.7% (33)	66.7% (20)	6.47	=.01
Both child and adult physical assault	19.4% (7)	3.0% (1)	4.52	<.05
Both child and adult rape	25.0% (9)	6.1% (2)	4.60	<.05

Walker. Psychosomatic Medicine 59:572-577 (1997)

Sexueller Missbrauch bei FMS-Patienten in der Meta-Analyse konform



Outcome	Studies, no.	Subjects, no.	OR (95% CI)	*P* for overall effect	Heterogeneity, I^2 (%)	*P* for interaction
Sexual abuse, childhood and/or adulthood						
Study population						
Population based	2	10,347	1.69 (1.00–1.88)	0.05	52	0.88
Clinical setting	6	773	1.61 (0.92–2.80)	0.09	29	
Sexual abuse, childhood						
Continent						
America	7	753	2.15 (1.49–3.11)	< 0.0001	13	0.34
Europe	3	734	1.41 (0.69–3.29)	0.43	16	
Sexual abuse, childhood						
Type of assessment						
Interview	3	256	2.23 (0.56–8.85)	0.25	64	0.87
Questionnaire	7	1,231	1.98 (1.43–2.74)	< 0.0001	0	
Sexual abuse, childhood						
Sex composition of samples†						
Only women	6	1,366	1.85 (1.28–2.66)	0.001	25	0.27
Mixed	2	121	3.84 (1.10–13.41)	0.03	30	
Sexual abuse, childhood and/or adulthood						
Sex composition of samples†						
Only women	2	187	1.34 (0.75–2.39)	0.33	0	0.19
Mixed	4	10,600	2.04 (1.62–2.56)	< 0.0001	1	
Sexual abuse, childhood						
Type of controls						
Healthy controls	2	163	3.06 (1.17–8.04)	0.02	0	0.34
Diseases	8	1,324	1.85 (1.27–2.70)	0.001	25	
Sexual abuse, childhood						
Type of FMS diagnosis						
ACR	6	1,057	1.61 (0.96–2.71)	0.07	33	0.21
Other criteria	4	430	2.49 (1.60–3.89)	< 0.0001	0	

* OR = odds ratio; FMS = fibromyalgia syndrome; 95% CI = 95% confidence interval; ACR = American College of Rheumatology.
† Sex composition of the samples is not reported in 2 studies.

Häuser. Arthritis Care & ResearchVol. 63, No. 6, June 2011, pp 808–820

Die "Gefahr" in dir

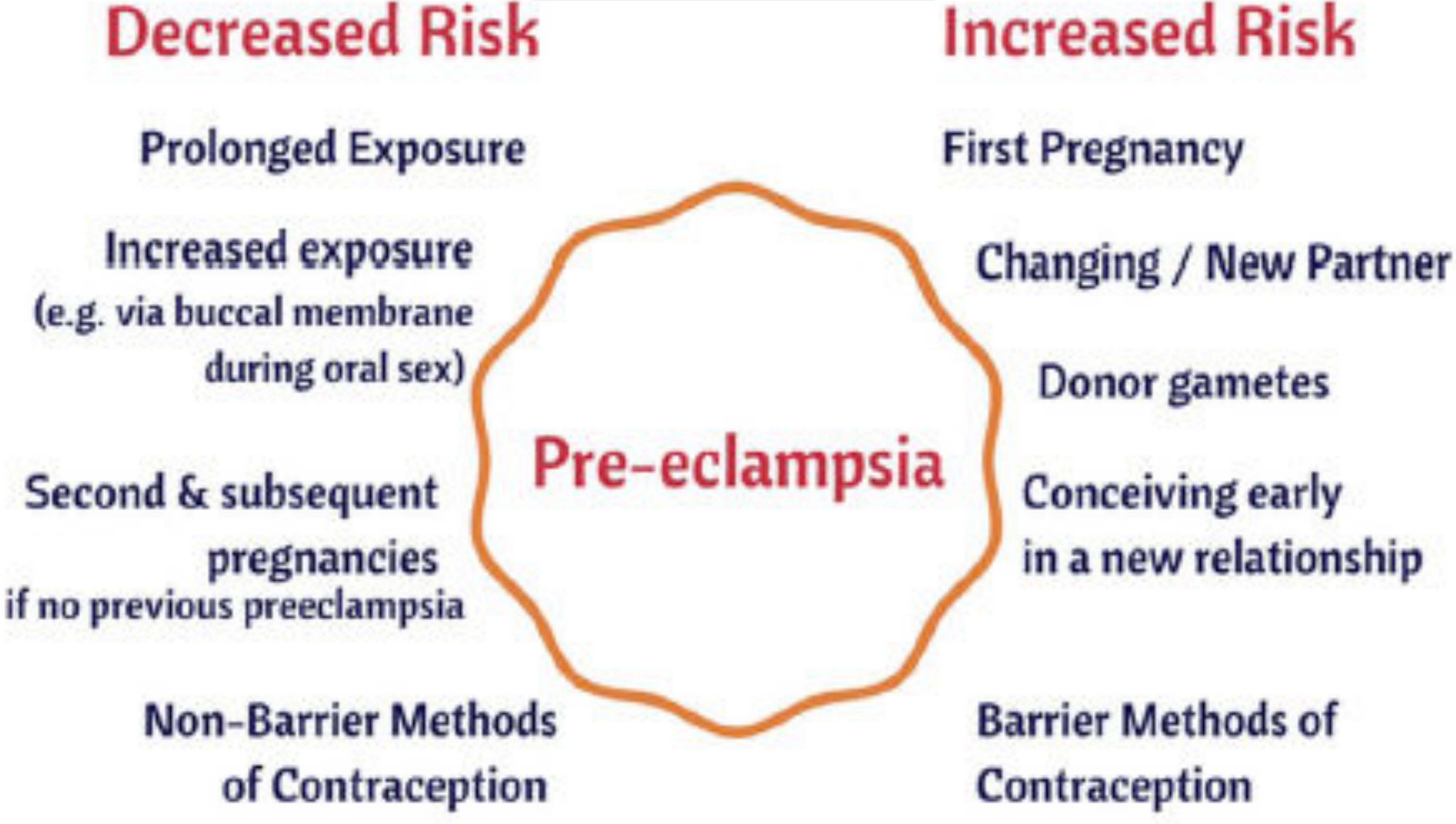

Decreased Risk
Increased Risk
Prolonged Exposure
Increased exposure (e.g. via buccal membrane during oral sex)
Second & subsequent pregnancies if no previous preeclampsia
Non-Barrier Methods of Contraception
Pre-eclampsia
First Pregnancy
Changing / New Partner
Donor gametes
Conceiving early in a new relationship
Barrier Methods of Contraception

FIGURE 5 | Some epidemiological risk factors for preeclampsia.

Kenny LC and Kell DB (2018) Immunological Tolerance, Pregnancy, and Preeclampsia: The Roles of Semen Microbes and the Father. Front. Med. 4:239.

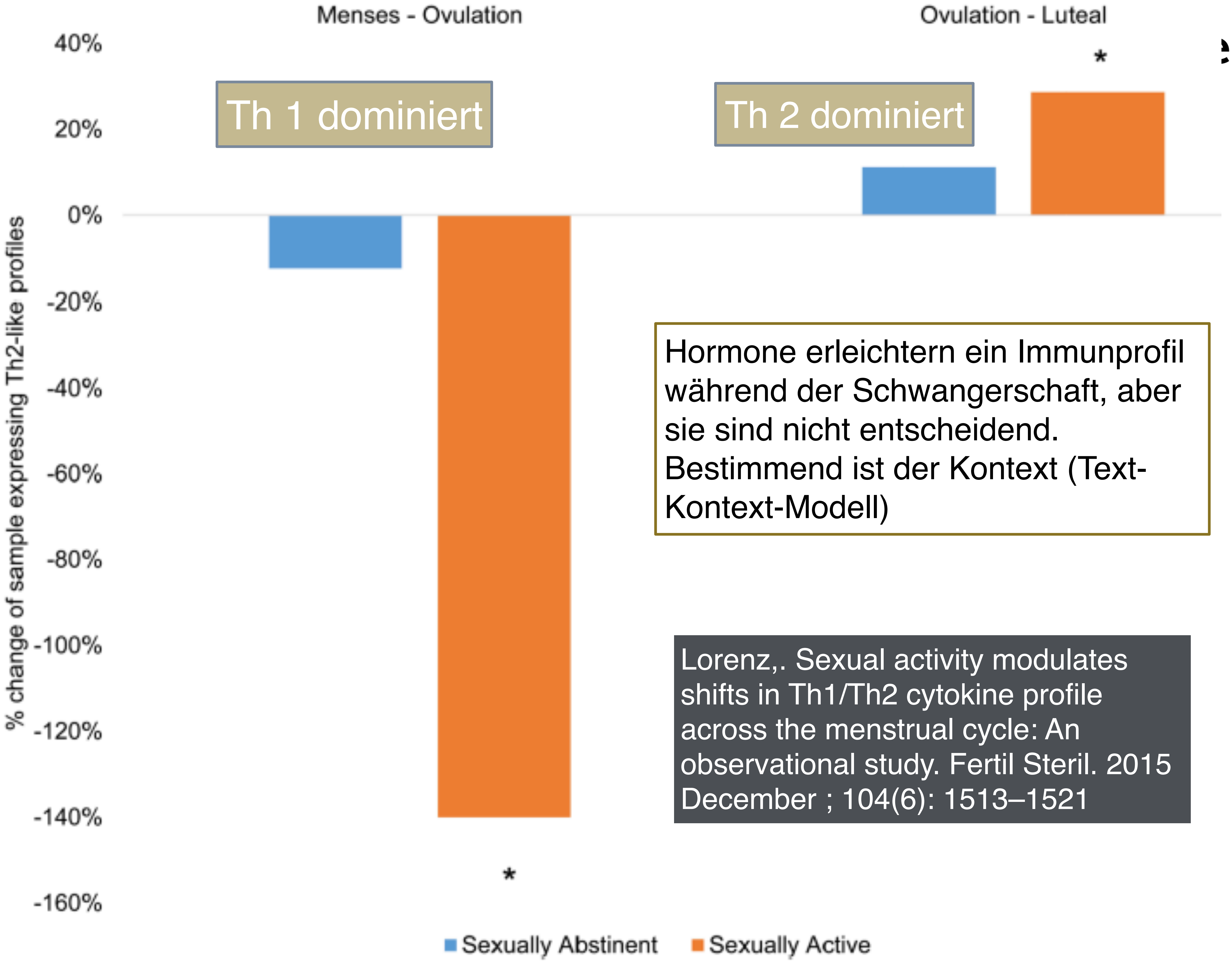
The most thorough analyses are for Canada, where data in a national archive of all homicides known to police indicate that children under 5 years of age were beaten to death by their putative genetic fathers at a rate of 2.6 deaths per million child-years at risk (residing with their fathers) in 1974-1990, while the corresponding rate for stepfathers was over 120 times greater at 321.6 deaths per million child-years at risk (Daly & Wilson 2001). Note that because few small children *have* stepfathers, this rate differential does not, in itself, convey anything about the absolute numbers of victims; what these rates represent are 74 fatal batterings by genetic fathers in 28.3 million child-years at risk, and 55 by stepfathers in 0.17 million child-years at risk.

(1) 9 fathers and 6 *de facto* stepfathers (live-in "mothers' boyfriends") were identified as killers of small children (median age 1 year) in a Birmingham, Alabama sample (Lyman et al. 2003);

(2) 4 fathers and 4 "mothers' boyfriends" were killers of infants (median age 6.5 months) in a Dayton, Ohio sample (Hicks & Gaughan 1995);

(3) 11 fathers and 15 (registered marriage plus *de facto*) stepfathers (plus an additional 2 mothers' boyfriends who did not coreside with their victims) inflicted fatal injuries on preschool-age children in Missouri over a 3-year period (Stiffman et al. 2002); and

(4) 14 fathers and 9 (registered marriage plus *de facto*) stepfathers were killers of preschool-age children in an analysis of such murders by U.S. Air Force personnel (Lucas et al. 2002).



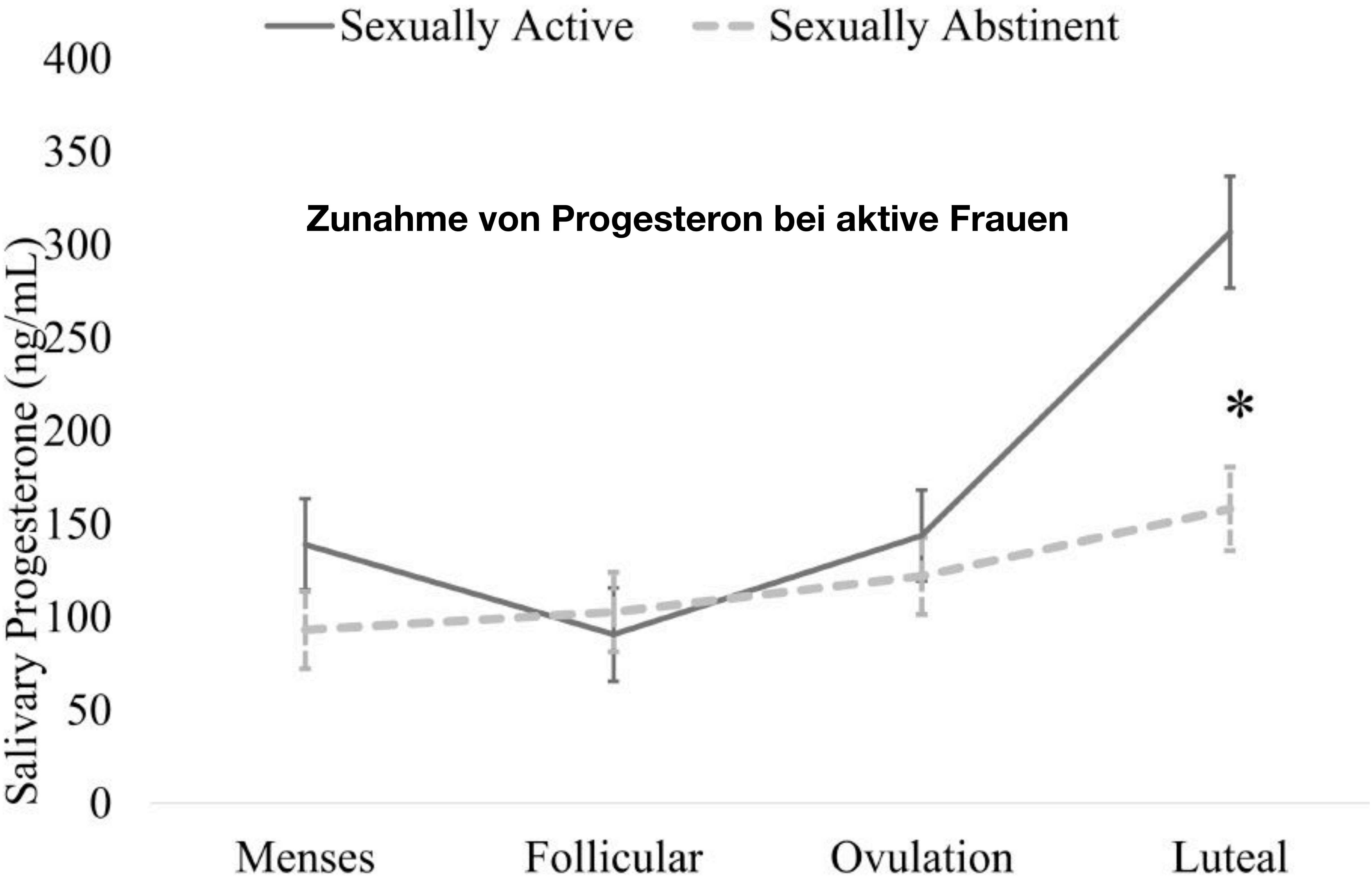
Th 1 dominiert

Th 2 dominiert

Hormone erleichtern ein Immunprofil während der Schwangerschaft, aber sie sind nicht entscheidend. Bestimmend ist der Kontext (Text-Kontext-Modell)

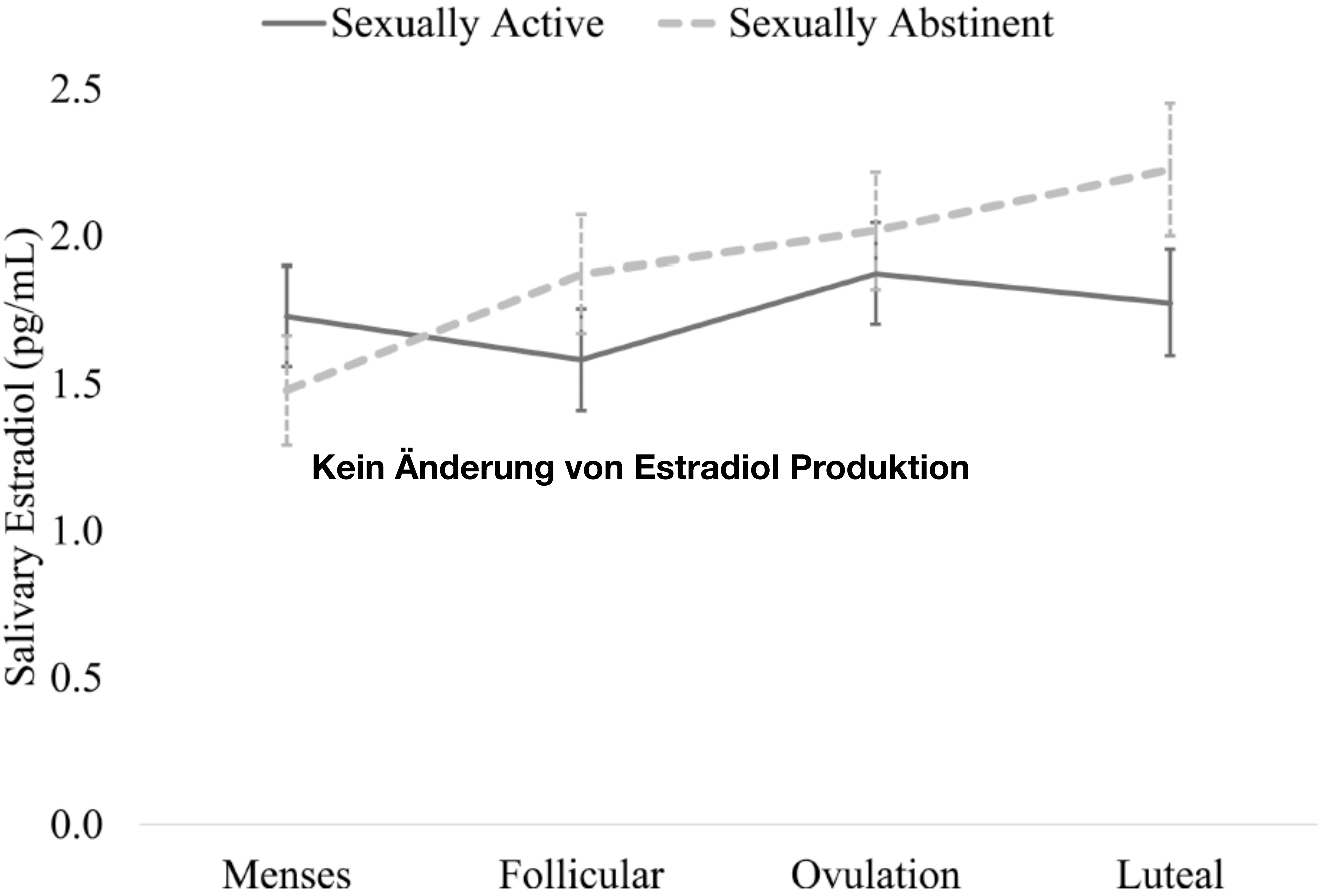
Lorenz,. Sexual activity modulates shifts in Th1/Th2 cytokine profile across the menstrual cycle: An observational study. Fertil Steril. 2015 December ; 104(6): 1513–1521

PNI Europe



Zunahme von Progesteron bei aktive Frauen

Lorenz,. Sexual activity modulates shifts in Th1/Th2 cytokine profile across the menstrual cycle: An observational study. Fertil Steril. 2015 December ; 104(6): 1513–1521



Kein Änderung von Estradiol Produktion

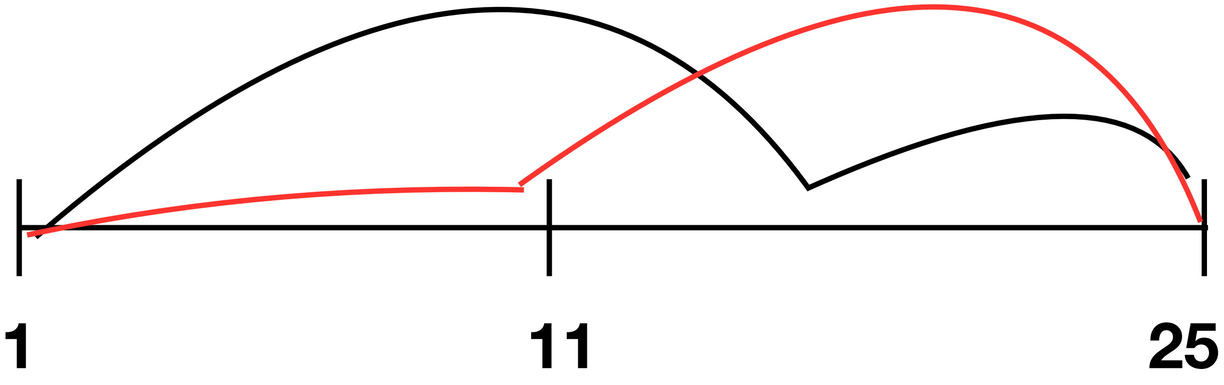
Lorenz,. Sexual activity modulates shifts in Th1/Th2 cytokine profile across the menstrual cycle: An observational study. Fertil Steril. 2015 December ; 104(6): 1513–1521

Text =
Charakter =
Persönlichkeit + Identität
23 : 77

Th1 Th2

Estradiol **Progesteron**

Sexuell aktive Frau



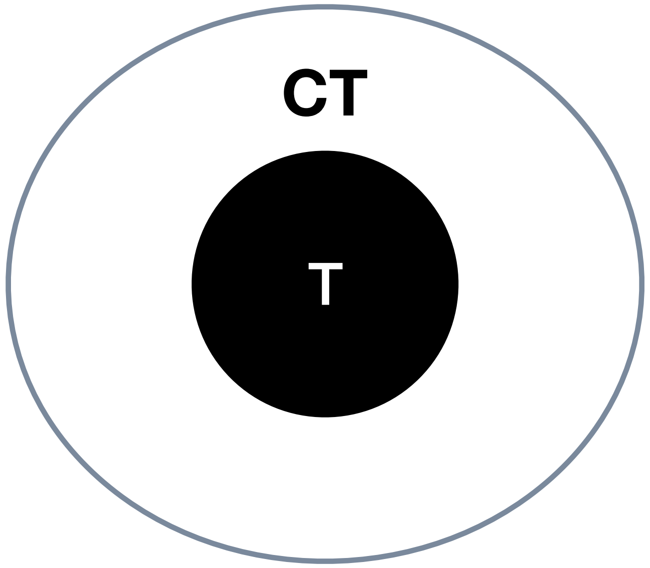
Eisprung

Sexuell inaktive Frau

Th1★ **Alfa** Th1★

Schwangere Frau **Estradiol** Th2 **Progesteron**

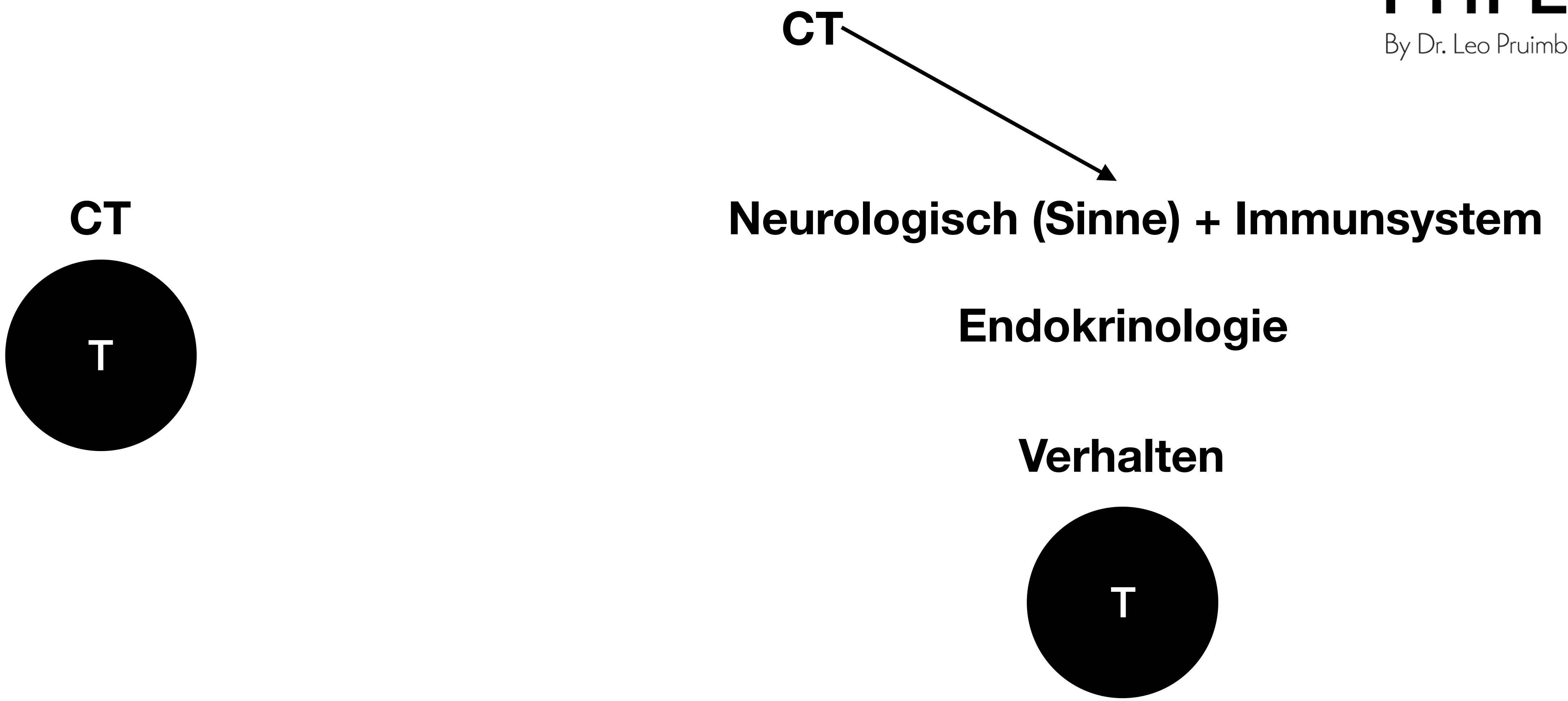
Beta



Neurologisch (Sinne) + Immunsystem

Endokrinologie

Verhalten



CT

T

CT

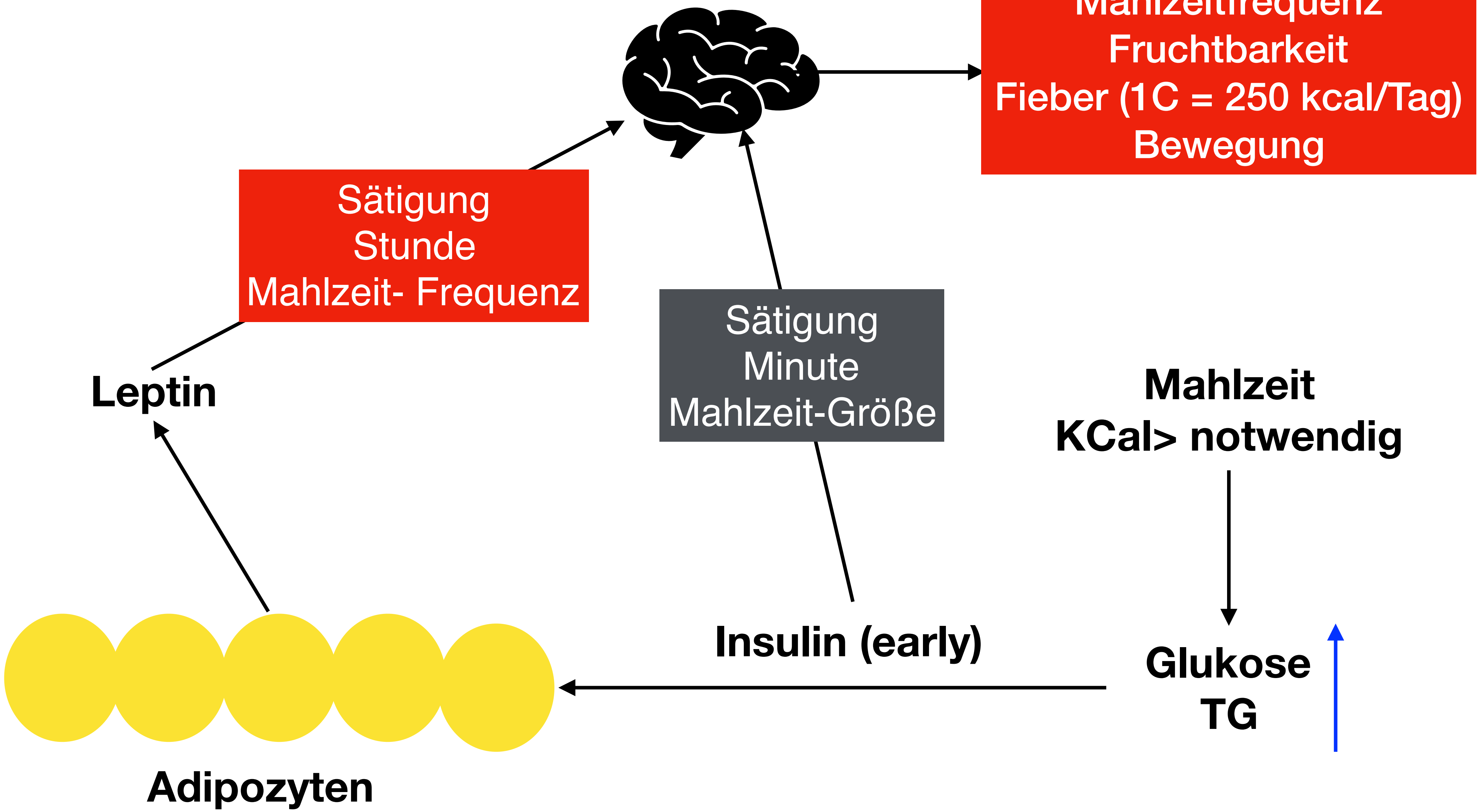
Neurologisch (Sinne) + Immunsystem

Endokrinologie

Verhalten

T

Leptin Funktion



Mahlzeitfrequenz
Fruchtbarkeit
Fieber (1C = 250 kcal/Tag)
Bewegung

Sättigung
Stunde
Mahlzeit- Frequenz

Leptin

Sättigung
Minute
Mahlzeit-Größe

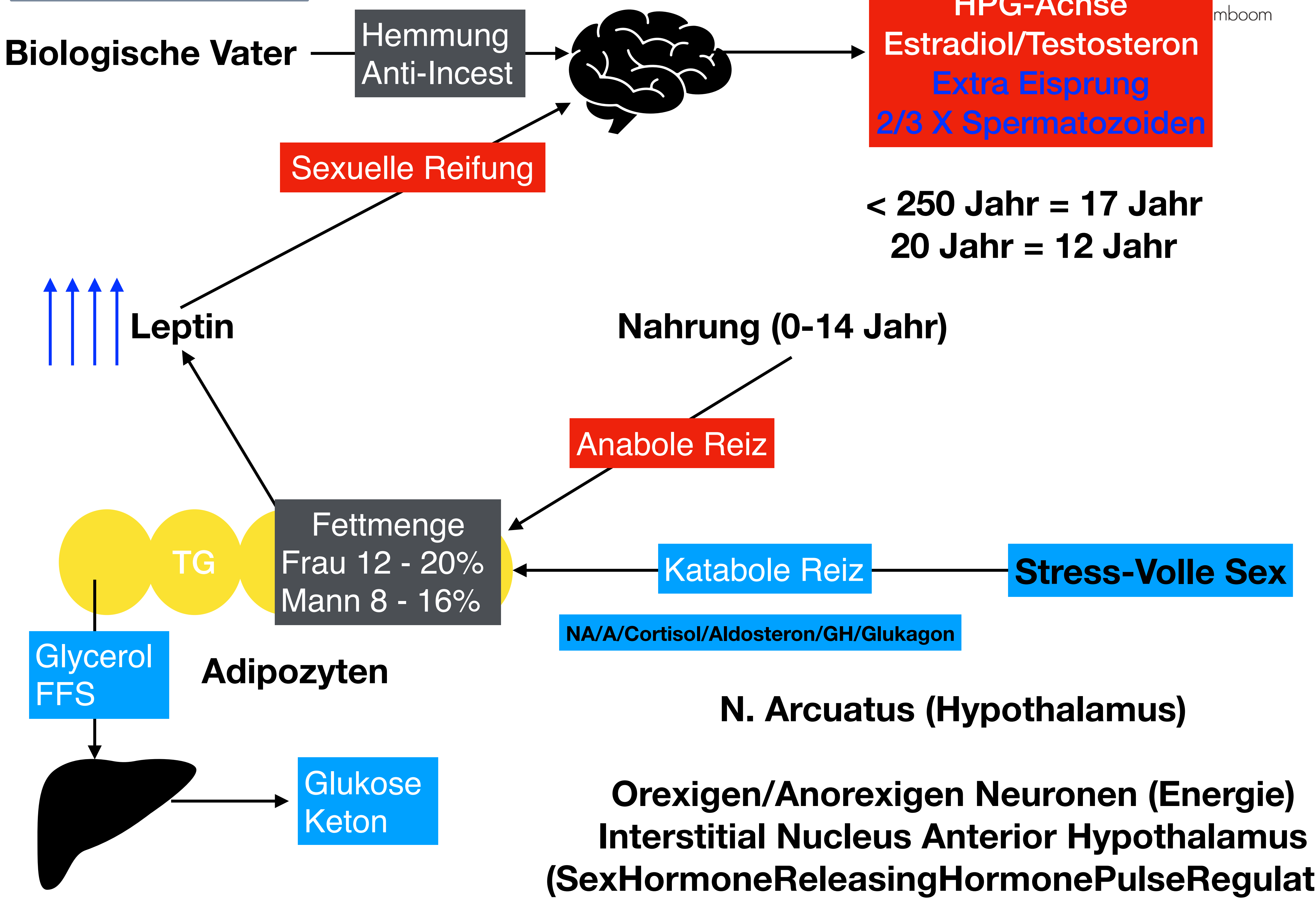
Mahlzeit
KCal> notwendig

Insulin (early)

Glukose
TG

Adipozyten

Leptin Funktion



N. Arcuatus
INAH

Biologische Vater

Hemmung
Anti-Incest

HPG-Achse
Estradiol/Testosteron
Extra Eisprung
2/3 X Spermatozoiden

Sexuelle Reifung

< 250 Jahr = 17 Jahr
20 Jahr = 12 Jahr

Leptin

Nahrung (0-14 Jahr)

Anabole Reiz

TG

Fettmenge
Frau 12 - 20%
Mann 8 - 16%

Katabole Reiz

Stress-Volle Sex

NA/A/Cortisol/Aldosteron/GH/Glukagon

Glycerol
FFS

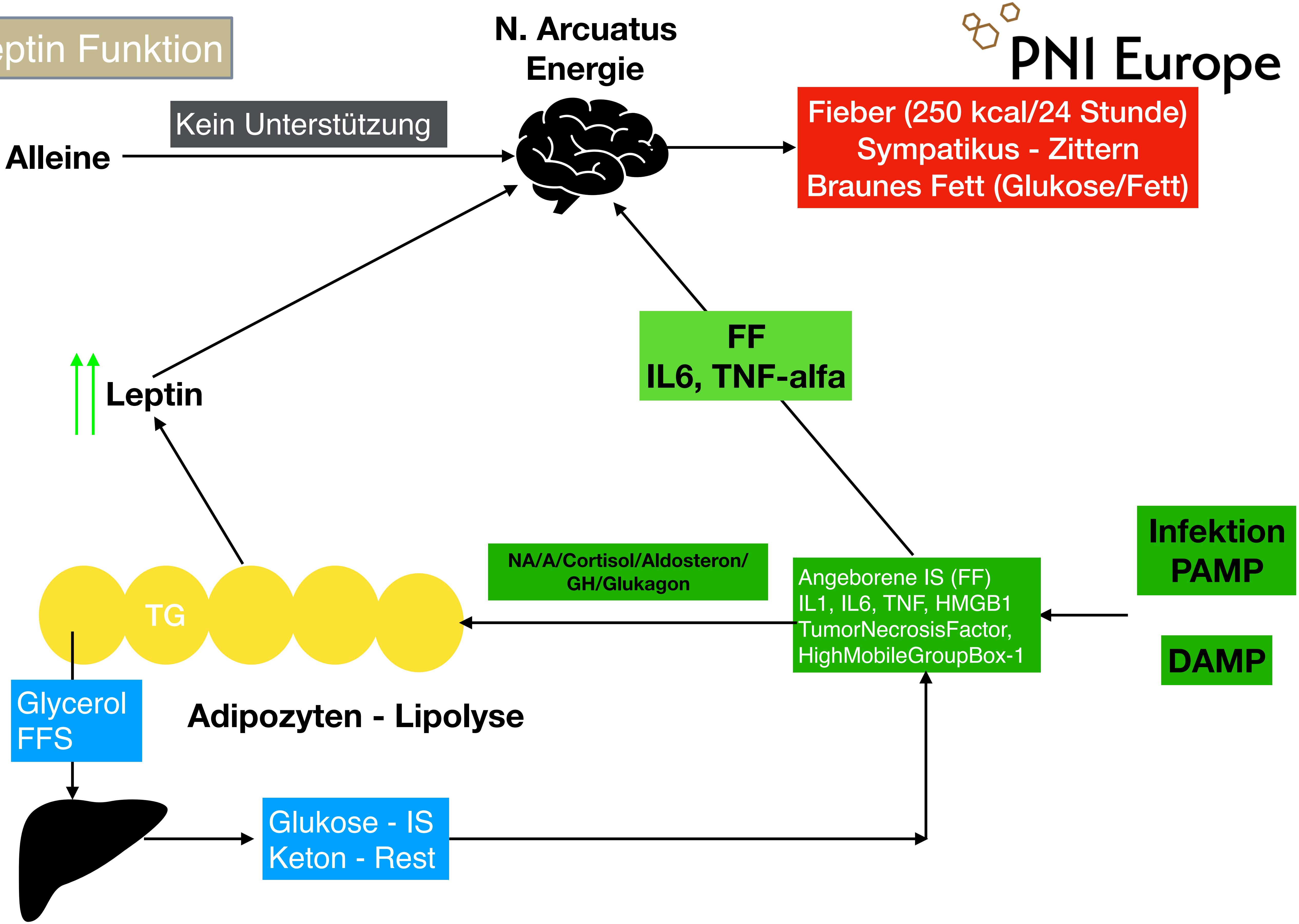
Adipozyten

Glukose
Keton

N. Arcuatus (Hypothalamus)

Orexigen/Anorexigen Neuronen (Energie)
Interstitial Nucleus Anterior Hypothalamus
(SexHormoneReleasingHormonePulseRegulator)

Leptin Funktion



N. Arcuatus Energie

Alleine

Kein Unterstützung

Fieber (250 kcal/24 Stunde)
Sympatikus - Zittern
Braunes Fett (Glukose/Fett)

↑↑ **Leptin**

FF
IL6, TNF-alfa

Infektion
PAMP

DAMP

Angeborene IS (FF)
IL1, IL6, TNF, HMGB1
TumorNecrosisFactor,
HighMobileGroupBox-1

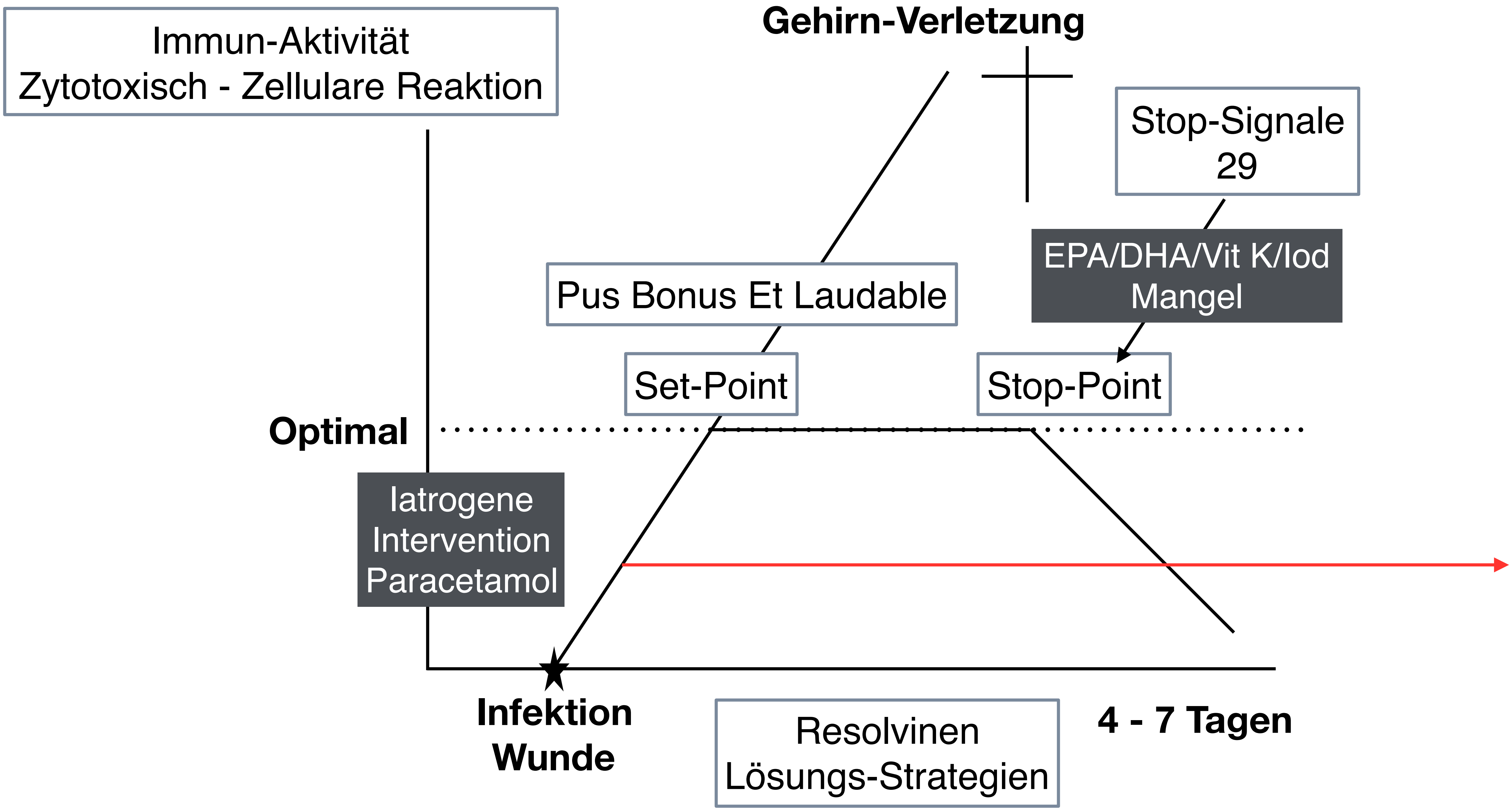
NA/A/Cortisol/Aldosteron/GH/Glukagon

TG

Adipozyten - Lipolyse

Glycerol
FFS

Glukose - IS
Keton - Rest



Sepsis
Knochenbrüche
Gehirn-Verletzung

Immun-Aktivität
Zytotoxisch - Zellulare Reaktion

Stop-Signale
29

EPA/DHA/Vit K/Iod
Mangel

Pus Bonus Et Laudable

Set-Point

Stop-Point

Optimal

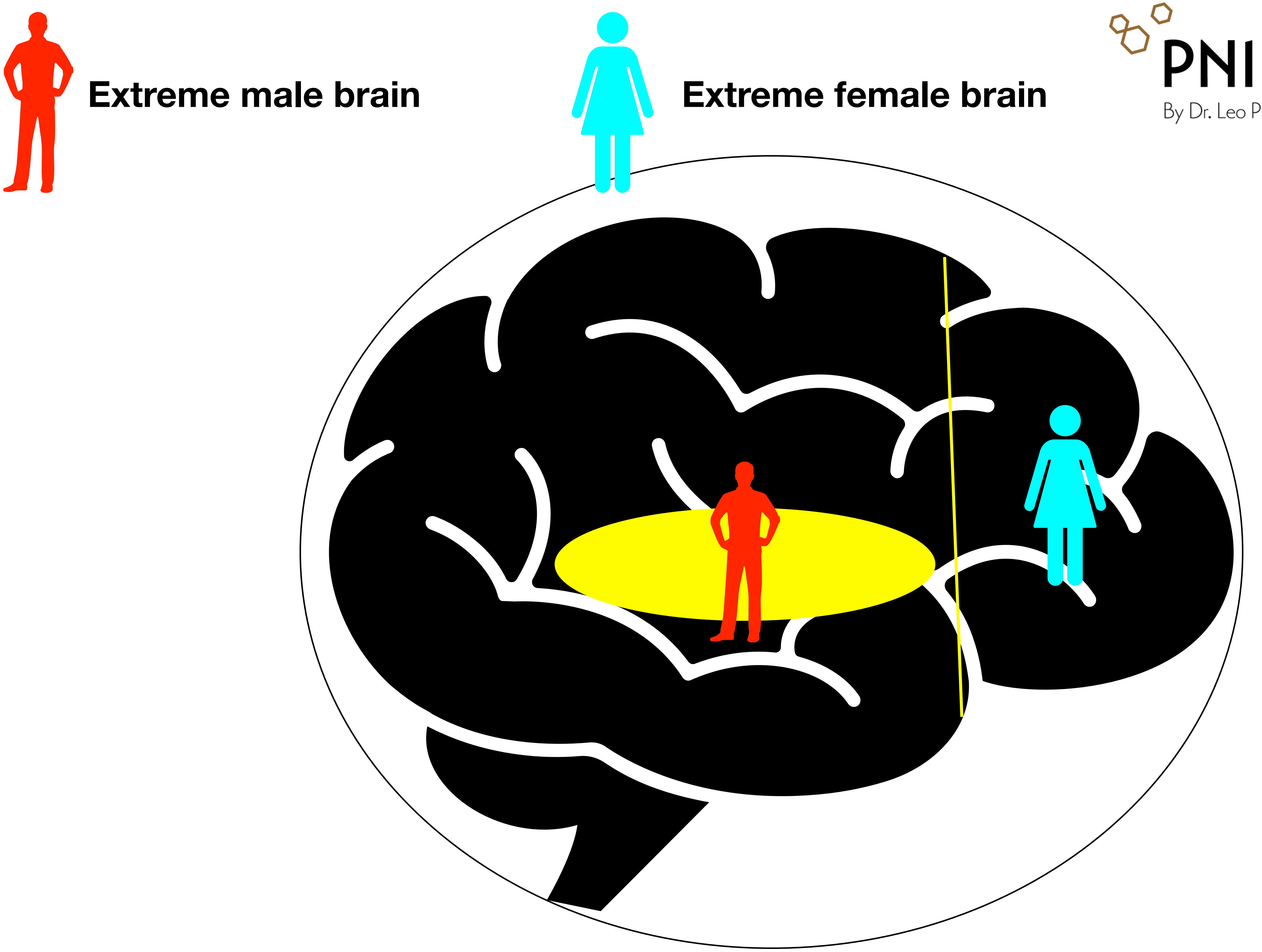
Iatrogene
Intervention
Paracetamol

Infektion
Wunde

Resolvinen
Lösungs-Strategien

4 - 7 Tagen

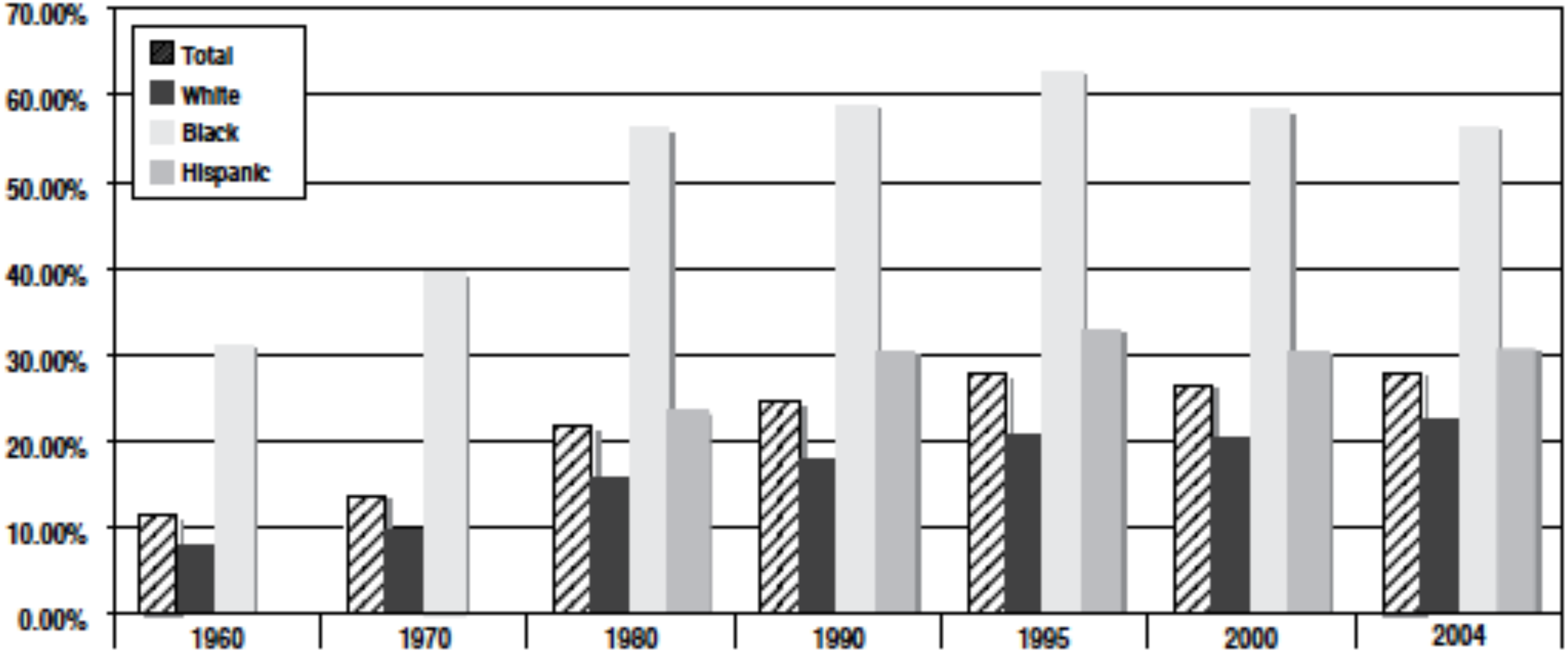
PNI Europe
By Dr. Leo Pruimboom


Extreme male brain
Extreme female brain

Father absence…

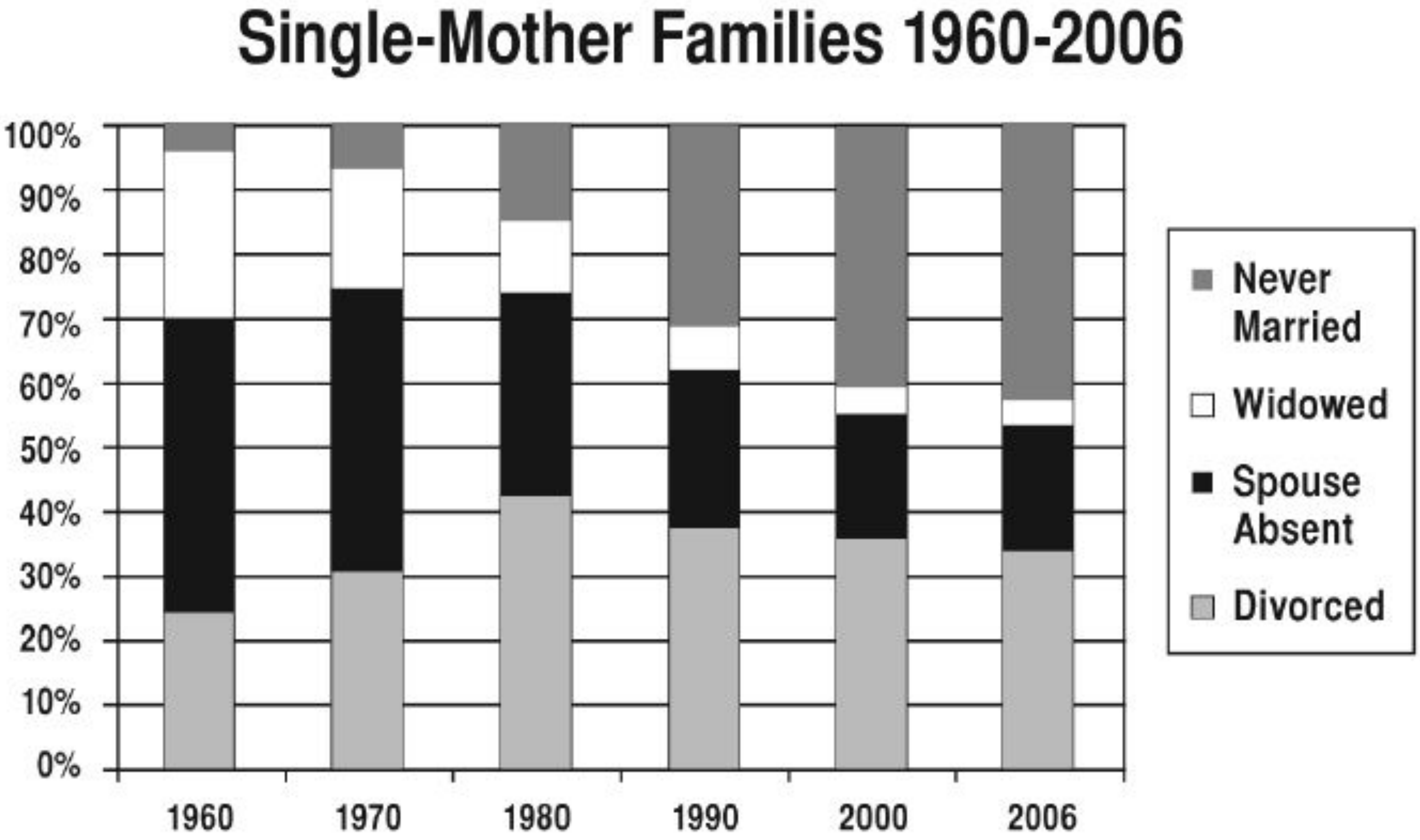
Vater-Abwesenheit führt zu Motivation und Muskeln

Percentage of Children Living in Father-Absent Homes, 1960 to 2004



Nock. National Fatherhood Initiative | www.fatherhood.org | The Costs of Father Absence. 2008

Father absence



Nock. National Fatherhood Initiative | www.fatherhood.org | The Costs of Father Absence. 2008

Father absence syndrome

The Hundred Billion Dollar Man The hundred billion dollar man. No, he’s not a new superhero with bionic limbs who can run through walls and is more powerful than a locomotive. The hundred billion dollar man is the personification of the annual cost of absentee fathers to American society. That was the conclusion of a 2008 report written by Christopher Einolf and the late Steven Nock for the National Fatherhood Initiative. The greatest plague to ever hit this country: it is the root cause for the greatest psychological, physical, emotional, mental, and social devastation in the history of the world. The disease is Father Deficiency. It goes beyond just being fatherless but also includes fathers who were present yet absent. Considered by most Americans the number-one social ill in the country, the devastation can be seen in the following statistics about fatherless homes compiled by the Department of Justice. 63 percent of youth suicides are from fatherless homes. 90 percent of all homeless and runaway youths are from fatherless homes. 85 percent of children who exhibit behavioral disorders are from fatherless homes. 71 percent of high school dropouts are from fatherless homes. 70 percent of youths in state institutions are from fatherless homes. 75 percent of adolescent patients in substance abuse centers are from fatherless homes. 85 percent of rapists motivated by displaced anger are from fatherless homes. 71 percent of teenage pregnancies are to children of single parents. U.S. Dept. of Health and Human Services Nearly 75 percent of American children living in single-parent families will experience poverty before they turn eleven.

Tag 1
Mittagspause
12.30 - 13.30

Tag 1
13.30 - 14.00
Aktives Lernen
Bestandsaufnahme Ihres Wissens

Aufträge

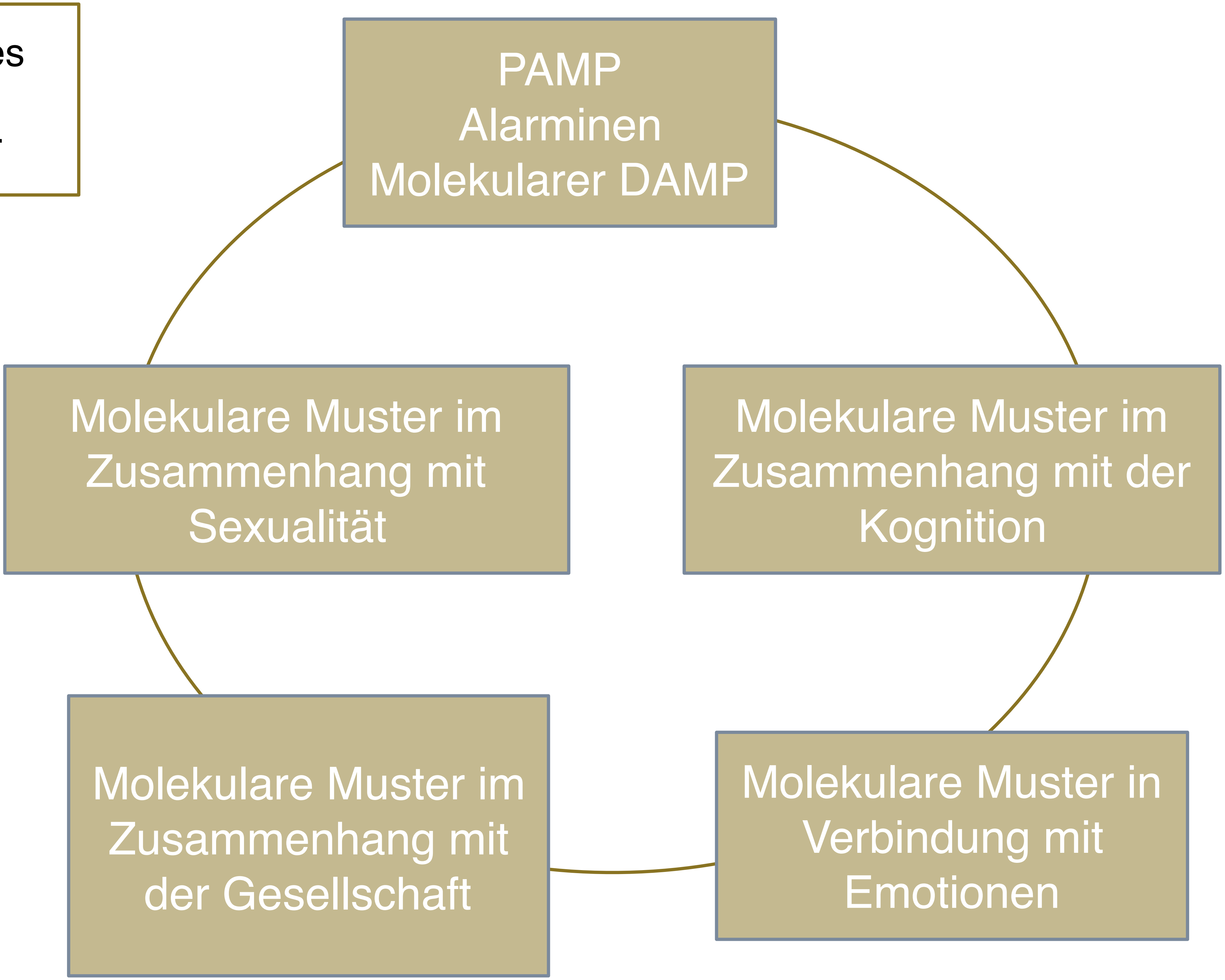
Welche Teile des Körpers gehören zu den Schleimhäuten?
Wie ist die Darmwand aufgebaut
Was ist die Rolle des enterischen Nervensystems
Welche Rolle spielen Bakteriom, Viroid und Fungoom?
Was ist die normale Laufzeit des Stuhls
Was ist ein leaky gut?
Was ist das Hyperpermeabilitätssyndrom?
Gibt es ein Gewebe-Mikrobiom?
Was ist eigentlich ein LGI?

Der Darm
Leaky Gut und Leaky Brain Syndrom
Wo Gesundheit beginnt

0. metamodel = Risikofaktoren

PNI Europe
By Dr. Leo Pruimboom

Transgenerationelles assoziiertes molekulares Muster



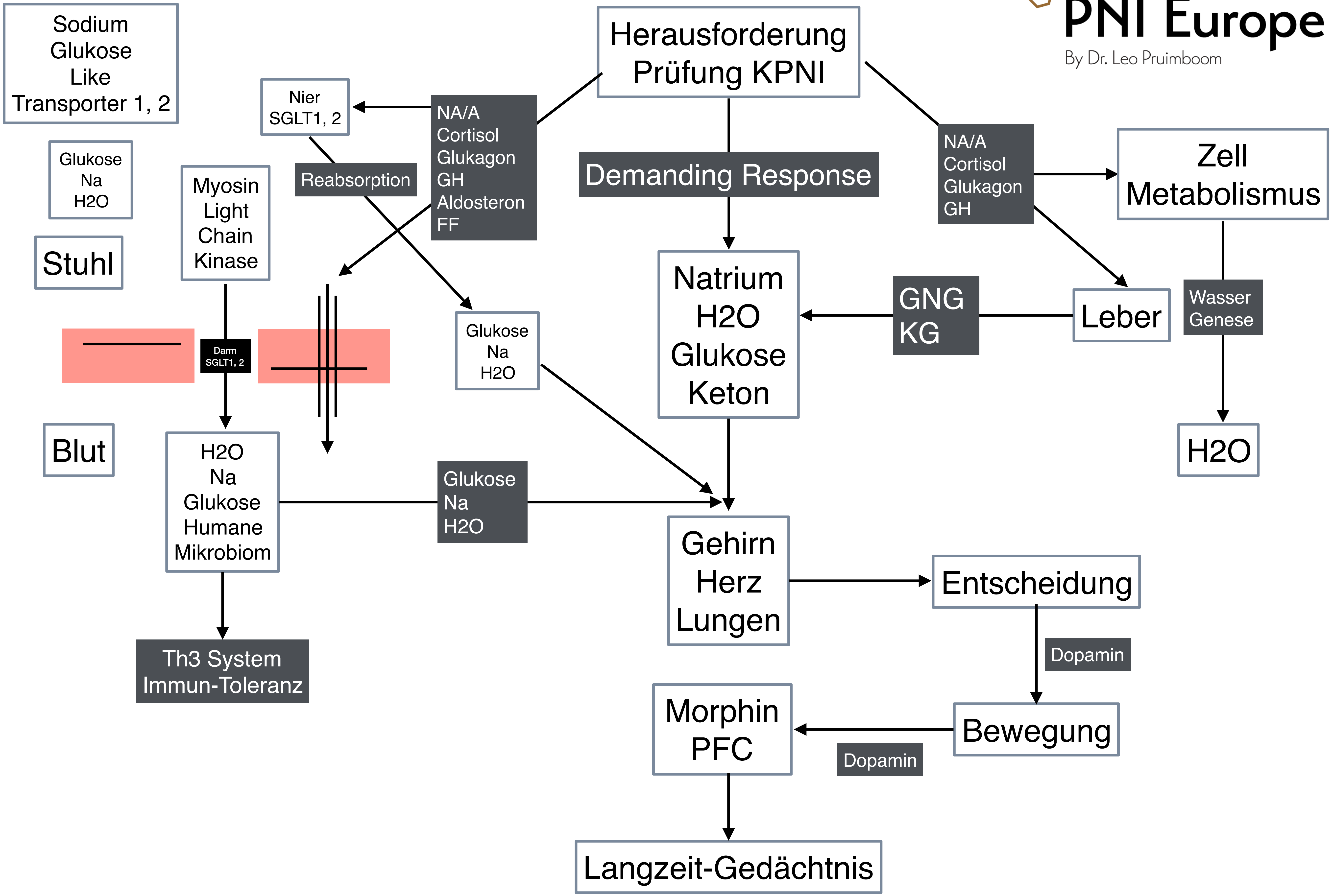
PAMP
Alarminen
Molekularer DAMP

Molekulare Muster im Zusammenhang mit der Kognition

Molekulare Muster in Verbindung mit Emotionen

Molekulare Muster im Zusammenhang mit der Gesellschaft

Molekulare Muster im Zusammenhang mit Sexualität



Herausforderung Prüfung KPNI

Demanding Response

Natrium
H2O
Glukose
Keton

NA/A
Cortisol
Glukagon
GH
Aldosteron
FF

Nier
SGLT1, 2

Reabsorption

Glukose
Na
H2O

NA/A
Cortisol
Glukagon
GH

Zell Metabolismus

Leber

GNG
KG

Wasser Genese

H2O

Sodium
Glukose
Like
Transporter 1, 2

Glukose
Na
H2O

Stuhl

Myosin
Light
Chain
Kinase

Darm
SGLT1, 2

Blut

H2O
Na
Glukose
Humane
Mikrobiom

Glukose
Na
H2O

Th3 System
Immun-Toleranz

Gehirn
Herz
Lungen

Entscheidung

Dopamin

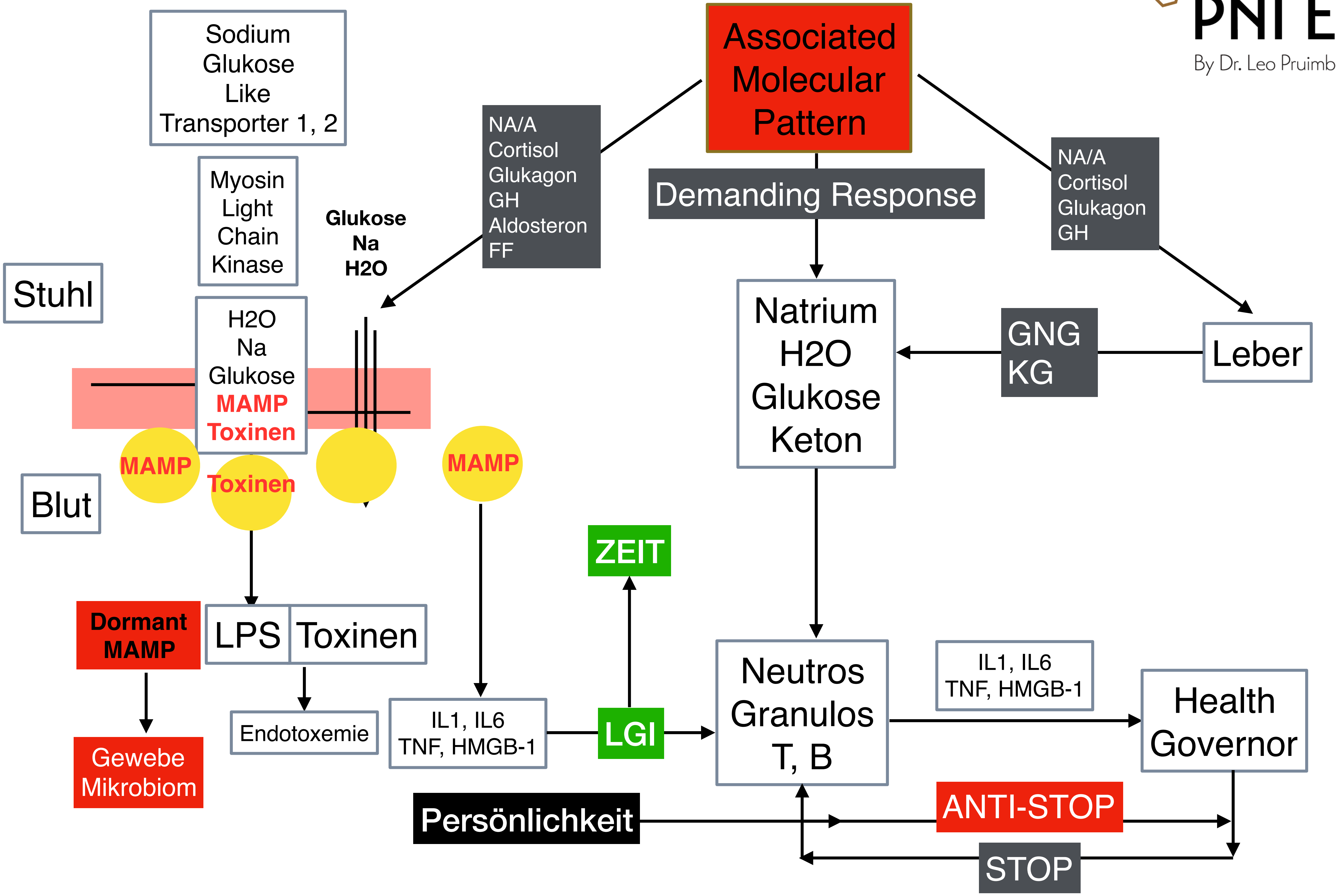
Bewegung

Dopamin

Morphin
PFC

Langzeit-Gedächtnis

PNI Europe
By Dr. Leo Pruimboom



Associated Molecular Pattern

Demanding Response

NA/A
Cortisol
Glukagon
GH
Aldosteron
FF

NA/A
Cortisol
Glukagon
GH

Sodium Glukose Like Transporter 1, 2

Myosin Light Chain Kinase

Glukose
Na
H2O

Stuhl

H2O
Na
Glukose
MAMP
Toxinen

MAMP

Toxinen

MAMP

Blut

Natrium
H2O
Glukose
Keton

GNG
KG

Leber

ZEIT

Dormant MAMP

Gewebe Mikrobiom

LPS

Toxinen

Endotoxemie

IL1, IL6
TNF, HMGB-1

LGI

Neutros
Granulos
T, B

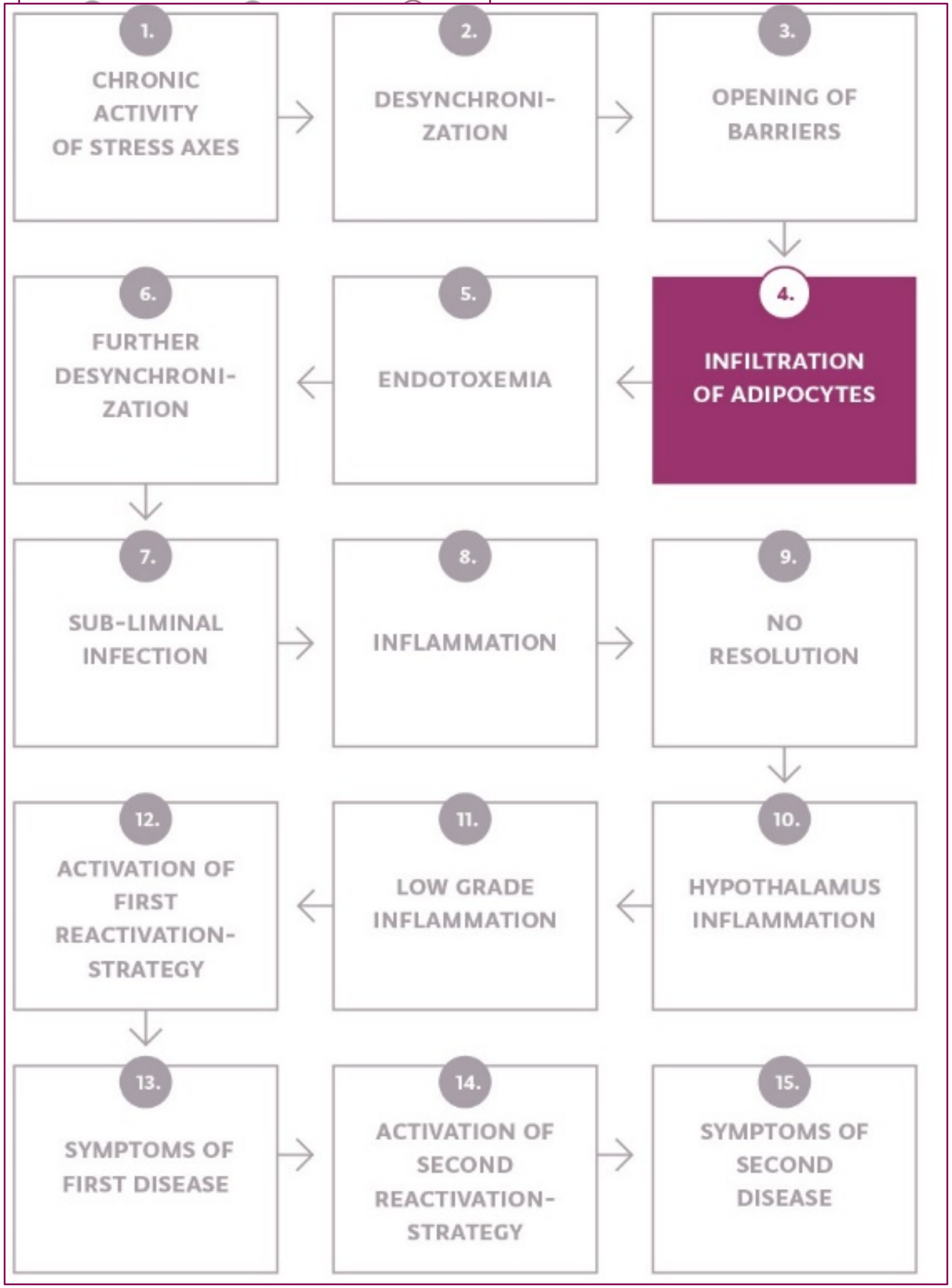
IL1, IL6
TNF, HMGB-1

Health Governor

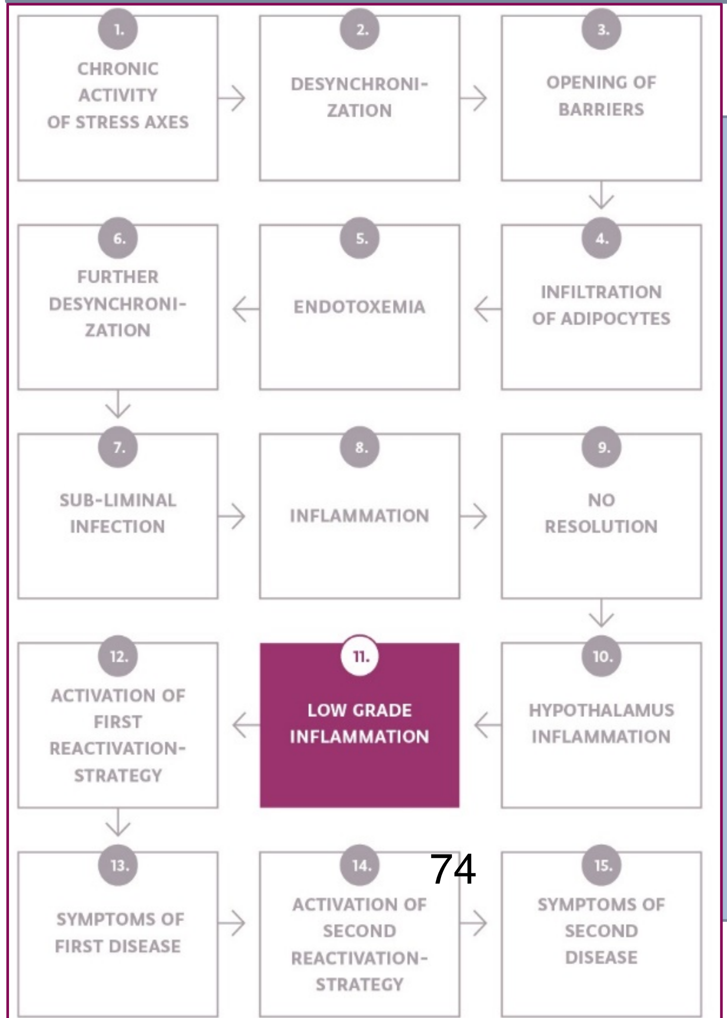
Persönlichkeit

ANTI-STOP

STOP


1. CHRONIC ACTIVITY OF STRESS AXES
2. DESYNCHRONIZATION
3. OPENING OF BARRIERS
4. INFILTRATION OF ADIPOCYTES
5. ENDOTOXEMIA
6. FURTHER DESYNCHRONIZATION
7. SUB-LIMINAL INFECTION
8. INFLAMMATION
9. NO RESOLUTION
10. HYPOTHALAMUS INFLAMMATION
11. LOW GRADE INFLAMMATION
12. ACTIVATION OF FIRST REACTIVATION-STRATEGY
13. SYMPTOMS OF FIRST DISEASE
14. ACTIVATION OF SECOND REACTIVATION-STRATEGY
15. SYMPTOMS OF SECOND DISEASE

Das Öffnen von Barrieren wird vom Körper als "Loch" erlebt. Jedes Loch wird mit Fettzellen gefüllt, um eine Sepsis zu verhindern. Dies führt zu einer Phagozytose von Toxinen und Krankheitserregern durch diese Fettzellen, die dann LPS und Toxine in das Blut freisetzen Aufgrund der Abwesenheit von lebenden Organismen ist das Immunsystem nur mäßig aktiviert --> geringgradige Entzündung


1. CHRONIC ACTIVITY OF STRESS AXES
2. DESYNCHRONIZATION
3. OPENING OF BARRIERS
4. INFILTRATION OF ADIPOCYTES
5. ENDOTOXEMIA
6. FURTHER DESYNCHRONIZATION
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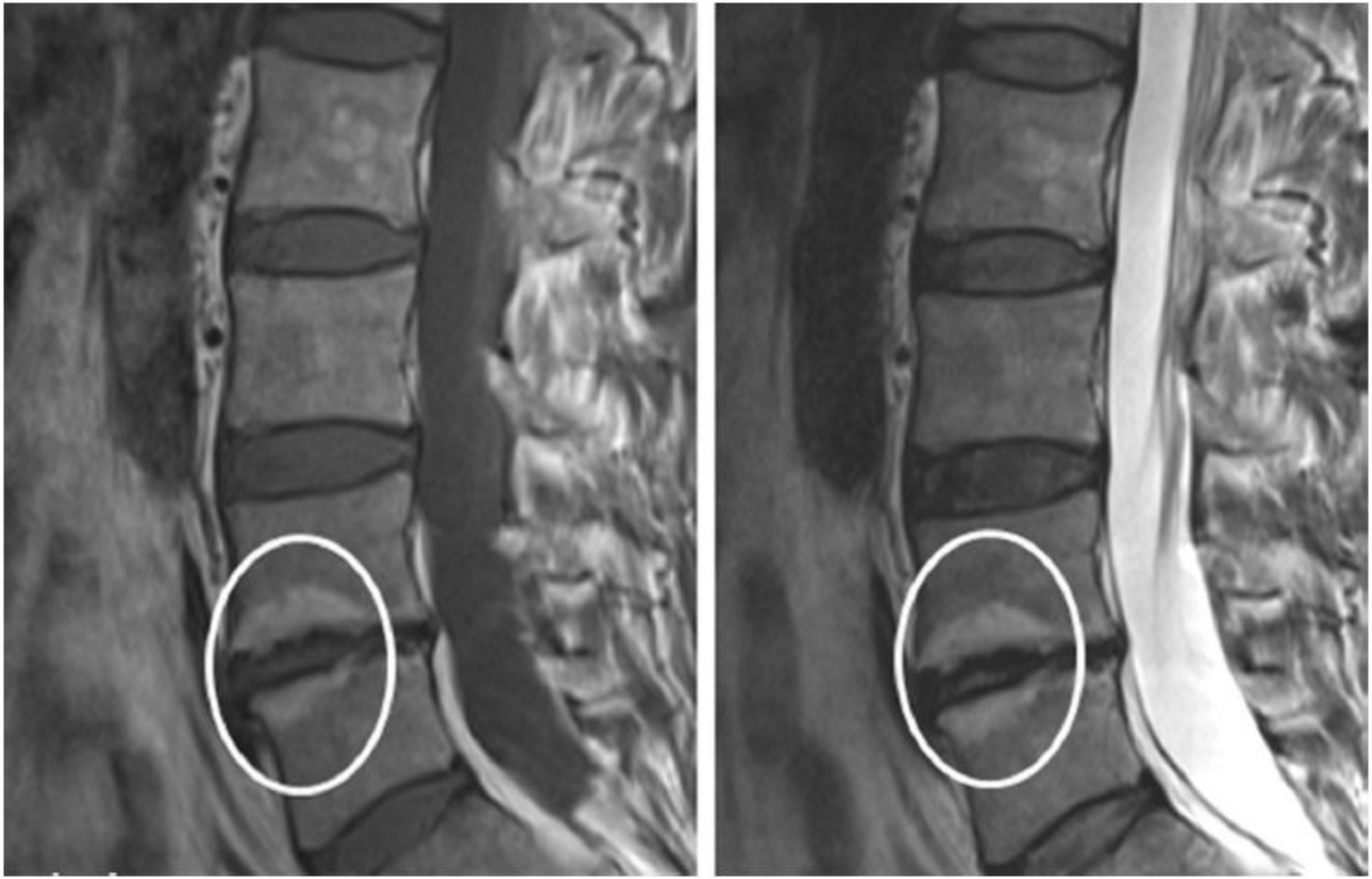
13. SYMPTOMS OF FIRST DISEASE
14. ACTIVATION OF SECOND REACTIVATION-STRATEGY
15. SYMPTOMS OF SECOND DISEASE

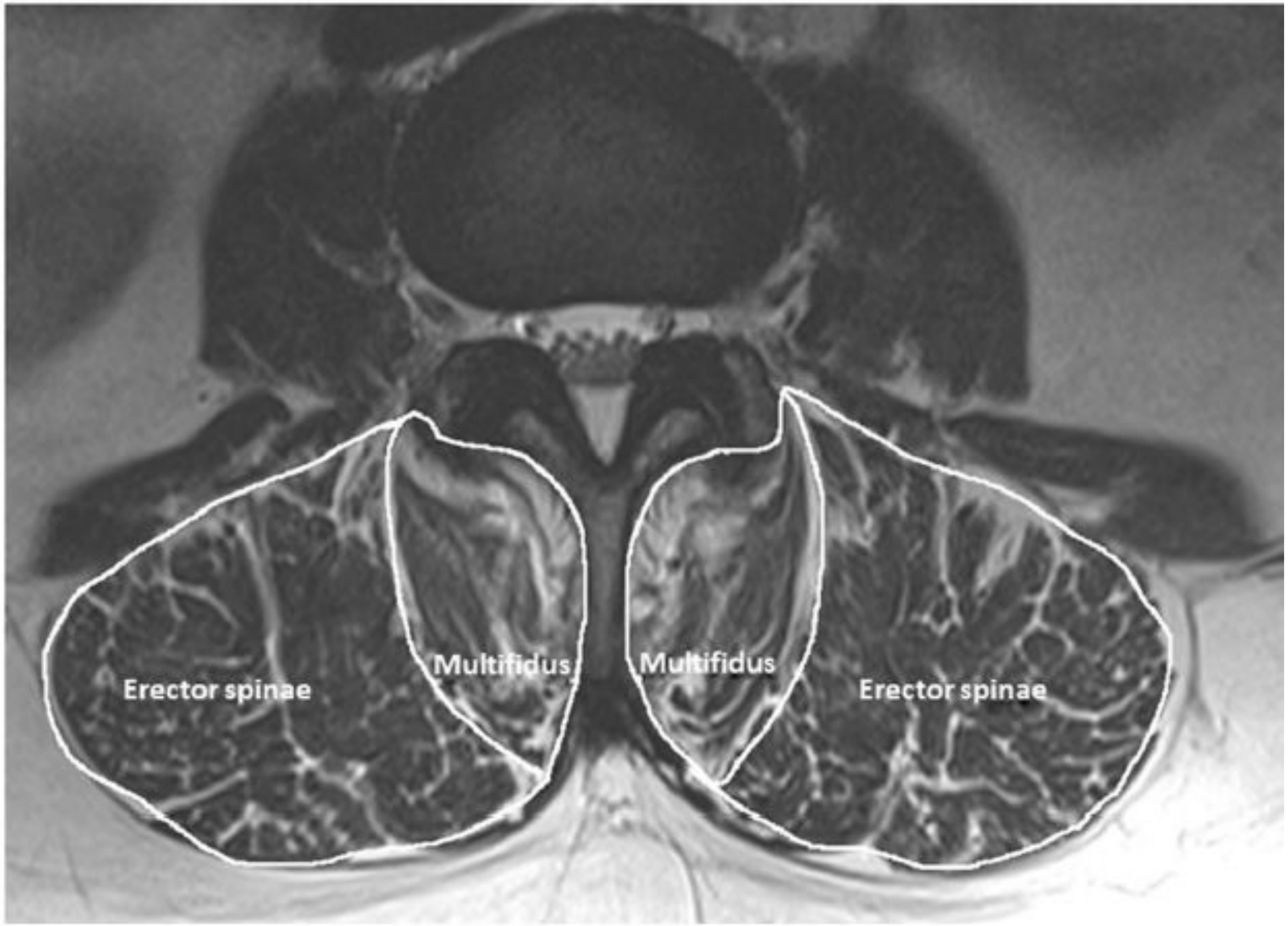
Es kommt also zu einer Kälte Entzündung, die durch eine INDIREKTE (über FAT) Aktivierung des Immunsystems hervorgerufen wird.

Fat infiltration of paraspinal muscles is associated with low back pain, disability, and structural abnormalities in community-based adults

Teichtahl.The Spine Journal 15 (2015) 1593–1601



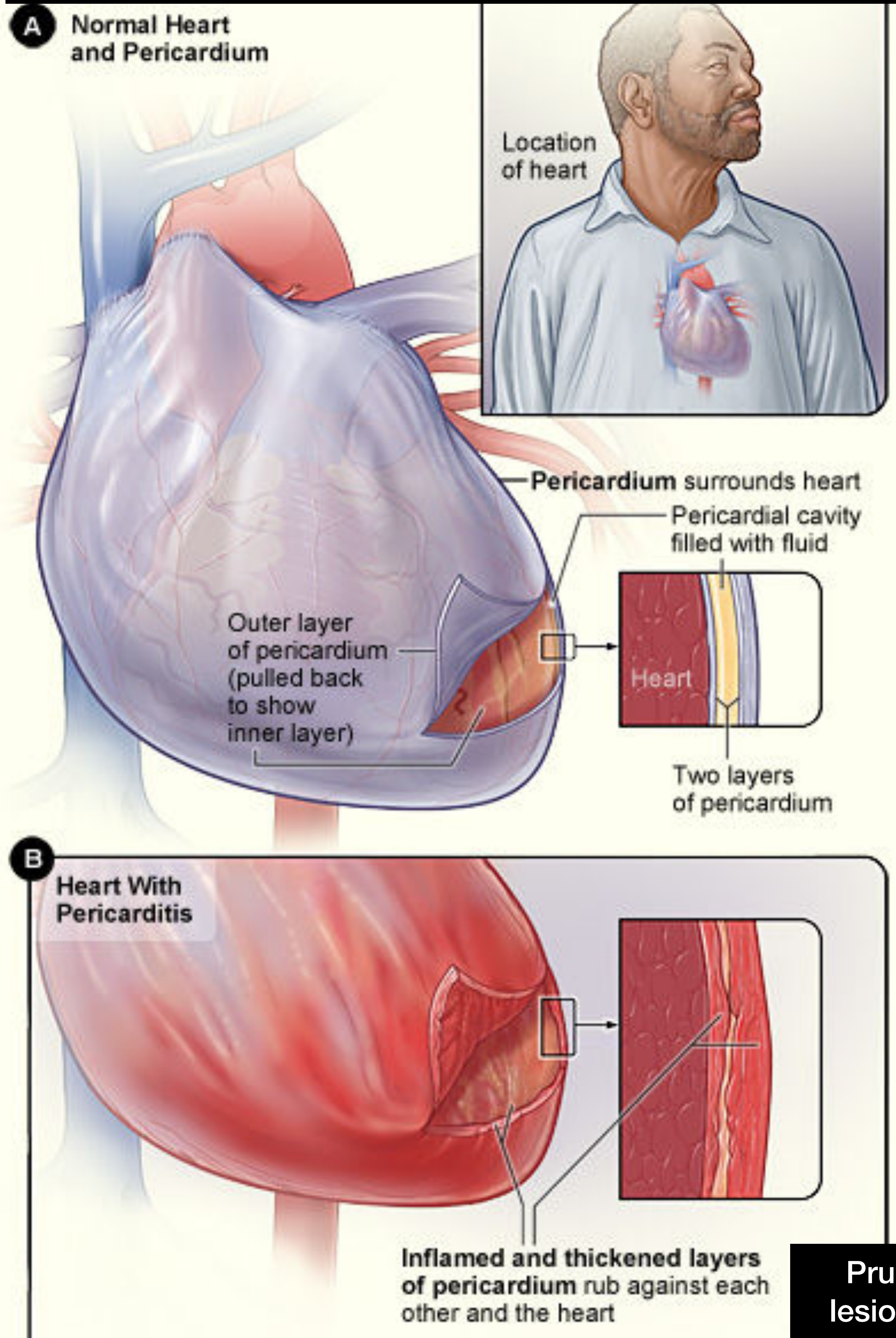
Physical inactivity is associated with narrower lumbar intervertebral discs, high fat content of paraspinal muscles and low back pain and disability

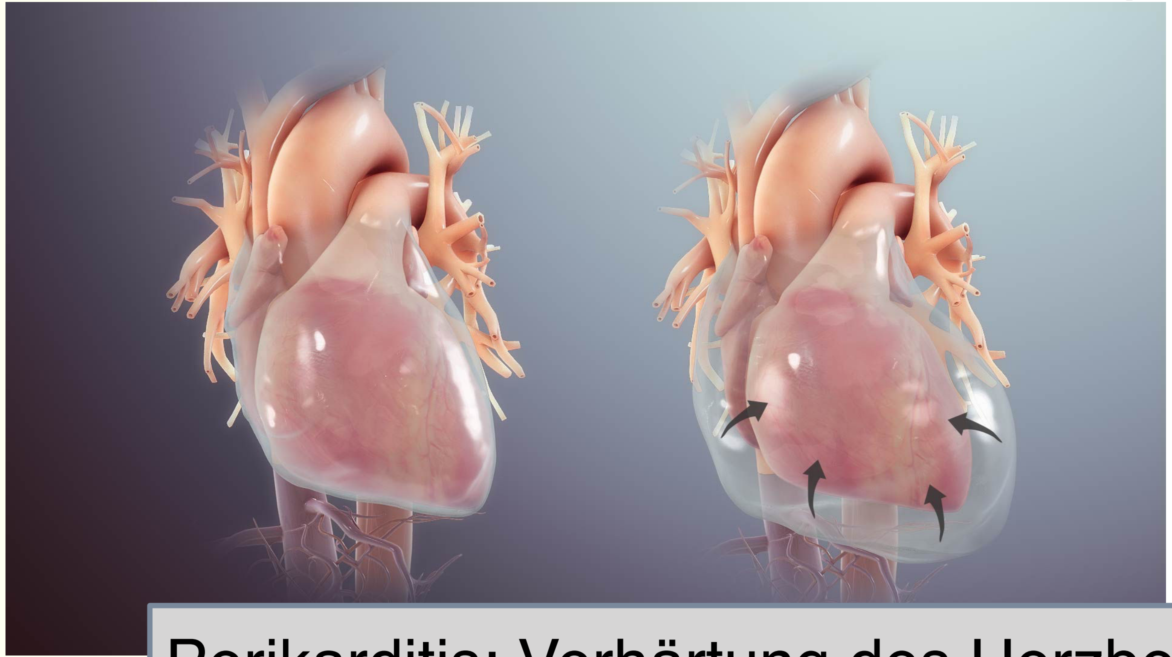

Erector spinae
Multifidus
Multifidus
Erector spinae

Teichtahl et al. Arthritis Research & Therapy
(2015) 17:114

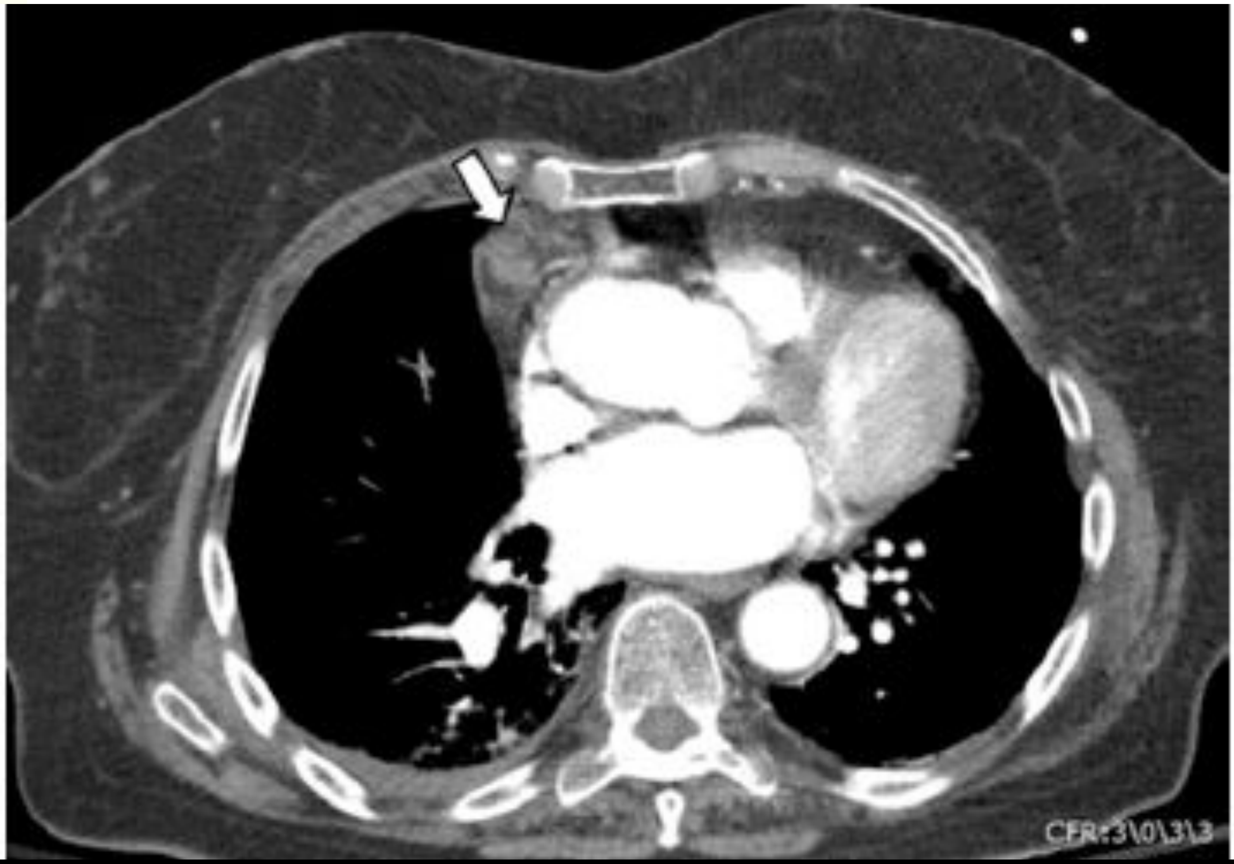
Lopez.. Rev Esp Cardiol. 2014;67:425-7 - Vol. 67 Num.06

PNI Europe


A
Normal Heart and Pericardium
Location of heart
Pericardium surrounds heart
Pericardial cavity filled with fluid
Outer layer of pericardium (pulled back to show inner layer)
Heart
Two layers of pericardium
B
Heart With Pericarditis
Inflamed and thickened layers of pericardium rub against each other and the heart

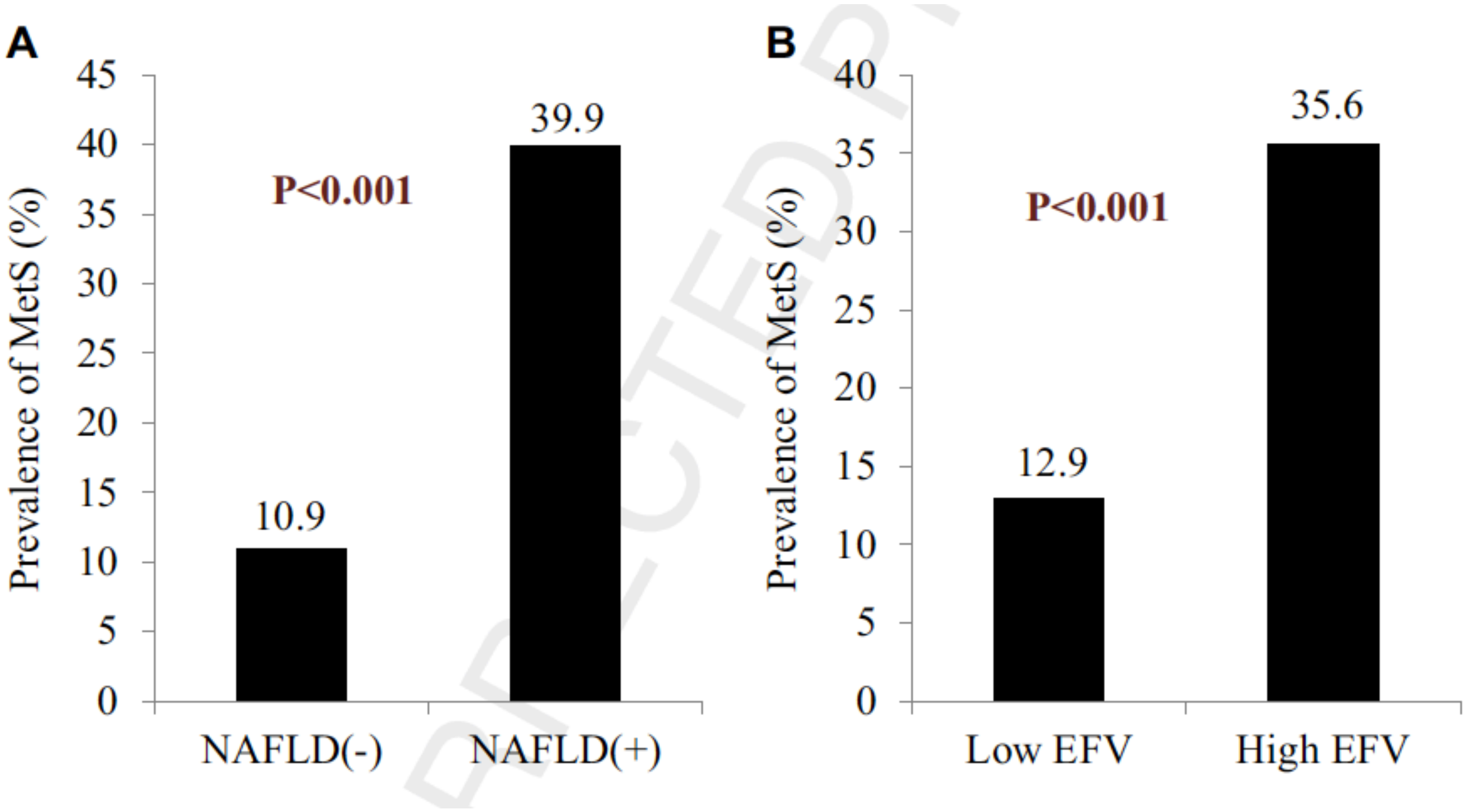


Perikarditis; Verhärtung des Herzbeutels und erhöhter Flüssigkeitsdruck auf den Herzmuskel. Infiltration von Fettzellen



Pruente R, Restrepo CS, Ocazionez D, Suby-Long T, Vargas D. Fatty lesions in and around the heart: a pictorial review. Br J Radiol 2015;88:

Zusammenhang zwischen NAFLD, METS und Perikardfettspeicherung



Kim. Journal of Clinical Lipidology (2016)

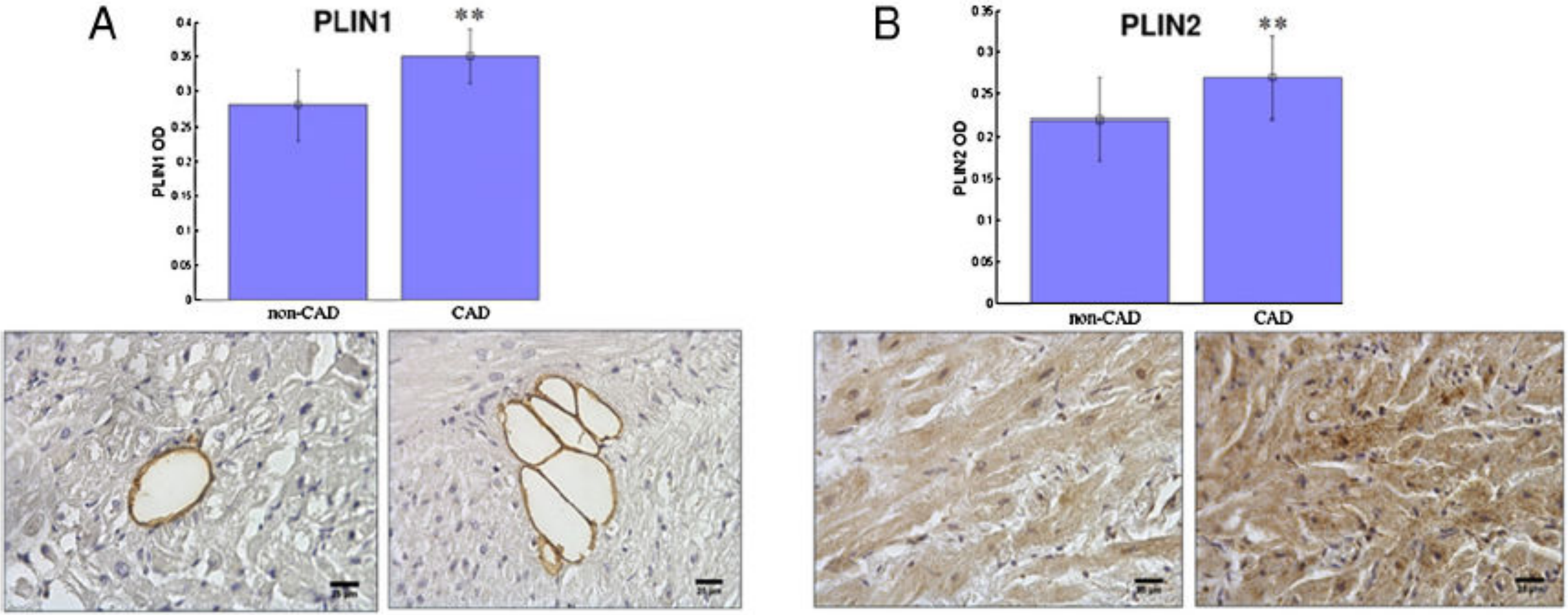
Insulinresistenz und Reihenfolge des Auftretens

1. Leber
2. Herz
3. Muskeln (3 Wochen)
4. Fettgewebe (20 Wochen)

IEMC
Healthy
Unhealthy
(Visceral Fat)

Park SY, et al. Unraveling the temporal pattern of diet-induced insulin resistance in individual organs and cardiac dysfunction in C57BL/6 mice. Diabetes. 2005; 54:3530–3540

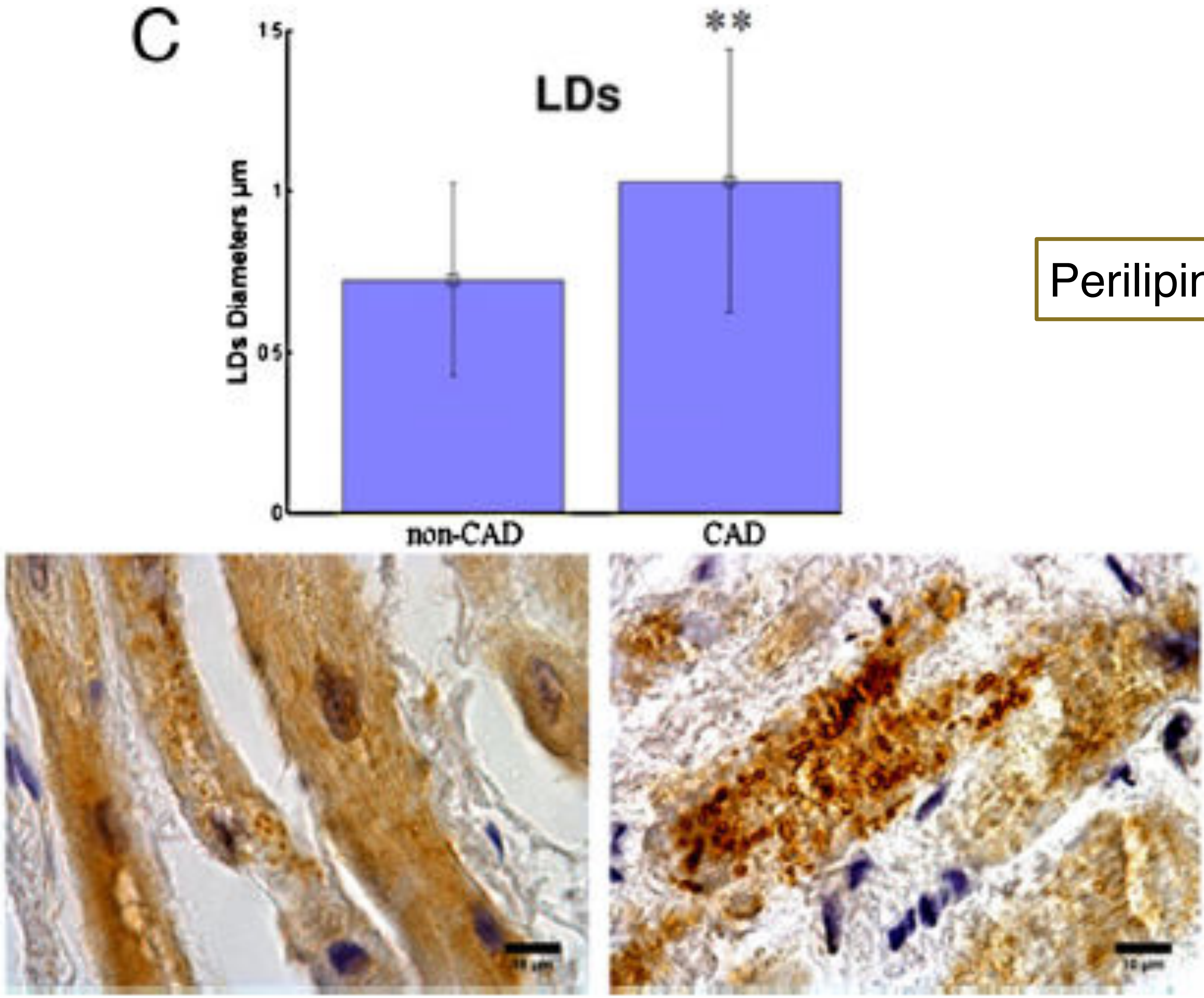
Fettspeicherung im Herzen



Perilipin (PLIN) 1 = Adipozyten = zwischen
Perilipin (PLIN) 2 = Herzmuskelzellen = innen

Mazzali. J Clin Endocrinol Metab, September 2015, 100(9):3364–3371

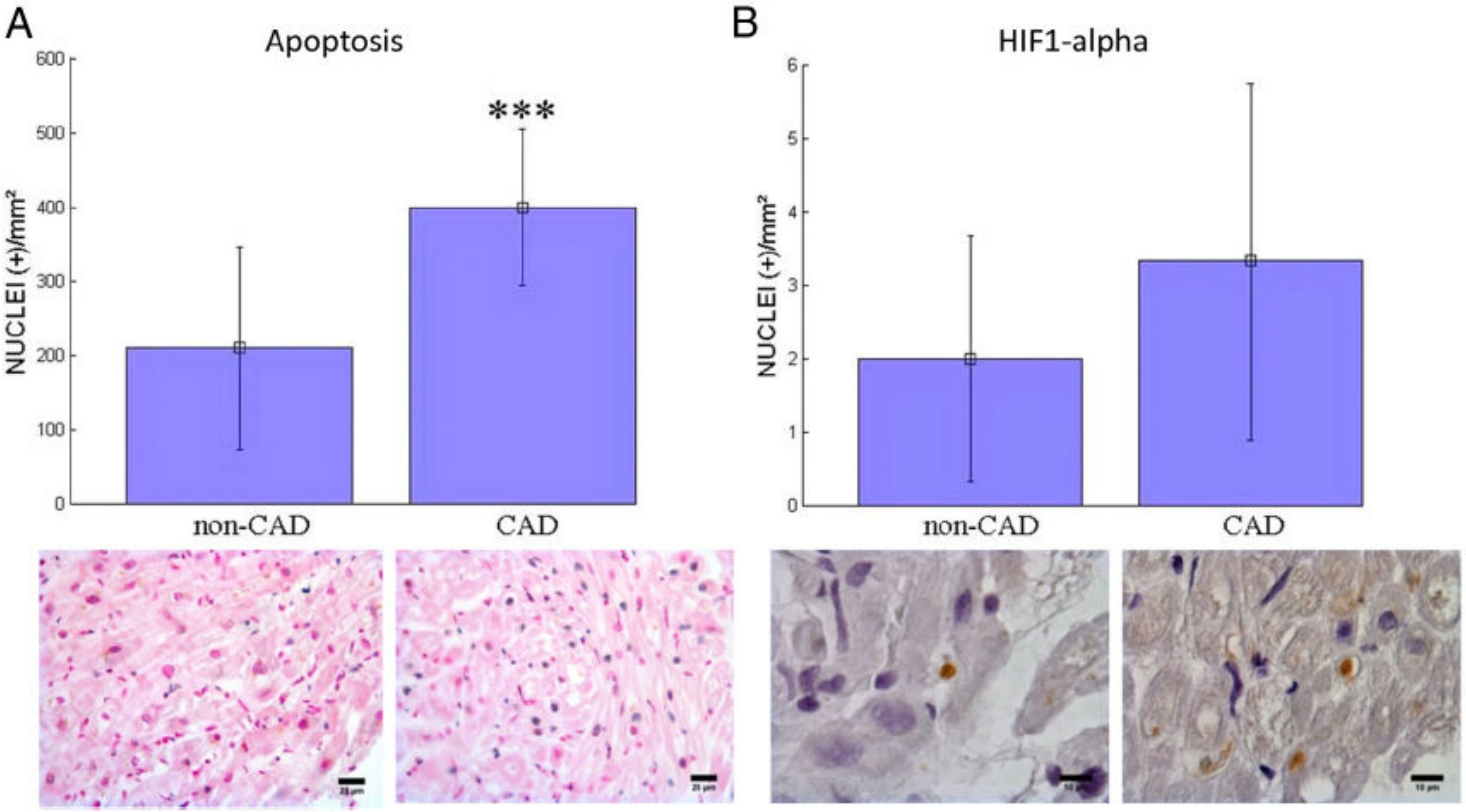
Fettspeicherung im Herzen bei Herzinsuffizienz



Perilipin (PLIN) 2 = Herzmuskelzellen

Mazzali. J Clin Endocrinol Metab, September 2015, 100(9):3364–3371

Fettspeicherung führt zu Zellapoptose und chronischer HIF1-Aktivität, die das Herz veranlasst, Gewebe zu verbinden



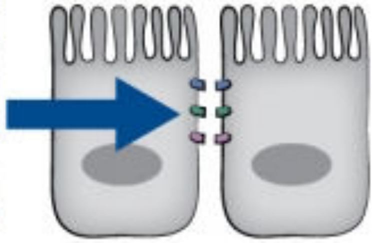
Mazzali. J Clin Endocrinol Metab, September 2015, 100(9):3364–3371

Leaky gut, leaky brain: the role of zonulin

fx Medicine

The discovery of **ZONULIN** began with a failed attempt to develop a cholera vaccine[1]

ZONULIN is a protein that can **OPEN TIGHT JUNCTION PROTEINS**[2]



GLIADIN & INTESTINAL BACTERIA are the main triggers for **ZONULIN RELEASE**[2]

ZONULIN has been identified as a biomarker for many conditions including:

COELIAC DISEASE, INFLAMMATORY BOWEL DISEASE, TYPE 1 DIABETES, ASTHMA, MULTIPLE SCLEROSIS, SCHIZOPHRENIA AND CANCER[2,3]

ZONULIN AND THE LEAKY BRAIN HYPOTHESIS[2-14]

① ZONULIN RELEASE

- Release of zonulin triggered by endothelial cells exposure to gliadin and pathogenic bacteria.
- Zonulin stimulates opening of TJs.
- Increase in intestinal permeability.
- Increased passage of stressors into lamina propria.

L. RHAMNOSUS (LGG) increasesTJ protein gene expression, inhibits zonulin release and restores intestinal permeability.[8]

L. PLANTARUM, L. ACIDOPHILUS and *B. LONGUM* increase TJ protein gene expression, inhibits zonulin release and restores intestinal permeability.[9]

ZINC enhancesTJ barrier function.[10]

PROBIOTICS may competitively inhibit pathogenic bacteria from stimulating zonulin release.

② IMMUNE RESPONSE DEVELOPMENT OF LEAKY GUT

- Increased exposure to stressors triggers immune response and inflammation.
- A vicious cycle develops where inflammation and tissue damage further increase intestinal permeability, leading to even greater passage of stressors therefore perpetuating the cycle.
- Altered immune responses and increased inflammation in the gut also interact with HPA axis and neurotransmitter metabolism.

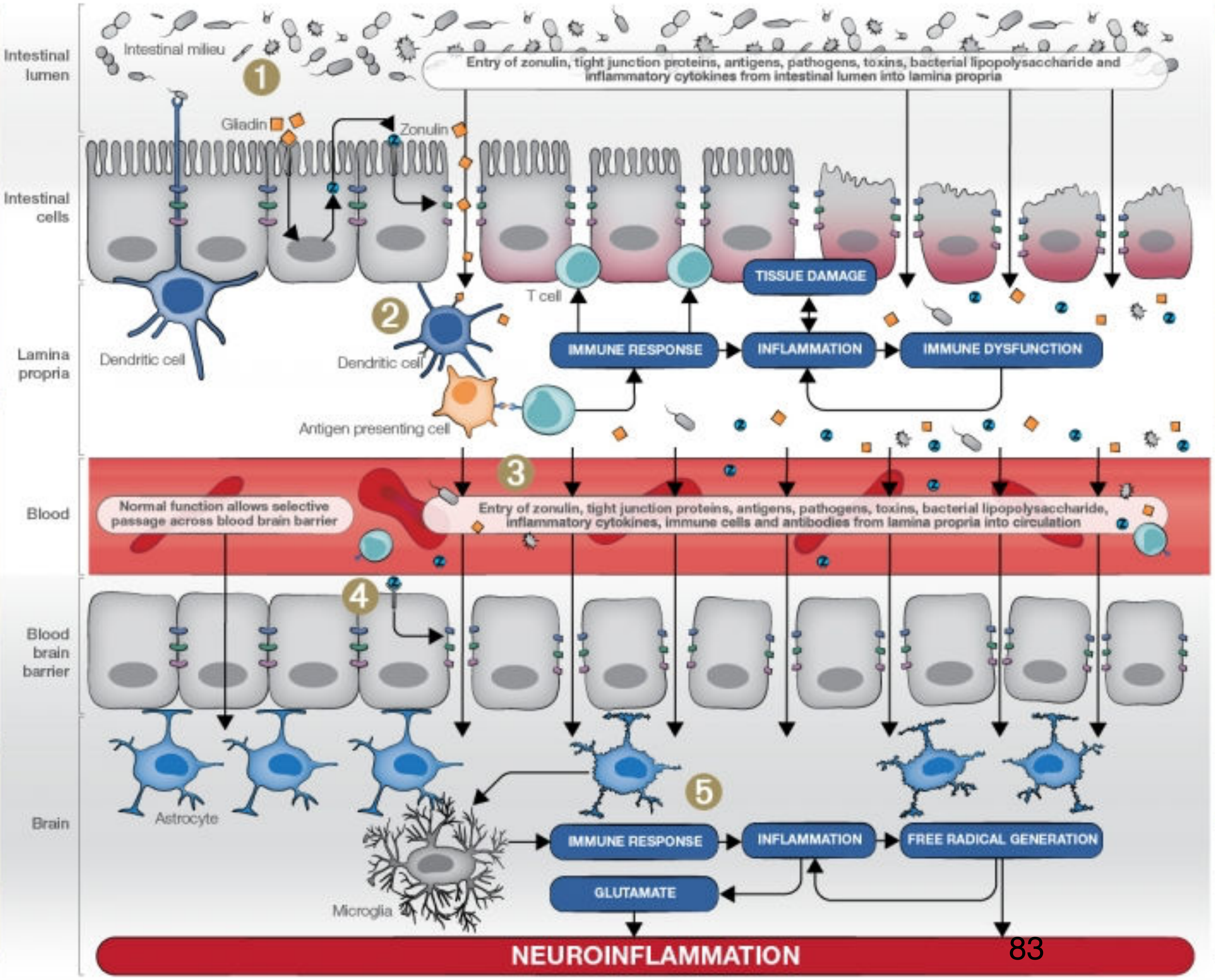
PROBIOTICS modulate immune response and down-regulate inflammation, thereby promoting healthy gut barrier function.[4]

ZINC supports healthy immune function and aids healing.[11]

③ STRESSORS ENTER CIRCULATION

- Stressors, including zonulin, TJ proteins, antigens, pathogens, toxins, bacterial lipopolysaccharide, inflammatory cytokines and antibodies enter into circulation.

PROBIOTICS reduce systemic inflammatory cytokines and lipopolysaccharide burden.[12]



Intestinal lumen
Intestinal milieu
1
Entry of zonulin, tight junction proteins, antigens, pathogens, toxins, bacterial lipopolysaccharide and inflammatory cytokines from intestinal lumen into lamina propria
Gliadin
Zonulin
Intestinal cells
T cell
TISSUE DAMAGE
2
Lamina propria
Dendritic cell
Dendritic cell
IMMUNE RESPONSE
INFLAMMATION
IMMUNE DYSFUNCTION
Antigen presenting cell
Blood
3
Normal function allows selective passage across blood brain barrier
Entry of zonulin, tight junction proteins, antigens, pathogens, toxins, bacterial lipopolysaccharide, inflammatory cytokines, immune cells and antibodies from lamina propria into circulation
4
Blood brain barrier
Brain
Astrocyte
5
IMMUNE RESPONSE
INFLAMMATION
FREE RADICAL GENERATION
GLUTAMATE
Microglia
NEUROINFLAMMATION

④ BLOOD BRAIN BARRIER DYSFUNCTION – LEAKY BRAIN

- The BBB includes endothelial cells and TJs.
- Astrocytes located beneath endothelial cells prevent entry of unwanted molecules across the BBB.
- Zonulin from the blood binds to zonulin receptors on the BBB.
- Zonulin stimulates opening of TJs.
- Similar to what happens in leaky gut, stressors, including zonulin, TJ proteins, antigens, pathogens, toxins, bacterial lipopolysaccharide, inflammatory cytokines and antibodies are allowed passage into the brain.

Gut microbiota may regulate BBB via modulation of TJ protein expression and production of short chain fatty acids.[13] PROBIOTICS may be beneficial.

ZINC enhances TJ barrier function.[10]

⑤ IMMUNE RESPONSE NEUROINFLAMMATION

- Increased passage of unwanted molecules causes damage to astrocytes.
- Immune response is stimulated by microglia.
- A vicious cycle of increased passage of stressors and inflammation develops, leading to neuroinflammation.
- Neuroinflammation can also impact on brain communication with the gut and HPA axis.
- Chronic neuroinflammation has been associated with various conditions including mood disorders, Alzheimer's disease, autism spectrum disorders, dementia, schizophrenia, cognitive decline and mental fatigue.

Short chain fatty acids may reverse detrimental effects on brain cells.[14] PROBIOTICS may be beneficial.

Intestinal milieu (including bacteria, viruses, fungi, toxins, lipopolysaccharide)

🟧 Gliadin

Ⓩ Zonulin

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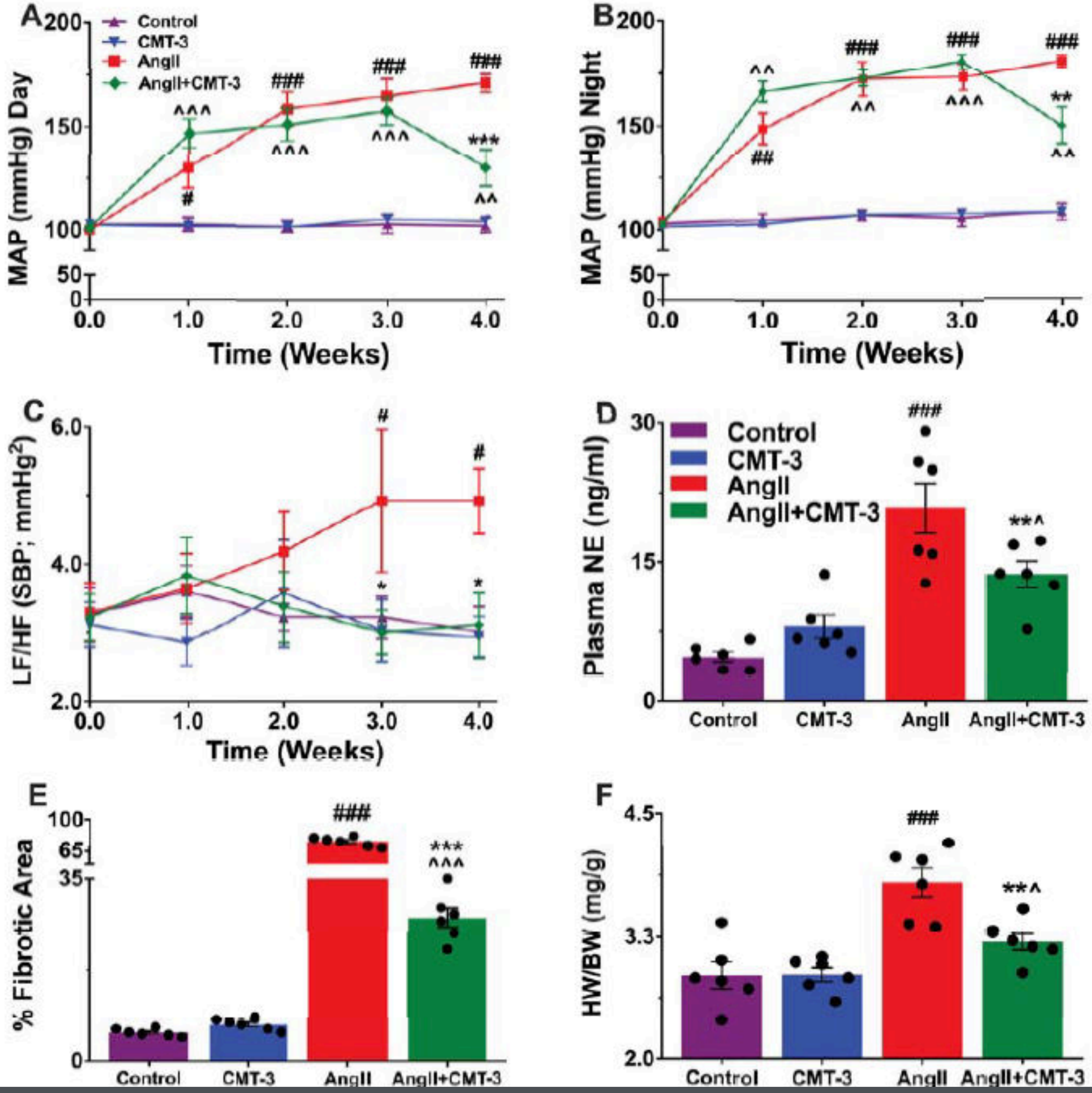
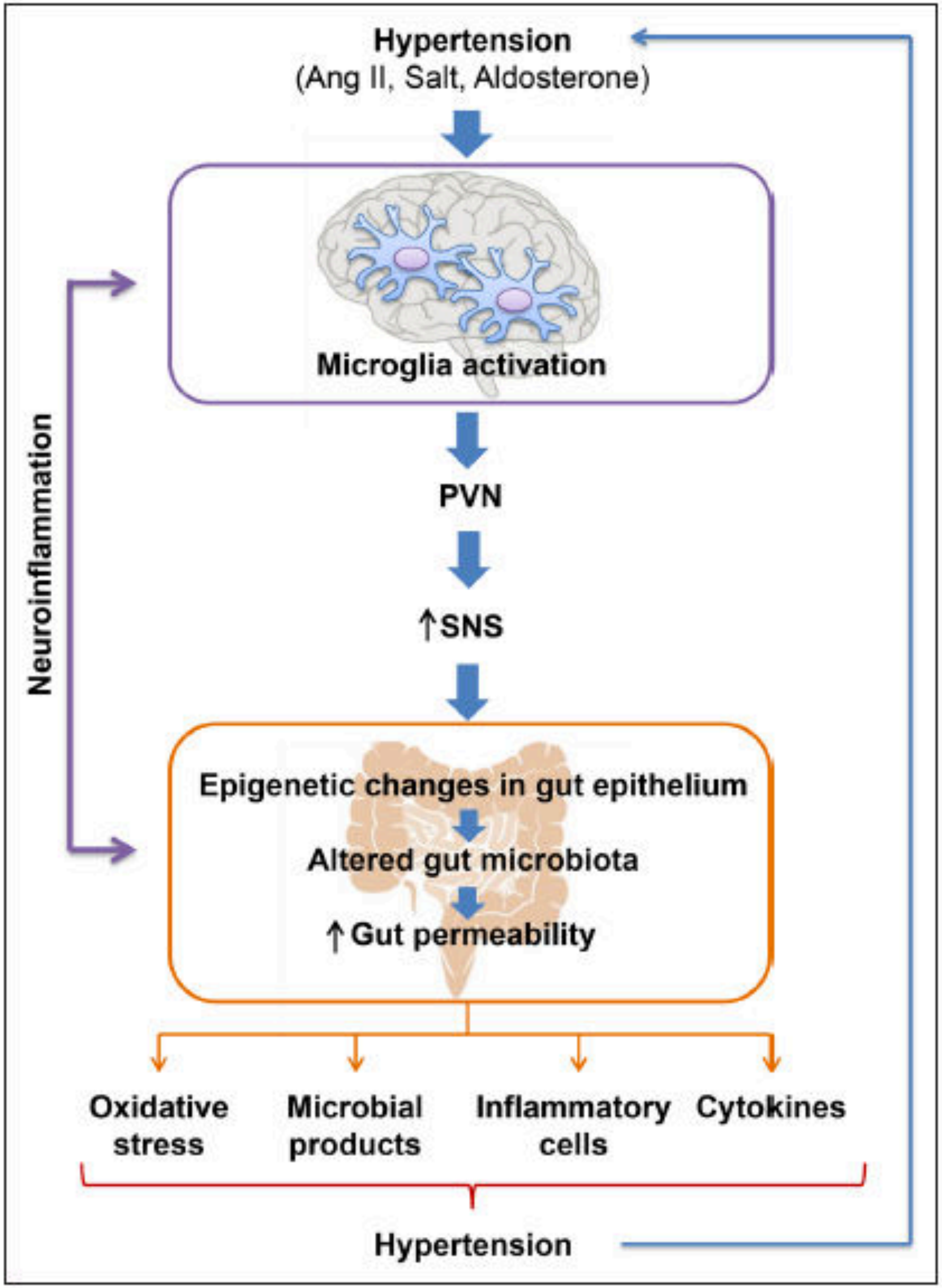
Die Hemmung der Aktivität der Gliazellen stellt den Blutdruck wieder her



Die Achse Bluthochdruck - Gehirn - Darm.

Erstmals wird gezeigt, dass die Hemmung der Neuroinflammation durch die Behandlung der Mikrogliazellen den Bluthochdruck beseitigt und die Darmflora verändert. Klinische PNI auf höchstem Niveau

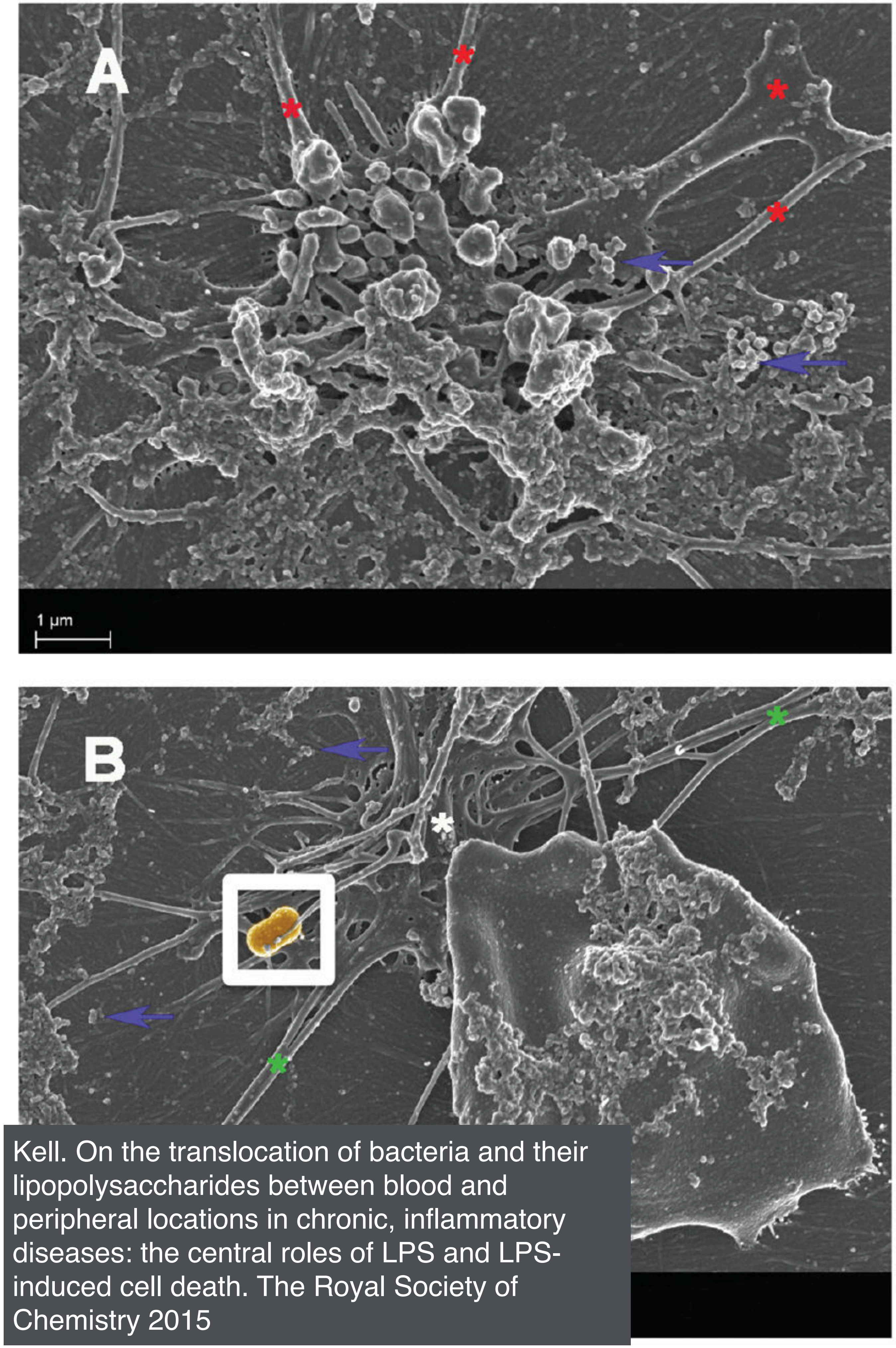
Sharma. Microglial Cells Impact Gut Microbiota and Gut Pathology in Angiotensin II-Induced Hypertension. AHA-journals 2019 . DOI: 10.1161/CIRCRESAHA.118.313882


Hypertension
(Ang II, Salt, Aldosterone)
Microglia activation
PVN
↑SNS
Epigenetic changes in gut epithelium
Altered gut microbiota
↑Gut permeability
Neuroinflammation
Oxidative stress
Microbial products
Inflammatory cells
Cytokines
Hypertension

Die schaltungstechnische Beziehung zwischen prohypertensiven Faktoren, Mikrogliaaktivierung, Sympathikusausfluss und Darmflora in der Pathophysiologie der Hypertonie. Neurogene Entzündungen und oxidativer Stress sind wichtige molekulare Prozesse, die die Darmachse des Gehirns antreiben. Ang = Angiotensin, PVN, paraventrikulärer Kern, und SNS, sympathisches Nervensystem.

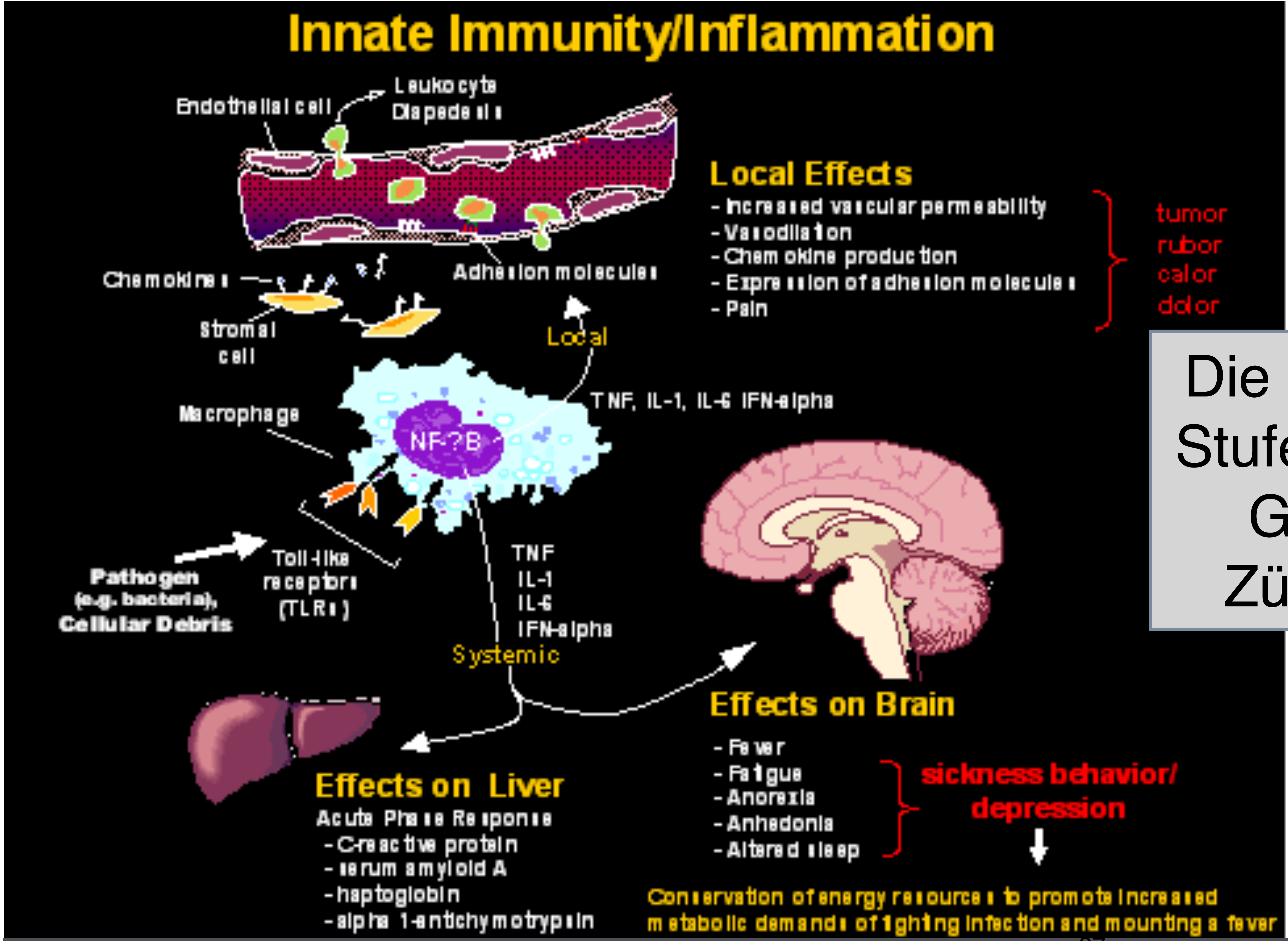
Touyz. Microglia, the Missing Link in the Brain-Gut-Hypertension Axis. Circ Res. 2019;124:671-673.

Nachweis, dass die Krankheitserreger tatsächlich das Gewebe erreichen und zur Pathophysiologie chronischer Krankheiten beitragen



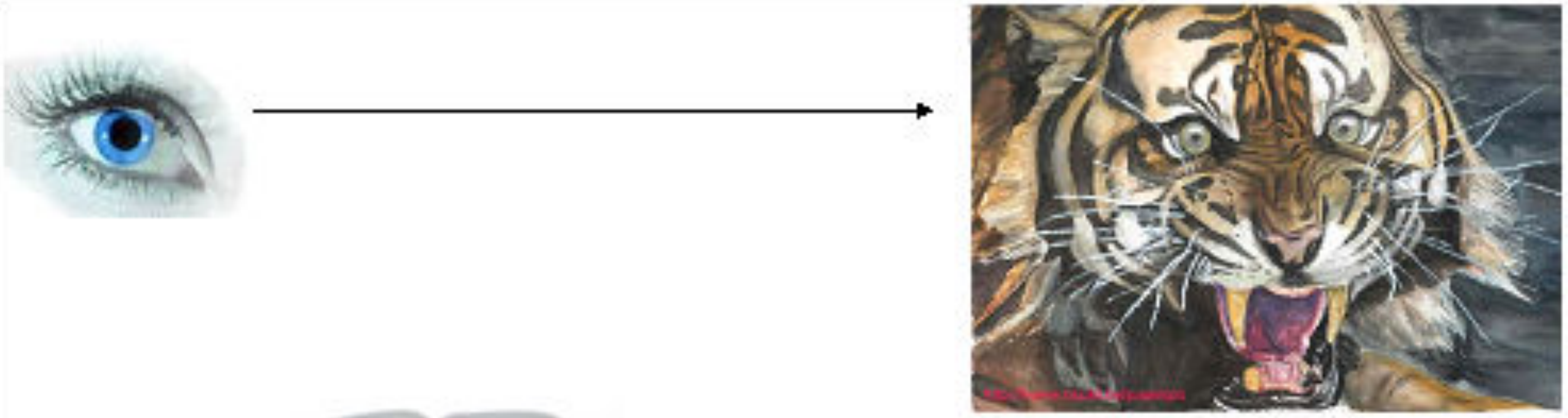
Kell. On the translocation of bacteria and their lipopolysaccharides between blood and peripheral locations in chronic, inflammatory diseases: the central roles of LPS and LPS-induced cell death. The Royal Society of Chemistry 2015

Vollblutausstriche von einem thromboembolischen ischämischen Schlaganfall. (A) Hyperaktivierte Thrombozytenmasse mit Pseudopodien und Mikropartikelbildung. (B) Hyperaktivierte Masse von Thrombozyten mit Fusion und spontan gebildete Fibrin-Fasern, im Vollblut. Diese aktivierte Masse ist eng mit einem abnormal gebildeten Erythrozyten verwandt, der mit Plasmaproteine/Mikroparate, die aus apoptotischen, hyperaktiven Plasmaproteinen/Mikroparaten, Thrombozyten oder geschädigten Erythrozyten gewonnen werden. Erläuterung der Sterne und Pfeile: in (A): rotes Sternchen: Pseudokörperbildung; blaue Pfeile: Mikropartikel.
In (B): blaue Pfeile: Mikropartikel; grünes Sternchen: Fibrinbildung, die mit dem Pseudopodion einer hyperaktivierten Fibrinfaser verschmilzt, gestaffelte Thrombozyten (weißes Sternchen). Beachten Sie wichtige Pseudopodien/Fibrine, die aus der dispergierten Thrombozytenmasse (weißes Sternchen) austreten. Bakterium (pseudo-farbig in gelb-braun) wird durch einen weißen Block dargestellt

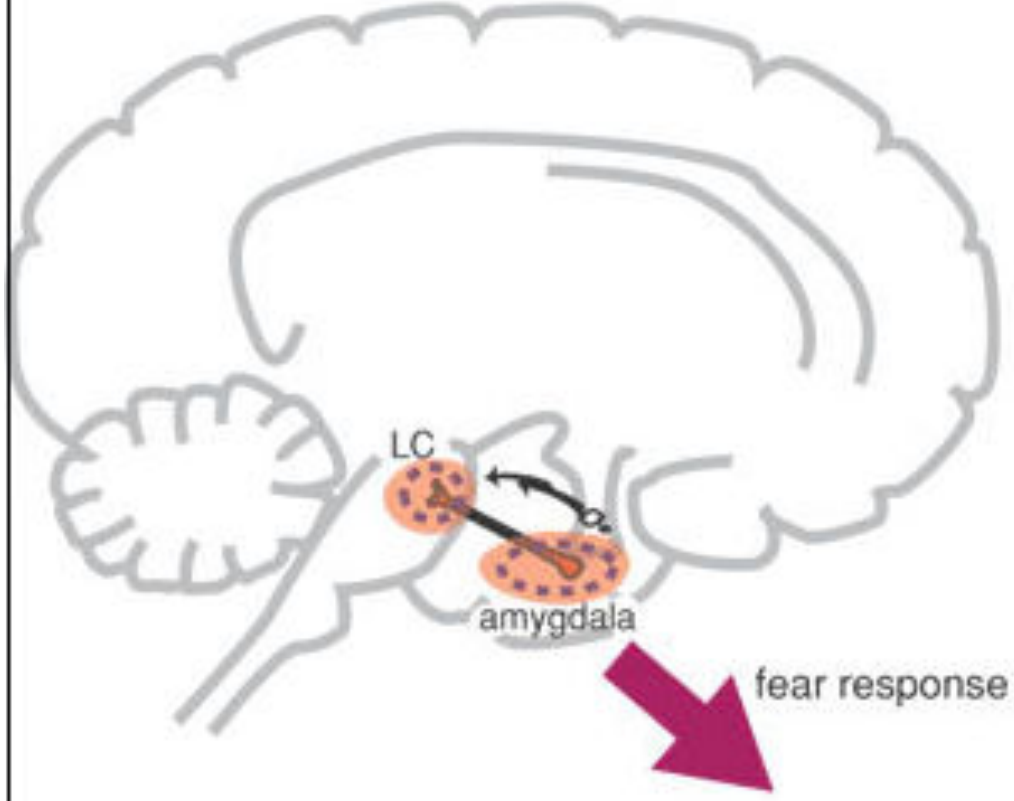

Innate Immunity/Inflammation
Endothelial cell
Leukocyte Diapedesis
Chemokines
Stromal cell
Adhesion molecules
Local
Macrophage
NF-?B
TNF, IL-1, IL-6 IFN-alpha
Pathogen (e.g. bacteria), Cellular Debris
Toll-like receptors (TLRs)
TNF
IL-1
IL-6
IFN-alpha
Systemic
Local Effects
- Increased vascular permeability
- Vasodilation
- Chemokine production
- Expression of adhesion molecules
- Pain
tumor
rubor
calor
dolor
Effects on Brain
- Fever
- Fatigue
- Anorexia
- Anhedonia
- Altered sleep
sickness behavior/ depression
Conservation of energy resources to promote increased metabolic demands of fighting infection and mounting a fever
Effects on Liver
Acute Phase Response
- C-reactive protein
- serum amyloid A
- haptoglobin
- alpha 1-antichymotrypsin

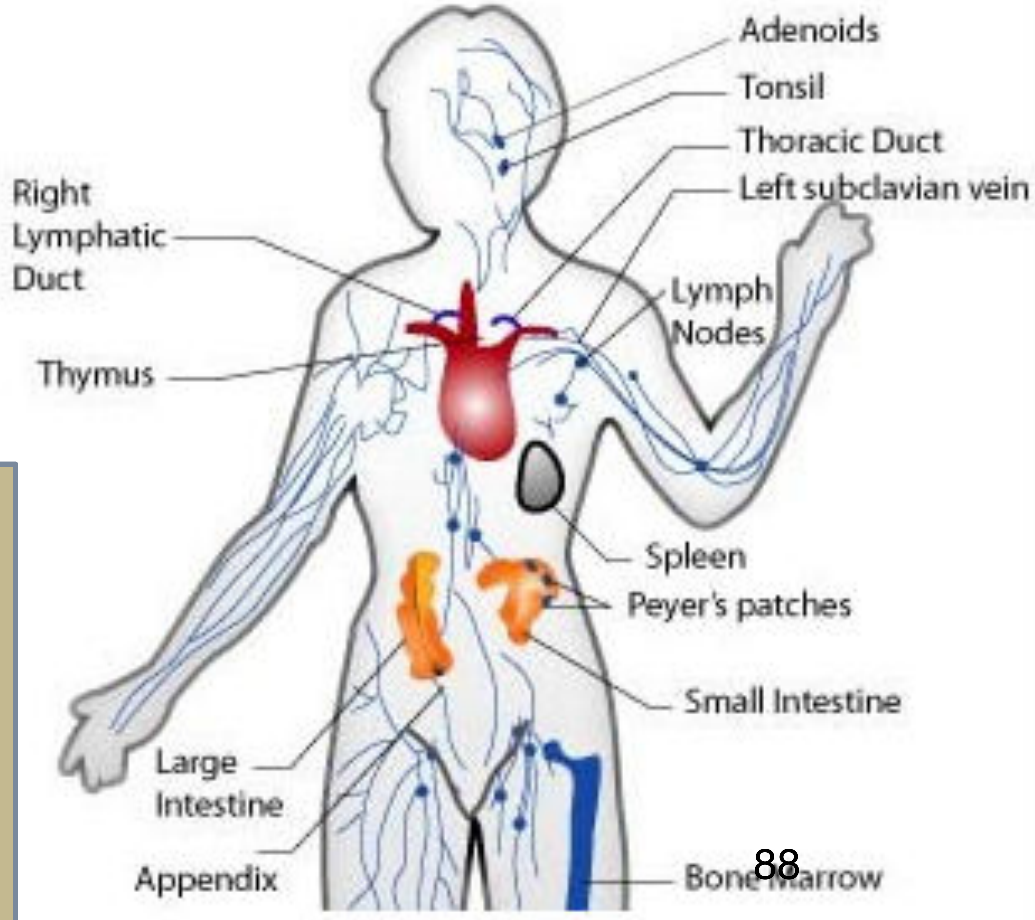
Die zentrale Stufe = Low-Grade-Zündung

Miller, A. H., V. Maletic, et al. (2009). "Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression." Biol Psychiatry **65**(9): 732-41.



Pruimboom, L. The universal pathways of chronic western disease. Van Nature 2009

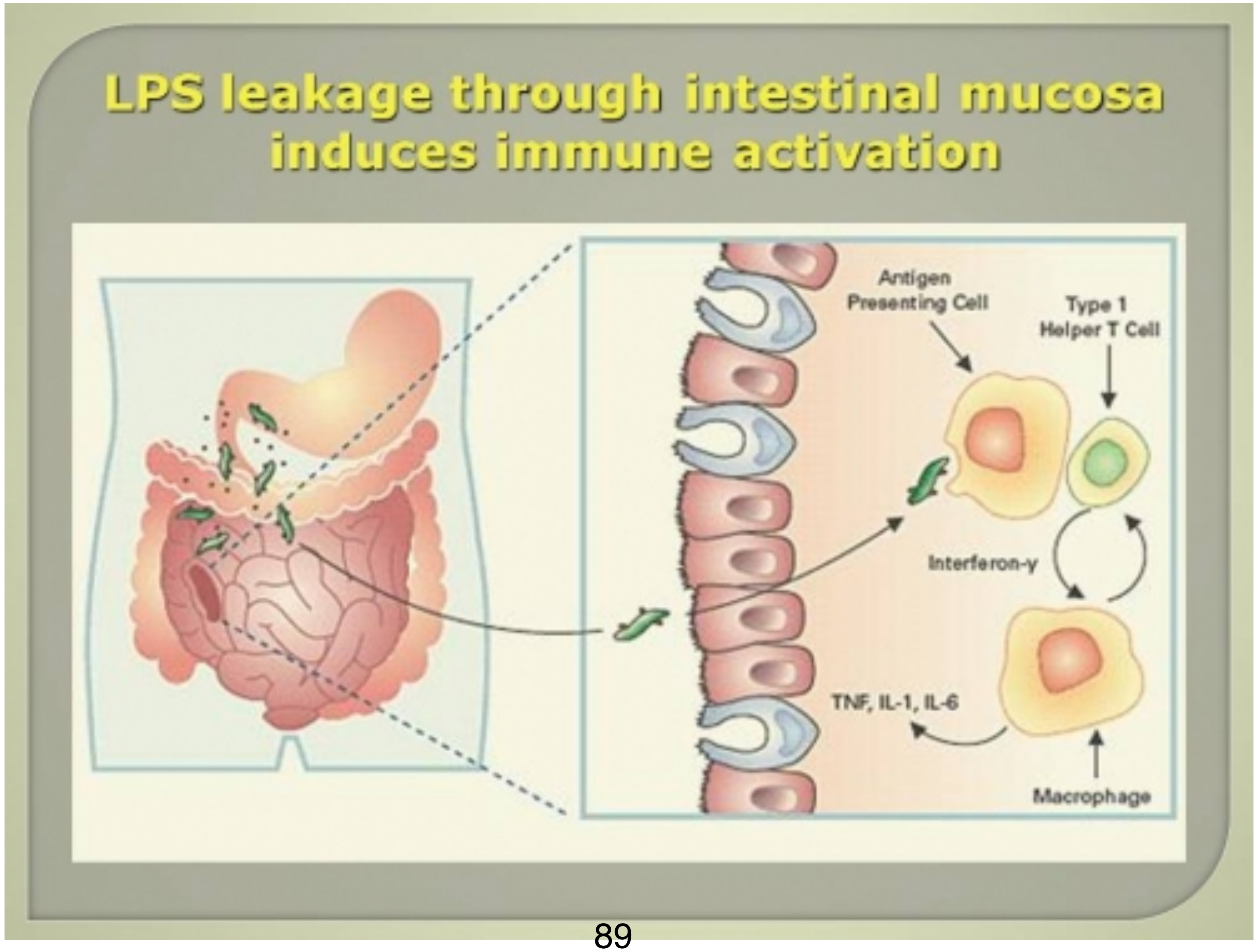

LC
amygdala
fear response


Adenoids
Tonsil
Thoracic Duct
Left subclavian vein
Right Lymphatic Duct
Lymph Nodes
Thymus
Spleen
Peyer's patches
Small Intestine
Large Intestine
Appendix
Bone Marrow

Auch neurogene Entzündungen führen zu LGI

Die undichten Barrieren

Die wichtigsten Barrieren sind die Blut-Hirn-Schranke, die Blut-Gastrointestinal-Schranke (GBB), Blut-, Augen- und Blutnetzwerkbarrieren, Blutplazenta- und Bluthodenbarrieren, die Blut-Thymus-Schranke und die Blut-Lungen- oder Atemwegsbarriere. Jede dieser Barrieren schützt verletzliche und empfindliche Organe und Systeme.


LPS leakage through intestinal mucosa induces immune activation
Antigen Presenting Cell
Type 1 Helper T Cell
Interferon-γ
TNF, IL-1, IL-6
Macrophage

Obrenovich. Leaky gut, Leaky brain?Microorganisms 2018, 6, 107

Erhöhte Darmdurchlässigkeit und Erkrankungen
1 Mechanismus für fast alle chronischen Krankheiten

- Disease Tissue/Organ Citation
- 1. Allergies Various Liu et al. Acta Paediatrica 2005;94:386-93
- 2. Ankyllosing Spondylitis Skeletal system Vaile JH et al. J Rheumatol 1999;26:128-35
- 3. Apthous stomatis Mouth Veloso FT et al. Hepatogastroenterol 1987;34:36-7
- 4. Asthma Lungs Benard A et al. J Allergy Clin Immun 1996;97:1173-
- 5. Autism Nerve/Brain White JF. Exp Bio Med 2003;228:639-49
- 6. Autoimmune gastritis GI Tract Greenwood DL et al. Eur J Pediatr 2008;167:917-25
- 7. Autoimmune hepatitis Liver Terjung B Clin Rev Allergy Immunol 2009;36:40-51
- 8. Behcet's Syndrome Small blood vessels Fresko I et al. Ann Rheum Dis 2001;60:65-6
- 9. Celiac Disease Gut Schulzke JD et al. Pediatric Res 1998;43:435-41
- 10. Chronic Fatigue Synd Multiple Maes M et al. Neuroendol Lett 2007;28;739-44
- 11. Crohn's disease Gut Caradonna L et al. J Endotoxin Res 2000;6:205-14
- 12. Depression Brain Maes M et al. Neuroendocrinol Lett 2008;29:117-24
- 13. Dermatitis
- herpetiformis Skin Kieffer M et al. Br J Dermatol 1983;108:673-8
- 14. Diabetes, Type 1 Pancreas Sapone A et al. Diabetes 2006;55:1443-49
- 15. Eczema Skin Hamilton et al. Q J Med 1985;56:559-67
- 16. Gut migraine children Gut Amery WK et al. Cephalalgia 1989;9:227-9

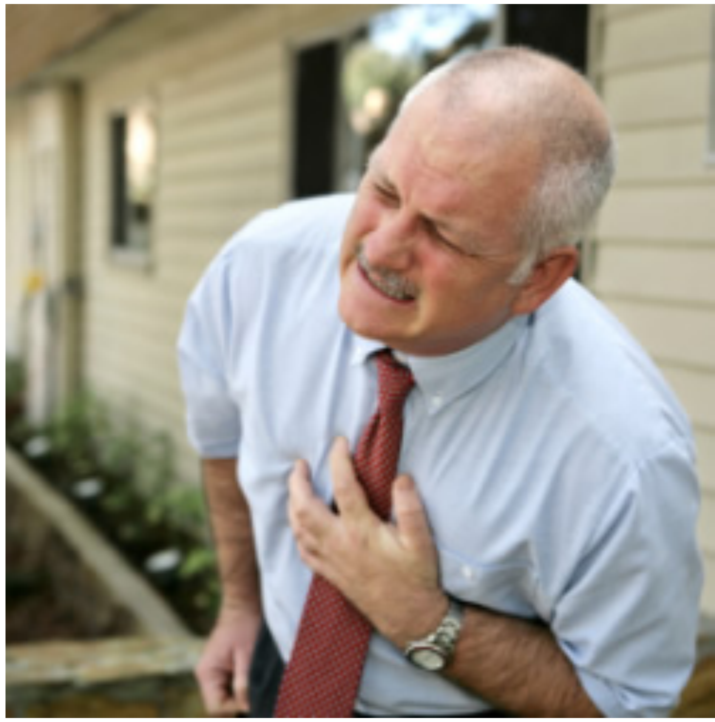
Verhoogde darm doorlaatbaarheid en ziekten
1 mechanisme voor zo goed als alle chronische aandoeningen

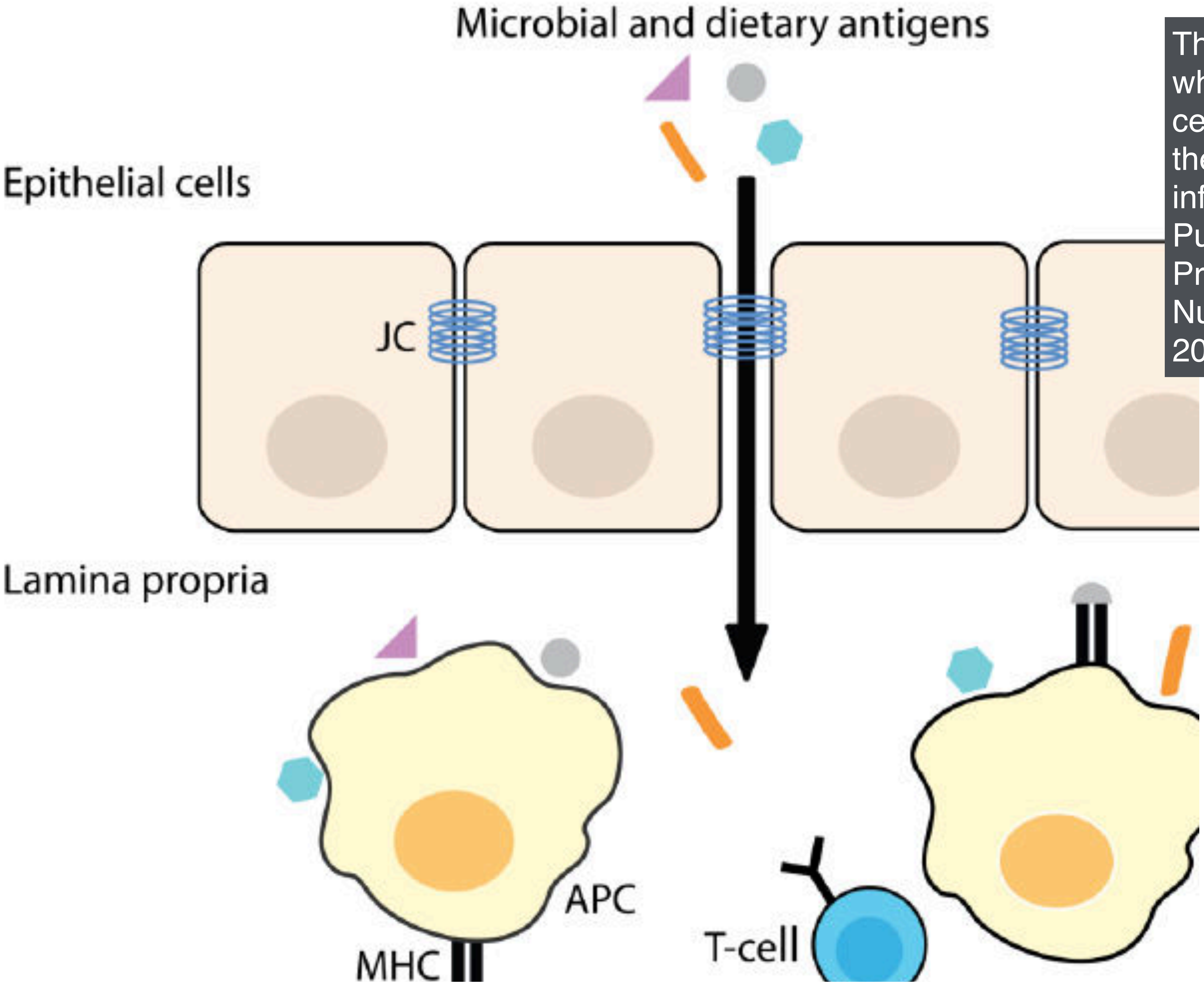
- Disease Tissue/Organ Citation
- 17. Hashimoto’s ThyroiditisThyroid Sasso FC et al. Gut 2004;53:1878-80
- 18. IgG Nephropathy Kidney Rostoker G et al. Nephron 1993;63:286-290.
- 19. Intrahepatic cholestasis
- of pregnancy Liver Reyes H et al. Hepatology 2006;43:715-22
- 20. Juvenile Arthritis Collagen/joints Picco P et al. Clin Exp Rheumatol 2000;18:773-8
- 21. Lupus erythmatosis Multiple Apperloo HZ et al. Epidemiol Infect 1994;112:367-73
- 22. Multiple sclerosis Nerve/Brain Yacyshyn B et al. Dig Dis Sci 1996;41:2493-98
- 23. Pemphigus Skin Kieffer M et al. Br J Dermatol 1983;108:673-8
- 24. Primary Biliary Cirrh Liver Di Leo V et al. Eur J Gastro Hepatol 2003;15:967-73
- 25. Psoriasis Skin Hamilton et al. Q J Med 1985;56:559-67
- 26. Rheumatoid arthritis Joints Smith MD et al. J Rheumatol 1985;12:299-305
- 27. Rosacea Skin Kendall SN. Exp Dermatol 2004;29:297-99
- 28. Schizophrenia Brain Wood NC et al. Br J Psychiatry 1987;150:853-6
- 29. Scleroderma Connective tissue Caserta L et al. Rheumatol Int 2003;23:226-30
- 30. Sclerosing Cholangitis Liver Terjung B Clin Rev Allergy Immunol 2009;36:40-51
- 31. Spontaneous abortion Uterus Friebe A Int J Biochem Cell Biol 2008;40:2348-52
- 32. Ulcerative colitis Gut Caradonna L et al. J Endotoxin Res 2000;6:205-14
- 33. Urticaria Skin Buhner S et al. Allergy 2004;59:1118-23
- 34. Uveitis Eye Benitez JM et al. Eye 2000 14(pt 3A):340-3

Erhöhte Darm- und LGI-Durchlässigkeit und Krankheiten
2 Mechanismen für fast alle chronischen Krankheiten

-Krankheit Gewebe/Organ Zitat

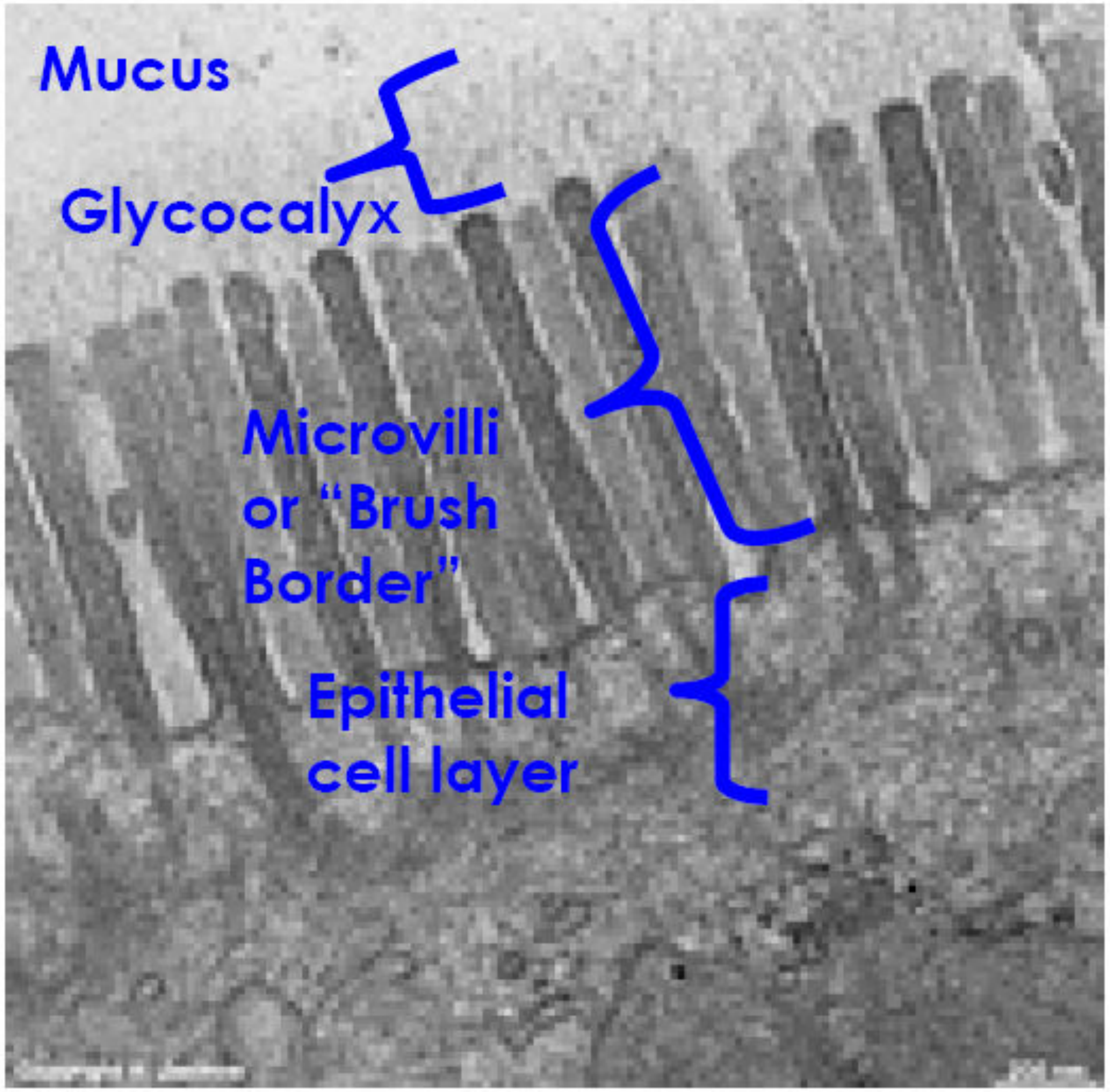
- **35. CVD Blood vessels Orr JS et al. Hypertension 2008;51(6):1519 - 1524**
- **36. Alzheimer Brain Watkins L. Brain Beh Imm 2008**



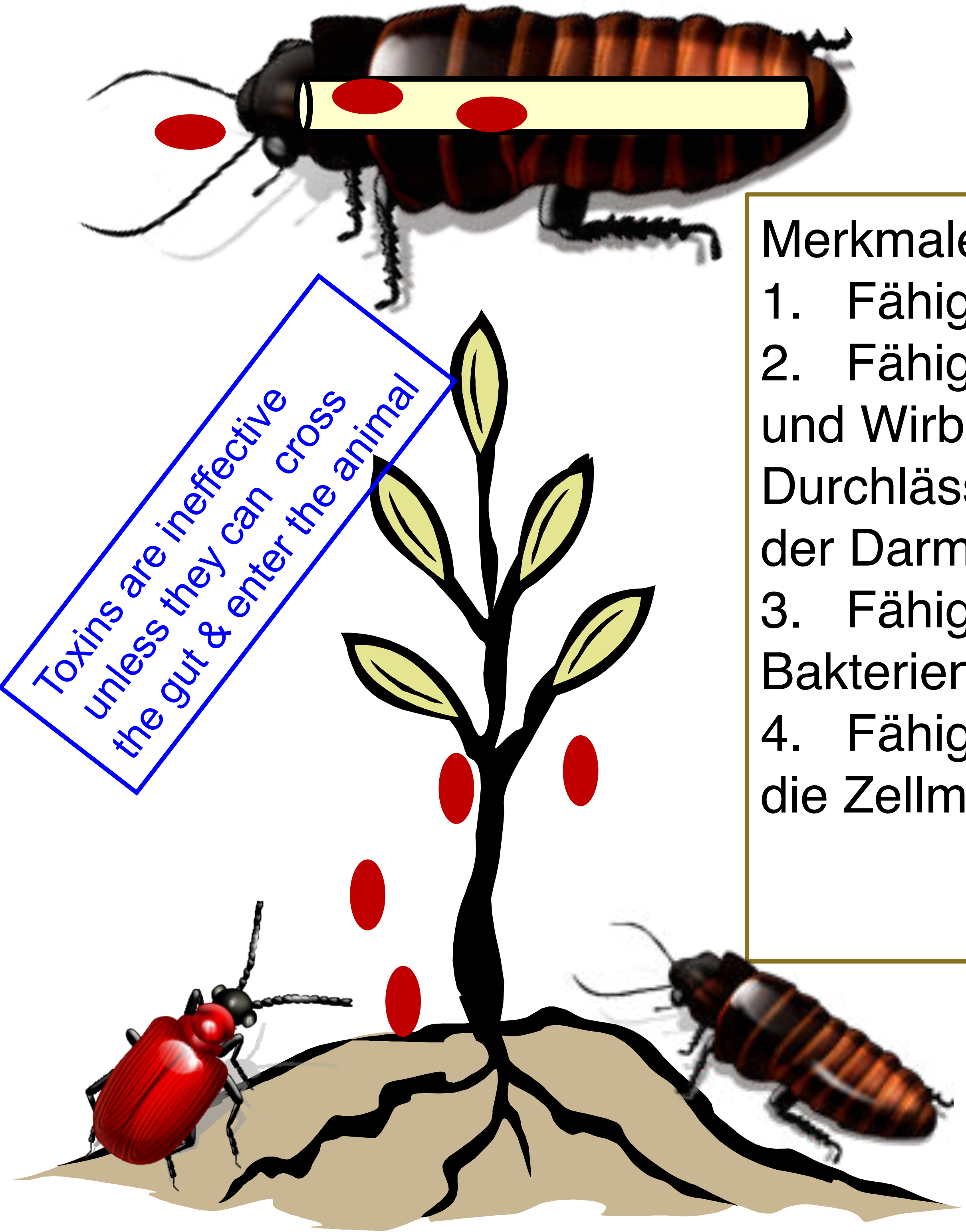

Microbial and dietary antigens
Epithelial cells
JC
Lamina propria
APC
MHC
T-cell

The dietary intake of wheat and other cereal grains and their role in inflammation. de Punder K, Pruimboom L. Nutrients 2013;5:771-87.

1. Schleimhaut
2. Glykokalyx: Transmembran-Glykokonjugatschicht
Glykokalyx-Abmessungen: (400-500 nm dick) & Pore Durchmesser:(7,4 - 28,8 nm)
Funktion: Selektiv Barriere gegen passive Diffusion von Bakterien, Viren & seltsame Material, mit dem Kontakt mit Enterozyten verhindert
3. Microvili
4. Zellmembran (Enterozyten, "M"-Zellen, Becherzellen, Paneth-Zellen oder enteroendokrine Zellen)


Mucus
Glycocalyx
Microvilli or "Brush Border"
Epithelial cell layer

The Agricultural Revolution:
Major Plant Choices for Domestication

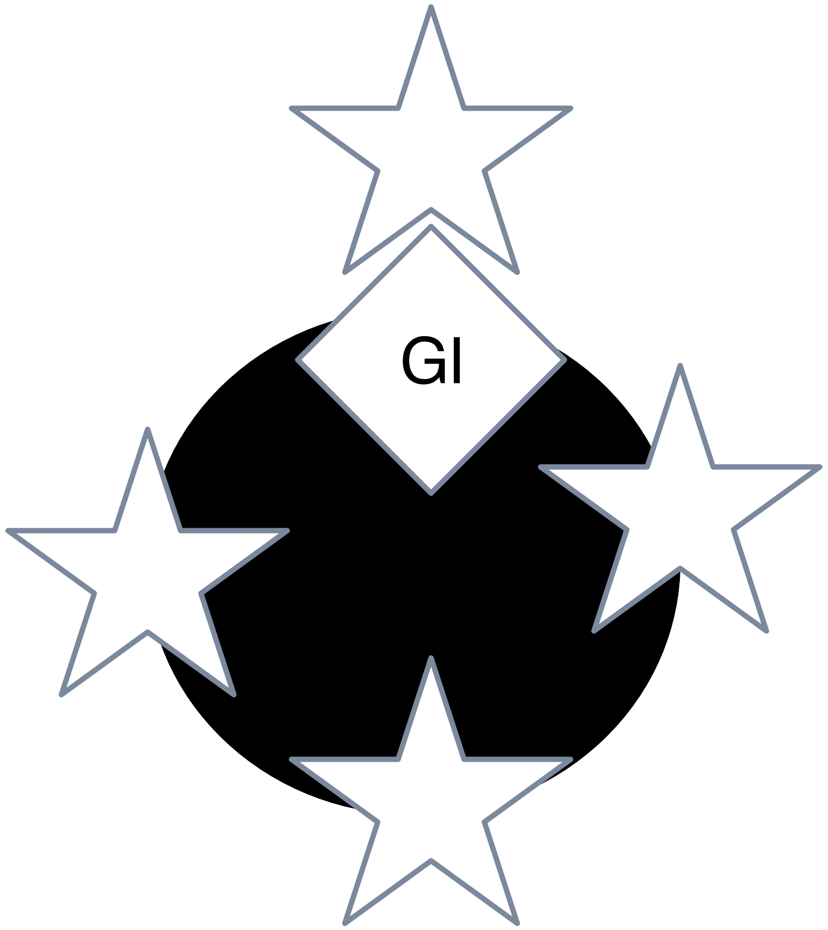


Toxins are ineffective unless they can cross the gut & enter the animal

Merkmale erfolgreicher Sekundärstoffe:

1. Fähigkeit zur Resistenz gegen Darmprotease-Enzyme
2. Fähigkeit, die Auskleidung der Darmzellen von Insekten und Wirbeltieren zu durchbrechen, indem die Durchlässigkeit der Darmzellen erhöht oder die Membran der Darmzellen aufgelöst wird.
3. Fähigkeit zur Zerstörung der Zellmembranen von Bakterien, Pilzen und anderen einfachen Zellorganismen.
4. Fähigkeit, zusätzliche Toxine zu verabreichen, sobald die Zellmembranen durchbrochen sind.

Baobab = 500 Glucanen
= Mucus - Schicht



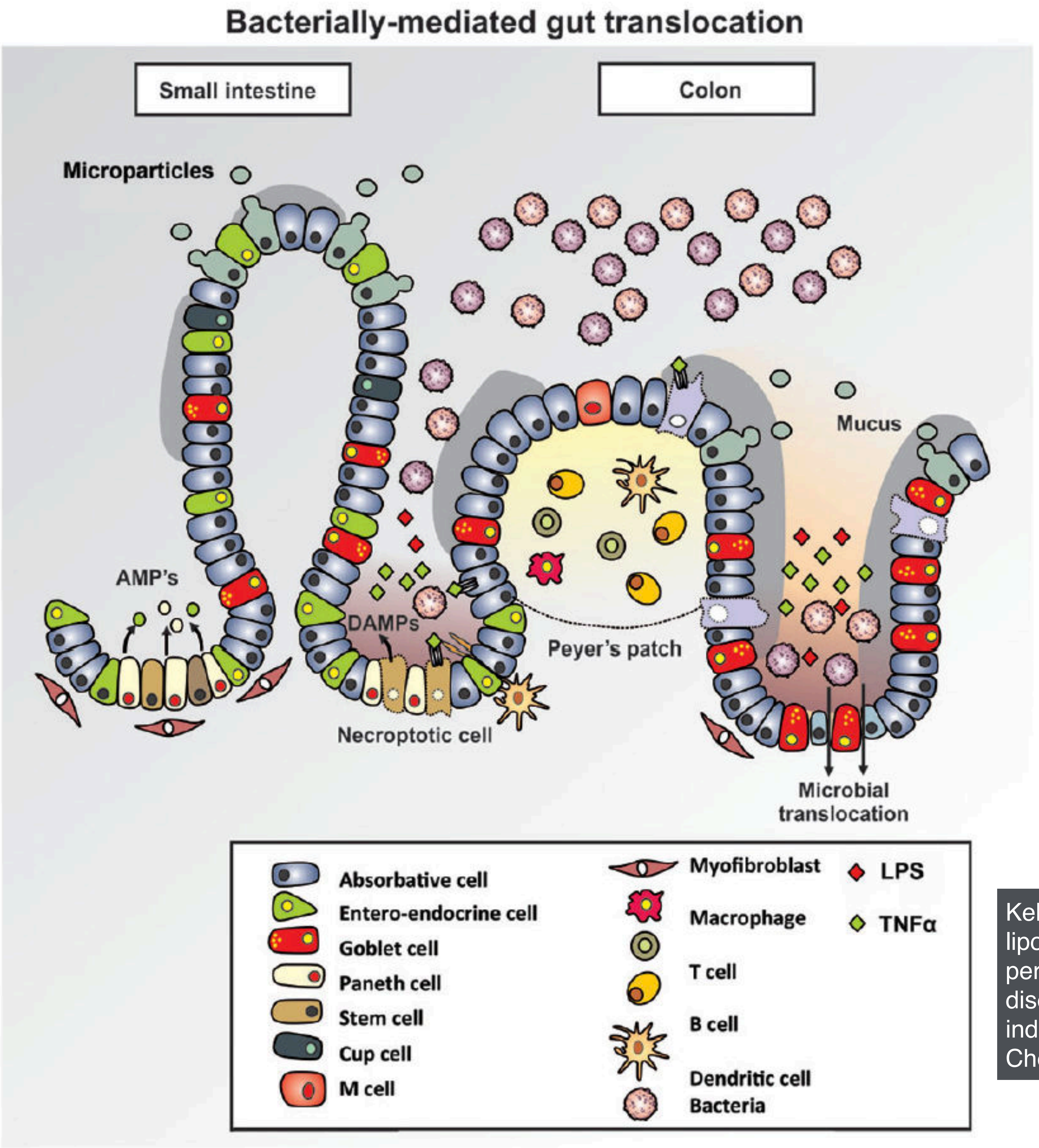
Sacrifice food
Mango
Algen
Honig = > 10 Glucanen
Okra
Pilzen

Lektine und Organempfindlichkeit

PNI Europe
By Dr. Leo Pruimboom

Gewebe/Organ	Weizen-Agglutinin	Soja-Agglutinin	Erdnuss-Agglutinin	Linsen agglutinin	Erbsen - Agglutinin	Bohnen - Agglutinin
Haut	*	*	*	*		*
Mundschleimhaut	*	*	*	*		
Magen	*					
Parietalzellen		*	*			
Darmschleimhaut	*	*				*
Kolonschleimhaut	*			*		
Bindegewebe	*			*	*	*
Schilddrüse	*	*		*		*
Knorpel	*	*	*			
Leber	*	*	*			*
Bauchspeicheldrüse	*					*
Niere	*			*		*
Prostata	*		*	*		
Skelettmuskulatur	*	*	*		*	
Herzmuskel	*	*				
Bruste	*	*	*			
Zirbeldrüse	*		*			
Auge		*	*		*	*
Gehirn (Myelin)	*			*		*

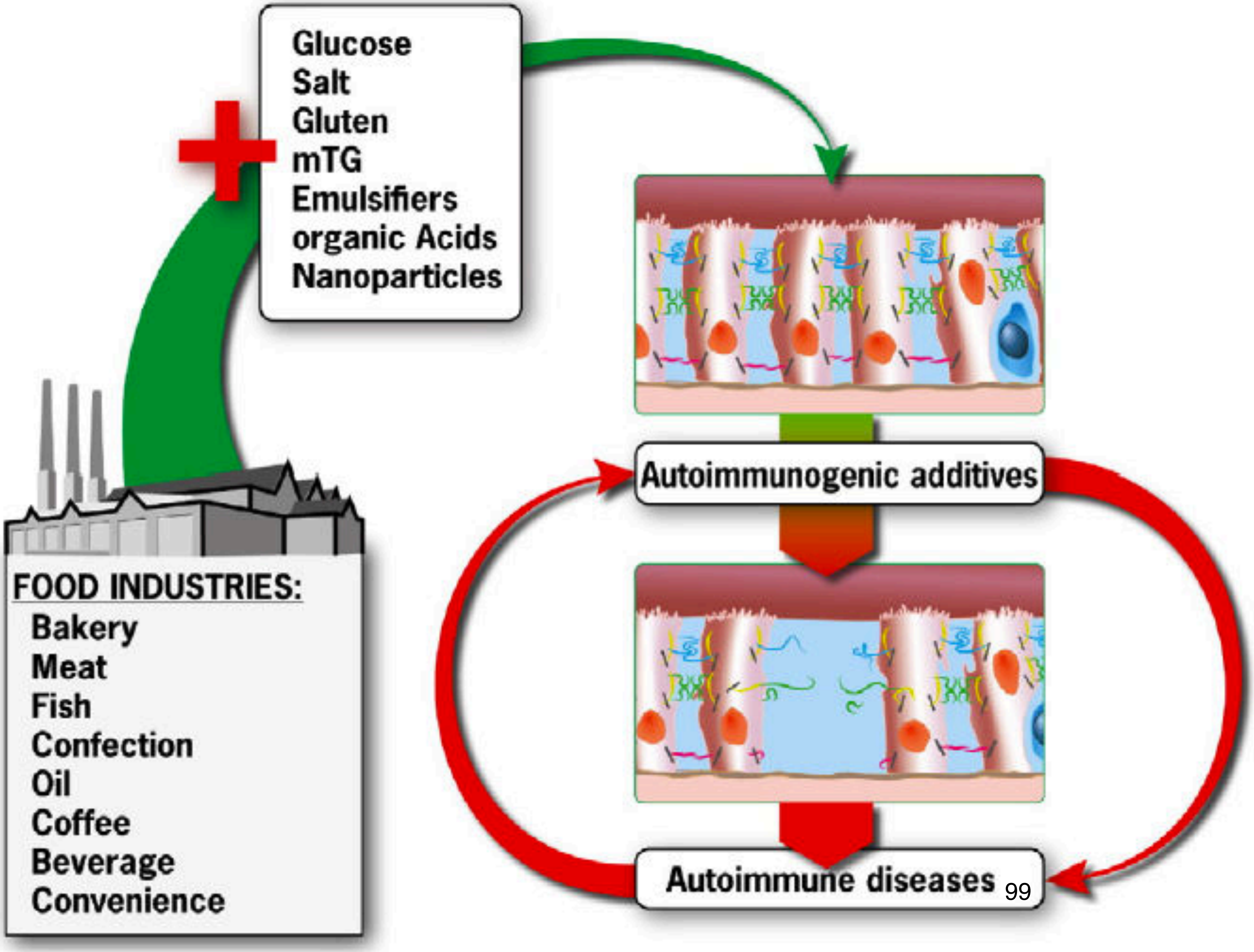
Pruimboom L. Plantenlectinen; vrienden of vijanden? Orthophyto juni 2019


Bacterially-mediated gut translocation
Small intestine
Colon
Microparticles
Mucus
AMP's
DAMPs
Peyer's patch
Necroptotic cell
Microbial translocation
Absorbative cell
Entero-endocrine cell
Goblet cell
Paneth cell
Stem cell
Cup cell
M cell
Myofibroblast
Macrophage
T cell
B cell
Dendritic cell
Bacteria
LPS
TNFα

Die Mechanismen sind vielfältig und es führt zu einer Infiltration des Mikrotoms in alle Gewebe.

Kell. On the translocation of bacteria and their lipopolysaccharides between blood and peripheral locations in chronic, inflammatory diseases: the central roles of LPS and LPS-induced cell death. The Royal Society of Chemistry 2015

A. Lerner, T. Matthias / Autoimmunity Reviews 14 (2015) 479–489



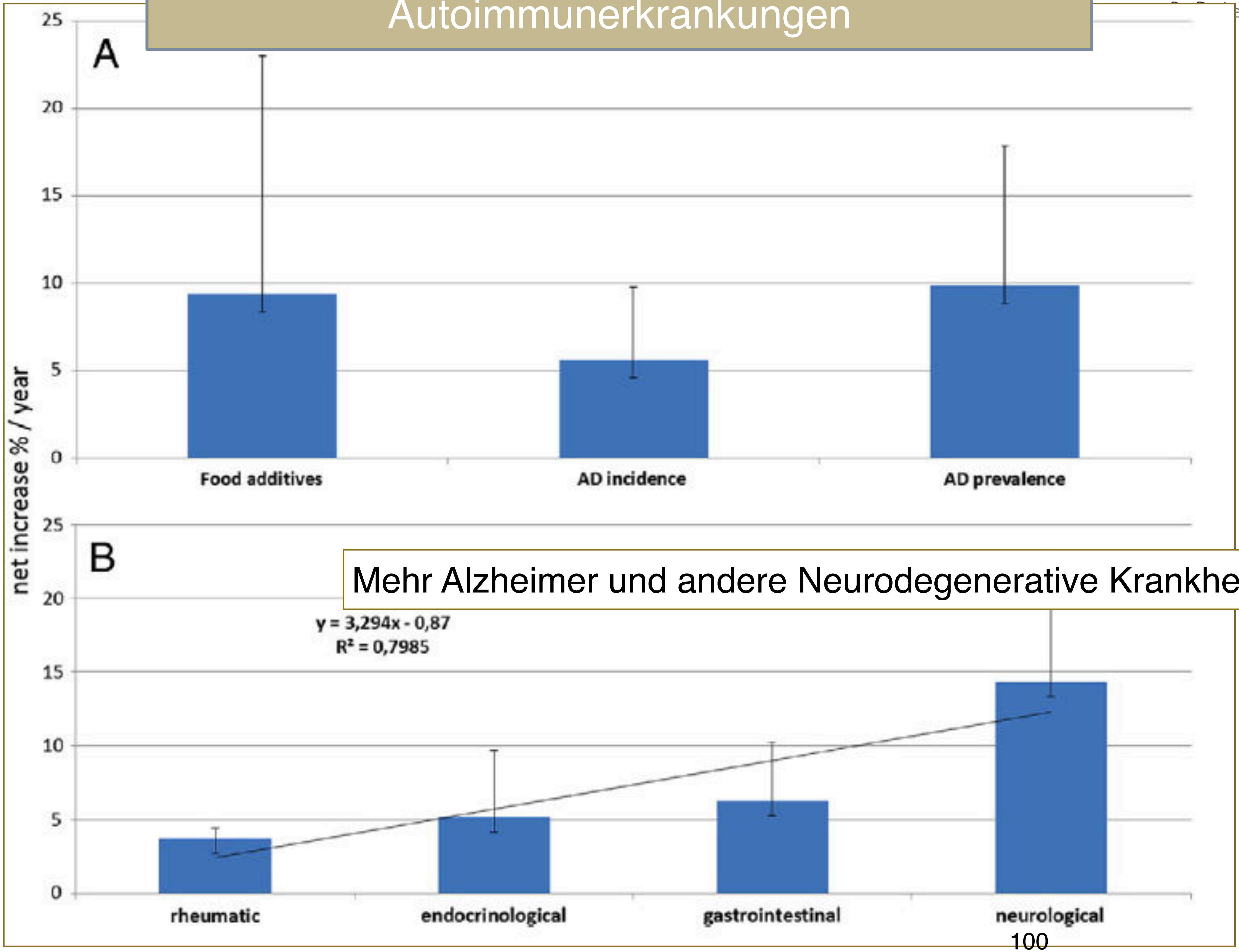
Glucose
Salt
Gluten
mTG
Emulsifiers
organic Acids
Nanoparticles

FOOD INDUSTRIES:
- Bakery
- Meat
- Fish
- Confection
- Oil
- Coffee
- Beverage
- Convenience

Autoimmunogenic additives

Autoimmune diseases

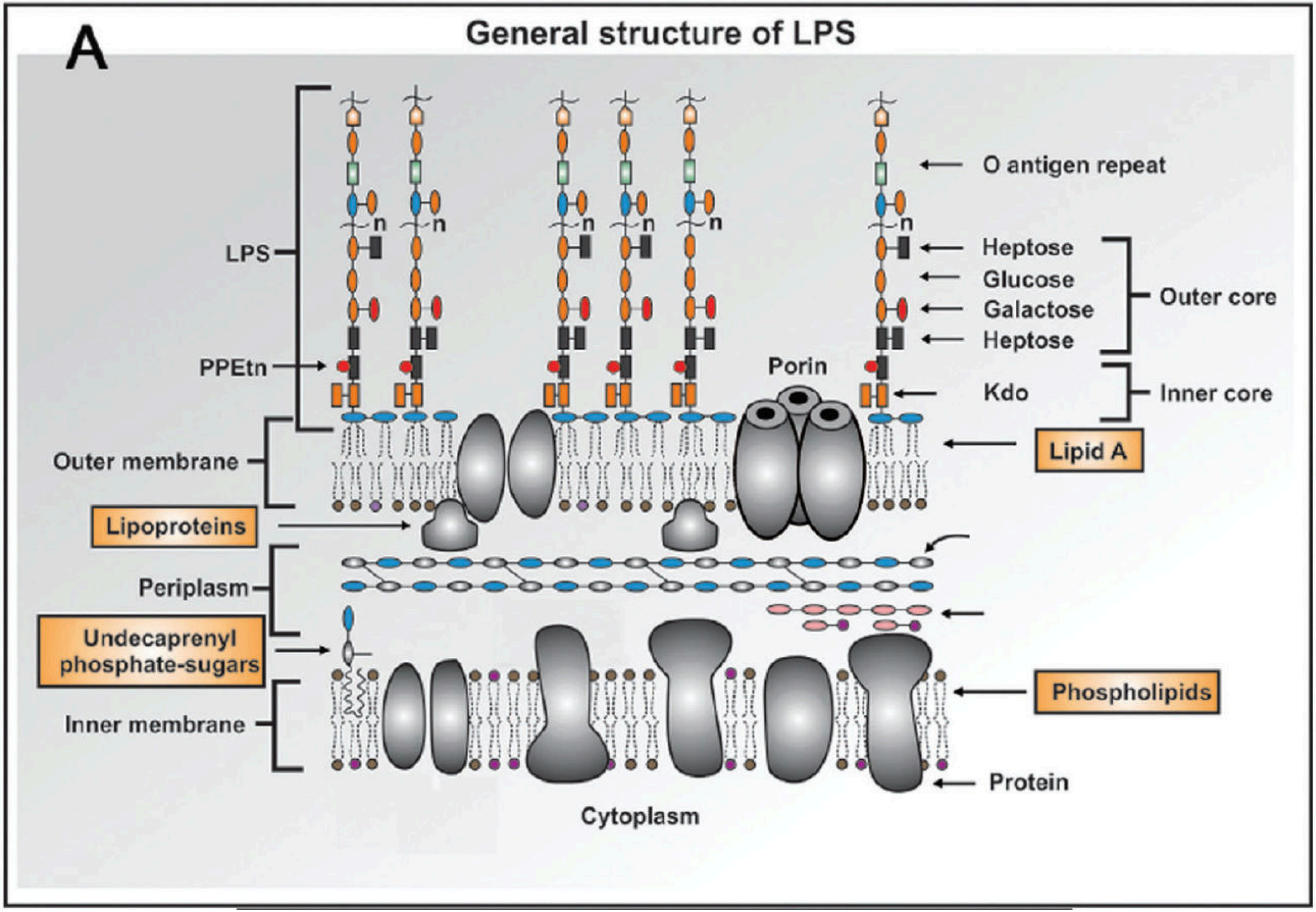
Lebensmittelzusatzstoffe erhöhen die intestinale Permeabilität und das Risiko von Autoimmunerkrankungen

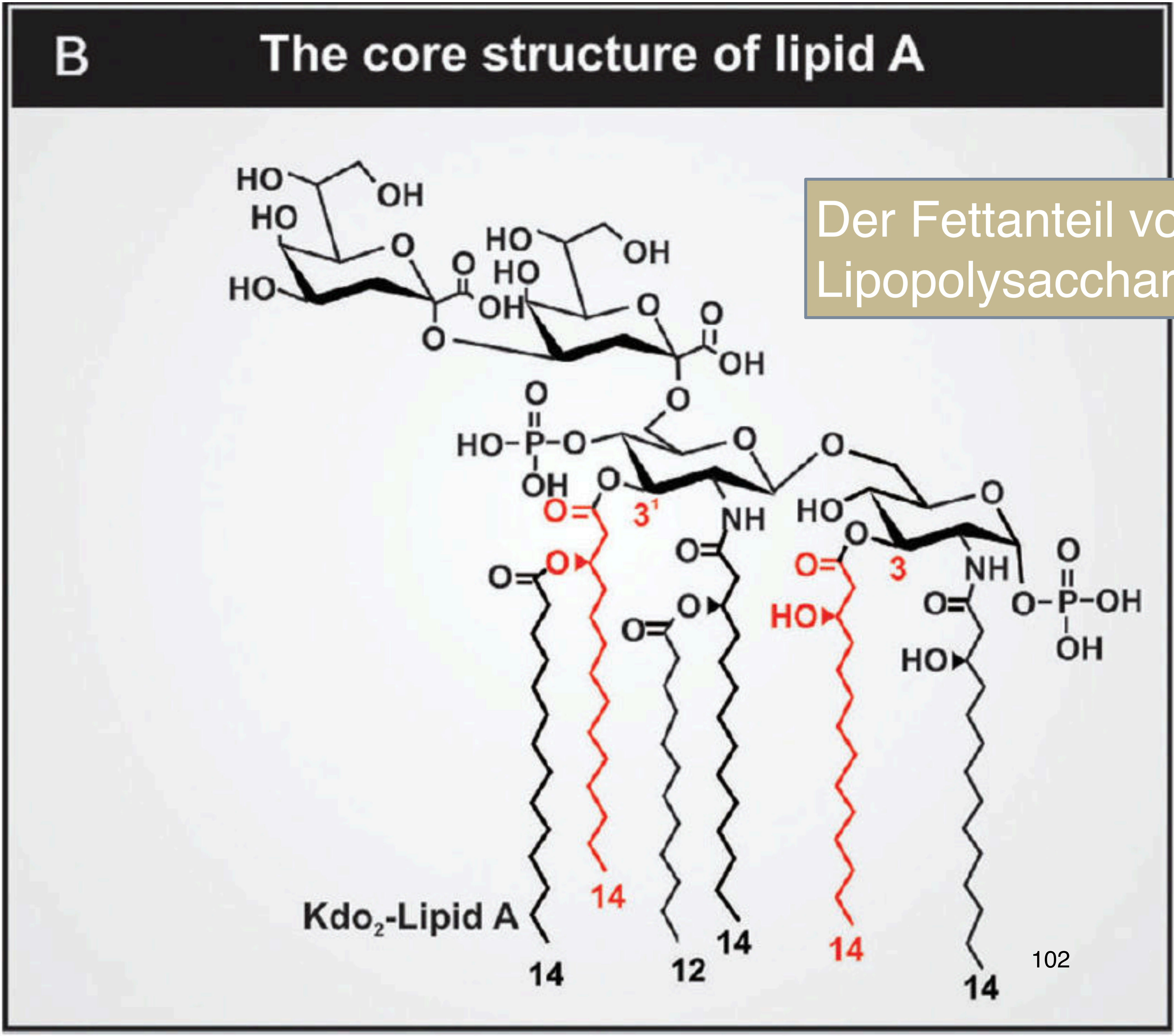


Mehr Alzheimer und andere Neurodegenerative Krankheiten

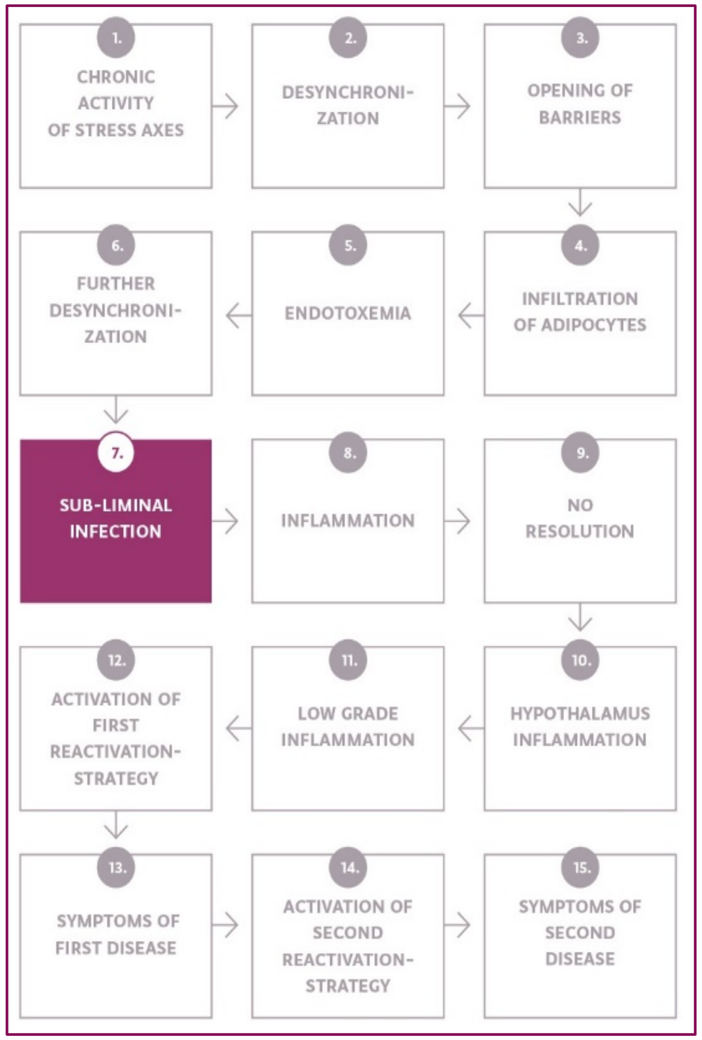
A. Lerner, T. Matthias / Autoimmunity Reviews 14 (2015) 479–489

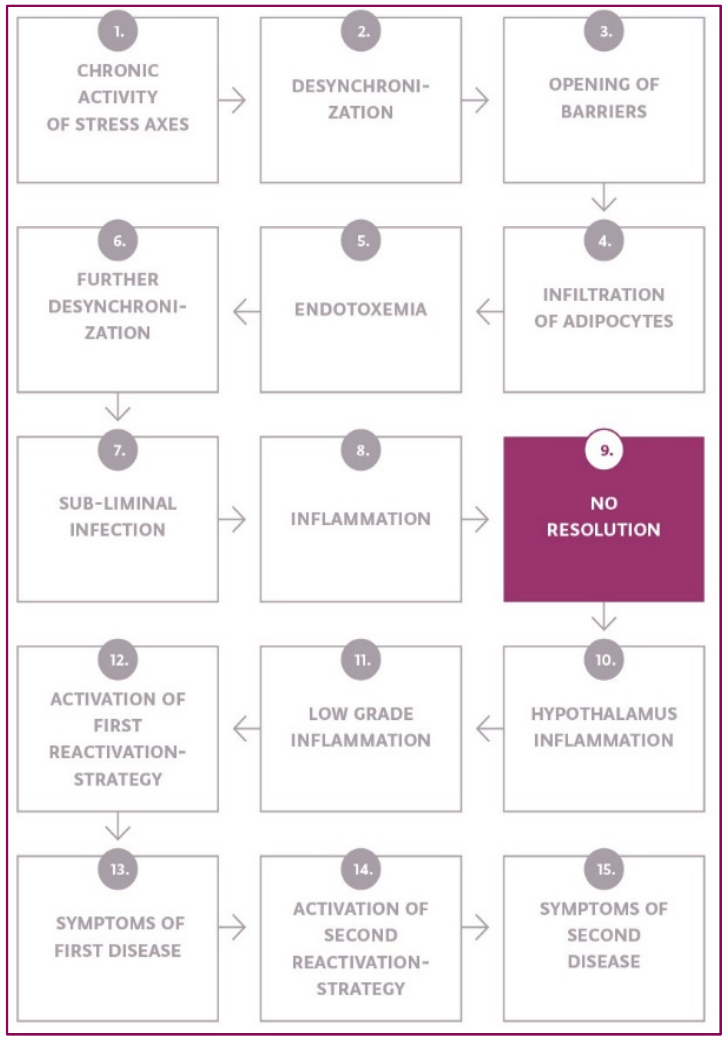
Lipopolysaccharid


A
General structure of LPS
LPS
PPEtn
Outer membrane
Lipoproteins
Periplasm
Undecaprenyl phosphate-sugars
Inner membrane
n
Porin
O antigen repeat
Heptose
Glucose
Galactose
Heptose
Outer core
Kdo
Inner core
Lipid A
Phospholipids
Protein
Cytoplasm


B
The core structure of lipid A
HO
OH
HO
HO
O
O
OH
HO
OH
HO
O
O
OH
O
O
HO-P-O
OH
O
O
O
3'
NH
HO
O
O
O=
O
3
NH
O
O=
O-P-OH
OH
O=
O
O=
HO
O=
HO
14
12
14
14
14
14
Kdo₂-Lipid A

Der Fettanteil von Lipopolysaccharide


1. CHRONIC ACTIVITY OF STRESS AXES
2. DESYNCHRONIZATION
3. OPENING OF BARRIERS
4. INFILTRATION OF ADIPOCYTES
5. ENDOTOXEMIA
6. FURTHER DESYNCHRONIZATION
7. **SUB-LIMINAL INFECTION**
8. INFLAMMATION
9. NO RESOLUTION
10. HYPOTHALAMUS INFLAMMATION
11. LOW GRADE INFLAMMATION
12. ACTIVATION OF FIRST REACTIVATION-STRATEGY
13. SYMPTOMS OF FIRST DISEASE
14. ACTIVATION OF SECOND REACTIVATION-STRATEGY
15. SYMPTOMS OF SECOND DISEASE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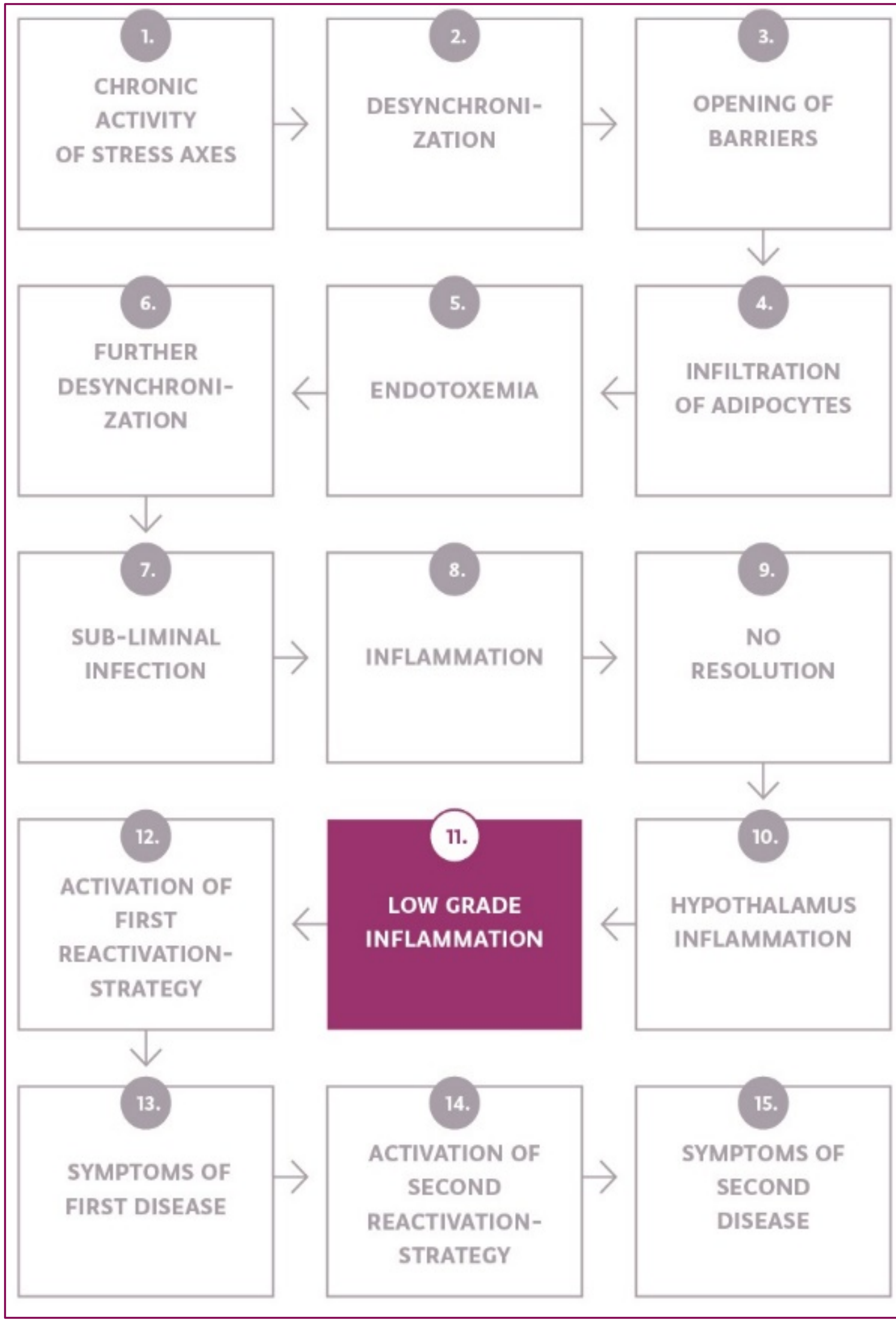
14. ACTIVATION OF SECOND REACTIVATION-STRATEGY
15. SYMPTOMS OF SECOND DISEASE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2. DESYNCHRONIZATION
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4. INFILTRATION OF ADIPOCYTES
5. ENDOTOXEMIA
6. FURTHER DESYNCHRONIZATION
7. SUB-LIMINAL INFECTION
8. INFLAMMATION
9. NO RESOLUTION
10. HYPOTHALAMUS INFLAMMATION
11. **LOW GRADE INFLAMMATION**
12. ACTIVATION OF FIRST REACTIVATION-STRATEGY
13. SYMPTOMS OF FIRST DISEASE
14. ACTIVATION OF SECOND REACTIVATION-STRATEGY
15. SYMPTOMS OF SECOND DISEASE

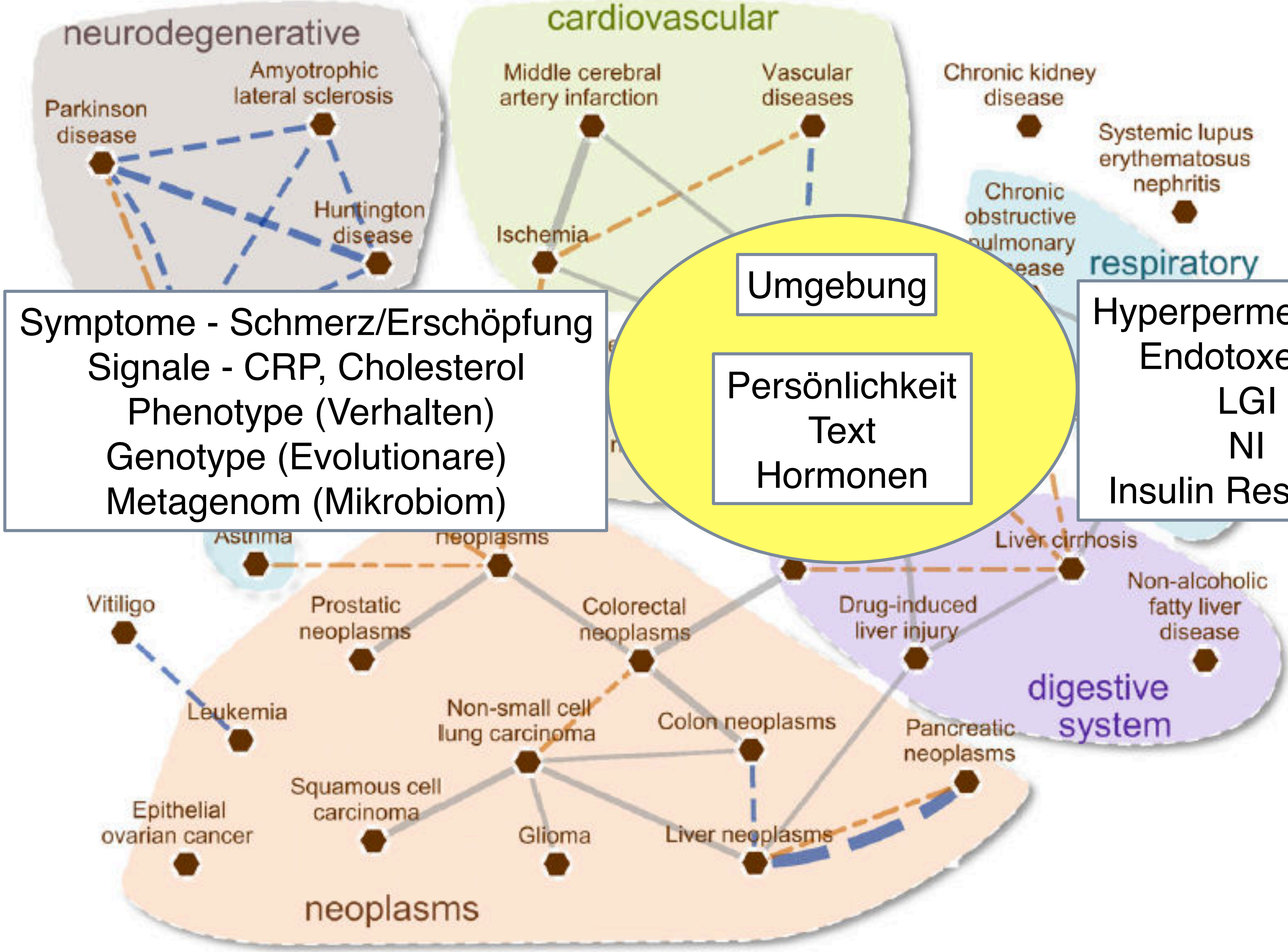
Es kommt also zu einer Kälteentzündung, die durch eine INDIREKTE (über FAT) Aktivierung des Immunsystems hervorgerufen wird.

Stress induces endotoxemia and low-grade inflammation by increasing barrier permeability. de Punder K, Pruimboom L. Front Immunol 2015;6:223. Epub 2015 May 15

PNI - Systemmedizin

Die meisten, wenn nicht alle chronischen Erkrankungen sind über das Leaky Gut Syndrom und LGI miteinander verbunden.

PNI Europe
By Dr. Leo Pruimboom


neurodegenerative
Amyotrophic lateral sclerosis
Parkinson disease
Huntington disease
cardiovascular
Middle cerebral artery infarction
Vascular diseases
Ischemia
Chronic kidney disease
Systemic lupus erythematosus nephritis
Chronic obstructive
ulmonary
ease
respiratory
Asthma
neoplasms
Vitiligo
Prostatic neoplasms
Colorectal neoplasms
Leukemia
Non-small cell lung carcinoma
Colon neoplasms
Squamous cell carcinoma
Epithelial ovarian cancer
Glioma
Liver neoplasms
Pancreatic neoplasms
Liver cirrhosis
Drug-induced liver injury
Non-alcoholic fatty liver disease
digestive system
neoplasms

Symptome - Schmerz/Erschöpfung
Signale - CRP, Cholesterol
Phenotype (Verhalten)
Genotype (Evolutionare)
Metagenom (Mikrobiom)

Umgebung

Persönlichkeit
Text
Hormonen

Hyperpermeabilität
Endotoxemia
LGI
NI
Insulin Resistenz

Tag 1

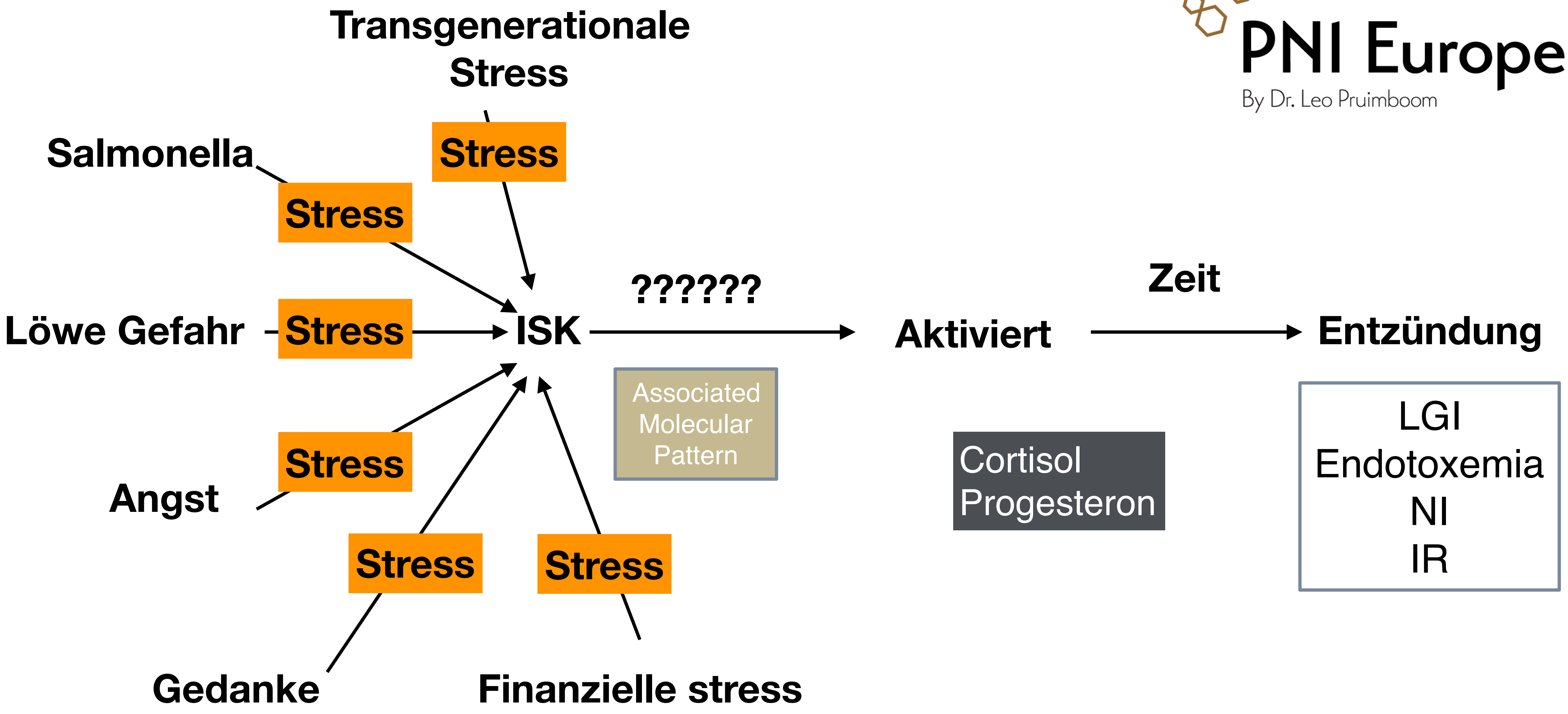
15.00 - 15.15

Die Kaffeepause

Tag 1

15.15 - 15.45

Erste Behandlung



Transgenerationale Stress

Stress

Salmonella

Stress

Löwe Gefahr

Stress

ISK

??????

Associated Molecular Pattern

Aktiviert

Cortisol
Progesteron

Zeit

Entzündung

LGI
Endotoxemia
NI
IR

Stress

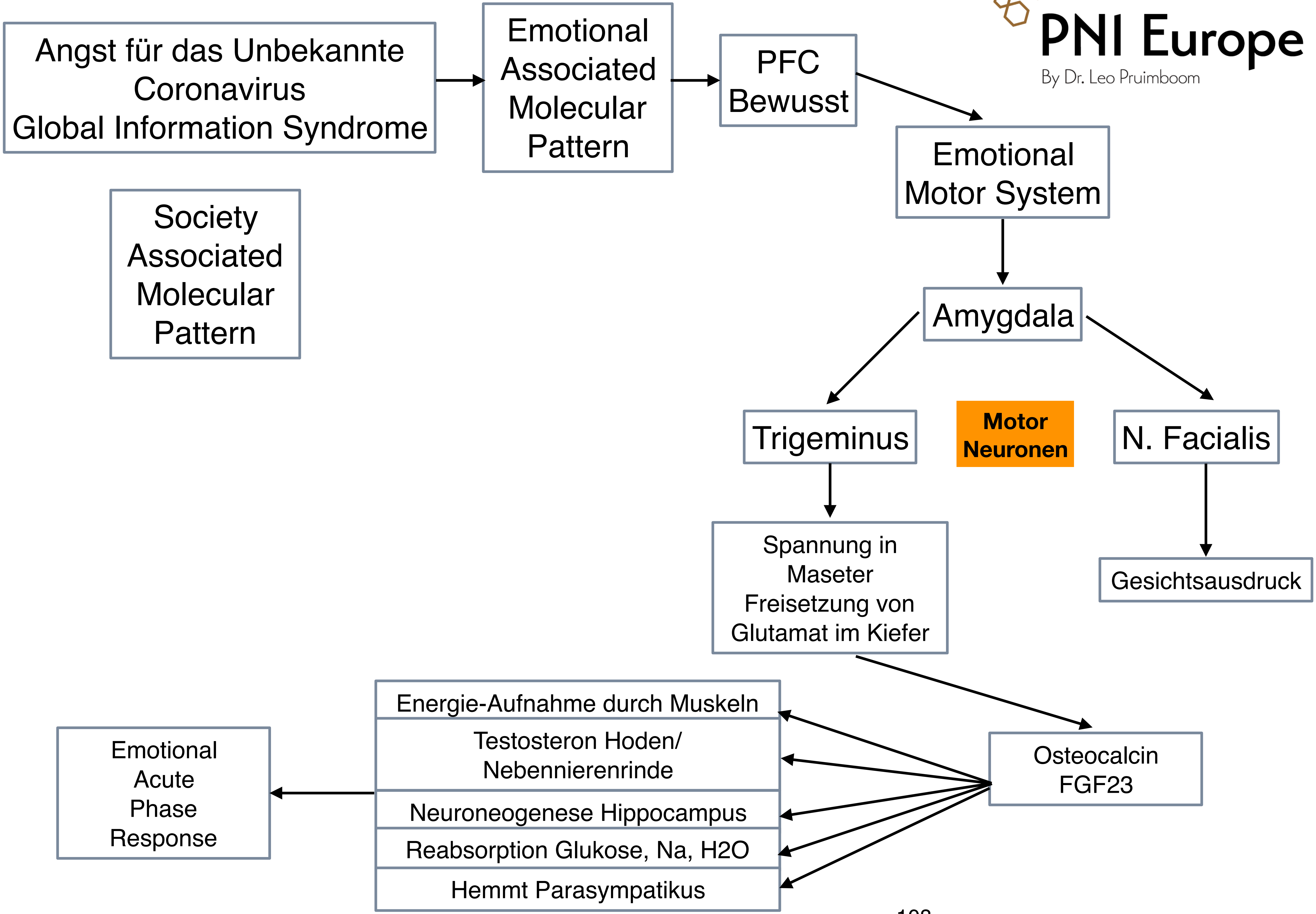
Angst

Stress

Stress

Gedanke

Finanzielle stress



Angst für das Unbekannte
Coronavirus
Global Information Syndrome

Emotional Associated Molecular Pattern

PFC Bewusst

Emotional Motor System

Society Associated Molecular Pattern

Amygdala

Trigeminus

Motor Neuronen

N. Facialis

Spannung in Maseter
Freisetzung von Glutamat im Kiefer

Gesichtsausdruck

Osteocalcin
FGF23

Energie-Aufnahme durch Muskeln

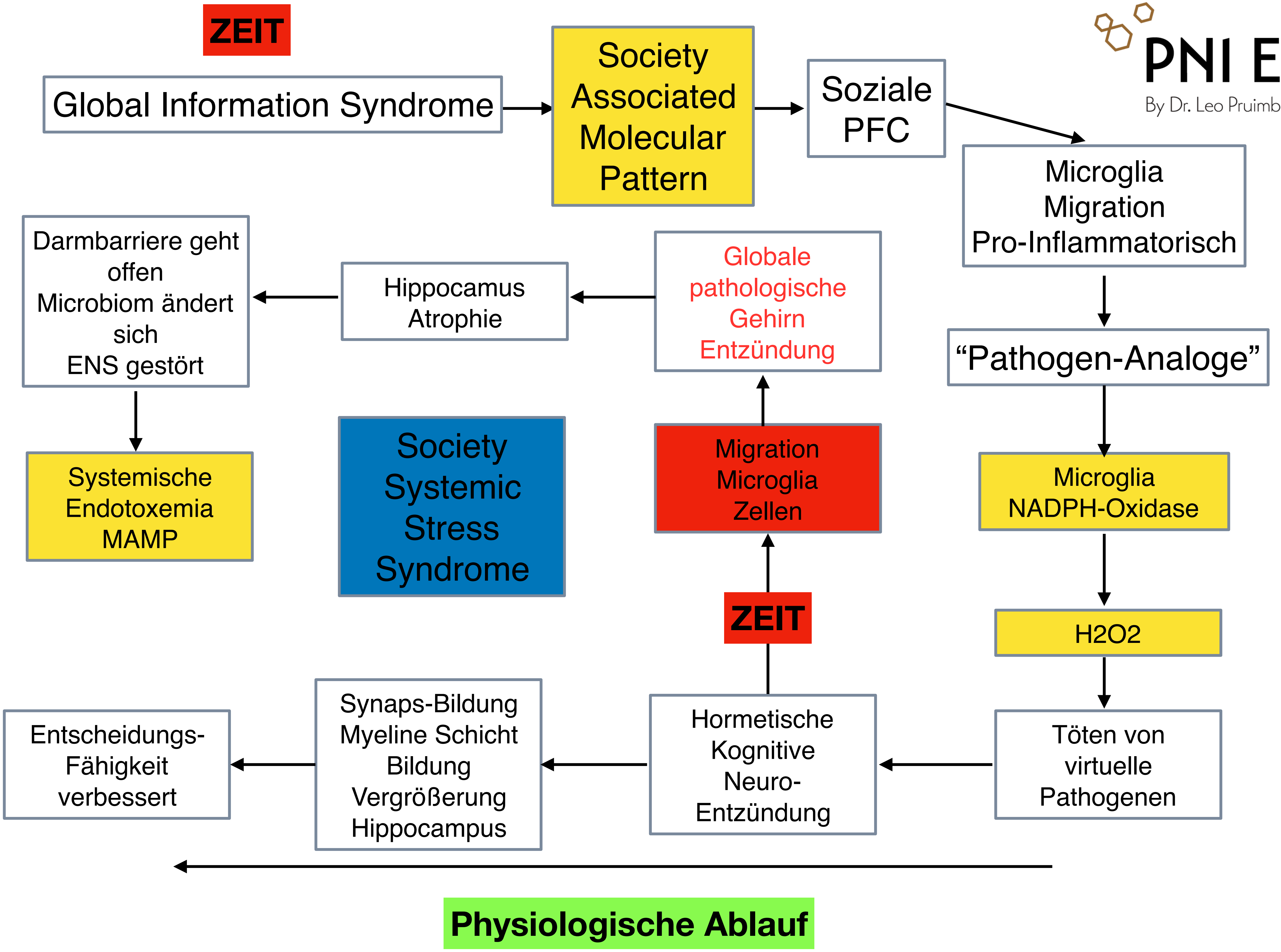
Testosteron Hoden/ Nebennierenrinde

Neuroneogenese Hippocampus

Reabsorption Glukose, Na, H2O

Hemmt Parasympatikus

Emotional Acute Phase Response



ZEIT

Global Information Syndrome

Society Associated Molecular Pattern

Soziale PFC

Microglia Migration Pro-Inflammatorisch

“Pathogen-Analoge”

Microglia NADPH-Oxidase

H2O2

Töten von virtuelle Pathogenen

Hormetische Kognitive Neuro-Entzündung

ZEIT

Migration Microglia Zellen

Globale pathologische Gehirn Entzündung

Hippocamus Atrophie

Darmbarriere geht offen
Microbiom ändert sich
ENS gestört

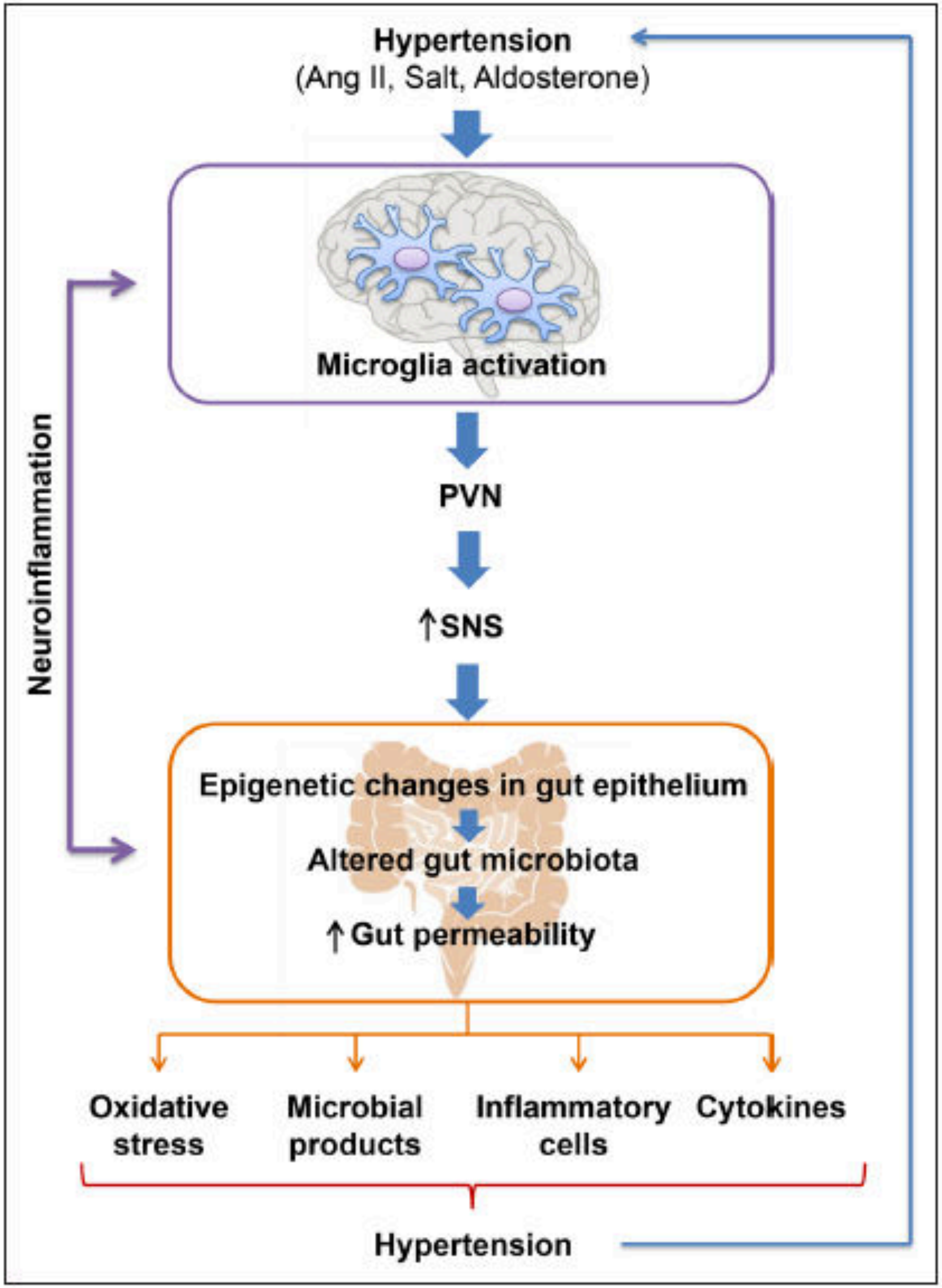
Systemische Endotoxemia MAMP

Society Systemic Stress Syndrome

Synaps-Bildung
Myeline Schicht Bildung
Vergrößerung Hippocampus

Entscheidungs-Fähigkeit verbessert

Physiologische Ablauf



Hypertension
(Ang II, Salt, Aldosterone)

Microglia activation

PVN

↑SNS

Epigenetic changes in gut epithelium

Altered gut microbiota

↑Gut permeability

Neuroinflammation

Oxidative stress

Microbial products

Inflammatory cells

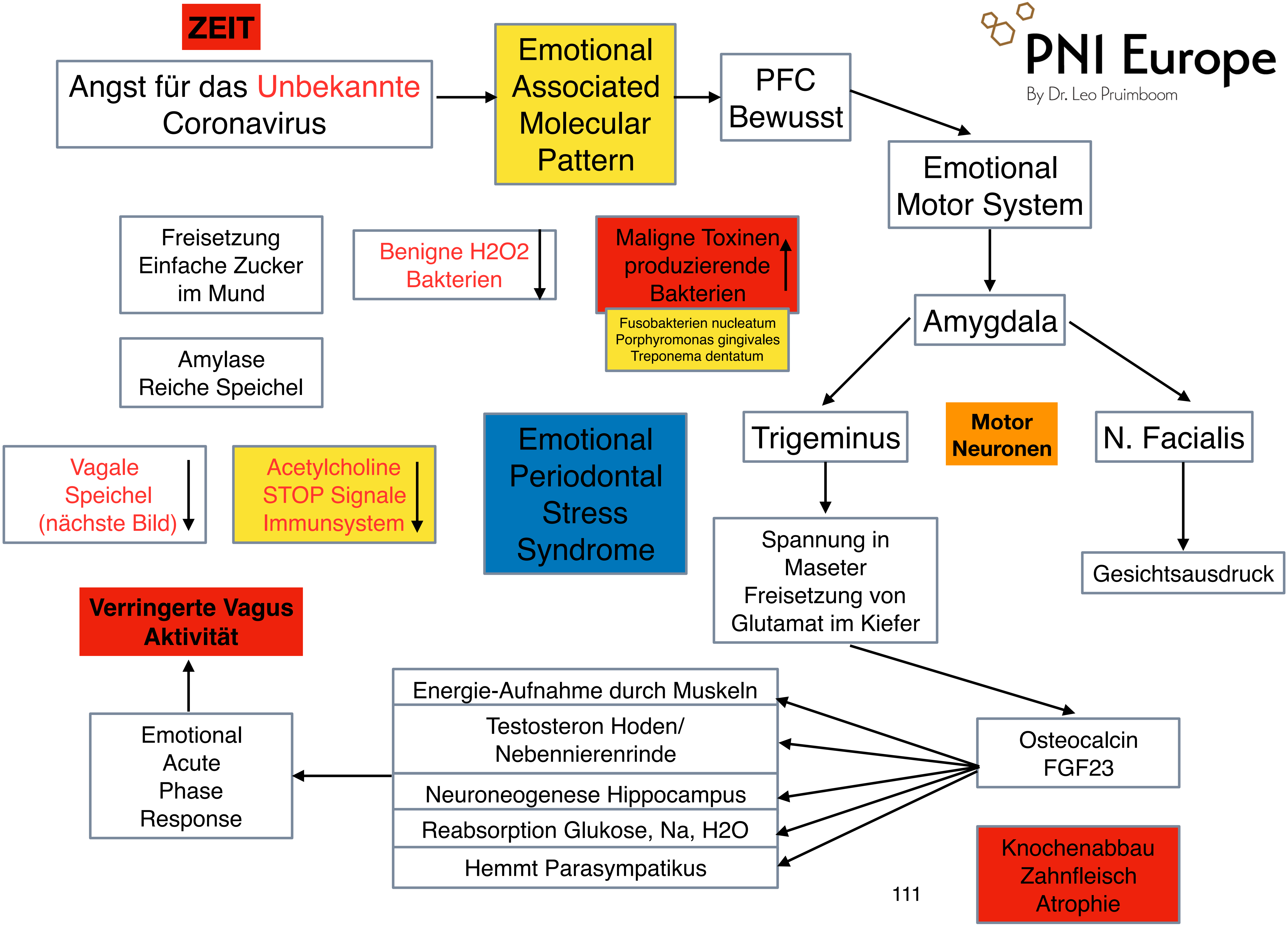
Cytokines

Hypertension

Die schaltungstechnische Beziehung zwischen prohypertensiven Faktoren, Mikrogliaaktivierung, Sympathikusausfluss und Darmflora in der Pathophysiologie der Hypertonie. Neurogene Entzündungen und oxidativer Stress sind wichtige molekulare Prozesse, die die Darmachse des Gehirns antreiben. Ang = Angiotensin, PVN, paraventrikulärer Kern, und SNS, sympathisches Nervensystem.

Touyz. Microglia, the Missing Link in the Brain-Gut-Hypertension Axis. Circ Res. 2019;124:671-673.

PNI Europe
By Dr. Leo Pruimboom



ZEIT

Angst für das Unbekannte Coronavirus

Emotional Associated Molecular Pattern

PFC Bewusst

Emotional Motor System

Amygdala

Trigeminus

Motor Neuronen

N. Facialis

Spannung in Maseter Freisetzung von Glutamat im Kiefer

Gesichtsausdruck

Freisetzung Einfache Zucker im Mund

Benigne H2O2 Bakterien ↓

Maligne Toxinen produzierende Bakterien ↑

Fusobakterien nucleatum
Porphyromonas gingivales
Treponema dentatum

Amylase Reiche Speichel

Vagale Speichel (nächste Bild) ↓

Acetylcholine STOP Signale Immunsystem ↓

Emotional Periodontal Stress Syndrome

Verringerte Vagus Aktivität

Emotional Acute Phase Response

Energie-Aufnahme durch Muskeln
Testosteron Hoden/ Nebennierenrinde
Neuroneogenese Hippocampus
Reabsorption Glukose, Na, H2O
Hemmt Parasympatikus

Osteocalcin FGF23

Knochenabbau Zahnfleisch Atrophie

N. Vagus Speichel

H2O

Lactoperoxidase

Thiocyanat
SCN-

sIgA

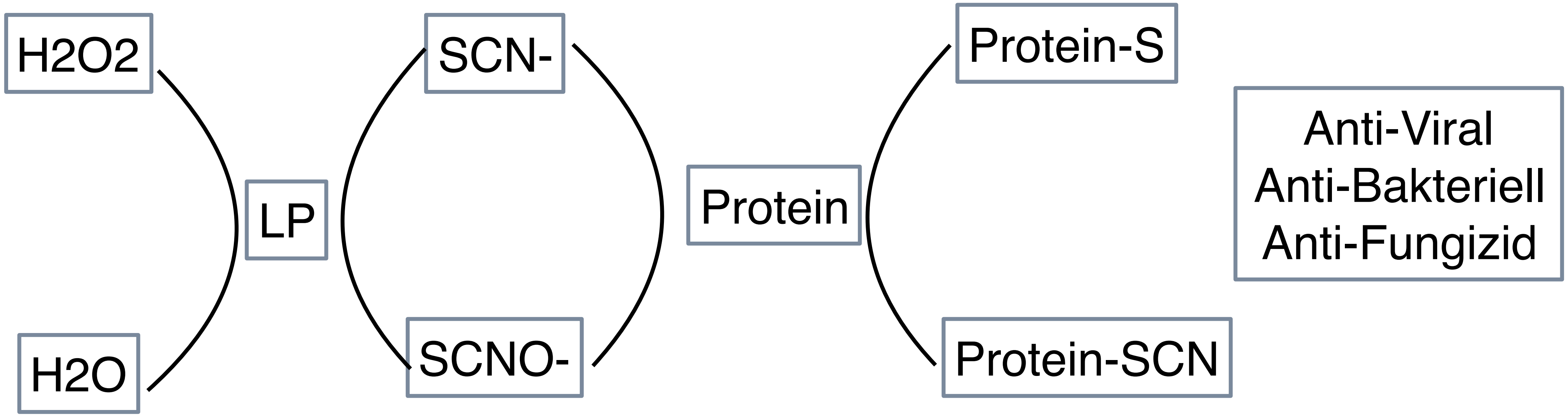
Amylase gering

Langsame
Kohlenhydrate

Benigne Pathogenen
S. mitis
S. mutans
S. sobrinus

Verpflichte
Multi-Zucker
Bakterien

Oxidase
H2O2

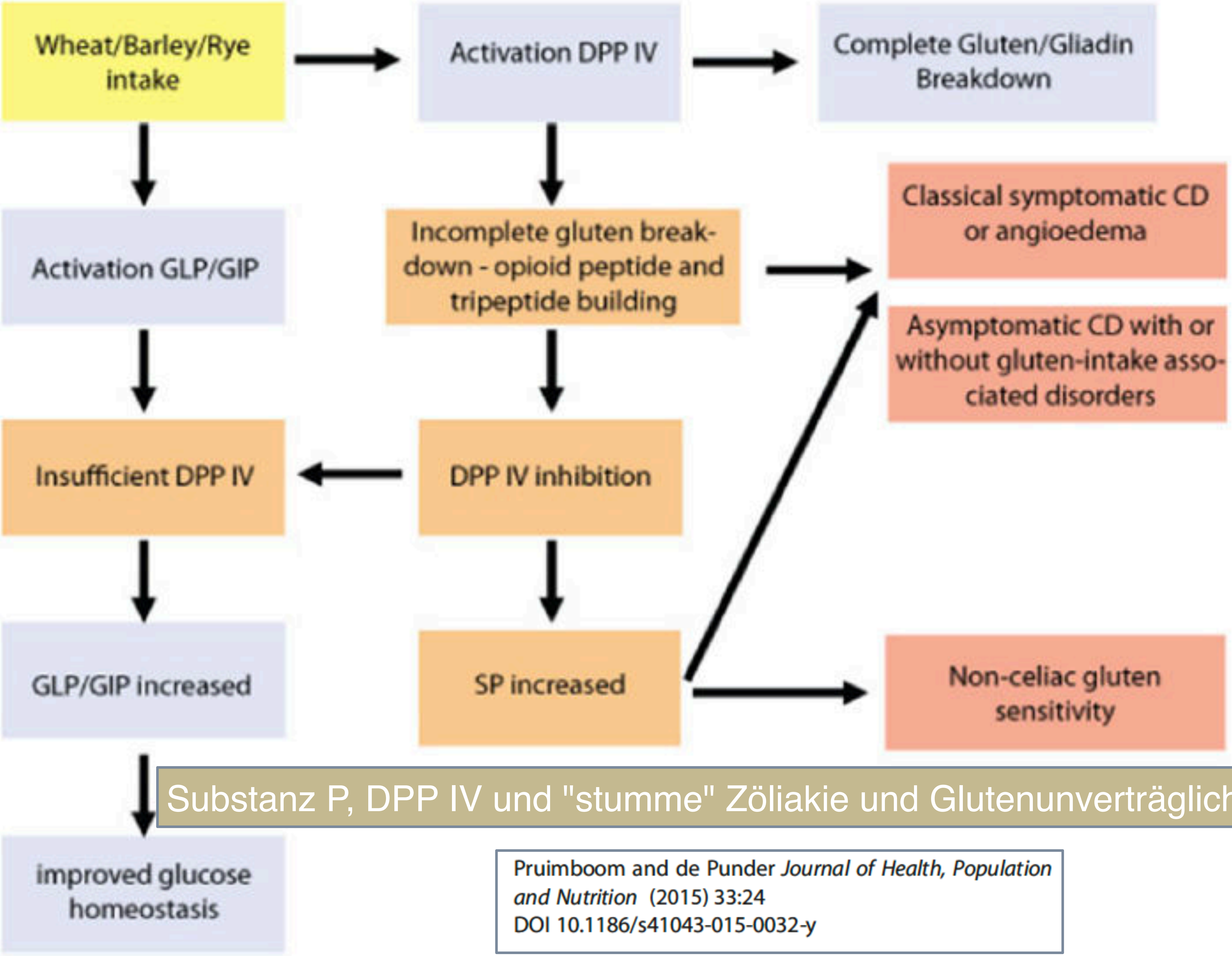

H2O2
H2O
LP
SCN-
SCNO-
Protein
Protein-S
Protein-SCN
Anti-Viral
Anti-Bakteriell
Anti-Fungizid

Fahrplan

1. Problembestimmung
2. SIBO
3. Pathogene Flora
4. Pankreas-Problem
5. Lieferproblem
6. Antibiotika
7. Leckagen im Darm
8. Stressdarm
9. Weitere offene Barrieren
10. Systemische 'Darm'-Symptome

2. Lösungen
Glutamin
Prebiotika
Probiotika
Stressabbau
SGLT-Hemmung
Laktoferrin
Antibiotikum für den Darm
DPP IV-Behandlung

Substanz P, DPP IV und "stumme" Zöliakie und Glutenunverträglichk



Wheat/Barley/Rye intake

Activation DPP IV

Complete Gluten/Gliadin Breakdown

Activation GLP/GIP

Incomplete gluten breakdown - opioid peptide and tripeptide building

Classical symptomatic CD or angioedema

Asymptomatic CD with or without gluten-intake associated disorders

Insufficient DPP IV

DPP IV inhibition

GLP/GIP increased

SP increased

Non-celiac gluten sensitivity

improved glucose homeostasis

Pruimboom and de Punder *Journal of Health, Population and Nutrition* (2015) 33:24
DOI 10.1186/s41043-015-0032-y

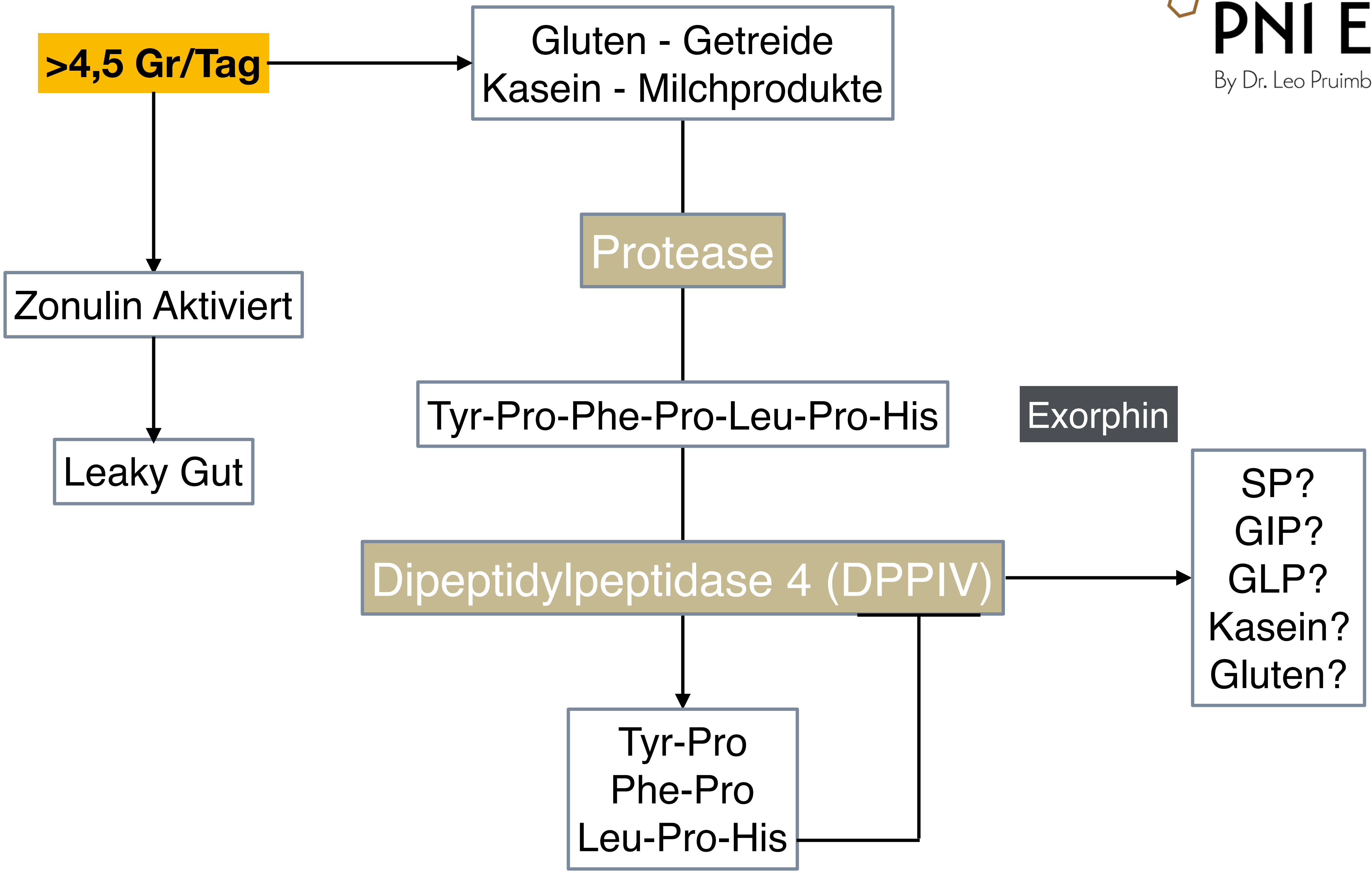
Substanz P. = Arg Pro Lys Pro Gln Gln Phe Phe Gly Leu M
Glucose Induced Protein = Insulin Produktion, Insulin Empfindlichkeit
Glucagon Like Peptide = Muskeln, Leber und Fett

Dipeptidylpeptidase 4 (DPPIV)

Arg-Pro
Lys-Pro
Gln-Gln-Phe-Phe-Gly-Leu-Met

Protease

Arg, Pro, Lys, Pro
Gln, Gln, Phe, Phe, Gly, Leu, Met



>4,5 Gr/Tag

Gluten - Getreide
Kasein - Milchprodukte

Zonulin Aktiviert

Leaky Gut

Protease

Tyr-Pro-Phe-Pro-Leu-Pro-His

Exorphin

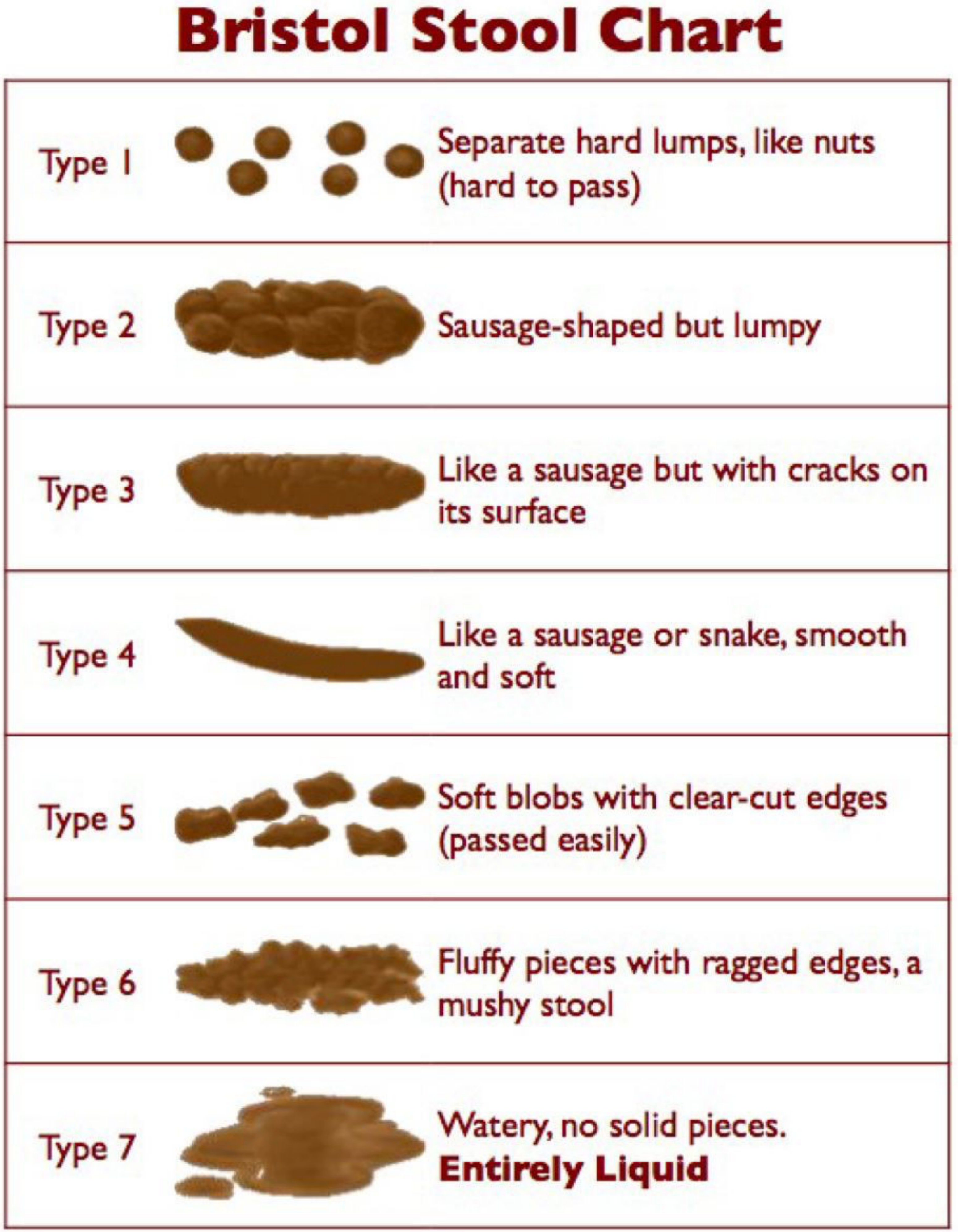
Dipeptidylpeptidase 4 (DPPIV)

SP?
GIP?
GLP?
Kasein?
Gluten?

Tyr-Pro
Phe-Pro
Leu-Pro-His

Stuhl

Farbe - Leichtbraun
Menge - 200 Gr/Tag
Komposition - Typ 4
Geruch - Geruchlos
Gas - ‘Geruchlos - Methangas’
Krämpfe - Pathologie - SP
‘Stille Verstopfung” - Exorphin
“Schmerzhafte Verstopfung”
SCFA, Mikrobiom
Magnesium Mangel



Bristol Stool Chart

Type 1	Separate hard lumps, like nuts (hard to pass)
Type 2	Sausage-shaped but lumpy
Type 3	Like a sausage but with cracks on its surface
Type 4	Like a sausage or snake, smooth and soft
Type 5	Soft blobs with clear-cut edges (passed easily)
Type 6	Fluffy pieces with ragged edges, a mushy stool
Type 7	Watery, no solid pieces. **Entirely Liquid**

DPPIV Mangel
Capsaicin/Senf/Wasabi
Äpfel - Baobab - Rucola

1. Substance P werd normal abgebaut, Exorphinen nehmen zu

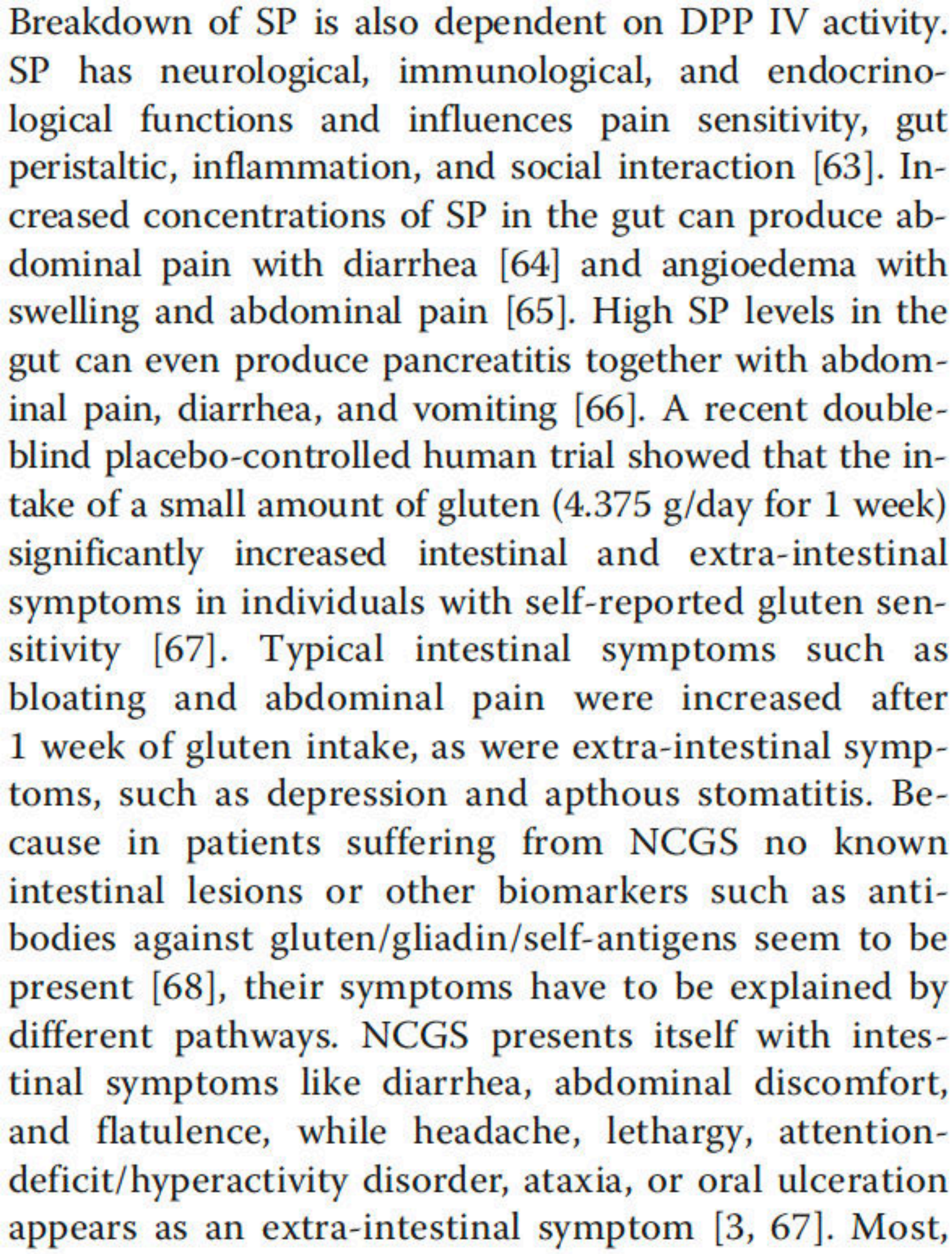
   Morphin Darm - Stille Verstopfung

2. Substance P nehmt zu (Leaky gut)
   Exorphinen Abbau

Krämpfe Verstopfung (SCFA)
Krämpfe Durchfall (Substanz P)
Extra-Intestinal Disorders = Migraine, Schmerz, Depression, Hautkrankheiten, Erschöpfung

3. Substance P Abbau Normal
   GIP und GLP nehmen zu
   Exorphine nehmen zu und kommen in die Blutbahn

Stille Verstopfung
Zombies
Glucose Spiegel Perfekt
Körpergewicht prima
Diabetes Gefahr verringert
Alzheimer/Demenz/Autismus



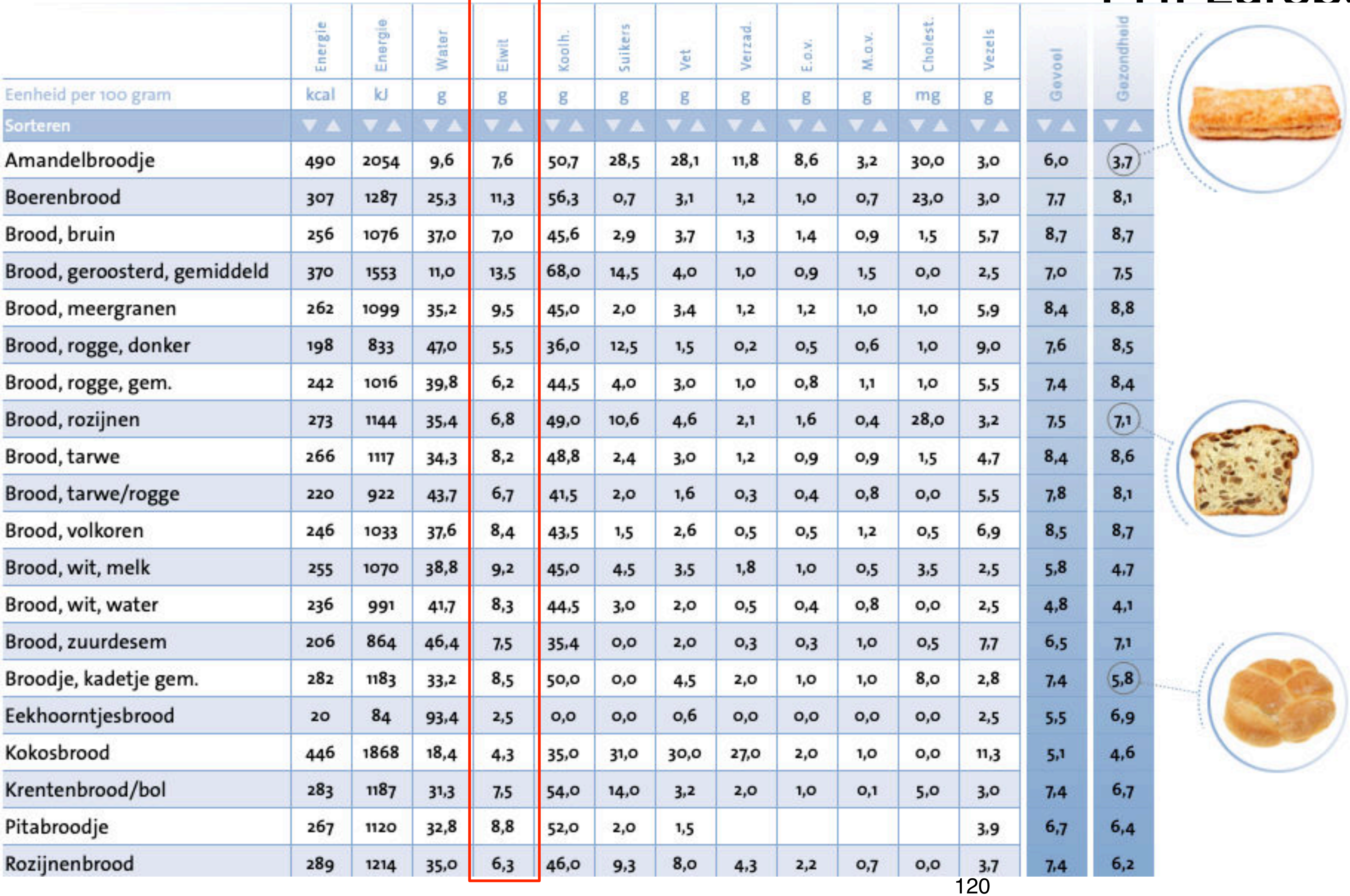
Breakdown of SP is also dependent on DPP IV activity. SP has neurological, immunological, and endocrinological functions and influences pain sensitivity, gut peristaltic, inflammation, and social interaction [63]. Increased concentrations of SP in the gut can produce abdominal pain with diarrhea [64] and angioedema with swelling and abdominal pain [65]. High SP levels in the gut can even produce pancreatitis together with abdominal pain, diarrhea, and vomiting [66]. A recent double-blind placebo-controlled human trial showed that the intake of a small amount of gluten (4.375 g/day for 1 week) significantly increased intestinal and extra-intestinal symptoms in individuals with self-reported gluten sensitivity [67]. Typical intestinal symptoms such as bloating and abdominal pain were increased after 1 week of gluten intake, as were extra-intestinal symptoms, such as depression and apthous stomatitis. Because in patients suffering from NCGS no known intestinal lesions or other biomarkers such as anti-bodies against gluten/gliadin/self-antigens seem to be present [68], their symptoms have to be explained by different pathways. NCGS presents itself with intestinal symptoms like diarrhea, abdominal discomfort, and flatulence, while headache, lethargy, attention-deficit/hyperactivity disorder, ataxia, or oral ulceration appears as an extra-intestinal symptom [3, 67]. Most,

Die maximale Aufnahme von Kasein und Gluten sollte niemals 4,5 Gramm/Tag überschreiten.

Pruimboom and de Punder *Journal of Health, Population and Nutrition* (2015) 33:24
DOI 10.1186/s41043-015-0032-y

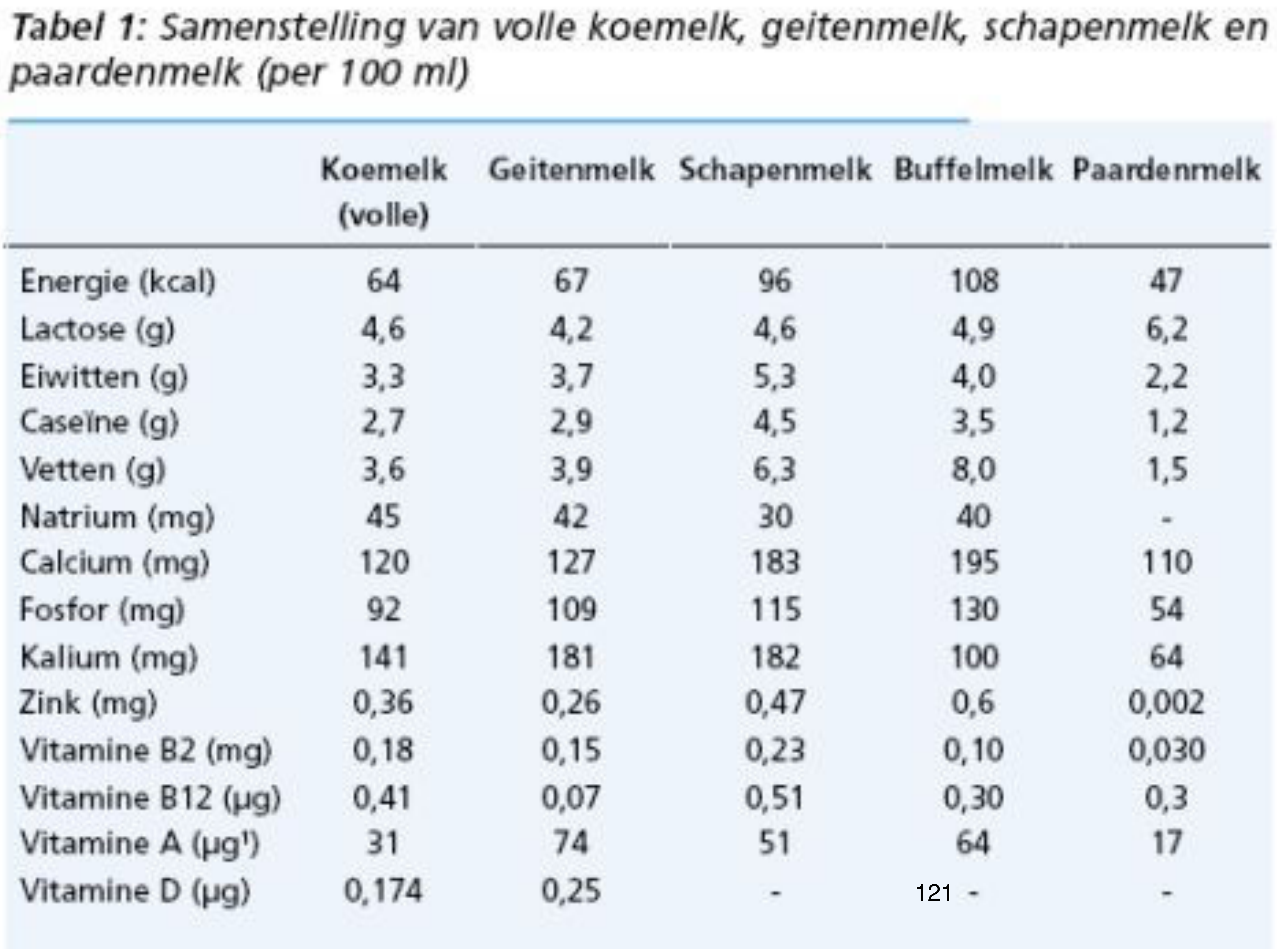
Ungefähr 60 % aller Proteine sind Gluten.

PNI Europe



	Energie	Energie	Water	Eiwit	Koolh.	Suikers	Vet	Verzad.	E.o.v.	M.o.v.	Cholest.	Vezels	Gevoel	Gezondheid
Eenheid per 100 gram	kcal	kJ	g	g	g	g	g	g	g	g	mg	g		
Sorteren	▼▲	▼▲	▼▲	▼▲	▼▲	▼▲	▼▲	▼▲	▼▲	▼▲	▼▲	▼▲	▼▲	▼▲
Amandelbroodje	490	2054	9,6	7,6	50,7	28,5	28,1	11,8	8,6	3,2	30,0	3,0	6,0	3,7
Boerenbrood	307	1287	25,3	11,3	56,3	0,7	3,1	1,2	1,0	0,7	23,0	3,0	7,7	8,1
Brood, bruin	256	1076	37,0	7,0	45,6	2,9	3,7	1,3	1,4	0,9	1,5	5,7	8,7	8,7
Brood, geroosterd, gemiddeld	370	1553	11,0	13,5	68,0	14,5	4,0	1,0	0,9	1,5	0,0	2,5	7,0	7,5
Brood, meergranen	262	1099	35,2	9,5	45,0	2,0	3,4	1,2	1,2	1,0	1,0	5,9	8,4	8,8
Brood, rogge, donker	198	833	47,0	5,5	36,0	12,5	1,5	0,2	0,5	0,6	1,0	9,0	7,6	8,5
Brood, rogge, gem.	242	1016	39,8	6,2	44,5	4,0	3,0	1,0	0,8	1,1	1,0	5,5	7,4	8,4
Brood, rozijnen	273	1144	35,4	6,8	49,0	10,6	4,6	2,1	1,6	0,4	28,0	3,2	7,5	7,1
Brood, tarwe	266	1117	34,3	8,2	48,8	2,4	3,0	1,2	0,9	0,9	1,5	4,7	8,4	8,6
Brood, tarwe/rogge	220	922	43,7	6,7	41,5	2,0	1,6	0,3	0,4	0,8	0,0	5,5	7,8	8,1
Brood, volkoren	246	1033	37,6	8,4	43,5	1,5	2,6	0,5	0,5	1,2	0,5	6,9	8,5	8,7
Brood, wit, melk	255	1070	38,8	9,2	45,0	4,5	3,5	1,8	1,0	0,5	3,5	2,5	5,8	4,7
Brood, wit, water	236	991	41,7	8,3	44,5	3,0	2,0	0,5	0,4	0,8	0,0	2,5	4,8	4,1
Brood, zuurdesem	206	864	46,4	7,5	35,4	0,0	2,0	0,3	0,3	1,0	0,5	7,7	6,5	7,1
Broodje, kadetje gem.	282	1183	33,2	8,5	50,0	0,0	4,5	2,0	1,0	1,0	8,0	2,8	7,4	5,8
Eekhoorntjesbrood	20	84	93,4	2,5	0,0	0,0	0,6	0,0	0,0	0,0	0,0	2,5	5,5	6,9
Kokosbrood	446	1868	18,4	4,3	35,0	31,0	30,0	27,0	2,0	1,0	0,0	11,3	5,1	4,6
Krentenbrood/bol	283	1187	31,3	7,5	54,0	14,0	3,2	2,0	1,0	0,1	5,0	3,0	7,4	6,7
Pitabroodje	267	1120	32,8	8,8	52,0	2,0	1,5					3,9	6,7	6,4
Rozijnenbrood	289	1214	35,0	6,3	46,0	9,3	8,0	4,3	2,2	0,7	0,0	3,7	7,4	6,2

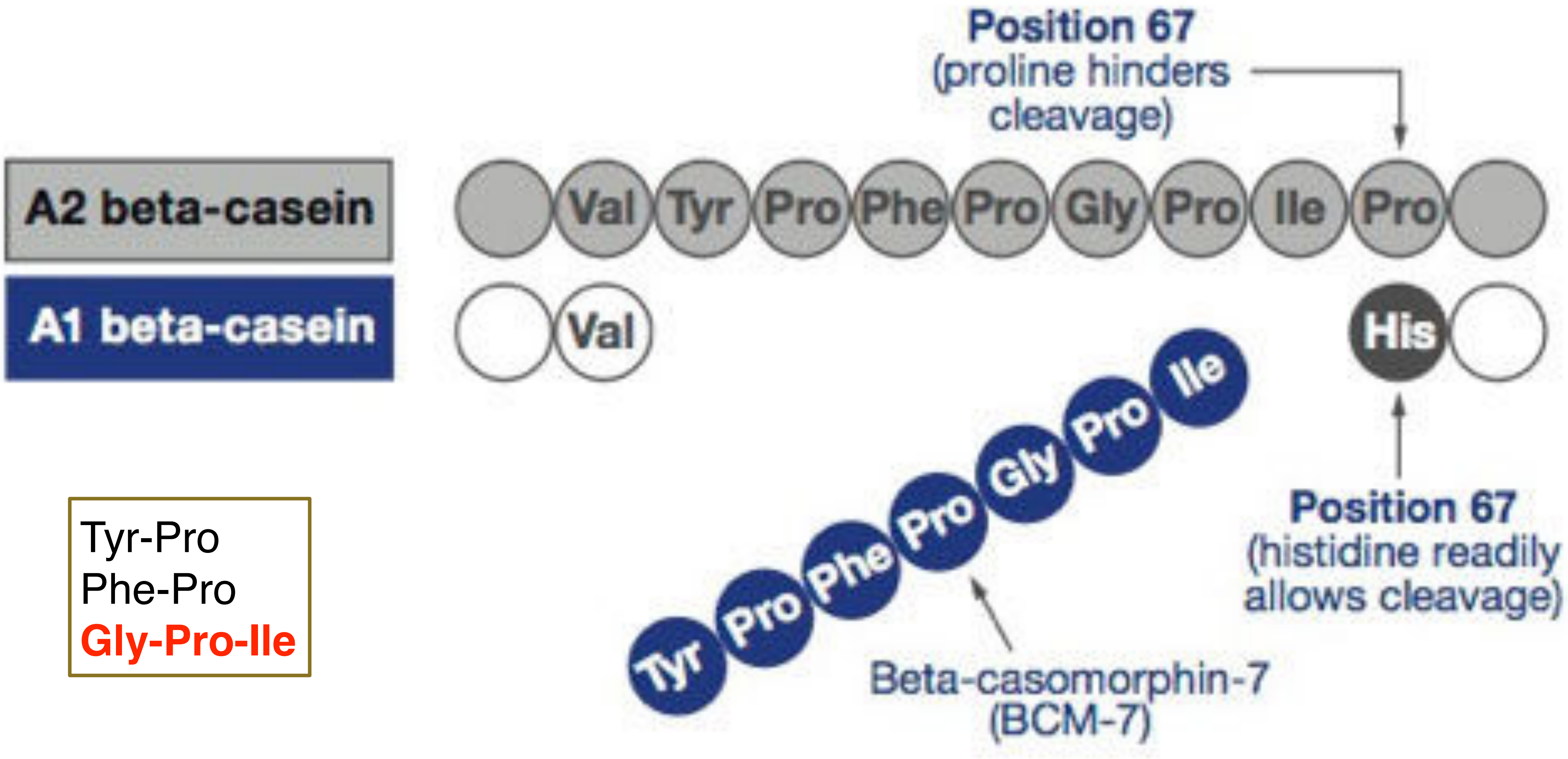
Kaseinmenge pro 100 ml



Tabel 1: Samenstelling van volle koemelk, geitenmelk, schapenmelk en paardenmelk (per 100 ml)

	Koemelk (volle)	Geitenmelk	Schapenmelk	Buffelmelk	Paardenmelk
Energie (kcal)	64	67	96	108	47
Lactose (g)	4,6	4,2	4,6	4,9	6,2
Eiwitten (g)	3,3	3,7	5,3	4,0	2,2
Caseïne (g)	2,7	2,9	4,5	3,5	1,2
Vetten (g)	3,6	3,9	6,3	8,0	1,5
Natrium (mg)	45	42	30	40	-
Calcium (mg)	120	127	183	195	110
Fosfor (mg)	92	109	115	130	54
Kalium (mg)	141	181	182	100	64
Zink (mg)	0,36	0,26	0,47	0,6	0,002
Vitamine B2 (mg)	0,18	0,15	0,23	0,10	0,030
Vitamine B12 (µg)	0,41	0,07	0,51	0,30	0,3
Vitamine A (µg[1])	31	74	51	64	17
Vitamine D (µg)	0,174	0,25	-	-	-

DPP IV wird durch das verbleibende

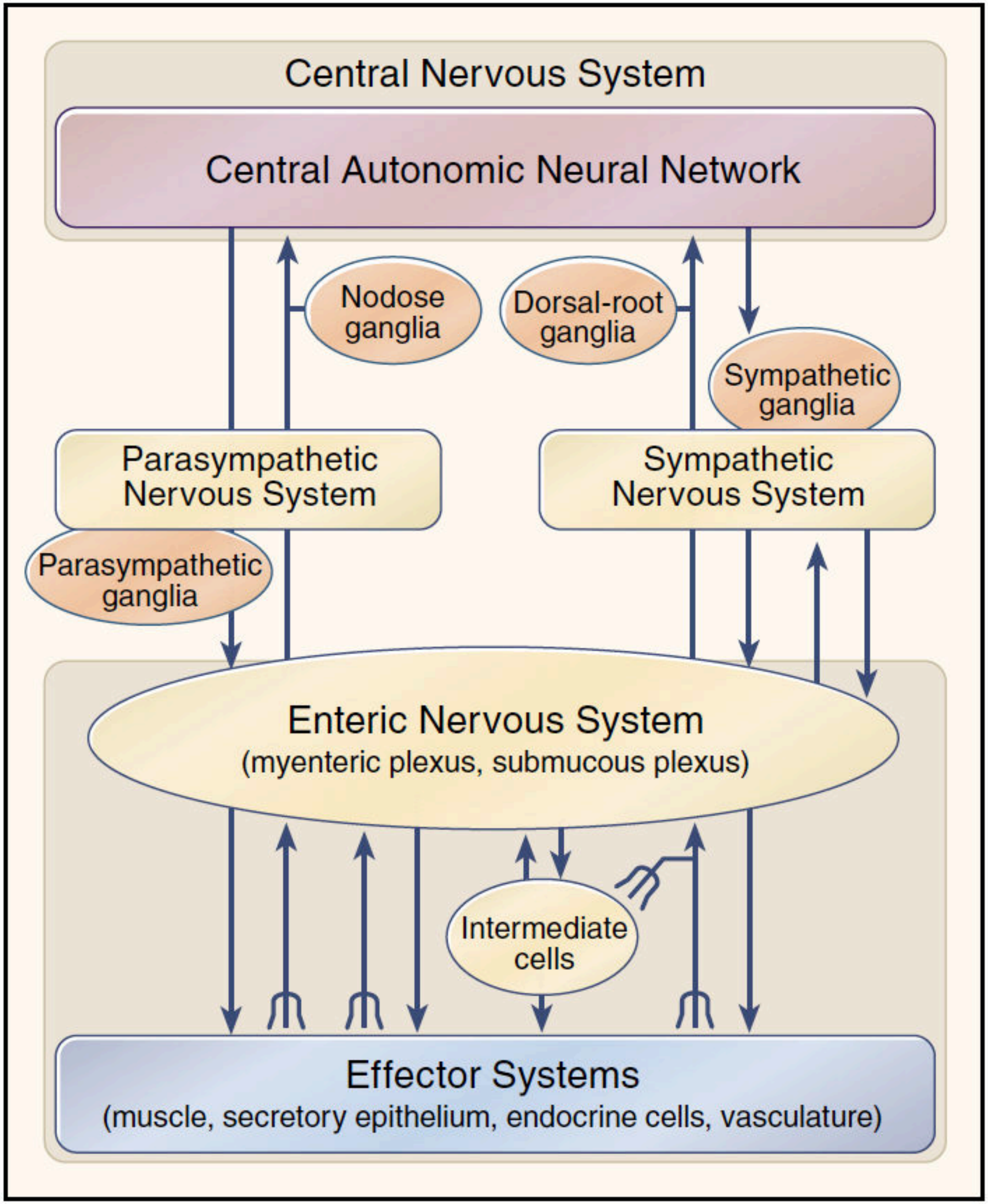

Position 67
(proline hinders cleavage)
A2 beta-casein
Val
Tyr
Pro
Phe
Pro
Gly
Pro
Ile
Pro
A1 beta-casein
Val
His
Tyr
Pro
Phe
Pro
Gly
Pro
Ile
Position 67
(histidine readily allows cleavage)
Beta-casomorphin-7
(BCM-7)

Tyr-Pro
Phe-Pro
Gly-Pro-Ile

Tag 1

15.45 - 17.00

Das enterische Nervensystem



Central Nervous System

Central Autonomic Neural Network

Nodose ganglia

Dorsal-root ganglia

Sympathetic ganglia

Parasympathetic Nervous System

Sympathetic Nervous System

Parasympathetic ganglia

Enteric Nervous System
(myenteric plexus, submucous plexus)

Intermediate cells

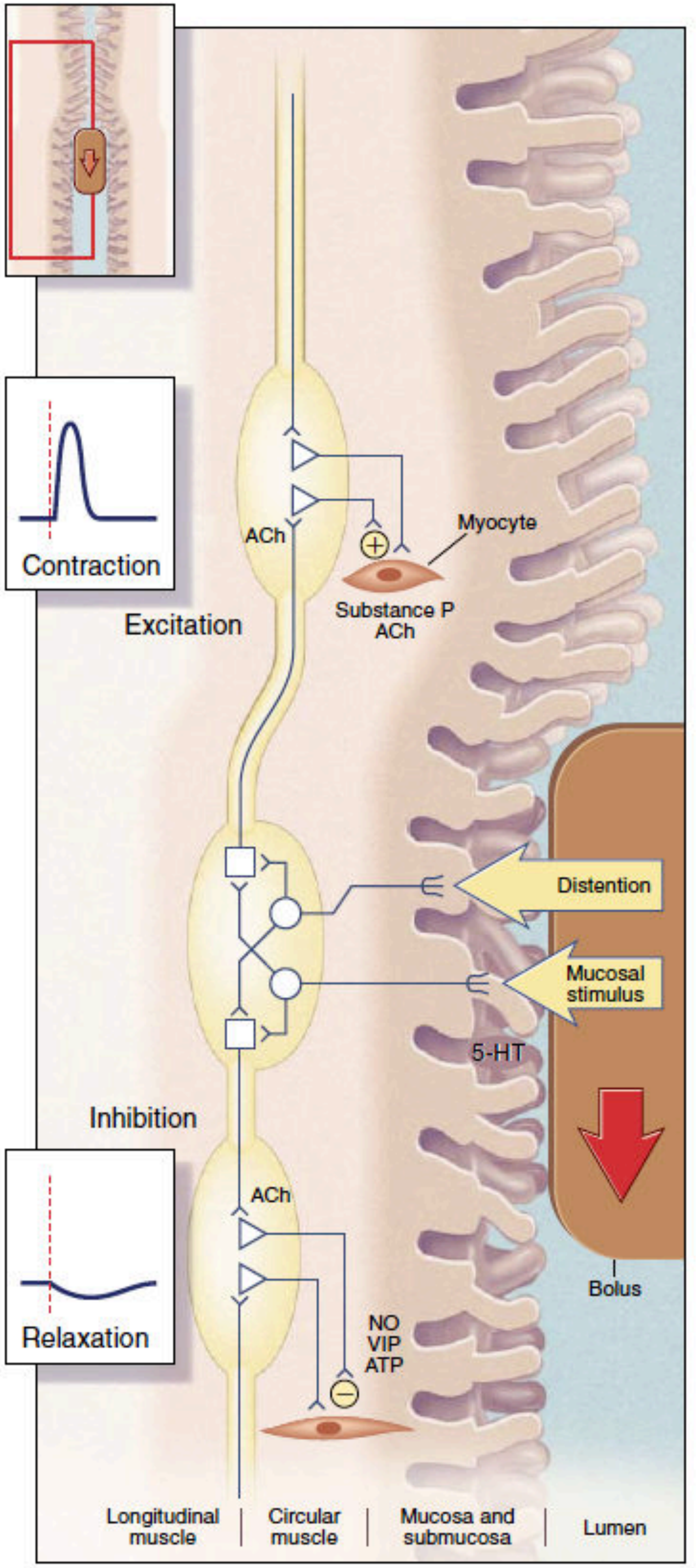
Effector Systems
(muscle, secretory epithelium, endocrine cells, vasculature)

PNI Europe
By Dr. Leo Pruimboom

Der neuronale Plexus im Darm stellt ein selbständig funktionierendes Netzwerk, das sogenannte enterische Nervensystem, dar, das über den Parasympathikus und den Sympathikus mit dem zentralen autonomen neuronalen Netzwerk im Zentralnervensystem verbunden ist. Das enterische Nervensystem kann die Effektorensysteme im Darm direkt oder indirekt durch seine Wirkung auf die Interneurone beeinflussen, zu denen die endokrinen Zellen, die Zwischenzellen von Cajal und Zellen des Immunsystems, wie z.B. Mastzellen, gehören. Die Zellkörper der primären vagalen und primären splanchnian-afferenten Neuronen befinden sich in den knötchenförmigen Ganglien bzw. den dorsalen Wurzelganglien, die jeweils unterschiedliche Informationen vom Darm zum Zentralnervensystem transportieren. Das Symbol repräsentiert die Enden des Afferenten und die Pfeile stellen die Antwort der neuronalen Übertragung dar.

THE ENTERIC NERVOUS SYSTEM. NEJM 1996
RAJ K. GOYAL, M.D., AND IKUO HIRANO, M.D

PNI Europe
By Dr. Leo Pruimboom


Contraction
Excitation
ACh
Myocyte
Substance P
ACh
Distention
Mucosal stimulus
5-HT
Inhibition
ACh
Relaxation
NO
VIP
ATP
Bolus
Longitudinal muscle
Circular muscle
Mucosa and submucosa
Lumen

5-HT = Serotonin = 85% Darm
NO = Stickstoff Monoxid
VIP = Vasoactive Intestine Peptide
ATP = Energie

Die Peristaltik ist das Ergebnis einer Reihe von lokalen Reflexen, die sich jeweils aus
einer Kontraktion des Darmmuskels über eine intraluminale Stimulation und Entspannung der Muskeln unter dem Stimulus (Einsatz, linke obere Ecke). Die Freisetzung von 5-HT durch die Schleimhaut
Die Stimulation oder mechanische Ausdehnung des Darmlumens (Hauptpanel) löst die Aktivität der intrinsisch afferenten Neuronen aus (). Oberhalb der Reizstelle geben aufsteigende cholinerge Interneuronen () dieses Signal an erregende Motoneuronen () weiter, die Acetylcholin (ACh) und Substanz P enthalten. Dadurch kontrahiert das kreisförmige Muskelbündel hinter dem Bolus, während vor dem Bolus alle Muskeln entspannen.

THE ENTERIC NERVOUS SYSTEM. NEJM 1996
RAJ K. GOYAL, M.D., AND IKUO HIRANO, M.D

Tryptophan Mangel (Serotonin) - Eier, Milch
Arginin Mangel (NO) - Mandeln, Cashewkerne, Lachs

Acetylcholin Mangel - Cholin Mangel (Eier, Fisch, Schalentiere)
PS Aktivität Mangel

ATP Mangel - 5000 Zucker-Molekule
Short Chain Fatty Acids - Mikrobiom

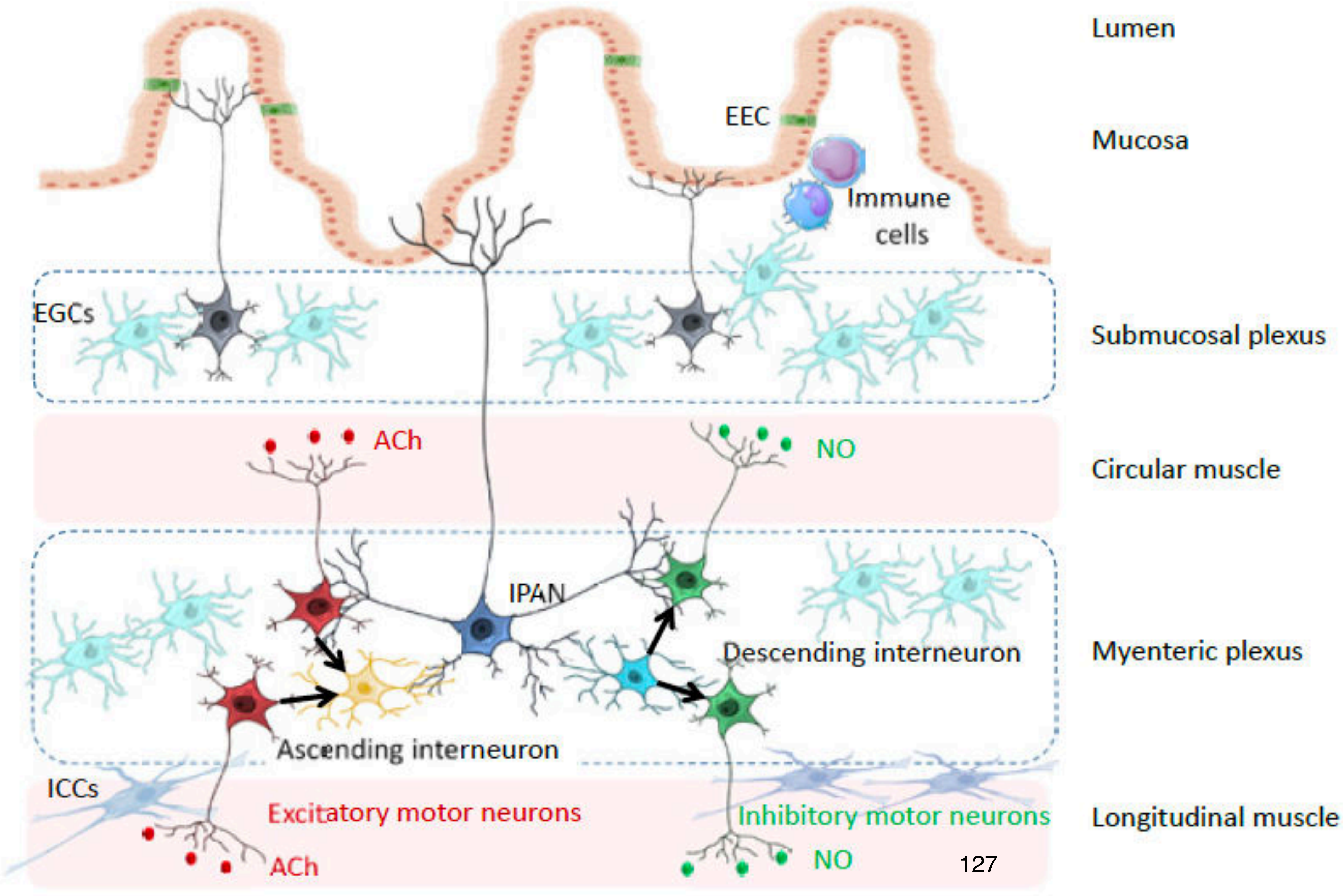
Stress - Chronisch/Unbekannte/Unausweichbar

Substanz P Erhöhung = Gluten/Kasein

Wasserhaushalt Störung

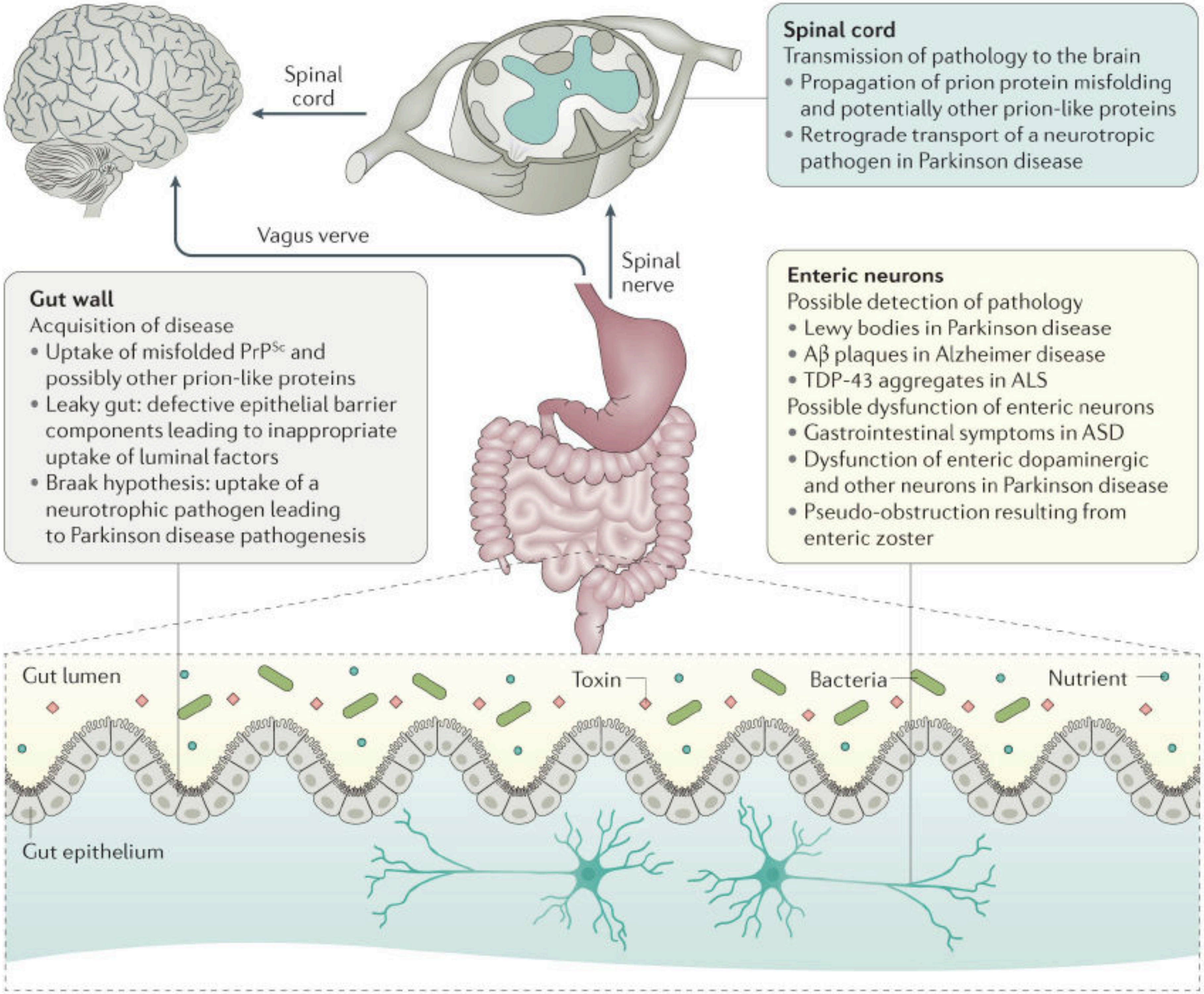
Gehirn-Entzündung

Das ENS; ein hochkomplexes Nervensystem, das einen großen Einfluss auf alle Syndrome hat.


Lumen
Mucosa
EEC
Immune cells
EGCs
Submucosal plexus
ACh
NO
Circular muscle
IPAN
Descending interneuron
Myenteric plexus
Ascending interneuron
ICCs
Excitatory motor neurons
Inhibitory motor neurons
ACh
NO
Longitudinal muscle

Darm-microbioma-Hersen-als

Neurodegeneratie ter wille van de consistentie



Spinal cord
Transmission of pathology to the brain
- Propagation of prion protein misfolding and potentially other prion-like proteins
- Retrograde transport of a neurotropic pathogen in Parkinson disease

Gut wall
Acquisition of disease
- Uptake of misfolded PrP^{Sc} and possibly other prion-like proteins
- Leaky gut: defective epithelial barrier components leading to inappropriate uptake of luminal factors
- Braak hypothesis: uptake of a neurotrophic pathogen leading to Parkinson disease pathogenesis

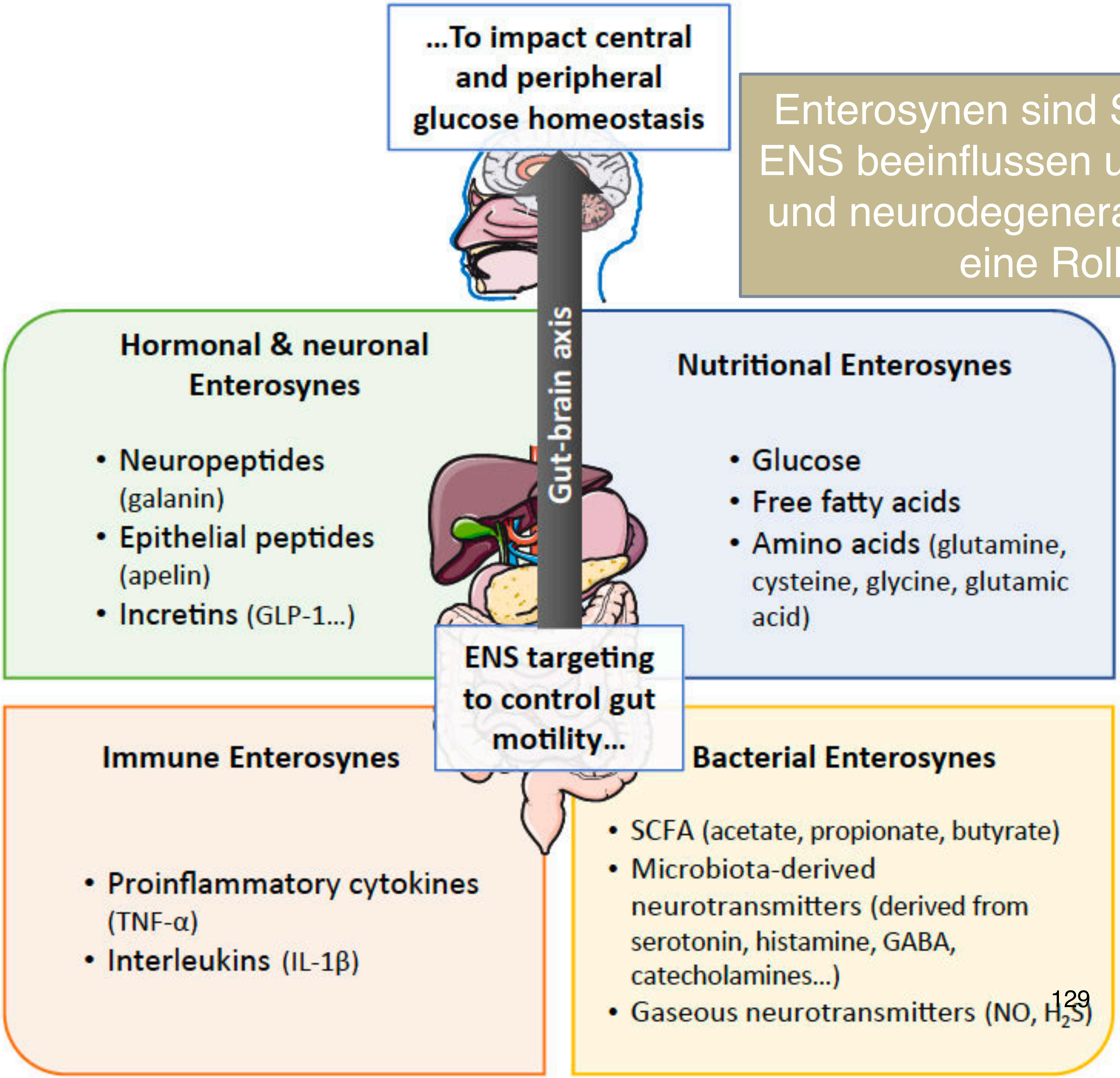
Enteric neurons
Possible detection of pathology
- Lewy bodies in Parkinson disease
- Aβ plaques in Alzheimer disease
- TDP-43 aggregates in ALS

Possible dysfunction of enteric neurons
- Gastrointestinal symptoms in ASD
- Dysfunction of enteric dopaminergic and other neurons in Parkinson disease
- Pseudo-obstruction resulting from enteric zoster

Figure 4. Summary of primary disease interactions between the gut and brain
Aβ, amyloid-beta; ALS, amyotrophic lateral sclerosis; ASD, autism spectrum disorder; PrP^{Sc}, prion protein scrapie.

Meenakshi Rao1 and Michael D. GershonThe bowel and beyond: the enteric nervous system in neurological disorders. Nat Rev Gastroenterol Hepatol. 2016 September ; 13(9): 517–528

Enterosynen sind Substanzen, die das ENS beeinflussen und bei Stoffwechsel- und neurodegenerativen Erkrankungen eine Rolle spielen.



…To impact central and peripheral glucose homeostasis

Gut-brain axis

Hormonal & neuronal Enterosynes

- **Neuropeptides** (galanin)
- **Epithelial peptides** (apelin)
- **Incretins** (GLP-1…)

Nutritional Enterosynes

- **Glucose**
- **Free fatty acids**
- **Amino acids** (glutamine, cysteine, glycine, glutamic acid)

ENS targeting to control gut motility…

Immune Enterosynes

- **Proinflammatory cytokines** (TNF-α)
- **Interleukins** (IL-1β)

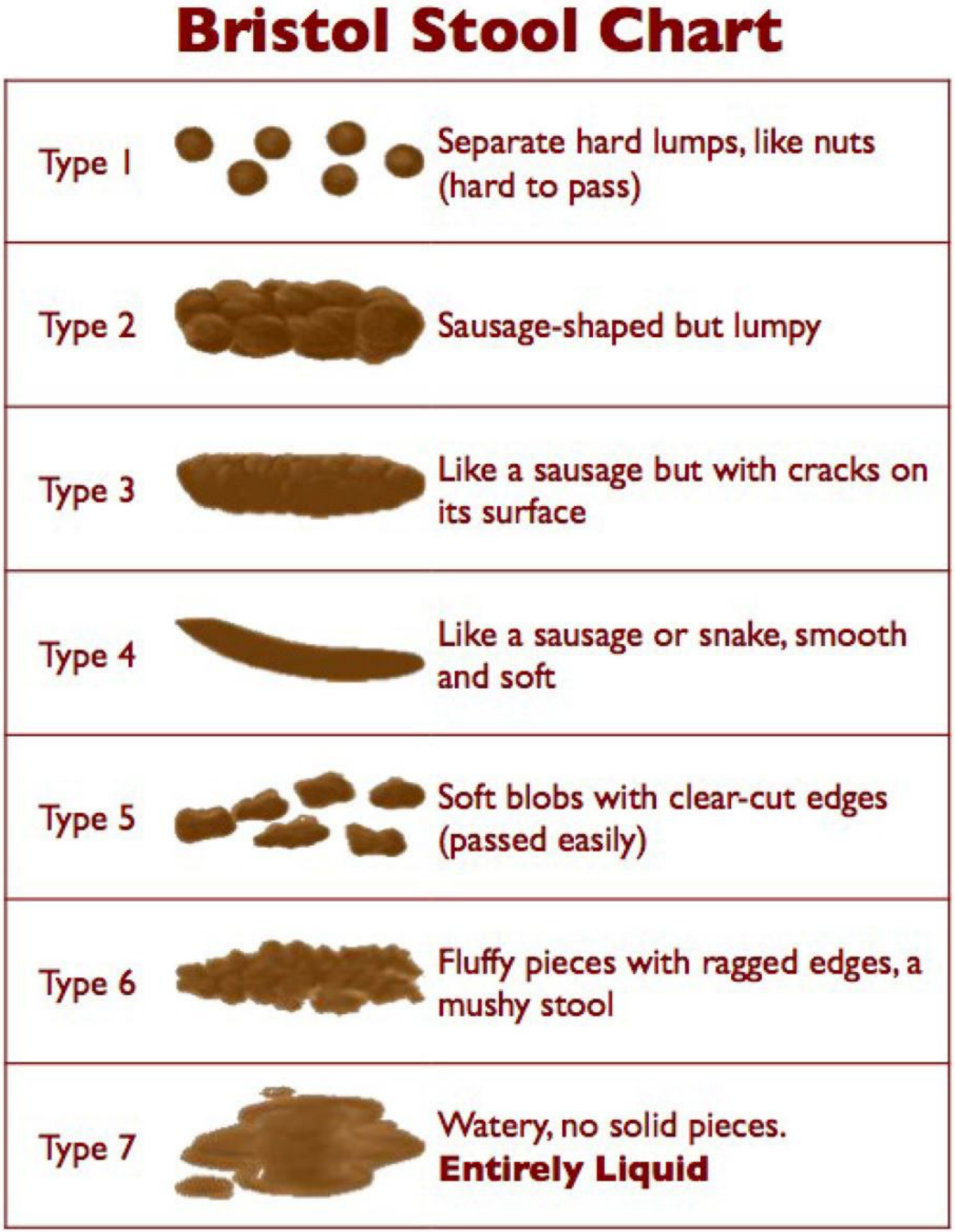
Bacterial Enterosynes

- SCFA (acetate, propionate, butyrate)
- Microbiota-derived neurotransmitters (derived from serotonin, histamine, GABA, catecholamines…)
- Gaseous neurotransmitters (NO, H_2S)

Claude Knauf et al.
Targeting the Enteric Nervous System
to Treat Metabolic Disorders?
“Enterosynes”
as Therapeutic Gut Factors.
Neuroendocrinology 2019

Stuhl

Farbe - Leichtbraun
Menge - 200 Gr/Tag
Komposition - Typ 4
Geruch - Geruchlos
Gas - ‘Geruchlos - Methangas’
Krämpfe - Pathologie - SP
‘Stille Verstopfung” - Exorphin
“Schmerzhafte Verstopfung”
SCFA, Mikrobiom
Magnesium Mangel



Bristol Stool Chart

Type 1	Separate hard lumps, like nuts (hard to pass)
Type 2	Sausage-shaped but lumpy
Type 3	Like a sausage but with cracks on its surface
Type 4	Like a sausage or snake, smooth and soft
Type 5	Soft blobs with clear-cut edges (passed easily)
Type 6	Fluffy pieces with ragged edges, a mushy stool
Type 7	Watery, no solid pieces. **Entirely Liquid**

Tag 1

17.00 - 17.15

kahoot.it