

Neuroinflammation: An important New Insight into Complex Brain Disorders

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Our Topics

- What is **neuroinflammation** (NI)?
- What drives NI
- Complex brain disorders and NI: schizophrenia, bipolar, autism, Alzheimer's, depression
- How herbs can help



Bottom Line

- Mentally Fuzzy
- Anhedonia
- Poor Brain Plasticity
- Memory fails
- Depressed
- Higher risk of Dementia



A Recent Headline

Ground-breaking study links immune system to mental health

“ The key issue there is what’s driving the mental ill health is not so much a change in the brain but a change in the immune system...”



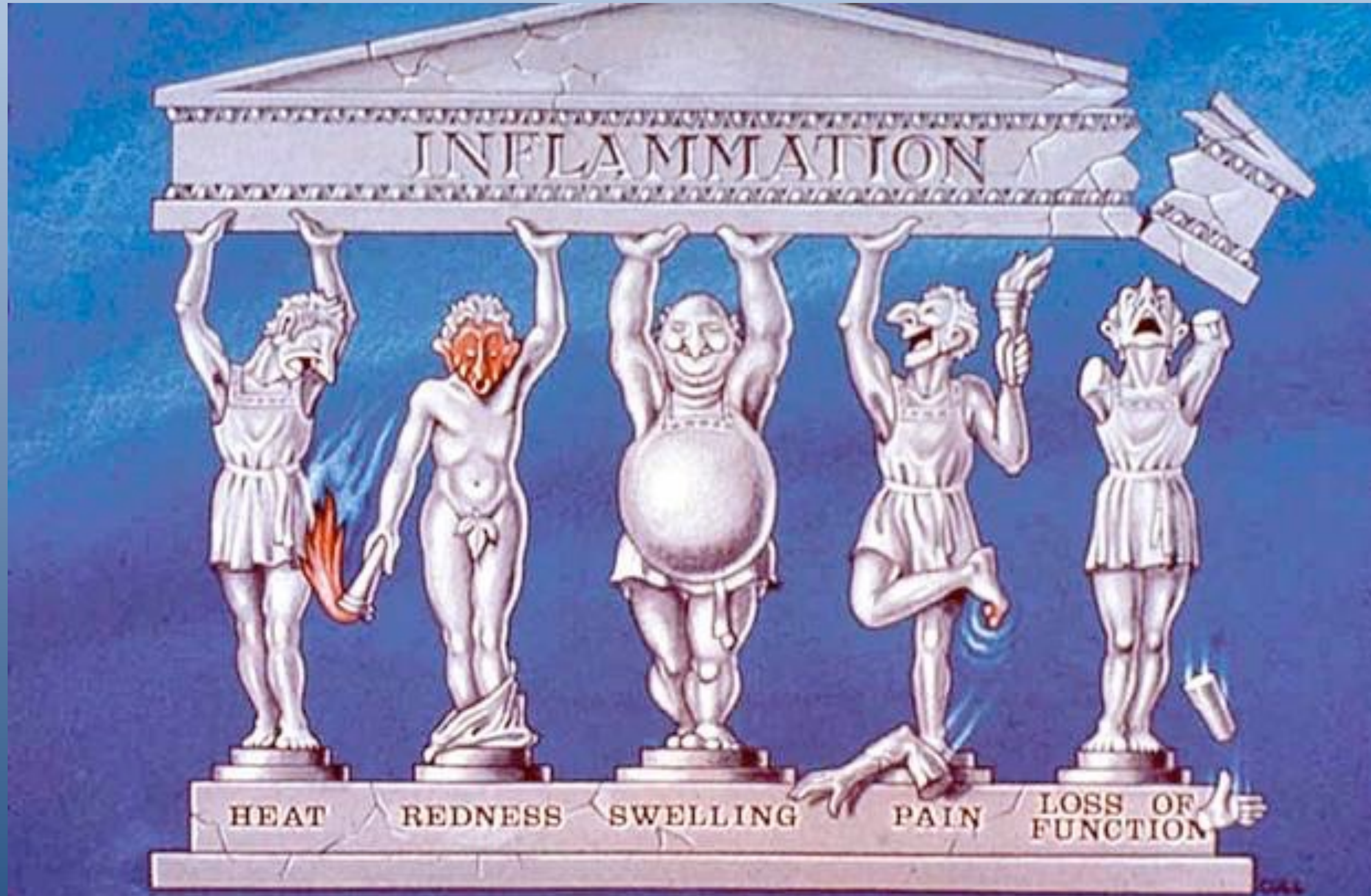
Professor Ian Hick of the University of Sydney’s Brain and Mind Center

Body and Brain

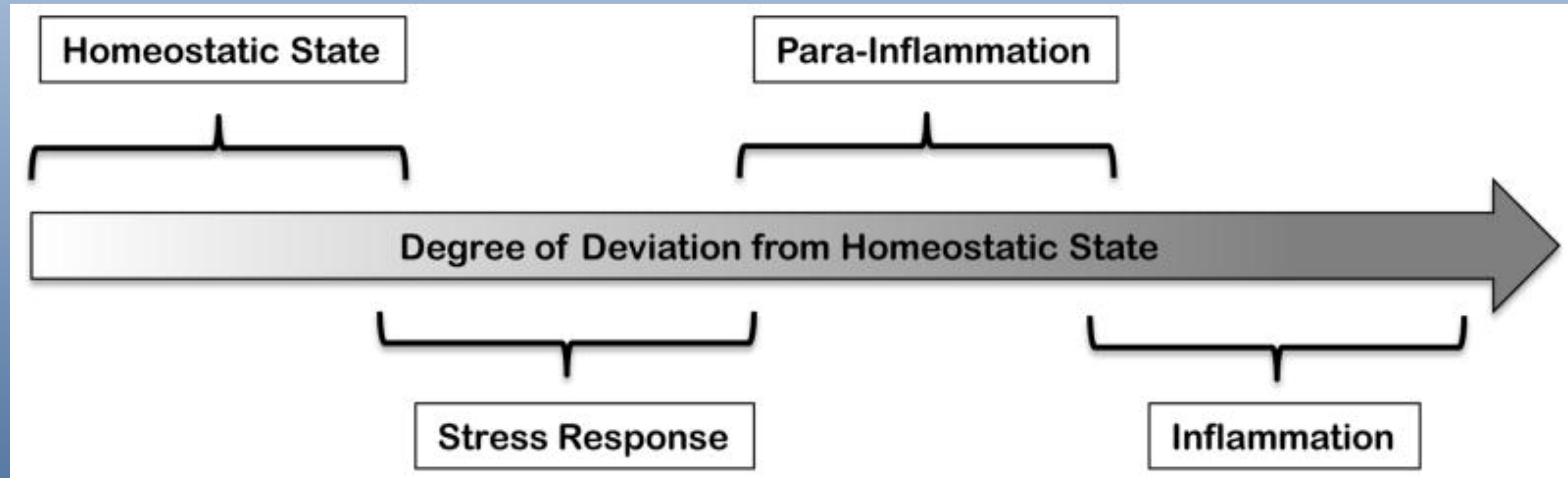
Healthy Body

Healthy Brain

Inflammation

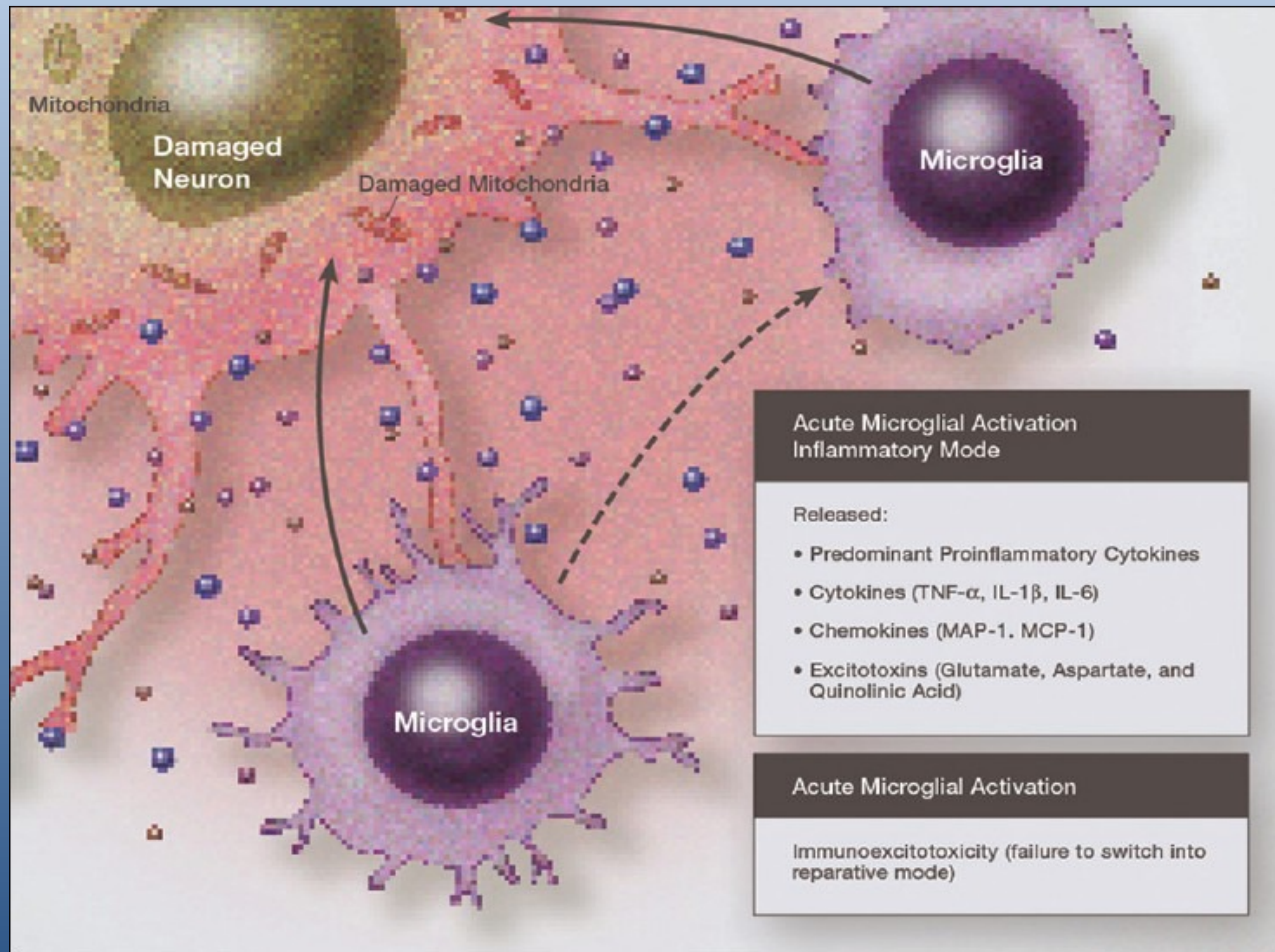


Stages of Tissue Response



Chovatiya R, Medzhitov R. *Mol Cell* 2014 ; **54**(2): 281-288 PMID 24766892

Brain and Immunity



IL-1 β =
interleukin
1beta

Direct Causes of NI

- Neurotoxins (endogenous, environmental)
- Pathogens
- Head trauma
- Autoimmunity
- Aging (eg decline in melatonin)
- Vascular (eg microbleeds etc)

Najjar S, Pearlman DM, Alper K et al. *J Neuroinflammation* 2013; **10**: 43 PMID 23547920

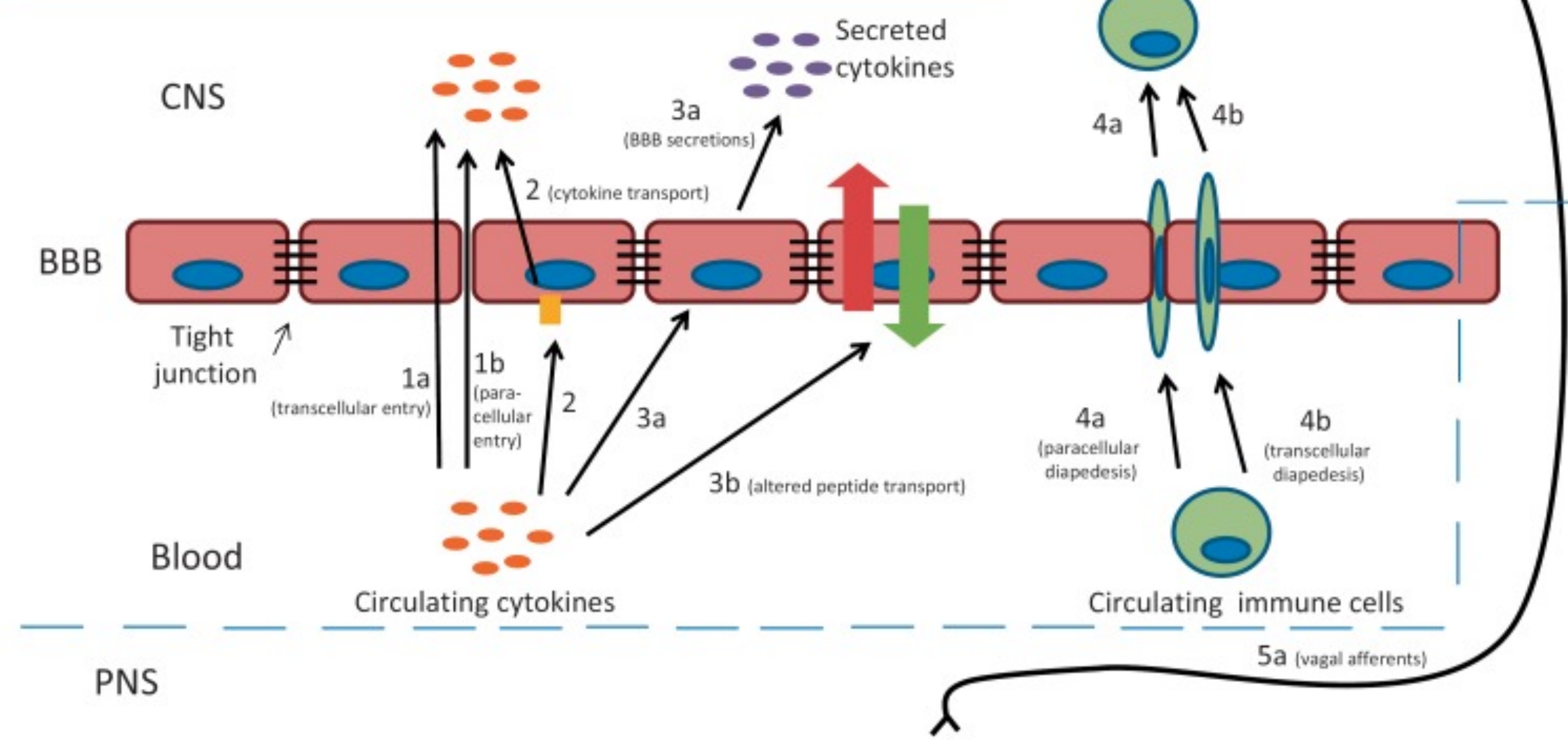
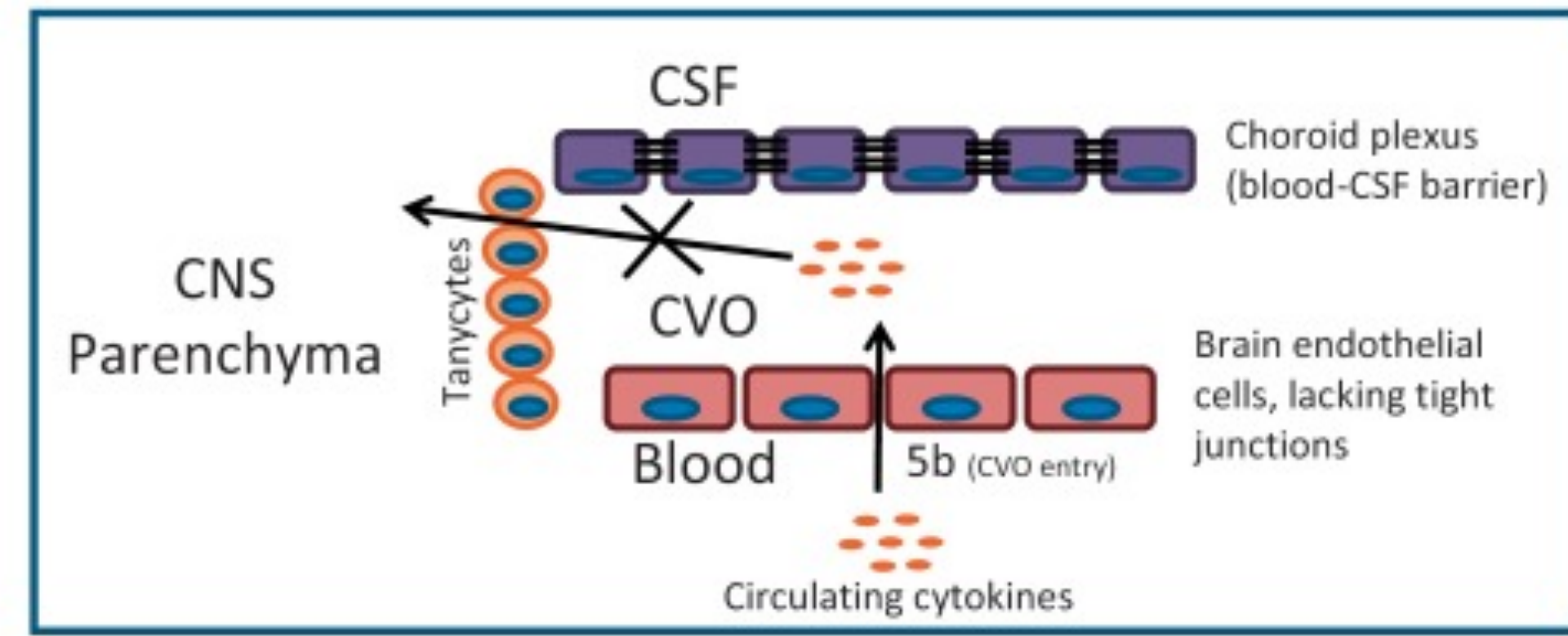
Hardeland R, Cardinali DP, Brown GM et al. *Prog Neurobiol* 2015; **127-128**: 46-63 PMID 25697044

Stone J, Johnstone DM, Mitrofanis J et al. *J Alzheimers Dis* 2015; **44**(2): 355-373
PMID25318547

Viviani B, Boraso M, Marchetti N et al. *Neurotoxicology* 2014; **43**: 10-20 PMID 24662010

Marošová L, Neradil P, Zilka N. *Acta Virol* 2013; **57**(3): 273-281 PMID 24020754

Body and Brain



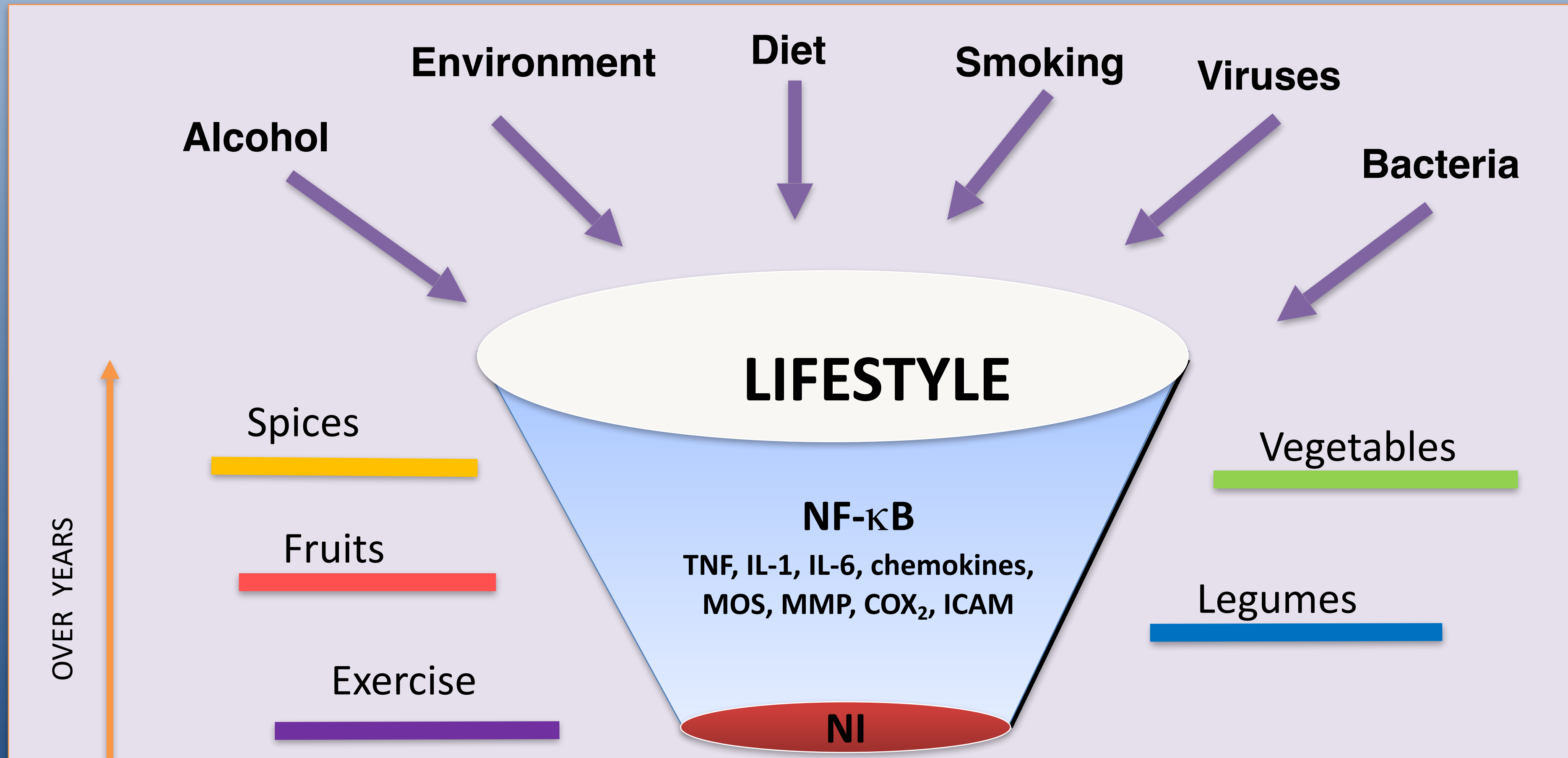
Erickson MA, Dohi K, Banks WA. *Neuroimmunomodulation* 2012; **19**(2):

121-130

PMID 22248728

What Drives NI?

- All the drivers of systemic inflammation



Systemic Inflammation (SI) Drives NI

Dysbiosis

Chronic
infections

Stealth pathogens
and occult viruses

Diet

Autoimmunity and other chronic
inflammatory conditions

Systemic Inflammation Drives NI

Stress

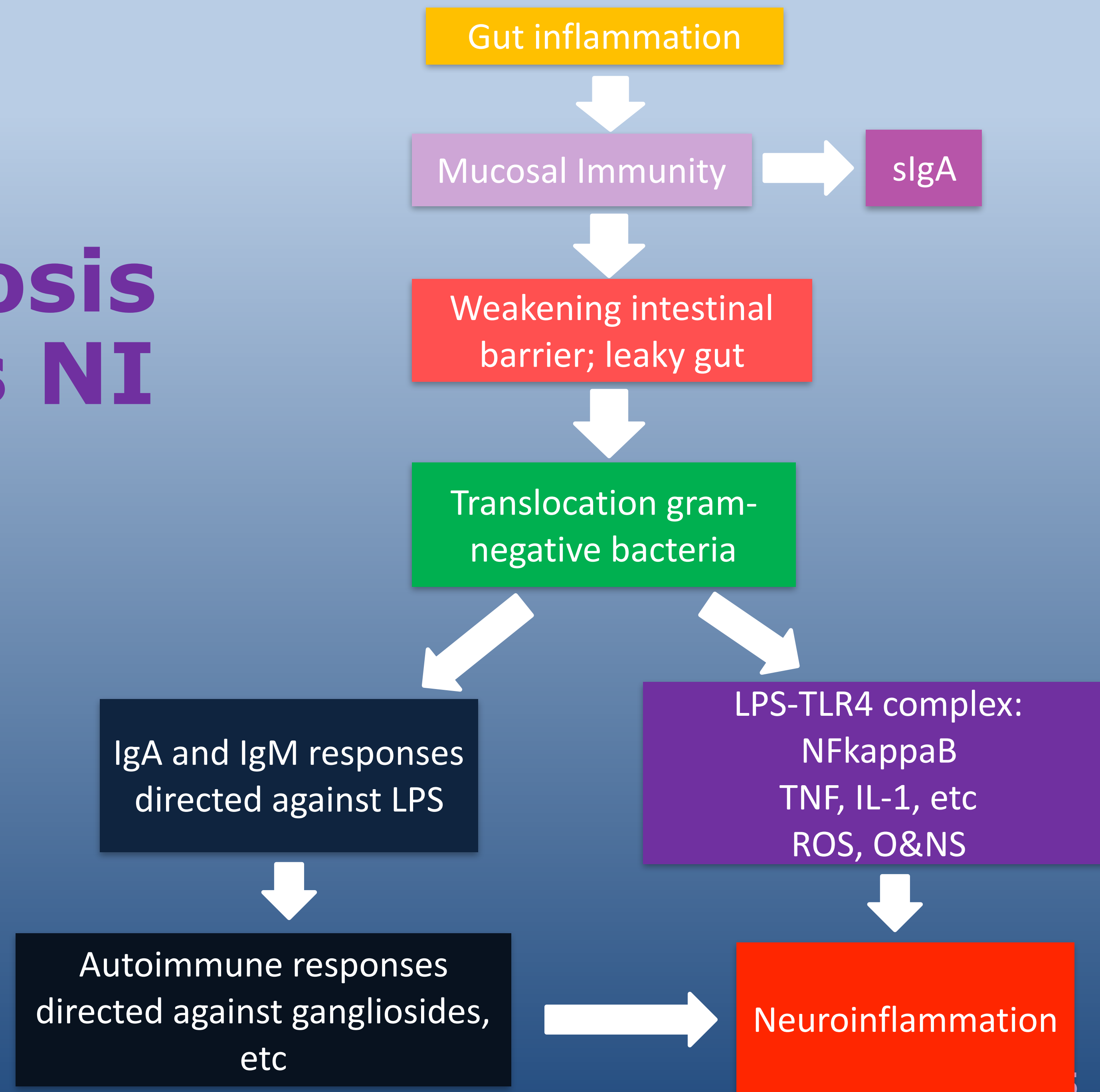
O & NS

Fatty
Liver

Trauma

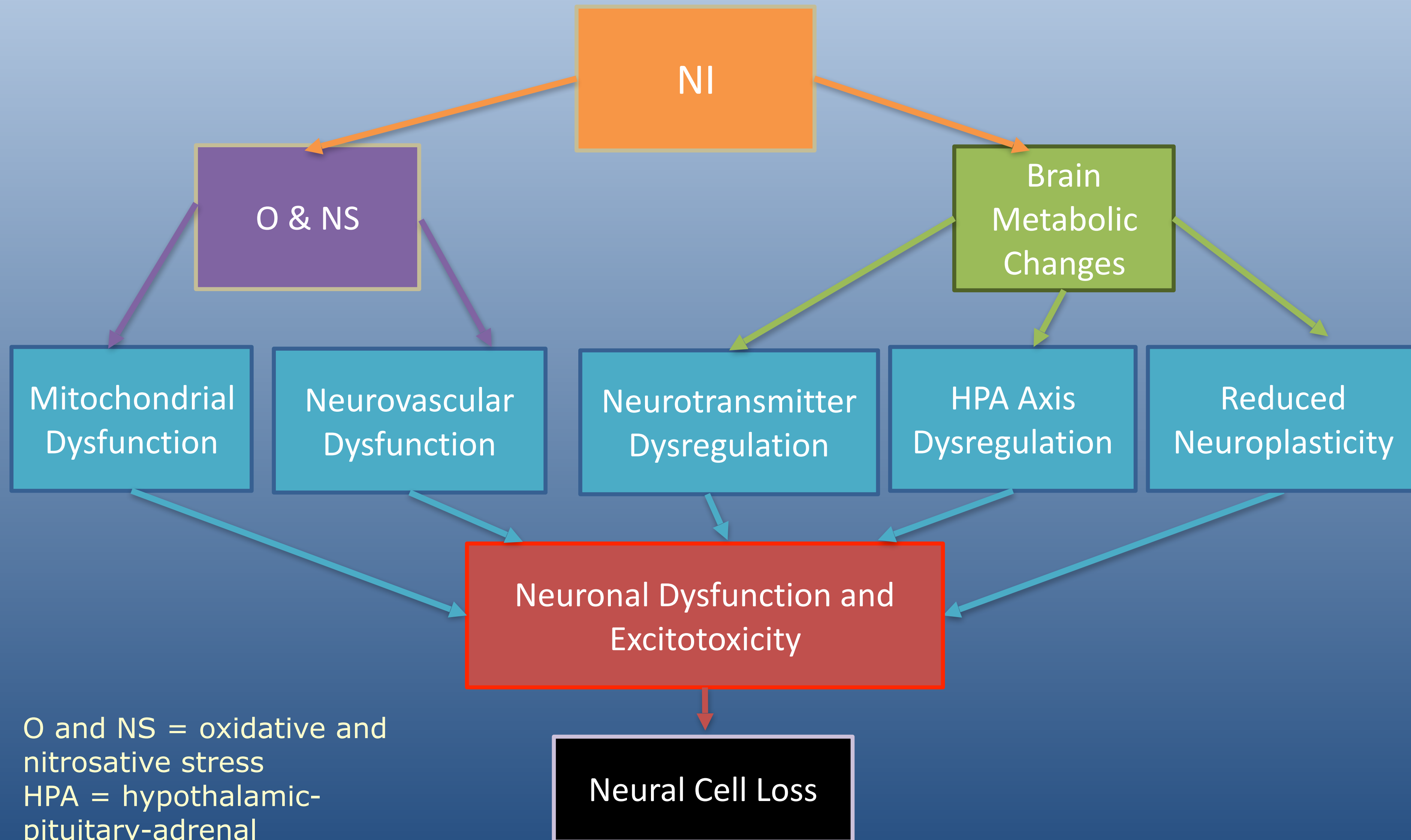
Drugs and Toxins

Dysbiosis Drives NI

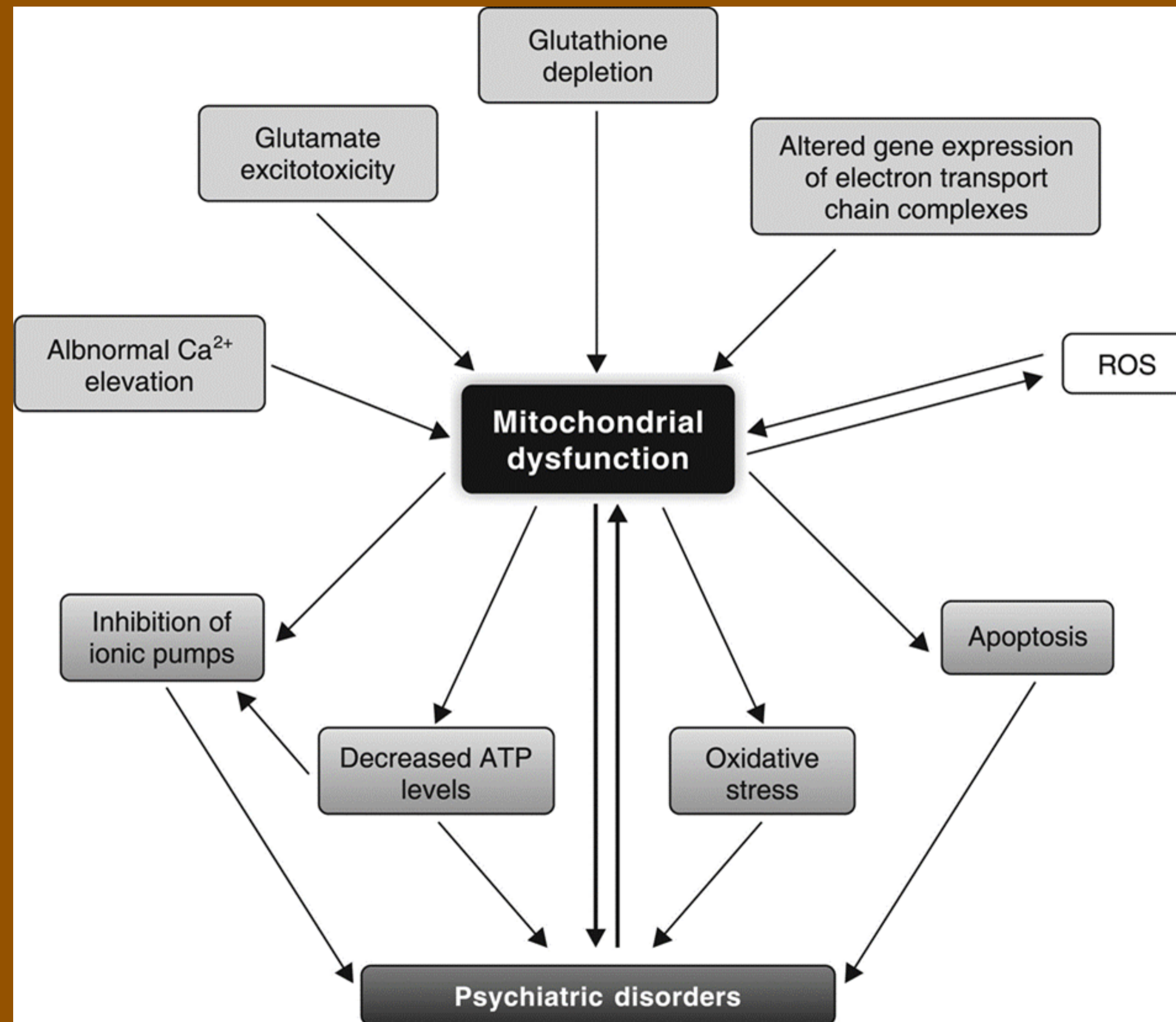


Maes M, Twisk FN, Kubera M et al. *J Affect Disord* 2012; **136**(3) :909-917 PMID 21967891

NI Consequences



NI Disrupts Mitochondria

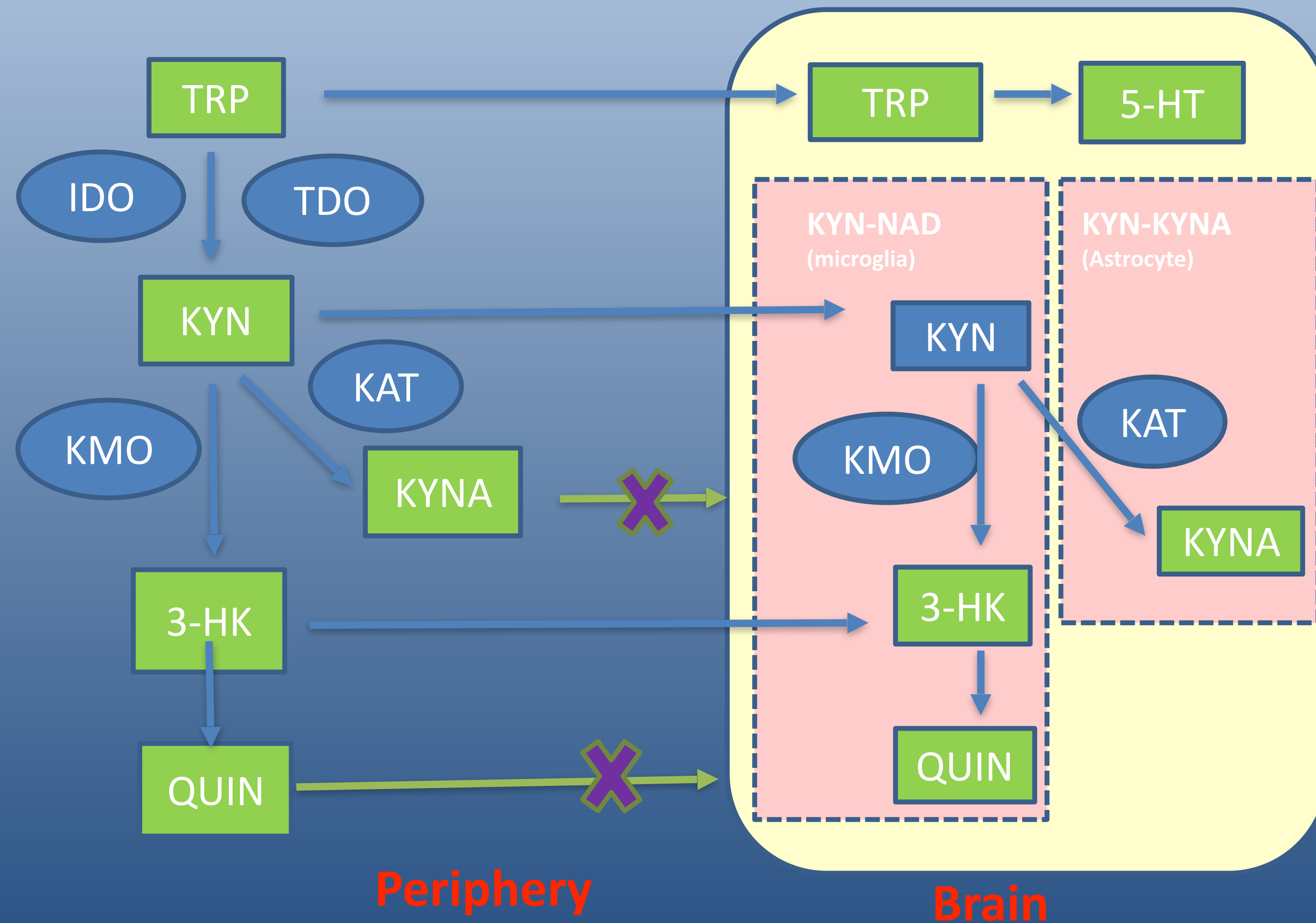


Streck EL, Gonçalves CL, Furlanetto CB et al. *Rev Bras Psiquiatr* 2014; **36**(2):156-167. PMID: 24845118

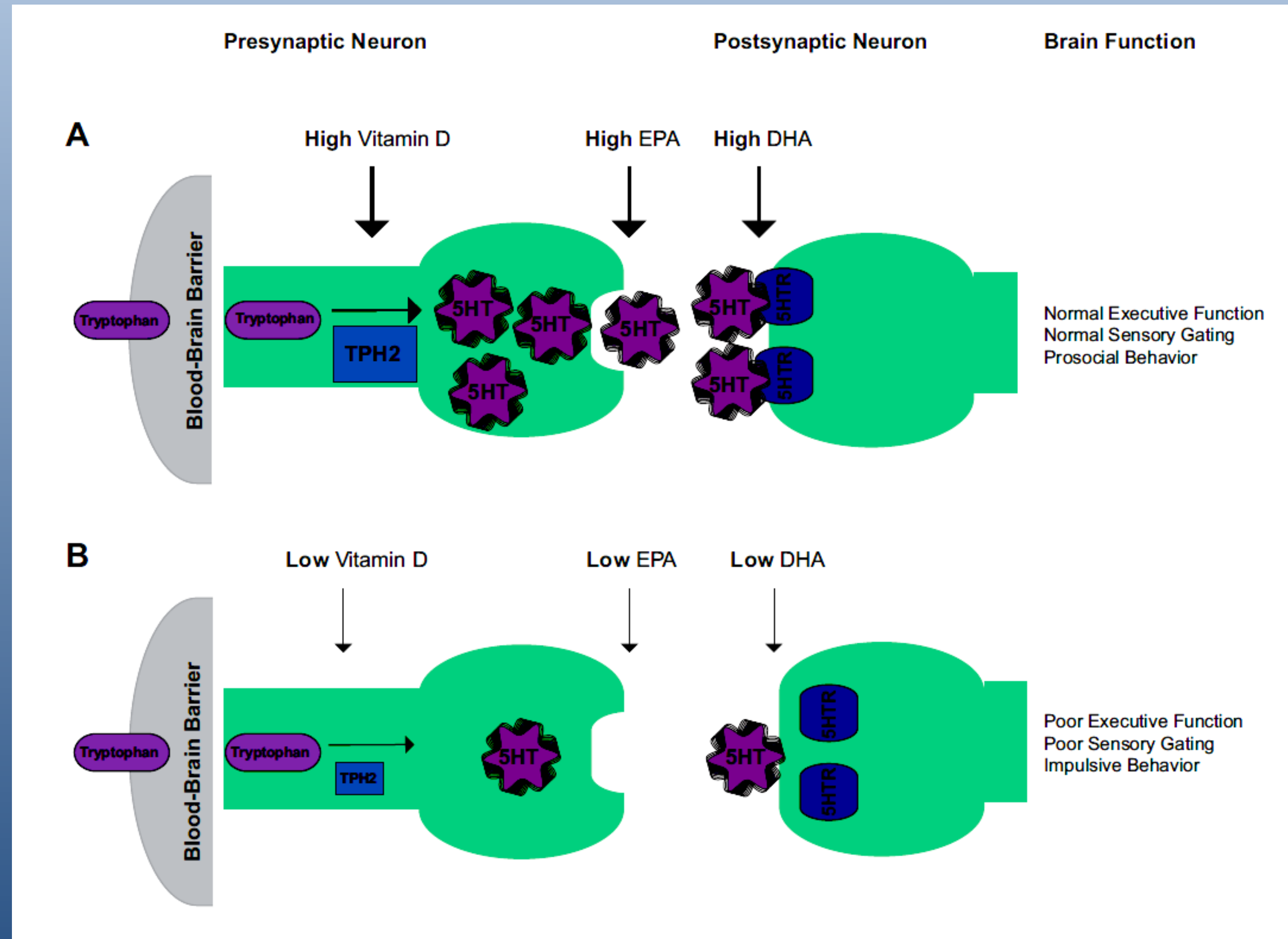
NI Disrupts Tryptophan (TRP) Metabolism

Peripheral cytokines imbalance brain TRP metabolism

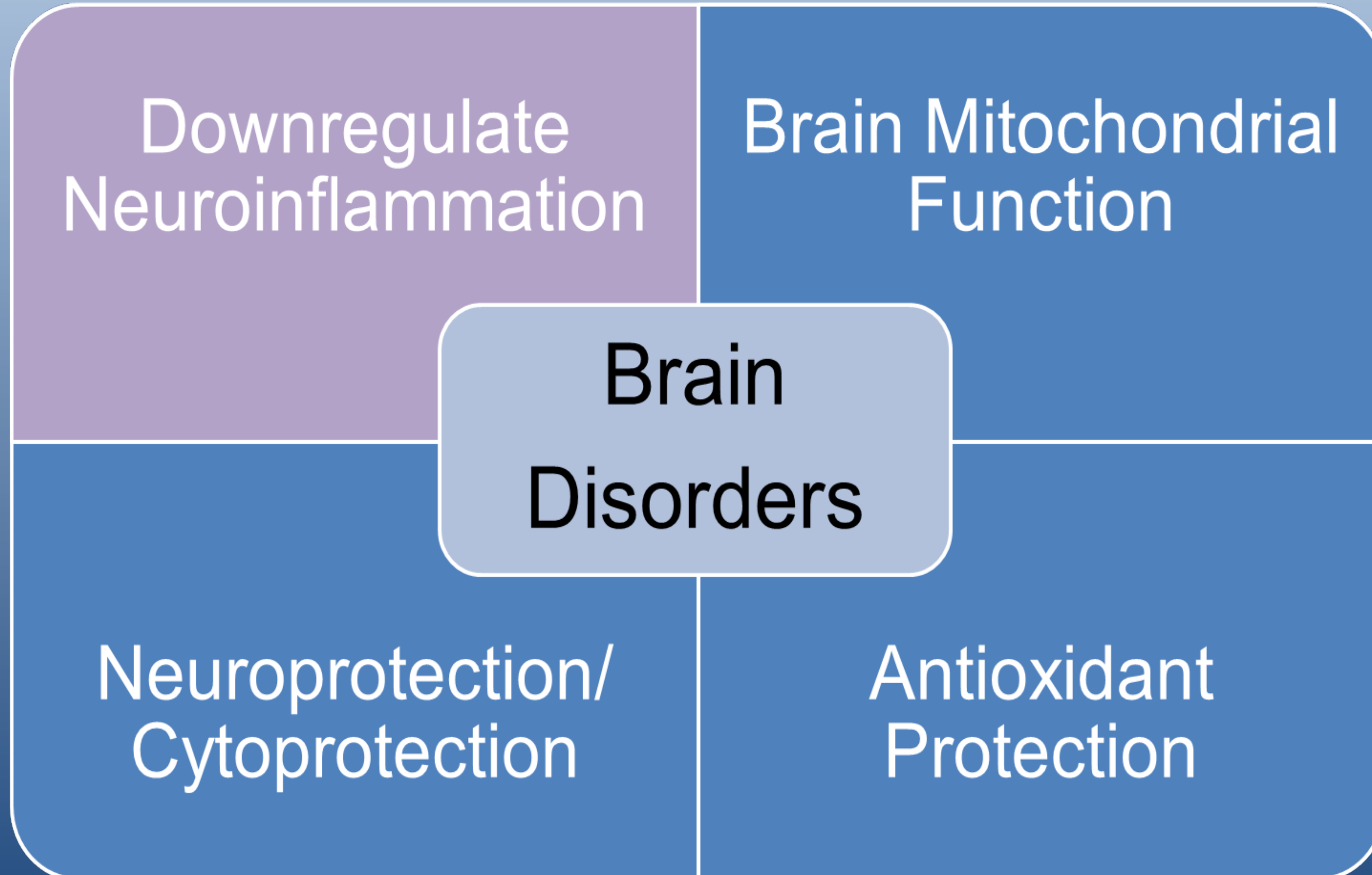
KYNA = kynurenic acid



Nutrient Deficiencies Fan the Flame



Core Support Strategy

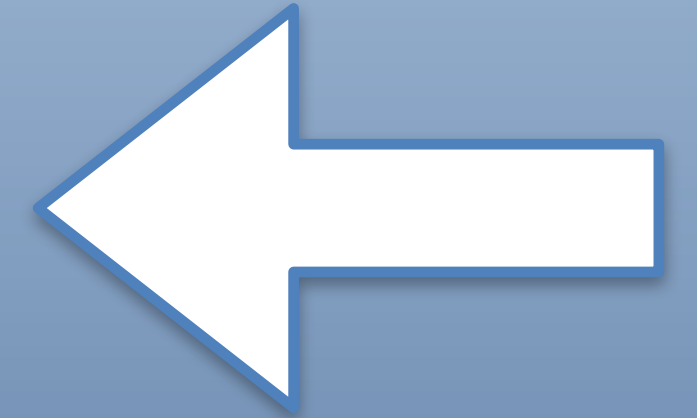
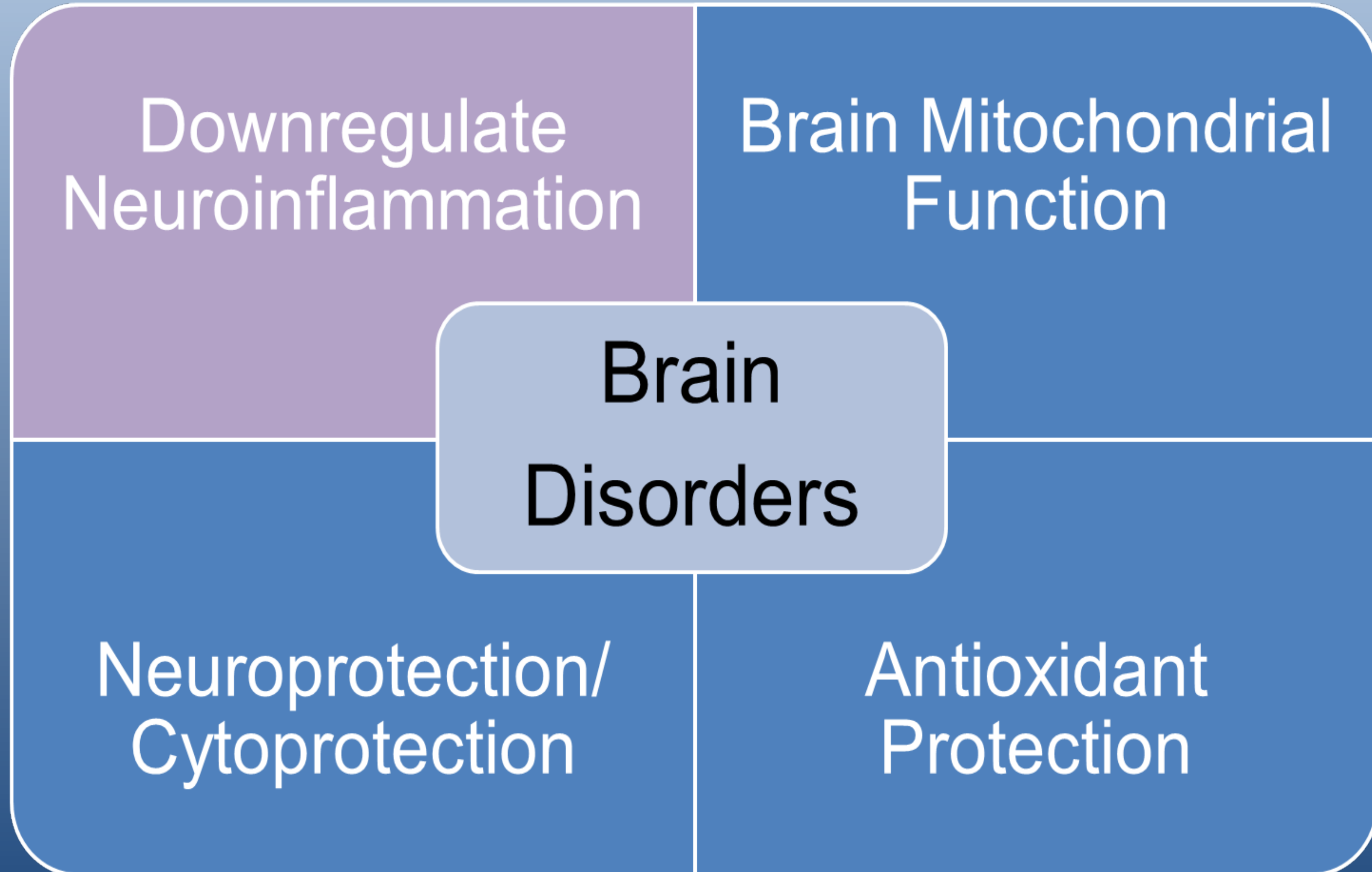


Switching off NI

- ↓ Brain inflammation: **Boswellia, Turmeric and omega-3 fatty acids**
- ↓ Systemic inflammation and its drivers especially:
 - Dysbiosis: GI Flora Balance Protocol
 - Stealth pathogens
 - Detoxification
 - HPA axis support: adrenal tonics, adaptogens

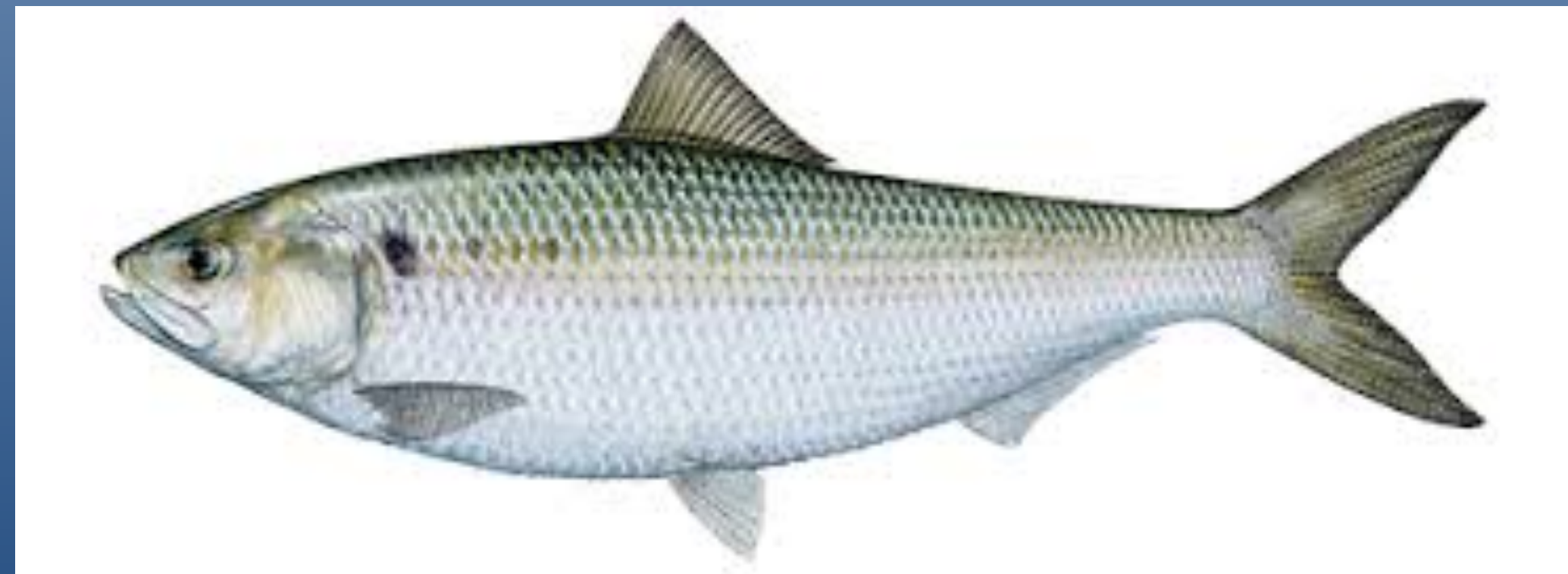


Core Support Strategy

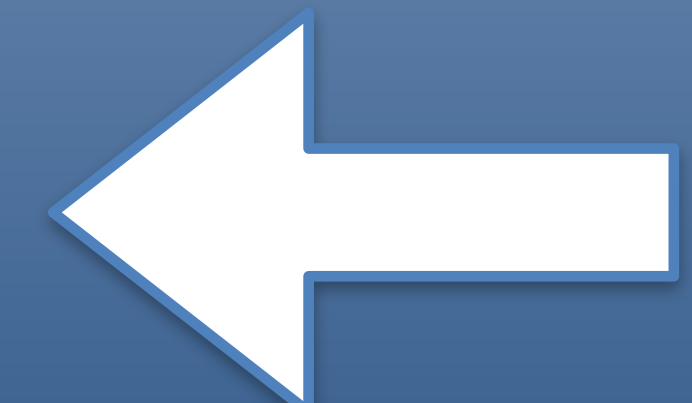
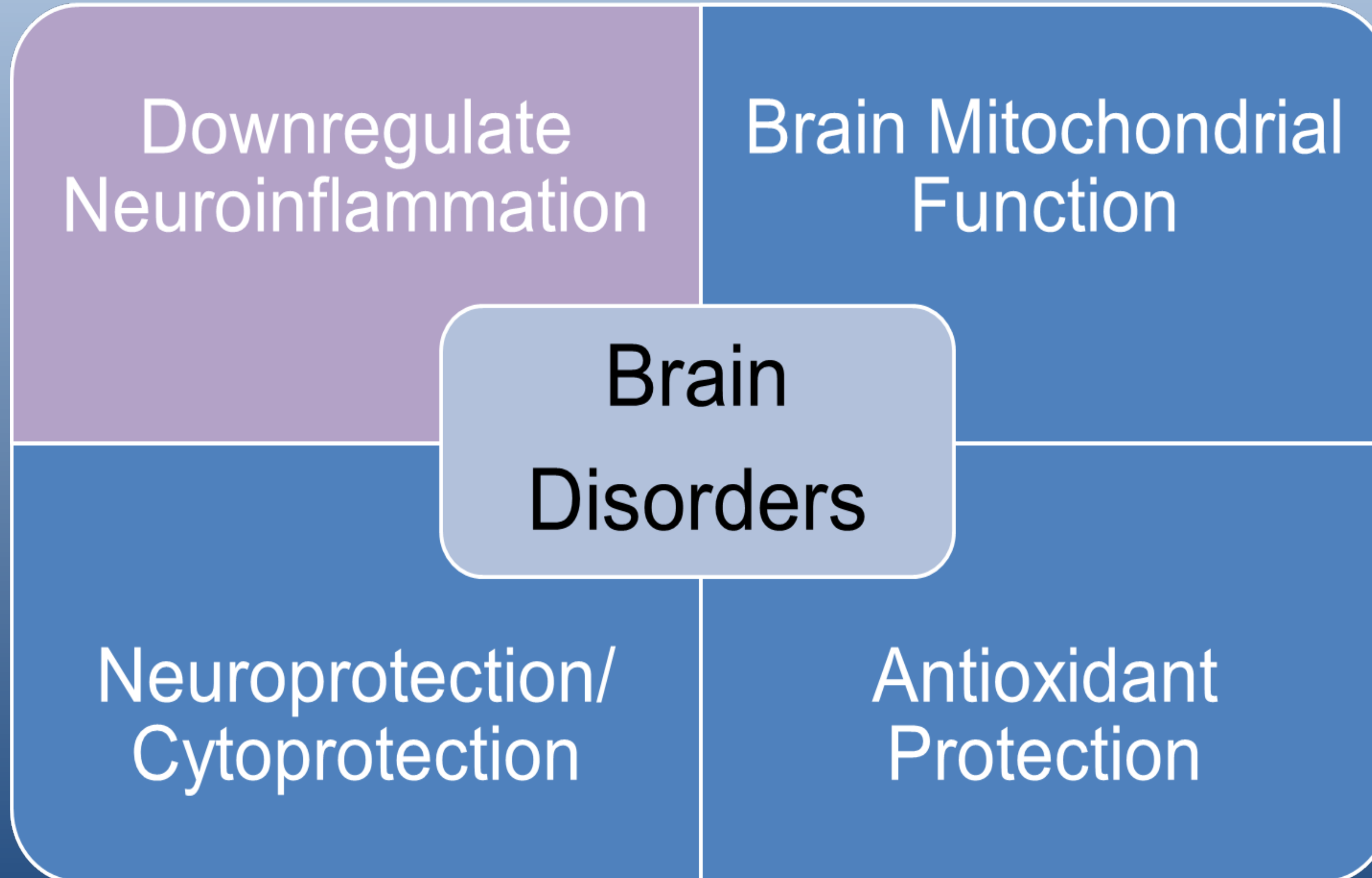


↑ Brain Mitochondrial Function

- Magnesium
- Omega-3 fatty acids
- Vitamin B co-factors (including B6, folate, B12)
- Medium chain fatty acids (MCFA), eg coconut oil
- Key herbs: Hawthorn, Polygonum (resveratrol) and Ginkgo
- Other Nrf2 herbs



Core Support Strategy

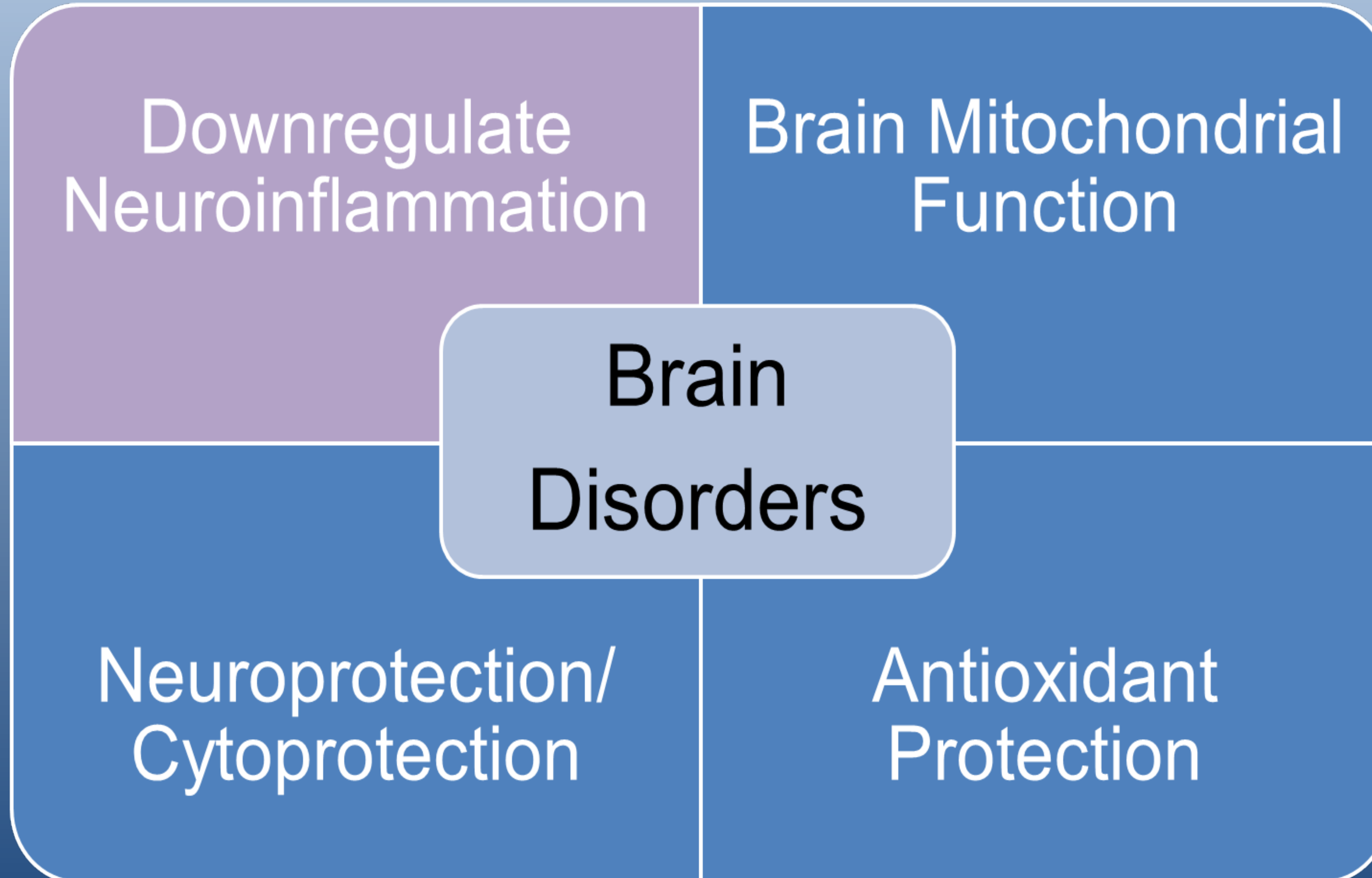


↑ Antioxidant Protection

- Key Nrf2 herbs: Ginkgo, Turmeric, Rosemary, Green Tea, Garlic , Grape Seed, Schisandra
- Whey



Core Support Strategy



↑ Neuroprotection/ Cytoprotection

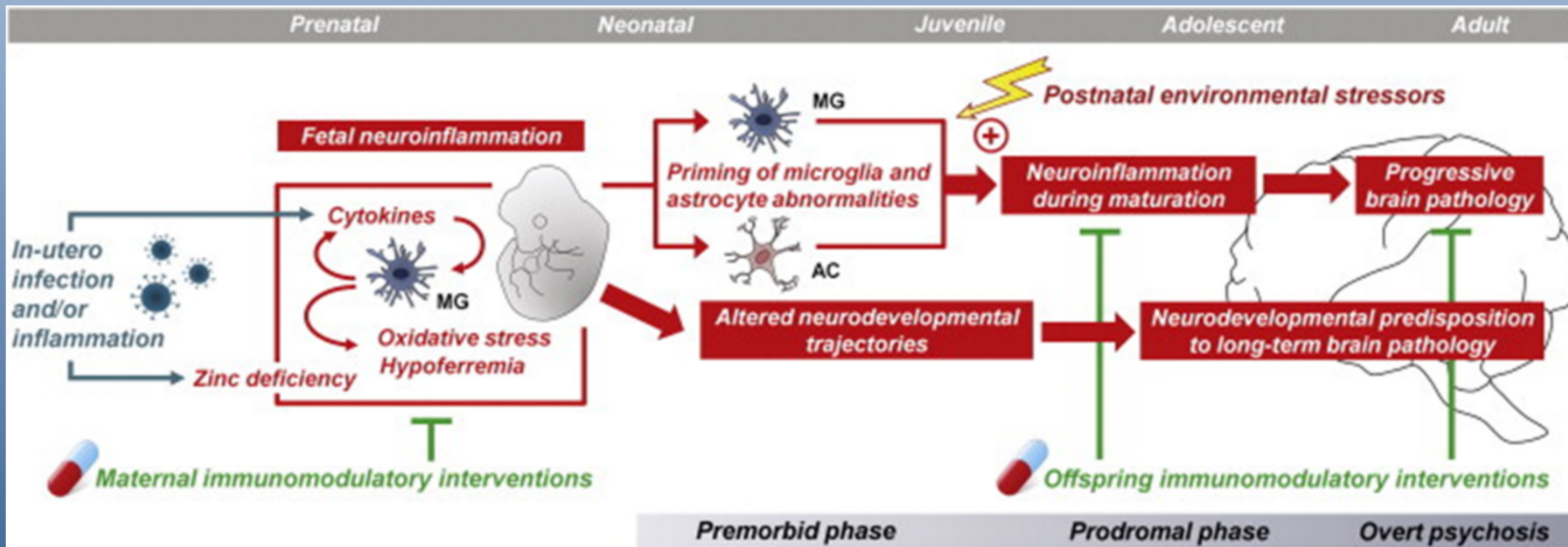
- Key neuroprotective herbs: Ginkgo and Saffron; and nutrients: B12
- ↓ O & NS via Nrf2 herbs: Ginkgo, Turmeric, Rosemary, Green Tea etc
- ↑ Heat shock proteins: adaptogens?, Echinacea root?
- ↑ SIRT1: Polygonum (resveratrol)
- ↑ Microcirculation protection: Gotu Kola, Grape Seed, Ginkgo and 5-Point Dietary Plan

NI in Complex Brain Disorders

| Abnormalities | Depression and Stress | Bipolar disorder | Schizophrenia | Autism | Reference |
|------------------------|--|------------------------------------|--------------------------------------|----------------|--|
| Astrocyte Density | ↓ | ↓ | ↓ | - | Steiner et al. (2009), Correa et al. (2011), Diz-Chaves et al. (2012) |
| Microglial Activation | ↑ | ↑ | ↑ | ↑ | Tetreault et al. (2012), Morgan et al (2012), Suzuki et al. (2013), Haarman et al. (2014), Torres-Platas et al. (2014) |
| Inflammatory Mediators | ↑IL-6, IL-8, IL-12, IFN- γ , IL-1 β and TNF- α | ↑IL-1 β and IL-1 receptor | ↑IL-1 β , IL6 and TGF- β | ↑ IL-1 β | Young et al. (2011), Miller et al. (2011), Schiepers et al. (2005), O'Brien et al. (2007), Rao et al. (2010), Reus et al. 2013b) |
| Microglial Stimulators | ↑ Lba1 | ↑[11c]-(R)-PK11195, iNOS and c-fos | ↑ iNOS and DAMPs | - | Ribeiro et al. (2013), Haarman et al. (2014), Rao et al. (2010), Diz-Chaves et al. (2012) |

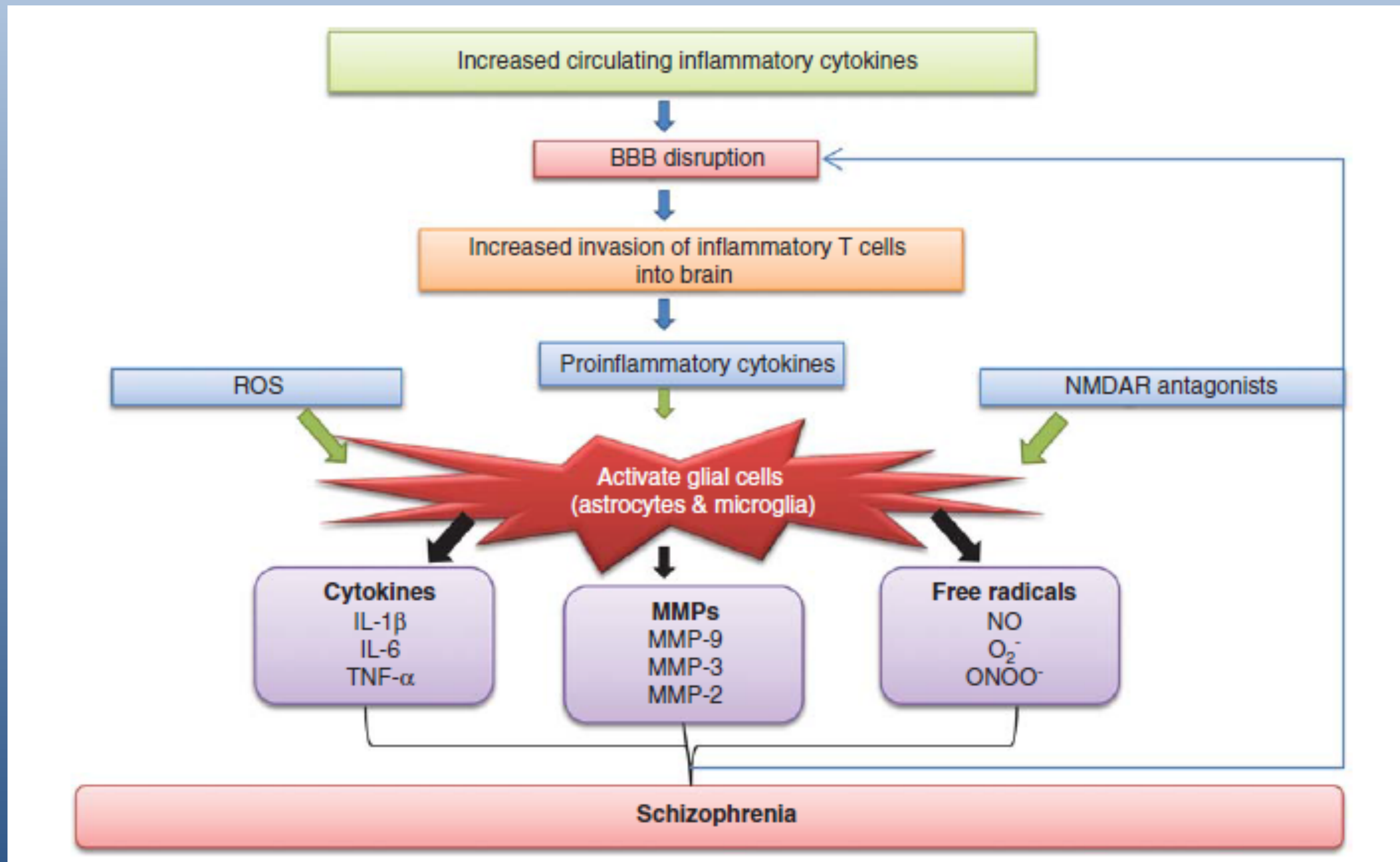
Réus GZ, Fries GR, Stertz L et al. *Neuroscience* 2015; **300**: 141-54. PMID:25981208.

Schizophrenia as NI



Meyer U. *Neuropsychopharmacol Biol Psychiatry* 2013; 42: 20-34. PMID: 22122877

Schizophrenia as NI

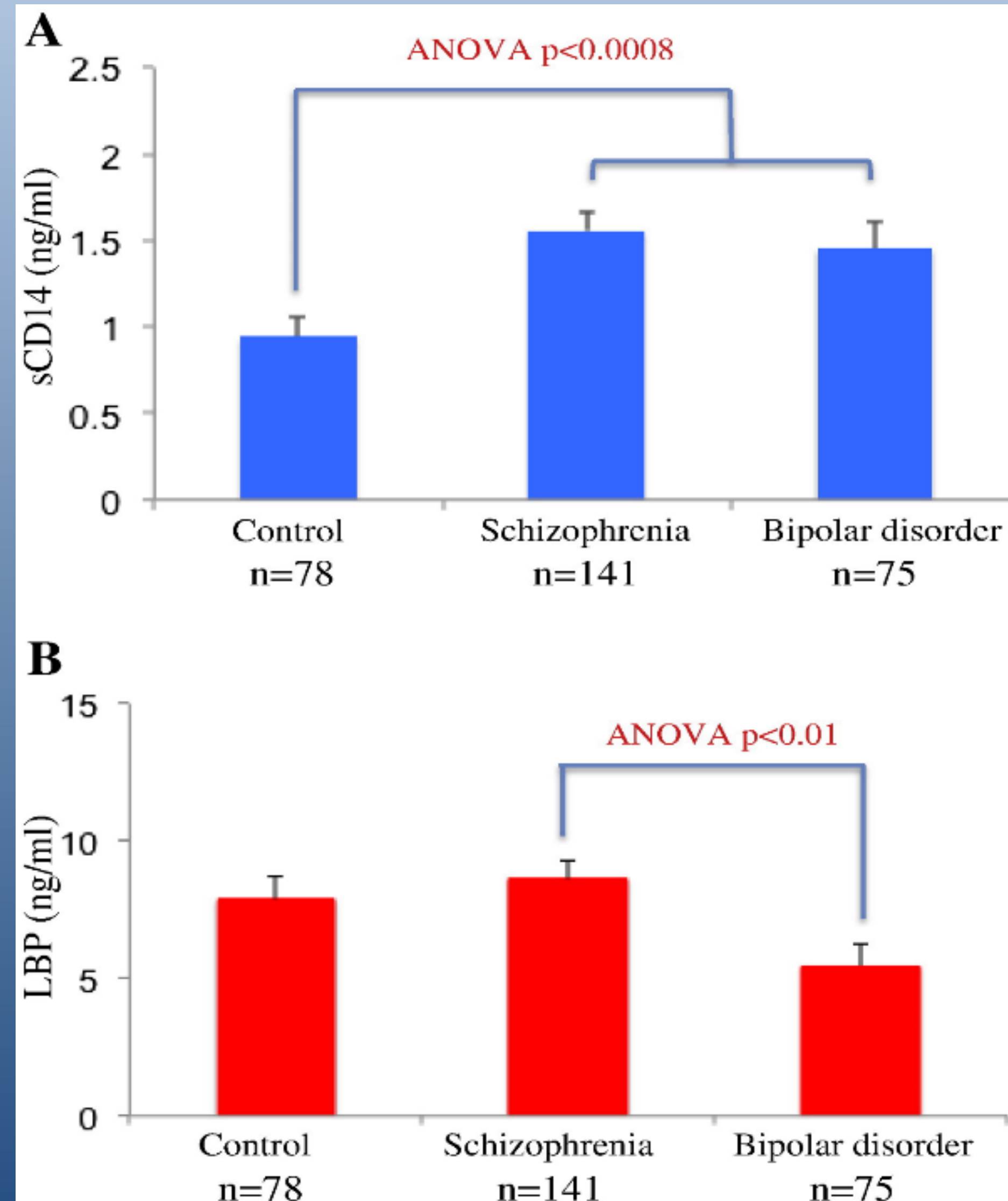


Chopra K, Baveja A, Kuhad A. *Expert Opin Ther Targets* 2015; **19**(1): 77-85.
PMID: 25214056

Schizophrenia and the Gut

Evidence for bacterial translocation

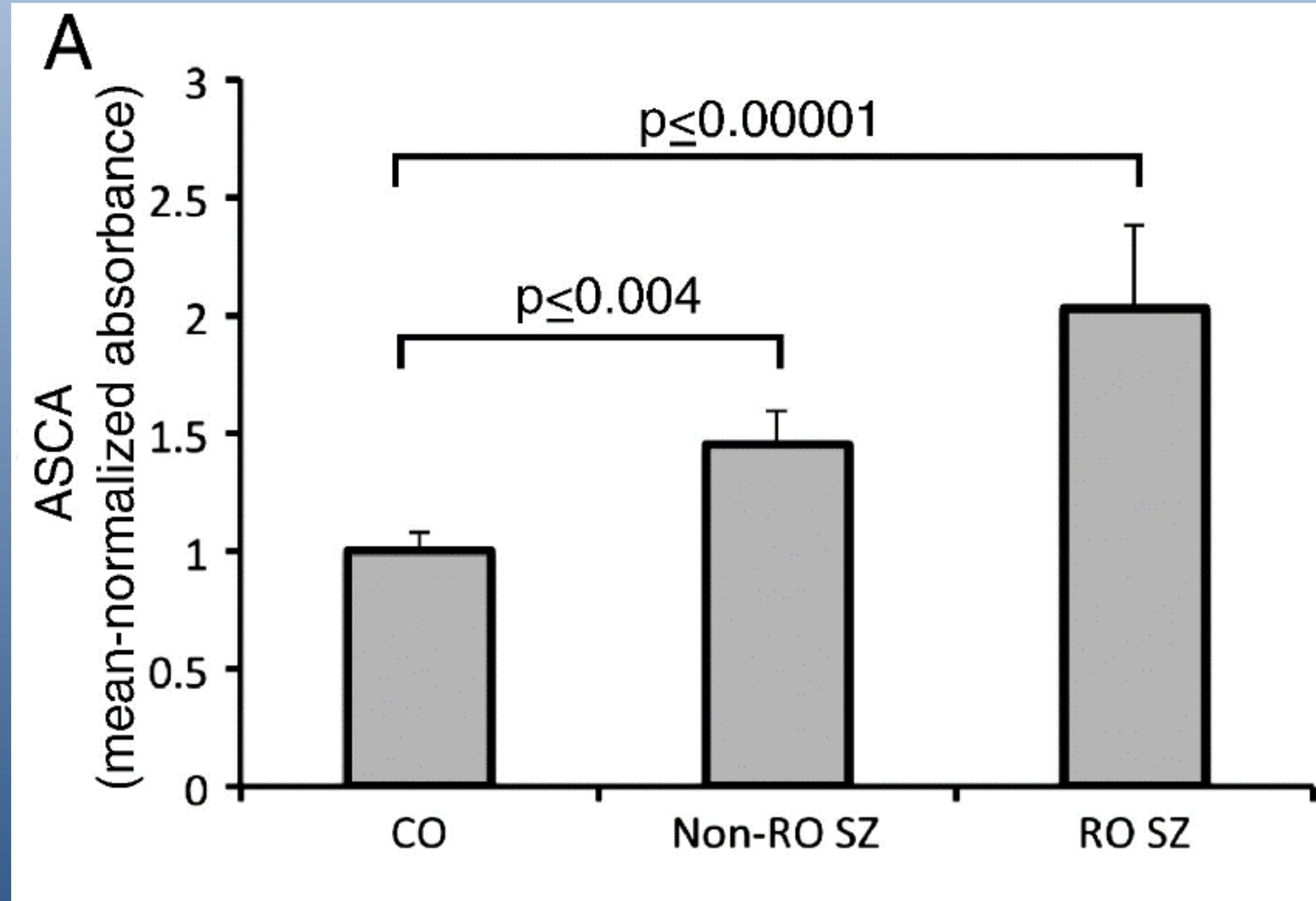
Severance EG, Gressitt KL, Stallings CR et al. *Schizophr Res* 2013; **148**(1-3): 130-137.
PMID: 23746484



Schizophrenia and the Gut

Evidence for a leaky gut

ASCA = antibodies against dietary yeast

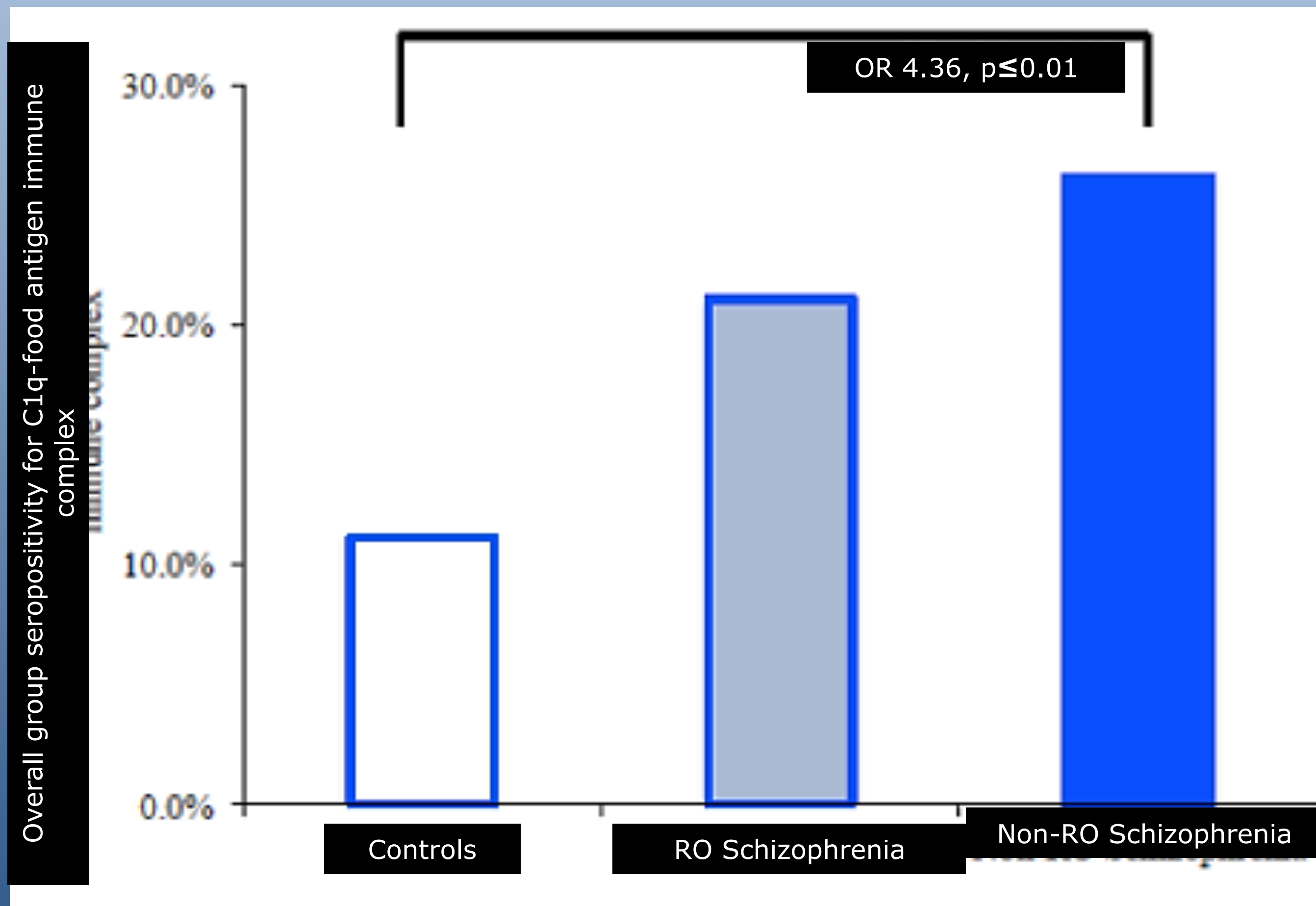


Severance EG, Alaedini A, Yang S et al. *Schizophr Res* 2012; **138**(1): 48-53.
PMID: 22446142

Schizophrenia and the Gut

Evidence for food protein reactions

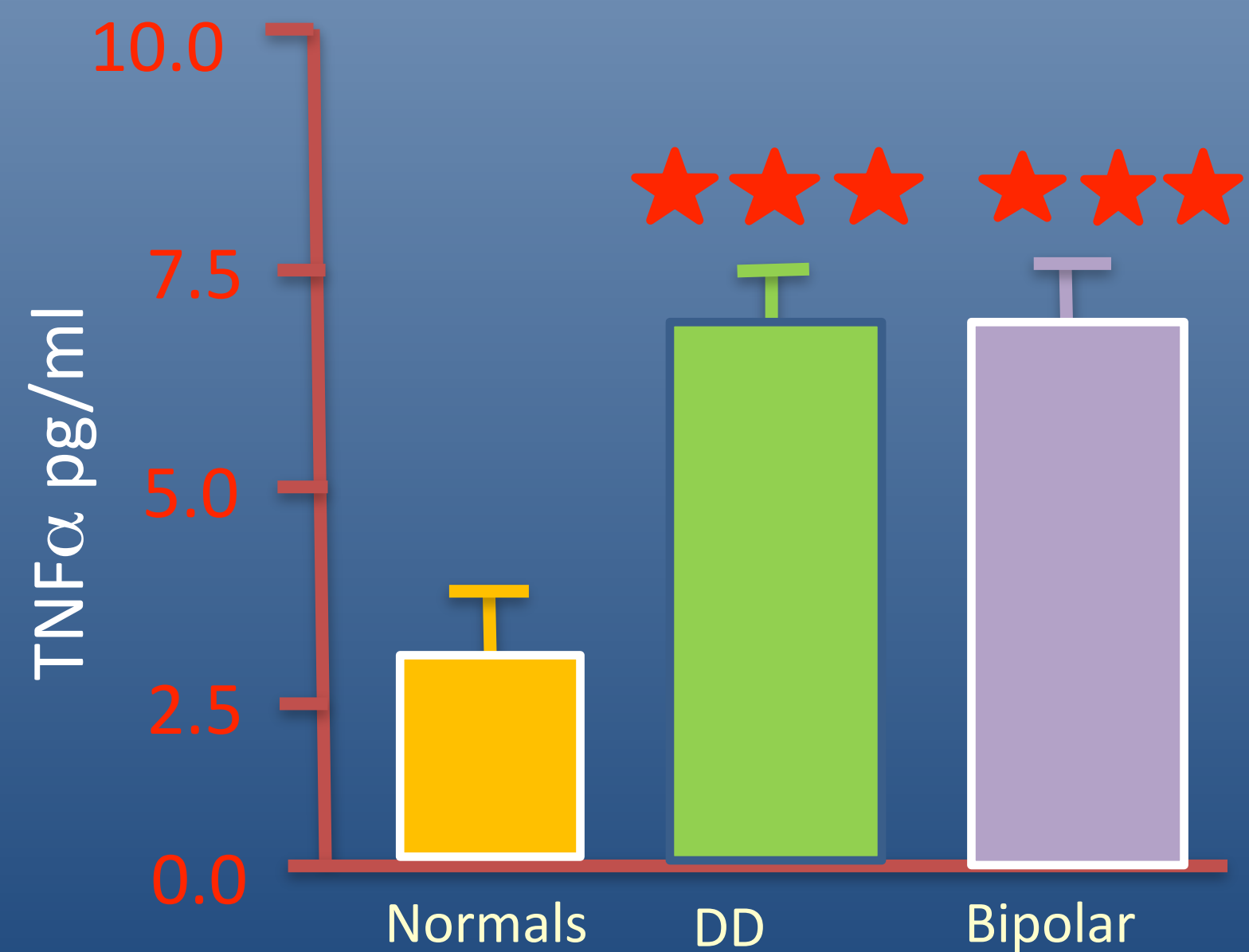
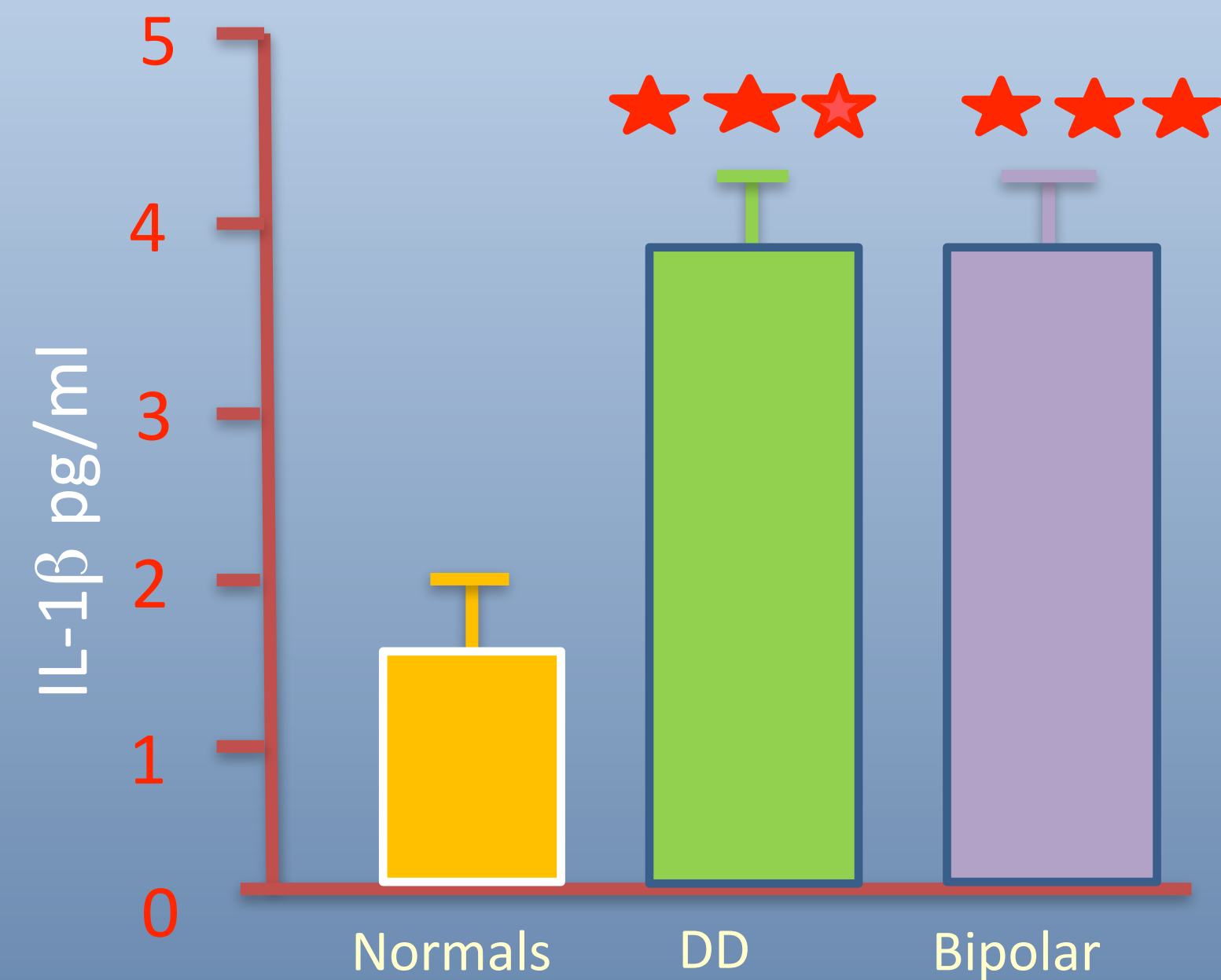
RO refers to recent onset
OR refers to odds ratio
C1q is a complement protein



Depression and Cytokines

DD =
Depressive
Disorder

Jones KA, Thomsen C. *Mol Cell Neurosci* 2013; **53**:
52-62 PMID 23064447



Toxins and Autism

Key issues are:

- Heavy metals
- Pesticides and other chemicals
- Reduced defenses: methylation, sulfation, glutathione, mitochondrial function
- Dysbiosis → toxicity



Reduced Toxin Defences in Autism

- Significantly decreased plasma levels of reduced glutathione (GSH), sulfate and cysteine¹ and S-adenosylmethionine (SAMe)²
- Several recent studies: children with autism have **abnormal sulfation** chemistry, limited thiol availability and decreased GSH reserve capacity^{2,3,4}

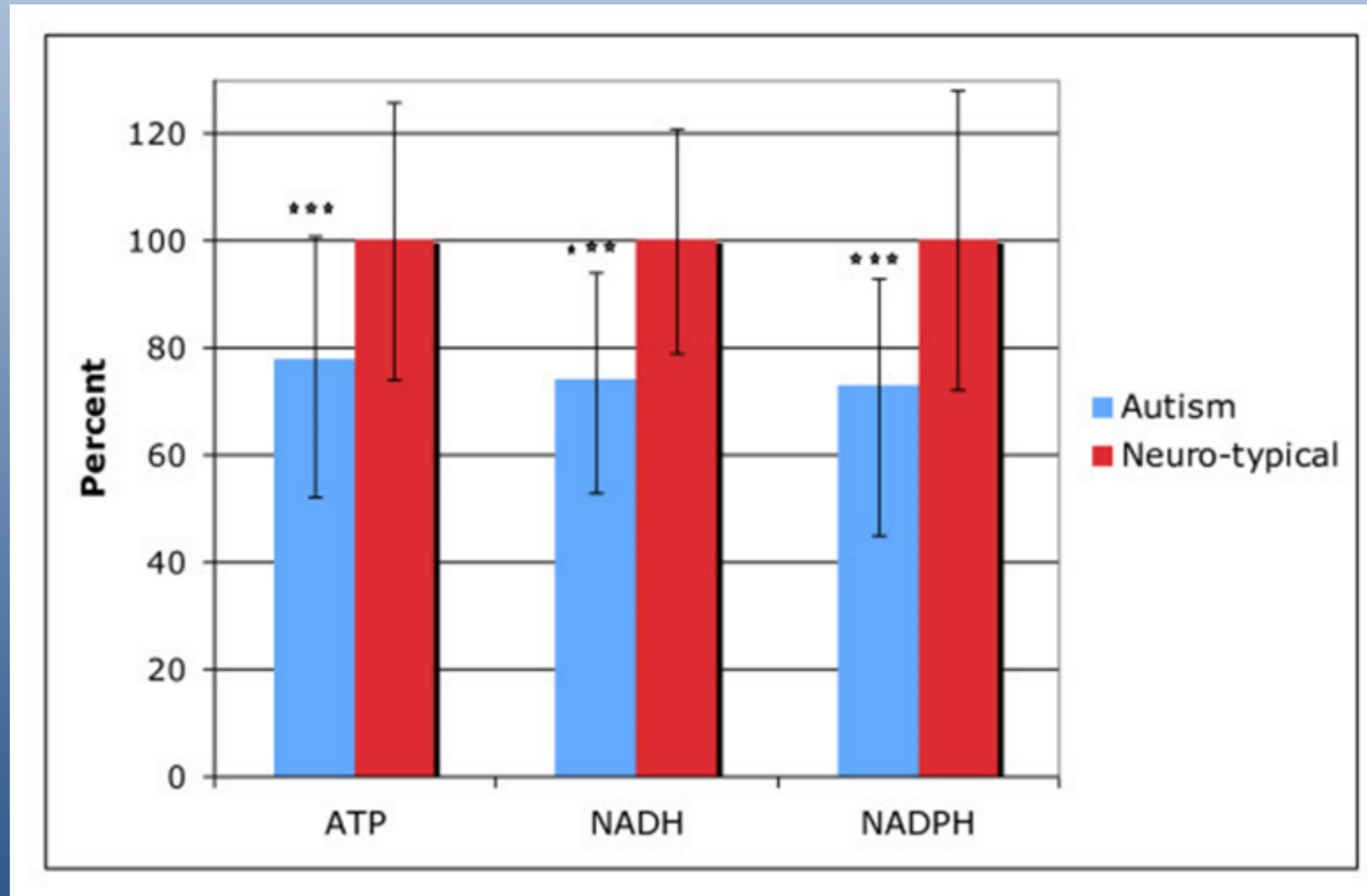
1. Geier DA, Kern JK, Garver CR et al. *J Neurol Sci* 2009; **280**(1-2): 101-108. PMID: 18817931

2. Adams JB, Audhya T, McDonough-Means S et al. *Nutr Metab (Lond)* 2011; **8**(1): 34. PMID: 21651783

3. Kern JK, Haley BE, Geier DA et al. *Int J Environ Res Public Health* 2013; **10**(8):3771-3800. PMID: 23965928

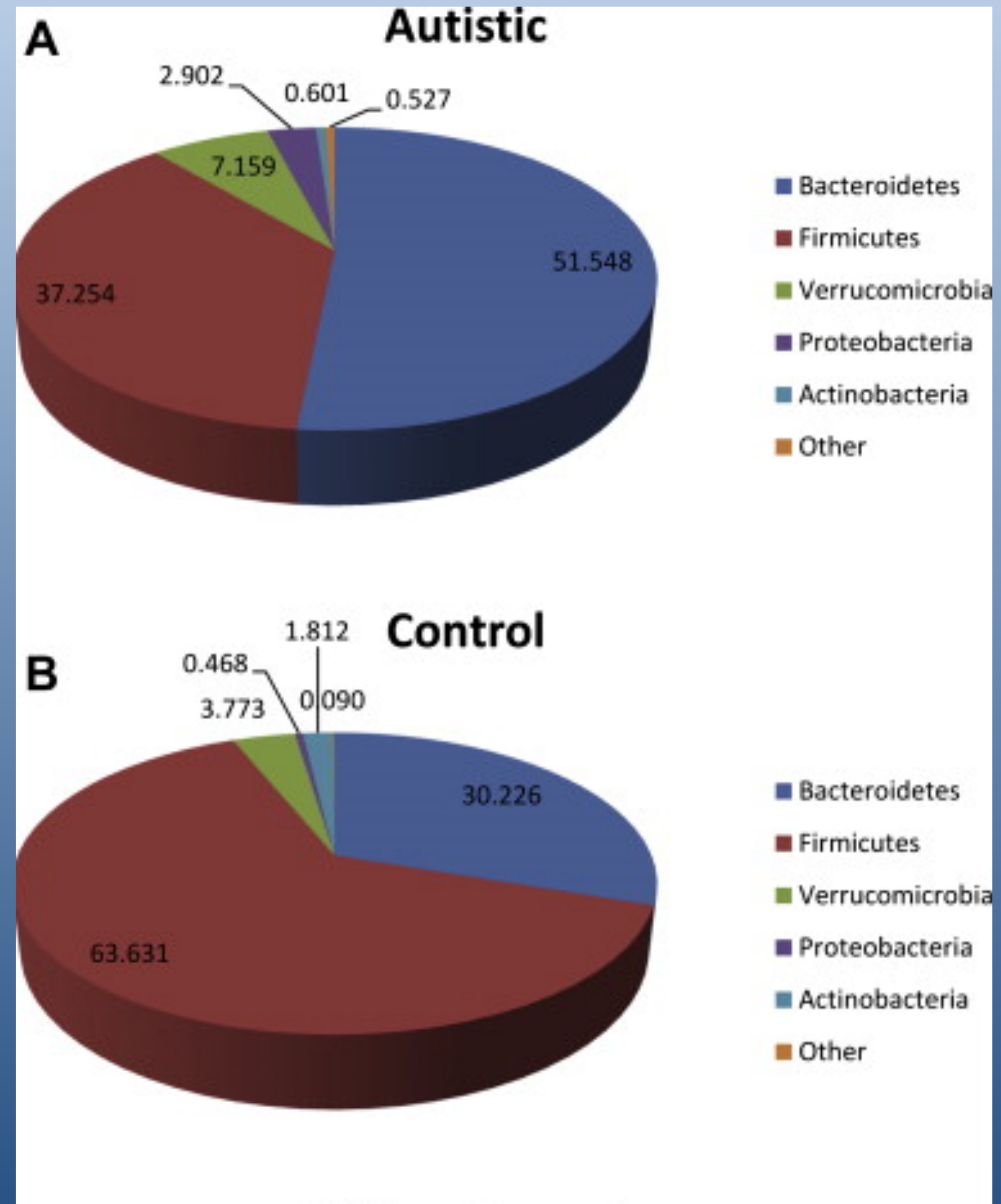
4. Esparham AE, Smith T, Belmont JM et al. *Integr Med (Encinitas)* 2015; **14**(2): 40-53. PMID: 26770138

Mitochondrial Dysfunction in Autism



Adams JB, Audhya T, McDonough-Means S et al. *Nutr Metab (Lond)* 2011; **8**(1): 34. PMID: 21651783

The Autism Microbiome



Finegold SM, Dowd SE, Gontcharova V et al. *Anaerobe* 2010; **16**(4): 444-453. PMID: 20603222

Autism: A Natural Overview

- Address the 3 key metabolic impairments: methylation, transulfuration and mitochondrial dysfunction¹
- Address sympathetic dominance¹
- Boost detoxification pathways
- Address neuroinflammation and its drivers
- Support a healthier microbiome

1. Mumper E, Bedell Cook S. <http://www.naturalmedicinejournal.com/journal/2015-02/metabolic-considerations-autism-spectrum-disorder>. Accessed 20/04/2016

Autism: Herb Summary

- Nrf2 activator herbs for detoxification (see later)
- Sleep herbs as needed (see later)
- GI Flora Balance Protocol
- Boswellia/Turmeric (NI)
- Ginkgo/Hawthorn (mitochondria)
- Other drivers of NI via SI

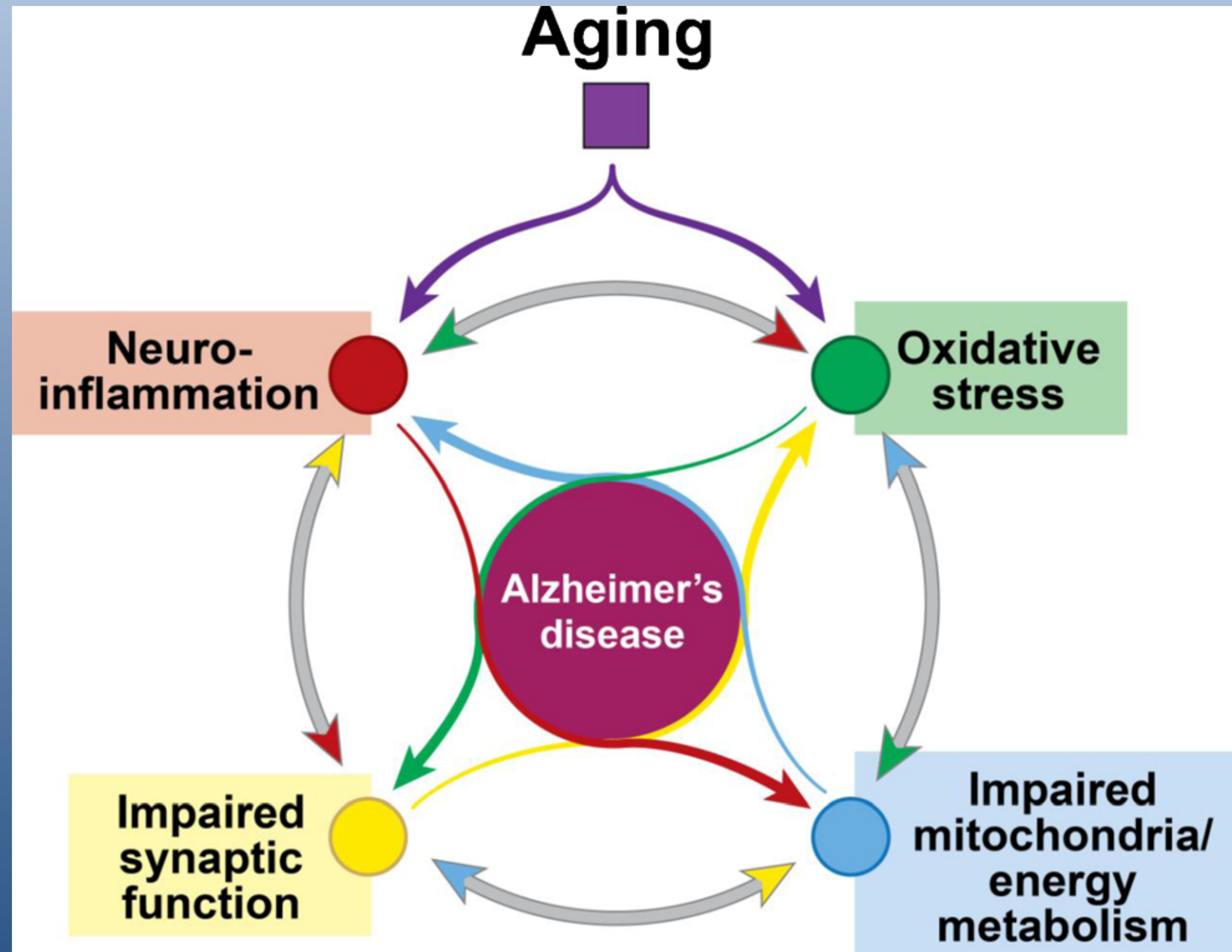


Autism: Practical Support

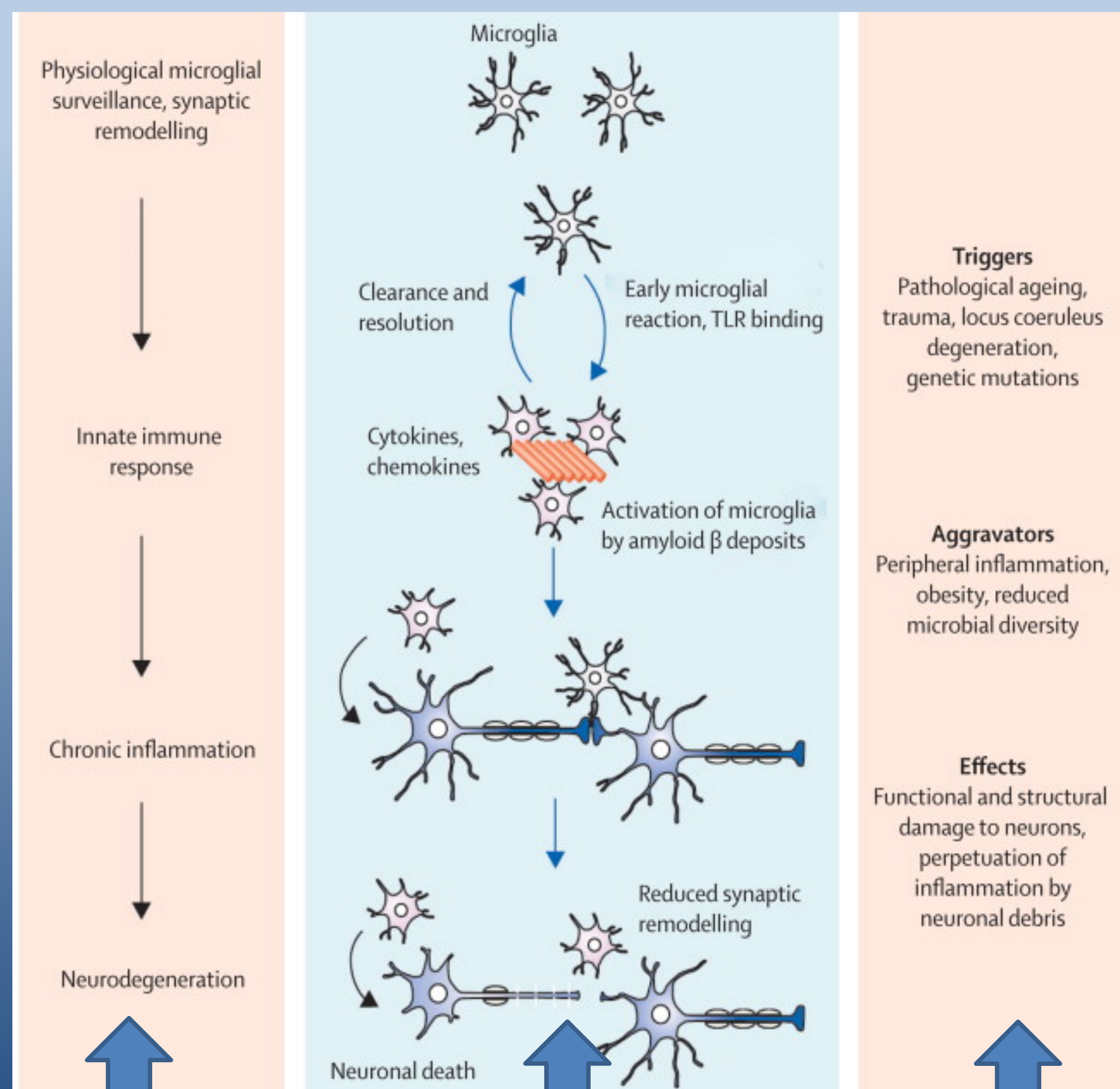
- Vitanox 2/day
- Sleep herbs as needed (see later)
- GI Flora Balance Protocol
- Turmeric Forte 4/day (NI)
- Other drivers of NI via SI



Neuroinflammation (NI) and Alzheimer's (AD)



NI and AD



Heneka MT, Carson MJ, El Khoury et al. *Lancet Neurol.* 2015; **14**(4):388-405. PMID 2592098

AD: Herb Summary

- Bacopa/Saffron/Gotu Kola
- Boswellia/Turmeric (NI)
- Ginkgo/Hawthorn
- Other Nrf2 herbs,
especially Rosemary
- Adaptogens and nervine
tonics (eg Schisandra,
Rhodiola, St John's Wort)
- 5-Point Microcirculation Phytonutrient Protocol
- Other drivers of NI via SI



AD: Practical Support

- Bacopa Complex 3/day
- **Turmeric Forte 4/day (NI)**
- **Vitanox 2/day**
- Nevaton Forte 3/day
- 5-Point Microcirculation Phytonutrient
- Other drivers of NI via SI



The 5-Point Microcirculation Phytonutrient Protocol

📁 📄 Boost dietary nitrate - beets

📄 📄 Increase cocoa intake

















📄 📄 Increase berry
anthocyanin intake

📄 📄 Raw crushed garlic:
½ to 1 clove/day

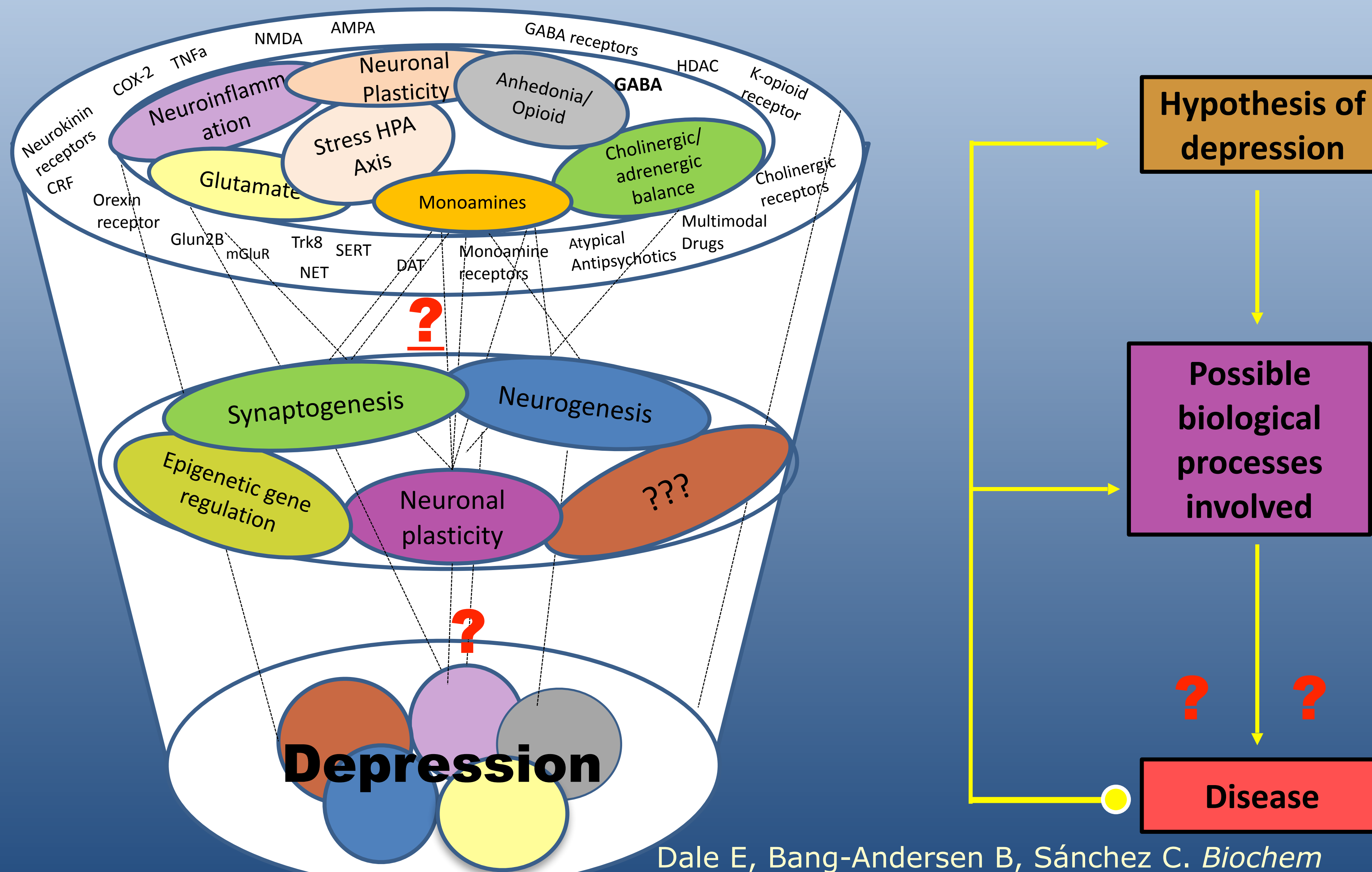
📄 📄 Increase herbs and spices: green tea, turmeric and
ginger



Major Depression

-   Depressed mood most of the day
-   Anhedonia
-   Appetite changes or significant weight loss or gain
-   Difficulty sleeping nearly every day
-   Psychomotor agitation or difficulty
-   Fatigue or loss of energy
-   Feelings of worthlessness or guilt
-   Diminished ability to think or concentrate or indecisiveness

What Leads to Depression?



Key Features of Depression

- 📁 📁 HPA axis dysregulation
- 📄 📁 Neuroinflammation (NI)
- 📄 📁 Tryptophan depletion and resultant neurotransmitter imbalance



Natural Solutions for Depression

- Lifestyle
- Herbs and nutrients
- Supporting sleep in depression
- Treating depression as NI, including mitochondrial support





- PDFs
- DATASETS
- INFOGRAPHICS
- AUDIO/VIDEO




BMJ. 2016; 352: i65.

PMCID: PMC4729837

Published online 2016 Jan 27. doi: [10.1136/bmj.i65](https://doi.org/10.1136/bmj.i65)

PMID: [26819231](https://pubmed.ncbi.nlm.nih.gov/26819231/)

Suicidality and aggression during antidepressant treatment: systematic review and meta-analyses based on clinical study reports

Tarang Sharma, student,^{1,2} Louise Schow Guski, student,^{1,2} Nanna Freund, medical student,^{1,2} and Peter C Gøtzsche, professor^{1,2}

▶ Author information ▶ Article notes ▶ Copyright and License information [Disclaimer](#)

This article has been [cited by](#) other articles in PMC.

Associated Data

▶ Supplementary Materials

Abstract

Go to: 

Objective To study serious harms associated with selective serotonin and serotonin-norepinephrine reuptake inhibitors.

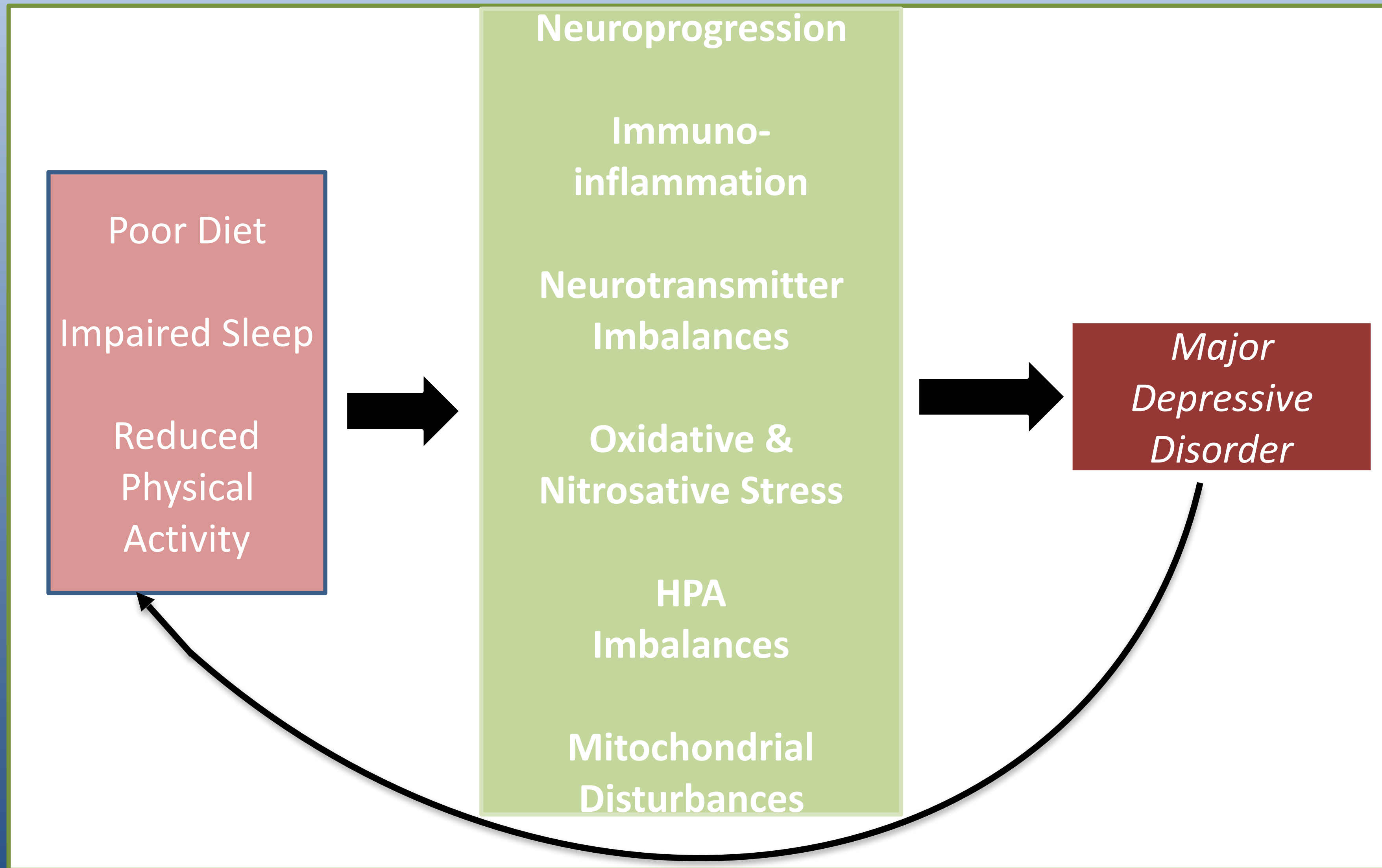
Design Systematic review and meta-analysis.

Main outcome measures Mortality and suicidality. Secondary outcomes were aggressive behaviour and akathisia.

“Therefore we suggest minimal use of antidepressants in children, adolescents, and young adults, as the serious harms seem to be greater, and as their effect seems to be below what is clinically relevant.^{4 45 46 47} Alternative treatments such as exercise^{48 49} or psychotherapy^{4 50} may have some benefit and could be considered...”⁵¹



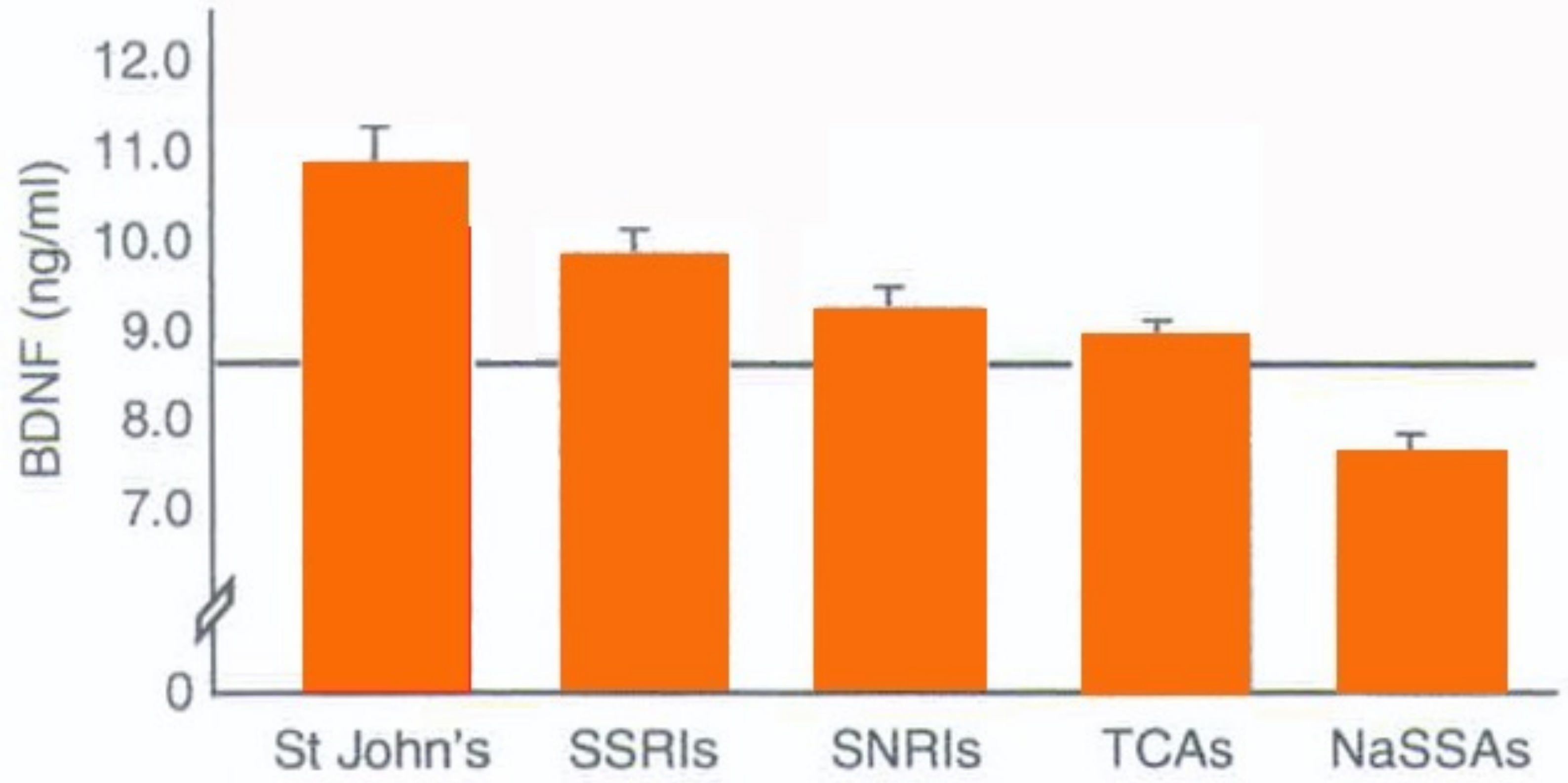
Lifestyle and Depression



Depression: Key Herbs

- Gold standard evidence for **St John's Wort**
- Other key herbs: **Saffron, Rhodiola and Kava**
- Address NI drivers
- ↑ Nrf2, sleep quality and additional mitochondrial support as per the case





Saffron and Depression

- Systematic review of Saffron (30 mg/day extract) in depression: 6 studies, concluded evidence was positive¹
- Since then, Saffron (30 mg/day extract) and fluoxetine (40 mg/day) were equivalent in 6-week RCT of 40 patients with moderate to severe depression, recently undergone a coronary procedure²

1. Lopresti AL, Drummond PD. *Hum Psychopharmacol* 2014; **29**(6): 517-527 PMID 25384672
2. Shahmansouri N, Farokhnia M, Abbasi SH et al. *J Affect Disord* 2014; **155**: 216-222 PMID 24289892

Saffron Mechanisms in Depression

- NMDA-R antagonism
- Antioxidant and anti-inflammatory
- Neuroprotective activity
- Monoamine neurotransmission \Rightarrow probably negligible effects



Bone K, MediHerb e-Monitor No.42, July 2012, P1

Lopresti AL, Drummond PD. *Hum Psychopharmacol* 2014; **29**(6): 517-527 PMID 25384672

Saffron and Alzheimers

- Saffron (30 mg/day stigma extract) versus donepezil (10 mg/day) in 54 patients with moderate AD ⇒ equal efficacy after 22 weeks¹
- More effective than placebo (same dose) in 46 AD patients over 16 weeks²
- Recently, saffron (same dose) versus memantine (20 mg/day) in 68 patients with moderate to severe AD ⇒ equal efficacy after 12 months³

1. Akhondzadeh S, Shafiee Sabet M, Harirchian MH et al. *Psychopharmacology (Berl)* 2010; **207**(4) :637-643

2. Akhondzadeh S, Sabet MS, Harirchian MH et al. *J Clin Pharm Ther* 2010; **35**(5): 581-588

3. Farokhnia M, Shafiee Sabet M, Iranpour N et al. *Hum Psychopharmacol* 2014; **29**(4): 351-359

Rhodiola and Depression

- 6-week RCT (n=99): two doses (340 or 680 mg/day extract) versus placebo ⇒ depression, insomnia and emotional instability all improved in both Rhodiola groups¹
- 12-week RCT (n=57): Rhodiola extract (340 mg/day) versus sertraline (50 mg/day) versus placebo ⇒ Rhodiola active but less than drug, but fewer side effects²

1. Darbinyan V, Aslanyan G, Amroyan E et al. *Nord J Psychiatry* 2007; **61**(5): 343-348. PMID: 17990195

2. Mao JJ, Xie SX, Zee et al. *J Phytomedicine* 2015; **22**(3): 394-399 PMID 25837277

The Kava Anxiety Depression Spectrum Study (KADSS): a randomized, placebo-controlled crossover trial using an aqueous extract of *Piper methysticum*

J. Sarris • D. J. Kavanagh • G. Byrne • K. M. Bone •
J. Adams • G. Deed

Anxiety Outcome

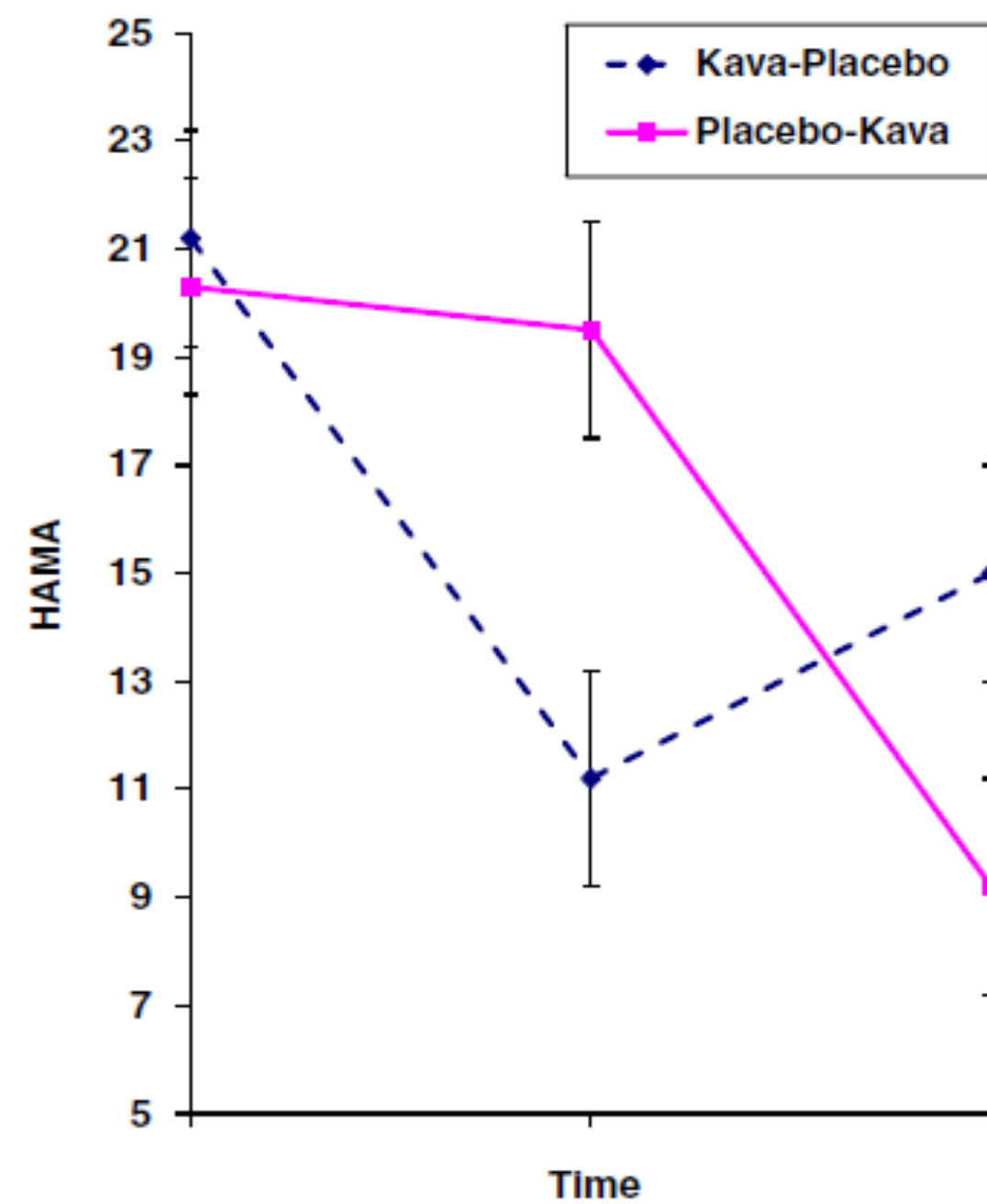


Fig. 2 Results on the Hamilton Anxiety Scale (HAMA)

Depression Outcome

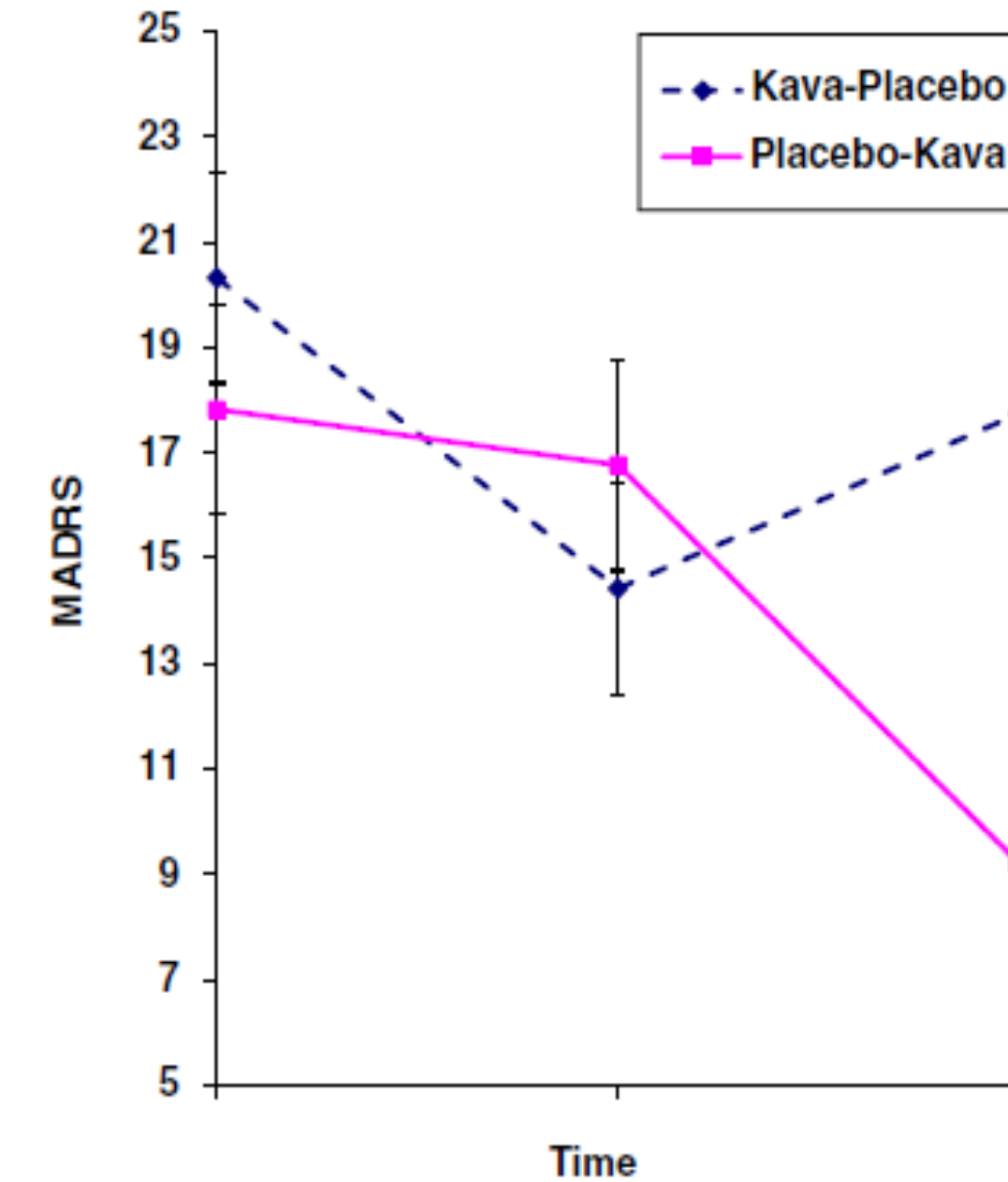


Fig. 4 Results on the Montgomery-Asberg Depression Rating Scale (MADRS)

Key Herbs for Healthy Sleep

Sleep Onset

- Valerian, Kava, Passion Flower, Spiny Jujube, Corydalis, Chaste Tree, Californian Poppy, Chamomile

▪ Sleep Maintenance

- St John's Wort, Chaste Tree, Valerian, Kava, Licorice and/or Rehmannia

▪ Restorative Sleep

- Withania, Rhodiola, Korean Ginseng, Licorice, Rehmannia

Key Herbs for Healthy Sleep- Practical

Sleep Onset

- Valerian Complex 6/day, Kava Forte 2 before bed, Chaste Tree Tablets 2 at 8pm, Nervagesic Complex 2-3 at bedtime

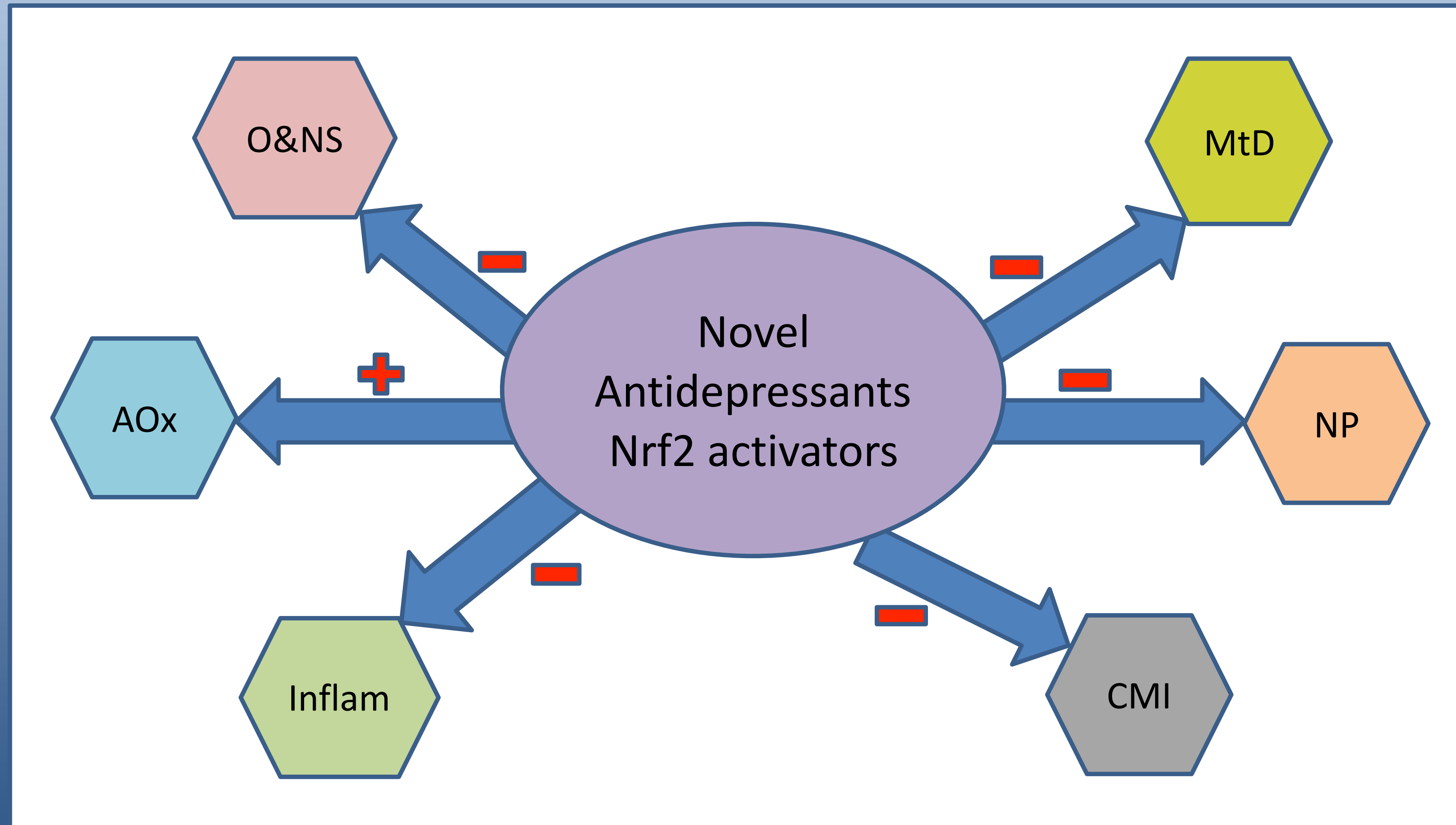
■ Sleep Maintenance

- St John's Wort 3/day, Chaste Tree 2 at 8pm, Valerian Complex 6/day, Adrenal Complex Tablets 3-4/day

■ Restorative Sleep

- Ashwaganda Complex 4/day, Rhodiola /Ginseng 3/day, Adrenal Complex Tablets 3-4/day

Treating Depression as NI



Key Nrf2 Activators

- Turmeric
- Rosemary
- Green tea
- Grape Seed
- Ginkgo
- Resveratrol
(Polygonum)
- Garlic



Key Nrf2 Activators-Practical

- Turmeric Forte 2-3/day
- Vitanox 3/day
- Garlic Forte 1-2/day



Switching off NI

- ↓ Systemic inflammation and its drivers
- ↓ Brain inflammation, eg Boswellia, Turmeric and omega-3 fatty acids



Support Mitochondrial Function

- Omega-3 fatty acids
- Medium chain fatty acids (MCFA), eg coconut oil
- Key herbs: Hawthorn, resveratrol (Polygonum) and Ginkgo
- Magnesium and B vitamins
- Other Nrf2 herbs



Depression: Herb Summary

- St John's Wort/Saffron
- Rhodiola
- Kava
- Sleep herbs as needed
- Boswellia/Turmeric (NI)
- Ginkgo/Hawthorn (mitochondria)
- Other Nrf2 herbs
- Other drivers of NI via SI



Depression: Herb- Practical

- Nevaton Forte 3-4/day
 - If anxiety present Kava might be helpful
- Rhodiola/Ginseng 3-4/day
- Sleep herbs as needed
- Turmeric Forte(NI)
- Ginkgo/ Forte 2-3/day
- Other Nrf2 herbs (Vitanox 2-3/day)
- Other drivers of NI via SI



Case History 1: Depression

- Male patient aged 36 complaining of low mood and anhedonia
- Sleep was good and recently started exercising
- Some anxiety, but improved now exercising
- Brain clarity good, but energy not
- Prescribed as tablets: Licorice, Rehmannia, St John's Wort, Rhodiola and Schisandra
- After 3 weeks: mood ↑ , energy ↑ , anxiety ↓
- After 9 weeks, ran out of herbs and noticed difference

Case History 2: Depression

- Female patient aged 63 years, long history (7 years) of antidepressant drug use (SSRIs, SNRIs)
- Was undergoing natural treatment for other issues when decided to discontinue her antidepressant medication (venlafaxine, SNRI)
- June 2015: started to taper off slowly, prescribed **Saffron**

Case History 2: Depression

- Early October 2015: completely off drug “not in a good place”: mood low, no energy, anxious, sleep disturbed.
- Added **Rhodiola and Schisandra** in tablet form at 3 per day
- Late October 2015: feels is just coping, also arthritis now very bad (currently on **Boswellia** herb combination tablet)
- Continue treatment

Case History 2: Depression

- November 2015: still struggling and feeling anxious. **Kava** at 2 tablets twice a day to replace Saffron, Rhodiola and Schisandra. Also added a probiotic
- Arthritis still bad so added **Willow Bark** tablets at 3 to 4 per day

Case History 2: Depression

- December 2015: much improved, mood good, sleep good, anxiety less, big reduction in joint pain
- Comments: 1) the value of **Kava** is demonstrated in this patient for her depression **comorbid** with anxiety
- 2) **Boswellia** in the joint combination and the probiotic would help NI (maybe even Willow Bark?)
- 3) **Willow Bark** can be a handy alternative for arthritic pain

Worked Case Study

- A female patient aged 74 years
- Recently diagnosed with early stages of AD (MMSE 22)
- Diagnosis confirmed by MRI, which also showed white matter hyperintensities
- Low mood present, which predated the AD diagnosis
- Generally had a good diet
- Outline your dietary and herbal recommendations for this woman
- How might this work in terms of products and doses?

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