Gut inflammation and Mental Health: The missing link?

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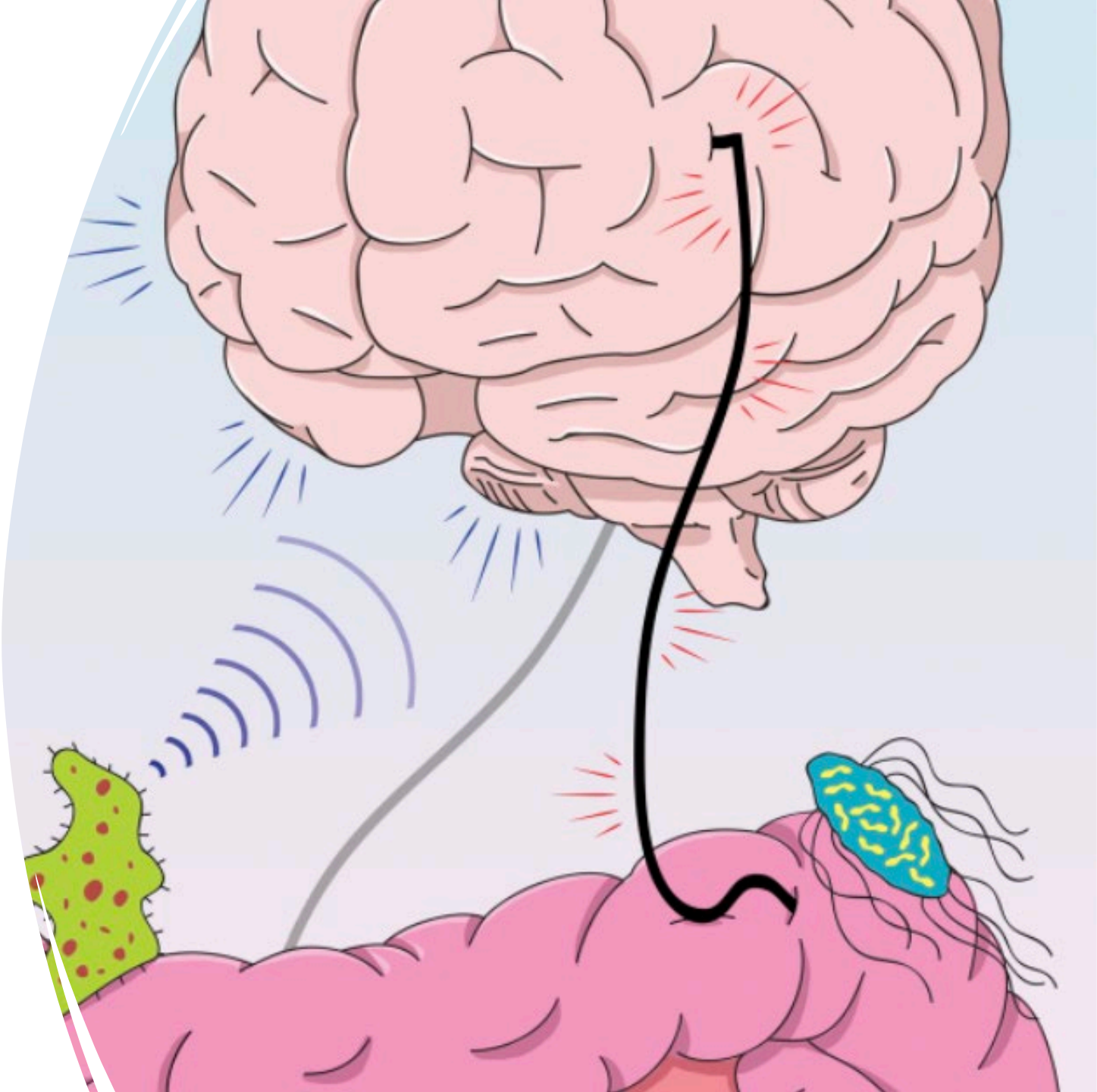

Objectives

- Examine the pathogenesis of mental illness in IBD
- Discuss how inflammation is linked to mental health
- Review the use of novel mental illness treatments in IBD

AUTOINTOXICATION
OR
INTESTINAL TOXEMIA

By

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Medical Director of the Battle Creek Sanitarium

BATTLE CREEK, MICHIGAN
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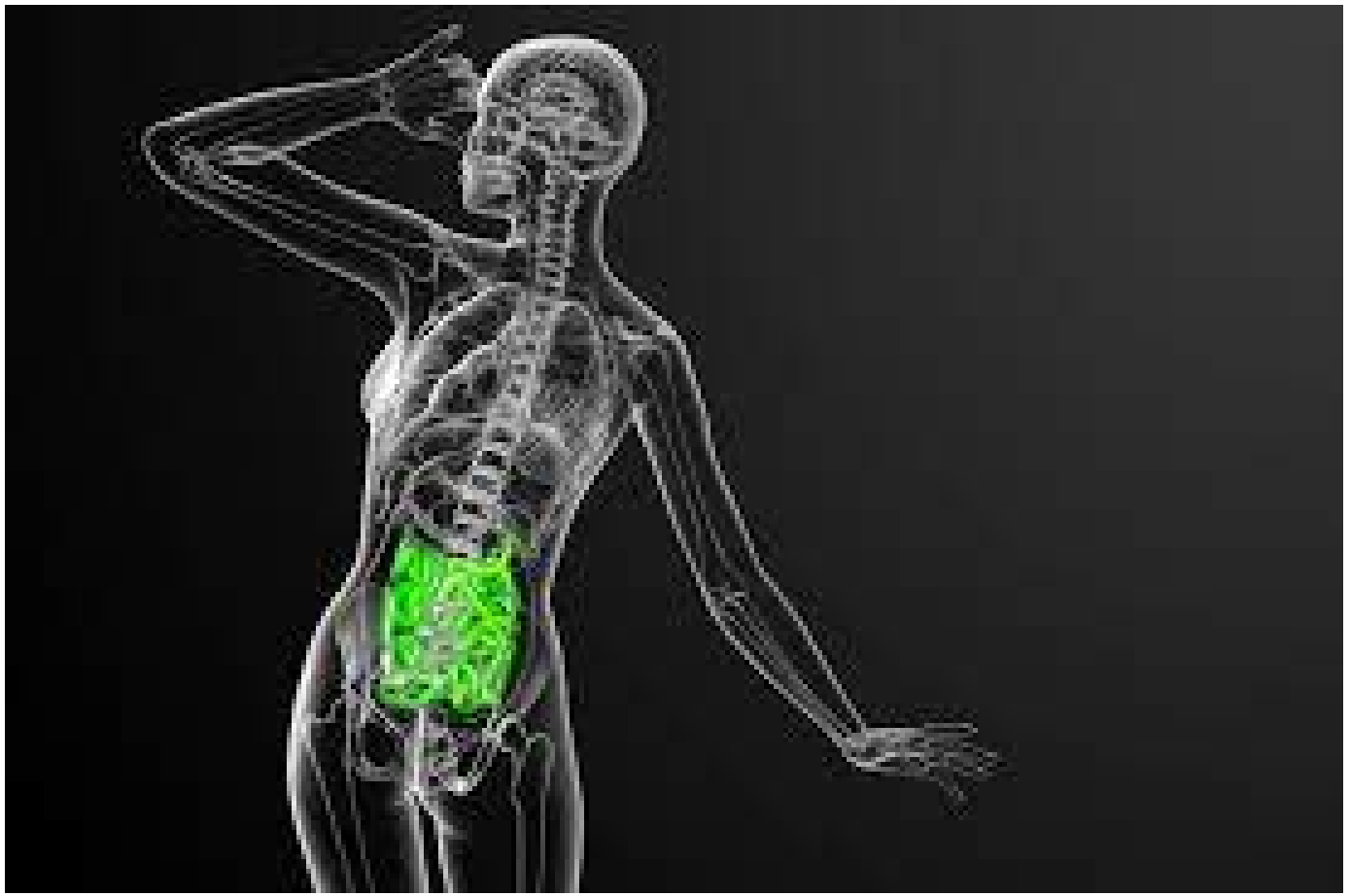
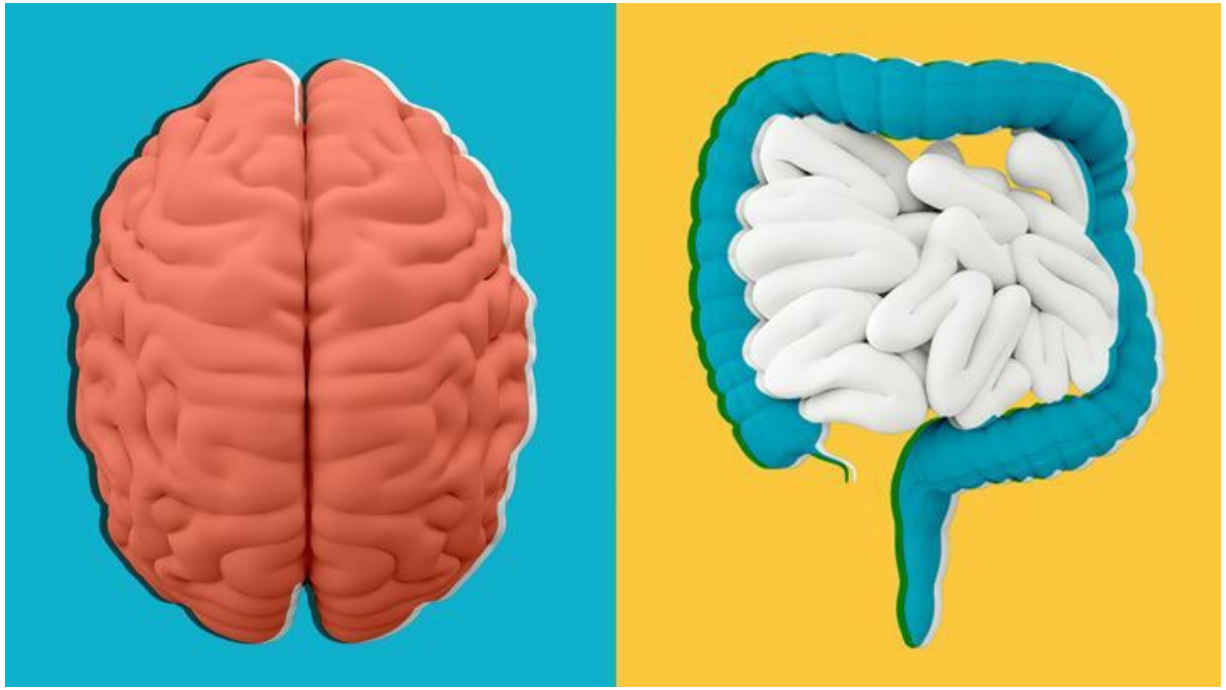


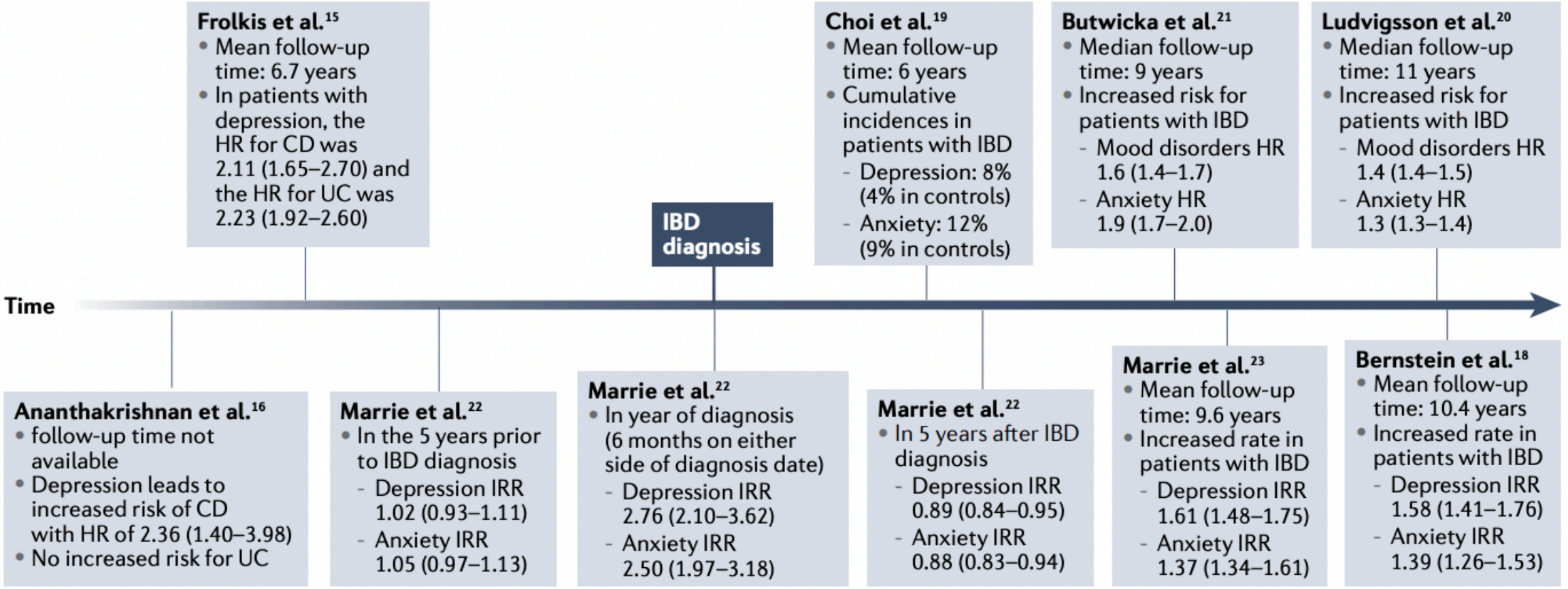
Mental Illness and Inflammatory Bowel Disease



- The pooled prevalence of symptoms of depression from three reviews was 21%, 21.6% and 25.2%, while the pooled prevalence of symptoms of anxiety was 19.1% 35.1% and 32.1%
- One of the studies also summarized data from a subset of studies reporting diagnosis rather than symptoms of psychiatric disease and **found a pooled prevalence of depression of 15.2% and a pooled prevalence of anxiety of 20.7%**

Mikocka-Walus, A. et al Inflamm. Bowel Dis. 22, 752–762 (2016); Neuendorf, R et al J. Psychosom. Res. 87, 70–80 (2016). Barberio, B. et al Lancet Gastroenterol. Hepatol. 6, 359–370 (2021).

Temporal association b/w IBD and Depression/Anxiety



Modified from Nature Reviews 2022: 13, 701-712

Association b/w Depression and IBD

Table 1 Adverse outcomes related to IBD activity during longitudinal follow-up among patients with symptoms of anxiety or depression at baseline

	Number of studies	Total number of patients	Pooled RR (95% CI)	I^2 (%)	P value for χ^2
Adverse outcomes related to IBD activity among patients with symptoms of anxiety at baseline					
Flare of IBD activity	5	1244	1.20 (0.93 to 1.55)	53.7	0.071
Escalation of therapy due to uncontrolled IBD activity	2	670	1.68 (1.18 to 2.40)	0.0	0.513
Hospitalisation due to IBD	3	1553	1.72 (1.01 to 2.95)	73.4	0.023
Emergency department attendance due to IBD	3	1511	1.30 (1.21 to 1.39)	1.0	0.364
IBD-related surgery	1	423	1.62 (0.50 to 5.25)	N/A	N/A
Composite endpoint combining any of the above	3	2844	1.21 (1.08 to 1.36)	19.8	0.291
Adverse outcomes related to IBD activity among patients with symptoms of depression at baseline					
Flare of IBD activity	8	7606	1.60 (1.21 to 2.12)	73.5	<0.001
Escalation of therapy due to uncontrolled IBD activity	4	6957	1.41 (1.08 to 1.84)	43.1	0.135
Hospitalisation due to IBD	3	5151	1.35 (1.17 to 1.57)	40.7	0.168
Emergency department attendance due to IBD	3	1511	1.38 (1.22 to 1.56)	0.0	0.985
IBD-related surgery	3	6710	1.63 (1.19 to 2.22)	57.4	0.070
Composite endpoint combining any of the above	4	2906	1.26 (1.07 to 1.48)	19.8	0.289

N/A, not applicable – too few studies; RR, relative risk.

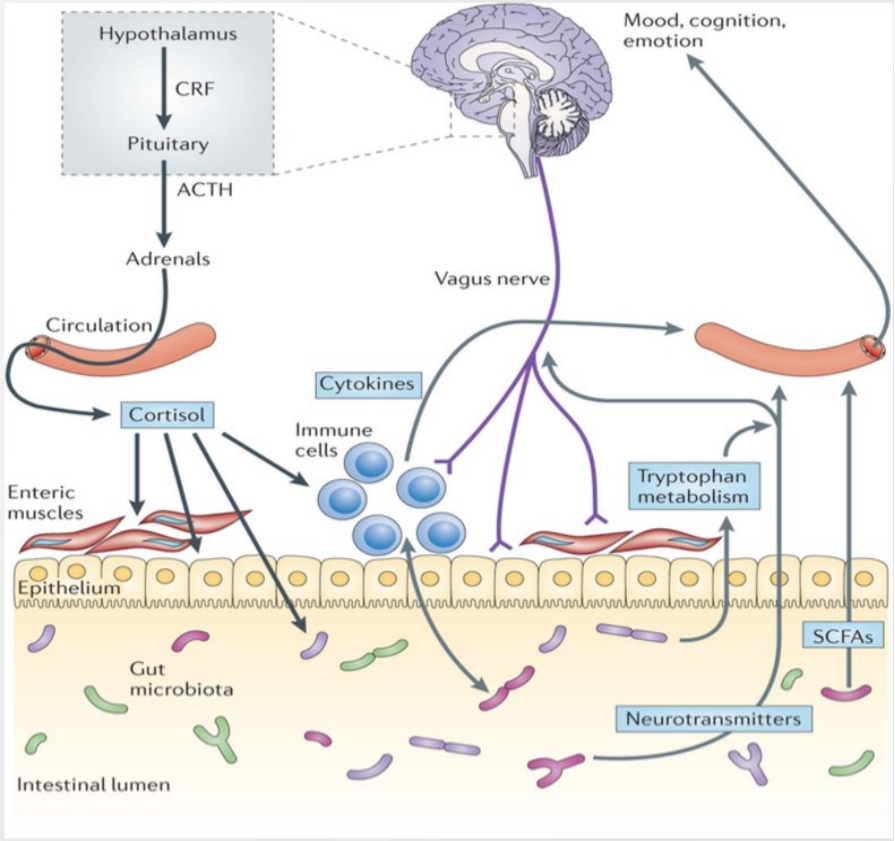
- Patients with IBD with symptoms of depression/anxiety had increased risk of flare, escalation of therapy, hospitalization, emergency department attendance and surgery

- Active IBD at baseline was associated with the development of symptoms of depression and anxiety

Fairbrass KM, et al. Gut 2022;71:1773–1780.

What is the link?

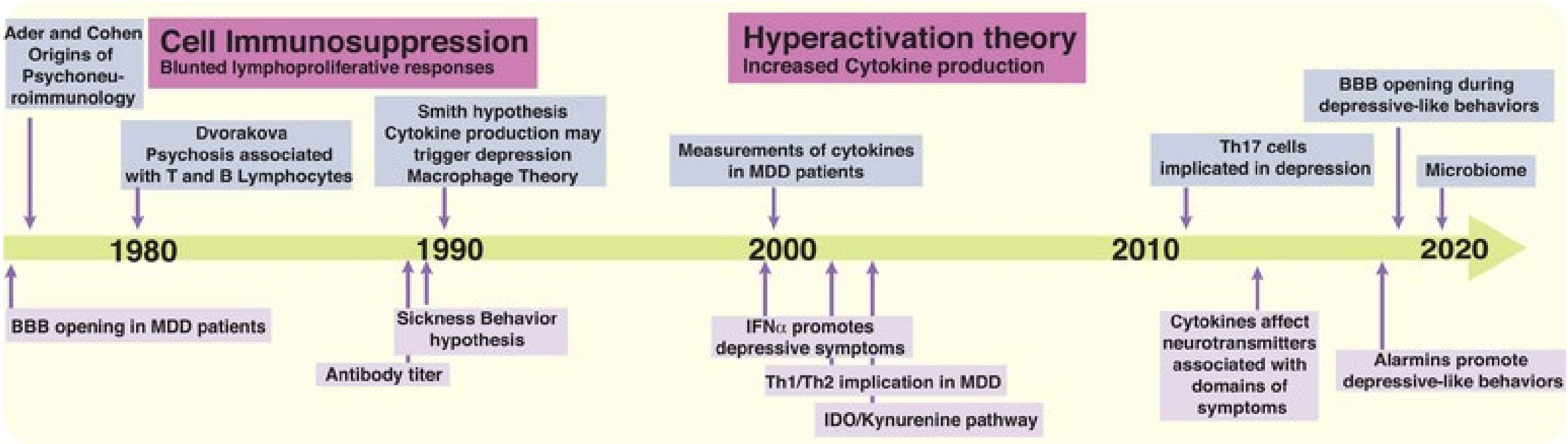
The Brain and Inflammation

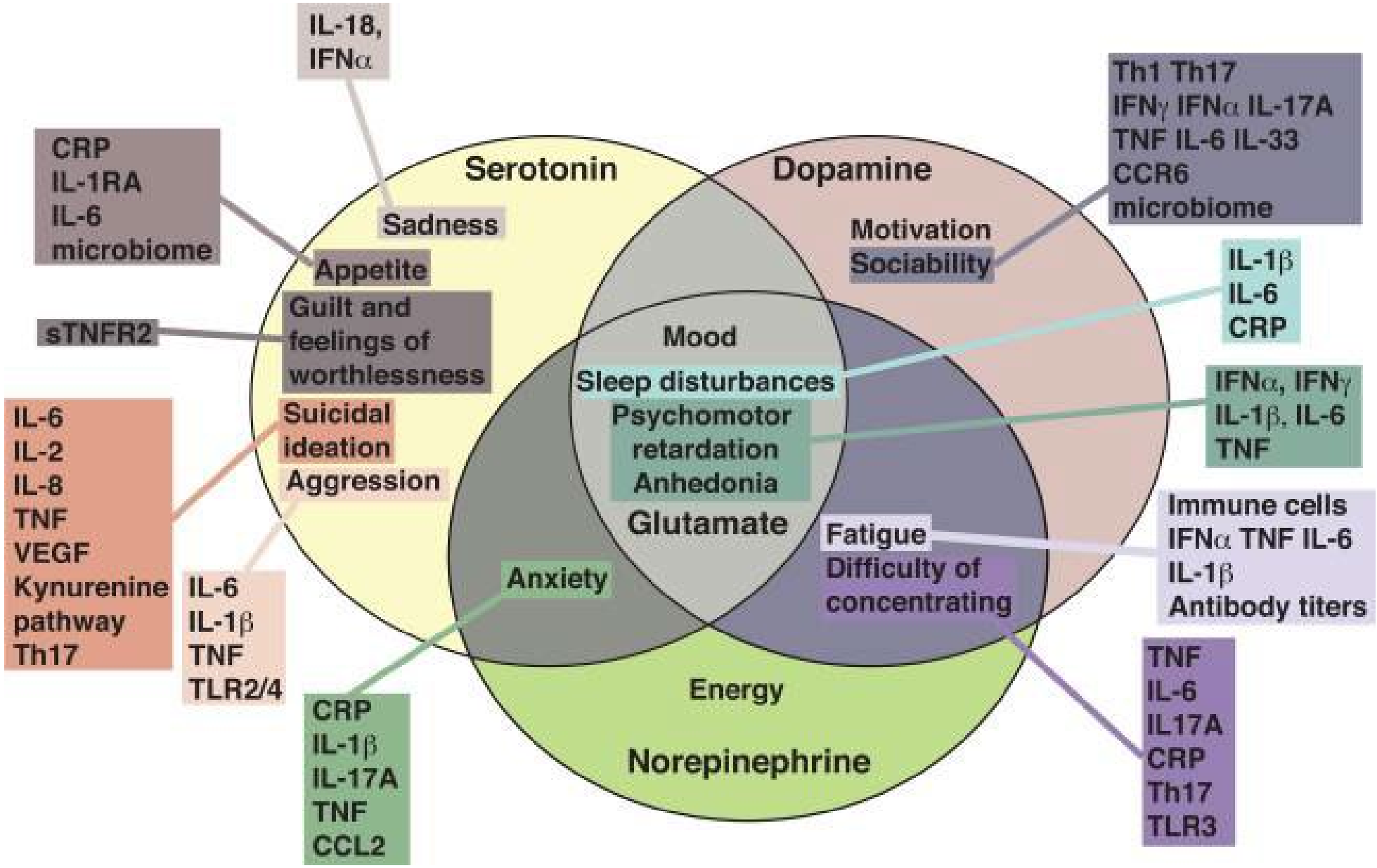


- Vagal Afferents
- Circulating cytokines signal via cerebral endothelial cells, causing cerebral production of prostaglandins and nitric oxide (NO)
- Circulating cytokines and leukocytes that enter the brain through the circumventricular organs
- Activation of Toll-like receptors on macrophages in the circumventricular organs, resulting in production of proinflammatory cytokines that diffuse into the brain

Cryan J, Dinan T. Nature Reviews Neuroscience 2012: 13, 701-712

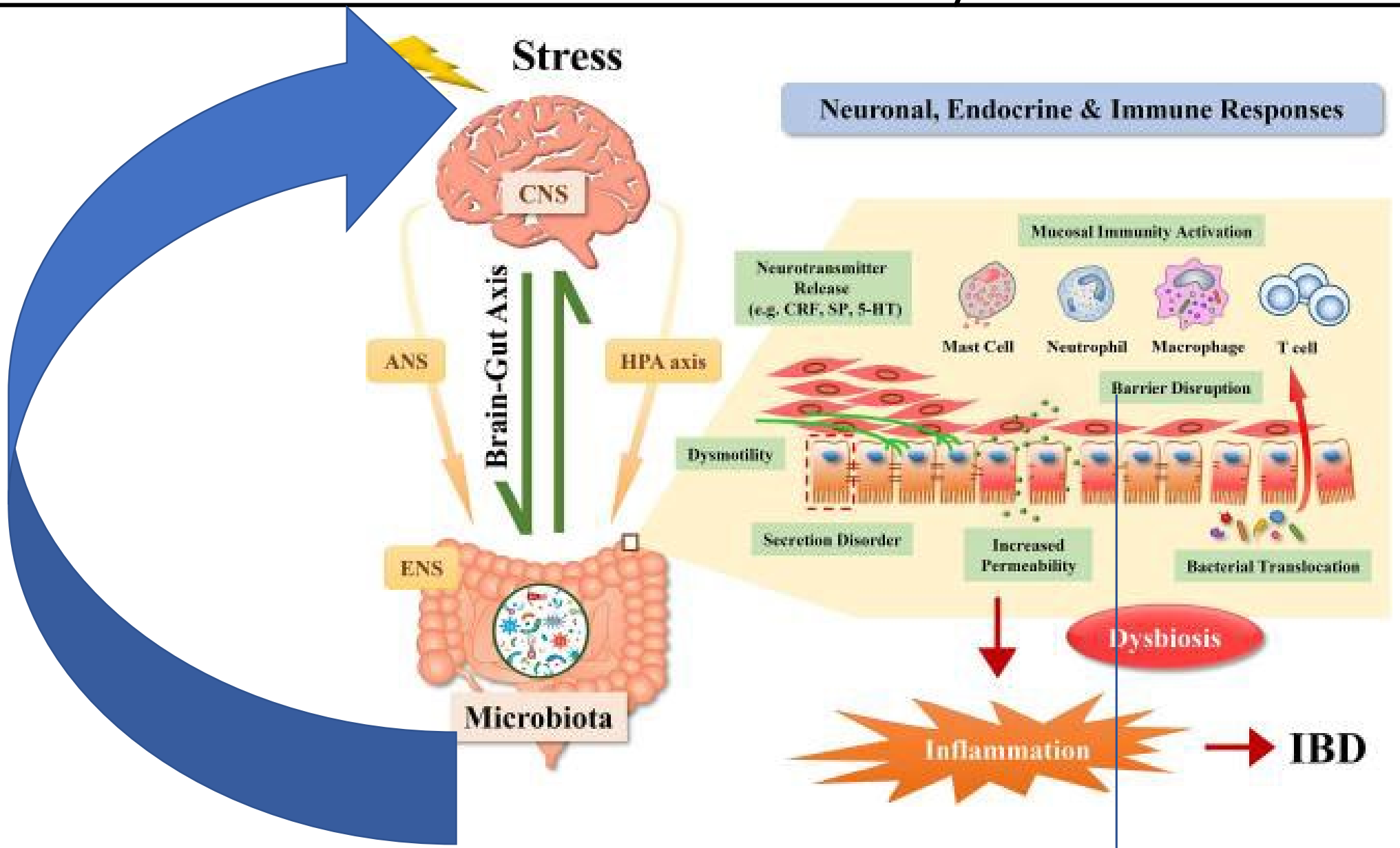
Neuroinflammation Hypothesis of Mental Illness



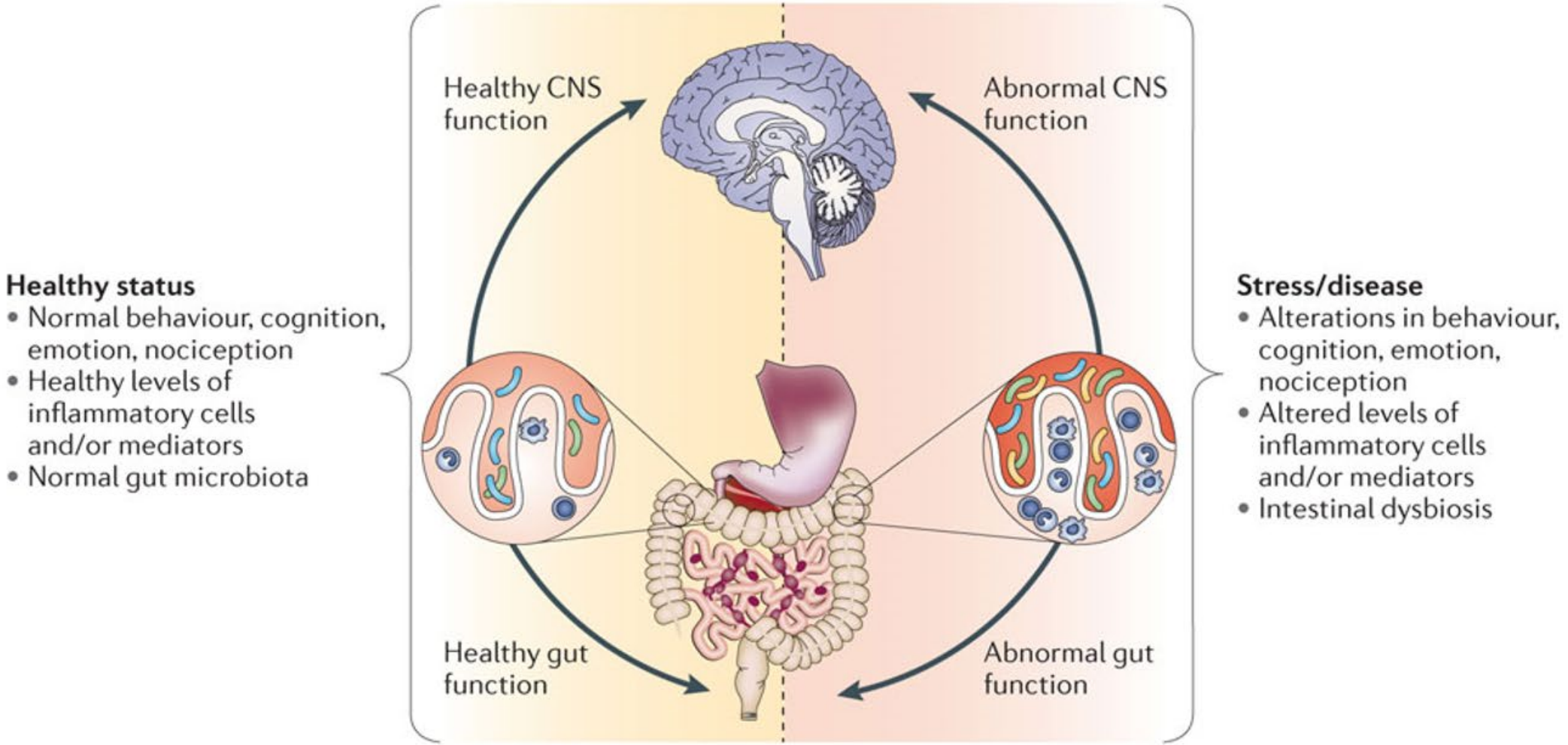


Beurel E, Toups M, Nemeroff CB. The Bidirectional Relationship of Depression and Inflammation: Double Trouble. Neuron. 2020 Jul 22;107(2):234-256.

Mental Illness and Inflammatory Bowel Disease



Treatment strategies for IBD and mental illness



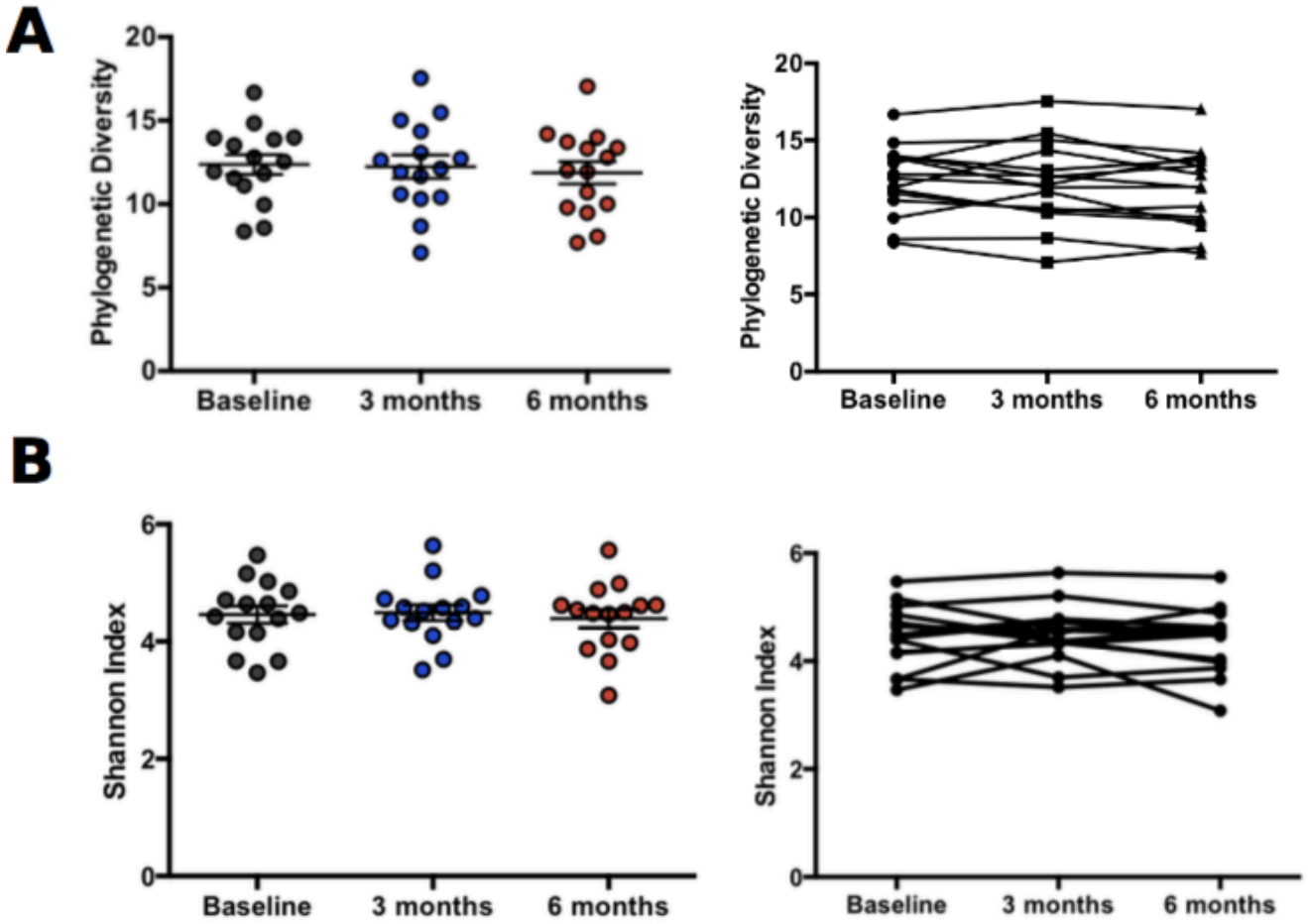
Cryan J, Dinan T. Nature Reviews Neuroscience 2012: 13, 701-712

The role of Antidepressants

- Approximately 30% of IBD patients take antidepressants
- Animal models of IBD show an improvement on inflammation similar to dexamethasone
- Human studies of the effect of antidepressants on the course of IBD are mixed but suggest benefit

Nature Reviews 2022: 13, 701-712

Gut microbiome changes in patients with Major Depressive Disorder

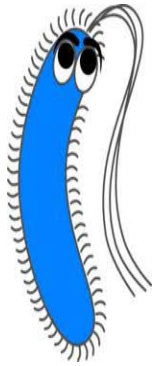


Bharwani A…Taylor VH, Canadian Journal of Psychiatry, Feb, 2020.

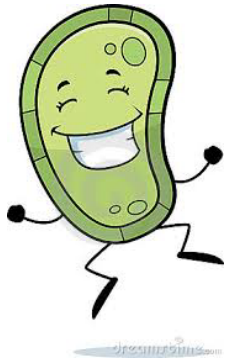
Gut microbiome changes in patients with Major Depressive Disorder

- When analyzed based on treatment response patients in the responder group exhibited greater phylogenetic diversity than non-responders(Mann- Whitney U= 5, p= 0.026).

- These observations indicate that antidepressant medications alter the gut microbiota of patients with MDD, with disparate effects in responders versus non-responders. This supports the concept of a microbiota phenotype associate with treatment response in MDD.



Bharwani A….Taylor VH et al, CJP, Feb, 2020.



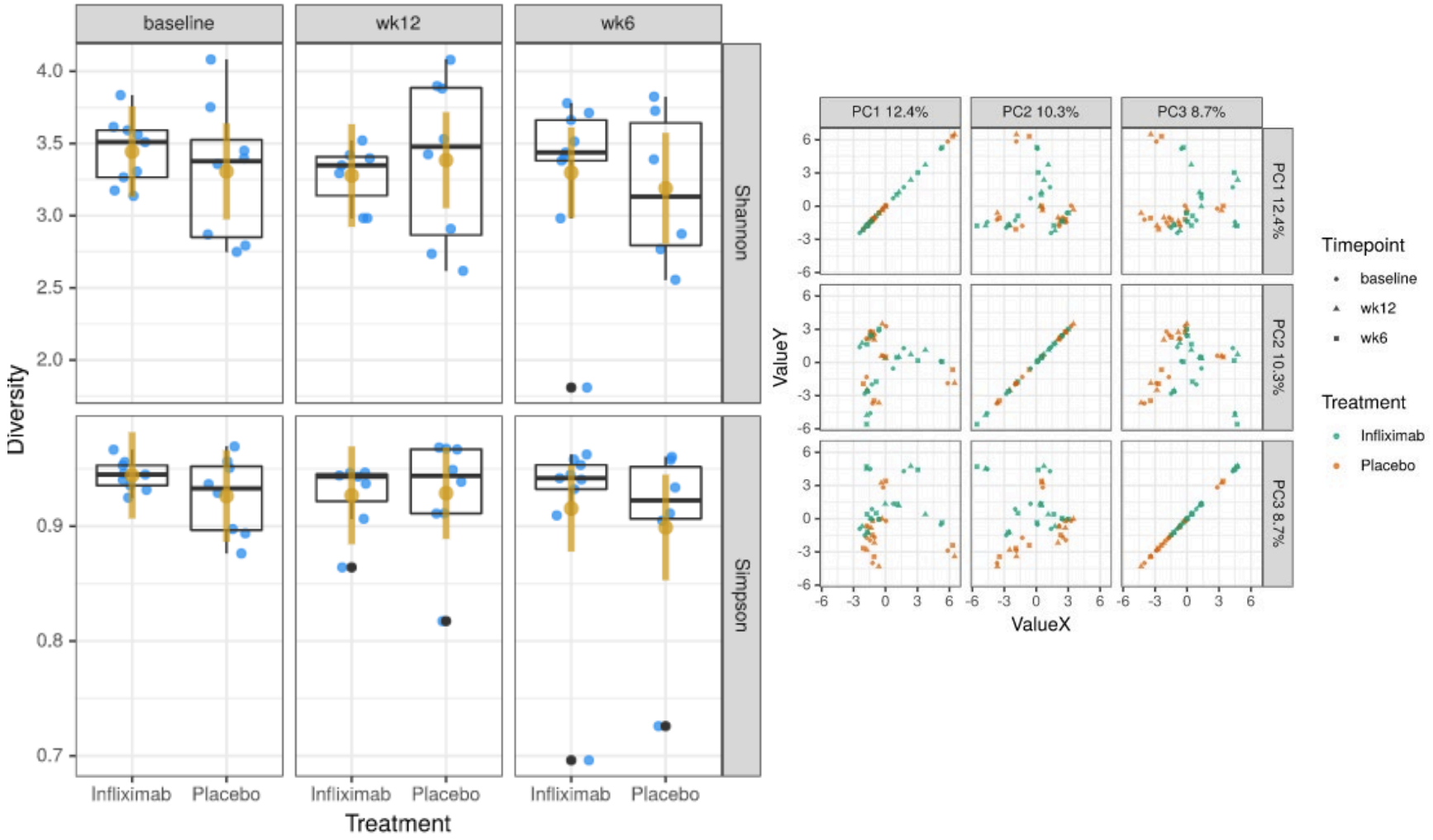
The impact of anti-inflammatory medications on mental illness

- Two studies found a decrease in depression and anxiety symptoms and an improvement in IBD symptoms with anti TNF therapy

- Other studies found no difference, a difference only with elevated CRP or actually found a worsening of depression with anti-TNF treatment

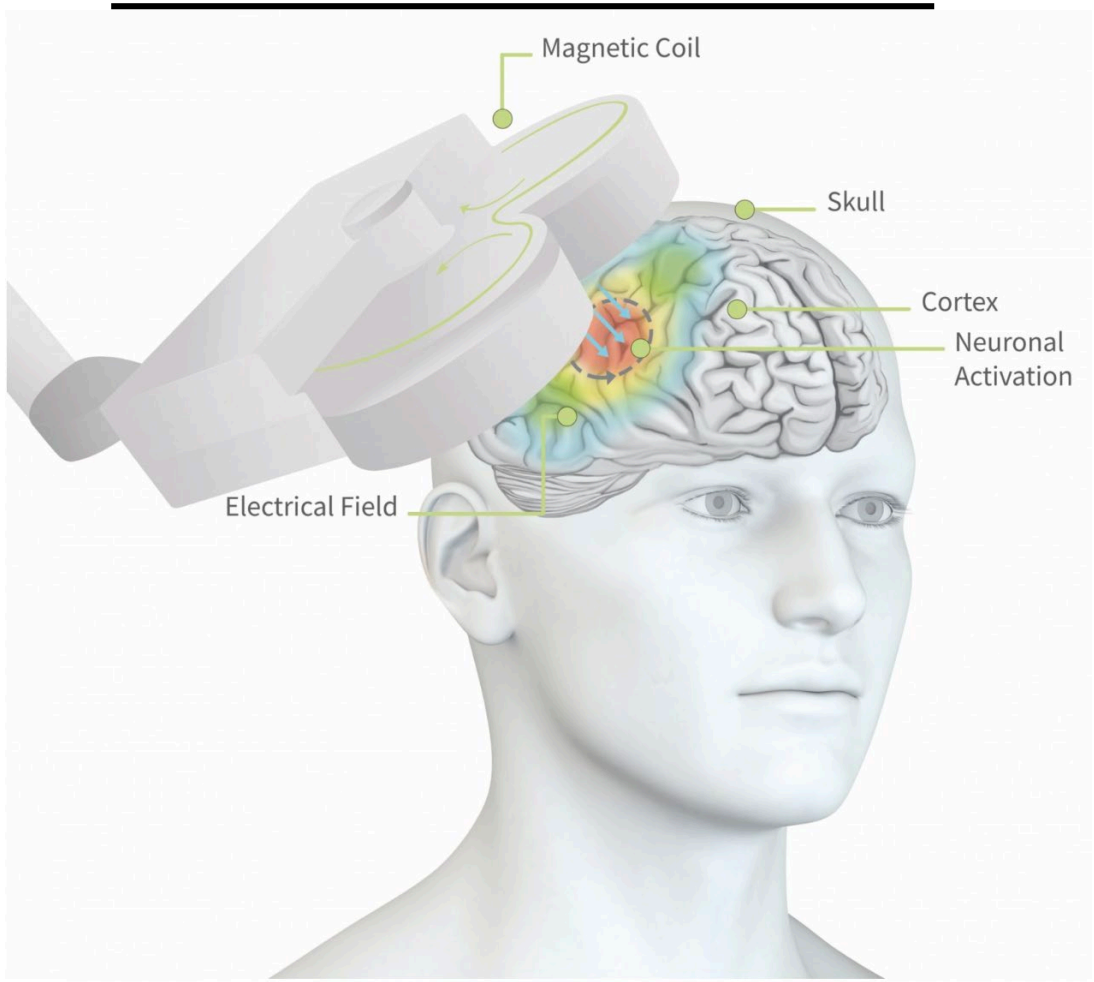
Nature Reviews 2022: 13, 701-712

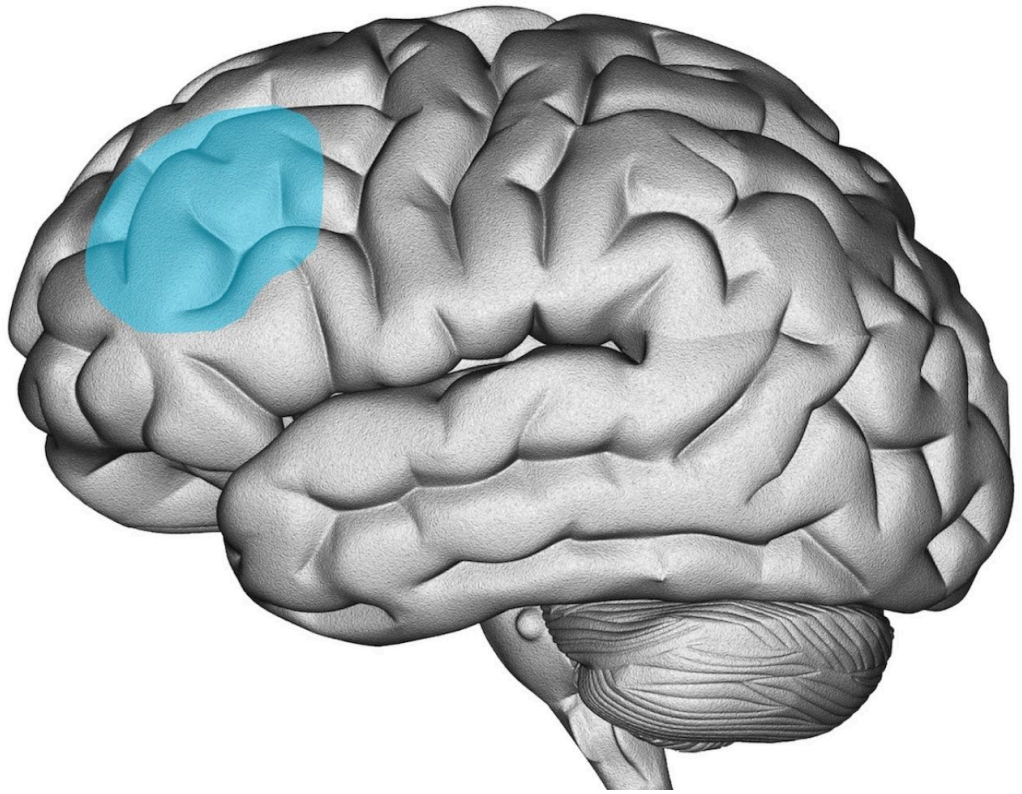
Infliximab for Depression



Bharwani A, Taylor VH et al Brain Behav. 2021 Aug;11(8)

Neurostimulation

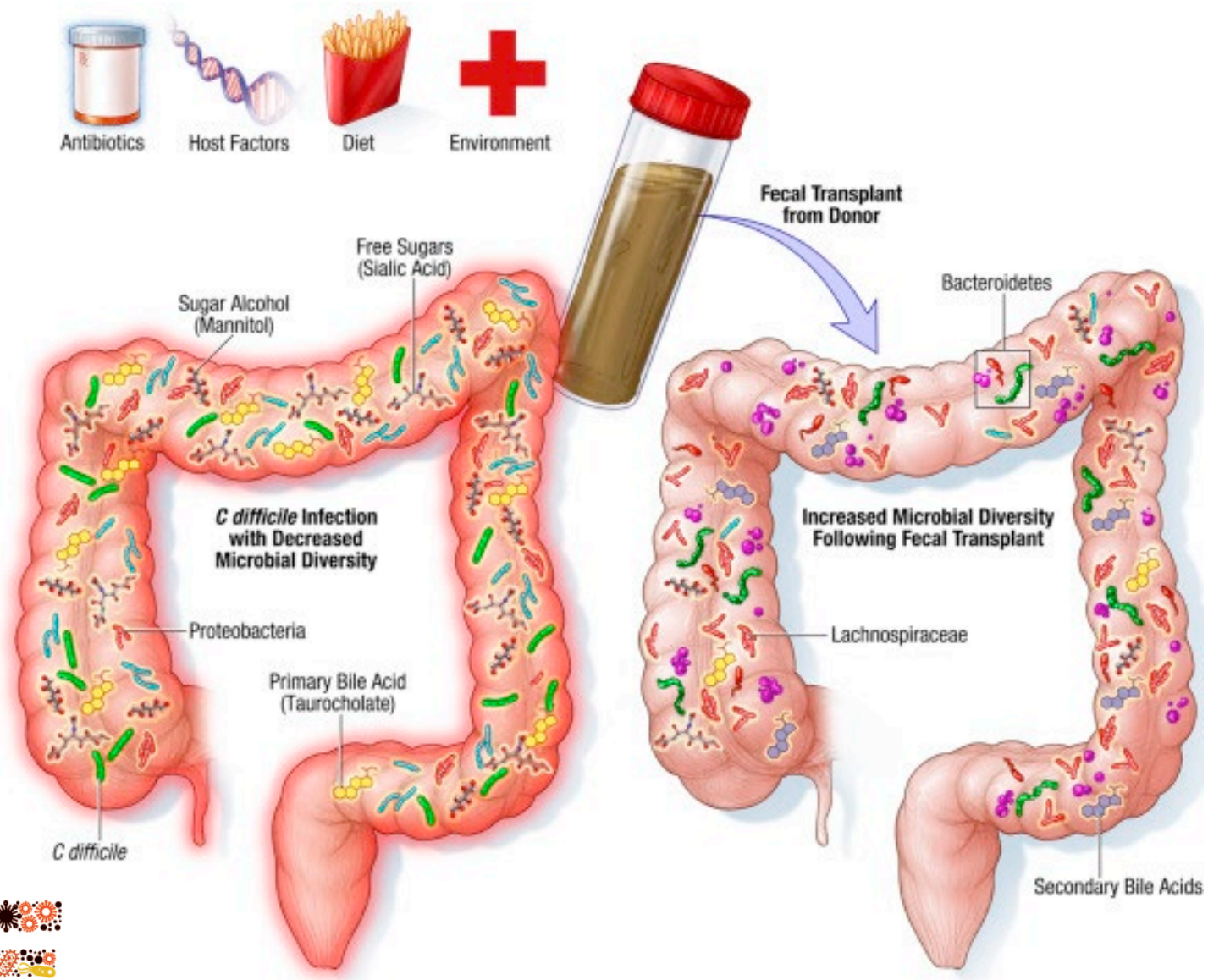




IMAGINE

Inflammation, Microbiome & Alimentation Gastro-Intestinal & Neuropsychiatric Effects

Fecal Microbial Transplant (FMT)



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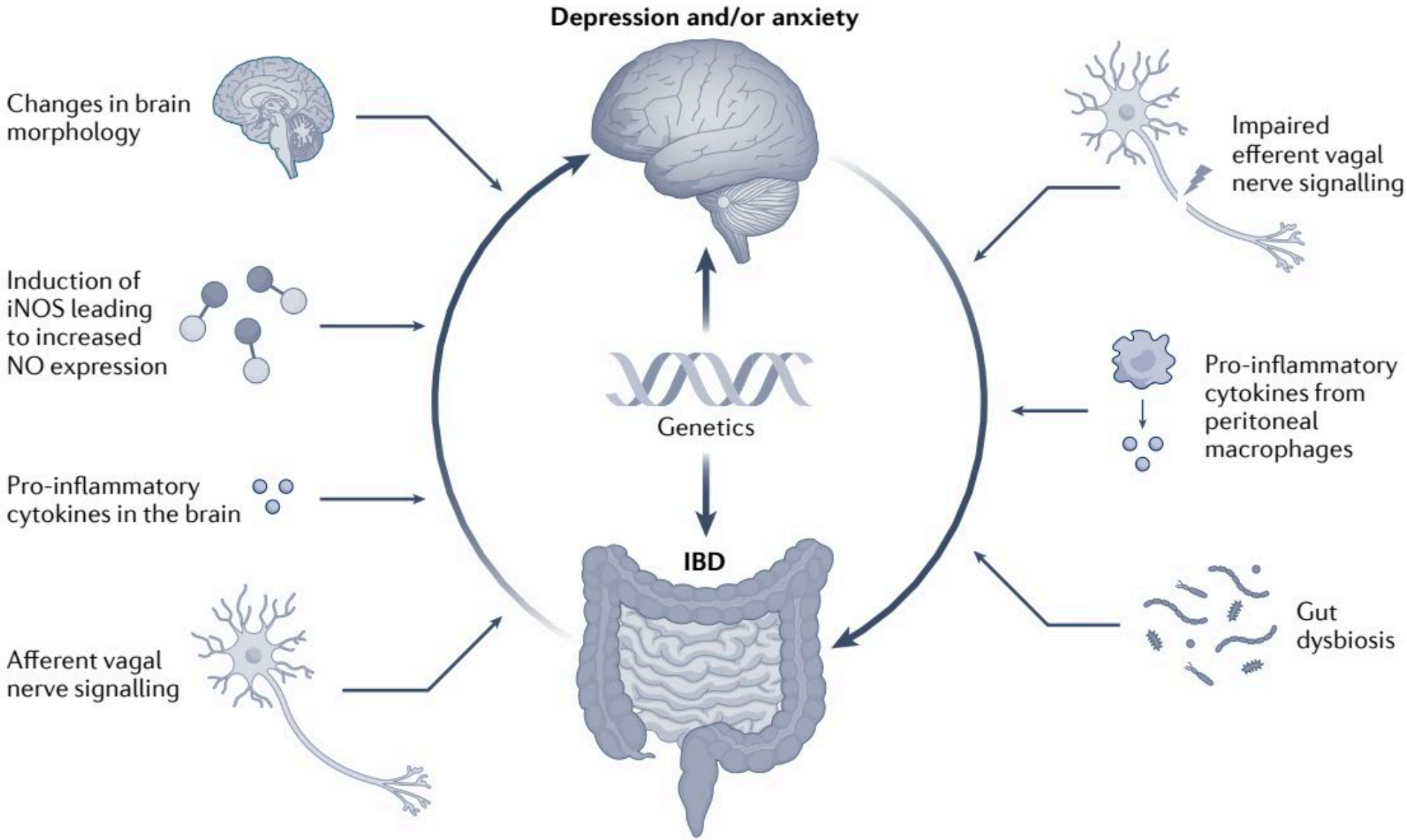
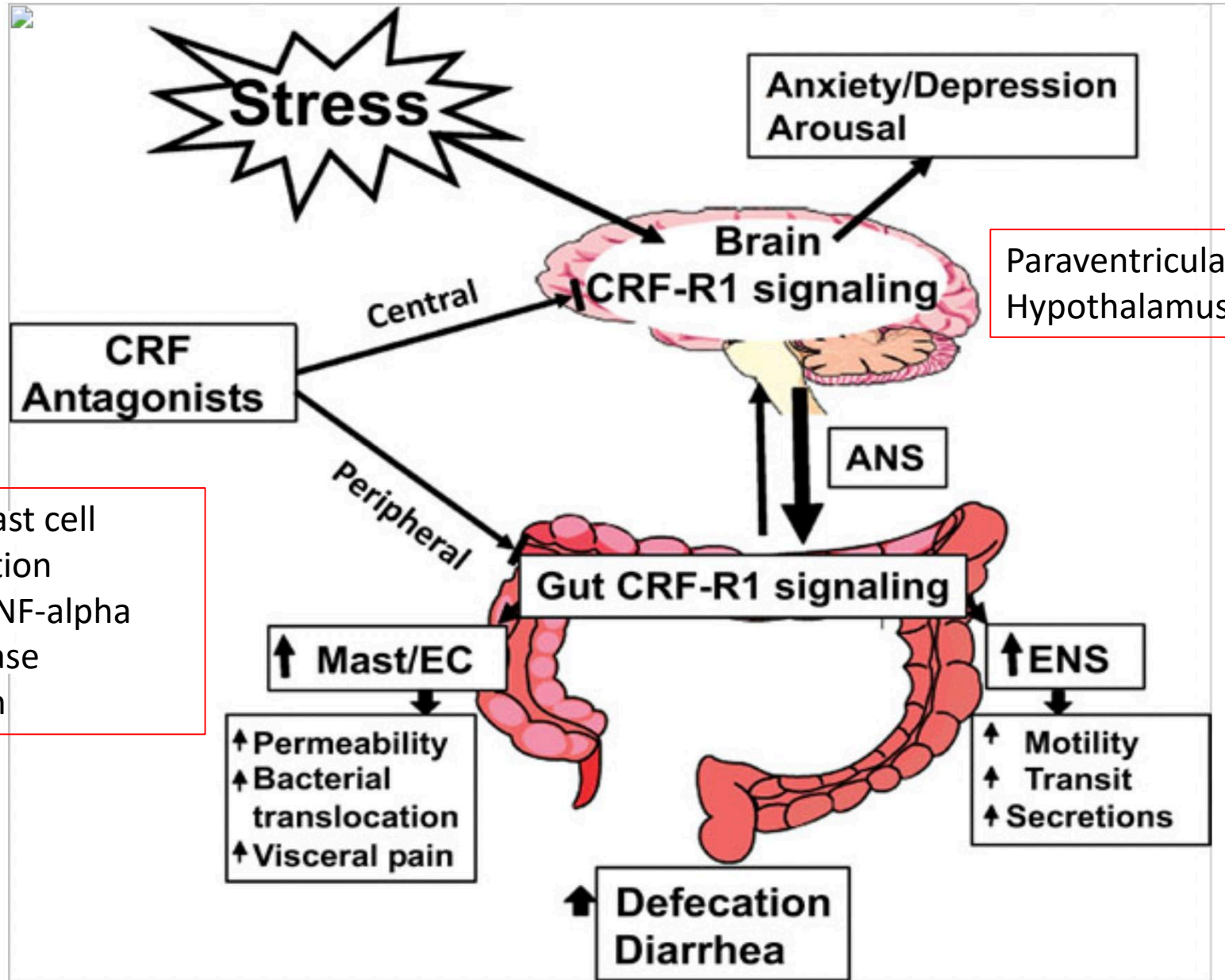
Inflammation, Microbiome & Alimentation Gastro-Intestinal & Neuropsychiatric Effects


Depression and/or anxiety
Changes in brain morphology
Induction of iNOS leading to increased NO expression
Pro-inflammatory cytokines in the brain
Afferent vagal nerve signalling
Impaired efferent vagal nerve signalling
Pro-inflammatory cytokines from peritoneal macrophages
Gut dysbiosis
Genetics
IBD

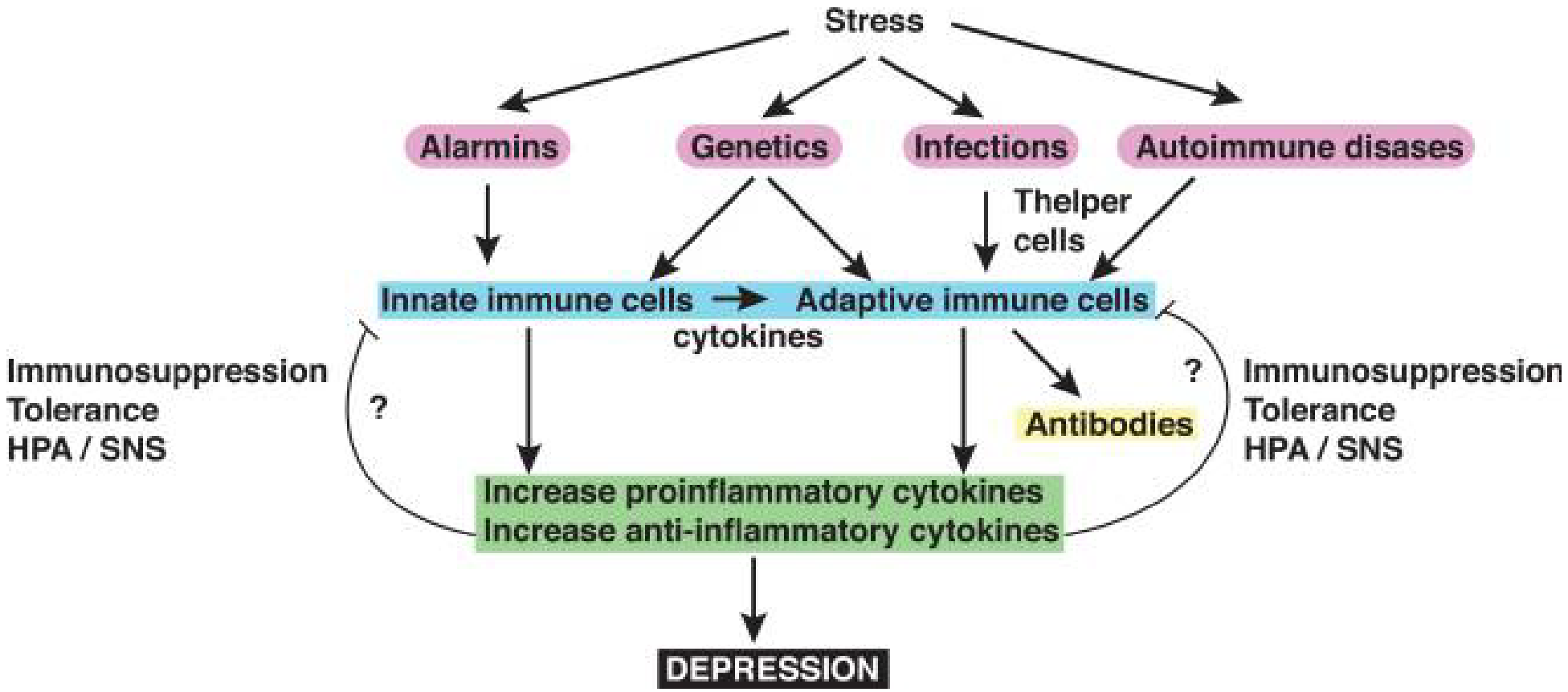


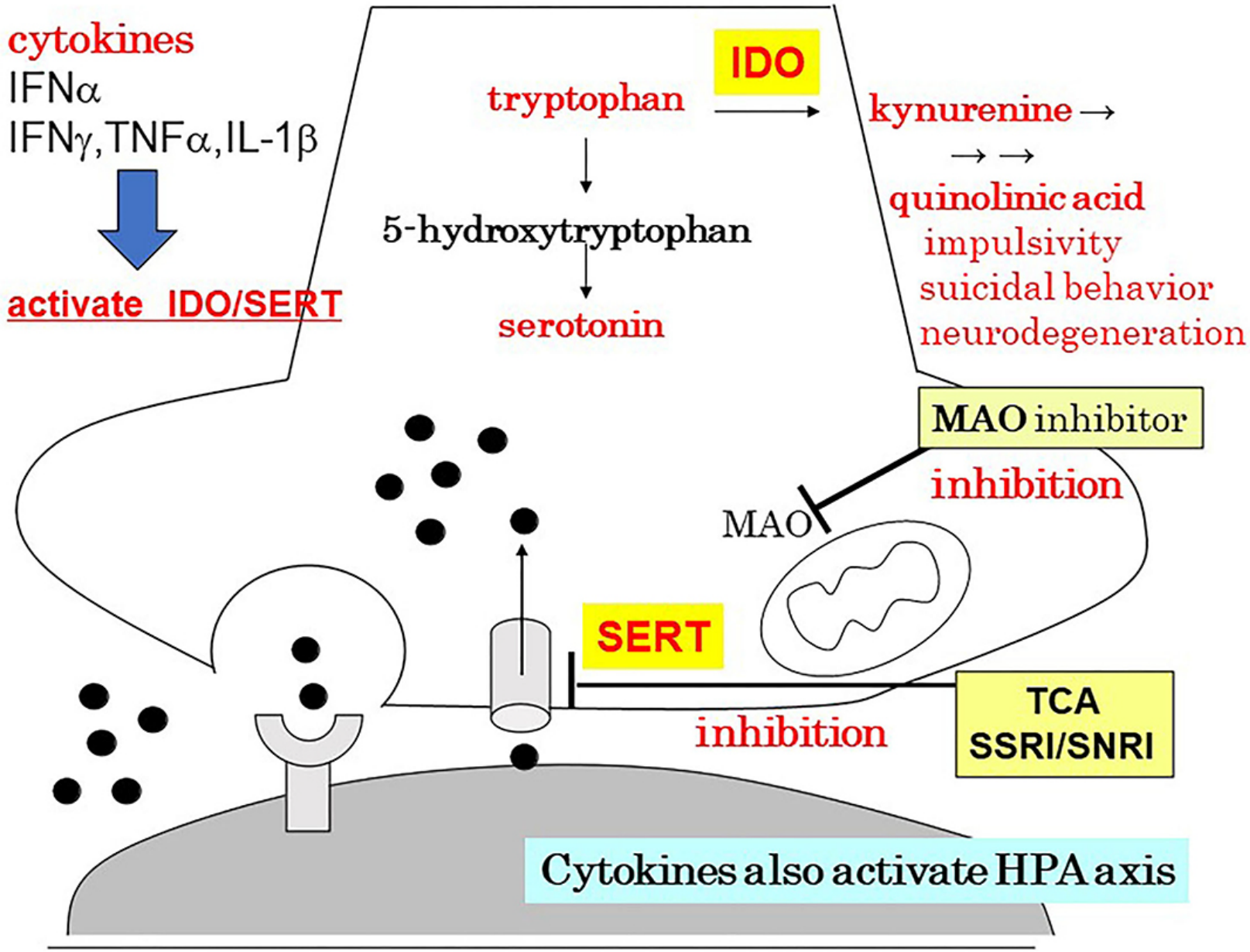
Paraventricular nucleus of the Hypothalamus

- Inhibits mast cell degranulation
- Reduces TNF-alpha and protease production

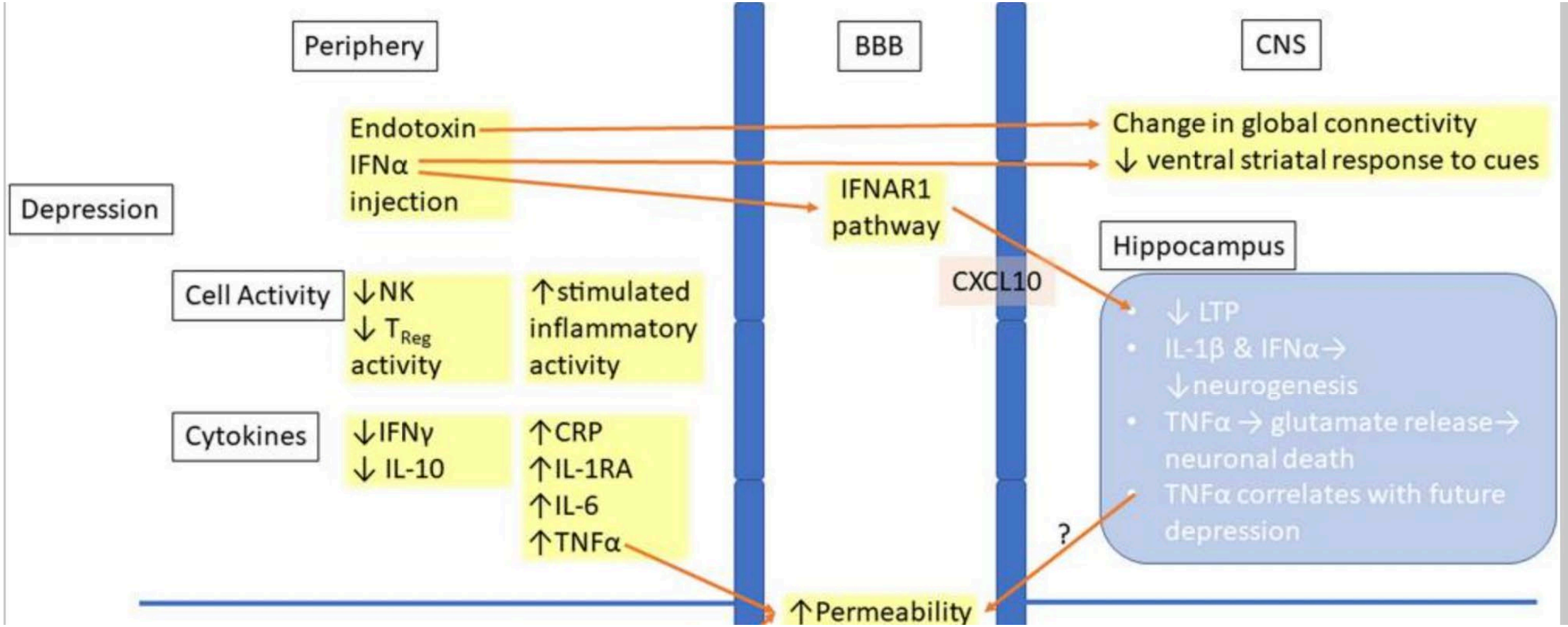
Yvette Tache et al Current Molecular Pharmacology 11, Issue 1, 2018, p51-71

Potential Immune Response Dysregulations in MDD Patients



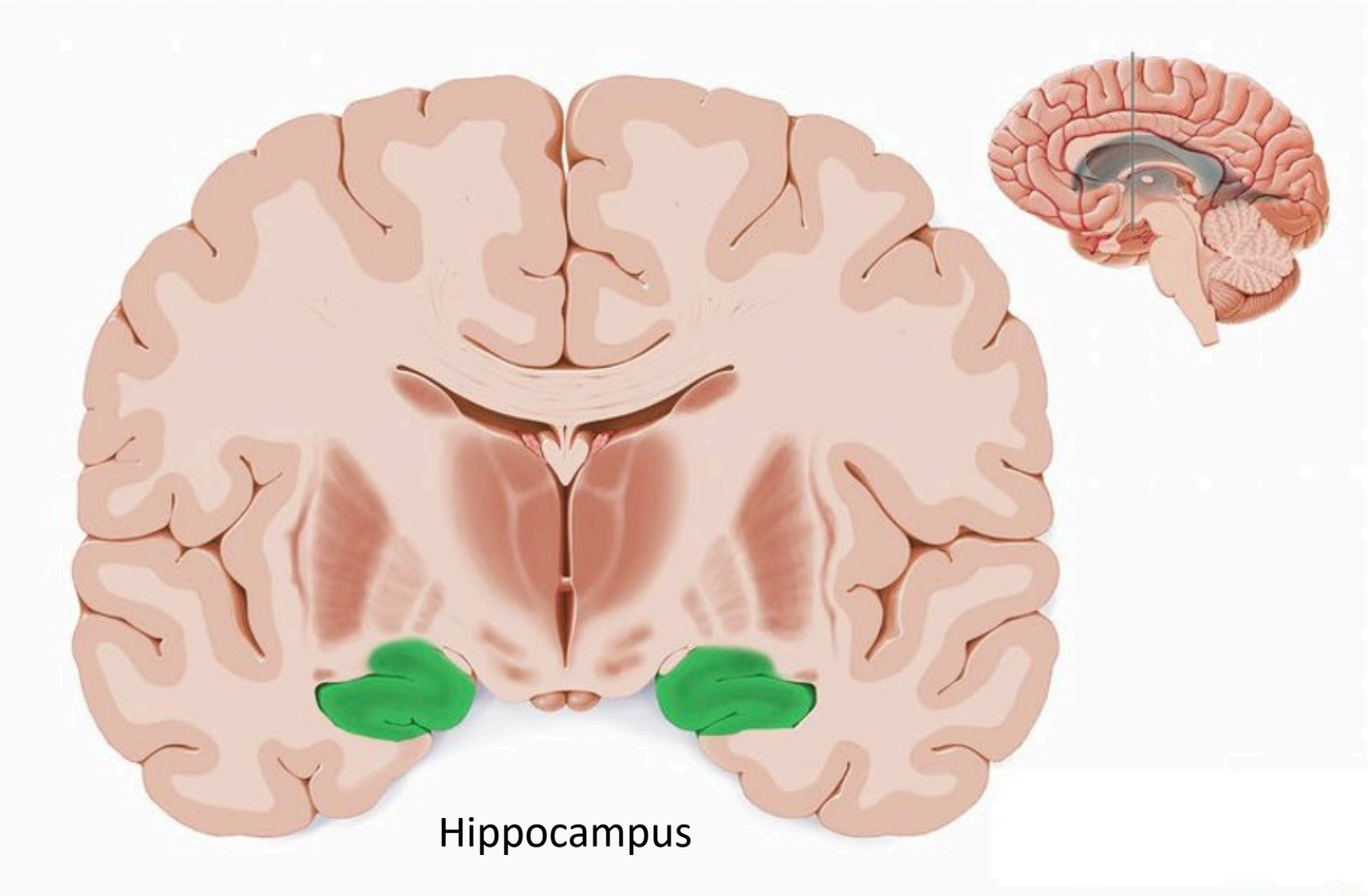

cytokines
IFNα
IFNγ,TNFα,IL-1β
activate IDO/SERT
IDO
tryptophan
kynurenine →
→ →
quinolinic acid
impulsivity
suicidal behavior
neurodegeneration
5-hydroxytryptophan
serotonin
MAO inhibitor
inhibition
MAO
SERT
inhibition
TCA
SSRI/SNRI
Cytokines also activate HPA axis

Mental Illness and Inflammation

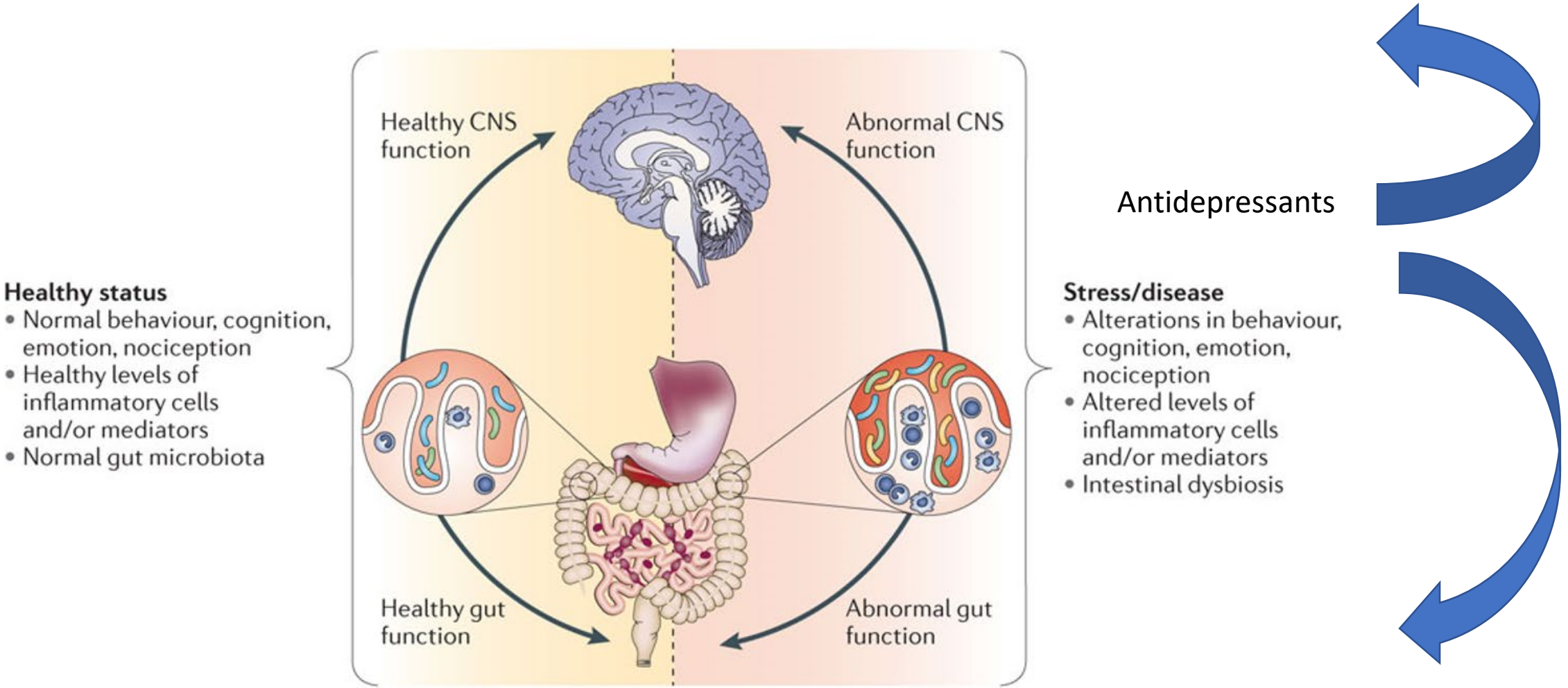


Lee CH, Giuliani F. The Role of Inflammation in Depression and Fatigue. Front Immunol. 2019 Jul 19;10:1696

Mechanisms linking IBD and Mental Illness



Treatment strategies for IBD and mental illness



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