The role of inflammation in depression

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I Brief introduction and Epidemiological considerations

What defines “Major Depression”?

Who is afflicted by it?

What are we currently doing to treat it?

Basic diagnostic criteria **Major Depressive Disorder**

TABLE 1. DSM-5 criteria for major depressive disorder

	DSM-5	
A	Five or more out of nine symptoms (including at least one of depressed mood and loss of interest or pleasure) in the same 2-week period. Each of these symptoms represents a change from previous functioning.	
		Frequency requirements:
	1. Depressed mood (subjective or observed); can be irritable mood in children and adolescents	Most of the day, nearly every day
	2. Loss of interest or pleasure	Most of the day, nearly every day
	3. Change in weight or appetite	Appetite: Nearly every day Weight: 5% change over 1 month
	4. Insomnia or hypersomnia	Nearly every day
	5. Psychomotor retardation or agitation (observed)	Nearly every day
	6. Loss of energy or fatigue	Nearly every day
	7. Worthlessness or guilt	Nearly every day
	8. Impaired concentration or indecisiveness	Nearly every day
	9. Thoughts of death or suicidal ideation or attempt	Thoughts: recurrent Attempt: any
B	Symptoms cause significant distress or impairment.	
C	Episode not attributable to a substance or medical condition.	
	Note 1: Criteria A–C represent a major depressive episode (MDE).	
	Note 2: Clinical judgement is inevitably required to distinguish if MDE is present in addition to a normal response to a significant loss.	
D	Episode not better explained by a psychotic disorder.	
E	There has never been a manic or hypomanic episode.	
	Note 3: Exclusion E does not apply if (hypo)manic episode was substance induced or attributable to medical condition.	

Table 1, from Usher, et al., 2013.

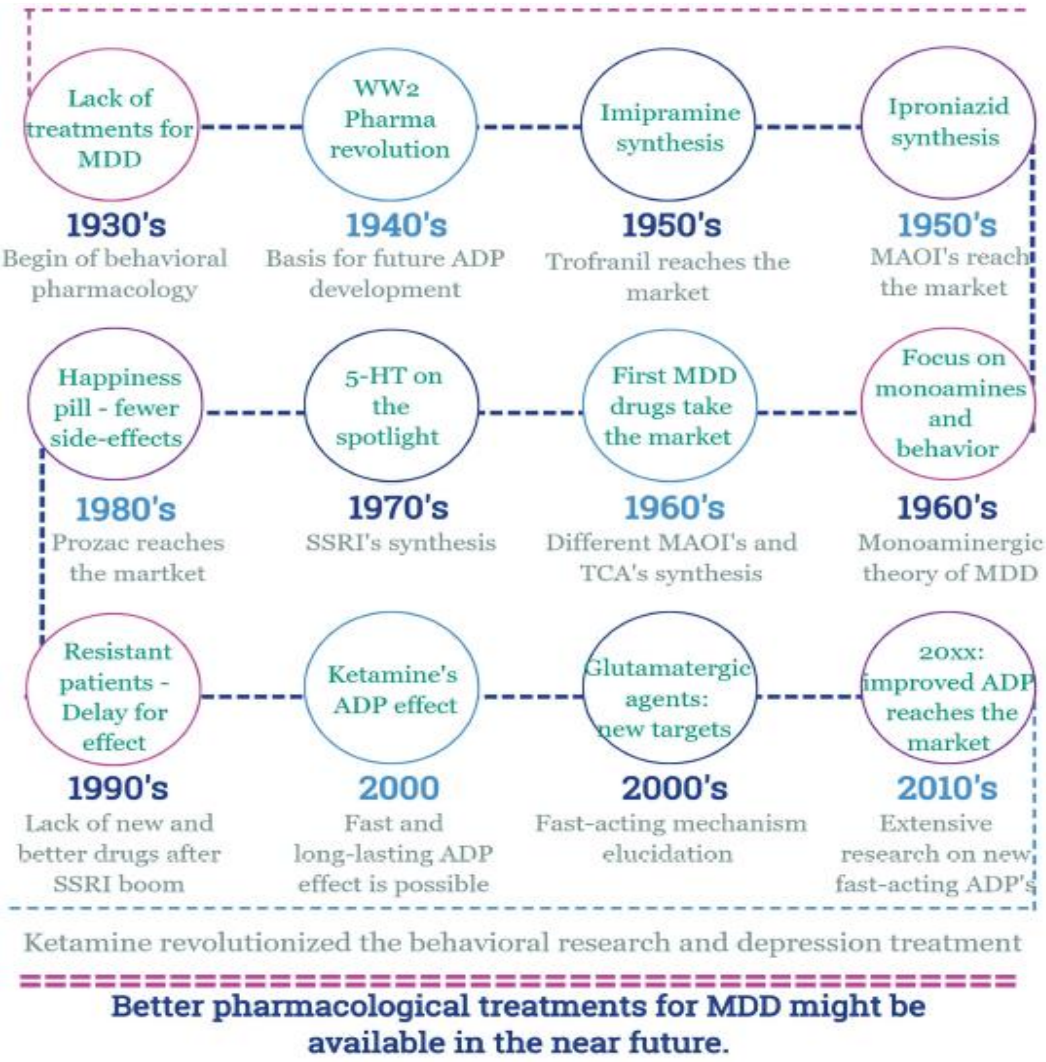
Depression – Epidemiological Considerations

Prevalence

Recent Meta Analysis, by Lim, G. Y., et al. (2018); with n=1,112,573 adults, 91 studies included, published between April 1994 and June 2014

- Aggregate **point prevalence: 12.9%**
- **One-year prevalence: 7.2%**
- **Lifetime prevalence: 10.8%**

According to the **WHO (2018)**:
→ **800 000** people die due to **suicide per year**, with suicide being the **second leading cause of death in 15-29-year-olds. Psychiatric disorders are prognosed to be the most significant global burden of diseases, by 2020.**



Timeline:
Milestones in pharmacological therapy.

Pereira, V., & Hiroaki-Sato, V. (2018).

Rather sluggish development, compared with other fields.

Only about half of patients achieve lasting remission under current treatment!
(Nemeroff, 2007)

Some unanswered questions?

→ Why is the prevalence of depression rising with the advent of modern, industrialized civilization?

→ Why does natural and/or sexual selection allow for a gene pool filled with depression associated allels in the first place ?

→ How does the pathophysiology of depression work ? (the elephant in the room)

→ How can we translate new insights into the pathophysiology of depression into clinical practice ? (the other elephant…)

New puzzle pieces from the realm of immunology?

1980-1990s: First systematic associations between pro-inflammatory cytokines and major depression: **increased haptoglobin plasma levels**
-> IL-1, IL-6 production associated with (mostly vegetative) symptoms of **depression**
(See Maes, 1993 for a review.)

Epidemiological cues (see Miller, & Raison, 2016 for a review):

- **CRP and IL-6 levels** (in peripheral blood) **predicted depressive symptoms** after 12 year follow up.
- **A CRP > 3mg/L predicted depressive symptoms**, but not vice versa.
- Cave: Not all studies replicate this link!
- Valid **associations between canonical psychosocial risk factors of depression**, like childhood trauma **and subsequent inflammation.**

II An Evolutionary Perspective

II Evolutionary perspective

"Nothing in Biology Makes Sense Except in the Light of Evolution" - Theodosius Dobzhansky

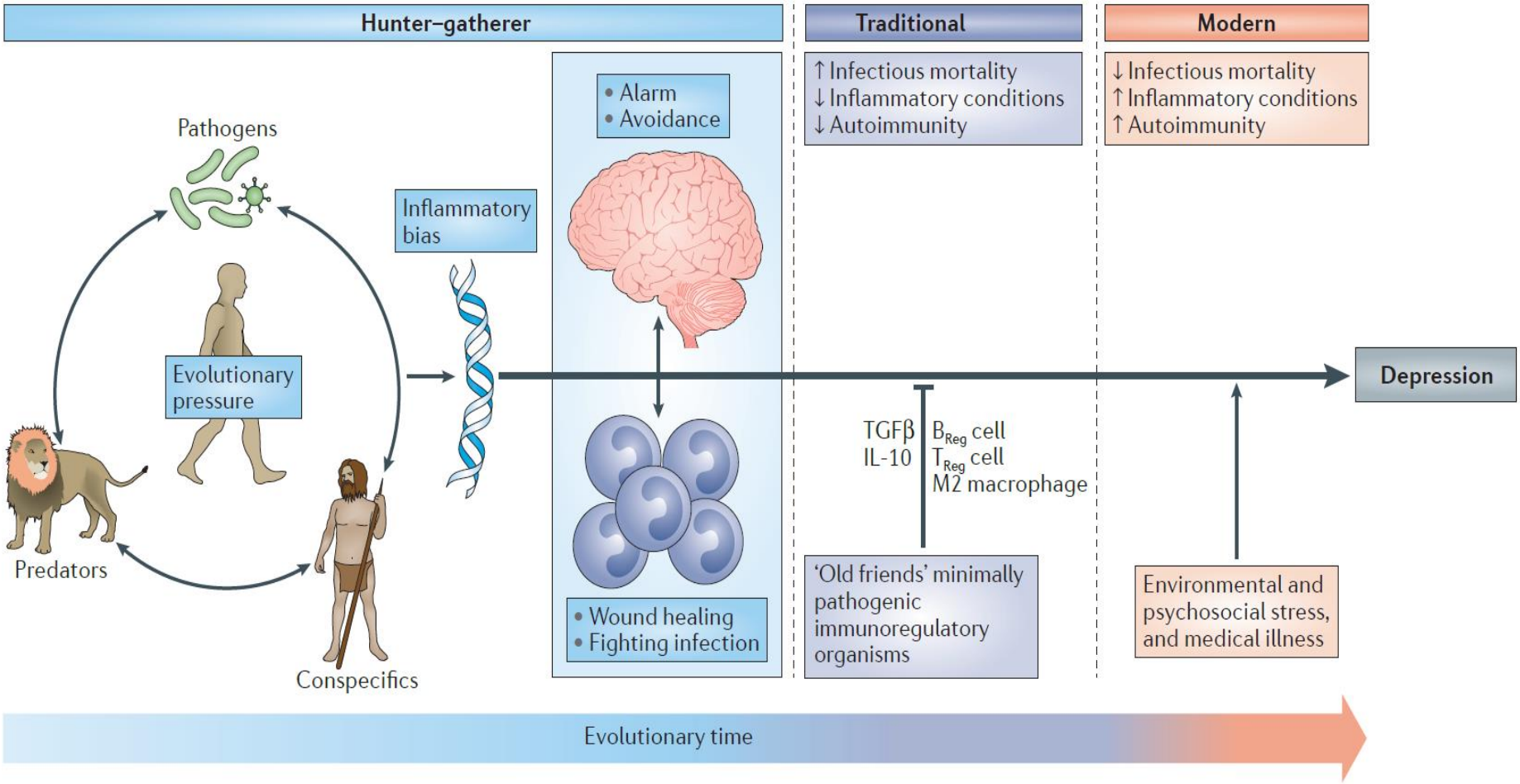
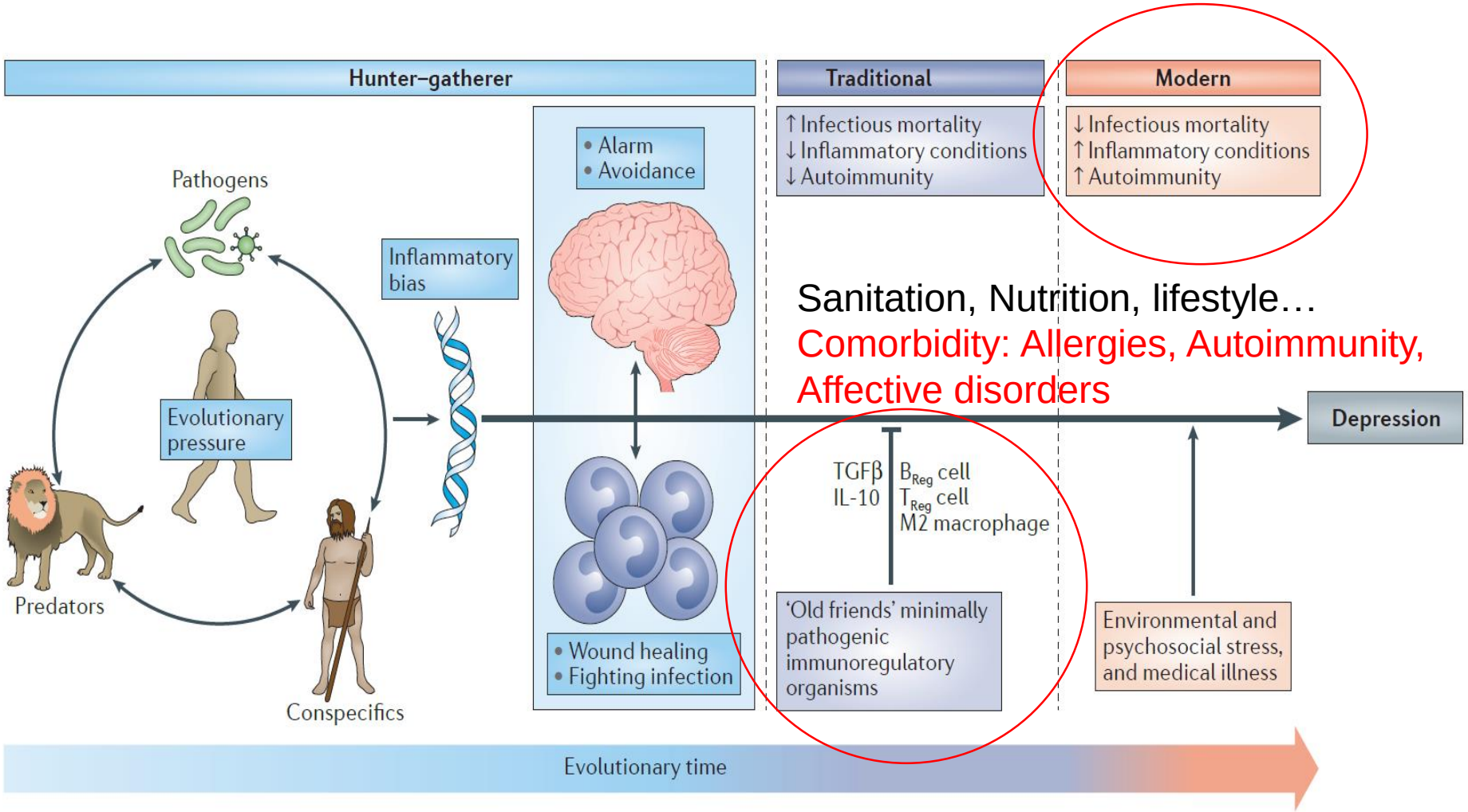


Figure 1 – The inflammatory bias, from Miller, A. H. and C. L. Raison (2016).

A question of timing – The rise of depression in modern and post modern societies



Key points so far

- Key features of „Sickness Behaviour“, e.g. social avoidance/withdrawal (->Anhedonia), lethargy, dismal mood, lowered cognitve and psychomotor acitvity, irritability and hypervigilance (->Anxiety), are also indicative of major depression.
- Unlike depression „Sickness Behaviour“ is an adaptive response.
- The accociation between stress perception and subsequent pathogen exposure was valid, for most of human history.
- Considering the strong selective pressure of infectious disease, a genomic bias towards inflammation makes sense.

The Pathogen host defence hypothesis of depression

In a nutshell:

Depression risk alleles and their associated phenomenological outcome (depressive symptoms) **are prevalent** in the human genepool, **because of their** former **role in** pathogen **host defense.**

... Cool story. But where´s your evidence?

Relevant lines of evidence (Miller, A. H. and C. L. Raison (2015)):

→ The best replicated **depression risk allels** are linked to **inflammation**

→ Environmental **risk factors of depression** (psychosocial, as well as metabolic, etc.) are uniformly **pro-inflammatory**

→ **Exposure to pro-inflammatory cytokines** can reliably induce „sickness behaviour“ phenotypes, overlapping with **depressive symptoms**.

→ **Alleviation** of depressive symptoms through **antiinflammatory drugs** (such as COX-2 Inhibitors) has been shown in animal models and clinically.

→ Consistently **raised** levels of **acute phase** proteins, **cytokines**, overrepresentation of **M1 macrophage** lineage in plasma and CSF of **patients**, compared to general population

→ Increased levels of **proinflammatory chemokines, TLR-3,4, hightend micor- and astroglia activation in post mortem brain** samples, of **suicide** victims.

→ **In vivo confirmation** of those signaling molecules in PET, TSPO studies

→ **Gen-Polymorphisms** prone to overexpression of said gen- products associated with depression and **resistance of depression to treatment**.

→ Patients with **CRP > 3mg/L are more likely NOT to respond to treatment** than „non-inflammed“ patients with depression.

III Putative pathways linking inflammation and major depression

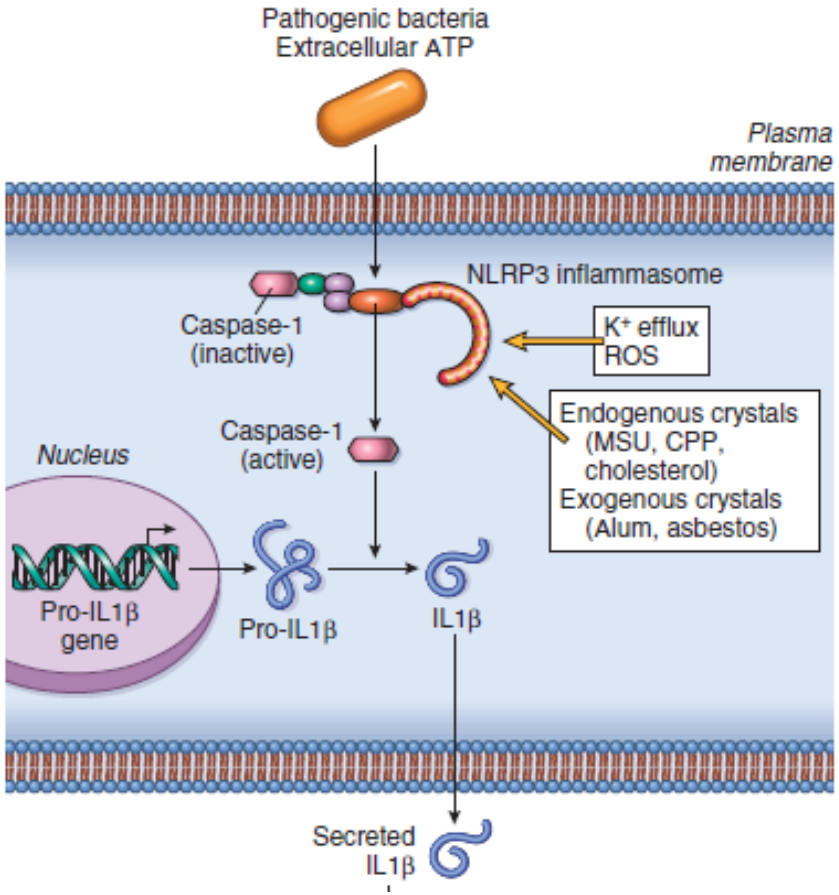
How do psychosocial stressors translate into inflammation?

- Canonical short to midterm stress reactions:

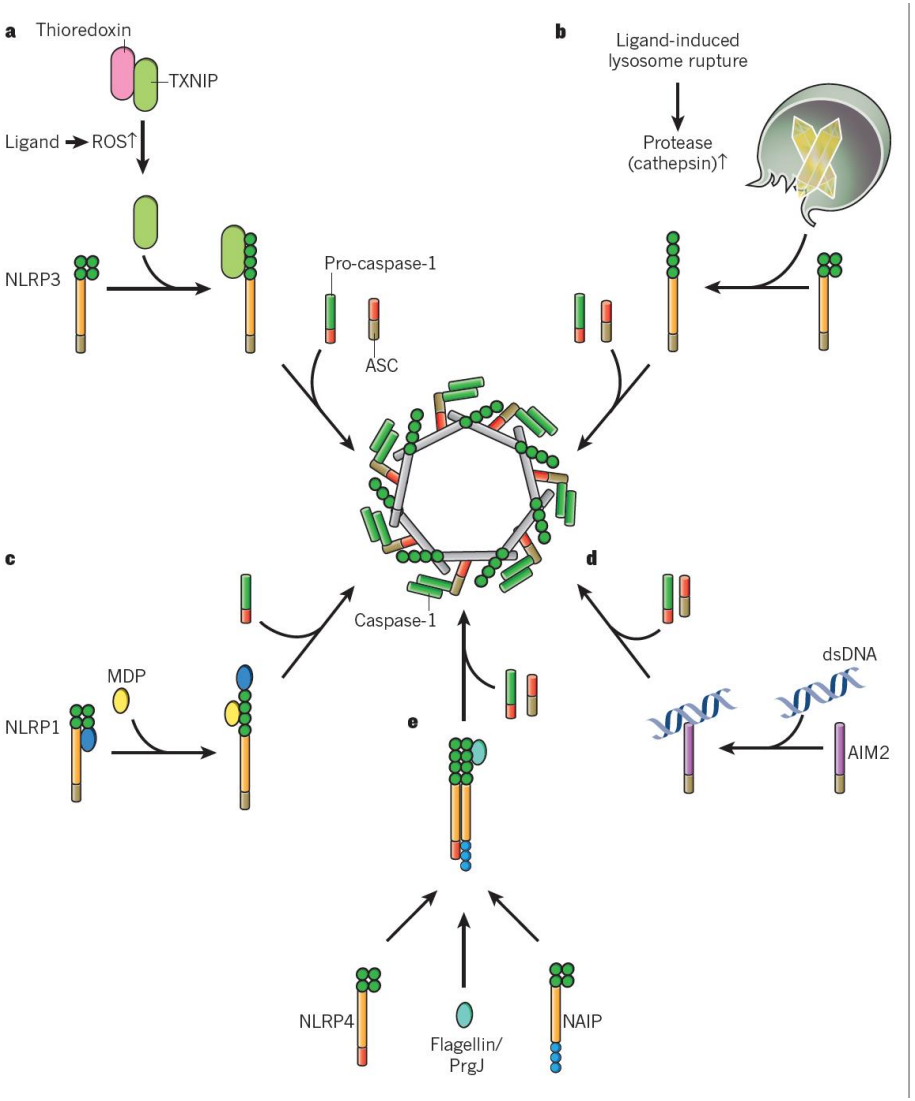
  -> Reactions of the Sympathetic nervous system and HPA-axis are associated with systemic low-grade inflammation!

- Key immunological interface: **The inflammasome**

Briefly, what is the inflammasomes job?

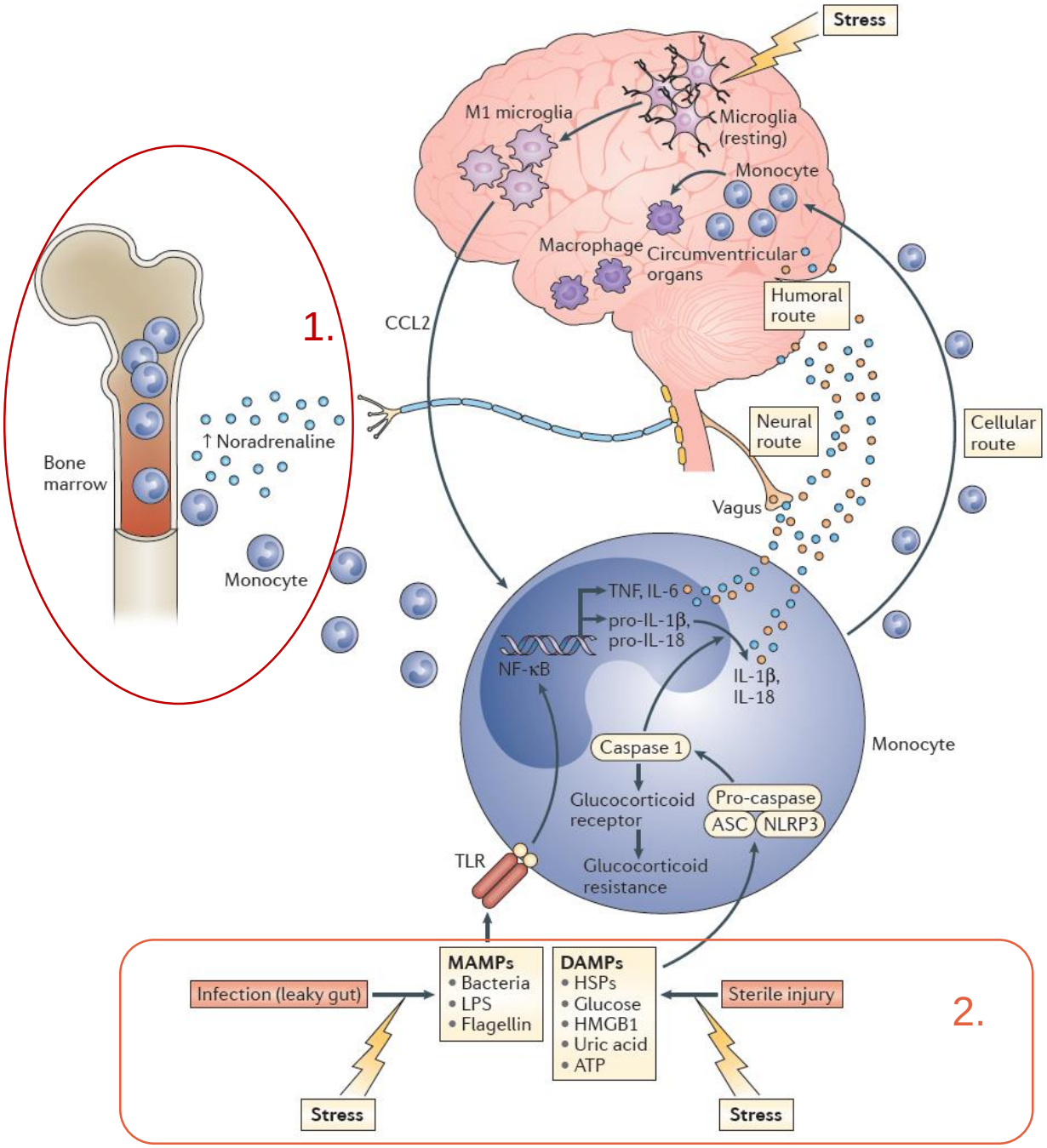


from Kumar, V., Abbas, A. K., & Aster, J. C. (2015).



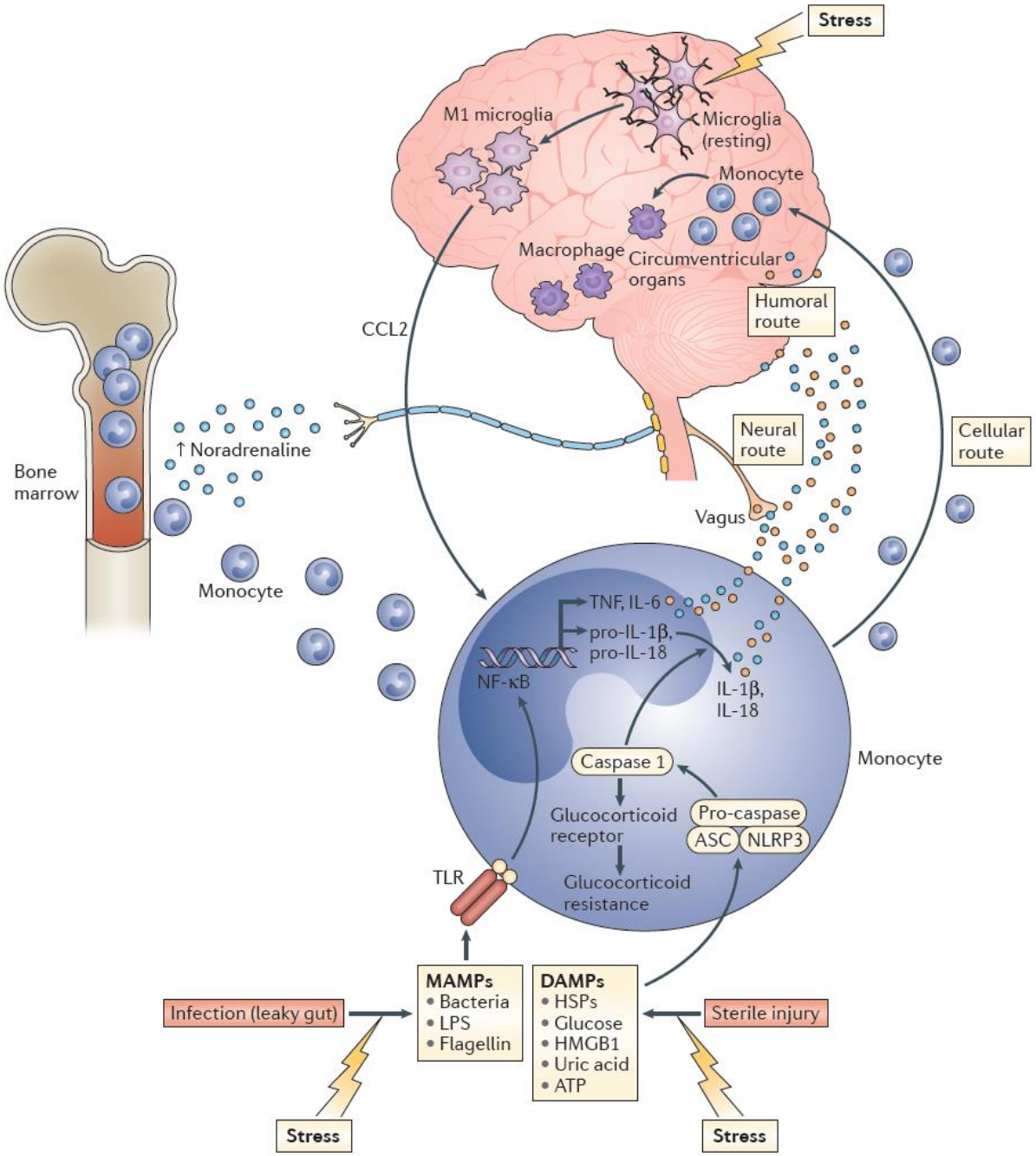
from Strowig, T., et al. (2012).

From initial evidence and hypothesis generation, towards a pathophysiological framework



1. Stimulation of production and release of myeloid cells through catecholaminergic stress response.

2. Higher probability of immune-cells (e.g. Monocytes) to encounter DAMPs and MAMPs in the periphery.



Transmission of inflammatory signals to the brain:

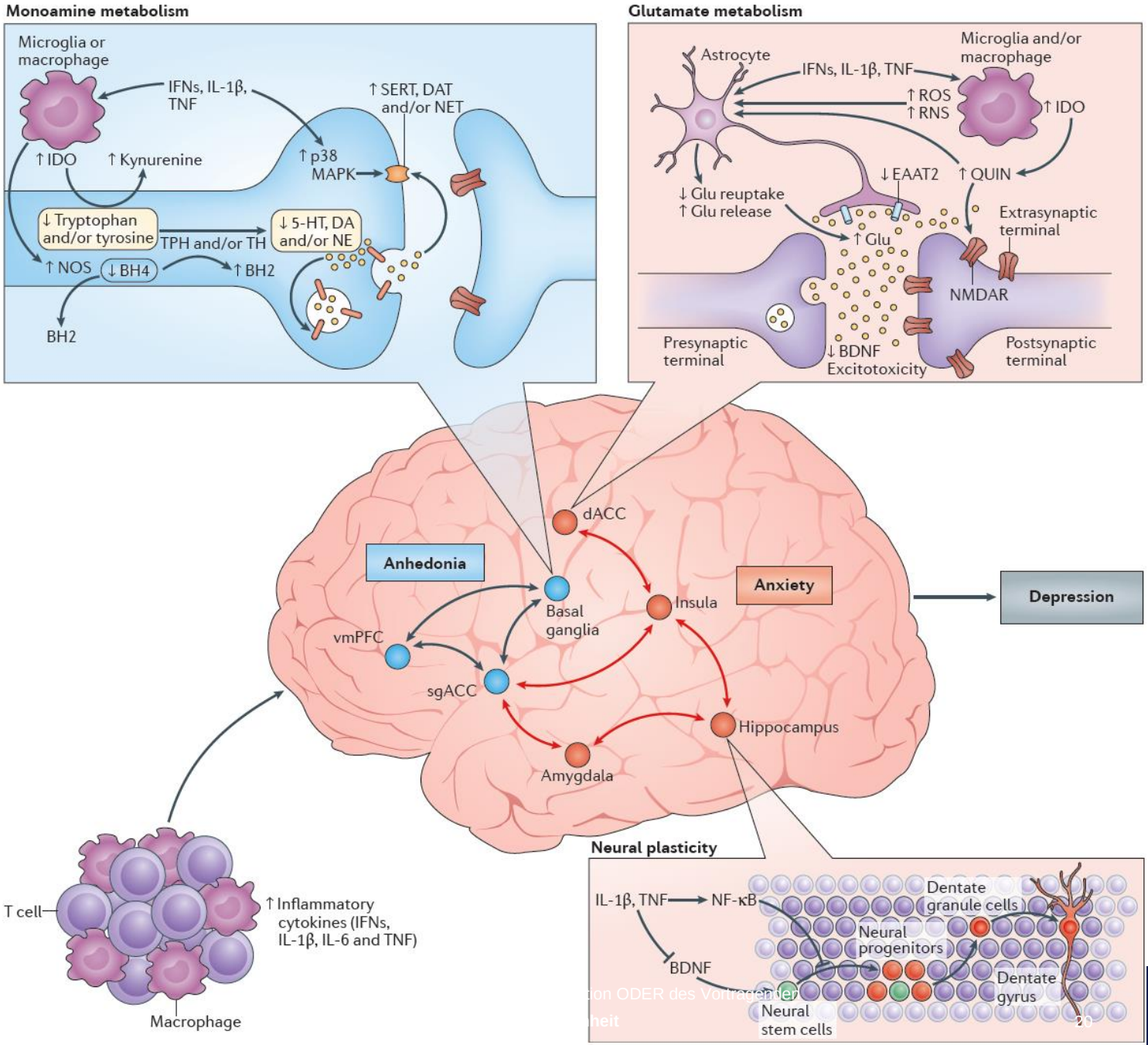
Putative pathways:

Humoral: "Leaky" BBB, and circumventricular organs as entry points of cytokines

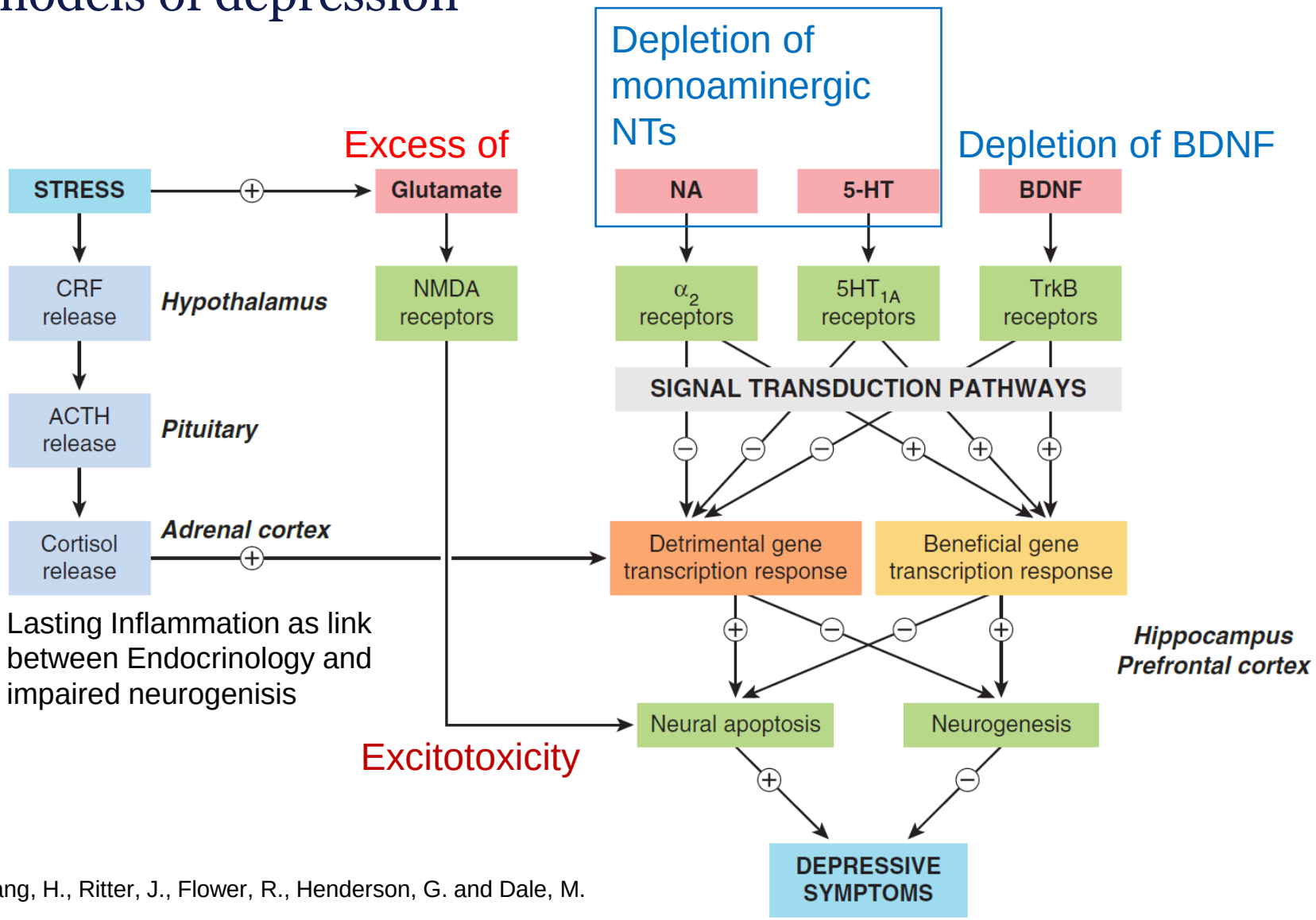
Neural: Binding to afferent vagus fibers -> Induction of central cytokine secretion; Stimulation of ascending sympathetic fibers -> more catecholamine secretion -> vicious cycle.

Cellular: Trafficking of activated immune cells (typically monocytes) into vasculature and brain parenchyma, facilitated by activated microglia.

Lasting effects of inflammation on CNS-function



Integrating immunological considerations into established models of depression



Lasting Inflammation as link between Endocrinology and impaired neurogenisis

From Rang, H., Ritter, J., Flower, R., Henderson, G. and Dale, M. (2016).

IV. Translational considerations

From bench to bedside – Translation in to new therapeutic strategies

Anti-inflammatory therapy should be aimed at the treatment of a subgroup of patients with depression!
Current guidline CRP cut off: >3mg/L

- **Dose-response relationship** between baseline levels of peripheral **inflammation and antidepressant response to infliximab** in a (first) double blind RCT. (Raison, et al. 2013)
- Rosenblat and McIntyre (2017):

  Quantitative synthesis including **three RCTs total N: 158** including 80 participants receiving **minocycline** and 78 participants receiving placebo.

  → **SMD** of minocycline in reducing depressive symptoms compared to placebo was **-0.78** [95% confidence interval (CI) -0.24 to -1.33 (P=0.005)]

(SMD = (Drug Improvement - Placebo Improvement) / Standard Deviation)

Husain, M. I., et al. (2017): **Quantitative analysis of six anti-inflammatory RCTs (n=214 participants with either MDD or bipolar depression) :**

Statistically significant moderate antidepressant effect (SMD=−0.71) (n=214, 95% CI −1.24 to −0.17, p=0.009)) of antiinflammatory treatment vs. Placebo.

BUT!

Severe Limitations:

-> Vastly different compounds used: Celecoxib, Aspirin, Infliximab, NAC…

-> Different symptom rating scales, not all of studies reported post-treatment symptom severity as an outcome measure; instead they provided data on change in symptom scores.

-> Generally small sample sizes, short durations of treatment, differing baseline symptomatology, comorbidity and poorly defined illness durations.

Keep an eye on:

- **Mino-TRD** -> Multicentric (at least 8 participating Centers) Clinical Trial, started in 2015

https://psychiatrie.charite.de/forschung/neurobiologisches_labor/studieninformation_fuer_interessenten_der_mino_trd_studie/

V. Q & A

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