

Inflammation in Chronic Brain Diseases

21st Annual International Integrative Medicine
Conference

Melbourne Australia

July 18, 2015

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Disclosure Statement

Robert Bransfield, MD, DLFAPA, PC

- Patients pay me money in return for trying to help them.
- Most of my income is paid directly from patients
- No psychoimmunology or infectious disease financial interests.
- No research grants or patents dependent upon a disease definition.
- Speakers Bureau (currently): Actavis, Astra Zeneca, Lundbeck, Sunovion, Takeda, Teva

Outline

- Introduction
 - Inflammation
- Pathophysiology
 - Autoimmunity
 - Biochemistry
 - Clinical Presentation
- Assessment
- Treatment
- Conclusion

Introduction

- Is Inflammation:
 - A friend?
 - A foe?
 - Both?
- What provokes and perpetuates it?
- What are the treatments?

Inflammation Definition

- A protective tissue response to injury or destruction of tissues, which serves to destroy, dilute, or wall off both the injurious agent and the injured tissues. The classical signs of acute inflammation are pain (dolor), heat (calor), redness (rubor), swelling (tumor), and loss of function (functio laesa).inflammatory

Neuroinflammation Definition

- The inflammatory response is an **early, non-specific immune reaction** to tissue damage or pathogen invasion. Inflammation of the central nervous system (CNS) is characterized by **increased glial activation, pro-inflammatory cytokine concentration, blood-brain-barrier permeability, and leukocyte invasion.**

The evolution of the danger theory

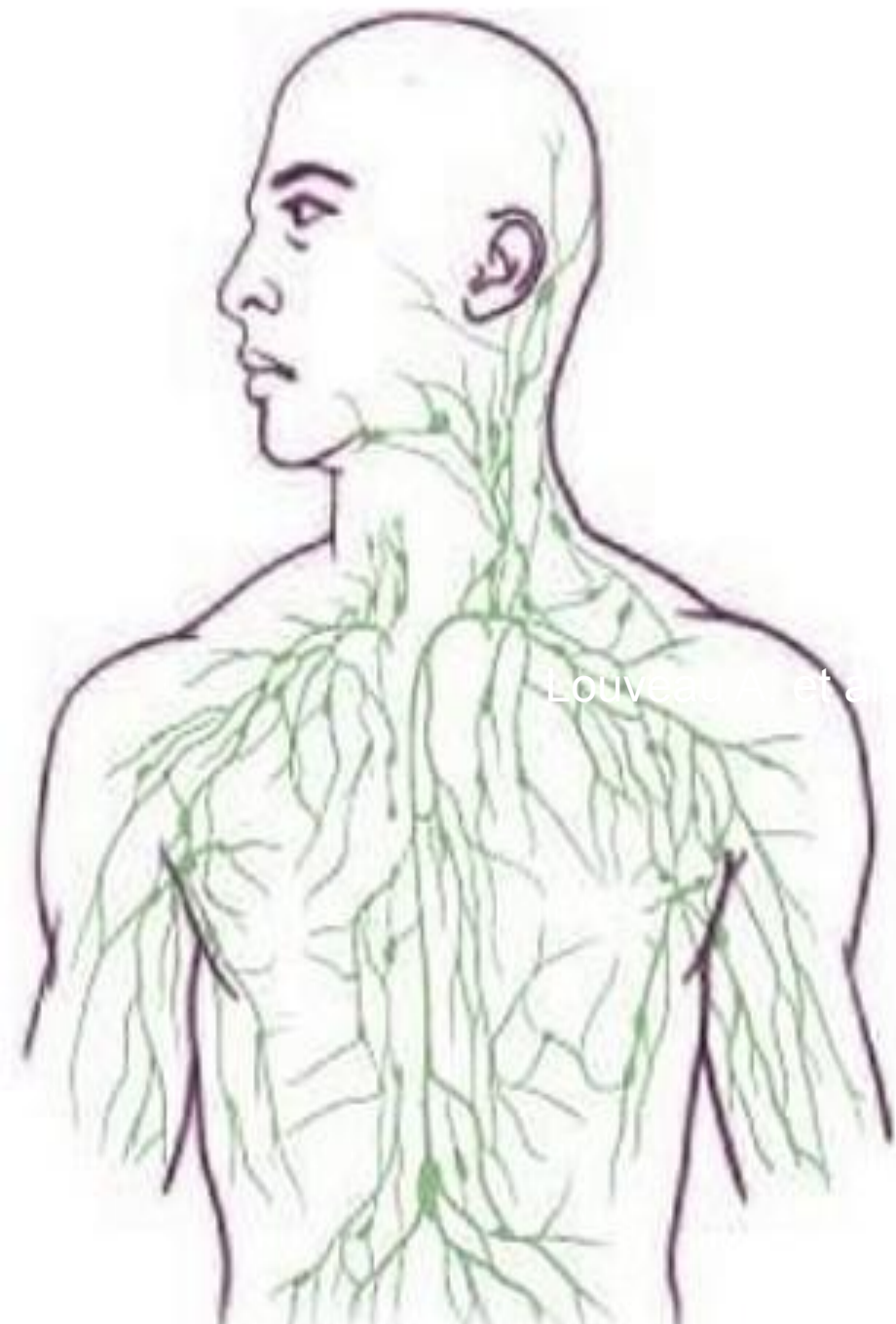
- The dominant model of immunity does not explain a wealth of accumulated data and has recently suggested an alternative, the **danger** model, which suggests that the immune system is far less concerned with things that are **foreign** than with those that do **damage**.

Immune System & Nervous System

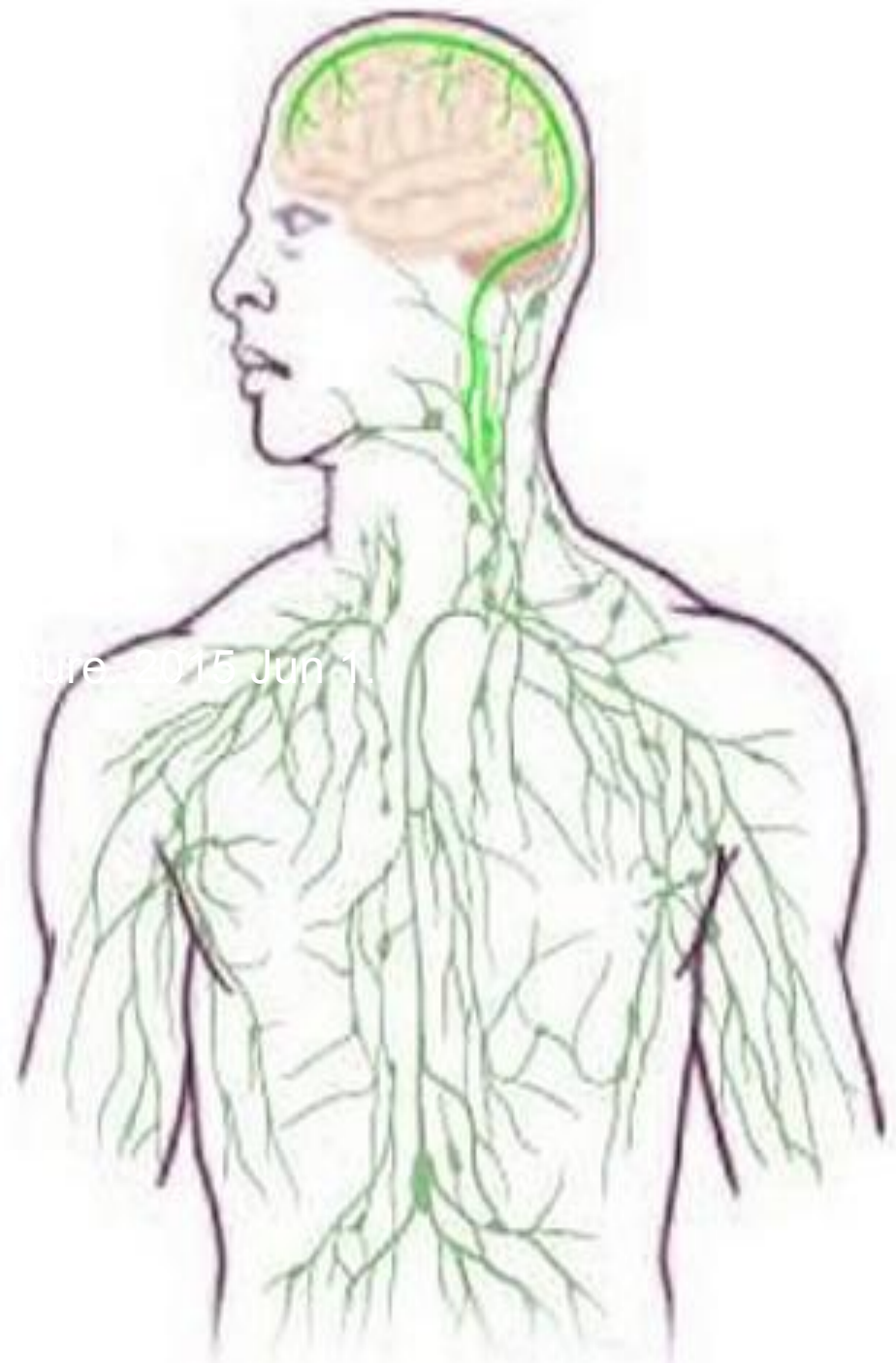
- They communicate with each other.
- Both respond to **danger**.
- Both have early, innate, as well as long term learned adaptive mechanisms.
- Pathology occurs with failure to adapt or excessive reactivity to danger or adaptive mechanisms gone awry, or chronic trauma from chronic reactivity to chronic stressors.

Structural and functional features of central nervous system lymphatic vessels

- We discovered functional lymphatic vessels lining the dural sinuses. These structures are able to carry both fluid and immune cells from the cerebrospinal fluid, and are connected to the deep cervical lymph nodes. The discovery of the central nervous system lymphatic system may call for a reassessment of basic assumptions in neuroimmunology and sheds new light on the aetiology of neuroinflammatory and neurodegenerative diseases associated with immune system dysfunction.



Louveau A, et al. Nature. 2015 Jun 1.

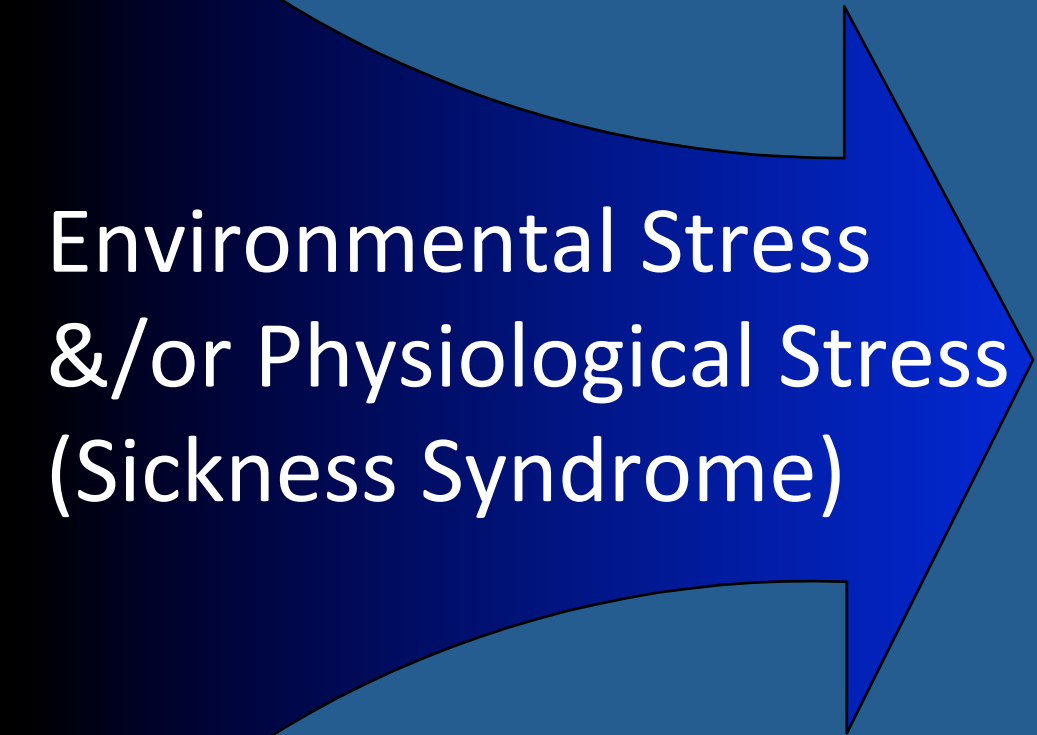


Louveau A, et al. Nature. 2015 Jun 1.

What Provokes & Weakens the Immune System?

- Infections
- Cancer
- Allergens
- Stress
- Early life stress
- Sleep deprivation
- Vaccinations
- Trauma
- Toxins
- Degenerative changes
- T cell dysfunction
- Foehn, barometric pressure drops
- Molecular mimicry
- Low glutathione levels
- Increased oxidative stress
- Metal toxicity
- Elevated leptin levels
- Obesity
- Diet
- Leaky gut
- Some medical treatments

Alostatic Load and Inflammation



Environmental Stress
&/or Physiological Stress
(Sickness Syndrome)

Inflammation

Progressive Inflammation is Associated with Increasing Encephalopathy & Increasing Mental Symptoms

Mild	Moderate	Severe
Executive dysfunction	Increasing cognitive deficits	Dementia
Reduced frustration tolerance, irritability, insomnia, dysthymia	Anxiety disorders, depression, impulsivity, personality disorders	Major psychiatric disorders, psychosis, suicide, homicide

Increasing Neurological, Multisystemic Symptoms & Fatigue



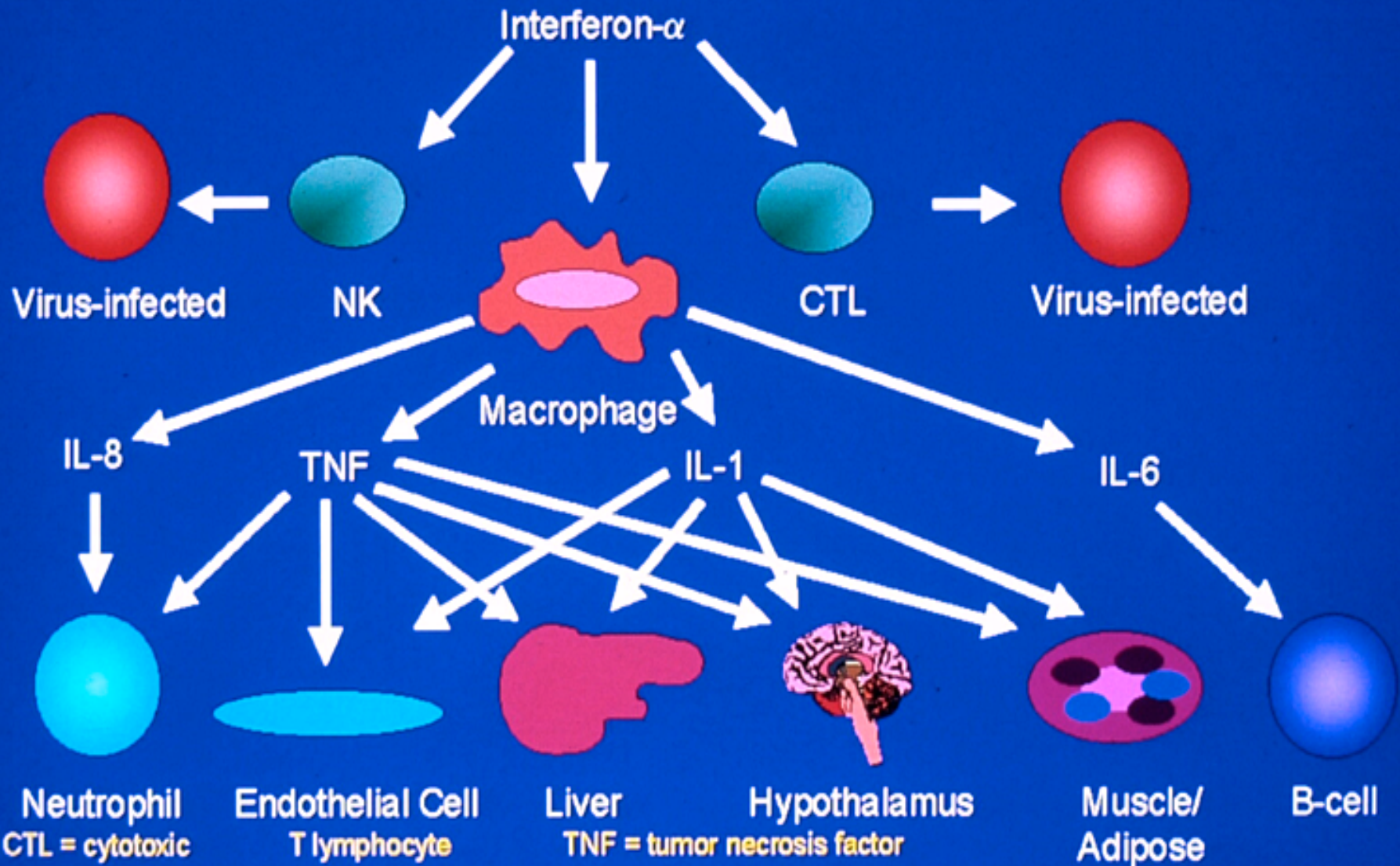
What Supports the Association?

- Inflammatory agents induce mental symptoms
- Inflammatory markers are elevated in mental disorders.
- Biochemistry
- Immune dysfunction adversely impact brain development.
- Psychotropics are anti-inflammatory.

Hepatitis C & Interferon Treatment

- A good model for inflammation mediated mental symptoms
- Cognitive impairments
- Symptoms include depression, anxiety, mania, irritability, impulsiveness, hostility, relapse of substance abuse & lassitude.[1]

IFN Cascade



Adapted courtesy of Sidney Grossberg, MD, Medical College of Wisconsin

Are Mood and Anxiety Disorders Inflammatory Diseases?

- Studies demonstrate increases in inflammatory markers in:
 - Sleep deprivation: IL-6 [1]
 - Stress: IL-1 beta, TNF-alpha, IL-6 [2]
 - PTSD: IL-1 beta, IL-6, TNF-alpha [3]
 - Depression: IL-6, CRP, IL-1, TNF-alpha [3]
 - Bipolar: IL-6, TNF-alpha, CRP, sIL-2R, sIL-6R [3]
 - Schizophrenia: IL-1 beta [4]
 - Autism: IL-6, autoimmune mechanisms [5]
 - Alzheimer's: IL-6, TNF-, IL-1, TGF-, IL-12 and IL-18 [6]

[1] M. Haack, E. Sanchez, J. Broussard, M. Regan, J. Mullington. *J Pain*. 2004;5(3)

[2] Raison et al, *Arch Gen Psychiatry*. 2010;67(12):1211-1224.

[3] Boorman E et al. *Psychiatric Annals*. 2015;45(5):240-248.

[4] Schwieler L, et al. *J Psychiatry Neurosci*. 2015 Mar;40(2):126-33

[5] Bransfield R. *Pediatric Health*. 3(2):125-140. (2009)

[6] Swardfager W, et al. *BIOL PSYCHIATRY* 2010.

Cytokine Activation Causes Psychiatric Symptoms

- Interleukin-6 Is Elevated in the Cerebrospinal Fluid of Suicide Attempters and Related to Symptom Severity (1)
- Interleukin-1Beta & Self-Inflicted Aggressive Behavior (2)
- Interleukin-1Beta Causes Fatigue (3)

(1) Lindqvist D, Janelidze S, Hagell P, Erhardt S, Samuelsson M, Minthon L, Hansson O, Björkqvist M, Träskman-Bendz L, Brundin L. Biol Psychiatry. 2009 Mar 6. [Epub] Lindqvist D. 10th Psychoimmunology Expert's Meeting, Gunzburg, 2009.

(2) Westling S et al. 10th Psychoimmunology Expert's Meeting, Gunzburg 2009.

(3) Corwin et al. Ann Behav Med 2003;25:41-47.

Inflammation in neurodegenerative diseases

- Neurodegeneration, the slow and progressive dysfunction and loss of neurons and axons in the central nervous system, is the primary pathological feature of acute and chronic neurodegenerative conditions such as Alzheimer's disease and Parkinson's disease, neurotropic viral infections, stroke, paraneoplastic disorders, traumatic brain injury and multiple sclerosis. **Despite different triggering events, a common feature is chronic immune activation, in particular of microglia**, the resident macrophages of the central nervous system.

LATE-STAGE IMMUNE CNS EFFECTS

- Mechanisms leading to the injury of neuronal cells include:
 - The secretion of cytotoxic substances by leucocytes and glial cells
 - Direct cytotoxicity
 - Autoimmune-triggered processes via molecular mimicry
 - An interaction between pathogens and the neural cells can cause dysfunction by adherence, invasion, and cytotoxicity of neural cells.

Balanced Inflammation

- Inflammation could have a protective role and promote regeneration of damaged neurons. We do not yet know how to achieve a "balanced" inflammation. Because some novel anti-inflammatory treatment might have detrimental consequences, carefully monitoring disease progress in patients treated with this category of drugs is indispensable.
- A variety of neurological diseases the initial triggers differ significantly, while the subsequent pathways involving inflammatory processes and causing brain damage share certain pathological mechanisms.

Pathophysiology: Autoimmunity

Autoimmune Encephalopathies

- Paraneoplastic limbic encephalopathy
 - autoantibodies directed against intracellular neuronal antigens
- Nonparaneoplastic limbic encephalitis
 - voltage-gated potassium channel limbic encephalitis
 - Hashimoto's encephalopathy
 - Anti-NMDA & other glutamate receptor encephalitis
- Encephalitis associated with GABAergic signaling

Antibodies to surface dopamine-2 receptor in autoimmune movement and psychiatric disorders

- Recent reports of autoantibodies that bind to neuronal surface receptors or synaptic proteins have defined treatable forms of autoimmune encephalitis.
- We conclude that assessment of dopamine-2 receptor antibodies can help define autoimmune movement and psychiatric disorders.

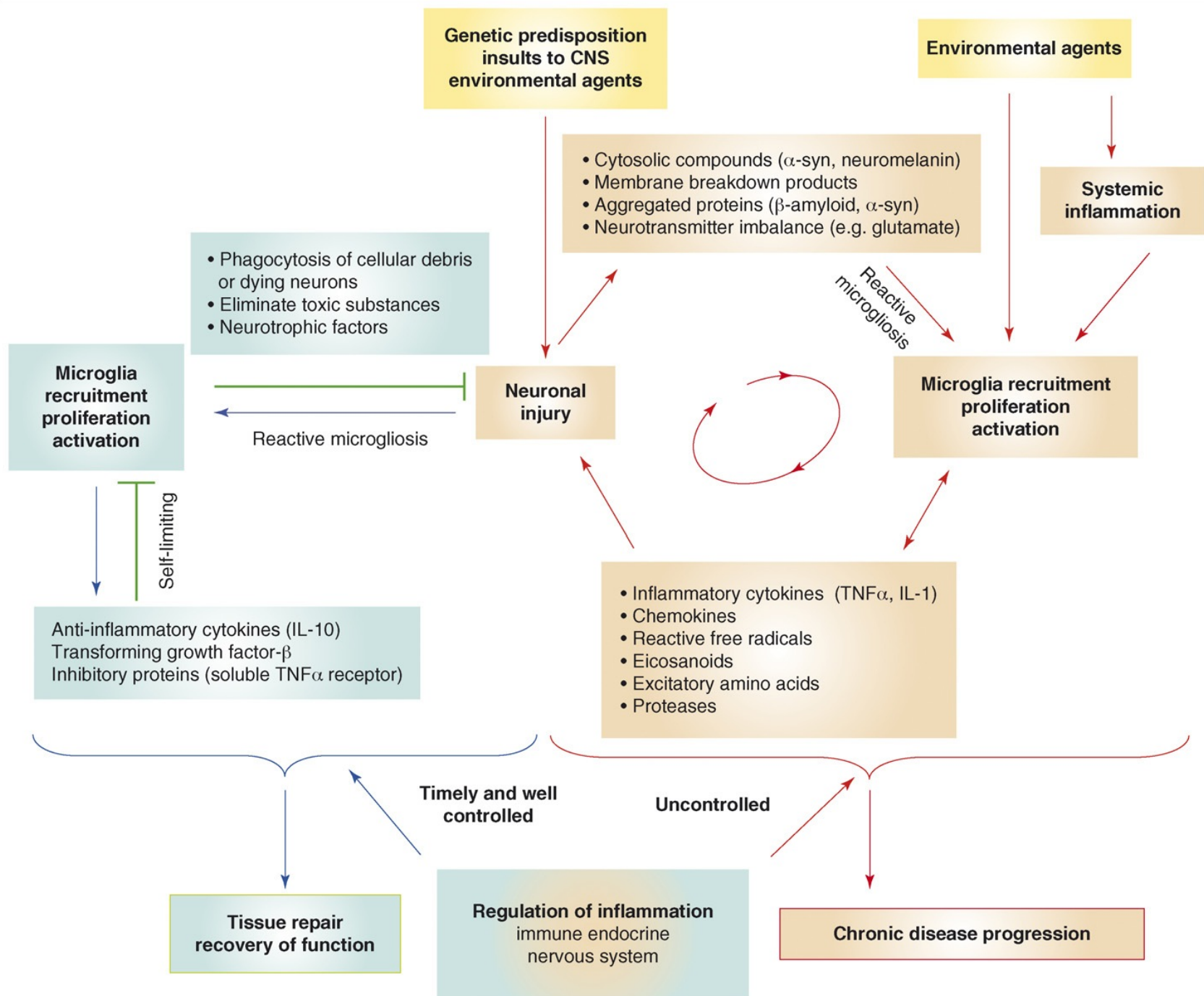
Pediatric Autoimmune Diseases Associated with Strep (PANDAS)

- Strep infections in a genetically susceptible individual at a young age can result in OCD, tics and sometimes attention span difficulties
- Often comorbid with Lyme/tick-borne disease
PITAND (Pediatric Infection-triggered Autoimmune Neuropsychiatric Disorders)
- Symptom flares follow a strep infection and correlate with increased antibody production
- ASO & anti-DNA titers may be elevated
- Antibiotics are effective in treating and preventing these symptoms
- IVIG & plasmapheresis can also be effective.

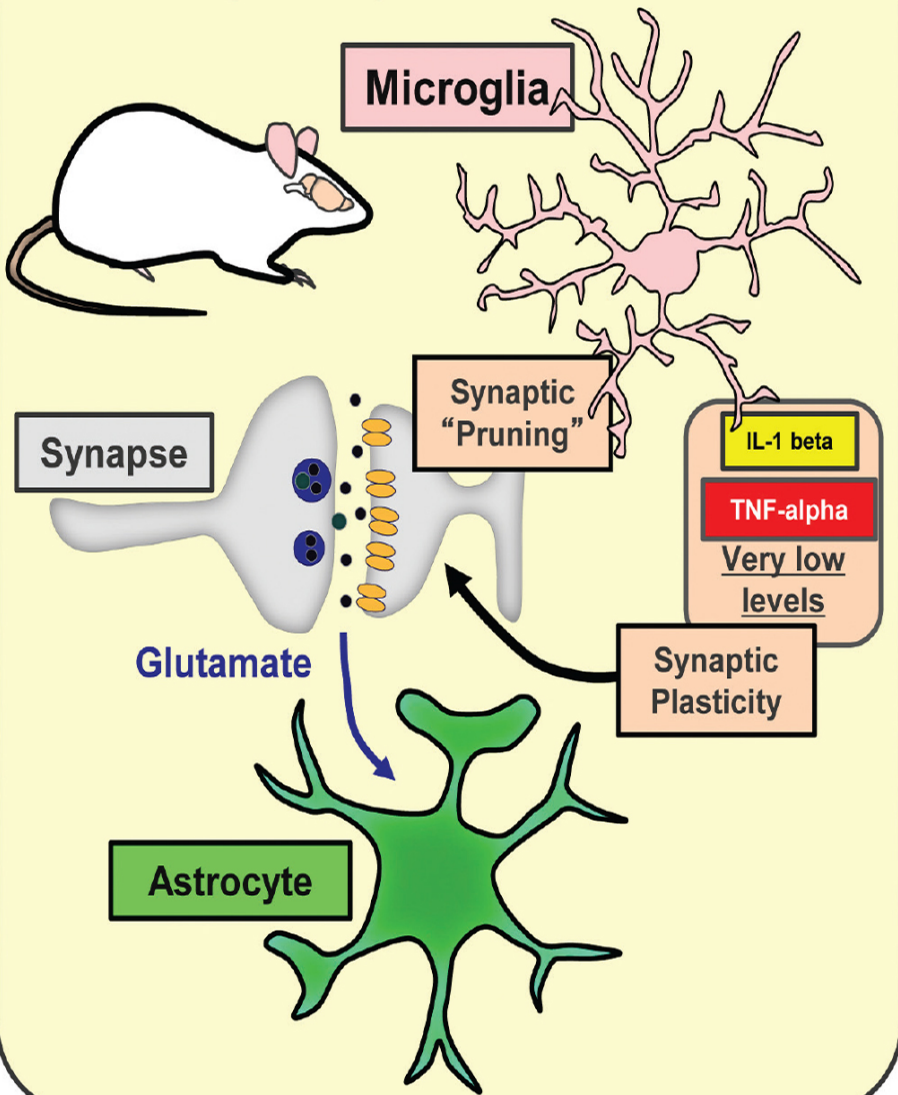
Pathophysiology: Biochemistry

Immune Provoked Pathophysiology

- Pathophysiologic changes are associated with oxidative stress, excitotoxicity, changes in homocysteine metabolism, mitochondrial dysfunction and altered tryptophan pathways.

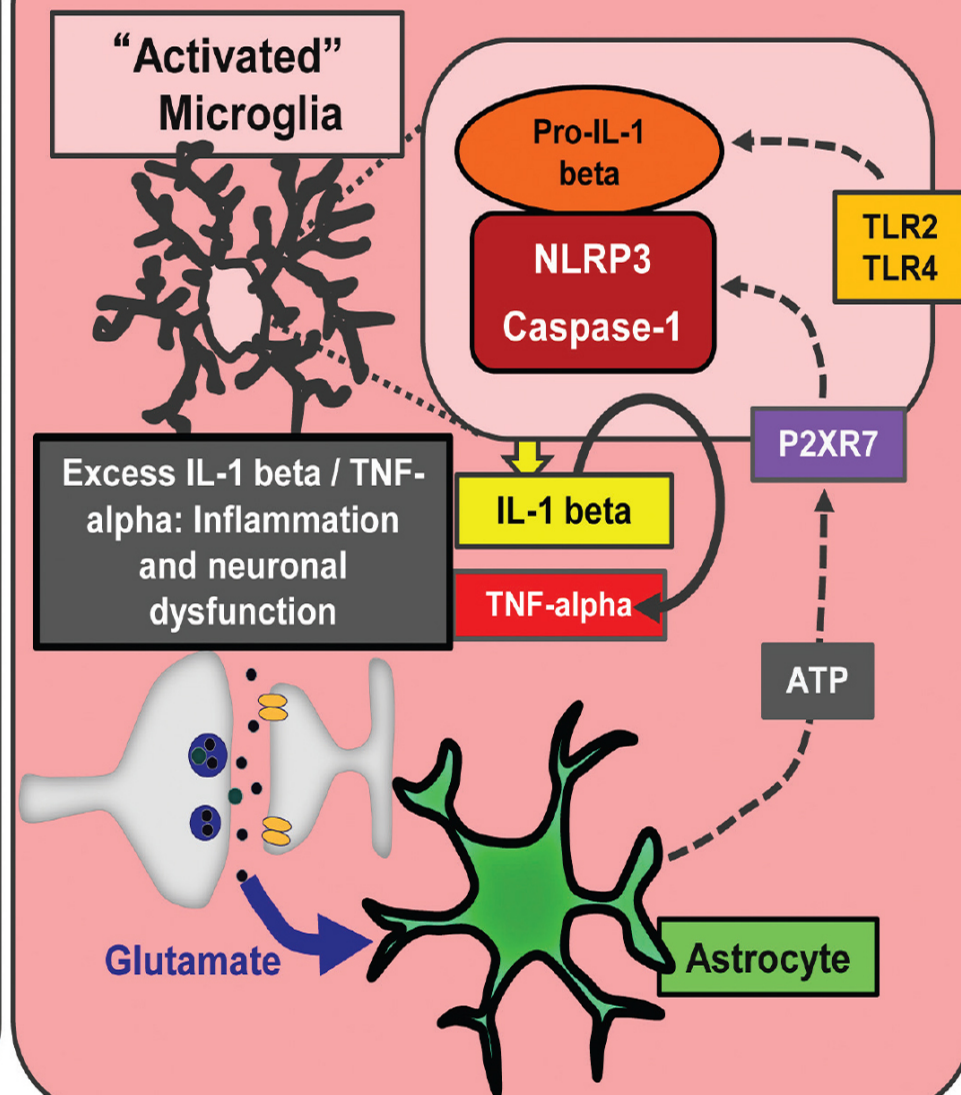


Physiological Conditions



Normal Behavior & Mood

"Stressed" Conditions

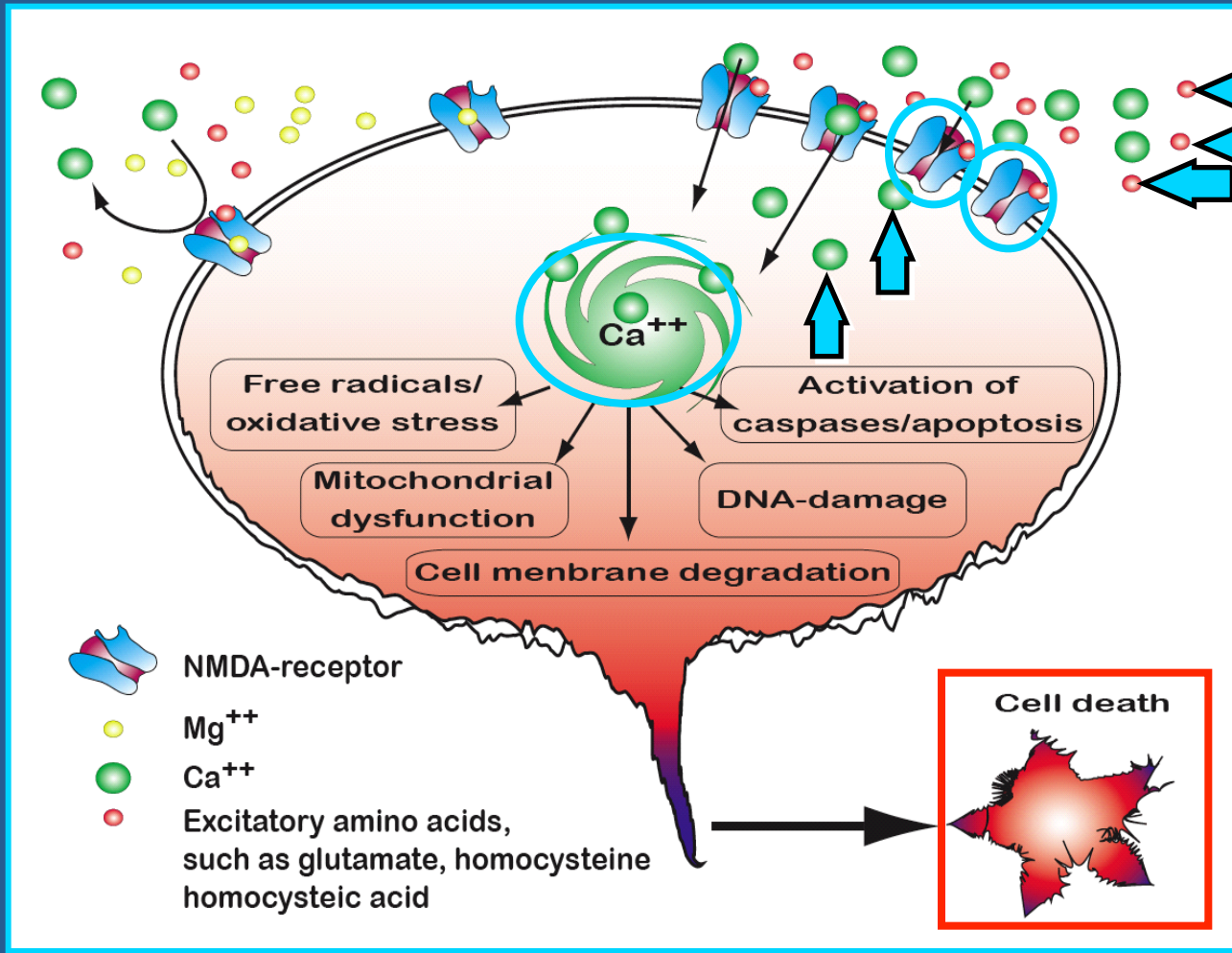


Prolonged Sickness, Depression, & Anxiety Behaviors

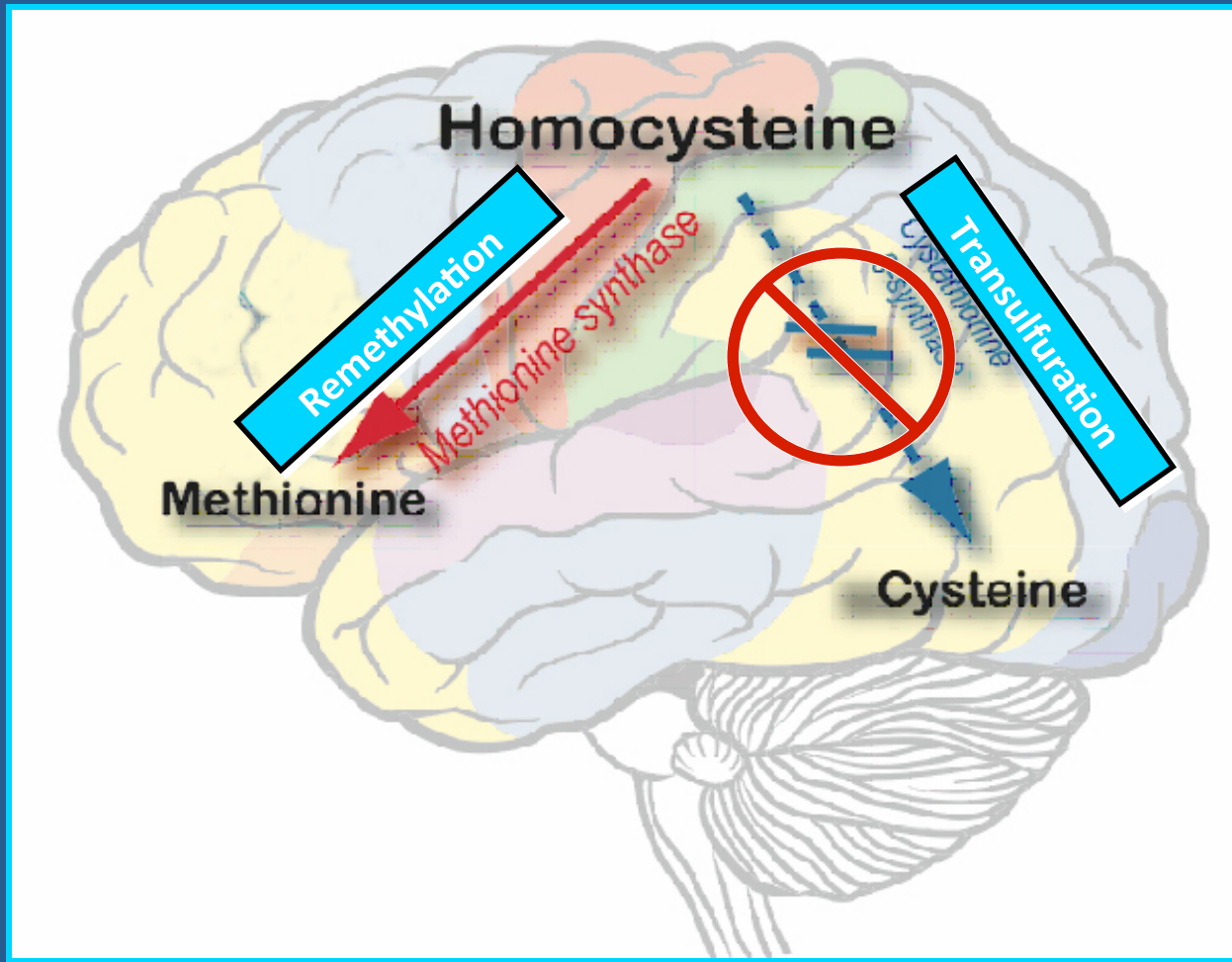
Oxidative Stress

- “Oxygen free radicals or activated oxygen has been implicated in diverse environmental stresses in plants and animals and appears to be a common participation in most, if not all, degenerative conditions in eukaryotic cells. The peroxidation of lipids, the cross-linking and inactivation of proteins and mutations in DNA are typical consequences of free radicals”

Excitotoxicity



Homocysteine Metabolism in the Brain

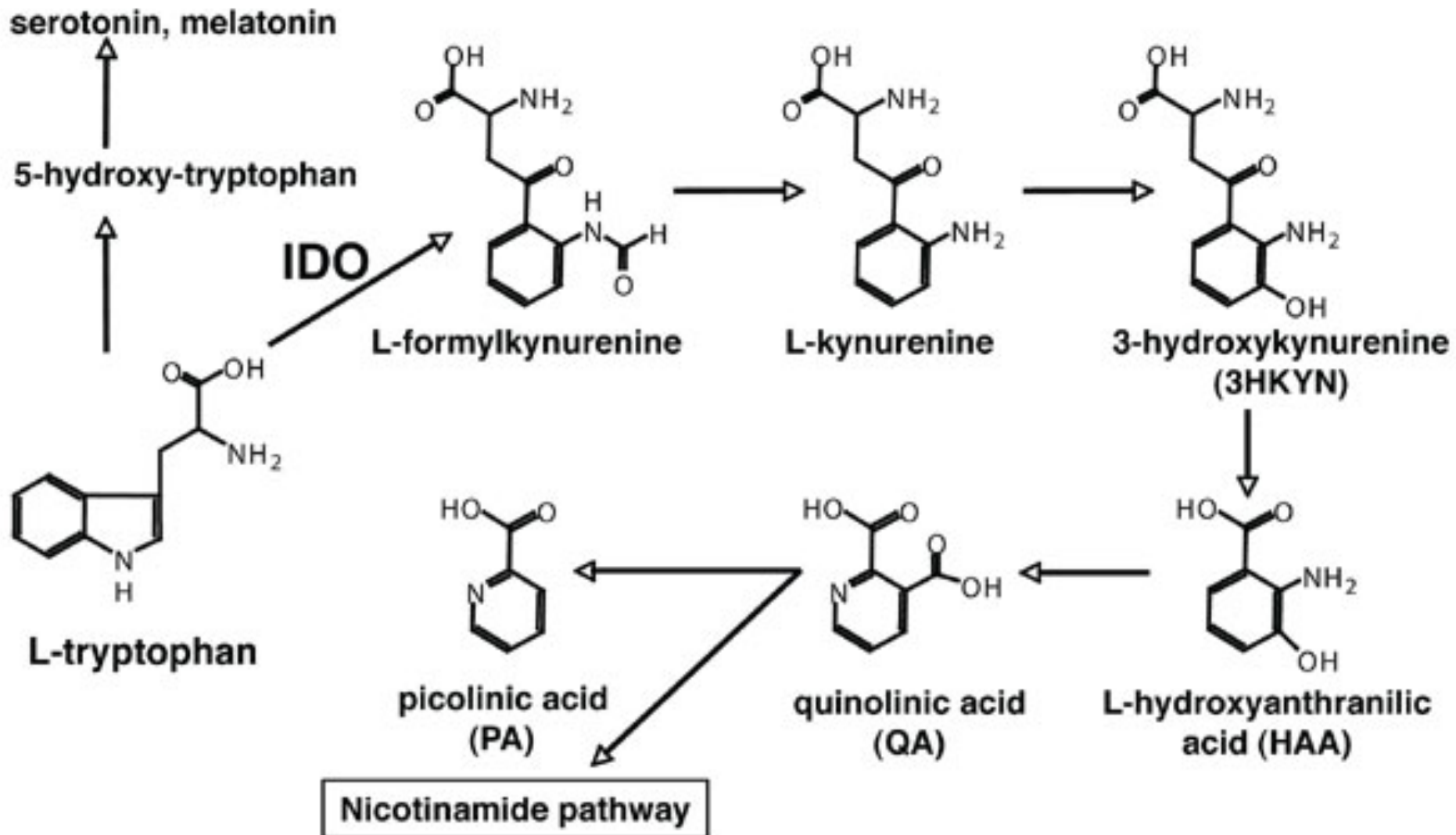


Inadequate remethylation leads to increased Hcy levels which are excitotoxic.

Homocysteine, depression and cognitive function in older adults

- Depression and high total plasma homocysteine are independently associated with cognitive impairment in older adults.
- Elevated total plasma homocysteine was associated with weaker performance in tests of immediate and delayed memory and global cognitive performance when compared to those with normal total plasma homocysteine independent of the presence of major depression or the severity of depressive symptoms.

IDO shifts tryptophan metabolism from serotonin to quinolinic acid



IDO and interferon--induced depressive symptoms: a shift in hypothesis from tryptophan depletion to neurotoxicity

- The enzyme indoleamine 2,3-dioxygenase (IDO), which converts tryptophan (TRP) into kynurenine (KYN) and which is stimulated by proinflammatory cytokines, may be implicated in the development of IFN--induced depressive symptoms, first by decreasing the TRP availability to the brain and second by the induction of the KYN pathway resulting in the production of neurotoxic metabolites.
- This study does support a role for IDO activity in the pathophysiology of IFN--induced depressive symptoms, through its induction of neurotoxic KYN metabolites.

Pathophysiology: Clinical Presentations

Chronic Stress, Insomnia, Sickness Syndrome & Fatigue



Disease Precipitation vs. Disease Perpetuation & Disease Progression

- What precipitates a disease process may not be exactly the same as what causes the perpetuation and progression of the disease.
- Chronic stress and non-restorative sleep contribute to disease perpetuation & are associated with:
 - Decreased regenerative functioning
 - Compromised immunity
 - Decreased resistance to infectious disease
 - Fatigue

Central pathways causing fatigue in neuro-inflammatory and autoimmune illnesses

- It is concluded that peripheral inflammation and immune activation, together with the subsequent activation of glial cells and mitochondrial damage, likely account for the severe levels of intractable fatigue and disability seen in many patients with neuroimmune and autoimmune diseases. This would also appear to be the case for many patients afforded a diagnosis of Chronic Fatigue Syndrome.

Sleep Drives Metabolite Clearance from the Adult Brain

- Sleep is associated with a 60% increase in the interstitial space, resulting in a striking increase in convective exchange of cerebrospinal fluid with interstitial fluid which increases clearance of β -amyloid. The restorative function of sleep may be a consequence of the enhanced removal of potentially neurotoxic waste products that accumulate in the awake central nervous system.

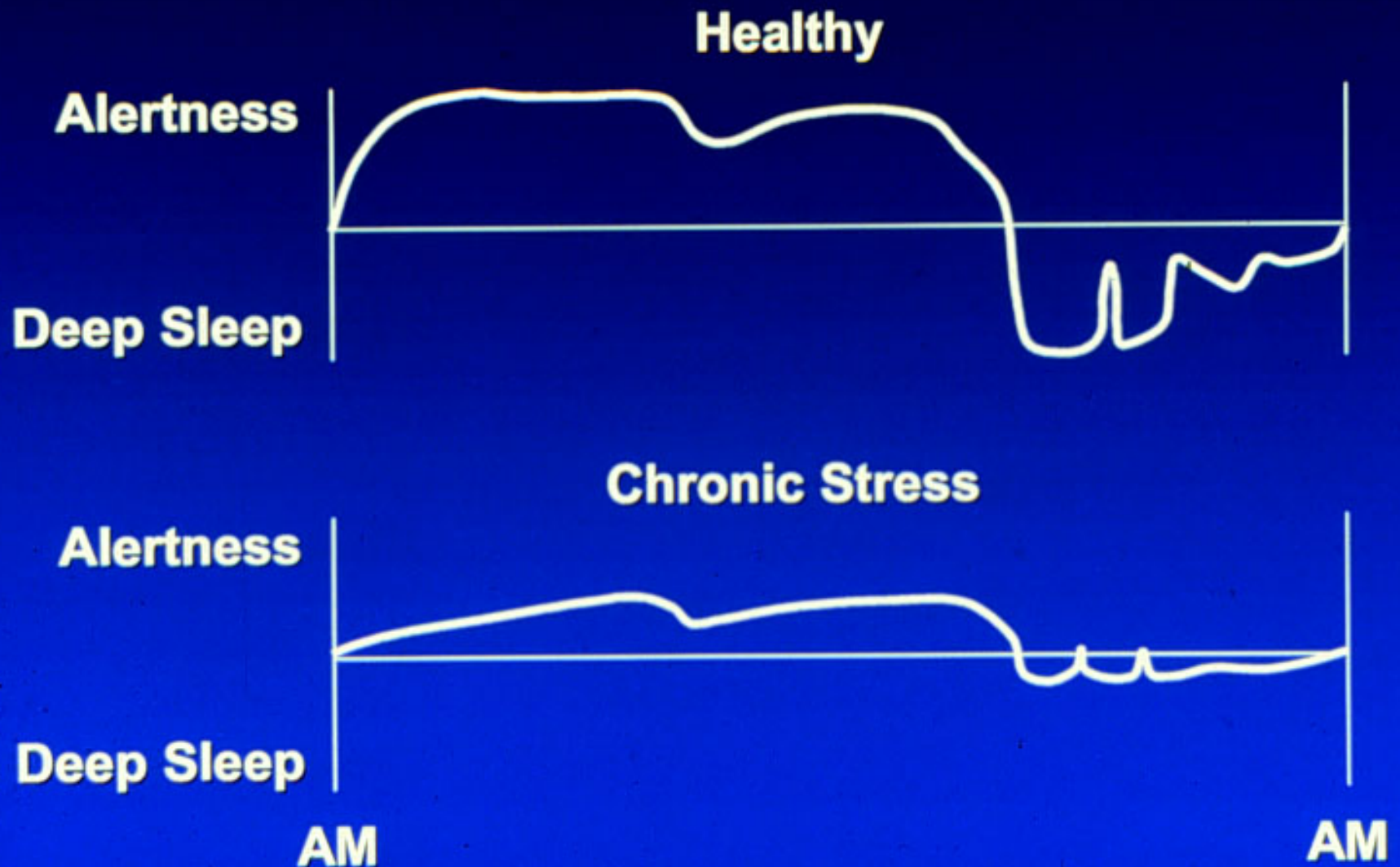
Diurnal Physiological Variation of Immune Parameters in Humans

- Sleep initiates Th1 response in lymph nodes.
- Early nocturnal sleep promotes T cell & proinflammatory cytokines & naïve T cell dendritic cell interaction.
- Sleep promotes immunosupportive hormones such as GH & prolactin to suppress anti-inflammatory hormones such as cortisol, norepinephrine and epinephrine.

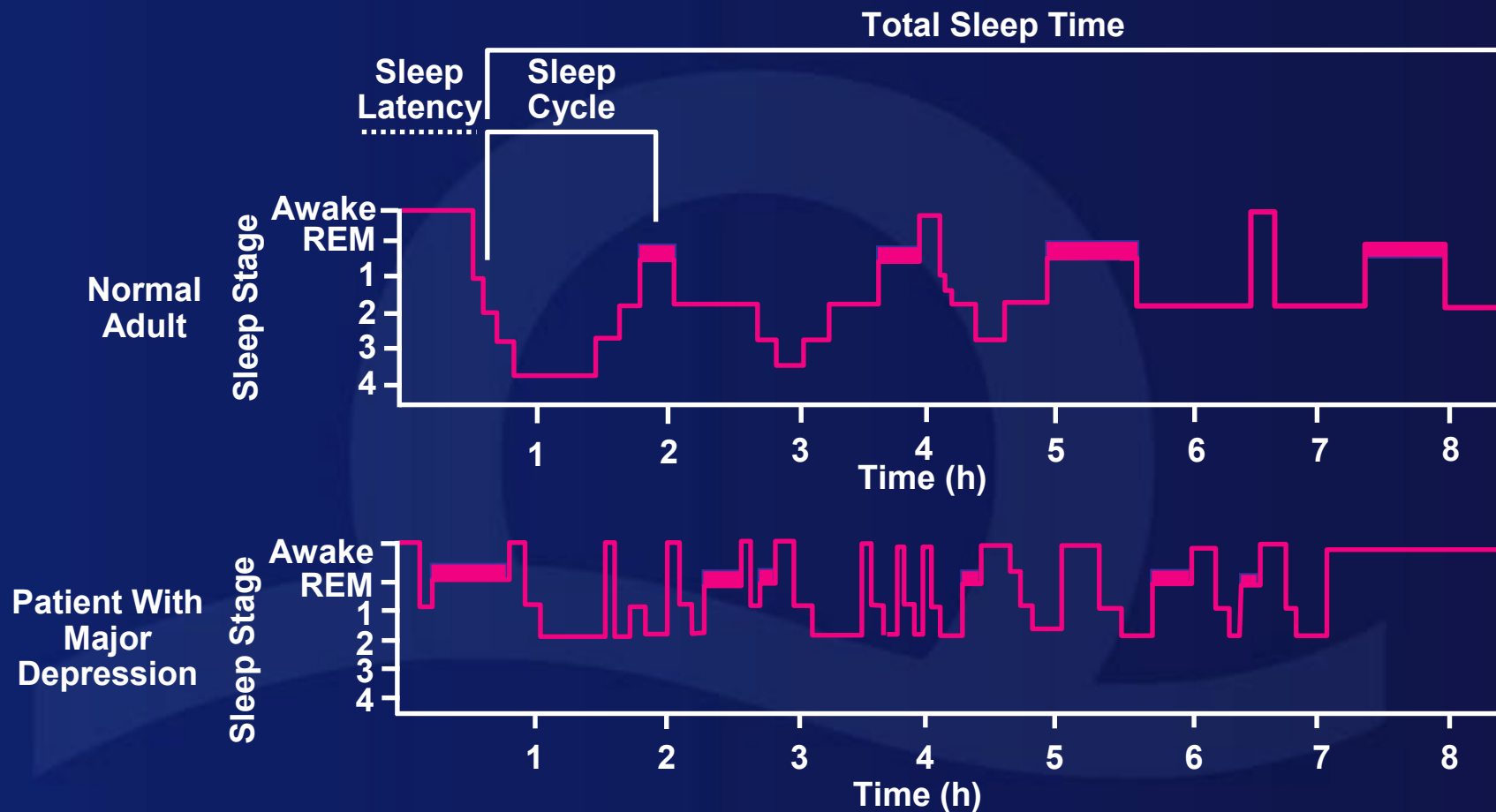
Bidirectional Communication between the Brain and the Immune System: Implications for Physiological Sleep and Disorders with Disrupted Sleep

- Cytokines produced by cells of the immune and nervous systems regulate sleep.
- particularly interleukin-1beta and tumor necrosis factor-alpha, signal neuroendocrine, autonomic, limbic and cortical areas of the CNS to affect neural activity and modify behaviors (including sleep), hormone release and autonomic function.
- Sleep disorders are commonly associated with chronic inflammatory diseases and chronic age- or stress-related disorders. The best studied are rheumatoid arthritis, fibromyalgia and chronic fatigue syndromes.

Circadian Rhythms



Variability in Sleep Patterns in a Normal Adult vs a Patient With Major Depression

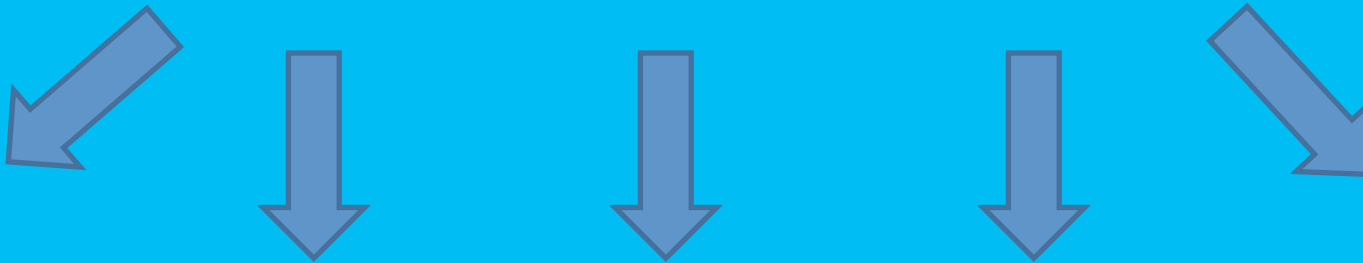


Adapted with permission from Winokur A, Reynolds CF III. *Primary Psychiatry*. Nov/Dec 1994:22-27.

Please see important safety information on accompanying slides and full prescribing information.

Disease Progression

**Non-Restorative
Sleep**



Fatigue

**Cognitive
Impairments**

**Emotional
Impairments**

**Pain
Sensitivity**

**Immune
Dysfunction**

Delta Sleep

- Sleep restriction increases IL-6 and pain-related symptoms in healthy volunteers (1)
- Impaired Sleep Correlates with Impaired Immune Functioning (2)
- Growth hormone is dependent upon delta sleep & modulates immune response (3)
- Increasing delta sleep is therapeutic

(1) M. Haack, E. Sanchez, J. Broussard, M. Regan, J. Mullington
J Pain; April 2004, Supplement 1 • Volume 5 • Number 3

(2) Modolfsy H. Sleep and the immune system. Int J Immunopharmacol 1995;17:649-54.

(3) Kelley KW. Ann N Y Acad Sci. 1990;594:95-103.

A Meta-Analysis of Cytokines in Major Depression

- This meta-analysis (**24 studies**) reports significantly higher concentrations of the proinflammatory cytokines TNF- α and IL-6 in depressed subjects compared with control subjects. While both positive and negative results have been reported in individual studies, this meta-analytic result strengthens evidence that depression is accompanied by activation of the inflammatory response system.

Autoimmune diseases and severe infections as risk factors for mood disorders: a nationwide study

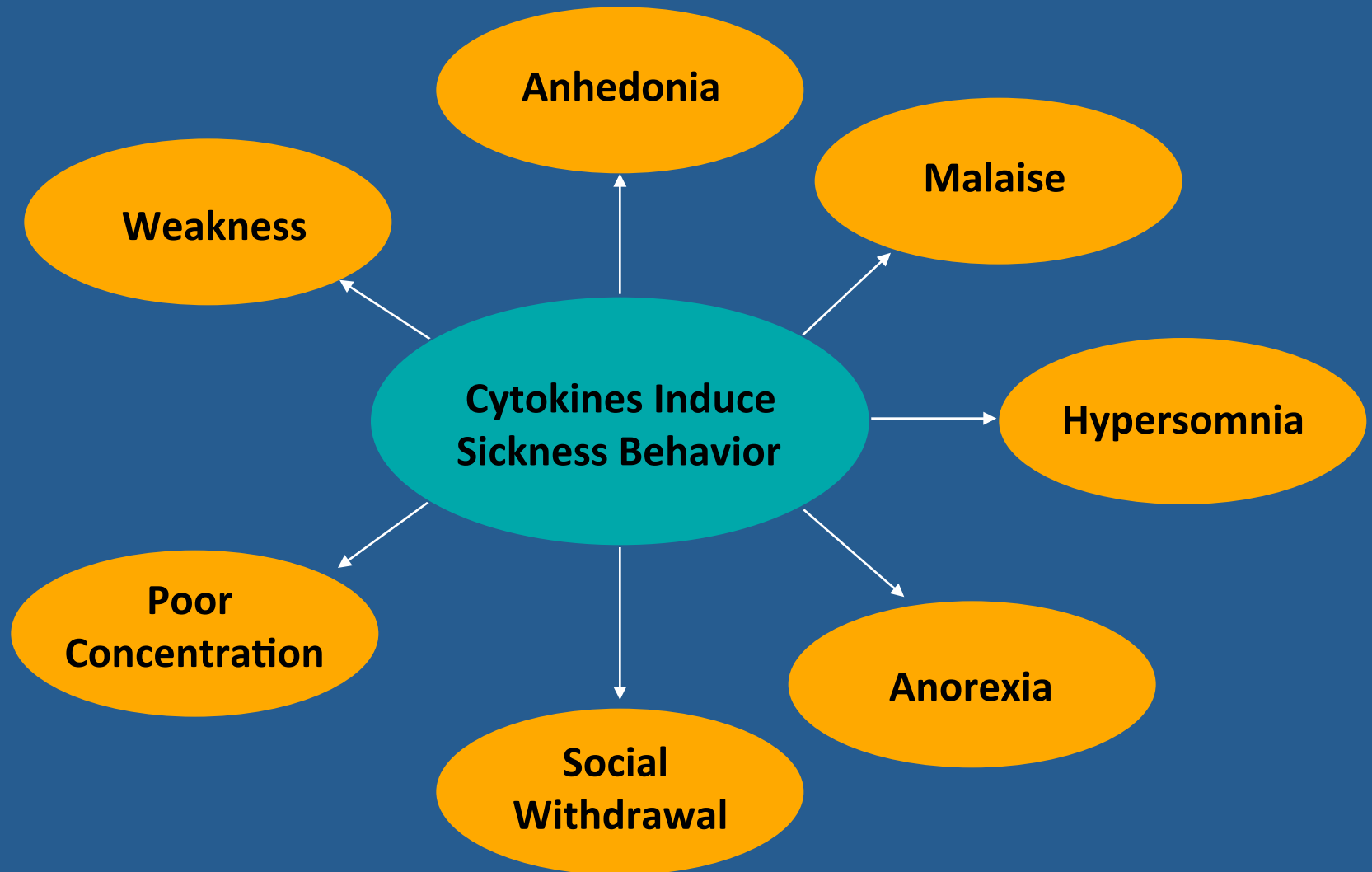
- Autoimmune diseases and infections are risk factors for subsequent mood disorder diagnosis. These associations seem compatible with an immunologic hypothesis for the development of mood disorders in subgroups of patients.

Cytokines, Stress, and Depression

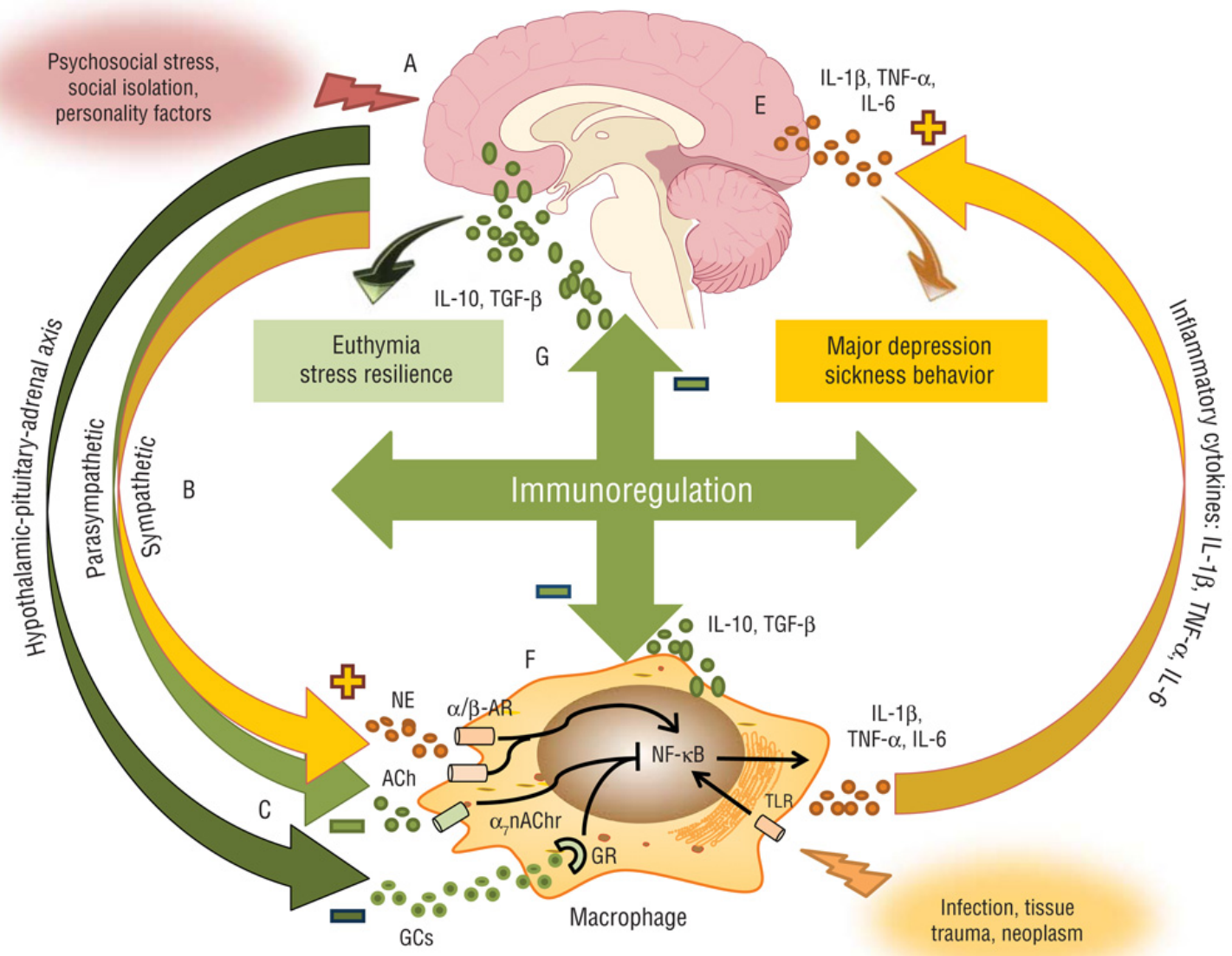
- Immune activation, and particularly increased activity of several cytokines, notably interleukin-1, interleukin-2, interleukin-6, tumor necrosis factor- as well as their soluble receptors is characteristic of depression.
- Affective changes may stem from the neuroendocrine and central neurochemical changes elicited by cytokines, as these are reminiscent of those associated thought to sub serve depression.

Sickness Syndrome Resembles Depression

(Mediated by Proinflammatory Cytokines IL-1, IL-6, and TNF)



Stress and inflammation in MDD



Inflammation and the phenomenology, pathophysiology, comorbidity, and treatment of bipolar disorder: a systematic review of the literature

- Available evidence indicates that bipolar disorder and inflammation are linked through shared genetic polymorphisms and gene expression as well as altered cytokine levels during symptomatic (i.e., mania and depression) and asymptomatic intervals. However, results are inconsistent. Several conventional mood stabilizers have anti-inflammatory properties. Inflammation is closely linked with behavioral parameters such as exercise, sleep, alcohol abuse, and smoking, as well as with medical comorbidities including coronary artery disease, obesity and insulin resistance, osteoporosis, and pain.
- **CONCLUSION: Inflammation appears relevant to bipolar disorder across several important domains.**

Inflammation, Psychosis, and the Brain

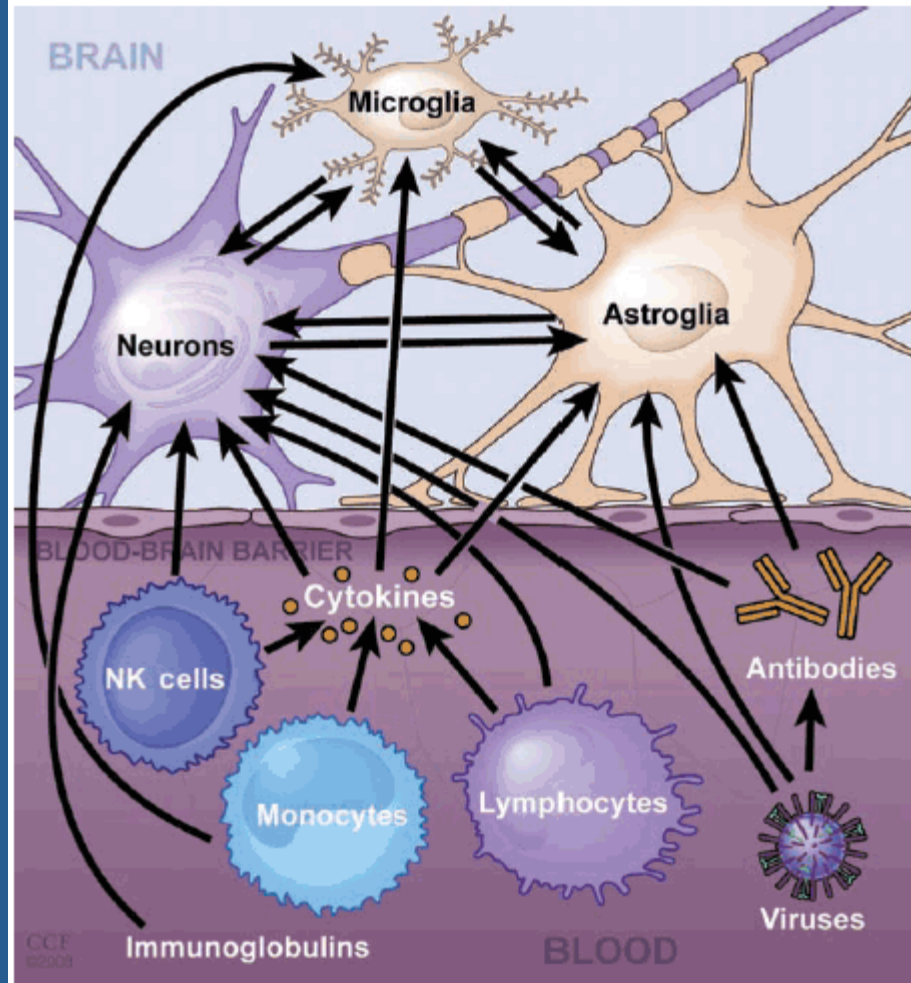
- **Hundreds of studies** of schizophrenic illness in adults have documented immunological abnormalities in these patients
- First-episode psychosis in children is associated with evidence of increased inflammation
- Increasing evidence now suggests that the glia, cerebral vasculature, and the BBB may be involved.
- Our results support the inflammatory theory of schizophrenia that was formulated over a 100 years ago and perhaps offer hope that prevention of chronicity can occur if the first episode of psychosis is rapidly and effectively controlled.

Increased levels of IL-6 in the cerebrospinal fluid of patients with chronic schizophrenia--significance for activation of the kynurenine pathway

- We have shown that IL-6, kynurenine (KYN) and KYNA are elevated in patients with chronic schizophrenia, strengthening the idea of brain immune activation in patients with this disease. Our concurrent cell culture and clinical findings suggest that IL-6 induces the KYN pathway, leading to increased production of the N-methyl-D-aspartate receptor antagonist KYNA in patients with schizophrenia.
- Interleukin-1beta can upset the dopamine system in rats in a similar way to schizophrenia in humans.

Figure 1

Interaction between the immune system and schizophrenia



Different immune reactions directly influence neuronal proliferation, differentiation, migration, and apoptosis. Microglia become activated after stress, trauma, or infection. They react with tissue repair or induction of immune responses: phagocytosis, secretion of cytokines, neuronal growth factors, and antigen presentation. Microglial activation may sustain chronic brain inflammation.²

NK, natural killer.

Rothermundt M, Arolt V. Schizophrenia and immunity. In: Adler R, ed. Psychoneuroimmunology. Burlington, MA: Elsevier Academic Press; 2007:563-577.

The role of inflammation in epilepsy

- Here, we focus on the rapidly growing body of evidence that supports the involvement of inflammatory mediators—released by brain cells and peripheral immune cells—in both the origin of individual seizures and the epileptogenic process. We explore the evidence from clinical and experimental studies for a relationship between inflammation and epilepsy. Subsequently, we discuss how seizures cause inflammation, and whether such inflammation, in turn, influences the occurrence and severity of seizures, and seizure-related neuronal death.

Autism: Brain Inflammation & Anti-Neural Antibodies

- The blood–brain barrier is permeable during fetal development and can be compromised by infections and environmental exposures throughout life. The absence of a complete barrier allows immune components access to the brain. Individuals with autism show increased pro-inflammatory cytokines in the brain, as well as activation of resident immune cells known as microglia. Additionally, antibodies that target brain tissues have been described in both children with autism and their mothers. These immunological phenomena may interfere with normal brain development and function, potentially contributing to the development and/or symptoms of autism spectrum disorders

A Meta-Analysis of Cytokines in Alzheimer's Disease

- A review of **86 studies** strengthen the clinical evidence that AD is accompanied by an inflammatory response, particularly higher peripheral concentrations of IL-6, TNF-, IL-1, TGF-, IL-12 and IL-18 and higher CSF concentrations of transforming growth factor.

Inflammatory Proteins in Plasma and the Risk of Dementia: The Rotterdam Study

- **Conclusion** Plasma levels of inflammatory proteins are increased before clinical onset of dementia, Alzheimer disease, and vascular dementia.

Cerebral inflammation is an underlying mechanism of early death in Alzheimer's disease: a 13-year cause-specific multivariate mortality study

- Our results suggest that inflammation, and not amyloid or tau pathology, is an independent underlying mechanism in the malignancy of AD.

Depression as a risk factor for Alzheimer disease: the MIRAGE Study

- Depression symptoms before the onset of AD are associated with the development of AD, even in families where first depression symptoms occurred more than 25 years before the onset of AD. These data suggest that depression symptoms are a risk factor for later development of AD.

Anxiety & Depression Increase Risk of Parkinson's Disease

- Gustafsson H, Nordström A, Nordström P. Depression and subsequent risk of Parkinson disease: A nationwide cohort study. *Neurology*. 2015 May 20.
- Lin CH, Lin JW, Liu YC, Chang CH, Wu RM. Risk of Parkinson's disease following anxiety disorders: a nationwide population-based cohort study. *Eur J Neurol*. 2015 May 29.

Lack Of Sleep Promotes Neurodegenerative Processes

- Increases of neuron-specific enolase and S100 calcium binding protein B that typically rise in blood under conditions of brain damage.[1]
- Increased cerebral β -amyloid 42 levels, which elevates the risk of Alzheimer disease.[2, 3]
- Mitochondrial stress and degeneration of Locus Ceruleus neurons.[4]

[1] Benedict C et al. Sleep. 2014 Jan 1;37(1):195-8.

[2] Ooms S et al. JAMA Neurol. 2014 Jun 2.

[3] Sprecher. Annual meeting of the Associated Professional sleep Societies. Minneapolis. 2014

Poor sleep quality is associated with increased cortical atrophy in community-dwelling adults

- Poor sleep quality was associated with reduced volume within the right superior frontal cortex in cross-sectional analyses, and an increased rate of atrophy within widespread frontal, temporal, and parietal regions in longitudinal analyses. Cortical atrophy was correlated with sleep quality. Poor sleep quality may be a cause or a consequence of brain atrophy.

Sleep is related to neuron numbers in the ventrolateral preoptic/intermediate nucleus in older adults with and without Alzheimer's disease

- The intermediate nucleus is the human homologue of the ventrolateral preoptic nucleus. More intermediate nucleus neurons are associated with better sleep while a paucity of intermediate nucleus neurons is accompanied by sleep fragmentation.

Elevated CRP Level Linked to Decline in Executive Function and Frontal Lobe Damage

- This study shows a link between elevated levels of high-sensitivity C-reactive protein (hs-CRP), an indicator of low-grade inflammation, and decline in executive function.

Assessment

Clinical Assessment

- In depth history, review of systems
- Thorough exam relevant to patient's complaints and findings
- Is there a point at which the patient's health declined, followed by a fluctuating progression and development of multi-systemic symptoms, including cognitive, psychiatric, neurological, and physical symptoms causing significant impairment?
- Pattern recognition, differential diagnosis
- Medical judgment
- (Laboratory confirmation)

Comprehensive Multi-Systemic Assessment

- **Cognitive:** Attention, sensory hyperacusis, working & short term memory, sequential memory, geographical memory, word finding, speech fluency, neologisms, comprehension, auditory & visual processing, processing speed, writing skills, math skills, dyslexia-like symptoms, imagery, executive functioning, “brain fog.”
- **Psychiatric:** Disinhibition, low frustration tolerance, irritability, hypervigilance, exaggerated startle, explosive anger, suicidal, aggressiveness, paranoia, hallucinations, depression, rapid cycling bipolar, panic disorder, obsessive compulsive disorder, intrusive symptoms, posttraumatic stress disorder, social anxiety, generalized anxiety, phobias, depersonalization, self mutilation, psychosis, decreased social & school functioning, accident prone, etc.
- **Vegetative:** Sleep, eating, sexual functioning, thermal dysregulation, fatigue.
- **Neurological:** Headaches (multiple types), cranial nerve neuritis & neuralgia, eye findings, migratory polyneuropathy, spinal cord signs, transverse myelitis, radiculopathy, peripheral neuropathies, motor neuropathies, movement disorders, tics, gait, balance, ataxia, seizures, white matter lesions,
- **Autonomic Nervous System:** POTS, nausea, orthostatic hypotension, anhydrosis, etc.
- **Musculoskeletal:** Migratory arthralgias, arthritis, crepitations, periostitis, fibro, stiffness, neck and back discomfort.
- **GU:** Spastic bladder, testicular pain/pelvic pain, menstrual irregularity, sexual dysfunction, decreased libido.
- **Cardiac/Pulmonary:** Chest pain, shortness of breath, palpitations, heart block, murmur.
- **Gastrointestinal:** GERD, irritable gut, reduced GI motility (gastro-paresis, ileus, etc.).
- **Immune:** Fevers, sweats or chills, lymphadenopathy.

What Symptoms Contribute to Disease Progression?

- Sleep disorders
- Fatigue
- Cognitive impairments
- Depression
- Anxiety
- Pain
- Others

Treatment Implications

Symptom Priority

- A complex, chronic, patient may have over 100 different symptoms.
- After completing an assessment, prioritize which symptoms are most severe and contribute the most towards perpetuating chronic illness.
- Treat the high priority symptoms first and work your way down the list.

Basic Treatment Strategies in Addition to Treating the Cause of Inflammation

- Three commonly associated symptoms are non-restorative sleep, fatigue and cognitive impairments. Treatments that increase delta sleep and normalize circadian rhythm helps these symptoms.
- Other strategies include treatments that further improve cognitive functioning, stress reduction, pain management, diet and exercise as well as traditional psychotropic interventions for depression, anxiety, psychosis, etc.

Benefit of Symptomatic Treatment

- Chronic stress, dysregulated hyper/hypo-arousal & impaired sleep cause compromised immune functioning (increased inflammation, decreased cellular immune response) & increased oxidative stress resulting in decreased neuroprotection and increased neurodegeneration
- Symptomatic treatments can prevent and sometimes reverse progression of illness

Drugs that Increase Delta Sleep Decrease Inflammation

- | Drug | Mechanism of Action | Reference |
|-----------------------|--|--------------------------|
| • Tiagabine | GAT-1 inhibitor | (Mathias et al., 2001) |
| • Gaboxadol | Selective extrasynaptic GABA A agonist | (Deacon et al., 2007) |
| • Gabapentin | $\alpha 2$ - δ site on voltage-gated calcium ion channels | (Bazil et al., 2005) |
| • Pregabalin | $\alpha 2$ - δ site on voltage-gated calcium ion channels | (Hindmarch et al., 2005) |
| • GHB | GABA _B /GHB agonist | (Pardi et al., 2006) |
| • Ritanserlin | Partially selective 5HT _{2A} receptor antagonist | (Dahlitz et al., 1990) |
| • Eplivanserin | Antagonist of Serotonin 2A Receptors | (Hindmarch et al, 2008) |
| • Mirtazapine | Multiple receptors, including 5HT ₂ antagonist | (Shen et al., 2006) |
| • Olanzapine | Multiple receptors, including 5HT ₂ antagonist | (Sharpley et al., 2005) |
| • Trazodone | Multiple receptors, including 5HT ₂ antagonist | (Mendelson, 2005) |
| • Quintiapine | Unpublished data | |

(GABA, γ -aminobutyric acid; GHB, γ -hydroxybutyrate; 5HT, serotonin)

Psychotropics are also Antimicrobial & Immune Modulating

- Antidepressants were developed from TB drugs
- Antidepressants modulate cytokine functioning (1)
- The immunostimulating and antimicrobial properties of lithium and antidepressants (2)
- Immunomodulatory effect of SSRIs on human T lymphocyte function and gene expression (3)
- Antiviral & immunomodulatory effect of lithium (4)

1 Janssen DG, Caniato RN, Verster JC, Baune BT. A psychoneuroimmunological review on cytokines involved in antidepressant treatment response. *Hum Psychopharmacol.* 2010 Apr;25(3):201-15.

2 Lieb J. *J Infect.* 2004 Aug;49(2):88-93

3 Taler, et al. *European Neuropsychopharmacology*

4 Rybakowski JK. *Pharmacopsychiatry.* 2000 Sep;33(5):159-64.

Treatment Options to Reduce Glutamate Mediated Excitotoxicity

- Ceftriaxone [1]
- Memantine [2]
- Acetylcarnitine [3]
- Dextromethorphan hydrobromide & quinidine sulfate [4, 5]
- N-acetyl cysteine [6]

[1] Knackstedt LA et al.

[2] Anathia M. et al.

[3] Famularo G. et al.

[4] Werling LL et al.

[5] Rosen H.

[6] Dean OM.

Minocycline as adjunctive therapy for schizophrenia: an open-label study

- Minocycline is a caspase inhibitor, decreases inducible nitric oxide synthase, and has been shown to delay disease in a mouse model of neuropsychiatric disorders. We administered minocycline (150 mg/d) for 4 weeks as an open-label adjunct to antipsychotic medication to 22 patients with schizophrenia. The Positive and Negative Syndrome Scale for schizophrenia showed statistically significant and robust clinical improvements with minocycline treatment, which were maintained at follow-up evaluation 4 weeks after the end of minocycline treatment. There were no adverse events. These results suggest that **minocycline may be a safe and effective adjunct to antipsychotic medications, and that augmentation with minocycline may prove to be a viable strategy for "boosting" antipsychotic efficacy and for treating schizophrenia.**

Clinical trial of adjunctive celecoxib treatment in patients with major depression: a double blind and placebo controlled trial

- The pathophysiology of depression is associated with the hyperactivity of immune inflammatory responses. Cyclooxygenase-2 inhibitors such as celecoxib reduce the production of pro-inflammatory cytokines.
- the combination of fluoxetine and celecoxib showed a significant superiority over fluoxetine alone in the treatment of symptoms of major depression.
- **CONCLUSION:** The results of this study suggest that celecoxib may be an effective adjuvant agent in the management of patients with major depression and anti-inflammatory therapies should be further investigated.

Inflammation & AT1 & AT2 receptors

- Regulation of the mutually antagonistic angiotensin II receptors (AT1 and AT2) is an essential in the management of inflammation & an imbalance in the expression of these receptors leads to disease.
- Manipulation of the angiotensin system with existing anti-hypertensive drugs could provide a new approach to the treatment of many of the diseases that afflict mankind. [1]
- Olmesartan inhibit TNF-alpha and IL-6.

13th Psychoimmunology Expert Meeting

3th – 6th March 2016

Neuroimmunology Meets Psychoimmunology

Focus on translational perspectives

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Scientific Institute of Ulm University



Conclusion

- Inflammation is a part of the acute stress response and sickness syndrome. It is beneficial and facilitates adaptation to an acute environmental or physiological stressor. However, in the presence of persistent stressors and adaptive failure chronic inflammation persists and has a gradually increasing degenerative effects. Chronic inflammation in the body can result in chronic inflammation in the brain with an increasing deleterious effect upon brain functioning.

Acknowledgement

- Thanks to Dr Gregory Bach for peer review from an Integrative Medicine perspective and his travelling to Australia to be available for discussion relevant to this presentation.
- Thanks to Dr Mualla McManus Dr Gull Herzberg and Dr Christabelle Yeoh for encouraging me to come to this meeting.

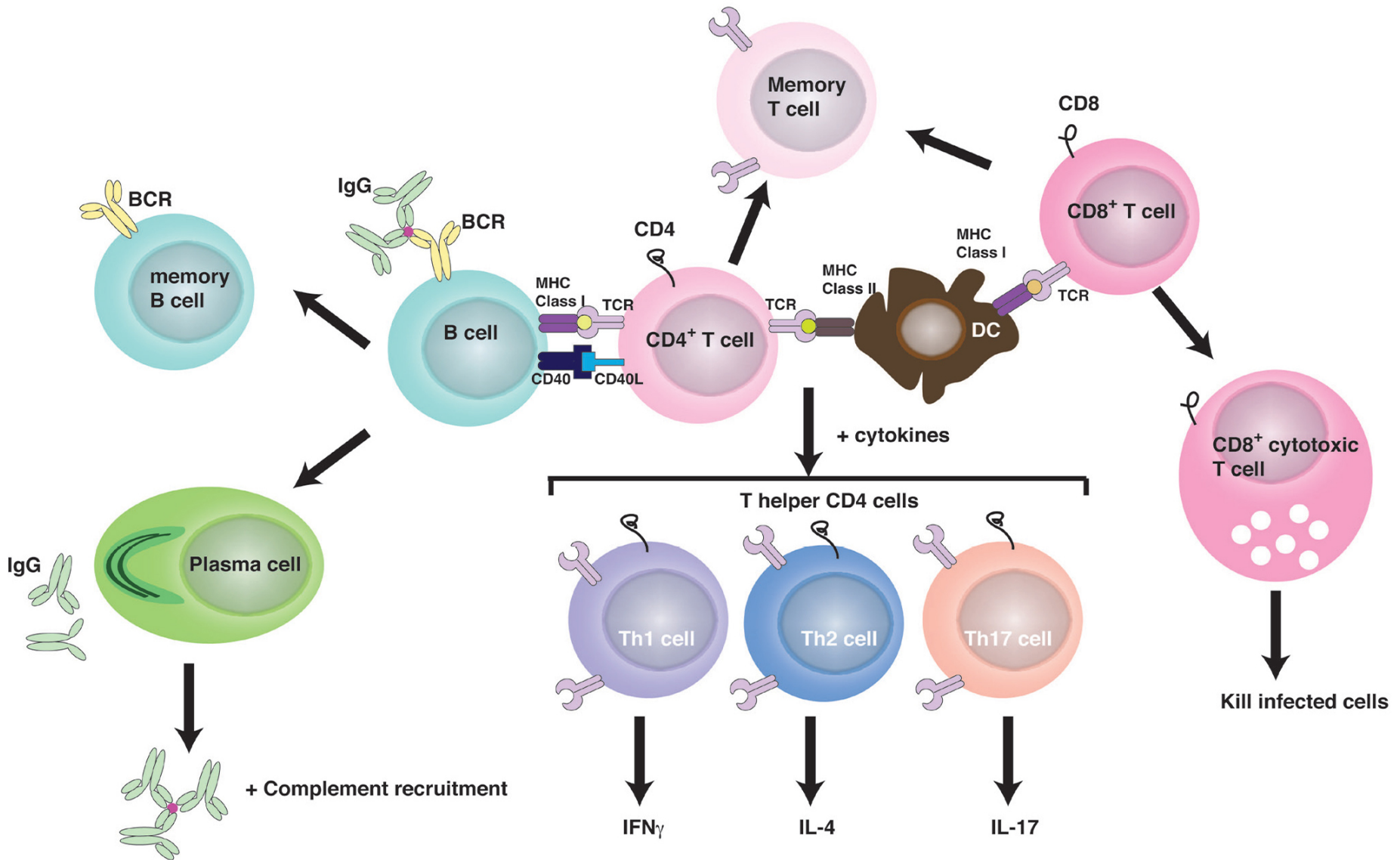
Thanks for Your Attention



Back-Up Slides if Needed

HUMORAL IMMUNITY

CELLULAR IMMUNITY



Activation/inhibition of other immune cells

TABLE 1.

A Summary of the Main Findings

Disorder	Type	Study	CRP	IL-1	IL-1 beta	IL-1RA	IL-2	sIL-2R	IL-4	IL-6	sIL-6R	IL-8	IL-10	TNF-alpha	sTNF-R1	IFN-gamma	CXCL8	CXCL3
Depressive symptoms	Meta-analysis	Valkanova et al. ⁹	↑							↑ ^a								
Major depressive disorder	Meta-analysis	Dowlati et al. ¹⁰			=		=		=	↑		=	=	↑		=		
	Meta-analysis	Howren et al. ¹¹	↑	↑		=				↑								
Bipolar disorder	Systematic review	Goldstein et al. ¹²	↑					↑	=	↑		↑	=	↑				
	Meta-analysis	Modabbernia et al. ¹³			↑ ^a	↑	=	↑	↑	↑ ^a	↑	=	↑	↑	↑	=		
	Systematic review	Munkholm et al. ¹⁴		=	=	=	=	↑	↑	=	↑	=	=	↑	↑	=		

Abbreviations: CRP, C-reactive protein; CXCL, C-X-C motif ligand; IFN, interferon; IL, interleukin; PBMC, peripheral blood mononuclear cells; PTSD, posttraumatic stress disorder; R, receptor; RA, receptor antagonist; s, soluble; TNF, tumor necrosis factor.

^aNot statistically significant, although a trend was reported.

^bSpontaneous production by isolated PBMCs; no difference found in plasma.

^cWomen with PTSD compared to traumatized and nontraumatized controls.

^dMen experiencing current anxiety.

^ePlasma levels measured at baseline as a predictor of future onset of PTSD.

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Disorder	Type	Study	CRP	IL-1	IL-1 beta	IL-1RA	IL-2	sIL-2R	IL-4	IL-6	sIL-6R	IL-8	IL-10	TNF-alpha	sTNF-R1	IFN-gamma	CXCL8	CXCL3
PTSD	Narrative review	Pace et al. ¹⁵	↑		↑					↑				↑				
	Study	Gill et al. ^{16c}			=					↑				↑				
	Study	Gola et al. ¹⁷			↑ ^b					↑ ^b / =		=	=	↑ ^b / =				
	Study	Heath et al. ¹⁸	↑															
	Study	Spitzer et al. ¹⁹	↑															
	Study	Eraly et al. ^{20e}	↑															
	Study	Baumert et al. ²¹	=															
OCD	Systematic review	Gray et al. ²³			↓					=				=				
	Study	Fon-tenelle et al. ²⁴													↑		↑	↑
Anxiety disorders	Study	Vogel-zangs et al. ^{25d}	↑							=				=				
	Study	Janelidze et al. ²⁶										↓						

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