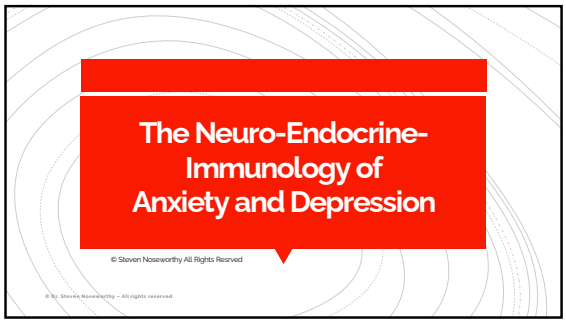
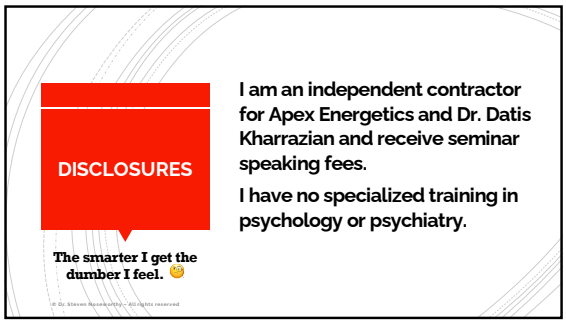
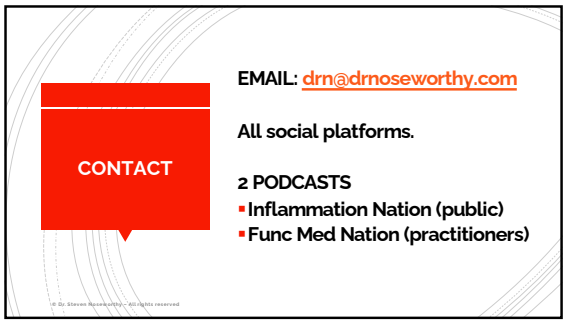

The Neuro-Endocrine-Immunology of Anxiety and Depression
© Steven Noseworthy All Rights Resrved

1


DISCLOSURES
I am an independent contractor for Apex Energetics and Dr. Datis Kharrazian and receive seminar speaking fees.
I have no specialized training in psychology or psychiatry.
The smarter I get the dumber I feel.

2


CONTACT
EMAIL: drn@drnoseworthy.com
All social platforms.
2 PODCASTS
Inflammation Nation (public)
Func Med Nation (practitioners)

3

A Mood Disorder is…

A pervasive and sustained feeling that is endured internally, which

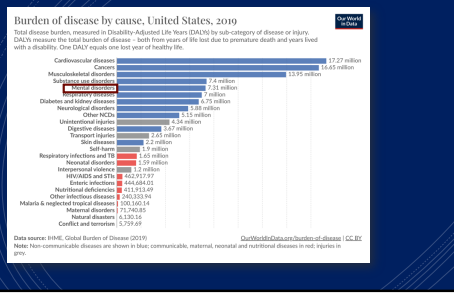
- Impacts nearly all aspects of a person's **behavior in the external world** (social, occupational etc.)
- Is described by **marked disruptions in emotions**

Anxiety – Depression – Bipolar – Schizophrenia

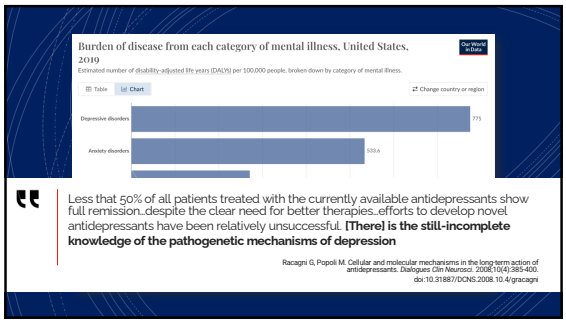
4

~300 million adults suffer from some combination of anxiety and depression

5



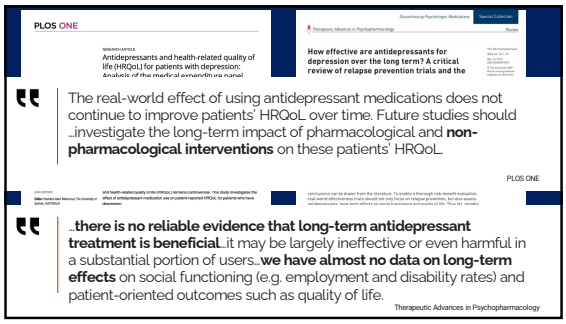
6



> Less that 50% of all patients treated with the currently available antidepressants show full remission…despite the clear need for better therapies…efforts to develop novel antidepressants have been relatively unsuccessful. **[There] is the still-incomplete knowledge of the pathogenetic mechanisms of depression**

Racagni G, Popoli M. Cellular and molecular mechanisms in the long-term action of antidepressants. *Dialogues Clin Neurosci*. 2008;10(4):385-400. doi:10.31887/DCNS.2008.10.4/gracagni

7



> The real-world effect of using antidepressant medications does not continue to improve patients' HRQoL over time. Future studies should …investigate the long-term impact of pharmacological and **non-pharmacological interventions** on these patients' HRQoL.

> …**there is no reliable evidence that long-term antidepressant treatment is beneficial**…it may be largely ineffective or even harmful in a substantial portion of users…**we have almost no data on long-term effects** on social functioning (e.g. employment and disability rates) and patient-oriented outcomes such as quality of life.

Therapeutic Advances in Psychopharmacology

8

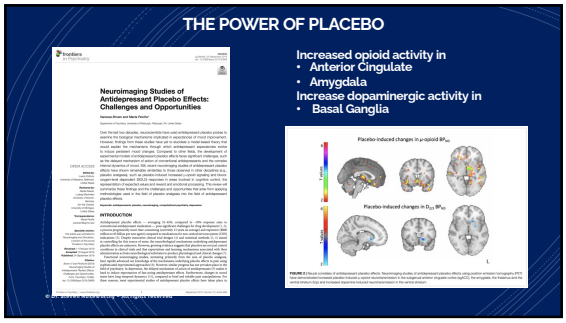
Conventional Medical Approach

Pharmaceutical	Cognitive Behavioral Therapy
Benzodiazepines • Hyperpolarize neurons to reduce activation **NT reuptake inhibitors** • Increase NT levels in synaptic cleft by inhibiting reuptake by the presynaptic neuron • SSRI – SNRI - SDRI	• **Challenging and changing** cognitive distortions in **thoughts, beliefs, and attitudes**, and their associated behaviors • Improve emotional regulation and develop personal **coping strategies** • Problem-focused and action-oriented as opposed to psychoanalytic (looking for hidden meanings)

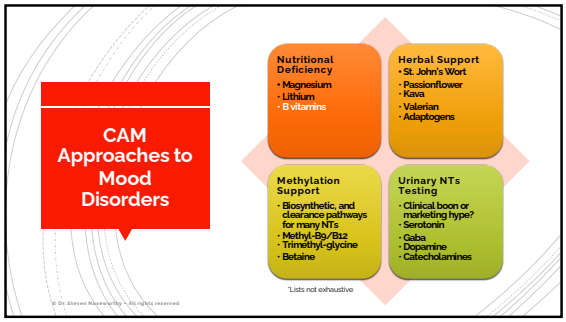
10


HHS Public Access
Author manuscript
JAMA Psychiatry. Author manuscript; available in PMC 2016 February 18.
Placebo-Activated Neural Systems are Linked to Antidepressant Responses:
Neurochemistry of Placebo Effects in Major Depression
Placebo-induced endogenous opioid release...was associated with better antidepressant treatment response, predicting 43% of the variance in symptom improvement at the end of the antidepressant trial.
Peciña M, Bohnert AS, Sikora M, et al. Association Between Placebo-Activated Neural Systems and Antidepressant Responses: Neurochemistry of Placebo Effects in Major Depression. JAMA Psychiatry. 2015;72(11):1087-1094. doi:10.1001/jamapsychiatry.2015.1335

11


THE POWER OF PLACEBO
Neuroimaging Studies of Antidepressant Placebo Effects: Challenges and Opportunities
Increased opioid activity in
• Anterior Cingulate
• Amygdala
Increase dopaminergic activity in
• Basal Ganglia
Placebo-induced changes in μ-opioid BPND
Placebo-induced changes in D2,3 BPND

12


CAM Approaches to Mood Disorders
Nutritional Deficiency
• Magnesium
• Lithium
• B vitamins
Herbal Support
• St. John's Wort
• Passionflower
• Kava
• Valerian
• Adaptogens
Methylation Support
• Biosynthetic, and clearance pathways for many NTs
• Methyl-B9/B12
• Trimethyl-glycine
• Betaine
Urinary NTs Testing
• Clinical boon or marketing hype?
• Serotonin
• Gaba
• Dopamine
• Catecholamines
*Lists not exhaustive

13

You CAN'T correlate urinary NT results to the brain. PERIOD.

CLINCAL PEARL

- Very few NTs cross the Blood Brain Barrier
- The brain makes its ALL of its own GABA, Serotonin, Dopamine, Acetylcholine
  - And MOST of its Catecholamines and Glutamate

Urinary NTs are primarily a reflection of GI production

14

MAJOR CATEGORIES OF MOOD DISORDERS

DEPRESSION

Major Depressive Disorder (MDD)
Minor Depressive Disorder
Recurrent Brief Depression (<2 weeks)
Dysthymia/Persistent Depressive Disorder (>2 years)

Depression With Known Triggers
- Premenstrual Dysphoric Disorder (PMDD)
- Seasonal Affective Disorder (SAD)

Nonspecific Depressive Disorder

ANXIETY & PHOBIAS

Primarily ANXIETY
- **Generalized Anxiety Disorder (GAD)**
- Anxiety 2° to other condition/substances

Primarily PHOBIA
- Panic Disorder (rapid onset, short duration with ANS concomitants)
- Post-traumatic Stress Disorder (PTSD)
- Phobias (avoidance behavior)
  - Social Anxiety Disorder
  - Separation Anxiety Disorder

OTHER
- Obsessive Compulsive Disorder (OCD)

Adapted from *Neurobiology of Brain Disorders Second Edition 2022*
Biological Basis of Neurological and Psychiatric Disorders

15

Five (or more) of the following present **nearly every day during the same 2-week period**
- At least one of the symptoms is either depressed mood or loss of interest or pleasure.

Major Depressive Disorder

Minor Depressive Disorder requires only 1-3 items.

1. **Depressed most of the day, nearly every day**
2. **Markedly diminished interest or pleasure in most activities**
3. Unintentional weight loss/gain (≥5% BW in one month); or decrease/increase in appetite
4. **Insomnia** or hypersomnia
5. Psychomotor agitation or retardation (observable by others)
6. **Fatigue**
7. Feelings of worthlessness or excessive/inappropriate guilt
8. **Diminished ability to think, concentrate, or indecisiveness**
9. Recurrent thoughts of death or recurrent suicidal ideation (without a specific plan, or a suicide attempt or a specific plan for committing suicide)

*Symptoms not attributable to the direct physiological effects of a substance or to another medical condition.

16

Poorly controlled excessive worry (apprehensive expectation) occurring **more days than not for at least 6 months**

Generalized Anxiety Disorder

Disproportionate and enduring fear where emotional response is larger than the actual/perceived threat

Associated with **three or more** of the following

1. Restlessness or feeling keyed up or on edge
2. Being easily **fatigued**
3. **Difficulty concentrating** or mind going blank
4. Irritability
5. Muscle tension
6. **Sleep** disturbance (difficulty falling or staying asleep, or restless unsatisfying sleep)

Where these symptoms not attributable to the direct physiological effects of a substance or to another medical condition such as:

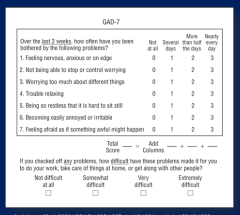
- Hyperthyroidism (Thyroiditis/Overmedication/Grave's Ds)
- Pheochromocytoma (Adrenal tumor)
- Cardiopulmonary disease
- Seizure Disorders
- **Vestibular disorder**

17

HOSPITAL ANXIETY AND DEPRESSION SCALE

Zigmond & Snaith (1983)

THE GENERALIZED ANXIETY DISORDER 7-ITEM (GAD-7) SCALE



Arch Intern Med. 2006;166(10):1092-1097. doi:10.1001/archinte.166.10.1092

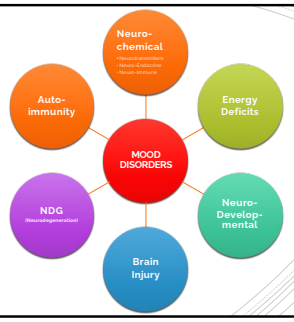
19

Psychological Causes of Mood Disorders

Psychological and Physiological mechanisms are intertwined (Psycho-Neuro-Immunology)

20

Physiological Causes of Mood Disorders



Psychological and Physiological mechanisms are intertwined (Psycho-Neuro-Immunology)

21

Age at Onset?

YOUNG ONSET/LIFELONG SYMPTOMS (WORSE PROGNOSIS)

- Genetics (strong family history → 3x risk
- Neuro-developmental issues → adulthood
- Acute onset at young age?: Think
  - Head injury
  - Infection (StrepA → PANDAS)

ADULT ONSET (BETTER PROGNOSIS)

- Less likely to be genetic
- Look at both psychological and physiological factors in a 6-month window before onset
- Consider age-related NDG if also see signs of cognitive decline

Palma-Gudiel H, Córdova-Palomera A, Navarro V, Fañanás L. Twin study designs as a tool to identify new candidate genes for depression. Neurosci Biobehav Rev. 2020 May;Epub ahead

22

EPISODIC VS PERSISTENT

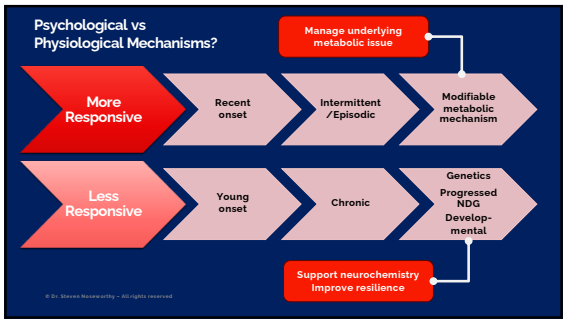
INTERMITTENT/EPISODIC (BETTER PROGNOSIS)

- Worse with stress or immune activation?
- Hormone control and stability
- Thyroid Dysfunction
- Lifestyle inconsistent and variable

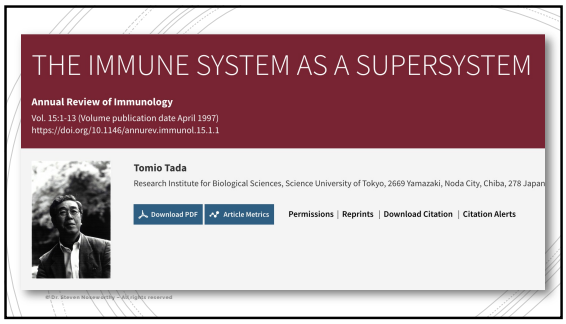
CHRONIC/PERSISTENT (WORSE PROGNOSIS)

- Prior brain injury → chronic microglial activation
- Neurodegeneration
- Unidentified or poorly managed metabolic issues
- Maladaptive/Negative Plasticity?

23


Psychological vs
Physiological Mechanisms?
Manage underlying metabolic issue
More Responsive
Recent onset
Intermittent /Episodic
Modifiable metabolic mechanism
Less Responsive
Young onset
Chronic
Genetics
Progressed NDG
Develop-mental
Support neurochemistry Improve resilience

24


THE IMMUNE SYSTEM AS A SUPERSYSTEM
Annual Review of Immunology
Vol. 15:1-13 (Volume publication date April 1997)
https://doi.org/10.1146/annurev.immunol.15.1.1
Tomio Tada
Research Institute for Biological Sciences, Science University of Tokyo, 2669 Yamazaki, Noda City, Chiba, 278 Japan
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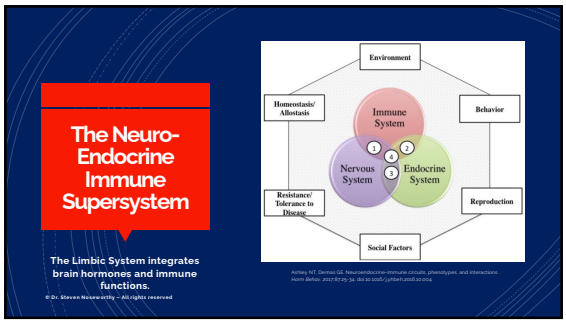
The Neuro-Endocrine Immune Supersystem
The Limbic System integrates brain hormones and immune functions.
Environment
Homeostasis/ Allostasis
Immune System
Behavior
Nervous System
Endocrine System
Resistance/ Tolerance to Disease
Reproduction
Social Factors

26

STRICTLY SPEAKING...

DEPRESSION IS DECREASED ACTIVATION OF THE FRONTAL LOBE
(PREFRONTAL/ORBITOFRONTAL CORTICES)

- Neuroinflammation
- Neurotransmitter dysregulation
- Hormonal imbalances
- Lack of input
  - ↓ Vestibulo-Cerebellar activation

ANXIETY IS INCREASED ACTIVATION OF THE AMYGDALA

- Neuronal energy deficits
- Stress chemistry
- Hyperthyroidism
- Loss of inhibition (GAD65/Purkinje/D2 receptors)

27

LIMBIC REGIONS

- Prefrontal Cortex
- Anterior Cingulate Gyrus
- Amygdala
- Hippocampus
- Mesencephalic Reticular Formation (Sympathetics)

CELLS

- Neurons (signaling)
- Glial Cells (supporting roles)
  - Oligodendrocytes (myelin)
  - Astrocytes (BBB, supplies glucose/glycogen/lactate)
  - Microglia (immune/inflammation)

THE LIMBIC SYSTEM

Mood disorders arise as a consequence of altered function(s) among the neurons, that make up the circuits, that connect multiple brain regions and structures of the Limbic System.

Adapted from: Neurobiology of Brain Disorders Second Edition 2022 Biological Basis of Neurological and Psychiatric Disorders

28

LIMBIC REGIONS

- Prefrontal Cortex
- Anterior Cingulate Gyrus
- Amygdala
- Hippocampus
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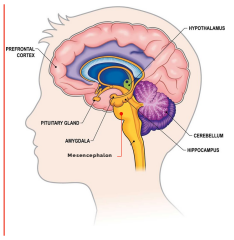
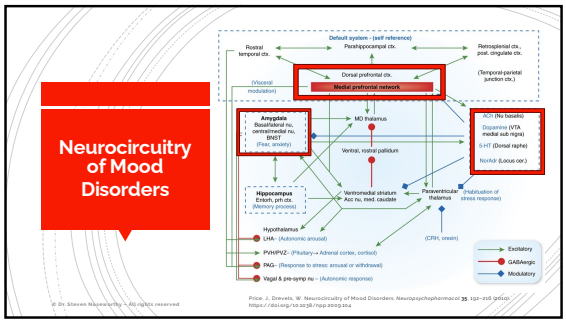
CELLS

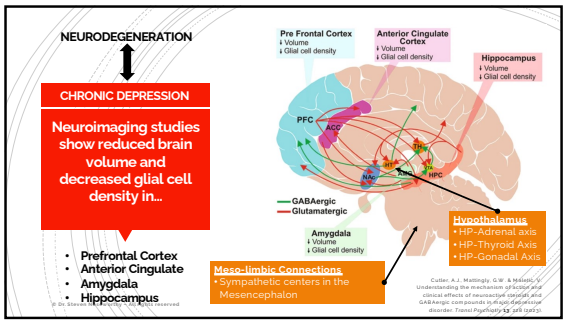
- Neurons (signaling)
- Glial Cells (supporting roles)
  - Oligodendrocytes (myelin)
  - Astrocytes (BBB, supplies glucose/glycogen/lactate)
  - Microglia (immune/inflammation)



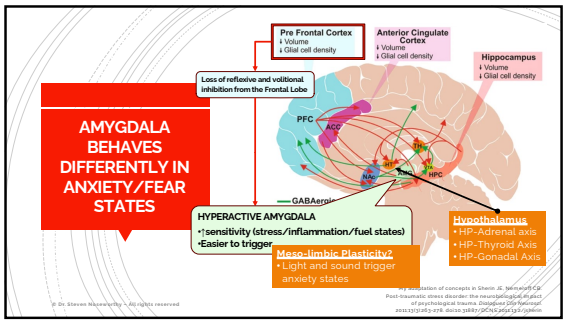
29


Neurocircuitry of Mood Disorders
Default system - (self reference)
Rostral temporal ctx.
Parahippocampal ctx.
Retrosplenial ctx., post. cingulate ctx.
Dorsal prefrontal ctx.
Medial prefrontal network
(Visceral modulation)
(Temporal-parietal junction ctx.)
Amygdala
Basal/lateral nu.
centra/medial nu.
BNST
(Fear, anxiety)
MD thalamus
Ventral, rostral pallidum
ACh (Nb basalis)
Dopamine (VTA medial sub-regns)
5-HT (Dorsal raphe)
NorAdr (Locus coer.)
Hippocampus
Entorh, prh ctx.
(Memory process)
Ventromedial striatum
Acc nu, med. caudate
Paraventricular thalamus
(Habituation of stress response)
Hypothalamus
LHA - (Autonomic arousal)
PVN/PVZ - (Pituitary→ Adrenal cortex, cortisol)
PAG - (Response to stress: arousal or withdrawal)
Vagal & pre-symp nu – (Autonomic response)
(CRH, orexin)
Excitatory
GABAergic
Modulatory

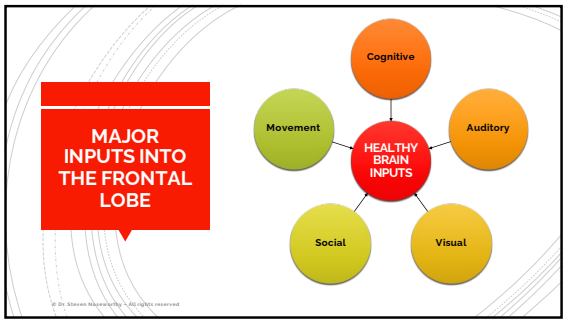
30


NEURODEGENERATION
CHRONIC DEPRESSION
Neuroimaging studies show reduced brain volume and decreased glial cell density in...
Prefrontal Cortex
Anterior Cingulate
Amygdala
Hippocampus
Pre Frontal Cortex
↓ Volume
↓ Glial cell density
Anterior Cingulate Cortex
↓ Volume
↓ Glial cell density
Hippocampus
↓ Volume
↓ Glial cell density
PFC
ACC
NAc
HPC
GABAergic
Glutamatergic
Amygdala
↓ Volume
↓ Glial cell density
Hypothalamus
• HP-Adrenal axis
• HP-Thyroid Axis
• HP-Gonadal Axis
Meso-limbic Connections
• Sympathetic centers in the Mesencephalon

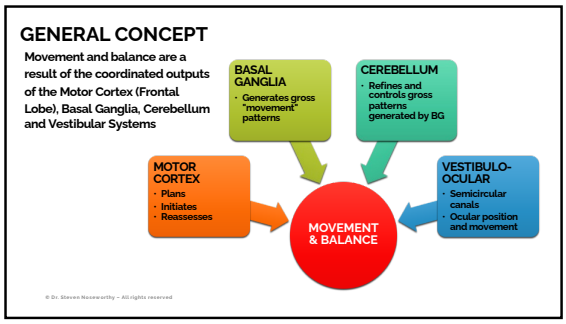
31


AMYGDALA BEHAVES DIFFERENTLY IN ANXIETY/FEAR STATES
Pre Frontal Cortex
↓ Volume
↓ Glial cell density
Anterior Cingulate Cortex
↓ Volume
↓ Glial cell density
Hippocampus
↓ Volume
↓ Glial cell density
Loss of reflexive and volitional inhibition from the Frontal Lobe
PFC
ACC
NAc
HPC
GABAergic
HYPERACTIVE AMYGDALA
•↑sensitivity (stress/inflammation/fuel states)
•Easier to trigger
Meso-limbic Plasticity?
• Light and sound trigger anxiety states
Hypothalamus
• HP-Adrenal axis
• HP-Thyroid Axis
• HP-Gonadal Axis

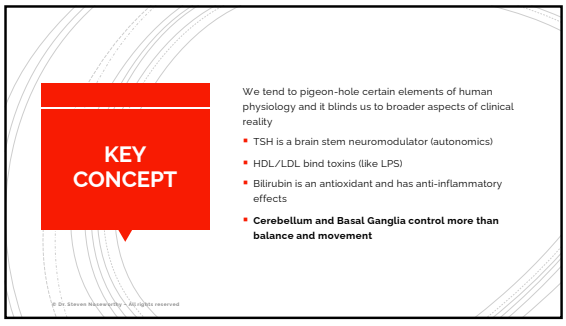
32


MAJOR INPUTS INTO THE FRONTAL LOBE
Cognitive
Movement
Auditory
HEALTHY BRAIN INPUTS
Social
Visual

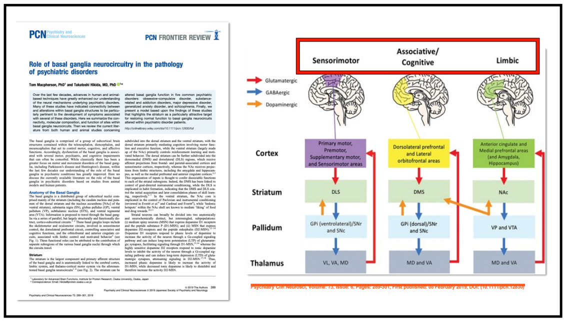
33


GENERAL CONCEPT
Movement and balance are a result of the coordinated outputs of the Motor Cortex (Frontal Lobe), Basal Ganglia, Cerebellum and Vestibular Systems
BASAL GANGLIA
· Generates gross "movement" patterns
CEREBELLUM
· Refines and controls gross patterns generated by BG
MOTOR CORTEX
· Plans
· Initiates
· Reassesses
MOVEMENT & BALANCE
VESTIBULO-OCULAR
· Semicircular canals
· Ocular position and movement

34


KEY CONCEPT
We tend to pigeon-hole certain elements of human physiology and it blinds us to broader aspects of clinical reality
TSH is a brain stem neuromodulator (autonomics)
HDL/LDL bind toxins (like LPS)
Bilirubin is an antioxidant and has anti-inflammatory effects
Cerebellum and Basal Ganglia control more than balance and movement

35


PCN Psychiatry and Clinical Neurosciences
PCN FRONTIER REVIEW
Role of basal ganglia neurocircuitry in the pathology of psychiatric disorders
Tom Macpherson, PhD and Takatoshi Hikida, MD, PhD
Anatomy of the Basal Ganglia
Striatum
Sensorimotor
Associative/ Cognitive
Limbic
Glutamatergic
GABAergic
Dopaminergic
Cortex
Striatum
Pallidum
Thalamus
Primary motor, Premotor, Supplementary motor, and Sensorimotor areas
Dorsolateral prefrontal and Lateral orbitofrontal areas
Anterior cingulate and Medial prefrontal areas (and Amygdala, Hippocampus)
DLS
DMS
NAc
GPi (ventrolateral)/SNr and SNc
GPi (dorsal)/SNr and SNc
VP and VTA
VL, VA, MD
MD and VA
MD and VA
Psychiatry Clin Neurosci, Volume: 73, Issue: 6, Pages: 289-301, First published: 08 February 2019, DOI: (10.1111/pcn.12830)

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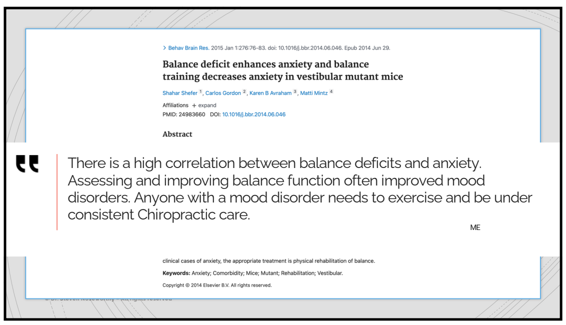
Behav Brain Res. 2015 Jan 1:276:76-83. doi: 10.1016/j.bbr.2014.06.046. Epub 2014 Jun 29.
Balance deficit enhances anxiety and balance training decreases anxiety in vestibular mutant mice
Shahar Shefer 1, Carlos Gordon 2, Karen B Avraham 3, Matti Mintz 4
Affiliations + expand
PMID: 24983660 DOI: 10.1016/j.bbr.2014.06.046
Abstract
There is a high correlation between balance deficits and anxiety. Assessing and improving balance function often improved mood disorders. Anyone with a mood disorder needs to exercise and be under consistent Chiropractic care.
ME
clinical cases of anxiety, the appropriate treatment is physical rehabilitation of balance.
Keywords: Anxiety; Comorbidity; Mice; Mutant; Rehabilitation; Vestibular.
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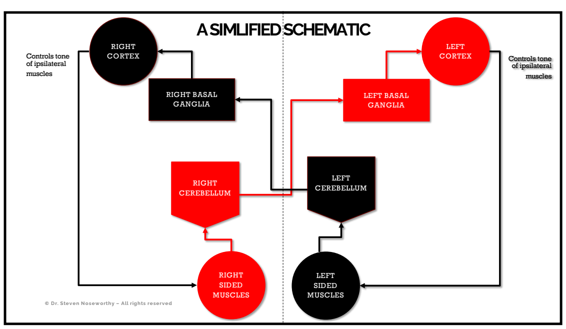
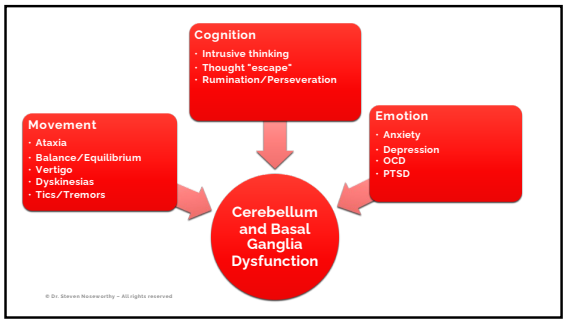

A SIMLIFIED SCHEMATIC
RIGHT CORTEX
Controls tone of ipsilateral muscles
RIGHT BASAL GANGLIA
LEFT CORTEX
Controls tone of ipsilateral muscles
LEFT BASAL GANGLIA
RIGHT CEREBELLUM
LEFT CEREBELLUM
RIGHT SIDED MUSCLES
LEFT SIDED MUSCLES
© Dr. Steven Noseworthy – All rights reserved

39


Cognition
· Intrusive thinking
· Thought "escape"
· Rumination/Perseveration
Movement
· Ataxia
· Balance/Equilibrium
· Vertigo
· Dyskinesias
· Tics/Tremors
Emotion
· Anxiety
· Depression
· OCD
· PTSD
Cerebellum and Basal Ganglia Dysfunction
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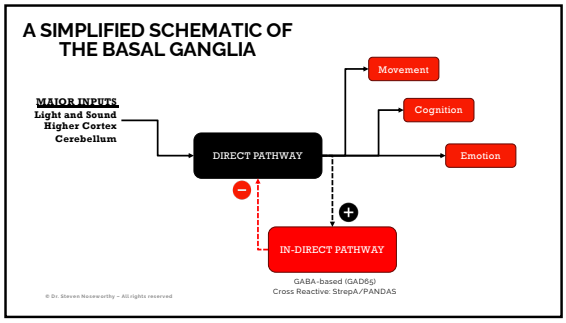
40


A SIMPLIFIED SCHEMATIC OF THE BASAL GANGLIA
MAJOR INPUTS
Light and Sound
Higher Cortex
Cerebellum
DIRECT PATHWAY
Movement
Cognition
Emotion
IN-DIRECT PATHWAY
GABA-based (GAD65)
Cross Reactive: StrepA/PANDAS
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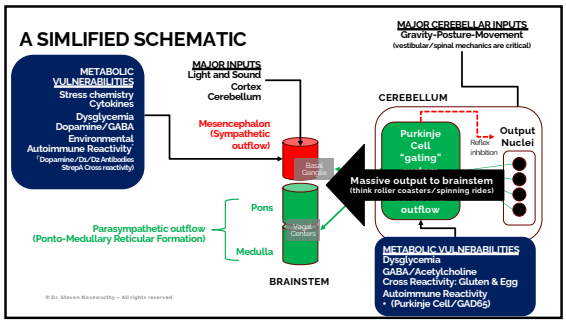
A SIMLIFIED SCHEMATIC
METABOLIC VULNERABILITIES
Stress chemistry
Cytokines
Dysglycemia
Dopamine/GABA
Environmental
Autoimmune Reactivity
†Dopamine/D1/D2 Antibodies
StrepA Cross reactivity)
MAJOR INPUTS
Light and Sound
Cortex
Cerebellum
Mesencephalon (Sympathetic outflow)
Basal Ganglia
Parasympathetic outflow (Ponto-Medullary Reticular Formation)
Pons
Medulla
Vagal Centers
BRAINSTEM
MAJOR CEREBELLAR INPUTS
Gravity-Posture-Movement
(vestibular/spinal mechanics are critical)
CEREBELLUM
Purkinje Cell "gating"
Reflex inhibition
Output Nuclei
Massive output to brainstem
(think roller coasters/spinning rides)
outflow
METABOLIC VULNERABILITIES
Dysglycemia
GABA/Acetylcholine
Cross Reactivity: Gluten & Egg
Autoimmune Reactivity
• (Purkinje Cell/GAD65)
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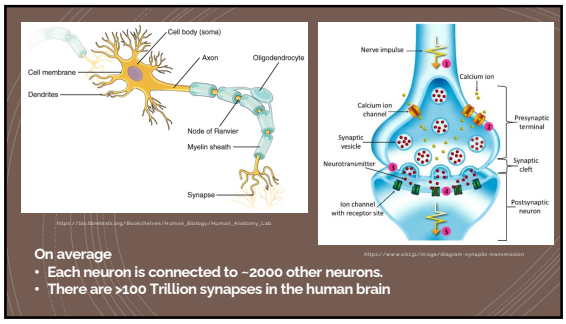

On average
- Each neuron is connected to ~2000 other neurons.
- There are >100 Trillion synapses in the human brain

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Do we really use only 10% of our brain?
- Brainstem: Glia outnumber neurons 10:1
- Cerebellum: Neurons outnumber Glia 20-30:1
- Cortex: 1:1 ratio

GLIAL CELL TYPES
- Oligodendrocytes
  - Myelination
  - ~75% of total
- Astrocytes
  - BBB and glucose/glycogen reserve
  - ~20% of total
- Microglia
  - Brain macrophages
  - ~5% of total

*%s and ratios vary by region & study

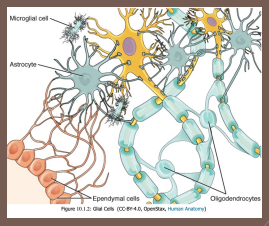

Figure 10.1.2: Glial Cells. (CC BY-4.0, OpenStax, Human Anatomy)

von Bartheld CS, Bahney J, Herculano-Houzel S. The search for true numbers of neurons and glial cells in the human brain: A review of 150 years of cell counting. J Comp Neurol. 2016;524(18):3865-3895. doi:10.1002/cne.24040

44

CLINCAL PEARL

THE RULE
- Neuroinflammation from Microglial activation causes LOSS of function related to whatever is inflamed
- Look for: Brain fog, Depression, Cognitive fatigue

THE EXCEPTION
- The Mesencephalon is very sensitive to stress chemistry and inflammation
- Negative plasticity → ↑ efficiency in creating stress chemistry and inflammation

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CRITICAL BRAIN CELL FUNCTIONS

- Microenvironment integrity (BBB)
- Inflammation control (microglial cells)
- ATP/Energy production
- NTs and Synaptic Transmission
- Plasticity

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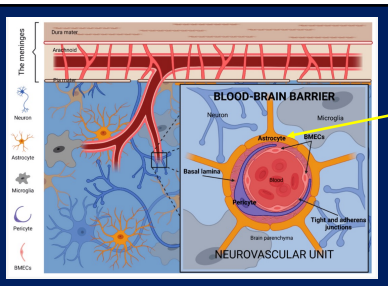
CRITICAL CELL FUNCTIONS

- Microenvironment integrity (BBB)
- Inflammation control
- Energy production
- Synaptic Transmission (NTs)
- Plasticity

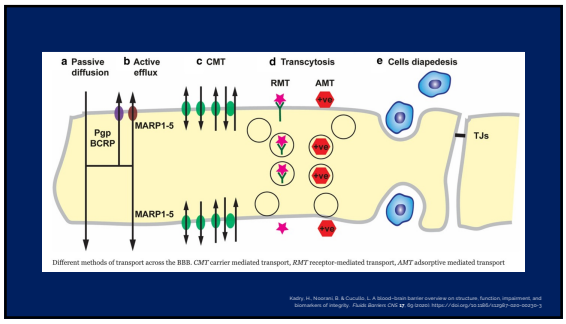
48



ASTROCYTES
- Modulate endothelial Tight Junction Proteins
- Control water and ion balance
- Produce both growth and apoptotic factors

Ruiz-López E, Schuhmacher AJ. Transportation of Single-Domain Antibodies through the Blood–Brain Barrier. *Biomolecules*. 2021; 11(8):1132. https://doi.org/10.3390/biom11081132

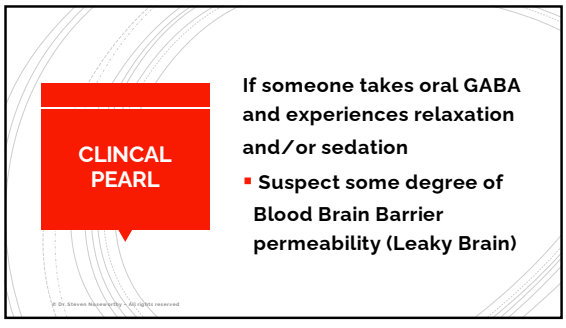
49


a Passive diffusion
b Active efflux
c CMT
d Transcytosis
e Cells diapedesis
RMT
AMT
Pgp
BCRP
MARP1-5
MARP1-5
TJs
Different methods of transport across the BBB. CMT carrier mediated transport, RMT receptor-mediated transport, AMT adsorptive mediated transport

50


Effects of Oral Gamma-Aminobutyric Acid (GABA) Administration on Stress and Sleep in Humans: A Systematic Review
GABA is critical to the functioning of the CNS, where ~60–75% of all synapses are GABAergic.
Front. Neurosci., 17 September 2020
Sec. Neuroenergetics and Brain Health
Volume 14 - 2020 |

51


CLINCAL PEARL
If someone takes oral GABA and experiences relaxation and/or sedation
Suspect some degree of Blood Brain Barrier permeability (Leaky Brain)

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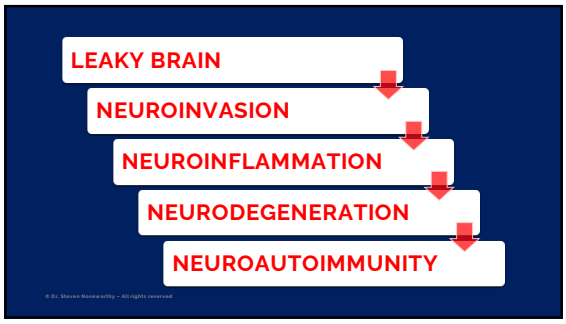
LEAKY BRAIN
NEUROINVASION
NEUROINFLAMMATION
NEURODEGENERATION
NEUROAUTOIMMUNITY
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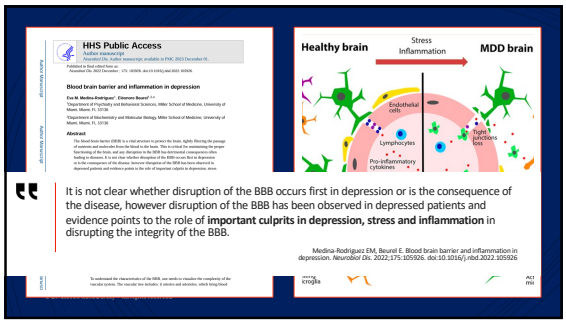
HHS Public Access
Blood brain barrier and inflammation in depression
Healthy brain
Stress
Inflammation
MDD brain
Endothelial cells
Lymphocytes
Pro-inflammatory cytokines
Tight junctions loss
It is not clear whether disruption of the BBB occurs first in depression or is the consequence of the disease, however disruption of the BBB has been observed in depressed patients and evidence points to the role of important culprits in depression, stress and inflammation in disrupting the integrity of the BBB.
Medina-Rodriguez EM, Beurel E. Blood brain barrier and inflammation in depression. Neurobiol Dis. 2022;175:105926. doi:10.1016/j.nbd.2022.105926

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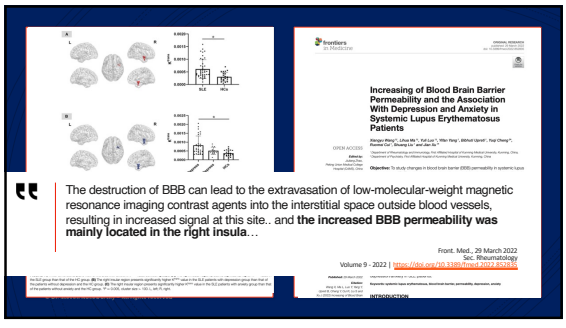
Increasing of Blood Brain Barrier Permeability and the Association With Depression and Anxiety in Systemic Lupus Erythematosus Patients
The destruction of BBB can lead to the extravasation of low-molecular-weight magnetic resonance imaging contrast agents into the interstitial space outside blood vessels, resulting in increased signal at this site.. and the increased BBB permeability was mainly located in the right insula…
Front. Med., 29 March 2022
Sec. Rheumatology
Volume 9 - 2022 | https://doi.org/10.3389/fmed.2022.852855

55

Things That Break The BBB

Anything that affects vascular and neuronal integrity

- Poor perfusion
- Insulin resistance and AGEs
- Inflammation & ROS
- Stress chemistry
- Lipopolysaccharides
- Environmental chemicals
- Mycotoxins – by ↓ Astrocyte mitochondrial function
- Concussion
- Aging/Senescence

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TESTING THE BBB

INDICATIVE

- GABA Challenge
- ~1000 mg GABA at onset of anxiety or 45 minutes before bed

DIAGNOSTIC

- Cyrex Array 2: Anti-BBB Protein Antibodies
- Vibrant Labs Neural Zoomer
  - Anti-Microglia
  - Anti-Glial fibrillary acidic protein
  - Anti-s100b
  - Ant-Glucose regulated protein 78

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NUTRIENTS TO SUPPORT BBB INTEGRITY

Manage/remove triggers and mechanisms

IMPROVE CEREBRAL BLOOD FLOW

- Feverfew
- Butcher's Broom
- Gingko Biloba
- Capsaicin
- Vinpocetine

DECREASE NEUROINFLAMMATION

- Green Tea Catechins
- Baicalein (Skullcap)
- Rutin
- Apigenin
- Luteolin

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CRITICAL CELL FUNCTIONS

- Microenvironment integrity (BBB)
- **Inflammation control**
- Energy production
- Synaptic Transmission (NTs)
- Plasticity

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Wang et al. Journal of Neuroinflammation (2022) 19:132
https://doi.org/10.1186/s12974-022-02492-0
Journal of Neuroinflammation
REVIEW Open Access

Microglia in depression: an overview of microglia in the pathogenesis and treatment of depression

Haixia Wang[1,2†], Yi He[1,2†], Zuoli Sun[1,2], Siyu Ren[1,2], Mingxia Liu[1,2], Gang Wang[1,2*] and Jian Yang[1,2*]

Abstract
Major depressive disorder is a highly debilitating psychiatric disorder involving the dysfunction of different cell types in the brain. Microglia are the predominant resident immune cells in the brain and exhibit a critical role in depression. Recent studies have suggested that depression can be regarded as a microglial disease. Microglia regulate inflammation, synaptic plasticity, and the formation of neural networks, all of which affect depression. In this review, we highlighted the role of microglia in the pathology of depression. First, we described microglial activation in animal models and clinically depressed patients. Second, we emphasized the possible mechanisms by which microglia recognize depression-associated stress and regulate conditions. Third, we described how antidepressants (clinical medicines and natural products) affect microglial activation. Thus, this review aimed to objectively analyze the role of microglia in depression and focus on potential antidepressants. These data suggested that regulation of microglial actions might

> Changes in microglia in different brain regions, including the PFC, HIP, anterior cingulate cortex (ACC), and amygdala, are involved in the development of depression.

Wang, H., He, Y., Sun, Z. *et al.* Microglia in depression: an overview of microglia in the pathogenesis and treatment of depression. *J Neuroinflammation* **19**, 132 (2022). https://doi.org/10.1186/s12974-022-02492-0

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Berk et al. BMC Medicine 2013, 11:200
http://www.biomedcentral.com/1741-7015/11/200
Current Controversies in Psychiatry
BMC Medicine
OPINION Open Access

So depression is an inflammatory disease, but where does the inflammation come from?

Michael Berk[1,2,3,4*], Lana J Williams[1,2], Felice N Jacka[1,2], Adrienne O'Neil[1,5], Julie A Pasco[1,6], Steven Moylan[1], Nicholas B Allen[7], Amanda L Stuart[1], Amie C Hayley[1], Michelle L Byrne[7] and Michael Maes[1,8]

Abstract
Background: We now know that depression is associated with a chronic, low-grade inflammatory response and activation of cell-mediated immunity, as well as activation of the compensatory anti-inflammatory reflex system. It is similarly accompanied by increased oxidative and nitrosative stress (O&NS), which contribute to neuroprogression in the disorder. The obvious question this poses is 'what is the source of this chronic low-grade inflammation?'
Discussion: This review explores the role of inflammation and oxidative and nitrosative stress as possible mediators of known environmental risk factors in depression, and discusses potential implications of these findings. A range of factors appear to increase the risk for the development of depression, and seem to be associated with systemic inflammation; these include psychosocial stressors, poor diet, physical inactivity, obesity, smoking, altered gut permeability, atopy, dental cares, sleep and vitamin D deficiency.
Summary: The identification of known sources of inflammation provides support for inflammation as a mediating pathway to both risk and neuroprogression in depression. Critically, most of these factors are plastic, and potentially amenable to therapeutic and preventative interventions. Most, but not all, of the above mentioned sources of inflammation may play a role in other psychiatric disorders, such as bipolar disorder, schizophrenia, autism and post-traumatic stress disorder.
Keywords: Depression, Inflammation, Cytokines, Diet, Obesity, Exercise, Smoking, Vitamin D, Dental cares, Sleep,

> There is now an extensive body of data showing that **depression is associated with both a chronic low-grade inflammatory response**, activation of cell-mediated immunity and activation of the compensatory anti-inflammatory reflex system (CIRS), characterized by negative immunoregulatory processes

BerketalBMCMedicine2013,11:200
http://www.biomedcentral.com/1741-7015/11/200

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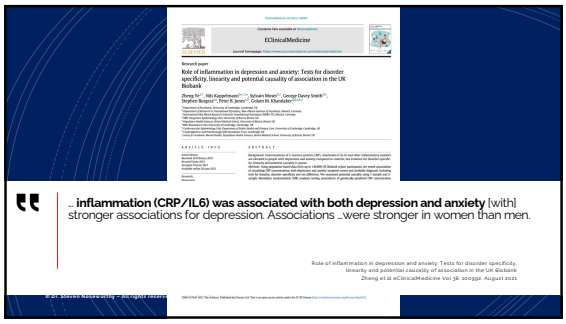

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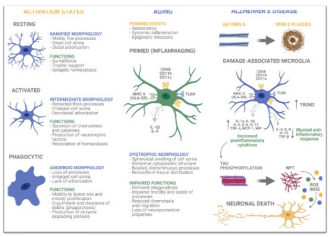
MICROGLIAL CELLS

- Brain macrophages
  - M1: Proinflammatory
  - M2: Anti-inflammatory & neurotrophic
- Have receptors for
  - Cytokines
  - Hormones (Cortisol, E2…)
  - ATP (extracellular)
  - NTs (many…GABA?)



Edler MK, Mhatre-Winters I, Richardson JR. Microglia in Aging and Alzheimer's Disease: A Comparative Species Review. Cells. 2021; 10(5):1138. https://doi.org/10.3390/cells10051138

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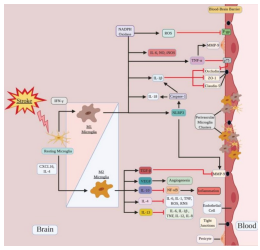
MICROGLIAL CELLS

- M1 Polarization
  - ↑Inflammatory cytokines → Tight junction damage
  - ↑ ROS → ↓ influx/efflux capacity
  - ↑MMP-9 → ↓ECM
  - ↑ iNOS
- M2 Polarization
  - ↓ NFkB/inflammation
  - ↓ MMP-9 → ↑ECM integrity
  - ↑VEGF and growth factors



Kang R, Gamdzyk M, Lenahan C, Tang J, Tan S, Zhang JH. The Dual Role of Microglia in Blood-Brain Barrier Dysfunction after Stroke. Curr Neuropharmacol. 2020;18(12):1237-1249. doi:10.2174/1570159X18666200529150907

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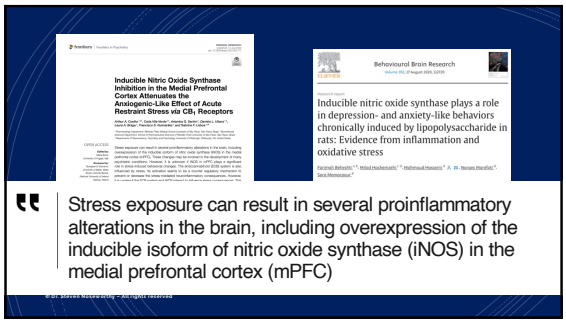
Inducible Nitric Oxide Synthase Inhibition in the Medial Prefrontal Cortex Attenuates the Anxiogenic-Like Effect of Acute Restraint Stress via CB1 Receptors
Behavioural Brain Research
Inducible nitric oxide synthase plays a role in depression- and anxiety-like behaviors chronically induced by lipopolysaccharide in rats: Evidence from inflammation and oxidative stress
Stress exposure can result in several proinflammatory alterations in the brain, including overexpression of the inducible isoform of nitric oxide synthase (iNOS) in the medial prefrontal cortex (mPFC)
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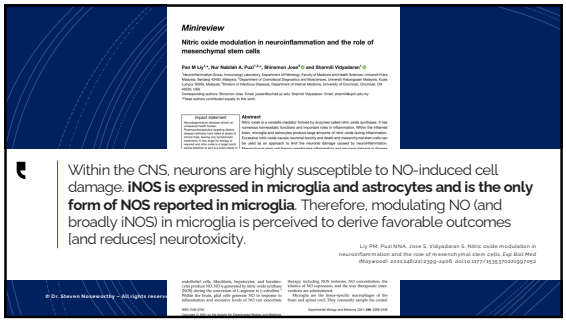
Minireview
Nitric oxide modulation in neuroinflammation and the role of mesenchymal stem cells
Within the CNS, neurons are highly susceptible to NO-induced cell damage. iNOS is expressed in microglia and astrocytes and is the only form of NOS reported in microglia. Therefore, modulating NO (and broadly iNOS) in microglia is perceived to derive favorable outcomes [and reduces] neurotoxicity.
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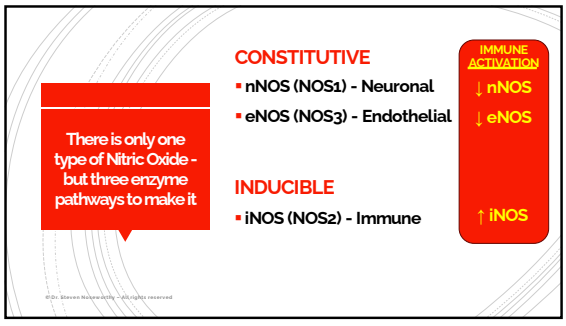
There is only one type of Nitric Oxide - but three enzyme pathways to make it
CONSTITUTIVE
nNOS (NOS1) - Neuronal
eNOS (NOS3) - Endothelial
INDUCIBLE
iNOS (NOS2) - Immune
IMMUNE ACTIVATION
↓ nNOS
↓ eNOS
↑ iNOS
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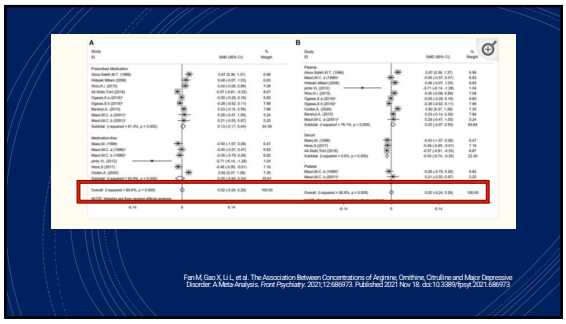

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> A growing body of evidence suggest that nNOS regulates the synthesis, release, and uptake of 5-HT.

Zhou QG, Zhu XH, Nemes AD, Zhu DY. Neuronal nitric oxide synthase and affective disorders. *IBRO Rep*. 2018;5:116-132. Published 2018 Nov 17. doi:10.1016/j.ibror.2018.11.004

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NUTRIENTS TO SUPPORT NOS-ISOMER BALANCE

Manage/remove immune triggers and mechanisms

GENERAL GOAL: ↓iNOS

- **↑eNOS ↑nNOS**

ATP
Xanthinol Nicotinate
N-Acetyl L-Carnitine
Alpha-GPC
Vinpocetine
Huperzine A

70

NUTRIENTS TO DAMPEN MICROGLIA

Manage/remove triggers and mechanisms

DECREASE NEUROINFLAMMATION

- Green Tea Catechins
- Baicalein (Skullcap)
- Rutin
- Apigenin
- Luteolin

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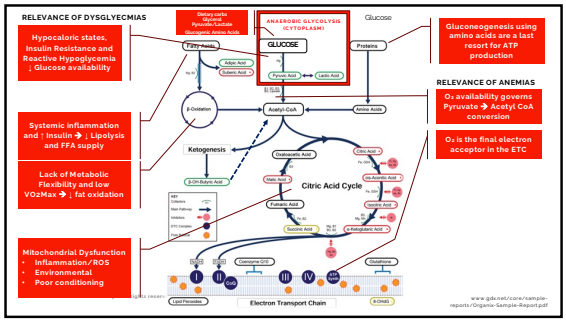
CRITICAL CELL FUNCTIONS

- Microenvironment integrity (BBB)
- Inflammation control
- **Energy production**
- Synaptic Transmission (NTs)
- Plasticity

72



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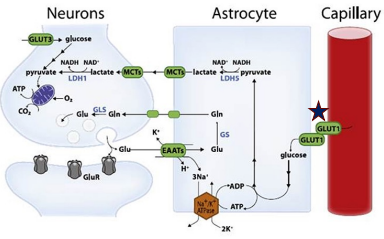
Astrocyte-Neuron Lactate Shuttle



Front. Neurosci., 02 February 2017 Sec. Neuroenergetics and Brain Health Volume 11 - 2017 | https://doi.org/10.3389/fnins.2017.00062

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Hyperinsulinemia drives anxiety and depression

- Alters brain mitochondrial function
  - ↓ ATP
  - ↑ ROS
  - ↑ lipid peroxidation
- ↑ MAO activity → ↓ Dopamine


Insulin resistance in brain alters dopamine turnover and causes behavioral disorders

https://www.pnas.org/doi/abs/10.1073/pnas.1515877112

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REACTIVE HYPOGLYCEMIA

- Activates Mesencephalic Reticular Formation
- Leads to ↑catecholamines and ↑Cortisol
- Dysregulates most NT biosynthetic pathways
- Neurons can't maintain Resting Membrane potential
  - Easier to fire with trivial inputs
- Lack of Metabolic Flexibility and adaptive responses leads to low fuel states
  - Prefrontal Cortex can't fire inhibitory signals
  - Amygdala activates "spontaneously"

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STRATEGIES AND NUTRIENTS THAT SUPPORT BLOOD SUGAR CONTROL

Keto and Intermittent Fasting are desirable if tolerated

INSULIN RESISTANCE

- Diet: Control calories and carbs; adequate protein
- Nutrients that support AMPK and Insulin Sensitivity
  - Berberine HCL
  - Alpha Lipoic Acid
  - Burdock Root
  - Rose Hips
  - Chromic Picolinate

REACTIVE HYPOGLYCEMIA

- Diet: Adequate calories and protein → Develop Metabolic flexibility
  - Careful of low carb and Intermittent Fasting
- Nutrients
  - Phytosterols-BCAA-Cinnamon extract
  - Adrenal co-support?

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CRITICAL CELL FUNCTIONS

- Microenvironment integrity (BBB)
- Inflammation control
- Energy production
- Synaptic Transmission (NTs)
- Plasticity

Fire or die.

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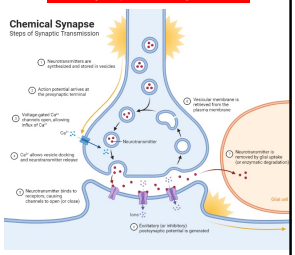
Fire or Die Means 3 things

1. Presynaptic neuron synthesizes & releases NT
2. NT crosses the Synapse & binds to post-synaptic receptor
3. Signal is terminated/reset to fire again

Cell body is up here and signals flow ↓



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MODULATION OF THE SYNAPSE

Homotropic Modulation

- NT system modulates itself
  - Honeymoon period of reuptake inhibitors

Heterotropic Modulation

- Modulation from outside the system
  - Hormones
  - Cytokines
  - Neuropeptides
    - e.g. CRH
  - Lipid mediators
    - e.g. Prostaglandins
  - Gas mediators
    - e.g. NO, CO_2

Plasticity Modulators

- BDNF
- Cytokines
- Steroid Hormones

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Brain Assessment Forms (NTAF and BFAF)


Neurotransmitter Assessment Form (NTAF)


Brain Function Assessment Form™ (BFAF)

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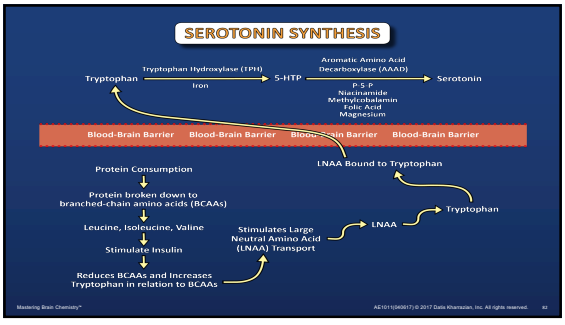
SEROTONIN SYNTHESIS



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INTELLLIGENT NT FORMULAE

- Amino Acid Precursors
- Pathway-specific nutrient cofactors
- Support for receptor sensitivity
- Support for NT clearance

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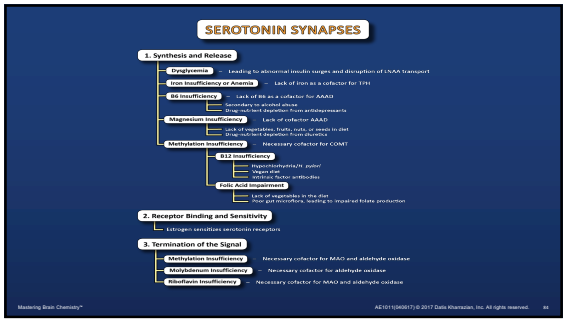

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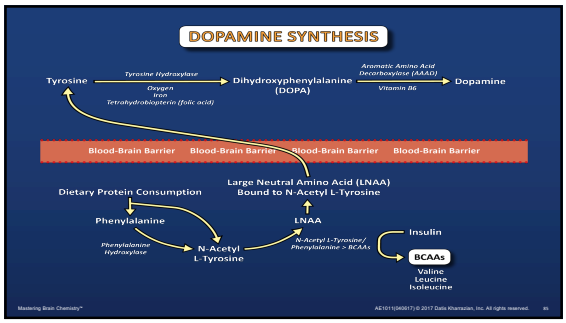

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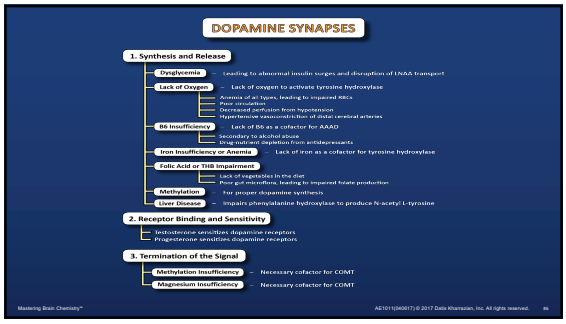
DOPAMINE SYNAPSES
1. Synthesis and Release
Dysglycemia
Leading to abnormal insulin surges and disruption of LNAA transport
Lack of Oxygen
Lack of oxygen to activate tyrosine hydroxylase
Anemia of all types, leading to impaired RBCs
Poor circulation
Decreased perfusion from hypotension
Hypertensive vasoconstriction of distal cerebral arteries
B6 Insufficiency
Lack of B6 as a cofactor for AAAD
Secondary to alcohol abuse
Drug nutrient depletion from antidepressants
Iron Insufficiency or Anemia
Lack of iron as a cofactor for tyrosine hydroxylase
Folic Acid or THB Impairment
Lack of vegetables in the diet
Poor gut microflora, leading to impaired folate production
Methylation
for proper dopamine synthesis
Liver Disease
Impairs phenylalanine hydroxylase to produce N-acetyl L-tyrosine
2. Receptor Binding and Sensitivity
Testosterone sensitizes dopamine receptors
Progesterone sensitizes dopamine receptors
3. Termination of the Signal
Methylation Insufficiency
Necessary cofactor for COMT
Magnesium Insufficiency
Necessary cofactor for COMT
Mastering Brain Chemistry™
AE101(040617)-© 2017 Dale Kharrazian, Inc. All rights reserved.
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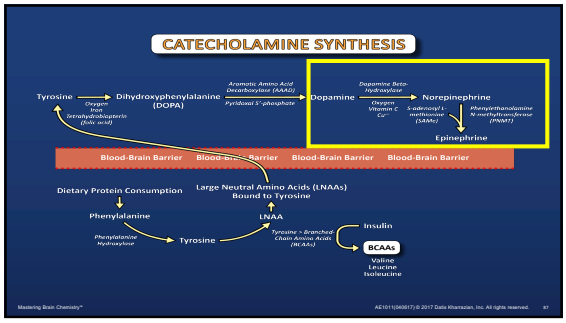
CATECHOLAMINE SYNTHESIS
Tyrosine
Oxygen
Iron
Tetrahydrobiopterin
(Folic acid)
Dihydroxyphenylalanine
(DOPA)
Aromatic Amino Acid
Decarboxylase (AAAD)
Pyridoxal 5'-phosphate
Dopamine
Dopamine Beta-
Hydroxylase
Oxygen
Vitamin C
Cu++
Norepinephrine
S-adenosyl-L-
methionine
(SAMe)
Phenylethanolamine
N-methyltransferase
(PNMT)
Epinephrine
Blood-Brain Barrier
Blood-Brain Barrier
Blood-Brain Barrier
Blood-Brain Barrier
Dietary Protein Consumption
Large Neutral Amino Acids (LNAAs)
Bound to Tyrosine
Phenylalanine
Phenylalanine
Hydroxylase
Tyrosine
LNAA
Tyrosine + Branched
Chain Amino Acids
(BCAAs)
Insulin
BCAAs
Valine
Leucine
Isoleucine
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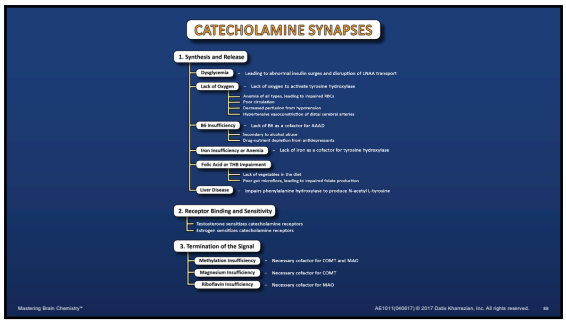
CATECHOLAMINE SYNAPSES
1. Synthesis and Release
Dysglycemia
Leading to abnormal insulin surges and disruption of LNAA transport
Lack of Oxygen
Lack of oxygen to activate tyrosine hydroxylase
Anemia of all types, leading to impaired RBCs
Poor circulation
Decreased perfusion from hypotension
Hypertensive vasoconstriction of distal cerebral arteries
B6 Insufficiency
Lack of B6 as a cofactor for AAAD
Secondary to alcohol abuse
Drug nutrient depletion from antidepressants
Iron Insufficiency or Anemia
Lack of iron as a cofactor for tyrosine hydroxylase
Folic Acid or THB Impairment
Lack of vegetables in the diet
Poor gut microflora, leading to impaired folate production
Liver Disease
Impairs phenylalanine hydroxylase to produce N-acetyl L-tyrosine
2. Receptor Binding and Sensitivity
Testosterone sensitizes catecholamine receptors
Estrogen sensitizes catecholamine receptors
3. Termination of the Signal
Methylation Insufficiency
Necessary cofactor for COMT and MAO
Magnesium Insufficiency
Necessary cofactor for COMT
Riboflavin Insufficiency
Necessary cofactor for MAO
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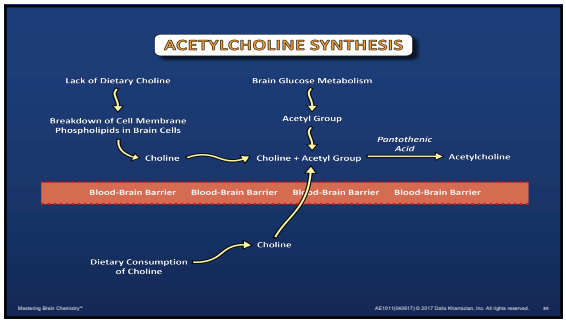
ACETYLCHOLINE SYNTHESIS
Lack of Dietary Choline
Brain Glucose Metabolism
Breakdown of Cell Membrane Phospholipids in Brain Cells
Acetyl Group
Choline
Choline + Acetyl Group
Pantothenic Acid
Acetylcholine
Blood-Brain Barrier
Blood-Brain Barrier
Blood-Brain Barrier
Blood-Brain Barrier
Choline
Dietary Consumption of Choline
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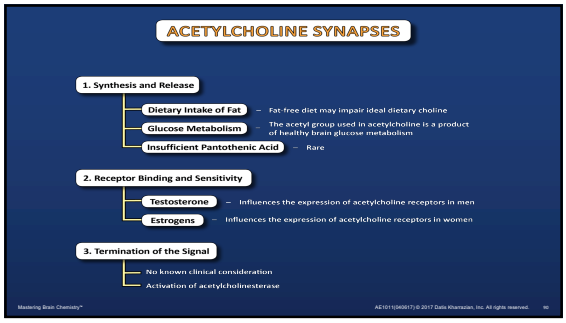
ACETYLCHOLINE SYNAPSES
1. Synthesis and Release
Dietary Intake of Fat – Fat-free diet may impair ideal dietary choline
Glucose Metabolism – The acetyl group used in acetylcholine is a product of healthy brain glucose metabolism
Insufficient Pantothenic Acid – Rare
2. Receptor Binding and Sensitivity
Testosterone – Influences the expression of acetylcholine receptors in men
Estrogens – Influences the expression of acetylcholine receptors in women
3. Termination of the Signal
No known clinical consideration
Activation of acetylcholinesterase
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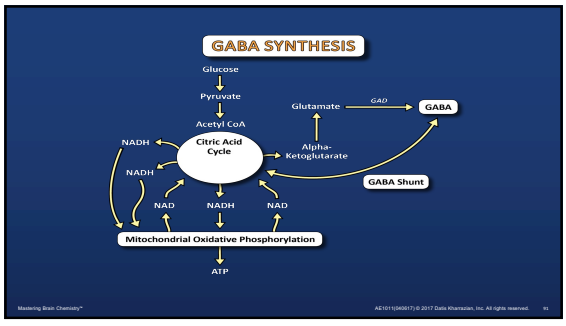
GABA SYNTHESIS
Glucose
Pyruvate
Acetyl CoA
Glutamate
GAD
GABA
NADH
Citric Acid Cycle
Alpha-Ketoglutarate
NADH
GABA Shunt
NAD
NADH
NAD
Mitochondrial Oxidative Phosphorylation
ATP
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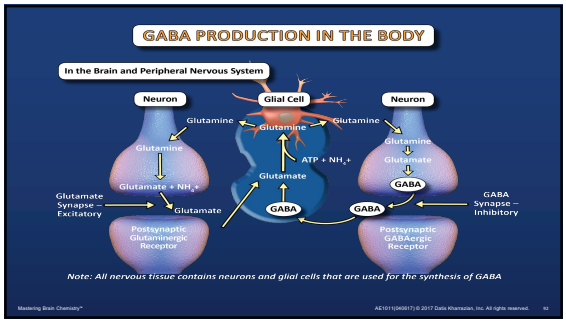

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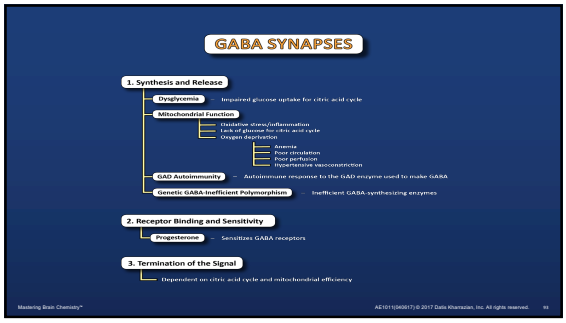

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CRITICAL CELL FUNCTIONS

- Microenvironment integrity (BBB)
- Inflammation control
- Energy production
- Synaptic Transmission (NTs)
- Plasticity

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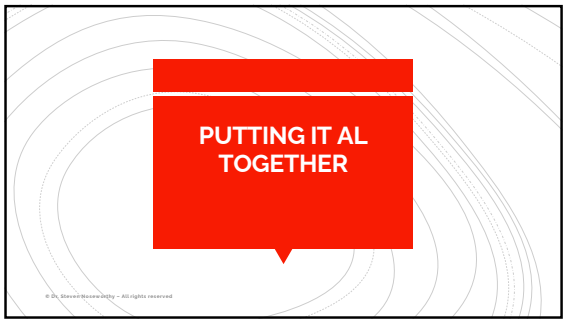
PUTTING IT AL TOGETHER

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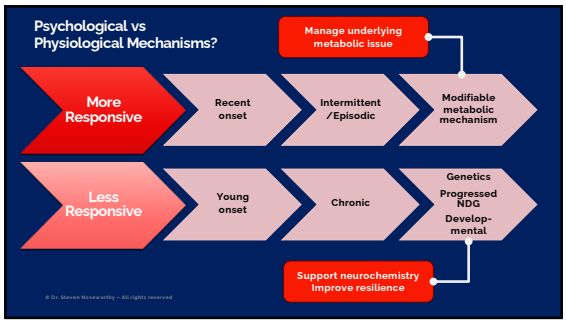
Psychological vs Physiological Mechanisms?
Manage underlying metabolic issue
More Responsive
Recent onset
Intermittent /Episodic
Modifiable metabolic mechanism
Less Responsive
Young onset
Chronic
Genetics
Progressed NDG
Develop-mental
Support neurochemistry Improve resilience

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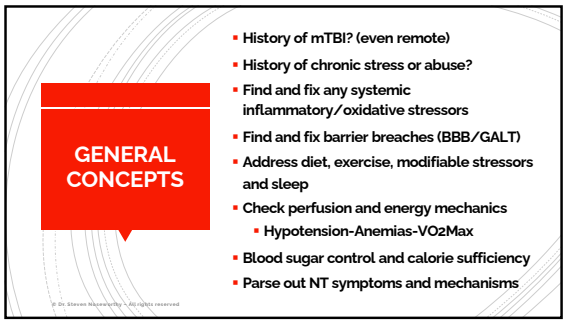
GENERAL CONCEPTS
History of mTBI? (even remote)
History of chronic stress or abuse?
Find and fix any systemic inflammatory/oxidative stressors
Find and fix barrier breaches (BBB/GALT)
Address diet, exercise, modifiable stressors and sleep
Check perfusion and energy mechanics
Hypotension-Anemias-VO2Max
Blood sugar control and calorie sufficiency
Parse out NT symptoms and mechanisms

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ANXIETY CORE CONCEPTS

Anxiety is inappropriate activation of the Amygdala

Goals:
- Stabilize neurochemistry
- Create plasticity in Frontal Lobe and Cerebellum

PRIMARY MECHANISMS TO CONSIDER

- Mesolimbic Plasticity? (light/sound sensitivity, easily startled)
- History of StrepA?
- Reactive Hypoglycemia and calorie sufficiency are VERY common
  - Often intolerant to low carb/Keto/IF
- Consider autoimmune reactivity
  - GAD65-Purkinje cells-GABA-D2 receptors
  - Gluten cross reactivity with GAD65 and/or Cerebellum
- Any mechanism that alters GABA
  - Consider Progesterone sufficiency
- Check for balance issues

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DEPRESSION CORE CONCEPTS

Depression is decreased activation of the Prefrontal Cortex

- Dampen microglial inflammation
- Stabilize general metabolic state

PRIMARY MECHANISMS TO CONSIDER

- Fire the Frontal Lobe
  - Exercise
  - Community
  - Purpose, Problem solving and Planning (75 Hard?!?!)
  - Sensory rich life
  - Control modifiable stressors
- Frontal Lobe heavily dependent on
  - Dopamine ad Catecholamines
  - Testosterone in men
  - Estrogens in women

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