NEUROPSYCHIATRIC EFFECTS OF MAST CELL ACTIVATION AND LIMBIC DYSREGULATION

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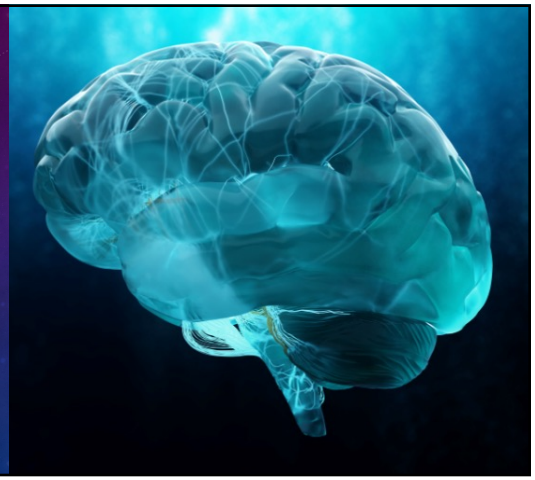


1

WHAT IS MAST CELL ACTIVATION DISORDER?

Chronic inappropriate production and release of the mast cells' large inventory of potent mediators, which upon interaction with other cells throughout the body, cause most of the symptoms of mast cell disease.

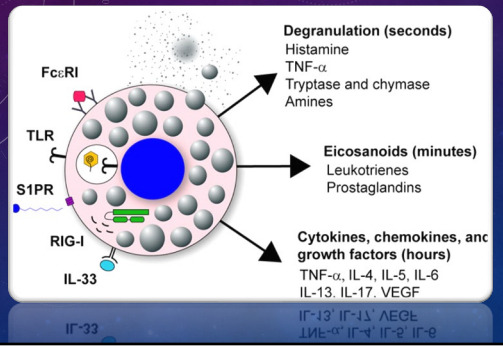
2

NOT A RARE ILLNESS

10 to 17 percent of population

3

MAST CELLS: OUR BODIES' FIRST RESPONDERS



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IMMUNE SYSTEM FIRST RESPONDERS

SKIN
Fulshing Rashes
Hives
Angioedema

AIRWAYS & LUNGS
Asthma
Anaphylaxis

GI TRACT
Leaky gut
Bloating
Reactivity Diarrhea

BLOOD BRAIN BARRIER
Leaky Brain
Limbic Dysregulation

BLADDER
Interstitial Cystitis

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NEUROINFLAMMATION AND THE COMPLEX PATIENT

TRIFECTA AND PENTAD

Most Common Grouping of Symptoms

1. MCAS which may not have yet been diagnosed.
2. Hypermobile/EDS body type
3. Symptoms consistent with Dysautonomia/POTS /Small Fiber Neuropathy
4. Autoimmunity
5. Gastroparesis
6. Sensitive to smells, sounds, EMFs or light
7. History of inability to tolerate most allopathic meds
8. Adverse childhood experiences (ACE's) Medical trauma and gaslighting

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HALSEY OPENS UP ABOUT BEING CALLED 'CRAZY, ANXIOUS AND LAZY' BEFORE RECENT HEALTH DIAGNOSES

Halsey is opening up about receiving a slew of new health diagnoses after previously informing fans they had spent time in the hospital.

"My health has changed a lot since I got pregnant and gave birth..."

"I just want to clarify, for the benefit of friends of friends who may have any of the diagnoses that I recently shared, I didn't 'just get sick' I've been sick. For a long time," the post read. "My sicknesses just have their names now. I went to doctors for 8 years. Trying to figure out what was wrong with me. I was called crazy and anxious and lazy amongst other things. I changed my entire lifestyle."

https://www.usatoday.com/story/entertainment/celebrities/2022/05/10/halsey-health-diagnosis-ehlers-danlos-mast-cell-activation-syndrome-pots/9722199002/

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MAST CELLS IN MY BRAIN!

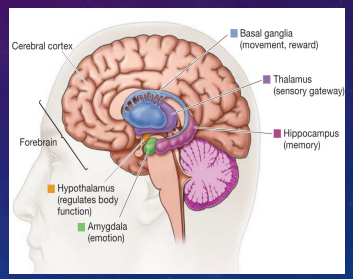
Blood Brain Barrier Permeability
- Neuroinflammation, "Leaky Brain"

Thalamus, Cerebellum, Amygdala
- Limbic System

Hypothalamus (Ventral Diencephalon)
- Hormones, HPA

Caudate, Putamen (Dorsal Striatum)
- OCD, Tourette's PANS, Parkinson's, Motivation

Brainstem (Substantia Nigra, Trigeminal Sensory and Motor, Noradrenergic and cholinergic neuron centers)
- Sleep wake cycles, Trigeminal neuralgia



Haas et al. Histamine in the nervous system. *Physiol Rev.* 2008; 88(3):1183-241. https://doi.org/10.1152/physrev.00043.2007

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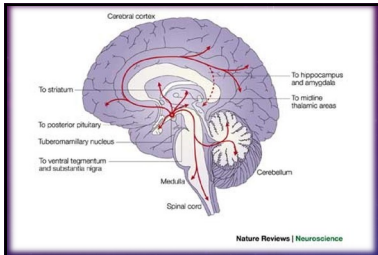

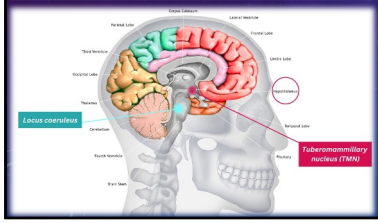

HISTAMINE IN THE BRAIN

The tuberomammillary nucleus of the posterior hypothalamus produces histamine.

Contributes to regulation of normal cognition and sleep-wakefulness in locus coeruleus.

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ROLE OF MAST CELLS IN BRAIN

- Activated by CRH made in hypothalamus and thalamus (stress hormones)
- Release inflammatory mediators (IL-6, TNF, mtDNA)
- Release IL-6 and TGFβ which promote IL-17 cell maturation
- Disrupt the BBB leading to hyperpermeability (aka Leaky Brain)
- Recruit circulating lymphocytes - neuroinflammation
- Stimulate microglial activation and proliferation - neuroinflammation
- Deplete histamine which promotes motivation

Theoharides, T., Stewart, J., Panagiotidou, S., & Melamed, I. (2015). Mast cells, brain inflammation and autism. *European Journal of Pharmacology*, *778*(5 May), 96–102

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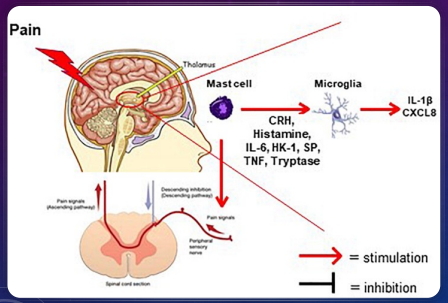
THALAMIC MAST CELL DEGRANULATION



Mast cells in the thalamus secrete pro-inflammatory and neuro-sensitizing mediators - CRH, histamine, IL-6, HK-1, SP, TNF, Tryptase. These mediators can then activate either microglia in thalamic nuclei or ascending nociceptive tracks creating the sensation of pain.

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NEUROPSYCHIATRIC DISEASES ASSOCIATED WITH MAST CELLS

Fibromyalgia
- Own observation & Lucas et al, 2006, e24

Migraine
- e48, e50, e51, e52

Neuropathic pain
- Own observation and Demir et al., 2013, e13, e53, e54

CRPS
- Prev. synonyms: Morbus Sudeck / Sudeck-dystrophia / Algodystrophia; e55, e56.

Vulvodynia
- Own observation and Bornstein et al., 2008

Autism
- Own observation and e46, e47, e48, e49.

Multiple Sclerosis
- Nelissen et al., 2013; Smith et al., 2011

Alzheimer's Disease
- Nelissen et al., 2013

Parkinsonism
- e57

Neurofibromatosis
- e58, e59

Bornstein et al. Involvement of heparanase in the pathogenesis of localized vulvodynia. *Int J Gynecol Pathol*. 2008 27(1):136-41. doi:10.1097/pgp.0b013e318140f2fb.
Nelissen et al. The role of mast cells in neuroinflammation. *Acta Neuropathol*. 2013. 125(5):637-50. doi:10.1007/s00401-013-1092-y. Smith et al. Neurologic symptoms and diagnosis in adults with mast cell disease. *Clin Neurol Neurosurg*. 2011. 113(7):570-4.
Alrin et al., 2015; Lucas et al. Fibromyalgia--new concepts of pathogenesis and treatment. *Int J Demir et al.* Perineural mast cells are specifically enriched in pancreatic neuritis and neuropathic pain in pancreatic cancer and chronic pancreatitis. *PLoS One*. 2013;8(3):e60529. doi:10.1371/journal.pone.0060529.
Immunopathol Pharmacol. 2006;19(1):1-10. PMID: 16569357.

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NEUROPSYCHIATRIC DISEASES ASSOCIATED WITH MAST CELLS

Gratuitous upset
- e.g. labile affect. Hermine et al., 2008; e32.

Motivation disorder
- Hermine et al., 2008; e30, e37, e69

Depressive episode
- Hermine et al., 2008; e30, e37, e60

ADHD / Bi-polar disorder
- Afrin, 2013; Afrin & Molderings, 2014

Anxiety disorder / Psychosis
- Own observation, Bornstein et al., 2008 / e73

PTSD/Panic Attacks
- Afrin et al., 2013; Afrin & Molderings, 2014

Visual hallucinations
- That disappear under blockade of mast cells (own observation) / Afrin et al., 2013

Hyperventilation tetany-like symp
- Afrin & Molderings, 2014

Disturbance of memory / Word-finding difficulties
- Afrin et al., 2013; Hermine et al., 2008, e31, 32, e70 / Afrin et al., 2013, e32

Difficulties in concentrating
- Hermine et al., 2008, e31, e32, 369, e70

Afrin & Molderings. A concise, practical guide to diagnostic assessment for mast cell activation disease. *World J Hematol* 2014 3(1):1-17. doi: 10.5315/wjh.v3.i1.1

Afrin et al., 2015; Hermine et al. Case-Control Cohort Study of Patients' Perceptions of Disability in Mastocytosis. *PLoS One*. 2008;3:e2266. doi: 10.1371/journal.pone.0002922

Afrin L. Presentation, diagnosis, and management of mast cell activation syndrome. In *Mast Cells: Phenotypic features, biological functions, and role in immunity*. Nova Science Publishers 2013: 155-231

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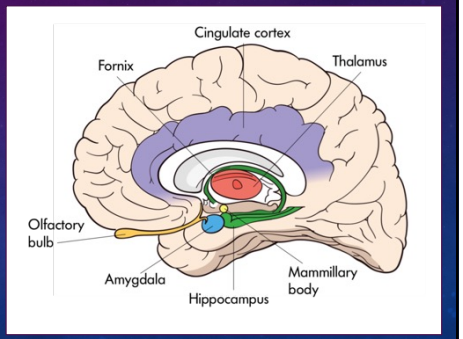
THE PERCEPTION OF DANGER TAKES PLACE IN THE LIMBIC SYSTEM

- LIMBIC SYSTEM CONSISTS OF THALAMUS, AMYGDALA, HIPPOCAMPUS, CINGULATE
- IT IS THE EMOTIONAL CENTER OF THE BRAIN
- "LOOPING" IS THE INCREASED SENSITIVITY OF THALAMUS
- THIS CAUSES AMPLIFICATION OF FEAR, ANGER AND STRESS



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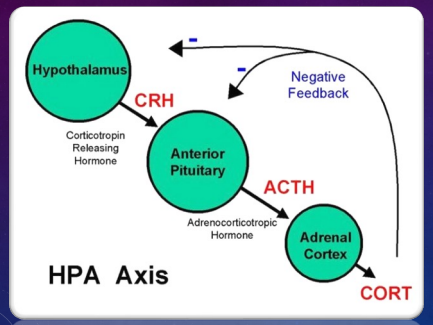
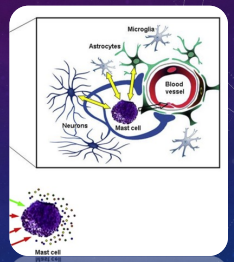
STRESS DESTABILIZES MAST CELLS





Afrin, L. B. *et al.* Mast cell activation disease: An underappreciated cause of neurologic & psychiatric symptoms and diseases (2015).

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TRAUMA RESPONSE OR HOW DOES THE AUTONOMIC NERVOUS SYSTEM BECOME DYSREGULATED

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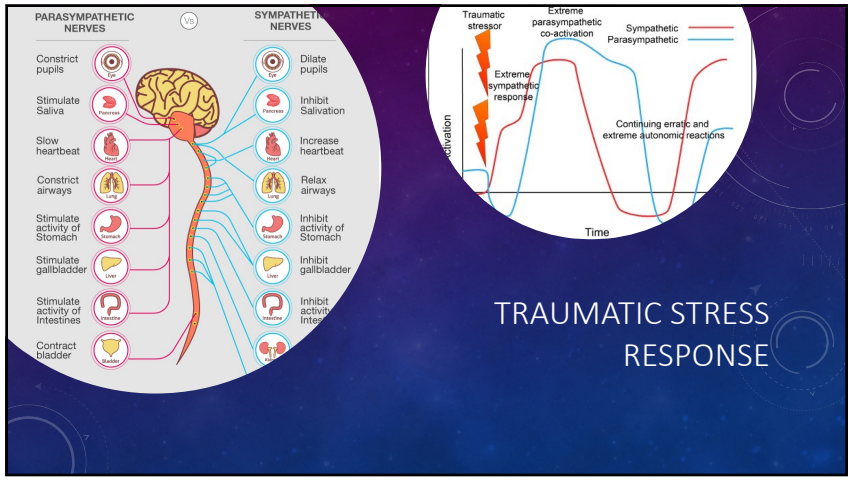
PARASYMPATHETIC NERVES
Vs
SYMPATHETIC NERVES
Constrict pupils
Stimulate Saliva
Slow heartbeat
Constrict airways
Stimulate activity of Stomach
Stimulate gallbladder
Stimulate activity of Intestines
Contract bladder
Dilate pupils
Inhibit Salivation
Increase heartbeat
Relax airways
Inhibit activity of Stomach
Inhibit gallbladder
Traumatic stressor
Extreme parasympathetic co-activation
Sympathetic
Parasympathetic
Extreme sympathetic response
Continuing erratic and extreme autonomic reactions
Time
TRAUMATIC STRESS RESPONSE

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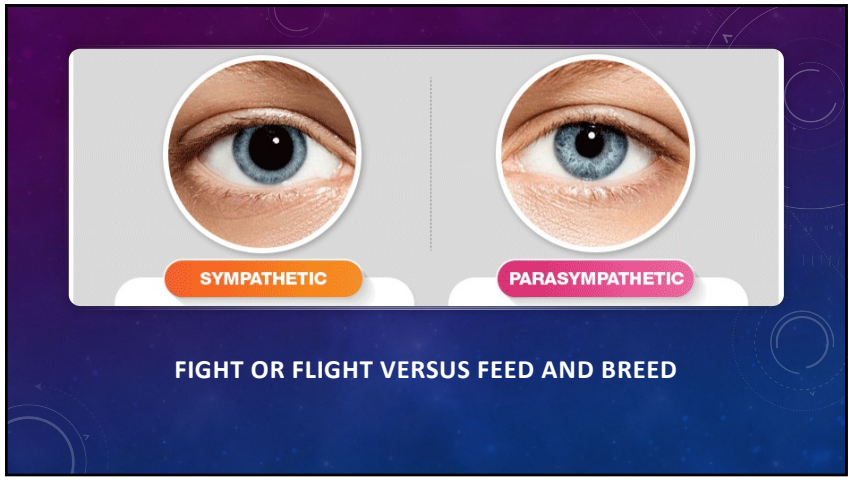
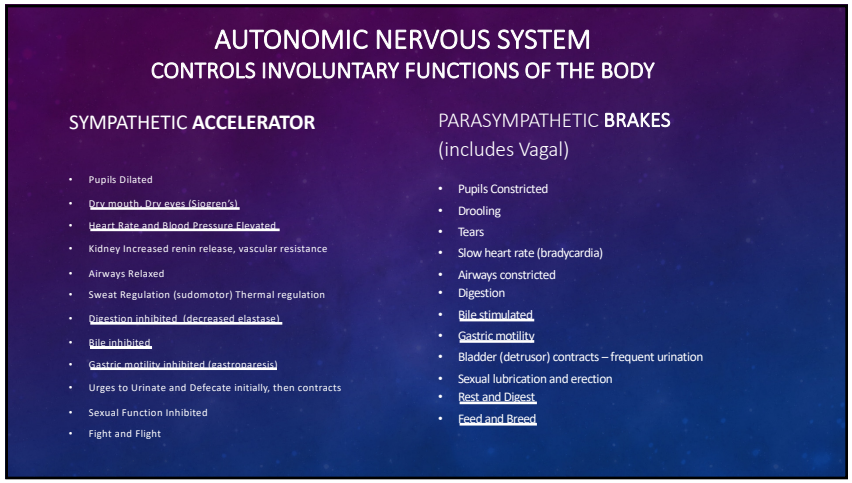

SYMPATHETIC
PARASYMPATHETIC
FIGHT OR FLIGHT VERSUS FEED AND BREED

18


AUTONOMIC NERVOUS SYSTEM
CONTROLS INVOLUNTARY FUNCTIONS OF THE BODY
SYMPATHETIC ACCELERATOR
Pupils Dilated
Dry mouth, Dry eyes (Sjogren's)
Heart Rate and Blood Pressure Elevated
Kidney Increased renin release, vascular resistance
Airways Relaxed
Sweat Regulation (sudomotor) Thermal regulation
Digestion inhibited (decreased elastase)
Bile inhibited
Gastric motility inhibited (gastroparesis)
Urges to Urinate and Defecate initially, then contracts
Sexual Function Inhibited
Fight and Flight
PARASYMPATHETIC BRAKES
(includes Vagal)
Pupils Constricted
Drooling
Tears
Slow heart rate (bradycardia)
Airways constricted
Digestion
Bile stimulated
Gastric motility
Bladder (detrusor) contracts – frequent urination
Sexual lubrication and erection
Rest and Digest
Feed and Breed

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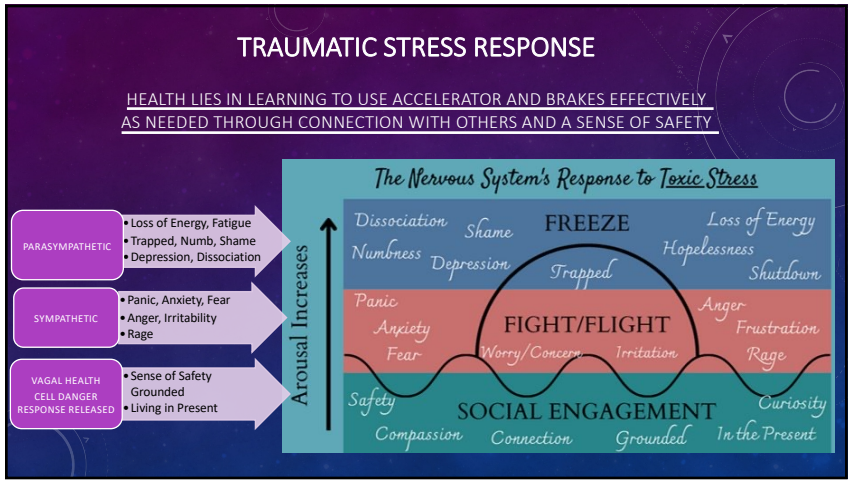
TRAUMATIC STRESS RESPONSE
HEALTH LIES IN LEARNING TO USE ACCELERATOR AND BRAKES EFFECTIVELY
AS NEEDED THROUGH CONNECTION WITH OTHERS AND A SENSE OF SAFETY
The Nervous System's Response to Toxic Stress
PARASYMPATHETIC
• Loss of Energy, Fatigue
• Trapped, Numb, Shame
• Depression, Dissociation
SYMPATHETIC
• Panic, Anxiety, Fear
• Anger, Irritability
• Rage
VAGAL HEALTH CELL DANGER RESPONSE RELEASED
• Sense of Safety
Grounded
• Living in Present
Arousal Increases
Dissociation
Shame
FREEZE
Loss of Energy
Numbness
Depression
Trapped
Hopelessness
Shutdown
Panic
Anxiety
Fear
FIGHT/FLIGHT
Anger
Frustration
Rage
Worry/Concern
Irritation
Safety
SOCIAL ENGAGEMENT
Curiosity
Compassion
Connection
Grounded
In the Present

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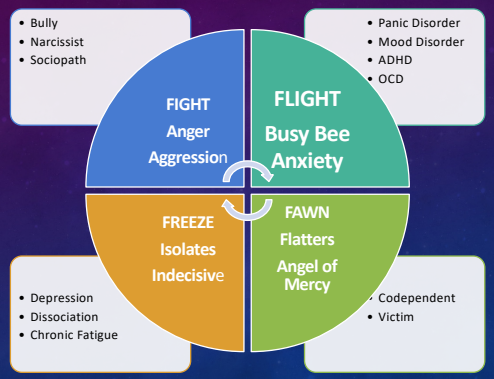
Psychiatric Diagnoses Corresponding to Trauma States



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NEUROQUANT MRI: WINDOW INTO LIMBIC DYSREGULATION & MAST CELLS

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VOLUMETRIC BRAIN IMAGING

STRUCTURAL PATHOLOGY OF THE BRAIN

Volumetric Imaging is an MRI of the brain with computerized volumetric analysis of multiple gray and white matter regions. In essence it takes 2D segmented images and reconstructs their 3D volumes.

- It can be used to diagnosis Alzheimer's
- Or to assess Traumatic Brain Injury patterns

Persson K, Barca ML, Cavallin L, et al. Comparison of automated volumetry of the hippocampus using NeuroQuant® and visual assessment of the medial temporal lobe in Alzheimer's disease. *Acta radiol*. 2018;598

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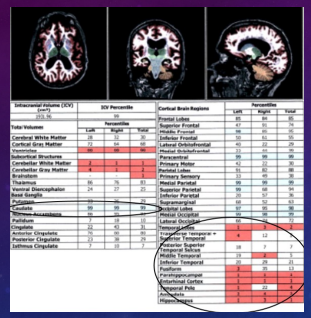
ALZHEIMER'S: SEA OF RED



Hippocampus 1%

Ventricles 99 %

Temporal Lobes 2%

Entorhinal 1%

Parahippocampus 1%

Amygdala 2%

Caudate 99%

2018

24

SYMPATHETIC AROUSAL BRAIN

Limbic Activation and Looping

Amygdala, Hippocampus, Thalamus,Cingulate

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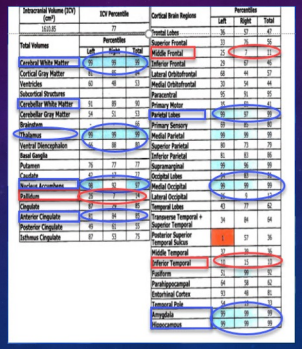
52 YO FEMALE – CIRS, TBI, EDS, MAST CELL MAJOR DEPRESSION REQUIRING TRANSCRANIAL & KETAMINE

White matter inflammation
Cerebral white 99%
Cerebellar white 90%

Limbic
Thalamus 99%
Some periventricular flairs
Anterior cingulate 85%
Amygdala 99%
Hippocampus 99%



Basal Ganglia (Striatum)
Nucleus accumbens 99%
Pallidum 14%

Cortical Gray 84%
Parietal 99%
Medial occipital 99%
Middle frontal 11%

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PANS, OCD AND MOLD: SEA OF BLUE & BASAL GANGLIA ATROPHY

Cortical Gray 99%
Frontal lobes 99%
Middle frontal 99%
INF frontal 99%
Primary motor 99%
Primary sensory 99%
Temporal lobes 99%

Limbic
Anterior cingulate 93%
Amygdala 81%
Hippocampus 68%
Thalamus 80%

Basal Ganglia (Striatum)
Putaman 9%
Caudate 6%
Nucleus accumbens 20%
Pallidum 10%

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BASAL GANGLIA, CIRS, PANS

- **Histamine plays a role in modulation of the corticostriatal circuitry**
- **Abnormal histaminergic transmission in caudate putamen is associated with Tourette's and OCD possibly by antagonizing dopamine transmission**

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High Pressure HBOT (2.2 atm)
77 y/o Male (Apr '22 – Nov '22)

Major Neurological Improvement & Increased Quality of Life

Intracranial Volume (ICV) (cm³)	ICV Percentile
1466.16	9

Total Volumes	Percentiles		
	Left	Right	Total
Cerebral White Matter	34	43	39
Cortical Gray Matter	98	96	97
Ventricles	67	69	68
Subcortical Structures			
Cerebellar White Matter	64	71	68
Cerebellar Gray Matter	76	80	78
Brainstem	-	-	5
Thalamus	49	65	57
Ventral Diencephalon	9	24	13
Basal Ganglia			
Putamen	87	90	89
Caudate	55	39	48
Nucleus Accumbens	83	94	82
Pallidum	48	71	61
Cingulate	78	72	76
Anterior Cingulate	68	72	73
Posterior Cingulate	73	80	78
Isthmus Cingulate	60	36	53

Cortical Brain Regions	Percentiles		
	Left	Right	Total
Frontal Lobes	79	73	76
Superior Frontal	63	45	55
Middle Frontal	37	47	34
Inferior Frontal	73	55	63
Lateral Orbitofrontal	89	97	96
Medial Orbitofrontal	62	41	48
Paracentral	86	81	86
Primary Motor	91	96	96
Parietal Lobes	84	78	82
Primary Sensory	91	92	80
Medial Parietal	94	69	85
Superior Parietal	74	80	76
Inferior Parietal	89	84	81
Supramarginal	25	40	27
Occipital Lobes	99	95	96
Medial Occipital	99	96	95
Lateral Occipital	95	82	93
Temporal Lobes	97	99	99
Transverse Temporal + Superior Temporal	76	97	92
Posterior Superior Temporal Sulcus	21	87	66
Middle Temporal	86	95	94
Inferior Temporal	74	99	95
Fusiform	95	99	98
Parahippocampal	96	56	85
Entorhinal Cortex	81	89	88
Temporal Pole	92	83	90
Amygdala	95	97	97
Hippocampus	51	63	58

White Matter +90%

Cortical Grey unchanged (97%)

Intracranial Volume (ICV) (cm³)	ICV Percentile
1480.25	12

Total Volumes	Percentiles		
	Left	Right	Total
Cerebral White Matter	77	70	74
Cortical Gray Matter	98	94	97
Ventricles	67	72	70
Subcortical Structures			
Cerebellar White Matter	85	76	82
Cerebellar Gray Matter	33	48	40
Brainstem	-	-	2
Thalamus	60	69	65
Ventral Diencephalon	3	13	5
Basal Ganglia			
Putamen	96	91	94
Caudate	92	77	87
Nucleus Accumbens	84	87	88
Pallidum	6	15	9
Cingulate	98	94	96
Anterior Cingulate	96	94	96
Posterior Cingulate	95	93	95
Isthmus Cingulate	69	45	59

Cortical Brain Regions	Percentiles		
	Left	Right	Total
Frontal Lobes	94	92	93
Superior Frontal	90	60	79
Middle Frontal	44	91	74
Inferior Frontal	65	64	66
Lateral Orbitofrontal	98	89	97
Medial Orbitofrontal	83	58	70
Paracentral	87	78	86
Primary Motor	98	99	99
Parietal Lobes	96	92	95
Primary Sensory	99	81	96
Medial Parietal	98	75	94
Superior Parietal	88	88	90
Inferior Parietal	82	87	89
Supramarginal	12	55	26
Occipital Lobes	99	75	97
Medial Occipital	99	72	95
Lateral Occipital	94	70	89
Temporal Lobes	75	88	83
Transverse Temporal + Superior Temporal	33	91	68
Posterior Superior Temporal Sulcus	72	93	88
Middle Temporal	15	42	25
Inferior Temporal	66	77	74
Fusiform	99	97	99
Parahippocampal	94	50	81
Entorhinal Cortex	66	86	76
Temporal Pole	90	51	77
Amygdala	78	68	76
Hippocampus	64	61	63

Middle Frontal +118%
(executive function)

Amygdala –22%

Hippocampus +7%

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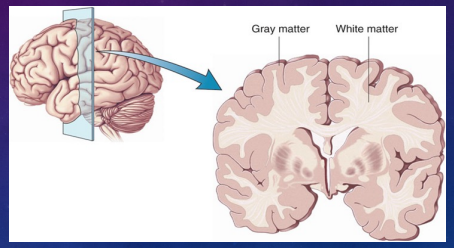
BRAIN STRUCTURE: GRAY MATTER

- Gray matter is composed of neuron cell bodies, dendrites, glial cells, and capillaries
- Regions of gray matter have very specific functions
- 6% of cerebrum
- Consumes 94% of oxygen



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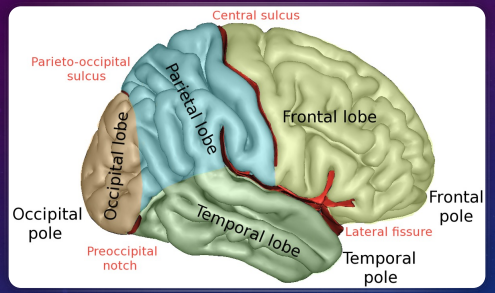

TEMPORAL POLE

Anger, Poor Comprehension, Visual Processing Issues, Memory Impairment, Paranoia, Feeling Spacey, (Auditory & Olfactory Hallucinations, Seizures)

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Bartonella IGENIX POSITIVE, Mold, EDS, MCAS
63 y/o Female (Mar '23)

Temporal Lobe Dysfunction
Anger, Poor Comprehension, Visual Processing Issues, Memory Impairment, Paranoia, Feeling Spacey, (Auditory & Olfactory Hallucinations, Seizures)

Structure	Total Volume (cm³)	Percentile
Intracranial Volume	1345	-
Whole Brain	1099	97
Forebrain Parenchyma	950	95

Total Volumes	Percentiles		
	Left	Right	Total
Cerebral White Matter	92	81	87
Cortical Gray Matter	80	80	80
Ventricles	82	75	80
Cerebral WM Hypointensities*	2	2	3
Subcortical Structures			
Cerebellar White Matter	75	78	77
Cerebellar Gray Matter	81	87	84
Brainstem			88
Thalamus	98	98	98
Ventral Diencephalon	56	40	48
Basal Ganglia			
Putamen	30	15	21
Caudate	55	39	47
Nucleus Accumbens	50	9	25
Pallidum	39	35	36
Cingulate	22	39	30
Anterior Cingulate	53	80	73
Posterior Cingulate	16	48	28
Isthmus Cingulate	28	2	8

Cortical Brain Regions	Percentiles		
	Left	Right	Total
Frontal Lobes	62	73	68
Superior Frontal	18	32	23
Middle Frontal	91	86	91
Inferior Frontal	97	95	97
Lateral Orbitofrontal	57	87	75
Medial Orbitofrontal	19	27	23
Paracentral	63	80	73
Primary Motor	24	58	39
Parietal Lobes	57	39	49
Primary Sensory	53	53	52
Medial Parietal	67	14	42
Superior Parietal	31	46	36
Inferior Parietal	67	68	69
Supramarginal	69	30	51
Occipital Lobes	98	98	99
Medial Occipital	99	99	99
Lateral Occipital	90	92	93
Temporal Lobes	74	74	75
Transverse Temporal + Superior Temporal	66	85	79
Posterior Superior Temporal Sulcus	50	59	56
Middle Temporal	35	70	52
Inferior Temporal	70	53	63
Fusiform	62	19	37
Parahippocampal	97	77	93
Entorhinal Cortex	81	35	62
Temporal Pole	88	99	98
Amygdala	66	33	50
Hippocampus	80	54	68

Temporal Pole 88L/99R 98%

Extreme overactivation of R temporal lobe associated with paranoia and mood issues

PATCHY ASYMMETRY POS

More than 30 percent difference between the left and right sides of same brain region. Possible causes are traumatic brain injury, infections such as Lyme or hypoperfusion of the underlying brain matter region.

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Bartonella, CIRS, MCAS, Hypermobility
60 y/o Female (Apr '18)

Owner of 7 Feral Cats, Mood Issues, Paranoia and Frank Hallucinations Requiring Court Ordered Hospitalization

Intracranial Volume (ICV) (cm³)	ICV Percentile		
1427.28	28		
Total Volumes	**Percentiles**		
	Left	Right	Total
Cerebral White Matter	58	80	69
Cortical Gray Matter	56	60	58
Ventricles	45	67	56
Subcortical Structures			
Cerebellar White Matter	88	98	95
Cerebellar Gray Matter	87	92	90
Brainstem	-	-	90
Thalamus	86	69	80
Ventral Diencephalon	32	26	28
Basal Ganglia			
Putamen	48	45	47
Caudate	65	64	65
Nucleus Accumbens	48	86	72
Pallidum	7	13	8
Cingulate	63	61	63
Anterior Cingulate	41	33	35
Posterior Cingulate	52	91	78
Isthmus Cingulate	75	43	64

Cortical Brain Regions	Percentiles		
	Left	Right	Total
Frontal Lobes	41	73	58
Superior Frontal	44	45	43
Middle Frontal	74	82	81
Inferior Frontal	12	53	26
Lateral Orbitofrontal	55	71	63
Medial Orbitofrontal	21	92	72
Paracentral	61	79	71
Primary Motor	52	69	55
Parietal Lobes	29	51	38
Primary Sensory	57	30	42
Medial Parietal	83	56	74
Superior Parietal	8	1	1
Inferior Parietal	42	99	92
Supramarginal	19	69	36
Occipital Lobes	53	48	46
Medial Occipital	99	77	96
Lateral Occipital	4	29	8
Temporal Lobes	94	55	81
Transverse Temporal + Superior Temporal	62	7	18
Posterior Superior Temporal Sulcus	98	94	98
Middle Temporal	99	27	86
Inferior Temporal	19	38	24
Fusiform	93	98	96
Parahippocampal	99	96	99
Entorhinal Cortex	38	39	24
Temporal Pole	99	99	99
Amygdala	35	35	21
Hippocampus	96	92	96

Temporal Pole 99%

Mood regulation
Personality (paranoid behavior)
Audiovisual processing (hallucinations)

Extreme overactivation of temporal lobe is consistent with paranoia and mood issues

Patchy Asymmetry

E.g. Inferior Frontal, Medial Orbitofrontal, Supramarginal, Middle Temporal

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PARASYMPATHETIC FREEZE

90 PERCENT BEDRIDDEN

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EDS, POTS, CIRS, MCAS
21 y/o Male (2017 vs. 2019)

90% bedridden initially. Marked improvement in gray matter. Neuroinflammation unchanged or worse. Now living alone and working.

Intracranial Volume (ICV) (cm³)	ICV Percentile		
2044.42	99		
Total Volumes	**Percentiles**		
	Left	Right	Total
Cerebral White Matter	96	96	96
Cortical Gray Matter	51	65	58
Ventricles	77	88	79
Subcortical Structures			
Cerebellar White Matter	81	86	84
Cerebellar Gray Matter	52	54	53
Brainstem	-	-	75
Thalamus	76	51	66
Ventral Diencephalon	27	39	32
Basal Ganglia			
Putamen	53	77	66
Caudate	52	35	43
Nucleus Accumbens	16	51	34
Pallidum	4	4	3
Cingulate	26	91	75
Anterior Cingulate	57	95	90
Posterior Cingulate	57	49	54
Isthmus Cingulate	10	35	16

Cortical Brain Regions	Percentiles		
	Left	Right	Total
Frontal Lobes	81	90	86
Superior Frontal	21	78	57
Middle Frontal	99	99	99
Inferior Frontal	52	39	43
Lateral Orbitofrontal	92	60	81
Medial Orbitofrontal	88	99	98
Paracentral	53	70	61
Primary Motor	48	12	30
Parietal Lobes	52	37	43
Primary Sensory	52	33	41
Medial Parietal	89	58	68
Superior Parietal	52	28	38
Inferior Parietal	67	62	65
Supramarginal	27	29	24
Occipital Lobes	18	29	21
Medial Occipital	63	73	69
Lateral Occipital	9	13	8
Temporal Lobes	35	55	45
Transverse Temporal + Superior Temporal	44	63	54
Posterior Superior Temporal Sulcus	39	8	14
Middle Temporal	3	78	28
Inferior Temporal	28	8	14
Fusiform	75	74	75
Parahippocampal	68	92	91
Entorhinal Cortex	98	90	94
Temporal Pole	44	21	28
Amygdala	86	36	68
Hippocampus	48	73	62

Occipital lobes 21%
Primary motor 40/12 20%
Middle temporal 3/78 28%

Cortical Gray 48%

Pallidum 3%

Structure	Total Volume (cm³)	Percentile
Intracranial Volume	1893	-
Whole Brain	1635	96
Forebrain Parenchyma	1424	94
Total Volumes	**Percentiles**	
	Left	Right	Total
Cerebral White Matter	50	46	48
Cortical Gray Matter	94	94	95
Ventricles	76	70	74
Cerebral WM Hyperintensities*	1	1	1
Subcortical Structures			
Cerebellar White Matter	37	51	44
Cerebellar Gray Matter	74	81	78
Brainstem	-	-	88
Thalamus	94	79	89
Ventral Diencephalon	25	23	23
Basal Ganglia			
Putamen	95	99	98
Caudate	48	38	43
Nucleus Accumbens	71	94	86
Pallidum	20	59	45
Cingulate	82	97	91
Anterior Cingulate	83	99	96
Posterior Cingulate	55	30	46
Isthmus Cingulate	38	20	28

Cortical Brain Regions	Percentiles		
	Left	Right	Total
Frontal Lobes	95	90	94
Superior Frontal	56	64	49
Middle Frontal	95	98	98
Inferior Frontal	95	75	90
Lateral Orbitofrontal	96	53	79
Medial Orbitofrontal	74	98	95
Paracentral	67	77	61
Primary Motor	84	52	71
Parietal Lobes	70	47	58
Primary Sensory	54	57	55
Medial Parietal	65	39	53
Superior Parietal	70	26	45
Inferior Parietal	76	68	75
Supramarginal	64	66	67
Occipital Lobes	90	95	93
Medial Occipital	96	98	98
Lateral Occipital	49	83	69
Temporal Lobes	91	82	87
Transverse Temporal + Superior Temporal	88	92	93
Posterior Superior Temporal Sulcus	58	19	30
Middle Temporal	82	84	77
Inferior Temporal	81	47	68
Fusiform	68	92	85
Parahippocampal	98	96	98
Entorhinal Cortex	99	97	99
Temporal Pole	57	68	77
Amygdala	91	78	87
Hippocampus	77	85	83

↓ Cerebral white 48%
↑ Occipital lobes 91%
↑ Primary motor 71%
↑ Middle temporal 62/84 77%

↑ Cortical Gray 95%
↑ Pallidum 45%

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ACE'S: MRI VOLUMETRIC CHANGES UNDERLY RISK FOR COGNITIVE AND EMOTIONAL DIFFICULTIES

- Reduced brain volumes overall
- Reduced amygdala volumes starting in childhood (limbic)
- Reduced hippocampal volumes seen in adulthood (limbic)
- Reduction prefrontal cortex (emotional control)
- Reduction orbitofrontal cortex (emotional control)
- Reductions dorsolateral prefrontal
- Reduction anterior cingulate cortex (salience network)
- Both increases and reduction in cerebellar white matter
- Increased risk of Alzheimer's

Bick J, Nelson CA. Early Adverse Experiences and the Developing Brain. Neuropsychopharmacology. 2016 Jan;41(1):177-96.
Corney KB, West EC, Quirk SE, Pasco JA, Stuart AL, Manavi BA, Kavanagh BE, Williams LJ. The Relationship Between Adverse Childhood Experiences and Alzheimer's Disease: A Systematic Review. Front Aging Neurosci. 2022 May 4;14:831378

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MCAS TREATMENTS

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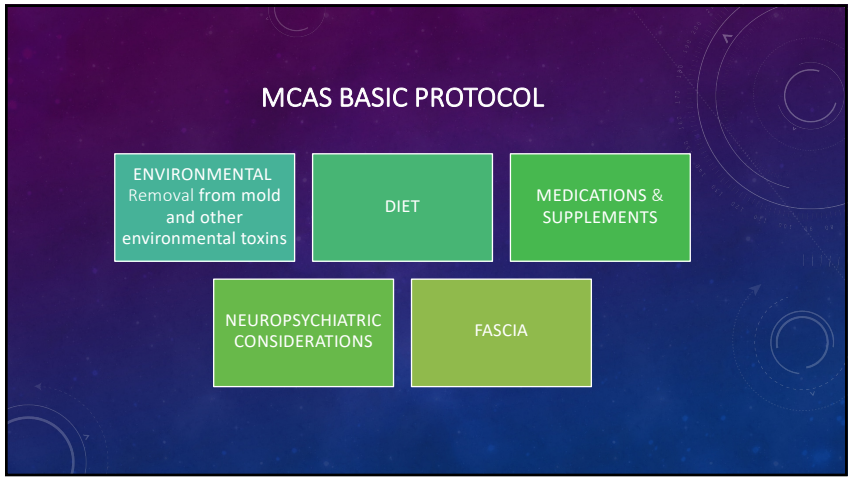
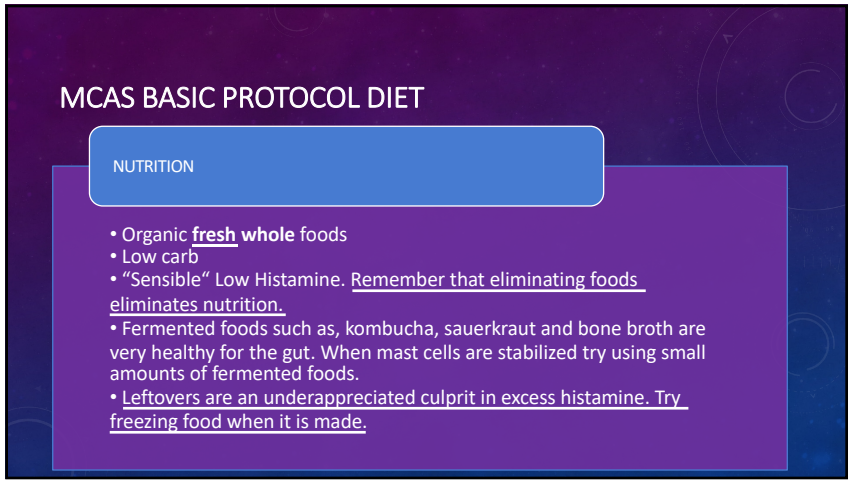

MCAS BASIC PROTOCOL
ENVIRONMENTAL Removal from mold and other environmental toxins
DIET
MEDICATIONS & SUPPLEMENTS
NEUROPSYCHIATRIC CONSIDERATIONS
FASCIA

38


MCAS BASIC PROTOCOL DIET
NUTRITION
• Organic fresh whole foods
• Low carb
• "Sensible" Low Histamine. Remember that eliminating foods eliminates nutrition.
• Fermented foods such as, kombucha, sauerkraut and bone broth are very healthy for the gut. When mast cells are stabilized try using small amounts of fermented foods.
• Leftovers are an underappreciated culprit in excess histamine. Try freezing food when it is made.

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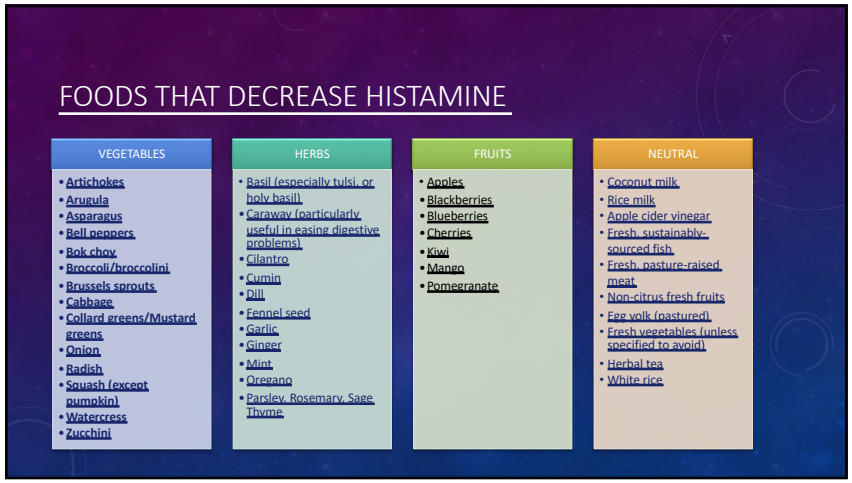
FOODS THAT DECREASE HISTAMINE
VEGETABLES
• Artichokes
• Arugula
• Asparagus
• Bell peppers
• Bok choy
• Broccoli/broccolini
• Brussels sprouts
• Cabbage
• Collard greens/Mustard greens
• Onion
• Radish
• Squash (except pumpkin)
• Watercress
• Zucchini
HERBS
• Basil (especially tulsi, or holy basil)
• Caraway (particularly useful in easing digestive problems)
• Cilantro
• Cumin
• Dill
• Fennel seed
• Garlic
• Ginger
• Mint
• Oregano
• Parsley, Rosemary, Sage, Thyme
FRUITS
• Apples
• Blackberries
• Blueberries
• Cherries
• Kiwi
• Mango
• Pomegranate
NEUTRAL
• Coconut milk
• Rice milk
• Apple cider vinegar
• Fresh, sustainably-sourced fish.
• Fresh, pasture-raised meat.
• Non-citrus fresh fruits
• Egg yolk (pastured).
• Fresh vegetables (unless specified to avoid)
• Herbal tea
• White rice

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MCAS BASIC PROTOCOL

Supplements

- Quercetin 500 to 1500 mg bid
- Luteolin – found in parsley, celery
- PEA (Palmitoylethanolamide) 500 mg tid
- N Acetyl Cysteine 600 mg bid
- DAO enzyme with meals.
- Vitamin C 500 mg bid
- Mg – glycinate, threonate, taurine well tolerated. Follow RBC levels for dosing (**1000 mg** not uncommon).

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MCAS BASIC PROTOCOL

H1 blockers such as Zyrtac (cetirizine), Xyzal (levocetirizine). Claritan (**loratadine**) up to tid. Have patients try multiple.

Ketotifen, H1 .5mg to 2mg tid po. Also found in OTC eyedrops. (Zaditor)

H2 blockers Famotidine, Cimetidine (Ranitidine removed 2019, may be available 2022). Start qhs, up to tid.

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MCAS BASIC PROTOCOL

Cromolyn 100-200 mg/ml qid for GI

Nasochrom one spray each nostril tid

Nebulized cromolyn 20 mg bid-qid)

Singular (montelukast) 10 mg qd, black box warning for neuropsych

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LOW DOSE NALTREXONE
GLIAL MODULATOR FOR NEUROINFLAMMATION

BASIC PROTOCOL

- Low Dose Naltrexone decreases microglial activation
- Useful dosages range from 1 to 4.5 mg.
- Usually start at 1.5 mg and increase slowly to 4.5 mg
- Sensitive patients can start at .25 and increase to .75 mg
- Should be tried in most MCAS patients
- Combining with lipoic acid 300 mg bid helps neuropathy

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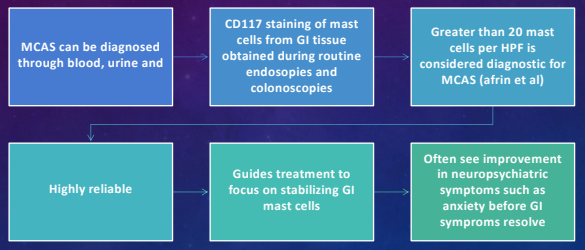
IN THE GASTROINTESTINAL TRACT, MUCOSAL MAST CELLS ARE LOCATED IN CLOSE PROXIMITY TO SENSORY NERVE FIBERS, WHICH COMMUNICATE BIDIRECTIONALLY.



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FAMOTIDINE (H2) AND COVID 19

Famotidine use in hospitalized patients with COVID-19 is associated with a lower risk of mortality, lower risk of combined outcome of mortality and intubation, and lower levels of serum markers for severe disease in hospitalized patients with COVID-19

Mather JF, Seip RL, McKay RG. Impact of Famotidine Use on Clinical Outcomes of Hospitalized Patients With COVID-19 [published online ahead of print, 2020 Aug 26]. *Am J Gastroenterol.*

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BIOACTIVE LIPIDS - CBD, PHOSPHATIDYLCHOLINE

- **PEA** available in synergistic combinations with luteolin or CBD.
- **CBD**: well-studied, effective for neuroinflammation, anxiety, pain, insomnia. Very well tolerated by sensitive patients. 1-100 mg. Available as oil, capsules, cream. Dosages usually reported as whole container.
- **PHOSPHATIDYLCHOLINE** (PC) major component cell membranes. Useful for neuroinflammation, cellular detoxification, focus, bile flow. Oral dosing usually 1300 mg tid. Most effective when used with the SCFA butyrate.

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HOMOCYSTEINE

- High homocysteine implies excess histamine
- Associated with low creatine
- "Under methylators"
- Associated with inflammation, oxidative stress, decreased cortical gray matter, DNA epigentic changes related to aging and toxic burden
- Can diminish the integrity of vascular **structures and neuron**

TREATMENTS

- Methyl B12 3 mg
- Methyl Folate 5 mg
- Riboflavin 90 mg
- B6 (P5P) 45 mg
- Betaine (TMG) 1.8
- Choline 250mg (2 egg yolks)
- Replenish creatine 1600 mg before exercise

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ADDITIONAL SUPPLEMENTS

Supplements

- *Red Sage (Salvia miltiorrhiza)*
- *Baikal Skullcap*
- *Boswellia*
- *Bromelain*
- Stinging nettle extract in tea or capsules (which studies have shown reduce inflammatory responses)
- N-acetyl cysteine
- Spirulina (limits the release of histamine)
- Bee pollen or honey (be careful)
- Moringa (capable of inhibiting 72% of all histamine released)

Probiotics

- Lactobacillus Rhamnosus
- Spore based
- Arabinogalactan (Lark Bark) Prebiotic

Peptides

- BPC 157 – gut, collagen, wound healing
- Thymosin – Immune modulation
- KPV Peptide analogue of MSH. Helps sleep, mast cells and IBS

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ANTIHISTAMINERGIC PSYCH MEDS

MIRTAZAPINE
- 3.75 to 15 mg Very useful for low weight

SEROQUEL
- 25 to 50 mg Sleep

NORTRIPTYLINE
- H1,H2,H3 blocker
- 10-30mg at bedtime

FLUVOXAMINE Antihistaminergic
- 25 to 50 mg Covid, Long Covid
- Used successfully for OCD
- Sigma 1 agonist, decreases cytokine production
- Antiviral, improves blood flow

TRAZADONE
- 25mg at bedtime

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BODYWORK APPROACHES

RESTORING VAGAL TONE & BALANCING PARASYMPATHETIC

Osteopathic manipulation Craniosacral (highly recommend for most patients with microvascular cerebral edema)	Lymphatic drainage Vibration plate helps microcirculation and neuropathy Coffee enemas, colonics	Qigong, Tai Chi (Yoga can worsen hypermobility if done incorrectly without trained supervision)	Somatic Experiencing, Organic Intelligence
Visual therapy – Optometry	Functional Neurology	Network Chiropractic (avoid forceful cervical adjustments)	Rolfing, myofascial can increase cytokine inflammation

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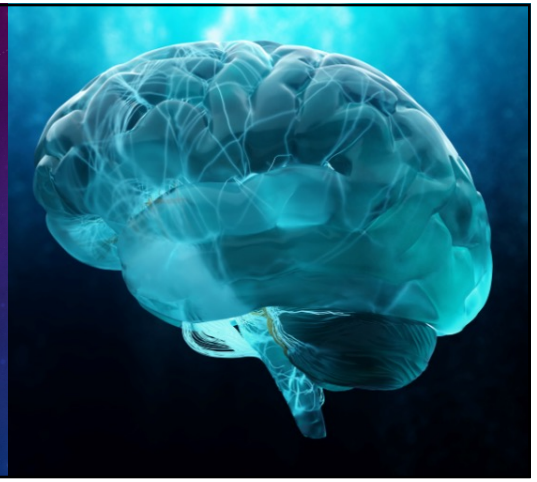
NEUROPSYCHIATRIC EFFECTS OF MAST CELL ACTIVATION AND LIMBIC DYSREGULATION

MARY ACKERLEY, MD, MD(H)
WWW.MYPASSION4HEALTH.COM
520-299-5694



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NEUROQUANT VOLUMETRIC IMAGING ORDER

- Brain MRI without contrast
- NeuroQuant Reports: Triage Brain Atrophy, General Morphometry, Age Related Atrophy
- Other reports available including Multistructure Atrophy (plots changes over time) and LesionQuant which shows periventricular flair count (useful for MS)
- Diagnostic Codes include patients actual symptoms such as:
  - TOX ENC G92
  - MEM LOSS R41.3
  - MCI G31.84
  - MIGRAINES G43.909
  - TBI+LOC SO6.9x95
  - TBI – LOC S06.9x05
  - Vertigo R42
  - Neuropathy G62.9

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VOLUMETRIC BRAIN IMAGING

STRUCTURAL PATHOLOGY OF THE BRAIN

To locate a radiology facility that offers the reports:

Use NEUROQUANT
https://www.cortechslabs.com/locations/

Or NEUROREADER
https://brainreader.net/

*NEUROQUANT is FDA 510(k) cleared

Persson K, Barca ML, Cavallin L, et al. Comparison of automated volumetry of the hippocampus using NeuroQuant® and visual assessment of the medial temporal lobe in Alzheimer's disease. *Acta radiol*. 2018;59(8):997-1001. doi:10.1177/0284185117743778

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BEST PRACTICES: APPROACHING THE NQ REPORT

Read the Radiologist's report first

- Findings such as Normal Pressure **Hydrocephalus**, AV Malformation, **Meningocele** best referred to neurosurgeon
- Hyperintensities or flairs represent micro ischemic damage. Causes can be migraines, CIRS, Lyme, apnea. **Contribute** to cognitive impairment. (Periventricular lesions imply BBB permeability.)

Check Age Related Atrophy Report for Alzheimer's pattern

- Alzheimer's 991, Ventricles 99, Hippocampus 1
- Neurocognitive testing to confirm
- Hippocampal <15, Ventricles >85 (Possible **Pre-Alzheimer's - Bredesen** candidates)

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BEST PRACTICES: APPROACHING THE NQ REPORT

GENERAL MORPHOMETRY

- **Look for Superior Lateral or Inferior Lateral Ventricular Asymmetry >15 % which can indicate there was a forceful impact to the brain**

Triage Brain Atrophy Report (TBAR)

- Adds more specific information on almost 50 Gray and White Matter Brain Regions.
  - The TBAR is age and sex matched **and** is reported in percentiles (50th percentile is the mean)
  - Blue indicates edema/inflammation and red indicates atrophy although need to look at non colour coded values as well for trends and patterns.
  - Correlate report with symptoms and other clinical findings. Can be extremely stable and reliable if done correctly. Common errors are retainer which will show unexpected atrophy, using research mode and slices not done correctly. Have CorTechs support review slices if doubtful.

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VOLUMETRIC BRAIN IMAGING

More accurate than a radiologist in assessing atrophy

Man vs Machine

Ross DE, Ochs AL, Desmit ME, et al. Man vs . Machine Part 2 : Comparison of Radiologists ' Interpretations and NeuroQuant® Measures of Brain Asymmetry and Progressive Atrophy in Patients with Traumatic Brain Injury. (804):1-23.

57

MCAS AND COVID 19

- Reznikov, L. R et al. (2021). Identification of antiviral antihistamines for COVID-19 repurposing. *Biochemical and Biophysical Research Communications*, *538*, 173–179.
- Theoharides, T. C. (2021). Potential association of mast cells with coronavirus disease 2019. Annals of Allergy, Asthma and Immunology, 126(3), 217–218.
- Mast cell stabilisers, leukotriene antagonists and antihistamines: A rapid review of the evidence for their use in COVID-19 - CEBM. https://www.cebm.net/covid-19/mast-cell-stabilisers-leukotriene-antagonists-and-antihistamines-a-rapid-review-of-effectiveness-in-covid-19/.
- Kempuraj D, Selvakumar GP, Ahmed ME, et al. COVID-19, Mast Cells, Cytokine Storm, Psychological Stress, and Neuroinflammation. *Neuroscientist*. 2020.
- Theoharides TC. COVID19, pulmonary mast cells, cytokine storms, and beneficial actions of luteolin. *BioFactors*. 2020;46(3):306-308. doi:10.1002/biof.1633.
- Gigante A, Aquili A, Farinelli L, et al. Sodium chromo-glycate and palmitoylethanolamide: A possible strategy to treat mast cell-induced lung inflammation in COVID-19. *Med Hypotheses*. 2020;143.

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