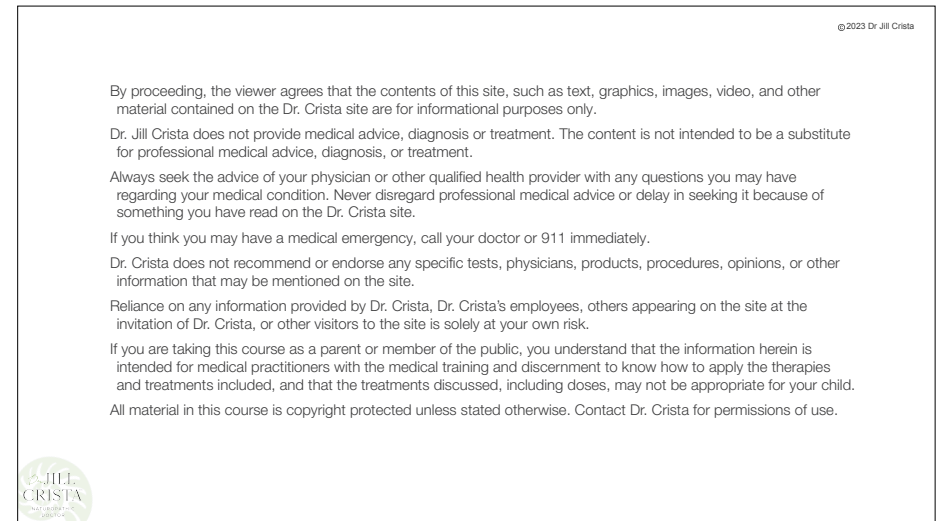




1



2



3



4

PANDAS/PANS mechanisms

Overview of what the research tells us to date ... (expect changes as our knowledge evolves)

- Pre-existing immune depleted state
- Microbiome alteration
- T-cell mediated damage to the brain triggered by infection AND toxicants
- Microglial activation → chronically “primed” neuroinflammation
- Damage to dopamine receptors & cholinergic interneurons
- Altered central dopamine, glutamate, ACh utilization → excitatory
- Impaired innate safety systems
- Cell danger response → limbic/vagal dysfunction
- CNS structural alterations



5

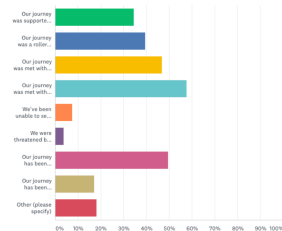
Bad parenting!???



6

Humanism in Medicine: In general, which phrase(s) best reflects your journey to support your child's medical condition? (Select ALL that apply)

Answered: 1,389 Skipped: 122



ANSWER CHOICES	RESPONSES
Our journey was supported by knowledgeable physicians with a positive attitude to help our child's medical issue.	34.52% 445
Our journey was a roller coaster ride to diagnosis, but we remain in good hands.	33.53% 350
Our journey was met with medical professionals who meant well, but were unable to help our child.	46.94% 605
Our journey was met with doubting medical professionals who made us feel like we were crazy.	57.72% 744
We've been unable to seek effective professional care due to lack of medical coverage.	7.80% 98
We were threatened by the medical professional(s) because they doubted the diagnosis of our child and forced our child into a psychiatric center against our wishes.	3.80% 49
Our journey has been supported by other families who've experienced PANDAS/PANS.	49.50% 638
Our journey has been supported by a non-profit(s) whose advice, recommendations or resources were pivotal in my child's health improvement.	17.07% 220
Other (please specify)	18.15% 234
Total Respondents: 1,389	Responses

PANDAS NETWORK PARENT SURVEY MAP 7/8



7



"It's impossible to know the feeling of losing a child, and have that child sitting right in front of you."

8

"Maybe you're just a little tired. Try taking a nap."
 "Have you considered parenting classes?"
 "You just need to be more strict."
 "Kids have tantrums."
 "Maybe she's just a picky eater, have you tried ice cream?"



9

PANDAS/PANS mechanisms

Overview of what the research tells us to date ... (expect changes as our knowledge evolves)

Pre-existing immune depleted state

Microbiome alteration

T-cell mediated damage to the brain triggered by infection AND toxicants

Microglial activation → chronically "primed" neuroinflammation

Damage to dopamine receptors & cholinergic interneurons

Altered central dopamine, glutamate, ACh utilization → excitatory

Impaired innate safety systems

Cell danger response → limbic/vagal dysfunction

CNS structural alterations



10

Pre-existing immune depleted state

Top 2 negative sequela for those with immune depletion ~

1. Increased risk of infections
2. Increased risk of developing an autoimmune disorder

↑ rate of IgA deficiency in pediatric OCD compared to children with ASD and anxiety.

↑ rate of IgA deficiency in pediatric OCD compared to adults with OCD.

Dendritic cell role. May have specificity to Strep &/or nasal infection. Strep inhibits dendritic cell maturation.

PMID: 30892924, 30516814, 26417101, 19712038



11

Infection and risk for mental disorders

Do infections increase the risk of subsequent mental disorders during childhood and adolescence?

Population-based cohort study using Danish nationwide registers.

>1 million individuals born in Denmark between 1995 and 2012

All treated infections were identified in a time-varying manner, including severe infections requiring hospitalizations and less severe infection treated with anti-infective agents in the primary care sector.

Findings ~

Severe infections requiring hospitalizations increased the risk of hospital contacts due to mental disorders by 84% and the risk of psychotropic medication use by 42%.

Less severe infection treated with anti-infective agents increased the risks by 40% and 22%, respectively; the risks differed among specific mental disorders.

PMID: 30516814, 26417101, 19712038



12

Immune system of the brain

2/3 of the brain is glial (immune), 1/3 is neurons

3 glial types - microglia, astrocytes, oligodendrocytes

Microglia ~

Brain "macrophages", scavengers

Modulate neurogenesis, influence synaptic remodeling, and regulate neuroinflammation by surveying the brain microenvironment

Astrocyte ~

Involved with glutamate and GABA activity, clean up synaptic cleft, BBB integrity

Oligodendrocyte ~

Myelinating, axonal metabolic support

Journal of Leukocyte Biology 2008, Dilger and Johnson



13

Innate activation



Innate I/S of brain can be activated in 4 ways ~

1. Pathogens
2. Vagal afferens pathway from enteric n.s./ hepatic projections (Kupffer cells)
3. Non-canulized pathway (inflam cytokines)- some xBBB through passive diffusion (IL-1 β)
4. Pathways involving blood vessels and astrocytes (ie: heat-shock proteins)

Journal of Leukocyte Biology 2008, Dilger and Johnson



14

Inflammasome

Systemic inflammation shifts the brain microenvironment towards a proinflammatory state.

OCD patients had higher levels of IL-18, IL-1Ra, and TNF, compared to the healthy controls.

Blood cells of OCD patients have increased expression of NLRP3 inflammasome - an important component of the innate immune system.

Expression of genes encoding for NLRP3, caspase-1, ASC, IL-1 β , IL-1RN, and TNF are significantly increased in peripheral whole blood of psychiatric patients compared to matched healthy controls.

"The findings support the inflammation hypothesis for markedly ill psychiatric patients across diagnostic groups."

The paradigm change in mental health.

PMD: 27149601, 31786499, 36911567



15

PANDAS/PANS mechanisms

Overview of what the research tells us to date ... (expect changes as our knowledge evolves)

Pre-existing immune depleted state

Microbiome alteration

T-cell mediated damage to the brain triggered by infection AND toxicants

Microglial activation → chronically "primed" neuroinflammation

Damage to dopamine receptors & cholinergic interneurons

Altered central dopamine, glutamate, ACh utilization → excitatory

Impaired innate safety systems

Cell danger response → limbic/vagal dysfunction

CNS structural alterations



16

What defines “self” vs “other”

Autoimmune = loss of tolerance to “self”

“Self” largely determined by our gut microbiome

We're **more microbe than man** - outnumbered by gut microbiome in both cell count and total DNA

Autoimmune dzs are linked to unique microbiome composition (ie: lower Firmicutes/Bacteroidetes ratio), reduction of gut commensals, altered gut integrity

Fecal microbiota transplantation (FMT) or inoculation with specific microbes in animal models of ADs support the hypothesis that alterations of gut microbiota influence autoimmune responses and disease outcome.

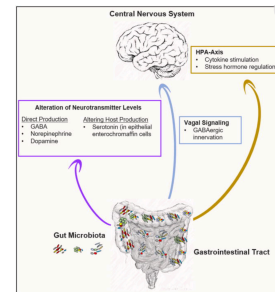
le: changes to the gut commensals and periodontal disease have been proposed as important factors in the pathogenesis of RA

PMID: 35534624, 32731813, 32038645, 29920643



17

Microbiome-Gut-Brain Axis



Bidirectional crosstalk between the gut and the brain

Various afferent and efferent pathways influence Dz pathogenesis - vagus n., I/S, bacterial metabolites

Bottom up ~

Antibiotics, environmental/infectious agents, intestinal NTs/neuromodulators, sensory vagal fibers, cytokines, metabolites all convey information to CNS about the intestinal state

Top down ~

Conversely, the HPA axis, CNS regulatory areas of satiety, and neuropeptides released from sensory nerve fibers affect the gut microbiota composition

Such interactions influence the pathogenesis of disorders where inflammation is implicated, such as mood disorder, ASD, ADHD, MS, obesity

Microbiome dysbiosis shown to affect cognitive function

PMID: 30892924, 28948967, 32130879, 35087123, 34205336, 29903615



18

Microbiome-microglial connection

Brain microglia not only respond to local brain signals but also input from the periphery, including the GI tract and microbiome

Microbiome plays a pivotal role in regulating brain microglial maturation and function in the brain, as well as production/consumption of NTs.

Microbial products (LPS) and microbially produced metabolites act as signalling molecules that have direct and indirect effects on the CNS and the ENS (motility)

Altered microbial composition is reported in neurological disorders with known brain microglial involvement in humans

Circadian rhythm: The composition of the gut microbiota is subject to diurnal variation and is entrained by host circadian rhythms. In turn, a diverse microbiota is essential for optimal regulation of host circadian pathways.

PMID: 30385457, 26046241, 30614568, 31478105, 29903615



19

Biomes, BBB, and OCD

During dysbiosis, gut-brain axis pathways are dysregulated and associated with altered permeability of the BBB and neuroinflammation

Post-prandial endotoxemia (plasma LPS) is found in approximately 1/3 of those eating Westernized diet, more common with dysbiosis

LPS caused the loss of dopaminergic neurons (in substantia nigra pars compacta) and microglia migration in a dose-dependent manner in a rat study

Imbalance in the gut and oropharyngeal microbiomes observed in OCD cases ~

Increase of bacteria from the Rikenellaceae family, associated with gut inflammation

Decrease of bacteria from the Coprococcus genus, associated with DOPAC synthesis

MS-twin study: FMT from MS-affected twin into mice promoted the dz in vivo vs FMT of twin unaffected by MS

PMID: 35087123, 33362788, 28893994, 31588712



20

Restricted eating

Certain gut microbiota-related compounds and food antigens can trigger the production of autoantibodies cross-reacting with appetite-regulating hormones and neurotransmitters.

Alterations in the gut microbiome and I/S may serve not only to maintain and exacerbate dysregulated eating behavior, but may serve as biomarkers of increased risk for developing an eating disorder.

Mice receiving FMT from those with anorexia nervosa (AN) displayed increased anxiety- and compulsive-like behavior relative to controls.

Conversely, case report of FMT from healthy control to pt with AN increased short chain fatty acids and serotonin, associated w normalized eating.

Increases in multiple Clostridium species belonging to the order Clostridiales.

Gastroparesis observed w neurotoxins: mycotoxins, Borrelia spp, Bartonella, algal blooms/aquariums

PMID: 33953692, 33652962, 33546416, 31504398, 31510101



© 2023 Dr Jill Crista



21

Restricted eating or self medicating?

Intermittent fasting increases microbiome diversity; significantly reduces the ratio of Firmicutes to Bacteroidetes and increases the relative abundance of Allobaculum.

Intermittent fasting attenuates LPS-induced neuroinflammation and memory impairment including enhancement of neurotrophic support.

Intermittent fasting contributes to aligned circadian rhythms through interactions with the gut microbiome.

β -hydroxybutyrate (BHB), a physiological ketone body produced by the liver in condition of fasting, low blood sugar, or carbohydrate-free (like ketogenic) diet consumption had an inhibitory effect on NLRP3-inflammasome.

Intermittent fasting attenuates LPS-induced acute lung injury in mice by modulating macrophage polarization.

PMID: 33223514, 24886300, 25686106, 36028098, 33530861



22

Lung microbiome effect on the brain

The lung tissue in particular has an important role in autoimmune diseases of the brain, such as MS.

There's a tight interconnection between the lung microbiota and immune reactivity in the brain.

A dysregulation in the lung microbiome significantly influenced the susceptibility of rats to developing autoimmune diseases of the CNS.

Shifting the microbiota towards LPS-enriched phyla induces a type-I-interferon-primed state in brain-resident microglial cells.

PMID: 35197636, 35417673, 35197592, 32140452, 19793773



© 2023 Dr Jill Crista



23

Gut-lung-immune axis

The gut-lung axis highlights both host-microbe interactions but also microbe-microbe interactions involving inter-kingdom microbial crosstalks (ie: bacterial and fungal.)

Water-damaged buildings host biofilm, including indoor airborne bacterial endotoxin, as well as fungi, modifying the lung microbiome.

LPS endotoxin enhances the negative health effects of many mycotoxins on respiratory and gastrointestinal tissue.

Further justification for both environmental + infection management.

PMID: 35197636, 35417673, 35197592, 32140452, 19793773



24

PANDAS/PANS mechanisms

Overview of what the research tells us to date ... (expect changes as our knowledge evolves)

Pre-existing immune depleted state

Microbiome alteration

T-cell mediated damage to the brain triggered by infection AND toxicants

Microglial activation → chronically “primed” neuroinflammation

Damage to dopamine receptors & cholinergic interneurons

Altered central dopamine, glutamate, ACh utilization → excitatory

Impaired innate safety systems

Cell danger response → limbic/vagal dysfunction

CNS structural alterations



25

T-cell mediation



Intranasal infections of all types preferentially generate Th17, not just Strep

Th17 → IL17 linked to increased risk for autoimmunity

Mouse studies: glyphosate, mold mycotoxins, and mercury exposure drives increase in Th17

Pts with depressive sx's had increased amyloid proteins + fecal IL-17

Mouse studies: microbiome regulates Th17 cell-mediated depressive-like behaviors and other CNS disorders

Naïve CD4 T-cell differentiates into either T-reg or Th17 depending on the Transforming Growth Factor (TGF) 'soup flavor'

Microbiome plays a role in TGF types/quantity

PMID: 32731813, 32038645, 29510522, 29920643, 28935500, 35963408, 20049214



26

Strep throat becomes “Strep nose”

From throat to nose ~

GAS-pharyngitis triggers Th17 response

Formation of Abs in cervical lymphatic chain dendritic cells

In turn sends these Abs back to throat *but also the nose*

Mouse study: repeated intranasal challenge w GAS-inoculated mice promoted migration of GAS-specific Th17 cells from NALT into the brain, BBB breakdown, serum IgG deposition, microglial activation, and loss of excitatory synaptic proteins under conditions in which no viable bacteria were detected in CNS tissue.

Proposed anti-GAS mimetic Abs affects DR1 & DR2 receptors, and/or cholinergic interneurons

Th1 may also play a role → strep, Herpes/EBV, H. Pylori

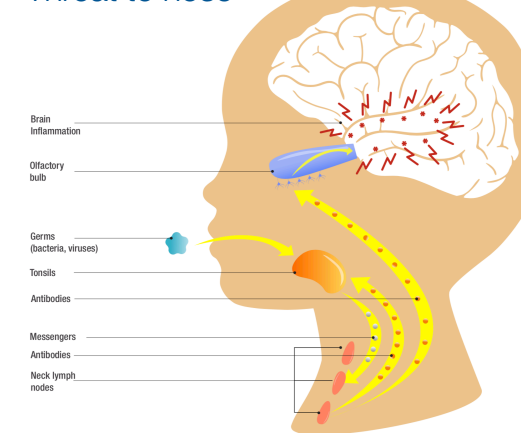
Discuss more about infectious triggers in next module

PMID: 28951419, 26657857, 26417101



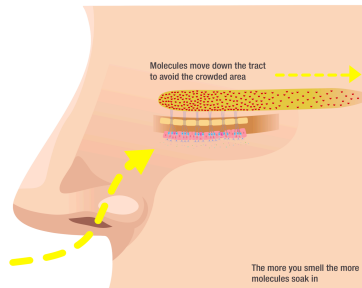
27

Throat to nose



28

Olfactory access



"Smelling is a form of physical contact."

Molecules interact with olfactory nerve terminals

Olfactory bulb void of BBB

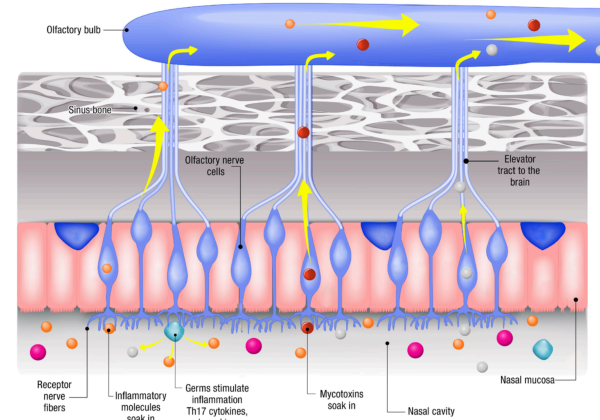
Part of limbic system

Terminates in nasal mucosa

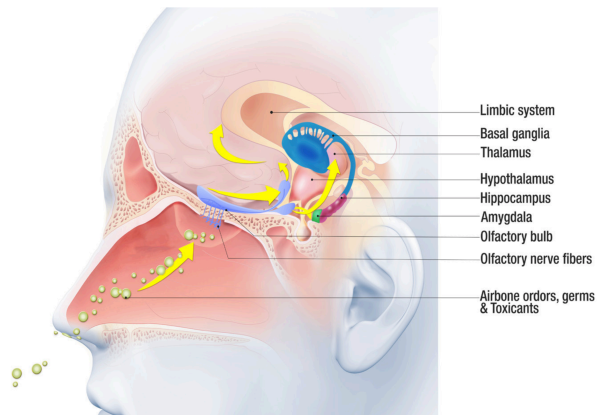
Th17 + mycotoxins uptake

Trigger microglia activation

The "elevator to the brain"



Basal ganglia



Strep antibody impacts on hypothalamus

Elevated anti-streptococcal antibodies more prevalent in patients with recent narcolepsy onset.

Narcolepsy; deficiency in hypocretin/orexin secretion from hypothalamus.

Thought to be largely genetically determined, but environmental factors were investigated based on the high discordance rate (approximately 75%) of monozygotic twins.

Retrospective, case-control study concluded that Streptococcal infections are probably a significant environmental trigger for narcolepsy.

Compared to age-matched controls, increased ASO found in 51% within 3 years of onset, compared to 19% ($P < 0.0005$) and 20% of patients with long-standing disease ($P < 0.0005$).

ASO and Anti-DNase B titers were highest close to narcolepsy onset, and decreased with disease duration.

PMID: 19725248

PANDAS/PANS mechanisms

Overview of what the research tells us to date ... (expect changes as our knowledge evolves)

Pre-existing immune depleted state

Microbiome alteration

T-cell mediated damage to the brain triggered by infection AND toxicants

Microglial activation → chronically “primed” neuroinflammation

Damage to dopamine receptors & cholinergic interneurons

Altered central dopamine, glutamate, ACh utilization → excitatory

Impaired innate safety systems

Cell danger response → limbic/vagal dysfunction

CNS structural alterations



33

Microglial activation

Microglia are the brain's resident immune cells, similar to macrophages. (#monkeys)

Activated microglia are classically associated with inflammation, neuronal damage, and neurodegeneration, and often secrete inflammatory cytokines in various neuro Dzs, including Alzheimers.

Microglial activation is not always associated with inflammation. Novel roles have emerged in brain development, homeostasis, and plasticity.

Microglial dysfunction has been implicated in the onset and progression of several neurodevelopmental and neurodegenerative diseases.

Activated or “primed” microglia lose their motility projections, get stuck in place and in the more inflammatory stage (M1, aka #monkeypoo.)

Once primed, the only way out is autophagy via maturation to M2 stage.

Primed glial cells may recruit adjacent microglia and mast cells, and *remain more sensitive to systemic inflammatory responses* for the rest of that cell's lifecycle (#monkeyseemoneydomoneypoo.)

Contrast to tumor-associated brain macrophages (partly derived from microglia,) express M2>M1 stage.

PMID: 24487234 , 27859676, 24303218, 22632727, 28948967



34

Microglial dysfunction

There's evidence for microglial dysregulation and neuroinflammatory etiology in PANDAS (also OCD, Tourette's.)

Defective microglia lead to OCD behaviors [mice]~ pathological grooming, hyperanxiety, social impairment deficits

Evidence from animal studies that synaptic pruning might be altered in PANDAS, though the evidence is limited.

Additional potential contributions of microglial abnormalities beyond neuroinflammation are failures in neuroprotection, lack of support for neuronal survival.

SSRIs may reduce this effect, but in a lab-induced condition, what about wild-type with different toxicant triggers?

Reiteration: the influential role of the microbiome-microglia axis.

The role of mast cells: histamine is both a neurotransmitter and an immune modulator. Can regulate microglia in vivo, via the H4 receptor.

PMID: 28053994, 36911567, 30385457, 29354029, 27859676



35

Mast cells

Reside in virtually all vascularized tissues. Differently differentiated based on recruitment trigger, location, milieu.

Secrete a wide variety of biologically active products in 50-200 granules, including diverse cytokines and growth factors, including histamine, heparin, a variety of cytokines, chondroitin sulfate, and neutral proteases.

MUCH more than, and not always, histamine, and not always degranulation.

Within 30 min releases heparin, etc but in the next 24 hours, releases cytokines and other inflammatory mediators without ever releasing histamine.

Non-redundant roles in many types of innate or adaptive immune responses, including immediate and chronic IgE-associated allergic disorders and enhancing host resistance to certain venoms, parasites, and fungi.

Influence many other biological processes, including responses to bacteria and virus, angiogenesis, wound healing, fibrosis, autoimmune and metabolic disorders, and cancer.

Functions reflect their ability to secrete, upon appropriate activation by a range of immune or non-immune stimuli, a broad spectrum of cytokines (including many chemokines) and growth factors, with potential autocrine, paracrine, local, and systemic effects.

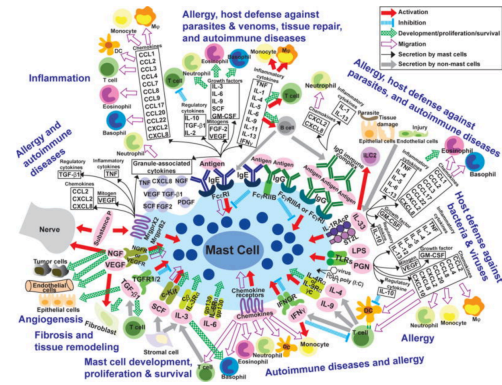
“Cluster bomb” effect.

PMID: 27381299, 19527167, 19201896, 29431211



36

Figure 1

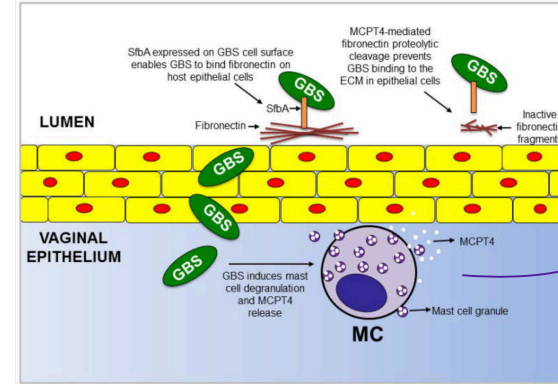


Highly simplified overview of the diverse stimuli and potential consequences of mast cell activation and secretion of cytokines, chemokines and growth factors

PMID: 29431212

37

Mast cells and Group B *Streptococcus*



Proposed mechanism for the protective effect of MCPT4 against Group B Streptococcus (GBS) dissemination and preterm birth. MCPT4, Mast cell protease 4; MC, mast cells; SfbA, streptococcal fibronectin binding protein; ECM, extracellular matrix

PMID: 29431211

38

Mast cells & the gut

Dr. Theoharides - "the gateway to inflammation in the body"

"It is well established that mast cell activation can ~

- Generate epithelial and neuromuscular dysfunction
- Promote visceral hypersensitivity
- Alter motility patterns in functional gastrointestinal disorders (FGIDs), postoperative ileus, food allergy, inflammatory bowel disease."

Colonic mast cell infiltration and mediator release from IBS patients, but not controls markedly enhanced the firing of mesenteric nerves, and stimulated mobilization of Ca^{2+} in dorsal root ganglia neurons known to mediate nociception.

Effects were inhibited by histamine **H(1)** receptor blockade.

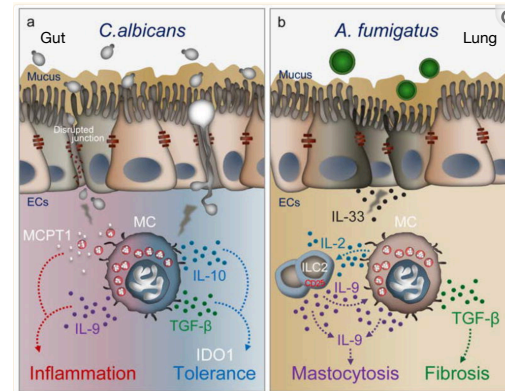
Can use biopsy from upper GI or colonoscopy. CD117 to look for mast cells. >20 mast cells significant for MCAS.

Symptoms related to eating ~

- Post-prandial flushing
- Post-prandial fatigue
- Post-prandial brain fog
- Post-prandial drop in bp
- Gastroparesis
- GI: heartburn, N/V, constipation, diarrhea
- Food avoidances related to histamine concentration, esp left-overs

PMID: 19527167, 19201896, 29431211

39



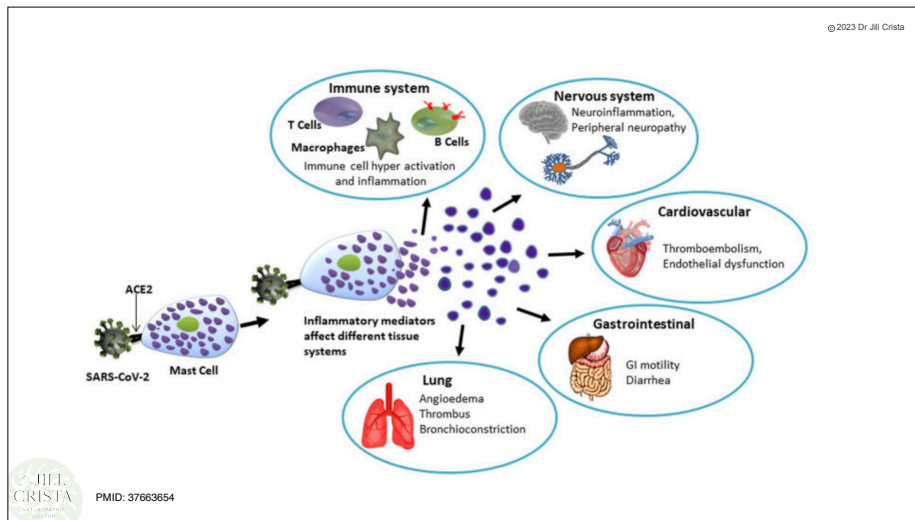
Mast cells are key players of *Candida* commensalism and pathogenicity at mucosal surfaces.

Empirically, increased recruitment at the stage of Evasion → Invasion of fungi.

Mold mycotoxins enhance mast cell recruitment, survival, and degranulation.

PMID: 27381299, 19527167, 19201896, 29431211

40



41

© 2023 Dr Jill Crista

PANDAS/PANS mechanisms

Overview of what the research tells us to date ... (expect changes as our knowledge evolves)

- Pre-existing immune depleted state
- Microbiome alteration
- T-cell mediated damage to the brain triggered by infection AND toxicants
- Microglial activation → chronically "primed" neuroinflammation
- Damage to dopamine receptors & cholinergic interneurons**
- Altered central dopamine, glutamate, ACh utilization → excitatory**
- Impaired innate safety systems
- Cell danger response → limbic/vagal dysfunction
- CNS structural alterations

42

© 2023 Dr Jill Crista

Dopamine receptor involvement

Dopa receptor1 & 2: posited targets of autoantibody attack, but don't forget LPS effect:
LPS caused the loss of dopaminergic neurons (in substantia nigra pars compacta) and microglia migration in a dose-dependent manner in a rat study

Dopamine excess (possibly during flare only?)

Possible dopamine deficiency when in remission

Synaptic pruning of excitatory connections may be increased in PANDAS

Glutamate excess

Cholinergic interneuron antibody binding

PMID: 26454143, 29233751, 26866234

43

© 2023 Dr Jill Crista

Cholinergic interneurons

Cholinergic interneuron (CIN) deficiency has been independently associated with tics in humans and with repetitive behavioral pathology in mice, making it a plausible locus of pathology.

Pilot work suggests that IgG antibodies from children with PANDAS bind to cholinergic interneurons (CINs) in the striatum.

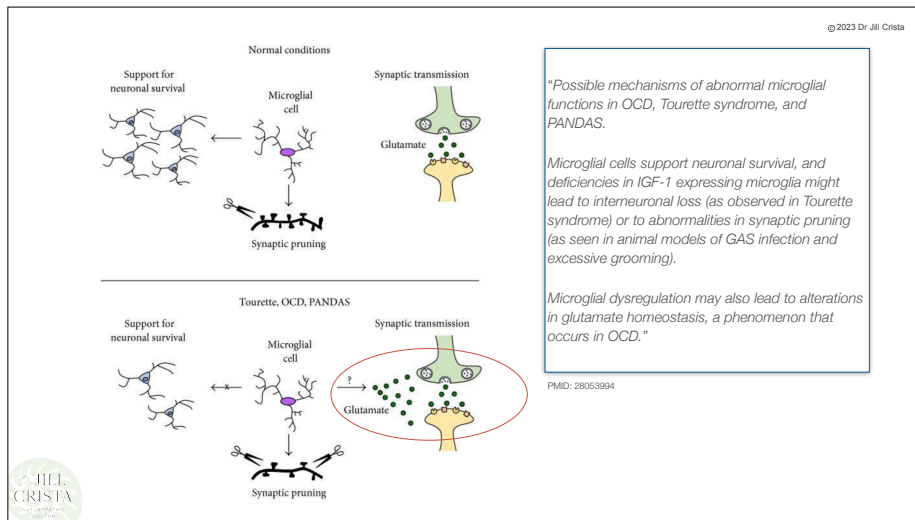
IgG from children with PANDAS bound to CINs, but not to several other neuron types, moreso than IgG from control subjects, in three independent cohorts of patients.

Post-IVIG serum had reduced IgG binding to CINs, and this reduction correlated with symptom improvement.

Baseline PANDAS sera decreased activity of striatal CINs and altered their electrophysiological responses, however post-IVIG PANDAS sera and IgG-depleted baseline sera did not alter the activity of striatal CINs.

PMID: 32539528

44



45

© 2023 Dr Jill Crista

Neurotransmitter dysregulation

End result - increased dopa, glutamate, dysregulated ACh

Gut microbiota regulate the production, transportation, and functioning of neurotransmitters.

Persistent message "unsafe" to limbic system.

PMID: 34205336

JILL CRISTA

46

© 2023 Dr Jill Crista

PANDAS/PANS mechanisms

Overview of what the research tells us to date ... (expect changes as our knowledge evolves)

- Pre-existing immune depleted state
- Microbiome alteration
- T-cell mediated damage to the brain triggered by infection AND toxicants
- Microglial activation → chronically "primed" neuroinflammation
- Damage to dopamine receptors & cholinergic interneurons
- Altered central dopamine, glutamate, ACh utilization → excitatory
- Impaired innate safety systems**
- Cell danger response → limbic/vagal dysfunction**
- CNS structural alterations

JILL CRISTA

47

© 2023 Dr Jill Crista

Cell danger response (CDR)

My thanks to Drs. Neil Nathan and Ben Lynch for "making me" learn this.

CDR is a universal response to environmental threat or injury that protects cells and hosts from harm.

Under direct control by ancient pathways in the brain that are ultimately coordinated by centers in the brainstem. (What happens if the basal ganglia is chronically inflamed?)

Expands the role of mitochondria beyond being the "powerhouse of the cell" to also being a protector and communicator of the cell status.

Mitochondria regulate the CDR (which controls innate immunity and healing), by monitoring and responding to the physical, chemical, and microbial/biological conditions within and around the cell.

Threats that exceed the cellular capacity for homeostasis trigger the CDR.

Chemical pollutants in the environment lower the threshold for CDR activation. In this way, mitochondria connect cellular health to environmental health.

Once triggered, healing cannot be completed until the the danger has been eliminated or neutralized, after which the CDR is reversed through a choreographed sequence of anti-inflammatory and regenerative pathways, and return to an updated state of readiness.

Although it's a cellular response, CDR has the power to change human thought and behavior, child development, physical fitness and resilience.

PMID: 31877376, 23981537, 28059333

JILL CRISTA

48

CDR “sickness behavior”/“sickness response”

When the CDR is triggered, the priorities of the organism are reset to optimize survival.

The response to danger involves an adaptive means of redirecting energy and includes ~

- Withdrawal from social contact
- Activation of innate immunity
- Decreased speech
- Fragmented sleep
- Head, muscle and abdominal aches
- Changes in the gut microbiome
- Increased sensitivity to touch, sound, and light

Similar to what many people experience when they have the flu or recovering from a serious injury.

It is the CDR that produces these familiar signs and symptoms.

Even though the term “sickness behavior” is a defined scientific term, I prefer “sickness response”, as “behavior” can be misconstrued as a choice.

PMID: 31877376, 23981537, 26056033, 25639499



49

CDR in chronic illness

Abnormal persistence of the CDR lies at the heart of many chronic diseases.

CDR produces a cascade of changes in cellular electron flow, oxygen consumption, redox, membrane fluidity, lipid dynamics, bioenergetics, carbon and sulfur resource allocation, protein folding and aggregation, vitamin availability, metal homeostasis, indole, pterin, 1-carbon and polyamine metabolism, and polymer formation.

Persistent activation of CDR inhibits healing, alters metabolism and gut microbiome, impairs the collective performance of multiple organ systems, changes behavior into “sickness response”, and chronic disease results.

CDR is different from the immune response which involves activation of the immune system. Instead this is a cellular response to the danger - “batten down the hatches” of the cell while the immune system takes on the danger. Possible to have one without the other?

Metabolic memory: past encounters with stressors are stored in the form of altered mitochondrial and cellular macromolecule content, resulting in metabolic memory of the past stressors.

PMID: 31877376, 37114062



50

Stages of CDR

3 sequential stages, separated by quality control checkpoints, CD1, CD2, CD3. (More about these details in bonus video by Dr. Neil Nathan.)

Abnormal persistence of any phase of the CDR inhibits the healing cycle.

Different tissues may be at different stages of the CDR.

The importance of water: changes in mitochondrial dynamics during cell stress in tissues link increasing cytoplasmic disorder with increasing disorder of water molecules, and an increase in CDR-associated functions. (MOA structured water tx?)

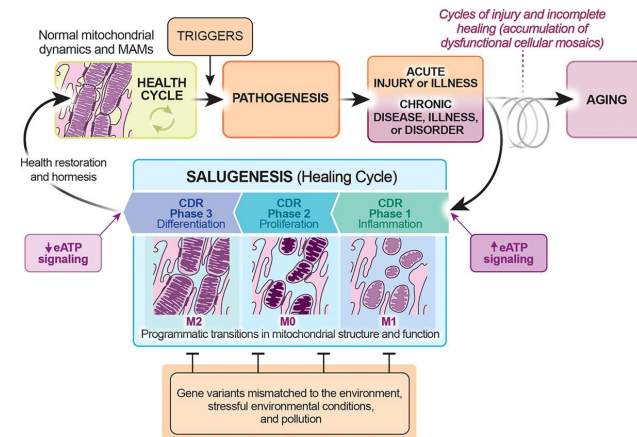
The rise and fall of extracellular ATP (eATP) signaling is a key driver of the mitochondrial and metabolic reprogramming required to progress through the healing cycle.

Sphingolipid and cholesterol-enriched membrane lipid rafts act as rheostats for tuning cellular sensitivity to *purinergic signaling*.

PMID: 37120082



51



Abbreviation: MAMs, mitochondria-associated membranes; eATP, extracellular ATP; CDR, cell danger response. © Naviaux Lab/UCSD
PMID: 37120082



52

Purinerergic signalling and oxidative shielding

Purinergetic signalling and oxidative shielding ~

First wave of danger signals consists of the release of metabolic intermediates like ATP and ADP, Krebs cycle intermediates, oxygen, and reactive oxygen species (ROS), and is sustained by purinergetic signaling (ie: ATP outside the cell as a signal of the state of the cell.)

Purinergetic signalling = ATP acting as an extracellular signalling molecule (eATP).

Purinergetic signalling maintains the CDR and appears to play an important role in neurodegeneration, neuroprotection and neuroregeneration.

Compelling evidence that ATP is a cotransmitter in most if not all nerves in the PNS and CNS (ie: co-released with Ach, dopa, glutamate, catecholamines.)

Additional alterations interfering with methylation, vitamin D and tryptophan metabolism, histamine and heme concentrations, lysine and P5P (pyridoxal 5-phosphate) utilization.

Antipurinergetic treatments may be an effective target. (Animal models - suramin)

SARS-CoV-2 spike protein alters microglial purinergetic signaling.

PMID: 31877376, 23981537, 26056033, 27573827, 23516405, 29253638, 37114062



53

Limbic dysregulation



More detailed and technical information, as well as treatment suggestions, can be found in the bonus video by Dr. Neil Nathan.



Limbic system in the brain gets stuck in hypervigilance.

Related to a sense of safety, or rather lack thereof.

Correlated to anxiety disorders and myofascial pain syndromes. Chronic pain and olfaction share common limbic cortical regions.

Autoimmune encephalitis describes a group of disorders characterised by symptoms of limbic and extra-limbic dysfunction occurring in association with antibodies against synaptic antigens and proteins localised on the neuronal cell surface.

Anorexia nervosa neural roots appear to be related to dysfunctional, primarily limbic, circuits driving pathological thoughts and behaviors. Key limbic modulatory structures, such as the subcallosal cingulate and insula.

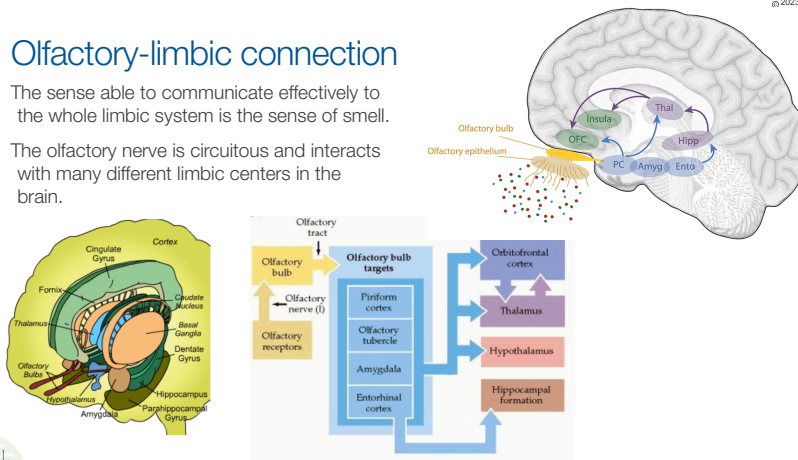
PMID: 28470168, 36307317, 25724849, 27330568, 24703713

54

Olfactory-limbic connection

The sense able to communicate effectively to the whole limbic system is the sense of smell.

The olfactory nerve is circuitous and interacts with many different limbic centers in the brain.



55



56

Polyvagal Theory: a science of safety

"Offers a neurophysiologic framework to consider why you act in the way you do. Actions are automatic and out of your conscious control."

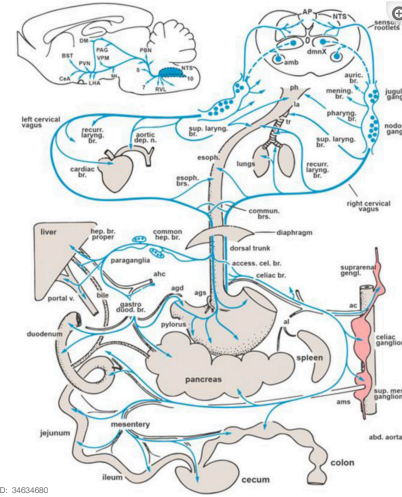
3 defining principles ~

1. The ANS has a hierarchy among which we move depending on sense of safety.
 - Ventral vagal
 - Sympathetic
 - Dorsal vagal
2. Neuroception: "safety scan". The process of your ANS unconsciously scanning for cues of safety, danger and threat. Your nervous system then uses that information to control your HR, RR, muscle tension, GI function, pain tolerance - almost every system in your body changes because your vagus nerve links them all together.
3. Co-regulation: "safer in community". Considered by PVT as a biological imperative in order to survive. Concept - your nervous system needs to be in connection with other nervous systems in order to feel both physical and psychological wellbeing. The key is coregulating with other nervous systems that have found their way to ventral vagal regulation.

PMID: 35645742, 30115210



57



PMID: 34634680



The wandering vagus nerve

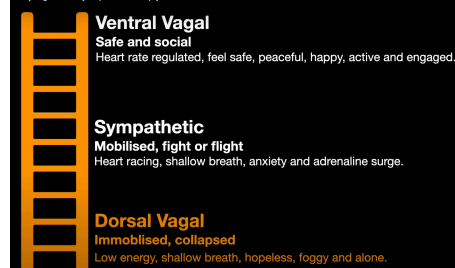
Vagus (Latin meaning wander)

Extends from brain stem, along arteries, through heart, lungs, diaphragm, digestive system, liver, gallbladder, spleen, pancreas and kidneys.

The neuroception of danger in one organ is very quickly transmitted to the other organs.

58

Polyvagal Theory Explained Simply



Healthy individuals can freely move between each state.

Trauma survivors and those with a chronically inflamed gut/brain can get stuck in a sympathetic or dorsal vagal state.

Possible link between prenatal events with neurodevelopment and the later onset of psychiatric disorder.

Natural pattern of connection is replaced with a pattern for protection.

Polyvagal Theory Explained Simply
Lewis Psychology YouTube channel
<https://www.youtube.com/watch?v=SiHFrBoEnxU>



59

PANDAS/PANS mechanisms

Overview of what the research tells us to date ... (expect changes as our knowledge evolves)

Pre-existing immune depleted state

Microbiome alteration

T-cell mediated damage to the brain triggered by infection AND toxicants

Microglial activation → chronically "primed" neuroinflammation

Damage to dopamine receptors & cholinergic interneurons

Altered central dopamine, glutamate, ACh utilization → excitatory

Impaired innate safety systems

Cell danger response → limbic/vagal dysfunction

CNS structural alterations



60

CNS structural alterations

Imaging studies distinguish OCD from normal controls

PANDAS children have MRI grey matter alterations in the cortex, subcortex, and cerebellum as compared to age-matched healthy controls "suggesting that the anatomical gray matter characteristics could have an immune origin."

PANDAS children have increased striatal volumes during acute illness, as well as increased microglia activity in the striatum compared to healthy adult controls

PET study with microglia tracer examined both PANDAS and Tourette syndrome (considered noninfectious)

- Inflammation was higher and more broadly spread through the bilateral caudate and lentiform nucleus in PANDAS than in age-matched non-PANDAS Tourette syndrome
- The observed differences support the notion that PANDAS is etiologically distinct from Tourette syndrome.

Alterations extend beyond the basal ganglia to include the cortico-striato-thalamo-cortical circuit

PMID: 30428956 , 28636705, 25117419, 10671403, 8768351



61

CNS structural alterations

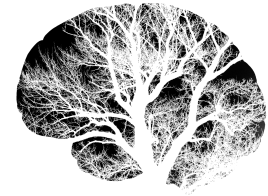
"Imaging and neurological signs suggest basal ganglia inflammation

Basal ganglia exerts an inhibitory influence on motor & behavior systems.

Inflammation/autoantibodies/injury causes disinhibition and thus disrupts the normal role of the basal ganglia in governing:

- Movements
- Mood & emotion
- Behavior
- Procedural learning
- Cognition"

Frankovich, Stanford PANS clinic, presentation Neuroimmune conference May23



62

PANDAS/PANS mechanisms

Overview of what the research tells us to date ... (expect changes as our knowledge evolves)

Pre-existing immune depleted state

Microbiome alteration

T-cell mediated damage to the brain triggered by infection AND toxicants

Microglial activation → chronically "primed" neuroinflammation

Damage to dopamine receptors & cholinergic interneurons

Altered central dopamine, glutamate, ACh utilization → excitatory

Impaired innate safety systems

Cell danger response → limbic/vagal dysfunction

CNS structural alterations



63

PANDAS/PANS Symptom Recap

Separation anxiety
 Inability to concentrate
 Urinary frequency, urgency, or urinary accidents
 Handwriting deterioration
 Alterations in sleep - insomnia, night terrors, inability to sleep alone
 Behavioral regression
 Hyper-alert appearance; enlarged pupils
 Hyperactivity
 Inattentiveness
 Tics
 Learning difficulties
 Short-term memory loss
 Aggression
 Sensory alterations - hypersensitive or insensitive
 Disordered eating
 Hallucinations, rarely



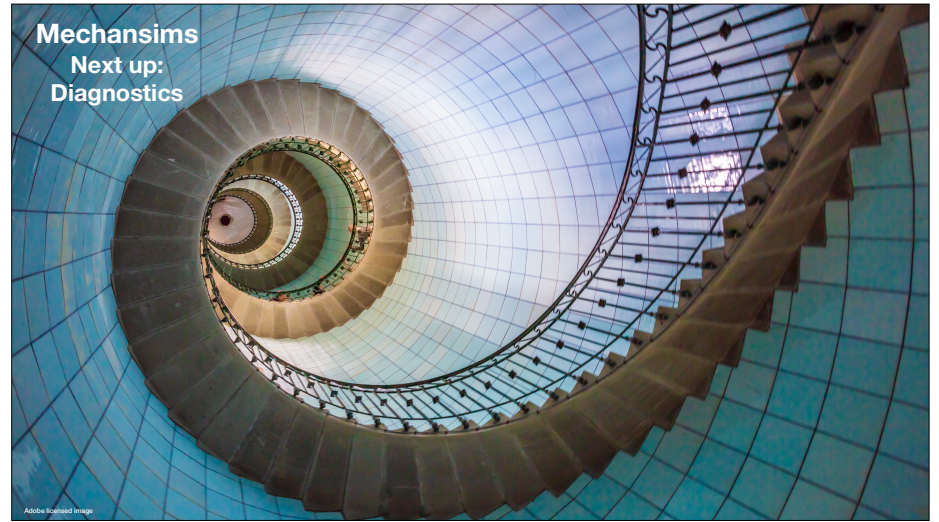
64

Take some parenting classes??



65

Mechansims
Next up:
Diagnostics



Adobe Stock image

66