

Casual Friday Presents

Seizures and Related Activity Part 2

FM Strategies: Physiology, Pathology, Interventions.

A BIOGENETIX CLINICAL PRESENTATION

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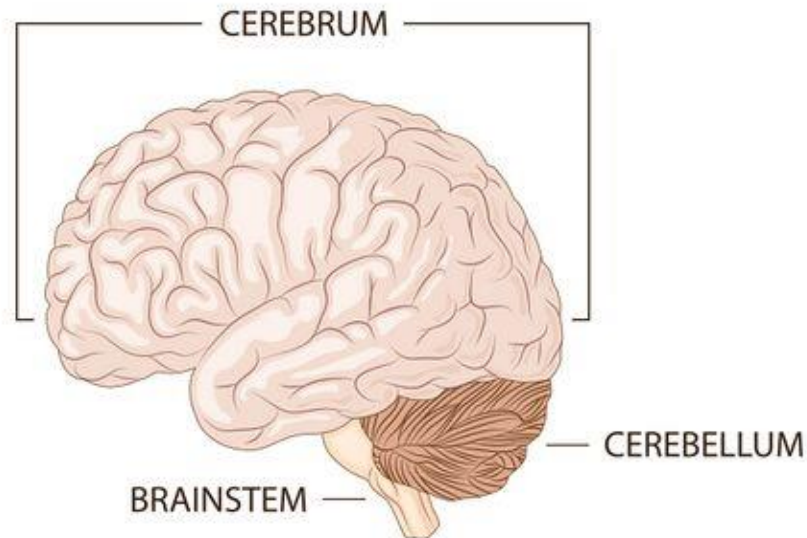




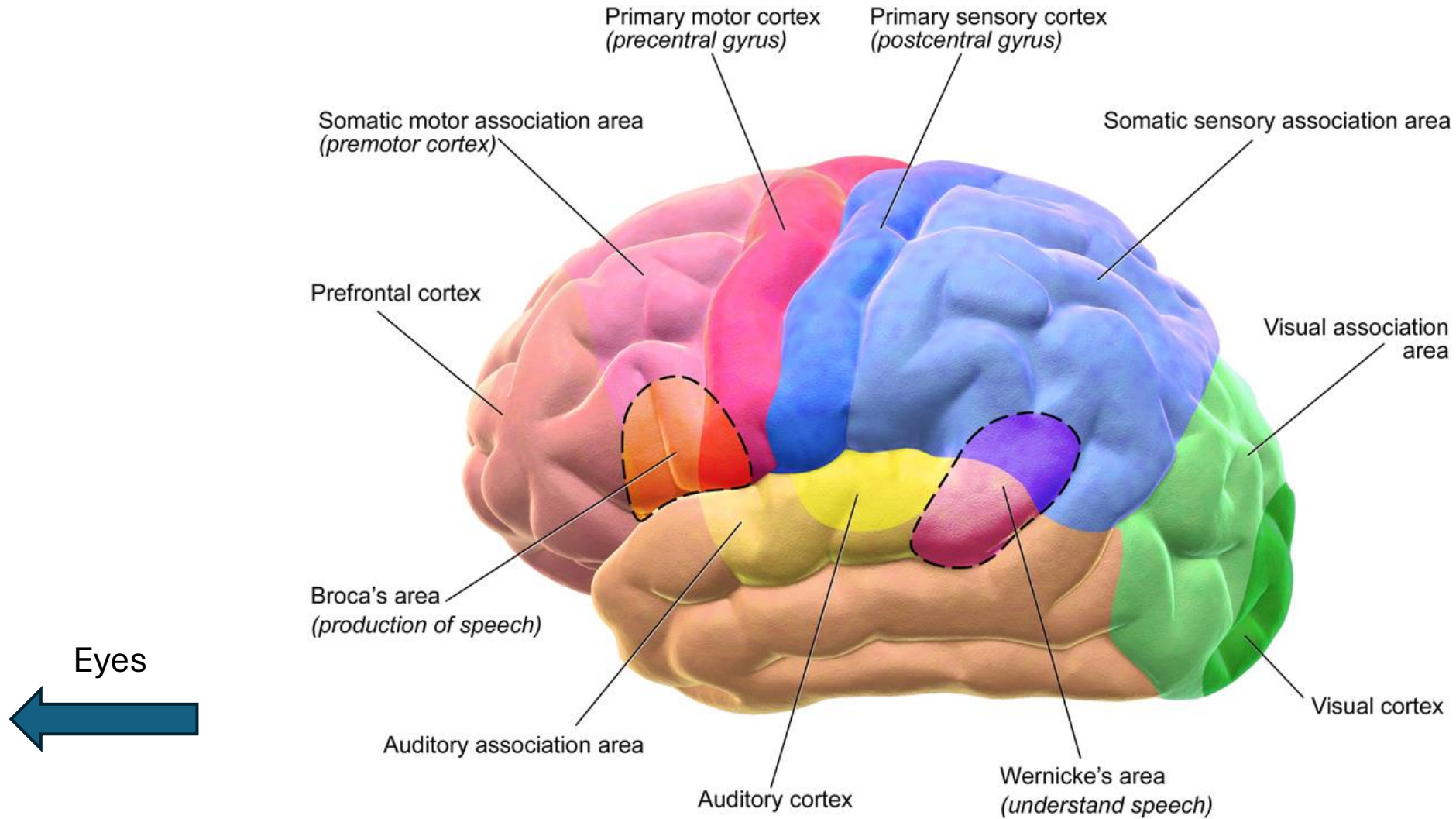
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A seizure represents the uncontrolled, abnormal electrical activity of the brain that may cause changes in the level of consciousness, behavior, memory, or feelings. Convulsive concussion, convulsive syncope, movement disorders, rigors, sleep-related events, or psychogenic non-epileptic spells are all in the differential diagnosis of an event. Seizures can classify as partial or generalized. In a partial seizure, the most common seizure type in adults, one area of the cortex activates first and may manifest through simple symptoms such as a motor or sensory phenomena. Generalized seizures result from diffuse cortical activation at seizure onset or generalization of partial seizure activity.



Motor and Sensory Regions of the Cerebral Cortex





Seizures may be either provoked or unprovoked. Provoked seizures, also known as acute symptomatic seizures, may result from electrolyte disorders, toxins, head injury, infectious processes, vascular anomalies, tumors or other mass lesions, and many other causes. A listing of provoked causes of seizures is lengthy and could include complications of almost any disease process. Some common causes are listed below:

- Electrolyte disturbances (hypoglycemia, hyponatremia, hypernatremia, hypocalcemia, others)
- Acute toxic effects (antidepressants, sympathomimetics, others)
- Withdrawal syndromes (ethanol, benzodiazepines, others)
- Irregularity with prescribed antiepileptic medications
- Sepsis
- CNS infections
- Hypoxic brain injury
- Traumatic brain injury
- Stroke, ischemic or hemorrhagic
- Neoplasm
- Inflammatory (lupus cerebritis, anti-NMDA receptor encephalitis, others)
- Fever
- Sleep deprivation



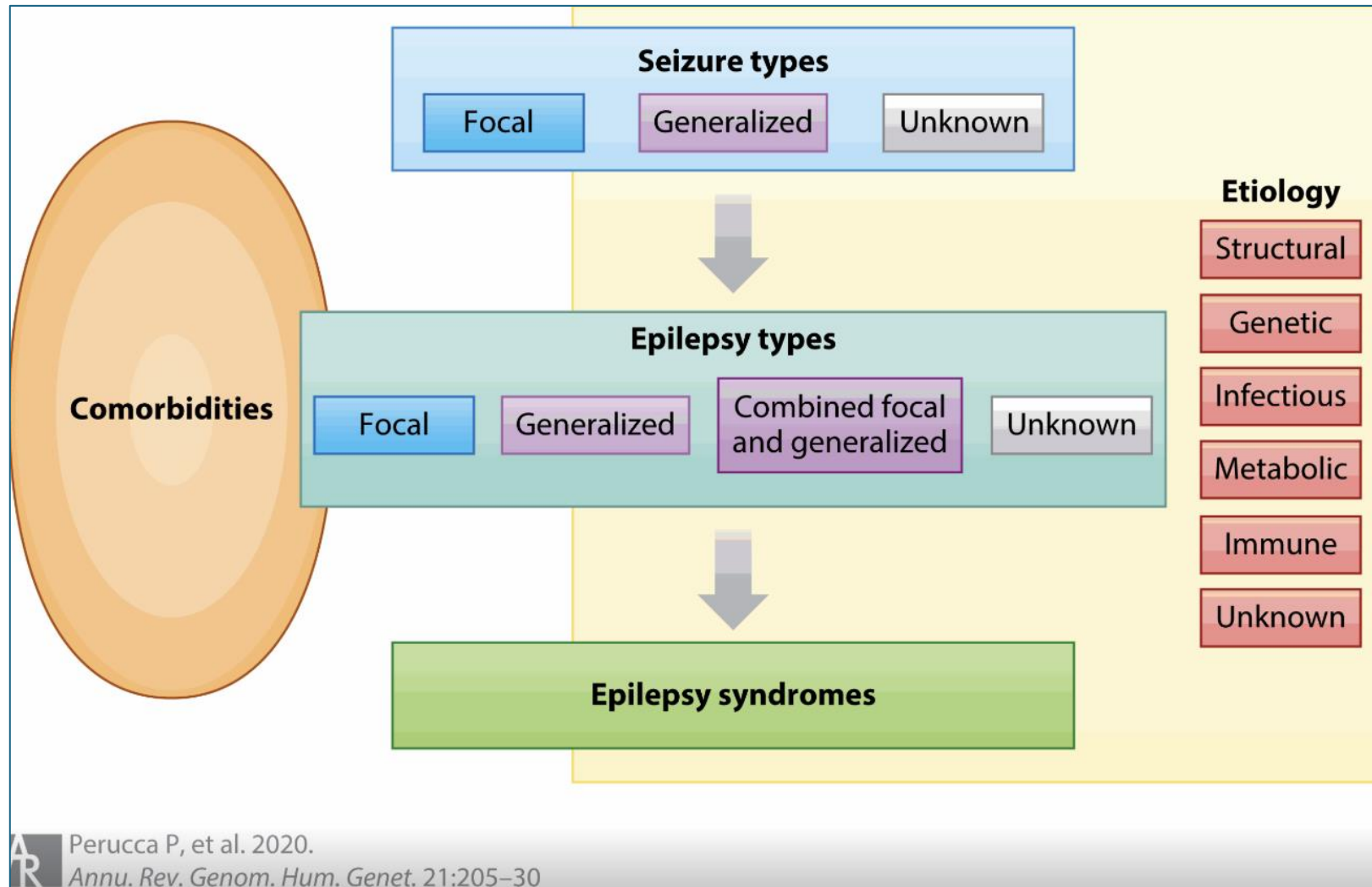
Ictal category	Examples	Commonly implicated region/network
Somatosensory	Tingling, numbness, burning, electric sensations	Contralateral primary sensory cortex; S2; posterior insula
Visual	Flashing lights, colored shapes, visual loss, distortion	Occipital cortex; visual association cortex
Auditory	Buzzing, ringing, distorted sound, occasionally voices	Superior temporal cortex
Olfactory/gustatory	Unpleasant smell or taste	Mesial temporal, amygdala, insula or operculum
Autonomic/visceral	Tachycardia, sweating, flushing, piloerection, nausea, throat constriction	Insula, amygdala, mesial temporal and autonomic networks
Abdominal	Rising epigastric sensation, butterflies, pressure or nausea	Often mesial temporal; also insular or frontal networks
Emotional	Sudden fear, dread, anxiety, joy or laughter	Amygdala, mesial temporal, cingulate or hypothalamic networks
Cognitive/experiential	Déjà vu, jamais vu, dreamlike state, forced thoughts, memory disturbance	Temporal and temporal-association networks
Language	Inability to speak, impaired comprehension, inability to name	Dominant frontal, temporal or parietal language networks
Motor	Tonic posturing, clonic jerking, myoclonus, automatisms, hypermotor movements	Primary motor, premotor, supplementary motor or frontal networks
Behavioral arrest	Sudden freezing, staring or cessation of activity	Frequently temporal or frontal network involvement
Awareness impairment	Reduced responsiveness or inability to recall the event	Usually bilateral network disruption rather than activation of one isolated location

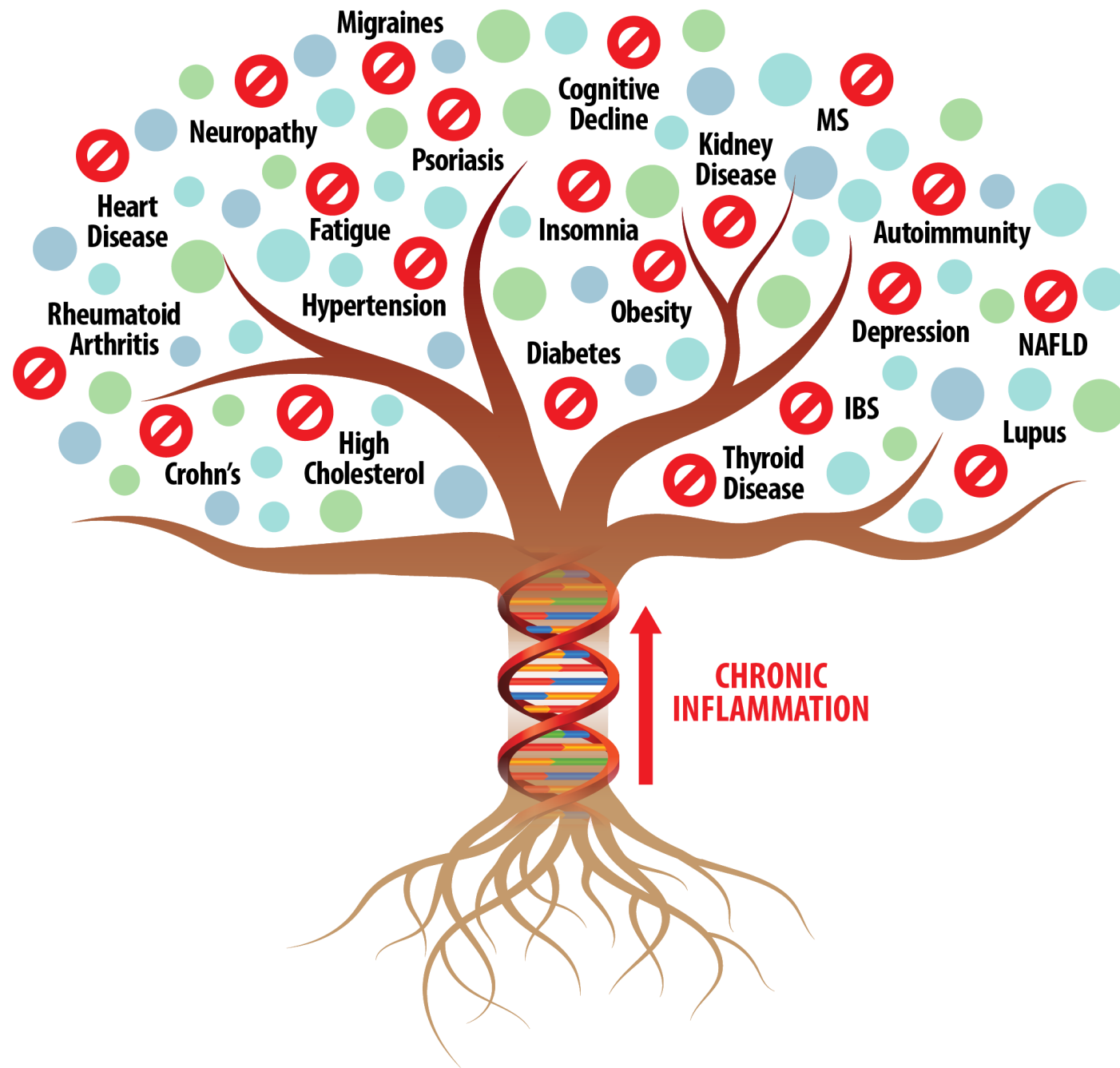
The Genetics of Epilepsy

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Mold and Mycotoxin Exposure and Brain Disorders

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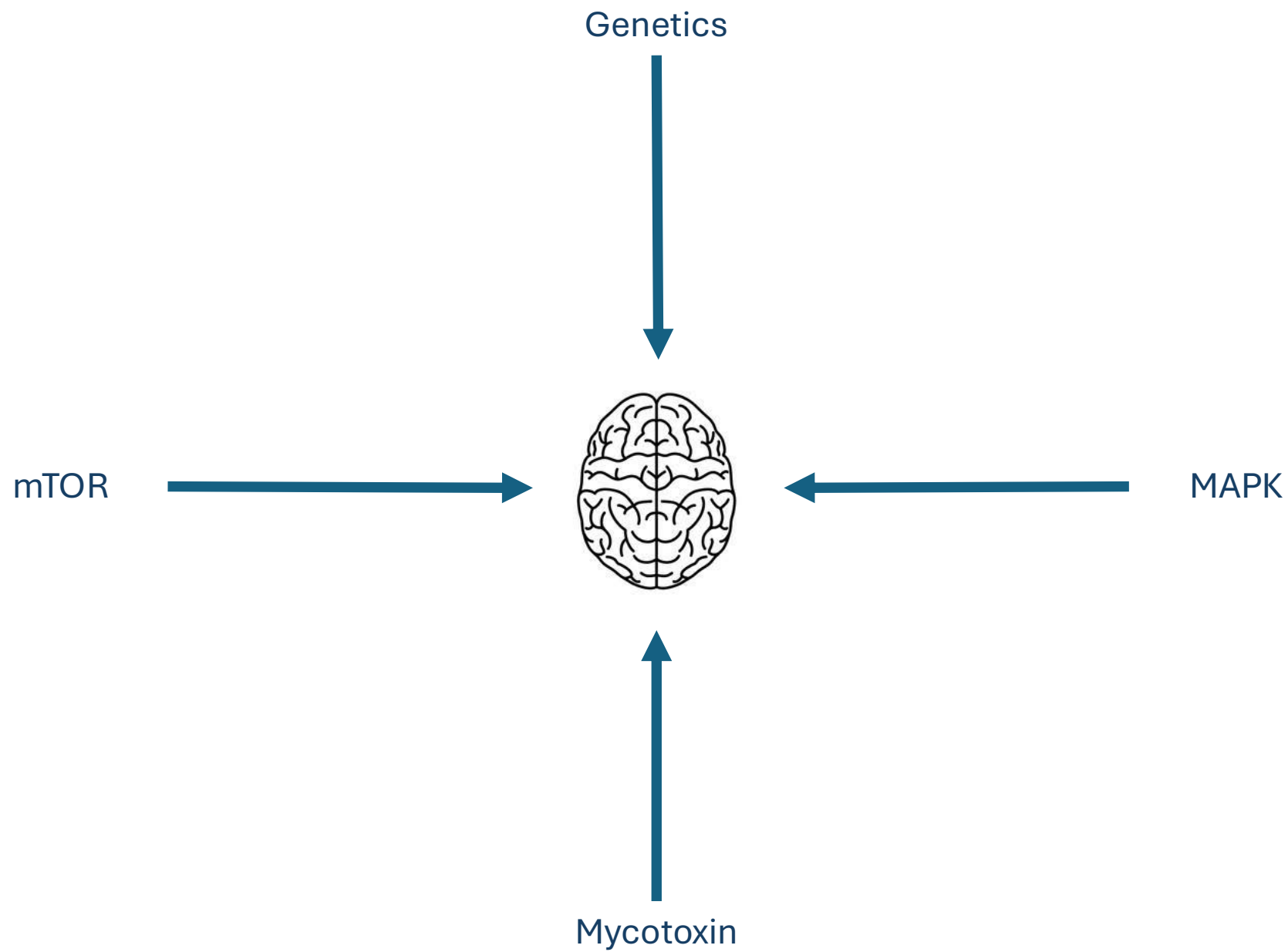
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Abstract

Gene-environment interaction is an emerging hypothesis to explain the increased incidence of neurological disorders. In this context, the health and clinical effects of exposure to air pollutants have received increasing attention. One of these pollutants is the growth of fungi and molds in the form of multicellular filaments, known as hyphae. Fungi and molds not only grow in outdoor environments, but they also thrive indoors with excessive moisture, producing mycotoxins. Mold enters the body through the nose via the olfactory neurons, which directly communicate with the brain. Mycotoxins induce toxicological effects similar to those associated with brain disorders such as oxidative stress and inflammation. One mold species can produce several different mycotoxins, and one mycotoxin can be produced by several different molds. Even a small amount of mold growth in the air conditioners and their ducts or the panels inside the buildings and even the cars cause the occupants to be chronically exposed to and constantly inhaling spores and mycotoxins, which causes illness. In this review, we focused on mold and mycotoxin exposure and brain disorders.



A scoping review on mycotoxin-induced neurotoxicity

Review |

Volume 2

Mycotoxins are toxic secondary metabolites produced by toxigenic fungi. Acute and chronic dietary exposure to toxigenic mycotoxins can cause various adverse health effects in humans and animals and thus are relevant food and feed contaminants. Despite many years of research and efforts on good agricultural and manufacturing practices, there remains a global challenge in the prevention of mycotoxin contamination and its effects on human and animal health. This leads to significant global economic losses. Research has established that these toxic mycotoxins are carcinogenic, genotoxic, mutagenic hepatotoxic and nephrotoxic. Toxigenic mycotoxins have a significant risk to the central nervous system, with potential long-term consequences on cognitive, and behavioural outcomes and neurological disorders, particularly in children. The most common mycotoxins aflatoxin B1, ochratoxin A, T-2 toxin, deoxynivalenol, zearalenone, and fumonisin B1 induces neurotoxicity via different mechanisms including disruption of neuronal signalling pathways, DNA damage, epigenetic modifications, impaired neurogenesis, oxidative stress, autophagy, disruption of neurotransmitter systems, mitochondrial dysfunction, and neuroinflammation. Exposure to mycotoxins has been associated with cognitive impairments, learning difficulties, behavioural abnormalities, and neurological disorders. The severity of neurological disorder outcomes associated with mycotoxin exposure can vary depending on the dose, duration, and timing of exposure. This review thus discusses the health effects of neurotoxic mycotoxins, their neurotoxicity and mechanisms of action.

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Exposures to mycotoxins through consumption of contaminated diets may lead to a variety of acute to chronic health conditions, depending on the type of toxin, exposure, duration, and age as well as health status of the exposed individual. Some of the health implications include hormonal imbalance, cancer, reproductive effects, genotoxicity, and neurotoxicity [4, 7, 8]. Recently, some studies have shown that some toxins can easily cross the blood–brain barrier (BBB) and reach the central nervous system particularly the glial cells and neurons to exhibit their harmful effects [9].

Some mycotoxins were found recently associated with neurotoxicity including T-2 toxins, OTA, Fs, ZEN, and AFs [10, 11]. AFs, especially aflatoxin B1 (AFB1), are of particular concern due to their high toxicity and are commonly found in food products. Studies have suggested the involvement of AFB1 in neurologic damage and OTA in the induction of neurotoxicity in human astrocytes by disrupting mitochondrial function [6]. Neurotoxic mycotoxins such as aflatoxins B1 cross the blood–brain barrier, accumulate in the brain, disrupt normal central nervous system function, and lead to neurological disorders. During the process, neurons and glial cells are particularly affected and may result in neuronal death and brain damage through various pathways [12,13,14]. Considering the implications of neurotoxicity on food safety and public health, this review has provided an overview of mycotoxin-induced neurotoxicity, which can lead to neurodegenerative diseases including Alzheimer's and Parkinson's diseases or neurodevelopmental disorders. This review therefore highlights the different mycotoxins and their neurotoxicity effects.

A scoping review on mycotoxin-induced neurotoxicity

Review | [Open access](#) | Published: 17 February 2025

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Some mycotoxins can cross the blood–brain barrier to the brain thus potentially causing harm to the brains of animals and humans [[77](#)]. In vitro and in vivo studies have revealed that mycotoxins can cause harm to neurons and glial cells causing neurotoxicity. Some of the mechanisms of action involved in the neurotoxicity of mycotoxins include induction of neuronal cell apoptosis, inflammation, oxidative stress, alteration of regional brain neurotransmitters [[78](#)]. It is worth noting that, as compared to other systems, very limited work has been done on the effect of mycotoxins on the brain. Table [2](#) summarises the various mechanisms involved in mycotoxin-induced neurotoxicity.



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Mycotoxins	Mycotoxin-induced neurotoxicity		Reference
	Mechanism	Description	
OTA	Gene expression regulation	Phosphorylation of signalling molecules can lead to the activation or inhibition of transcription factors, which in turn regulate the expression of specific genes. OTA-induced phosphorylation in human astrocytes could potentially modulate the expression of genes involved in various cellular processes, including inflammation, oxidative stress response, apoptosis, and cell cycle regulation	[78]
	Neuroinflammatory response	OTA has been shown to induce a neuroinflammatory response in different cell types. Activation of astrocytes and microglia by OTA contributes to the release of pro-inflammatory cytokines and chemokines, such as IL-1 β , IL-18, TNF- α , CXCL8 and IL-6, exacerbating neuroinflammation and promoting a pro-inflammatory environment in the brain	[24]
	Oxidative stress	OTA exposure is associated with increased oxidative stress levels in various cell types. OTA depletes antioxidants such as glutathione and antioxidant enzymes responsible for buffering the redox potential in cells	[79]
	Cell survival and apoptosis	Phosphorylation of signalling molecules can regulate cell survival and apoptotic pathways. OTA-induced phosphorylation in astrocytes may activate or inhibit specific signalling pathways involved in cell survival or apoptotic pathways, ultimately influencing cell fate and viability	[25]
	Calcium signalling	OTA disrupts calcium homeostasis in astrocytes. Phosphorylation events triggered by OTA may affect calcium-dependent signalling pathways, such as those involved in neurotransmitter release, synaptic plasticity, and intracellular calcium-dependent processes	[29]

mTOR and MAPK: from localized translation control to epilepsy

[Helena F Pernice](#)¹, [Rico Schieweck](#)¹, [Michael A Kiebler](#)¹, [Bastian Popper](#)^{1,✉}

Recently, it has been shown that the mechanistic target of rapamycin (mTOR) and mitogen-activated protein kinases (MAPK) are important regulators of synaptic excitability involved in cognitive impairment and epilepsy in animal models as well as human disease [14–16]. Those kinases regulate gene expression in neurons in a stimulus-dependent manner [17, 18]. Both pathways can be activated i.e. by long-term potentiation (LTP), a process characterized by enhanced transmission between simultaneously activated synapses. Still, not all neuronal stimulation paradigms lead to the activation of both mTOR and MAPK pathways [19, 20]. Further research is necessary to describe the exact mechanisms and kind of neuronal excitation that leads to hyperactivity. Regardless, multiple key studies show an effect of mTOR and MAPK on general expression control [21, 22]. Remarkably, recent research has shown that both mTOR and MAPK also act locally to regulate protein expression at activated synapses [17, 22]. Together, these findings provide new insight into the molecular mechanisms of epilepsy and explain how lack of pathway control results in seizures.



mTOR and MAPK: from localized translation control to epilepsy

Expression control by the MAPK pathway: a regulator of epileptic biomarkers

Helena

► Author

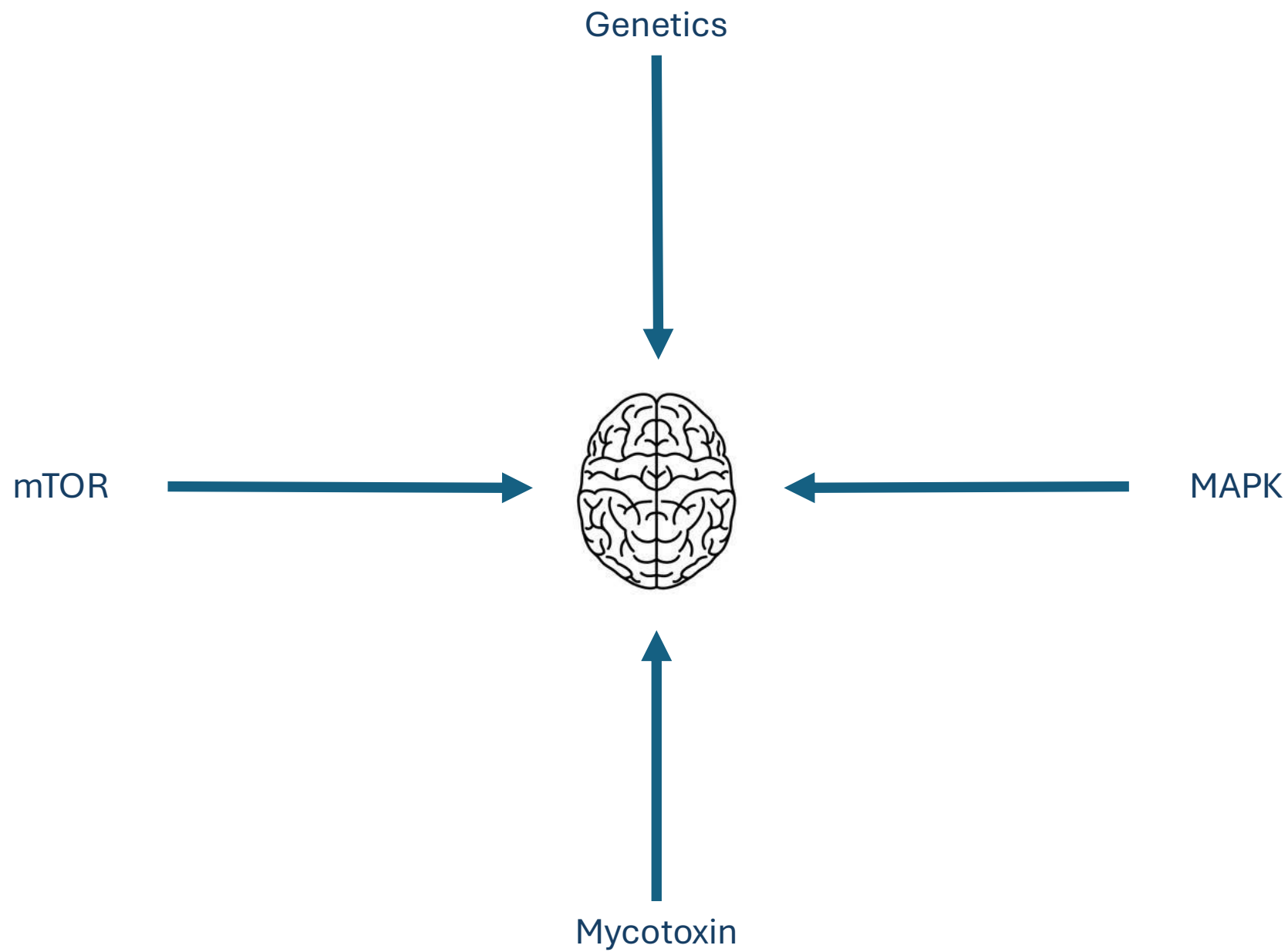
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The mitogen-activated protein kinase (MAPK) family consists of three pathways, the extracellular signal regulated kinase (ERK) pathway, the p38 pathway and C-Jun N-terminal kinases (JNK) pathway. All three are highly conserved serine-threonine kinases that respond to nutrition and growth factors availability as well as neuronal activation [38]. ERK stimulates the expression of *N*-methyl-D-aspartate (NMDA) receptors causing synaptic excitability. This, in turn, leads to seizures [38]. Moreover, the neuroprotective effect of NMDA injected in mice before seizure induction is diminished by inhibition of the MAPK pathway, further underlining the potential of MAPK to regulate neuronal excitability [39]. Also the induction of mossy fiber sprouting, an effect causally associated with epileptogenesis, by the ERK/MAPK pathway has been shown in rats after traumatic brain injury [40]. This further supports a role of MAPK pathway in epileptogenesis. Interestingly, MAPK responds to different seizures-inducing treatments: maximal electroshock seizures in mice [41], kainate [42], pilocarpine [43] and pentylenetetrazole [44] as well as dopamine D1 receptor (D₁R) agonist [45]. These findings suggest a role of MAPK in epileptogenesis.

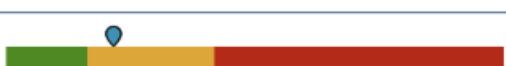
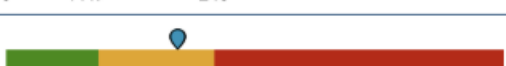
Strikingly, there is evidence that also the MAPK pathway involves RBPs that are misregulated in epilepsy, like FMRP and HuR. In this context, kinases regulate those proteins and, therewith, their ability to control posttranscriptional gene expression [22, 46].

mTOR and MAPK: from localized translation control to epilepsy

[Helen](#) It is generally believed that epilepsy results from hyperexcitability and synchronous firing of neurons [7]. In the last decade, many biomarkers such as potassium and sodium channels as well as GABA receptors have been identified (Table 1). Beside those, mTOR and MAPK also contribute to epileptogenesis. Very often they are key players of converging pathways. Nonetheless, the underlying molecular mechanism of hyperexcitability and, in consequence, synchronous firing remain elusive. Strikingly, it has been shown that transcripts encoding for some of epileptic biomarkers including *mTOR* are localized in dendrites. Additionally, RBPs, mediators of RNA localization and remote expression control, have been linked to epilepsy bridging mTOR signaling with spatially restricted expression. We propose that hyperactive mTOR and MAPK affect RBPs and RBP-mediated expression control locally (Fig. 2). Thereby, they influence transcript transport, stability and translation at or near synapses of RBP target mRNAs. Thus, increased, local expression of ion channels and receptors results in enhanced synaptic density of excitability regulating proteins and, eventually, in increased synaptic transmission. In turn, augmented synaptic stimulation further activates mTOR and MAPK. This spatially restricted misregulation of synaptic excitability may therefore represent an accelerator of synchronous, neuronal firing that eventually results in seizures. Thus, RBPs might represent a novel category of epileptic biomarkers that can help to diagnose epilepsy in patients. Furthermore, they also can serve as additional targets for therapeutics. However, future studies will elucidate their eligibility for diagnosis and therapy.



High (>95th percentile)					
TEST NAME	CURRENT RESULT	PREVIOUS RESULT	CURRENT RESULT	PREVIOUS RESULT	REFERENCE
 Aflatoxin B2 (AFB2)	22.76				≤8.13 ng/g
 Aflatoxin G1	15.43				≤6.53 ng/g
 Aflatoxin M1	9.65				≤6.4 ng/g
 Dihydrocitrinone	34.87				≤16.53 ng/g
 Fumonisin B1	17.02				≤6.13 ng/g
 Mycophenolic Acid	16.48				≤6.4 ng/g
 Roridin A	8.99				≤7.6 ng/g
 Aluminum	56.1				≤45.15 ug/g
 Barium*	9.22				≤5.59 ug/g
 Lead*	1.41				≤1.16 ug/g
 Bisphenol A (BPA)*	8.98				≤5.09 ug/g
 Perchlorate (PERC)*	21.83				≤10.7 ug/g
 Phenyl glyoxylic Acid (PGO)*	854.49				≤518 ug/g

Moderate (75th-95th percentile)					
 Mycotoxins  Heavy Metals  Environmental Toxins  PFAS					
TEST NAME	CURRENT RESULT	PREVIOUS RESULT	CURRENT RESULT	PREVIOUS RESULT	REFERENCE
 Aflatoxin B1 (AFB1)	4.45				≤6.93 ng/g
 Citrinin (CTN)	11.82				≤12.53 ng/g
 Fumonisin B3	8.16				≤10.8 ng/g
 Gliotoxin	191.93				≤207.87 ng/g
 Roridin L2	5.22				≤6.8 ng/g
 Sterigmatocystin (STC)	0.53				≤0.53 ng/g
 Zearalenone (ZEN)	0.49				≤0.67 ng/g
 Cesium*	7.26				≤10.3 ug/g
 Mercury*	1.38				≤1.61 ug/g
 Thallium*	0.28				≤0.43 ug/g
 Thorium	0.03				≤0.07 ug/g
 2-Methylhippuric Acid (2MHA)*	89.84				≤248 ug/g
 2,2-bis(4-Chlorophenyl) acetic acid (DDA)	16.62				≤19 ug/g

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