Research Article ISSN 2835-6276

American Journal of Medical and Clinical Research & Reviews

Biological Barriers and Severe Mental illness: Potential Novel Interventions

Adonis Sfera[1]*, Edelina Turturica[1]*, Dragos Turturica[2], Ioana Ciuperca[3], Daniel Ikhimiukor[1], Jacob J. Anton[4], Bernardo Boza[5] and Garth Nicolson[6]

1. Patton State Hospital; Loma Linda University
2. College Hospital of Long Beach
3. UCLA Medical Center
4. California Baptist University, Department of Biological Sciences
5. University of Florence, Patton State Hospital
6. Institute of Molecular Medicine, Huntington Beach

*Correspondence: Adonis Sfera, Edelina Turturica

Received: 05 Sep 2025; Accepted: 10 Sep 2025; Published: 15 Sep 2025

Citation: Adonis Sfera, Edelina Turturica, Dragos Turturica, et al. Biological Barriers and Severe Mental illness: Potential Novel Interventions. AJMCRR. 2025; 4(9): 1-19.

Abstract

Life is dependent on the separation of body compartments from each other and the environment. The permeability of biological barriers, including the gastrointestinal and blood-brain, depends on the integrity of cell membranes and intercellular tight junctions.

Severe mental illness is characterized by premature cellular senescence and subsequent gray matter loss in the central nervous system. Senescence-induced gut barrier disruption enables microbial migration outside the gastrointestinal tract. Systemic immune responses to gut microorganisms or their molecules may lead to neuroinflammation and the subsequent pathology.

This review discusses cellular senescence and microbial migration outside of the gastrointestinal tract along with potential strategies for restoring the gut barrier homeostasis. These approaches include membrane lipid replacement, gamma wave entrainment, red light therapy, and pulsed electromagnetic field therapy.

Keywords: gut microbes; Membrane Lipid Replacement; Oscillations; EEG gamma waves; severe mental illness.

Introduction

Life depends on the integrity of biological barriers, beginning with the cell membranes that separate the human body from the outside environment and the barriers that separate tissues and organs from each other.

Biological barrier homeostasis is of utmost importance as its disruption was demonstrated in many diseases, including severe mental illness (SMI). Aryl hydrocarbon receptor (AhR), a transcription factor abundantly expressed at the gut and blood-brain barrier (BBB), is the master regulator of both tight junctions (TJs) and cellular senescence, thus controlling both molecular aging and barrier permeability (1)(2). Conversely, dysfunctional AhR allows gut microbes to migrate through the paracellular spaces in-between intestinal epithelial cells (IECs), accessing the systemic circulation and reaching the brain. Dysfunctional TJs and premature cellular senescence were demonstrated in patients with SMI and inflammatory bowel disease (IBD), implicating AhR in these pathologies (3)(4). Indeed, patients with schizophrenia (SCZ), known to live 15-20 years less than the general population, exhibit shorter telomeres, a more porous BBB, and higher prevalence of IBD (5)(6). Since mitochondria express mitochondrial AhR (mAhR), aberrant activation of this receptor may lead to the elimination of healthy organelles, a phenomenon documented in both SCZ and cellular senescence (7).

Dysfunctional AhR can contribute to premature molecular aging in IECs, further increasing microbial translocation. Moreover, impaired AhR may respond aberrantly to microbial molecules, such as tryptophan catabolites, shifting the processing of this amino acid toward kynurenine and quinolinic acid associated with SCZ, autism spectrum disorder (ASD), major depressive disorder (MDD), posttraumatic stress disorder (PTSD), and suicide (8)(9). Interestingly, psychological stress has been shown to increase microbial translocation by disrupting indoleamine dioxygenase (IDO), an essential tryptophan catabolizing enzyme, known for promoting immunological tolerance. Furthermore, microbe-activated AhR, and premature cellular senescence are known to drive lipid peroxidation, plasmalogen depletion, and toxic ceramide formation in cell membranes, hastening neuronal demise.

Membrane lipid replacement (MLR) and plasmalogen replacement therapy (PRT) can remove oxidized phospholipids from plasma and mitochondrial membranes, re-placing them with healthy, natural phospholipids, preventing neuronal senescence and gray matter volume loss (Fig. 1). Electric, magnetic, and sound stimulation of Vagus nerve and/or spleen may further lower the permeability of biological membranes, preventing neuropathology.

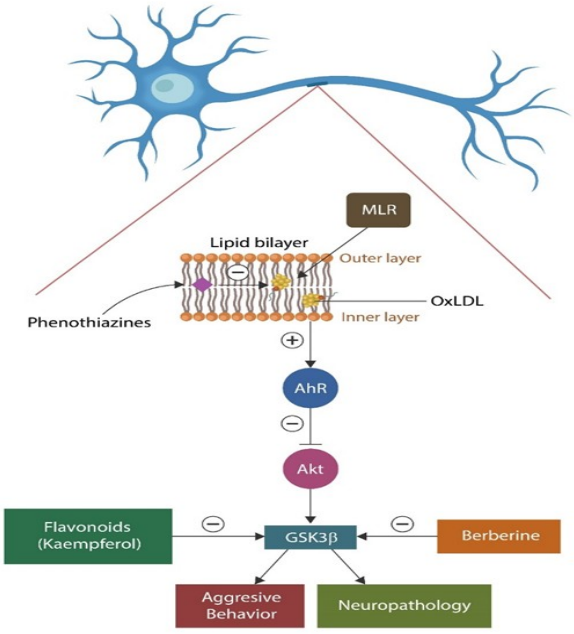

Figure 1. Neuronal cell lipid bilayer contains phospholipids, glycolipids, plasmalogen, and cholesterol. Oxidized lipids disrupt the cell and mitochondrial membranes, while pheno-thiazines exert antioxidant properties that can repair membrane lipids. This averts AhR activa-tion and the downstream GSK3β-mediated pathology. Two natural remedies, Kaempferol and Berberine, inhibit GSK3β, acting in synergy with lithium and some antipsychotic drugs.

Schizophrenia and dysfunctional cell membranes

A growing body of evidence suggests that membrane lipids, such as phosphatidylcholine (PC), phosphatidylethanolamine (PE), and plasmalogens, are significantly downregulated in patients with SCZ (10)(11). Lowered membrane lipids decrease fluidity and increase oxidative stress have been documented in SCZ (12).

Mitochondria contain a unique microbe-like double membrane structure, highlighting its likely bacterial origin. The membrane consists of an inner and outer leaflet, an intermembrane space, and a matrix containing mitochondrial enzymes, ribosomes, and mitochondrial DNA (mtDNA). The inner membrane harbors the electron transport enzymes involved in oxidative phosphorylation (OXPHOS). Like plasma membranes, the mitochondrial membrane contains an asymmetric lipid bilayer comprised of PE, cardiolipin (CL), and PC. CL is a unique lipid found primarily in the mitochondrial inner membrane that is crucial for maintaining the inner membrane fluidity and the transmembrane potential. In the CNS, CL is found in neurons and glial cells, where it maintains the energy homeostasis and drives damaged cells' apoptosis. Interestingly, anti-cardiolipin antibodies were documented in SCZ, while commensal gut flora, including *Muribaculum intestinale*, produces CL, suggesting that upon translocation, host antibodies may be directed at this microbe and not the mitochondrion itself (13).

Mitochondria contain mAhR that can be aberrantly activated by oxidized lipids, causing organelle demise. Excessive reactive oxygen species (ROS) can cause mem-brane damage, leakage of protons across the inner membrane, impaired ATP production, and cell death. For example, oxidized lipid-activated mAhR can drive glycogen synthase kinase 3 beta (GSK3β), a known SCZ pathogenetic mechanism (14)(Fig. 1).

Cellular and mitochondrial membranes exhibit asymmetric lipid bilayers marked by different lipidomes in each leaflet. For example, sphingomyelin is much more predominant in the outer leaflet, whereas PE and PS are predominantly located in the inner leaflet. The lipid asymmetry drives the physiological properties of cell membranes and their functional characteristics, including signal transduction, temperature adaptation, endocytosis, and apoptosis (15)(16). Conversely, loss of membrane asymmetry may lead to mitochondrial demise, a pathology described in SCZ. Membrane Lipid Replacement (MLR) refers to restoration of physiological membrane lipid composition to reverse pathology (17)(18).

Recent SCZ studies have linked dysmetabolism and obesity to reduced mitochondrial number, likely explaining the overall metabolic slowdown documented in this condition. Along this line, impaired mitochondrial fission, a process equivalent to microbial binary fission, reduces mitochondrial number and metabolism, a key characteristic of obesity and insulin resistance (19)(20)(21). Since metabolic dysfunction and cellular senescence co-occur, this program may contribute to both SCZ pathogenesis and dysmetabolism (22)(23)(24)(25).

When iron and fat get together

Cellular and mitochondrial lipid bilayer is susceptible to oxidation that can trigger cellular senescence, which may reflect a defense mechanism against ferroptosis (26, 27). Indeed, senescent cells upregulate intracellular iron, increasing the risk of

ferroptosis, a programmed cell death triggered by lipid peroxidation. Peroxidation-disrupted neuronal membranes can alter the biophysical properties of surface receptors, disrupting neurotransmission (Fig. 2).

Oxidized membrane lipids, especially sphingolipids, have been directly correlated with the vulnerability to mental illness and metabolic syndrome, suggesting that ferroptosis may play a significant role in these pathologies (28)(29). Together, this emphasizes once again the role of dysfunctional lipidome in neuropsychiatric disorders and metabolic syndrome. Indeed, increased ceramide and reduced mitochondria number have been documented in SCZ and insulin resistance, linking once more neuropathology to dysmetabolism (30)(31). Since ceramide is known for tagging defective mitochondria for mitophagy, it has been hypothesized that excess ceramide may contribute to the aberrant elimination of healthy mitochondria (32). Moreover, ceramide has been implicated in neuronal autophagy, a process in which microglia aberrantly engulfs and digests healthy neurons (33). This may explain why most patients with SCZ exhibit low white matter levels of phosphatidylcholine (PC) and high ceramide levels (34). Moreover, these findings suggest that correcting membrane lipidomes via MLR and PRT could ameliorate the SCZ outcome.

Ceramides are cell membrane phospholipids (composed of sphingosine and fatty acids) that play a key role in many cellular events, including growth, cell cycle, migration, autophagy, and response to stressors (35)

Under physiological circumstances, ceramides are obtained from three sources: the diet, de novo synthesis in human tissues, and production by gut commensal flora, such as *Bacteroidetes spp.* Along this line, the oral cavity *Bacteroidetes*, more abundant in patients with SCZ than healthy controls, emphasize the likely origin of ceramide (36). Moreover, several studies have shown that inflammation can convert ceramide into a toxin, leading to neuropathology, likely connecting this lipid to the neuroinflammation in SCZ (37). For example, novel preclinical studies have shown that gut microbes can metabolize dietary PC into a toxin, trimethylamine-N-oxide (TMAO), a biomolecule implicated in atherosclerosis, and SCZ (38). This is important not only for explaining the lower levels of PC in SCZ but also the high prevalence of coronary artery disease in people with this disorder (39). Indeed, proinflammatory cytokines and inflammation likely account for the presence of TMAO in SCZ and metabolic disorders. Indeed, earlier studies have shown that inflammation drives the formation of toxic ceramide species, resulting in CNS pathology, insulin resistance, and oxidative stress (39) (40).

Plasmalogens are a class of cell membrane glycerophospholipids with powerful antioxidant properties, including the ability to protect the membrane bilayer from peroxidation, a pathology documented in SCZ, Alzheimer's disease (AD), and metabolic syndrome (41). Asymmetrically displayed glycerophospholipids help maintain the biophysical properties of neuronal membranes, including their shape, fluidity, and thickness to stabilize membrane proteins, including cell surface receptors.

Phenazines and phenothiazines

Antipsychotic drugs with antioxidant properties, such as phenothiazines, were demonstrated to enter the lipid bilayers of cellular and mitochondrial

membranes, and repair the structural lipids (42)(43) (Fig.2).

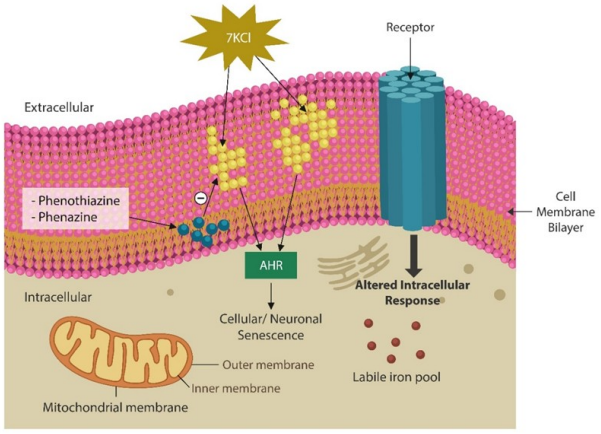

Figure 2. Natural phenazines and synthetic phenothiazines can ingress cell membrane lipid bilayer, reversing the oxidative damage caused by oxidants, such as 7-Ketocholesterol (7-KCl), preventing AhR activation. Toxic oxides alter the biophysical structures of membranes, altering neurotransmission by misaligning the surface receptors. Increased intracellular free iron in the presence of damaged lipids increases the risk of ferroptosis.

Indeed, reduced phospholipids in plasma membranes and platelets of patients with SCZ, mood disorders, and dysmetabolism are considered biomarkers of SMI and metabolic syndrome (44)(45)(46).

Naturally occurring phenazines, a class of phenothiazines produced by the marine and terrestrial microorganisms as well as by some gut microbes, can also act on neuronal membranes, likely comprising an inbuilt antipsychotic system, akin to the analgesic endogenous opioids. In addition, these agents exert antimicrobial, antiparasitic, neuroprotective, anti-inflammatory, and anticancer activities and are currently in clinical trials for these pathologies (42). At present, there are over 100 natural phenazines and about 6000 synthetic derivatives with antioxidant properties that can ingress cell membranes, protecting the lipid bilayer against peroxidation (42). Moreover, there are important new phenothiazines with strong antioxidant properties, that have been developed for cancer treatment, such as azaphenothiazines, that can be utilized in SCZ along with PRT or MLR (table 1).

Azaphenothiazines are modified phenothiazine compounds with antipsychotic and antioxidant properties that may be utilized in many conditions including psychosis and cancer. Biochemically, the benzene ring of phenothiazines is replaced in azaphenothiazines with one or more azine rings, resulting in: Monoazaphenothiazines: contain a single azine ring fused to the phenothiazine core. Diazaphenothiazines: contain two azine rings Triazaphenothiazines: three azine rings. Tetraazaphenothiazines: four azine rings. Azaphenothiazines can also be categorized based on the type of azine ring fused to the phenothiazine system. These include: Pyridobenzothiazines: fused with pyridine ring. Diazaphenothiazines (Dipyridothiazines): fused with two pyridine rings. Quinolinobenzothiazines: fused with quinoline. Other azaphenothiazine derivatives contain pyridazine, pyrimidine, pyrazine, 1,2,4-triazine, quinoxaline, benzoxazine, and benzothiazine rings. Biological activity: anti-inflammatory, hematopoietic, osteoclastogenic, neurogenic. It also has an influence on women's fertility and promotes development of T-cell-stimulated Ig-producing B cells. Some azaphenothiazines, including 10H-1,9-diazaphenothiazine and 10H-3,6-diazaphenothiazine, exhibit antitumor activity. Others are neuroprotective through various mechanisms, including free radical scavenging, anti-inflammatory effects, and autophagy induction. Many azaphenothiazines exhibit antipsychotic activity, including: prothipendyl and 1-Azaphenothiazine. These agents function as electron donors and prevent gray matter volume loss.

Table 1. Azaphenothiazines as the largest group of modified phenothiazines with antioxidant properties.

Cellular senescence and microbial translocation

SCZ is characterized by accelerated aging, shorter lifespan, decreased telomere length, and early onset of age-related diseases, indicating the involvement of cellular senescence, a program likely driven by AhR. Senescent cells arrest proliferation, re-wire their metabolism to protect against carcinogens and other endogenous or exogenous toxicants, and release a toxic secretome known as senescence-associated secretory phenotype (SASP) that can spread senescence to the neighboring healthy cells. Senes-cent IECs disrupt the gut barrier, leading to increased microbial translocation, and systemic inflammation (47). Indeed, the movement of microbes across the intestinal barrier, can promote inflammation by upregulating the levels of toxic ceramide (48).

Mitochondrial lipidome and rapid EEG frequences

Premature cellular senescence can occur in response to mitochondrial damage, impaired OXPHOS, and production of excessive ROS (49). Reduced mitochondrial number in neurons have been associated with the loss of EEG gamma waves (30-100Hz), frequences associated with cognition and higher intellectual functions (50).

The role of oscillations and vibrations in nature has been appreciated for thousands of years. For example, Pythagoras and his followers thought that celestial bodies vibrated in a musical rhythm. Nikola Tesla envisioned a universe governed by oscillatory frequencies, while in our time, two separate groups detected Universe-generated acoustic oscillations (51). Moreover, an Italian study found that 432 Hz tuned music can decrease heart rate, blood pressure, and respiratory rate compared to other frequencies (52). Others found that listening to 432 Hz music lowered stress measured by salivary cortisol levels, (53). This data shows that a quantum paradigm may explain the effects of gamma frequences on human tissues. Along this line, oscillations can lead to “synchronization”, bringing distant brain areas of in harmony with each other, a phenomenon believed to engender consciousness (54)(55). For example, several sound and light frequences were demonstrated to increase empathy and compassion, suggesting that it promotes the function of the anterior insular cortex (AIC) and anterior cingulate cortex (ACC)(56). In addition, certain oscillatory frequences were found to improve the overall health and wellbeing even in the absence of music, suggesting the beneficial effect of frequency itself rather than the delivering modality. Indeed, another study showed measurable improvement in depression and anxiety scores in college students who utilized a whole-body vibrating platform twice a week (57).

Interoceptive awareness and oscillations

The synchronization of oscillatory brain activity is thought to drive self -awareness, while desynchronization, inhibition of inter-regional CNS signaling, has been demonstrated in general anesthesia, linking intracerebral communication to consciousness (58)(59)(60). Gamma oscillations are believed to connect distant brain regions such as those in charge of movement, memory, and emotion, emphasizing the crucial role of synchronicity (61)(62). Moreover, gamma waves, likely drive interoceptive awareness and cognition, contributing to emotional intelligence, the ability to view one’s actions from another person’s perspective (63)(64). Furthermore, awareness of pain, well-being, or the position of one’s limbs and body parts, comprise interoception or perception of endogenous states. In psychopathology, including SCZ, anosognosia (lack of

insight) is a marker of higher severity of symptoms and frequently a marker of aggressive behaviors (65). For example, somatostatin (SST)-secreting γ -aminobutyric acid (GABA) neurons are depleted in SCZ, likely reflecting poor insight (anosognosia) (66). Along this line, loss of gamma oscillations was also documented in AD and PD, linking poor insight to the depletion of these interneurons (67) (68)(Fig. 3).

EEG desynchronization and violent crime

Several EEG studies on death row inmates with history of violent crime found diminished or absent gamma frequencies, probably highlighting impaired insight (69). Low electrophysiological activity in the right prefrontal cortex and increased striatal activity in these individuals likely mirror anosognosia, a previously described marker of violent crime (70)(71). Indeed, altered prefrontal coherence, especially hypo-frontality, is believed to reflect dysfunctional information processing and inability to distinguish reality from imaginary content , a characteristic trait of poor insight (72).

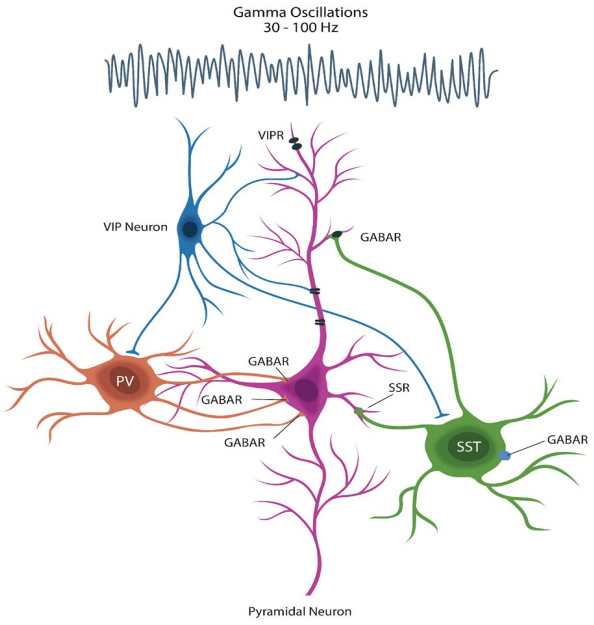

Figure 3. Gamma oscillations comprise a rapid brain rhythm believed to be generated by the synaptic "chatter" of inhibitory GABAergic interneurons, such as somatostatin (SST)-expressing cells which signal with the GABA receptors on other neurons. Loss of inhibitory interneurons disinhibits pyramidal cells, leading to psychosis. Vaso-intestinal peptide (VIP)-releasing neurons counteract this inhibition by inhibiting the inhibitory neurons, an action that leads to the disinhibition of pyramidal cells.

Potential novel interventions

It has been said that the 20th century was an era of biochemistry, when drugs were chosen to address illnesses. In contrast, the 21st century may be a time of biophysical interventions marked by recruiting physical forces, such as oscillations, or electromagnetic energy to influence various molecular pathways in tissues and organs. In addition, the 20th century was a time of specializing and overspecializing in most fields, with emphasis on details, often at the expense of the whole. Conversely, the 21st century appears to highlight healing, restoration, and repair.

MLR and PRT

PRT and MLR aim at restoring the physiological levels of membrane lipids in cell and mitochondrial membranes via natural fats and antioxidants. Altered membrane lipids and oxidation states have been observed in several conditions, including normal aging, SCZ, chronic inflammation, and other neurodegenerative and metabolic disorders.

PRT and MLR can replace and restore functional membrane lipids required for the barrier function. Natural glycerophospholipids, including plasminogen are administered orally to remove and replace toxic lipids and other detrimental hydrophobic molecules, re-storing the physiological permeability of membranes. This was recently demonstrated in vet-

erans with Gulph War Illness (GWI) treated with MLR (65). Likewise, PRT and MLR may have a role in SCZ in which premature molecular senescence appears to be triggered by lipid, especially plasmalogen, peroxidation in cellular and mitochondrial membranes (73). Since plasmalogen disrupts cholesterol biosynthesis, low levels of this lipid in SCZ may explain the cause of dyslipidemia (74). Along this line, a recent study determined the optimal oral dose of PRT as being 900 to 3,600 mg/day over a 4-month period. The authors of this study noted improved cognition and mobility in patients with neurocognitive disorders after about 120 days of PRT in the above doses (75).

PRT, MLR replace damaged membrane lipids in cells via oral intake of natural, unoxidized membrane lipid supplements. MLR has shown efficacy in various conditions involving loss of mitochondrial number and function as well as damage to plasma membranes (43).

PRT and MLR restores the physiological function of plasma membranes throughout the body, including the gut barrier and BBB. This lowers the permeability of epithelial and endothelial barriers, thus averting microbial migration and microbial translocation disorders.

Viruses, including SARS-CoV-2, damage cell membranes as they enter the intra-cellular compartment to replicate. Damaged membranes externalize PS, a universal signal that attracts phagocytes to eliminate infected cells. Cellular senescence upregulates cytosolic iron, predisposing to lipid peroxidation and ferroptosis (76).

Ferroptosis is an iron-induced form of programmed cell death caused by the intracellular accumulation of this biometal in the absence of glutathione peroxidase 4 (GPX4)(77), a lipid repair enzyme. Oxidized lipids have been shown to act as foreign molecules, activating host pattern recognition receptors (PRR), resulting in chronic inflammation, neuropathic pain, depression, and neurodegeneration (78).

Rescue from ferroptosis can be achieved by lowering intracellular iron, increasing GPX4, or replacing the oxidized lipids in cell membranes.

Membrane repair via MLR or PRT reduces neuropathic pain and chronic inflammation, upregulating the number of mitochondria by enhancing organelle dynamics, including fission (17).

Lipid peroxidation and ferroptosis have been associated with several conditions, including myalgic encephalomyelitis /chronic fatigue syndrome (ME/CFS), GWI, chronic pain, and neuropsychiatric disorders. In this regard, ferroptosis-disintegrating cells release proinflammatory alarmins, such as the high mobility group box 1 (HMGB1), known for disrupting the intestinal barrier and BBB (79). Natural membrane supplementation with glycerophospholipids was demonstrated to safely restore the homeostasis of biological barriers, limiting microbial translocation (18). In SCZ, substituting ferroptosis-driving oxidized lipids with healthy glycerophospholipids, may restore the physiological permeability of biological barriers (gut and BBB), averting microbial translocation grom the GI tract into the systemic circulation. Oxidized membrane lipids can also induce toxicity by aberrantly activating AhR, and the downstream GSK3β. Overactive GSK3β has been documented in various neuropsychiatric conditions, especially SCZ and bipolar disorder, as well as in perpetrators of violent crime.

Several antipsychotic drugs, lithium, and the natural compounds berberine and kaempferol, inhibit GSK3β, suggesting that these herbal remedies exert antipsychotic properties, without the adverse effects of conventional psychotropic drugs (Fig.1). In -deed, unlike the antipsychotic drugs that are symptomatic, MLR and PRT may com-prise etiopathogenetic treatments for SMI.

Oscillatory treatment

Oscillations or vibrations are fundamental properties of matter, including the biological systems (80)(81). rom yeast to humans, cells communicate via oscillations, indicating that this is likely a highly conserved mechanism (82)(83)(84). Indeed, it is believed that certain frequencies may be ideal for encoding and transmitting information, suggesting that oscillations may play a role in neurotransmission, functioning in parallel with the synaptic and exocrine/paracrine systems (85)(86).

How brain oscillatory frequencies relate to information processing in neuronal networks is not entirely clear. However, a growing body of evidence has demonstrated that neurons can function as oscillators, making cognition possible by synchronizing with the same frequency oscillators in other brain regions (87)(88). Adaptive resonance theory (ART) and communication through coherence (CTC) are two neurophysiological models which utilize inter-region brain signaling to explain information processing (89)(90). For example, the auditory cortex generates its own spontaneous oscillations in response to the exogenous oscillatory input, synchronizing with the environment (91).

Synchronized oscillations may engender a body-wide communication platform, connecting structures inside and outside the CNS. For example, GI tract microbes en-train “brain-like” oscillations, suggesting that the gut-brain axis may be driven by this modality (92). This is in line with another novel discovery, that oscillations drive the expression of microbial genes, replication, cell cycle progression, and antibiotic resistance (93). Furthermore, the GI tract microbiota oscillations are driven by metabolism, suggesting that the enteric nervous system (ENS) may function as an oscillatory sensor and direct this information to the CNS (94).

Auricular vagal nerve stimmulation (aVNS)

Electrical stimulation of auricular transcutaneous vagal nerve is a modality that can alter the functioning of the neural tissue for therapeutic benefits. Vagus nerve, links the brain directly with several visceral organs, providing a bridge to the GI tract.

Vagus nerve stimulation (VNS) is an invasive procedure which requires implantation of a pulse generator and electrodes close to the cervical vagus. As auricular nerve travels superficially and projects to the nucleus of the solitary tract (NTS) where the vagus nerve also reaches, this method could yield results comparable to those of VNS without being invasiveness (95)(96).

Aside from its central role of increasing norepinephrine, endorphins, and serotonin, VNS was shown to optimize the permeability of gut barrier, averting microbial translocation (97). This is significant as migration of commensal flora (or its components) outside the GI tract is a hallmark of SMI. For this reason, VNS should be used more often as an adjunct to psychiatric treatments.

Gamma band entrainment

Gamma oscillations on EEG have been involved in higher neural functions, including working

memory, attention, and likely consciousness (98). Gamma waves are generated by the GABA interneurons secreting SST, cells that are absent or disrupted in SCZ and MDD (99). Other studies have associated loss of gamma rhythm with aggressive behaviors in forensic psychiatric patients.

The question asked more and more frequently is can we induce gamma waves in a schizophrenic brain to lower psychotic symptoms? Most researchers and clinicians be-lieve that gamma band can be elicited by exposing the patient to this rhythm by various brain stimulatory techniques, including flickering light stimulation (FLS) or exposure to 40 Hz sounds (100).

Pulsed electromagnetic field therapy (PEMF)

Magnetotherapy can be static or pulsed and is produced by the electric current flowing through a coil, generating an electromagnetic field. Exposure to magnets is an old strategy which has been revisited as we learn more about biophysical treatments.

A recent large study, 8-weeks PEMF therapy in patients with treatment-resistant depression emphasized the beneficial role of this modality as an augmentation treatment to pharmacotherapy (101).

PEMF has been used in several conditions, including SMI, chronic pain, wound healing, postoperative pain, and depression (102)(103).

Red light therapy (RLT)

RLT has been used in various pathologies, including SCZ and metabolic disorders in which it was shown to be neuroprotective by improving mitochondrial function, mood, and cognition (104) (105). As higher number of mitochondria can be generated by fission, it has been suggested that fission-inducing modalities could benefit individuals with SCZ (106).

It is believed that RLT lowers inflammation and reduces oxidative stress. In obesity, RLT promotes lipolysis, lowers the adipocyte size, and enhances musculoskeletal system circulation thus, lowering insulin resistance (107).

More studies are needed to clarify the role of RLT in SCZ and dysmetabolism, especially on mitochondrial upregulation.

Other biophysical modalities

Several noninvasive stimulatory techniques, such as low-level laser therapy (LLLT), transcranial alternating current stimulation (tACS) or transcranial magnetic stimulation (TMS), may enhance gamma band synchronization, improving illness in-sight (108)(109)(110). Indeed, a recent study found that 40 Hz auditory steady-state response (ASSR), induced the brain to generate gamma waves, opening novel therapeutic avenues for anosognosia and negative symptoms of SCZ (111).

Aging downregulates SST and upregulates the non-pituitary growth hormone (npGH), lowering gamma band and inducing premature neuronal senescence (112). Since SST-generating GABAergic interneurons are depleted in SCZ, stimulation at 40 Hz may entrain this frequency in the cortex (113).

Conclusion

Both medicated and psychotropic naïve patients with SMI exhibit premature cellular senescence and a higher prevalence of metabolic syndrome, suggesting that both may be inherent components of psychopathology rather than separate entities.

At the cellular level, functional mitochondria likely delay senescence, suggesting that novel therapeutic strategies, addressing this pathology may repair dysfunctional biological barriers.

At the molecular level, aberrant AhR and mAhR activation by the translocated microbes and/or their components, triggers cellular senescence and TJ disruption, contributing to microorganismal migration from the gut lumen into the systemic circulation.

In summary, premature cellular senescence and reduced mitochondrial number may contribute to the pathogenesis of SMI by facilitating microbial translocation. Conversely, early detection of mitochondrial depletion and restoration of organelle number and function by various biophysical modalities may ameliorate neuropsychiatric pathology.

References

1. Yu M, Wang Q, Ma Y, Li L, Yu K, Zhang Z, Chen G, Li X, Xiao W, Xu P, Yang H. Aryl Hydrocarbon Receptor Activation Modulates Intestinal Epithelial Barrier Function by Maintaining Tight Junction Integrity. Int J Biol Sci. 2018 Jan 11;14(1):69-77. doi: 10.7150/ijbs.22259.
2. Nacarino-Palma A, Rico-Leo EM, Campisi J, Ramanathan A, González-Rico FJ, Rejano-Gordillo CM, Ordiales-Talavero A, Merino JM, Fernández-Salguero PM. Aryl hydrocarbon receptor blocks aging-induced senescence in the liver and fibroblast cells. Aging (Albany NY). 2022 May 26;14(10):4281-4304. doi: 10.18632/aging.204103.
3. Greene C, Hanley N, Campbell M. Blood-brain barrier associated tight junction disruption is a hallmark feature of major psychiatric disorders. Transl Psychiatry. 2020 Nov 2;10(1):373. doi: 10.1038/s41398-020-01054-3.
4. Sienkiewicz M, Sroka K, Binienda A, Jurk D, Fichna J. A new face of old cells: An overview about the role of senescence and telomeres in inflammatory bowel diseases. Ageing Res Rev. 2023 Nov;91:102083. doi: 10.1016/j.arr.2023.102083.
5. Papanastasiou E, Gaughran F, Smith S. Schizophrenia as segmental progeria. J R Soc Med. 2011 Nov;104(11):475-84. doi: 10.1258/jrsm.2011.110051. PMID: 22048679
6. Sung KY, Zhang B, Wang HE, Bai YM, Tsai SJ, Su TP, Chen TJ, Hou MC, Lu CL, Wang YP, Chen MH. Schizophrenia and risk of new-onset inflammatory bowel disease: a nationwide longitudinal study. Aliment Pharmacol Ther. 2022 May;55(9):1192-1201. doi: 10.1111/apt.16856. E
7. Wiley CD, Velarde MC, Lecot P, Liu S, Sarnoski EA, Freund A, Shirakawa K, Lim HW, Davis SS, Ramanathan A, Gerencser AA, Verdin E, Campisi J. Mitochondrial Dysfunction Induces Senescence with a Distinct Secretory Phenotype. Cell Metab. 2016 Feb 9;23(2):303-14. doi: 10.1016/j.cmet.2015.11.011.
8. Marx W, McGuinness AJ, Rocks T, Ruusunen A, Cleminson J, Walker AJ, Gomes-da-Costa S, Lane M, Sanches M, Diaz AP, Tseng PT, Lin PY, Berk M, Clarke G, O'Neil A, Jacka F, Stubbs B, Carvalho AF, Quevedo J, Soares JC, Fernandes BS. The kynurenine pathway in major depressive disorder, bipolar disorder, and schizophrenia: a meta-analysis of 101 studies. Mol Psychiatry. 2021 Aug;26(8):4158-4178. doi: 10.1038/s41380-020-00951-9
9. Tao, Kai ; Yuan, Yanling ; Xie, Qinglian ; Dong, Zaiquan. Relationship between human oral microbiome dysbiosis and neuropsychiatric

diseases: An updated overview Behavioural brain research, 2024-08, Vol.471, p.115111, Article 115111

10. Wood PL, Unfried G, Whitehead W, Phillipps A, Wood JA. Dysfunctional plasmalogen dynamics in the plasma and platelets of patients with schizophrenia. Schizophr Res. 2015 Feb;161(2-3):506-10. doi: 10.1016/j.schres.2014.11.032.
11. Nuss P, Tessier C, Ferreri F, De Hert M, Peuskens J, Trugnan G, Masliah J, Wolf C. Abnormal transbilayer distribution of phospholipids in red blood cell membranes in schizophrenia. Psychiatry Res. 2009 Sep 30;169(2):91-6. doi: 10.1016/j.psychres.2009.01.009. Epub 2009 Jul 30. PMID: 19646766.
12. Zhang Y, Yin J, Yan H, Yan L, Li Y, Zhang C, Li Y, Liu B, Lin J, Zhang L, Hu X, Song C. Correlations between omega-3 fatty acids and inflammatory/glial abnormalities: the involvement of the membrane and neurotransmitter dysfunction in schizophrenia. Front Cell Neurosci. 2023 Oct 23;17:1163764. doi: 10.3389/fncel.2023.1163764.
13. Bang S, Shin YH, Ma X, Park SM, Graham DB, Xavier RJ, Clardy J. A Cardiolipin from Muribaculum intestinale Induces Antigen-Specific Cytokine Responses. J Am Chem Soc. 2023 Nov 1;145(43):23422-23426. doi: 10.1021/jacs.3c09734.
14. Beaulieu JM, Zhang X, Rodriguiz RM, Sotnikova TD, Cools MJ, Wetsel WC, Gainetdinov RR, Caron MG. Role of GSK3 beta in behavioral abnormalities induced by serotonin deficiency. Proc Natl Acad Sci U S A. 2008 Jan 29;105(4):1333-8. doi: 10.1073/pnas.0711496105
15. Kimura AK, Kimura T. Phosphatidylserine biosynthesis pathways in lipid homeostasis: Toward resolution of the pending central issue for decades. FASEB J. 2021 Jan;35(1):e21177. doi: 10.1096/fj.202001802R.
16. Harayama T, Reizman H. Understanding the diversity of membrane lipid composition. Nat. Rev. Mol. Cell Biol. 2018; 19: 281-296.Nicolson, G.L. The Fluid—Mosaic Model of Membrane Structure: Still relevant to understanding the structure, function and dynamics of biological membranes after more than 40 years. Biochim. Biophys. Acta Biomembr. 2014; 1838: 1451–1466.
17. Nicolson, G.L.; Ferriera de Matos, G. A brief introduction to some aspects of the Fluid—Mosaic Model of cell membrane structure and its importance in Membrane Lipid Replacement. Membranes 2021; 11: 947.
18. Nicolson GL, Ferreira de Mattos G, Ash M, Settineri R, Escribá PV. Fundamentals of Membrane Lipid Replacement: A Natural Medicine Approach to Repairing Cellular Membranes and Reducing Fatigue, Pain, and Other Symptoms While Restoring Function in Chronic Illnesses and Aging. Membranes (Basel). 2021 Nov 29;11(12):944. doi: 10.3390/membranes11120944.
19. Jinling Wang, Xiufu Lin, Ningning Zhao, Guanping Dong, Wei Wu, Ke Huang, Junfen Fu. Effects of Mitochondrial Dynamics in the Pathophysiology of Obesity. Front. Biosci. (Landmark Ed) 2022, 27(3), 107. https://doi.org/10.31083/j.fbl2703107
20. Kim JA, Wei Y, Sowers JR. Role of mitochondrial dysfunction in insulin resistance. Circ Res. 2008 Feb 29;102(4):401-14. doi: 10.1161/CIRCRESAHA.107.165472.
21. Prasun P. Mitochondrial dysfunction in metabolic syndrome. Biochim Biophys Acta Mol Basis Dis. 2020 Oct 1;1866(10):165838. doi: 10.1016/j.bbadis.2020.165838.

22. Spinelli R, Baboota RK, Gogg S, Beguinot F, Blüher M, Nerstedt A, Smith U. Increased cell senescence in human metabolic disorders. J Clin Invest. 2023 Jun 15;133(12):e169922. doi: 10.1172/JCI169922. PMID: 37317964; PMCID: PMC10266774.
23. Zhang H, Zhou H, Shen X, Lin X, Zhang Y, Sun Y, Zhou Y, Zhang L, Zhang D. The role of cellular senescence in metabolic diseases and the potential for senotherapeutic interventions. Front Cell Dev Biol. 2023 Oct 6;11:1276707. doi: 10.3389/fcell.2023.1276707.
24. Palmer AK, Tchkonia T, Kirkland JL. Targeting cellular senescence in metabolic disease. Mol Metab. 2022 Dec;66:101601. doi: 10.1016/j.molmet.2022.101601.
25. Schafer MJ, Miller JD, LeBrasseur NK. Cellular senescence: Implications for metabolic disease. Mol Cell Endocrinol. 2017 Nov 5;455:93-102. doi: 10.1016/j.mce.2016.08.047.
26. Decker ST, Funai K. Mitochondrial membrane lipids in the regulation of bioenergetic flux. Cell Metab. 2024 Sep 3;36(9):1963-1978. doi: 10.1016/j.cmet.2024.07.024.
27. Oliveira MC, Yusupov M, Bogaerts A, Cordeiro RM. Lipid Oxidation: Role of Membrane Phase-Separated Domains. J Chem Inf Model. 2021 Jun 28;61(6):2857-2868. doi: 10.1021/acs.jcim.1c00104.
28. Zhuo C, Zhao F, Tian H, Chen J, Li Q, Yang L, Ping J, Li R, Wang L, Xu Y, Cai Z, Song X. Acid sphingomyelinase/ceramide system in schizophrenia: implications for therapeutic intervention as a potential novel target. Transl Psychiatry. 2022 Jun 23;12(1):260. doi: 10.1038/s41398-022-01999-7.
29. Adams JM 2nd, Pratipanawatr T, Berria R, Wang E, DeFronzo RA, Sullards MC, Mandarino LJ. Ceramide content is increased in skeletal muscle from obese insulin-resistant humans. Diabetes. 2004 Jan;53(1):25-31. doi: 10.2337/diabetes.53.1.25.
30. Fizíková I, Dragašek J, Račay P. Mitochondrial Dysfunction, Altered Mitochondrial Oxygen, and Energy Metabolism Associated with the Pathogenesis of Schizophrenia. Int J Mol Sci. 2023 Apr 28;24(9):7991. doi: 10.3390/ijms24097991.
31. Xia W, Veeragandham P, Cao Y, Xu Y, Rhyne TE, Qian J, Hung CW, Zhao P, Jones Y, Gao H, Liddle C, Yu RT, Downes M, Evans RM, Rydén M, Wabitsch M, Wang Z, Hakozaki H, Schöneberg J, Reilly SM, Huang J, Saltiel AR. Obesity causes mitochondrial fragmentation and dysfunction in white adipocytes due to RalA activation. Nat Metab. 2024 Feb;6(2):273-289. doi: 10.1038/s42255-024-00978-0.
32. Sentelle RD, Senkal CE, Jiang W, Ponnusamy S, Gencer S, Selvam SP, Ramshesh VK, Peterson YK, Lemasters JJ, Szulc ZM, Bielawski J, Ogretmen B. Ceramide targets autophagosomes to mitochondria and induces lethal mitophagy. Nat Chem Biol. 2012 Oct;8(10):831-8. doi: 10.1038/nchembio.1059. Erratum in: Nat Chem Biol. 2012 Dec;8(12):1008.
33. Mencarelli C, Martinez-Martinez P. Ceramide function in the brain: when a slight tilt is enough. Cell Mol Life Sci. 2013 Jan;70(2):181-203. doi: 10.1007/s00018-012-1038-x.
34. Schwarz E., Prabakaran S., Whitfield P., Major H., Leweke F. M., Keothe D., et al.. (2008). High troughput lipidomic profiling of schizophrenia and bipolar disorder brain tissue reveals alterations of free fatty acids, phosphatidylcolines and ceramides. J. Proteome Res. 7, 4266–4277. 10.1021/pr800188y
35. Bernal-Vega S, García-Juárez M, Camacho-Morales A. Contribution of ceramides metabo-

lism in psychiatric disorders. J. Neurochem.2023; 164: 708-724.
36. Zhu, F., Ju, Y., Wang, W. et al. Metagenome-wide association of gut microbiome features for schizophrenia. Nat Commun 11, 1612 (2020). https://doi.org/10.1038/s41467-020-15457-9
37. Johnson, E.L., Heaver, S.L., Waters, J.L. et al. Sphingolipids produced by gut bacteria enter host metabolic pathways, impacting ceramide levels. Nat Commun 11, 2471 (2020). https://doi.org/10.1038/s41467-020-16274-w
38. Schugar RC, Shih DM, Warrier M, Helsley RN, Burrows A, Ferguson D, Brown AL, Gromovsky AD, Heine M, Chatterjee A, Li L, Li XS, et al. The TMAO-Producing Enzyme Flavin-Containing Monooxygenase 3 Regulates Obesity and the Beiging of White Adipose Tissue. Cell Rep. 2017 Jun 20;19(12):2451-2461. doi: 10.1016/j.celrep.2017.05.077. Erratum in: Cell Rep. 2017 Jul 5;20(1):279. doi: 10.1016/j.celrep.2017.06.053.
39. Liu Y, Dai M. Trimethylamine N-Oxide Generated by the Gut Microbiota Is Associated with Vascular Inflammation: New Insights into Atherosclerosis. Mediators Inflamm. 2020 Feb 17;2020:4634172. doi: 10.1155/2020/4634172.
40. Nguyen TT, Kosciolek T, Daly RE, Vázquez-Baeza Y, Swafford A, Knight R, Jeste DV. Gut microbiome in Schizophrenia: Altered functional pathways related to immune modulation and atherosclerotic risk. Brain Behav Immun. 2021 Jan;91:245-256. doi: 10.1016/j.bbi.2020.10.003.
41. de la Monte SM. Triangulated mal-signaling in Alzheimer's disease: roles of neurotoxic ceramides, ER stress, and insulin resistance reviewed. J Alzheimers Dis. 2012;30 Suppl 2(02):S231-49. doi: 10.3233/JAD-2012-111727.
42. Voronova O, Zhuravkov S, Korotkova E, Artamonov A, Plotnikov E. Antioxidant Properties of New Phenothiazine Derivatives. Antioxidants (Basel). 2022 Jul 14;11(7):1371. doi: 10.3390/antiox11071371.
43. Egbujor MC, Tucci P, Buttari B, Nwobodo DC, Marini P, Saso L. Phenothiazines: Nrf2 activation and antioxidant effects. J Biochem Mol Toxicol. 2024 Mar;38(3):e23661. doi: 10.1002/jbt.23661.
44. Zhou X, Long T, Haas GL, Cai H, Yao JK. Reduced Levels and Disrupted Biosynthesis Pathways of Plasma Free Fatty Acids in First-Episode Antipsychotic-Naïve Schizophrenia Patients. Front Neurosci. 2020 Jul 29;14:784. doi: 10.3389/fnins.2020.00784.
45. Almsherqi ZA. Potential Role of Plasmalogens in the Modulation of Biomembrane Morphology. Front Cell Dev Biol. 2021 Jul 21;9:673917. doi: 10.3389/fcell.2021.673917.
46. Schooneveldt YL, Paul S, Calkin AC, Meikle PJ. Ether Lipids in Obesity: From Cells to Population Studies. Front Physiol. 2022 Mar 3;13:841278. doi: 10.3389/fphys.2022.841278.
47. Thevaranjan N, Puchta A, Schulz C, Naidoo A, Szamosi JC, Verschoor CP, Loukov D, Schenck LP, Jury J, Foley KP, Schertzer JD, et al. Age-Associated Microbial Dysbiosis Promotes Intestinal Permeability, Systemic Inflammation, and Macrophage Dysfunction. Cell Host Microbe. 2017 Apr 12;21(4):455-466.e4. doi: 10.1016/j.chom.2017.03.002. Erratum in: Cell Host Microbe. 2018 Apr 11;23(4):570. doi: 10.1016/j.chom.2018.03.006.
48. Johnson EL, Heaver SL, Waters JL, Kim BI, Bretin A, Goodman AL, Gewirtz AT, Worgall TS, Ley RE. Sphingolipids produced by gut bacteria enter host metabolic pathways impacting ceramide levels. Nat Commun. 2020 May

18;11(1):2471. doi: 10.1038/s41467-020-16274-w.
49. Miwa S, Kashyap S, Chini E, von Zglinicki T. Mitochondrial dysfunction in cell senescence and aging. J Clin Invest. 2022 Jul 1;132(13):e158447. doi: 10.1172/JCI158447.
50. Guan A, Wang S, Huang A, Qiu C, Li Y, Li X, Wang J, Wang Q, Deng B. The role of gamma oscillations in central nervous system diseases: Mechanism and treatment. Front Cell Neurosci. 2022 Jul 29;16:962957. doi: 10.3389/fncel.2022.962957
51. Miller CJ, Nichol RC, Batuski DJ. Acoustic oscillations in the early universe and today. Science. 2001 Jun 22;292(5525):2302-3. doi: 10.1126/science.1060440. Epub 2001 May 24. PMID: 11375481.
52. Calamassi D, Lucicesare A, Pomponi GP, Bambi S. Music tuned to 432 Hz versus music tuned to 440 Hz for improving sleep in patients with spinal cord injuries: a double-blind cross-over pilot study. Acta Biomed. 2020 Nov 30;91(12-S):e2020008. doi: 10.23750/abm.v91i12-S.10755.
53. Hohneck A, Rodríguez ÁM, Weingärtner S, Merx K, Sarodnick F, von Gagern F, Mavratzas A, Burkholder I, Schumacher G, Hofmann WK, Hofheinz RD. Differential effects of sound interventions tuned to 432 Hz or 443 Hz on cardiovascular parameters in cancer patients: a randomized cross-over trial. BMC Complement Med Ther. 2025 Jan 22;25(1):18. doi: 10.1186/s12906-025-04758-5.
54. Nani A, Manuello J, Mancuso L, Liloia D, Costa T, Cauda F. The Neural Correlates of Consciousness and Attention: Two Sister Processes of the Brain. Front Neurosci. 2019 Oct 31;13:1169. doi: 10.3389/fnins.2019.01169.
55. Arnulfo G, Wang SH, Myrov V, Toselli B, Hirvonen J, Fato MM, Nobili L, Cardinale F, Rubino A, Zhigalov A, Palva S, Palva JM. Long-range phase synchronization of high-frequency oscillations in human cortex. Nat Commun. 2020 Oct 23;11(1):5363. doi: 10.1038/s41467-020-18975-8.
56. Wallmark Z, Deblieck C, Iacoboni M. Neurophysiological Effects of Trait Empathy in Music Listening. Front Behav Neurosci. 2018 Apr 6;12:66. doi: 10.3389/fnbeh.2018.00066.
57. Chawla G, Azharuddin M, Ahmad I, Hussain ME. Effect of Whole-body Vibration on Depression, Anxiety, Stress, and Quality of Life in College Students: A Randomized Controlled Trial. Oman Med J. 2022 Jul 31;37(4):e408. doi: 10.5001/omj.2022.72
58. Biel AL, Minarik T, Sauseng P. EEG cross-frequency phase synchronization as an index of memory matching in visual search. Neuroimage. 2021 Jul 15;235:117971. doi: 10.1016/j.neuroimage.2021.117971
59. Chao JY, Gutiérrez R, Legatt AD, Yozawitz EG, Lo Y, Adams DC, Delphin ES, Shinnar S, Purdon PL. Decreased Electroencephalographic Alpha Power During Anesthesia Induction Is Associated With EEG Discontinuity in Human Infants. Anesth Analg. 2022 Dec 1;135(6):1207-1216. doi: 10.1213/ANE.0000000000005864.
60. Melloni L, Molina C, Pena M, Torres D, Singer W, Rodriguez E. Synchronization of neural activity across cortical areas correlates with conscious perception. J Neurosci. 2007 Mar 14;27(11):2858-65. doi: 10.1523/JNEUROSCI.4623-06.2007.
61. Guan A, Wang S, Huang A, Qiu C, Li Y, Li X, Wang J, Wang Q, Deng B. The role of gamma oscillations in central nervous system diseases: Mechanism and treatment. Front Cell Neurosci.

2022 Jul 29;16:962957. doi: 10.3389/fncel.2022.962957.
62. Buzsáki G, Schomburg EW. What does gamma coherence tell us about inter-regional neural communication? Nat Neurosci. 2015 Apr;18 (4):484-9. doi: 10.1038/nn.3952. Epub 2015 Feb 23. PMID: 25706474; PMCID: PMC4803441.
63. Angioletti L, Balconi M. EEG brain oscillations are modulated by interoception in response to a synchronized motor vs. cognitive task. Front Neuroanat. 2022 Sep 23;16:991522. doi: 10.3389/fnana.2022.991522.
64. Liberati G, Klöcker A, Algoet M, Mulders D, Maia Safronova M, Ferrao Santos S, Ribeiro Vaz JG, Raftopoulos C, Mouraux A. Gamma-Band Oscillations Preferential for Nociception can be Recorded in the Human Insula. Cereb Cortex. 2018 Oct 1;28(10):3650-3664. doi: 10.1093/cercor/bhx237.
65. Lehrer DS, Lorenz J. Anosognosia in schizophrenia: hidden in plain sight. Innov Clin Neurosci. 2014 May;11(5-6):10-7. PMID: 25152841; PMCID: PMC4140620.
66. Mahadevan V, Mitra A, Zhang Y, Yuan X, Peltekian A, Chittajallu R, Esnault C, Maric D, Rhodes C, Pelkey KA, Dale R, Petros TJ, McBain CJ. NMDARs Drive the Expression of Neuropsychiatric Disorder Risk Genes Within GABAergic Interneuron Subtypes in the Juvenile Brain. Front Mol Neurosci. 2021 Sep 14;14:712609. doi: 10.3389/fnmol.2021.712609.
67. Traikapi A, Konstantinou N. Gamma Oscillations in Alzheimer's Disease and Their Potential Therapeutic Role. Front Syst Neurosci. 2021 Dec 13;15:782399. doi: 10.3389/fnsys.2021.782399. PMID: 34966263; PMCID: PMC8710538.
68. Guerra A, Asci F, D'Onofrio V, Sveva V, Bologna M, Fabbrini G, Berardelli A, Suppa A. Enhancing Gamma Oscillations Restores Primary Motor Cortex Plasticity in Parkinson's Disease. J Neurosci. 2020 Jun 10;40(24):4788-4796. doi: 10.1523/JNEUROSCI.0357-20.2020.
69. McNally JM, McCarley RW. Gamma band oscillations: a key to understanding schizophrenia symptoms and neural circuit abnormalities. Curr Opin Psychiatry. 2016 May;29(3):202-10. doi: 10.1097/YCO.0000000000000244.
70. Pillmann F, Rohde A, Ullrich S, Draba S, Sannemüller U, Marneros A. Violence, criminal behavior, and the EEG: significance of left hemispheric focal abnormalities. J Neuropsychiatry Clin Neurosci. 1999 Fall;11(4):454-7. doi: 10.1176/jnp.11.4.454. PMID: 10570757.
71. De Carolis A, Cipollini V, Corigliano V, Comparelli A, Sepe-Monti M, Orzi F, Ferracuti S, Giubilei F. Anosognosia in people with cognitive impairment: association with cognitive deficits and behavioral disturbances. Dement Geriatr Cogn Dis Extra. 2015 Feb 17;5(1):42-50. doi: 10.1159/000367987. PMID: 25852731
72. Joseph B, Narayanaswamy JC, Venkatasubramanian G. Insight in schizophrenia: relationship to positive, negative and neurocognitive dimensions. Indian J Psychol Med. 2015 Jan-Mar;37 (1):5-11. doi: 10.4103/0253-7176.150797.
73. Murray AJ, Rogers JC, Katshu MZUH, Liddle PF, Upthegrove R. Oxidative Stress and the Pathophysiology and Symptom Profile of Schizophrenia Spectrum Disorders. Front Psychiatry. 2021 Jul 22;12:703452. doi: 10.3389/fpsyt.2021.703452.
74. Wood PL, Unfried G, Whitehead W, Phillipps A, Wood JA. Dysfunctional plasmalogen dynamics in the plasma and platelets of patients with schizophrenia. Schizophr Res. 2015

Feb;161(2-3):506-10. doi: 10.1016/j.schres.2014.11.032.
75. Goodenowe DB, Haroon J, Kling MA, Zielinski M, Mahdavi K, Habelhah B, Shtilkind L, Jordan S. Targeted Plasmalogen Supplementation: Effects on Blood Plasmalogens, Oxidative Stress Biomarkers, Cognition, and Mobility in Cognitively Impaired Persons. Front Cell Dev Biol. 2022 Jul 6;10:864842. doi: 10.3389/fcell.2022.864842.
76. Schmitt CA, Tchkonia T, Niedernhofer LJ, Robbins PD, Kirkland JL, Lee S. COVID-19 and cellular senescence. Nat Rev Immunol. 2023 Apr;23(4):251-263. doi: 10.1038/s41577-022-00785-2. Epub 2022 Oct 5. PMID: 36198912; PMCID: PMC9533263.
77. Ursini F, Maiorino M. Lipid peroxidation and ferroptosis: The role of GSH and GPx4. Free Radic Biol Med. 2020 May 20;152:175-185. doi: 10.1016/j.freeradbiomed.2020.02.027. Epub 2020 Mar 9. PMID: 32165281.
78. Zhivaki D, Kagan JC. Innate immune detection of lipid oxidation as a threat assessment strategy. Nat Rev Immunol. 2022 May;22(5):322-330. doi: 10.1038/s41577-021-00618-8. Epub 2021 Sep 21.
79. Wen Q, Liu J, Kang R, Zhou B, Tang D. The release and activity of HMGB1 in ferroptosis. Biochem Biophys Res Commun. 2019 Mar 5;510(2):278-283. doi: 10.1016/j.bbrc.2019.01.090.
80. Sage C. The implications of non-linear biological oscillations on human electrophysiology for electrohypersensitivity (EHS) and multiple chemical sensitivity (MCS). Rev Environ Health. 2015;30(4):293-303. doi: 10.1515/reveh-2015-0007. PMID: 26368042
81. Cheong R, Levchenko A. Oscillatory signaling processes: the how, the why and the where. Curr Opin Genet Dev. 2010 Dec;20(6):665-9. doi: 10.1016/j.gde.2010.08.007
82. Bier M, Bakker BM, Westerhoff HV. How yeast cells synchronize their glycolytic oscillations: a perturbation analytic treatment. Biophys J. 2000 Mar;78(3):1087-93. doi: 10.1016/S0006-3495(00)76667-7. PMID: 10692299; PMCID: PMC1300712.
83. Martinez-Corral R, Liu J, Prindle A, Süel GM, Garcia-Ojalvo J. Metabolic basis of brain-like electrical signalling in bacterial communities. Philos Trans R Soc Lond B Biol Sci. 2019 Jun 10;374(1774):20180382. doi: 10.1098/rstb.2018.0382
84. Vislova A, Sosa OA, Eppley JM, Romano AE, DeLong EF. Diel Oscillation of Microbial Gene Transcripts Declines With Depth in Oligotrophic Ocean Waters. Front Microbiol. 2019 Sep 24;10:2191. doi: 10.3389/fmicb.2019.02191.
85. Başar E. Brain oscillations in neuropsychiatric disease. Dialogues Clin Neurosci. 2013 Sep;15(3):291-300. doi: 10.31887/DCNS.2013.15.3/ebasar.
86. Chan D, Suk HJ, Jackson B, Milman NP, Stark D, Beach SD, Tsai LH. Induction of specific brain oscillations may restore neural circuits and be used for the treatment of Alzheimer's disease. J Intern Med. 2021 Nov;290(5):993-1009. doi: 10.1111/joim.13329.
87. Stiefel KM, Ermentrout GB. Neurons as oscillators. J Neurophysiol. 2016 Dec 1;116(6):2950-2960. doi: 10.1152/jn.00525.2015.
88. Singer W. Neuronal oscillations: unavoidable and useful? Eur J Neurosci. 2018 Oct;48(7):2389-2398. doi: 10.1111/ejn.13796.
89. González J, Cavelli M, Mondino A, Rubido N, Bl Tort A, Torterolo P. Communication Through Coherence by Means of Cross-

frequency Coupling. Neuroscience. 2020 Nov 21;449:157-164. doi: 10.1016/j.neuroscience.2020.09.019.
90. Grossberg S. Adaptive Resonance Theory: how a brain learns to consciously attend, learn, and recognize a changing world. Neural Netw. 2013 Jan;37:1-47. doi: 10.1016/j.neunet.2012.09.017.
91. Gourévitch B, Martin C, Postal O, Eggermont JJ. Oscillations in the auditory system and their possible role. Neurosci Biobehav Rev. 2020 Jun;113:507-528. doi: 10.1016/j.neubiorev.2020.03.030.
92. Martinez-Corral R, Liu J, Prindle A, Süel GM, Garcia-Ojalvo J. Metabolic basis of brain-like electrical signalling in bacterial communities. Philos Trans R Soc Lond B Biol Sci. 2019 Jun 10;374(1774):20180382. doi: 10.1098/rstb.2018.0382
93. Vislova A, Sosa OA, Eppley JM, Romano AE, DeLong EF. Diel Oscillation of Microbial Gene Transcripts Declines With Depth in Oligotrophic Ocean Waters. Front Microbiol. 2019 Sep 24;10:2191. doi: 10.3389/fmicb.2019.02191.
94. Spencer NJ, Hu H. Enteric nervous system: sensory transduction, neural circuits and gastrointestinal motility. Nat Rev Gastroenterol Hepatol. 2020 Jun;17(6):338-351. doi: 10.1038/s41575-020-0271-2.
95. Butt MF, Albusoda A, Farmer AD, Aziz Q. The anatomical basis for transcutaneous auricular vagus nerve stimulation. J Anat. 2020 Apr;236(4):588-611. doi: 10.1111/joa.13122.
96. Howland RH. Vagus Nerve Stimulation. Curr Behav Neurosci Rep. 2014 Jun;1(2):64-73. doi: 10.1007/s40473-014-0010-5.
97. Mogilevski T, Rosella S, Aziz Q, Gibson PR. Transcutaneous vagal nerve stimulation protects against stress-induced intestinal barrier dysfunction in healthy adults. Neurogastroenterol Motil. 2022 Oct;34(10):e14382. doi: 10.1111/nmo.14382.
98. Panagiotaropoulos TI, Deco G, Kapoor V, Logothetis NK. Neuronal discharges and gamma oscillations explicitly reflect visual consciousness in the lateral prefrontal cortex. Neuron. 2012 Jun 7;74(5):924-35. doi: 10.1016/j.neuron.2012.04.013. Erratum in: Neuron. 2012 Jun 21;74(6):1139. PMID: 22681695.
99. Dienel SJ, Fish KN, Lewis DA. The Nature of Prefrontal Cortical GABA Neuron Alterations in Schizophrenia: Markedly Lower Somatostatin and Parvalbumin Gene Expression Without Missing Neurons. Am J Psychiatry. 2023 Jul 1;180(7):495-507. doi: 10.1176/appi.ajp.20220676
100. Blanco-Duque C, Chan D, Kahn MC, Murdock MH, Tsai LH. Audiovisual gamma stimulation for the treatment of neurodegeneration. J Intern Med. 2024 Feb;295(2):146-170. doi: 10.1111/joim.13755.
101. Larsen ER, Licht RW, Nielsen RE, Lolk A, Borck B, Sørensen C, Christensen EM, Bizik G, Ravn J, Martiny K, Vinberg M, Jankuviené O, Jørgensen PB, Videbech P, Bech P. Transcranial pulsed electromagnetic fields for treatment-resistant depression: A multicenter 8-week single-arm cohort study. Eur Psychiatry. 2020 Feb 18;63(1):e18. doi: 10.1192/j.eurpsy.2020.3. PMID: 32093804; PMCID: PMC7315871.
102. Hattapoğlu E, Batmaz İ, Dilek B, Karakoç M, Em S, Çevik R. Efficiency of pulsed electromagnetic fields on pain, disability, anxiety, depression, and quality of life in patients with cervical disc herniation: a randomized controlled

study. Turk J Med Sci. 2019 Aug 8;49(4):1095-1101. doi: 10.3906/sag-1901-65.

103. Cole JC, Green Bernacki C, Helmer A, Pininti N, O'reardon JP. Efficacy of Transcranial Magnetic Stimulation (TMS) in the Treatment of Schizophrenia: A Review of the Literature to Date. Innov Clin Neurosci. 2015 Jul-Aug;12(7-8):12-9. PMID: 26351619; PMCID: PMC4558786.

104. Qiu K, Zou W, Fang H, Hao M, Mehta K, Tian Z, Guan JL, Zhang K, Huang T, Diao J. Light-activated mitochondrial fission through optogenetic control of mitochondria-lysosome contacts. Nat Commun. 2022 Jul 25;13(1):4303. doi: 10.1038/s41467-022-31970-5. PMID: 35879298; PMCID: PMC9314359.

105. Li JY, Zhang K, Xu D, Zhou WT, Fang WQ, Wan YY, Yan DD, Guo MY, Tao JX, Zhou WC, Yang F, Jiang LP, Han XJ. Mitochondrial Fission Is Required for Blue Light-Induced Apoptosis and Mitophagy in Retinal Neuronal R28 Cells. Front Mol Neurosci. 2018 Nov 27;11:432. doi: 10.3389/fnmol.2018.00432. PMID: 30538621; PMCID: PMC6277708.

106. Roopram SM, Burger AM, van Dijk DA, Enterman J, Haffmans J. A pilot study of bright light therapy in schizophrenia. Psychiatry Res. 2016 Nov 30;245:317-320. doi: 10.1016/j.psychres.2016.07.034. Epub 2016 Jul 19. PMID: 27568303.

107. Modena DAO, Soares CD, Martignago CCS, Almeida S, Cazzo E, Chaim EA. Effects of LED photobiomodulation therapy on the subcutaneous fatty tissue of obese individuals - histological and immunohistochemical analysis. J Cosmet Laser Ther. 2022 Nov 17;24(6-8):84-90. doi: 10.1080/14764172.2022.2109677. Epub 2022 Sep 8. PMID: 36074934.

108. Kheradmand A, Tabeie F, Seif P, Rezaei O, Yasamy MT. Effect of low-level laser therapy (LLLT) on cognitive impairment among patients with chronic schizophrenia: a double-blind randomized placebo-controlled clinical trial. Lasers Med Sci. 2022 Aug;37(6):2717-2725. doi: 10.1007/s10103-022-03545-9.

109. Dougall N, Maayan N, Soares-Weiser K, McDermott LM, McIntosh A. Transcranial magnetic stimulation (TMS) for schizophrenia. Cochrane Database Syst Rev. 2015 Aug 20;2015(8):CD006081. doi: 10.1002/14651858.CD006081.pub2

110. Agarwal SM, Shivakumar V, Bose A, Subramaniam A, Nawani H, Chhabra H, Kalmady SV, Narayanaswamy JC, Venkatasubramanian G. Transcranial direct current stimulation in schizophrenia. Clin Psychopharmacol Neurosci. 2013 Dec;11(3):118-25. doi: 10.9758/cpn.2013.11.3.118.

111. Grent-'t-Jong T, Brickwedde M, Metzner C, Uhlhaas PJ. 40-Hz Auditory Steady-State Responses in Schizophrenia: Toward a Mechanistic Biomarker for Circuit Dysfunctions and Early Detection and Diagnosis. Biol Psychiatry. 2023 Oct 1;94(7):550-560. doi: 10.1016/j.biopsych.2023.03.026. Epub 2023 Apr 21. PMID: 37086914.

112. Veit J, Hakim R, Jadi MP, Sejnowski TJ, Adesnik H. Cortical gamma band synchronization through somatostatin interneurons. Nat Neurosci. 2017 Jul;20(7):951-959. doi: 10.1038/nn.4562.

113. Choi KM, Im CH, Yang C, Lee HS, Kim S, Lee SH. Influence of inter-stimulus interval on 40-Hz auditory steady-state response in patients with schizophrenia. Schizophrenia (Heidelb). 2023 Jul 27;9(1):46. doi: 10.1038/s41537-023-00377-6.