American Journal of Neurology Research

Research Article

Local Hormones and Neurolipidomics in schizophrenia

Adonis Sfera[1]*, Sabine Hazan[2], Peter G Bota[3], Jonathan J Anton[4] and Garth L Nicolson[5]

[1]*Patton State Hospital, Loma Linda University, University of California at Riverside.*
[2]*Progenabiome.*
[3]*California university of Science and Medicine.*
[4]*California Baptist University, department of biology.*
[5]*Institute for Molecular Medicine in Huntington Beach, California.*

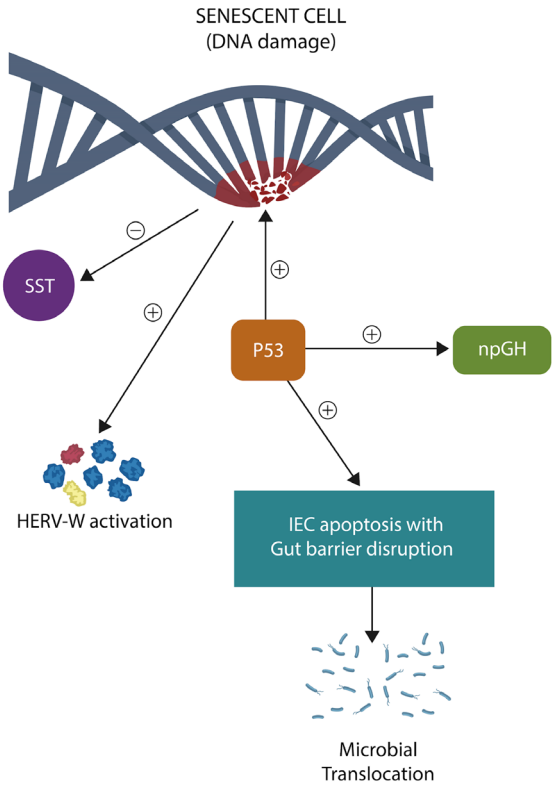
Corresponding Author Information

Adonis Sfera, MD
Patton State Hospital, Loma Linda University, University of California at Riverside, Email: dr.sfera@gmail.com.

Received: October 20, 2023; **Accepted:** November 22, 2023; **Published:** November 30, 2023

Citation: Adonis Sfera, Sabine Hazan, Peter G Bota, Jonathan J Anton, Garth L Nicolson. Local Hormones and Neurolipidomics in schizophrenia . American J Neurol Res. 2023; 2(1):1-4.

GRAPHICAL ABSTRACT



- SCZ is associated with genomic damage and premature cellular senescence, affecting both somatic and postmitotic cells.
- Premature neuronal senescence contributes to gray matter loss, involving the neurites and synapses of inhibitory interneurons.
- Loss of somatostatin-expressing GABA interneurons may drive the gray matter loss in schizophrenia.
- Deficient somatostatin upregulates non-pituitary growth hormone, inducing DNA damage and p53-mediated neuronal senescence.

ABSTRACT

Chronic mental illnesses, including schizophrenia, have been associated with premature brain aging manifested on neuroimaging as gray matter loss. This has been associated with impaired insight (anosognosia) and suboptimal treatment outcome. Novel strategies for addressing premature brain aging are urgently needed and somatostatin up regulation may avert gray matter loss. Recent studies, involving non-pituitary growth hormone and p53, have offered early glimpses into the molecular underpinnings of cellular senescence in SCZ. Moreover, age-downregulated somatostatin and activation of Human Endogenous Retroviruses likely drive the negative and cognitive symptoms of SCZ.

In this perspective article, we discuss the following: 1) neuropsychiatric implications of premature brain aging, 2) potential therapies for restoring the homeostasis of somatostatin and non-pituitary growth hormone.

Keywords

Schizophrenia, Neurodevelopmental diseases.

Introduction

Schizophrenia (SCZ) and schizophrenia-like disorders (SLDs) are neurodevelopmental diseases with an average global prevalence of 1%. Antipsychotic drugs, extremely effective for acute psychosis, are much less helpful in the chronic phase, marked primarily by negative and cognitive symptoms [1]. In addition, SCZ outcome studies show that a dismal 13.5% of patients achieve sustained recovery at any time after the first psychotic episode, suggesting that the currently available antipsychotic drugs do not target the central pathology of this illness [2-4].

SCZ neuroimaging studies have consistently reported progressive brain shrinkage, while microscopy found gray matter loss at the expense of dendritic spines and synapses. These findings comprise the proof of concept that the available treatment strategies do not address gray matter loss [5]. Indeed, several studies have found accelerated brain atrophy with some antipsychotic drugs, indicating that maintenance treatment may require different approaches than acute episodes.

Novel studies have emphasized the role of p53, somatostatin (SST), and non-pituitary growth hormone (npGH) in SCZ-associated neuronal senescence [6,7]. In addition, p53 and senescence can activate human endogenous retroviruses (HERVs), ancestral pathogens, residing in the human genome, previously linked to SCZ with negative symptoms [8].

The role of hormones in the etiology of neuropsychiatric disorders is well-established as these conditions often become manifest at puberty or postpartum, life milestones marked by significant stress and "hormonal storms". In addition, endocrinopathies, including Cushing's syndrome, hypopituitarism, and primary hyperparathyroidism (PHPT) have been associated with SCZ, emphasizing the intertwinement of endocrinology and neuropathology [9-12]. Moreover, gut microbes, synthesize several hormones, including SST and npGH, likely implicating the microbiome in SCZ [13-17]. Indeed, commensal flora can synthesize many SCZ-relevant neurotransmitters, including dopamine (DA), serotonin (5HT), norepinephrine (NE), acetylcholine (ACh), melatonin, somatostatin (SST), and oxytocin (OXT), further linking mental illness to various endocrinopathies [18-21].

Numerous studies have connected SCZ with the premature cellular (including neuronal) senescence, emphasizing that DNA damage or defective genomic repair is the likely cause of this pathology [22-24]. It is well-established that SCZ patients live on average 15 to 20 years shorter than their healthy counterparts and develop age-related diseases while still young, highlighting the role of premature aging in this disorder. Indeed, some scholars refer to SCZ as "segmental" progeria, to emphasize this correlation [25].

Gamma oscillations (30-100 Hz) on electroencephalogram (EEG) are altered in SCZ patients, probably reflecting the loss of SST-expressing gamma-aminobutyric acid (GABA) neurons, known for promoting network oscillations [26-29]. Interestingly, both GABA and SST are synthesized by the gut microbes, which are also known for entraining "brain-like" oscillations, linking the microbiome to the EEG waves [30-35]. This is not surprising as in bacteria, oscillations control gene expression, division, cell cycle progression, and antibiotic resistance [35-37].

Do gut microbes communicate with the host via synchronized oscillations? Many believe that certain frequencies may be ideal for low-energy encoding and transmitting information to distant body tissues, suggesting that this platform may be functioning in parallel with the synaptic and exocrine/paracrine neurotransmission [38,39]. Indeed, synchronized oscillations were documented in many tissues, including the endocrine glands, which are known for releasing hormones in regular spurs [40-

43]. At the molecular level, the DNA double helix as well as the p53 genomic repair system, generate spontaneous oscillations, suggesting that macromolecules may engender their own signaling platform - a global molecular network [44]. For example, genome oscillations and gamma waves may generate a quantum code for almost instant information transfer to distant tissues and cells [45,46]. Along this line, desynchronization or uncoupling of a brain region from other areas was demonstrated in general anesthesia or ketamine-induced dissociation states, indicating that awareness requires network synchronization [47,48]. Conversely, noninvasive stimulatory techniques, such as photobiomodulation or transcranial magnetic stimulation (TMS), may avert gray matter loss by optimizing synchronization [49,50]. Indeed, a 40 Hz auditory steady-state response (ASSR) is believed to be an insight biomarker of SCZ, suggesting novel therapeutic avenues for addressing anosognosia and the negative symptoms [51-54]. In addition, SST has been implicated not only in central nervous system (CNS) synchronization but also in brain plasticity, suggests that loss of this hormone may account for the negative and cognitive symptoms of SCZ [55,56]. Indeed, aging downregulates SST and upregulates npGH, linking local hormones to premature neuronal senescence and decreased gamma band [57-59]. Since SST-generating GABAergic interneurons are depleted in SCZ, desynchronization may explain the information processing difficulties [60].

In the GI tract, accumulation of npGH induces intestinal epithelial cells (IECs) senescence via p53 and insulin growth factor-1 (IGF-1), enabling microbes and/or their molecule to migrate into the systemic circulation, eventually reaching the brain [61,6]. Indeed, microbial translocation may be averted by novel approaches, such as lipid replacement therapy (LRT) and or 3-phosphoinositide-dependent protein kinase-1 (PDK1) inhibitors [62].

In this article, we take a closer look at the role of SST and npGH in neuronal senescence, microbial translocation, gray matter loss, and HERV-W activation. We also discuss some potential strategies for restoring the homeostasis of npGH and somatostatin.

Natural Progression of Schizophrenia

The gray matter loss in SCZ, demonstrated in both antipsychotic naïve patients and in those treated with these drugs, suggests that this disorder progresses despite the available therapeutics [63,64]. This is in line with the discouraging SCZ outcome studies, and the continuous need for long-term psychiatric hospitals [65,5].

SCZ starts with a premorbid phase with very few or no symptoms, followed by a prodrome with behavioral changes, but without overt psychosis, which gradually transitions into the psychotic phase marked by acute positive symptoms, multiple hospitalizations, and medication nonadherence. The last phase, beginning in the late 40s or early 50s, is characterized by negative and cognitive symptoms, significant disability and poor response to medications [66] (Figure 1).

Antipsychotics: Electron Donors or Receivers?

Several studies have found that psychotropic drugs which give away electrons do not deplete the CNS gray matter, while electron accepting therapeutics do, suggesting that biophysical properties of these drugs may be more important for the treatment outcome than their receptor affinity or agonist/antagonist status [67,68]. This quantum conceptualization of antipsychotics opens a new research vista - the development of electron donor drugs. For example, dopamine agonists and dopamine (DA) itself are electron donors, while most, but not all, antipsychotic drugs are electron acceptors, suggesting that partial DA antagonists may be preferable for SCZ maintenance treatment [69]. This is significant as electron donors, DA and DA agonists were shown to promote gamma oscillations, while antagonists had the opposite effect [70]. This raises the question of the "anionic brain": do externalized anionic phospholipids such as phosphatidylserine (PS), a marker of cellular senescence, contribute to the loss of gray matter? It has been established that PS on the cytoplasmic side of cell membranes binds several kinases, containing the pleckstrin homology (PH) domain. This molecular leitmotif regulates cell membrane-recruited kinases, including PDK1, implicated in SCZ [71]. Since PS is externalized in senescent cells, bringing about the "anionic brain", downstream PDK1-mediated phosphorylation is disrupted, likely disinhibiting glycogen synthase kinase 3 beta (GSK3β), a SCZ-associated enzyme (see below in Natural and synthetic PDK1 inhibitors). For this reason, LRT may stabilize the function of cell membranes, restoring the homeostasis of these kinases.

We construe, that SST downregulation and the subsequent surge in npGH contribute to premature neuronal senescence and the negative and cognitive symptoms of SCZ. This model is supported by the postmortem mRNA studies, demonstrating low SST and NMDA in patients with negative symptoms [72]. In addition, preclinical studies, have shown that knockdown of parvalbumin (PV) or SST neurons, resembles negative symptoms of SCZ [73].

Premature Senescence and Somatostatin Loss

The most consistent neuroimaging findings in SCZ, gray matter loss and enlargement of lateral ventricles, indicate that reversing this pathology could ameliorate the negative and cognitive symptoms, likely improving the outcome [74-76].

For example, in SCZ, reduced gamma oscillations due to the loss of gray matter volume may be a measurable marker of negative symptoms. At the molecular level, npGH-mediated DNA damage and p53-induced cellular senescence likely drive the gray matter loss [22]. In this regard, recent studies have shown that the interplay between npGH and p53 contributes to the accumulation of damaged DNA and premature senescence (77). Excessive genomic damage downregulates SST, increasing npGH, which in return, promotes brain aging and senescence-mediated pathology [72,78]. Moreover, p53 upregulation activates HERVs, viral fossils previously connected to SCZ [79].

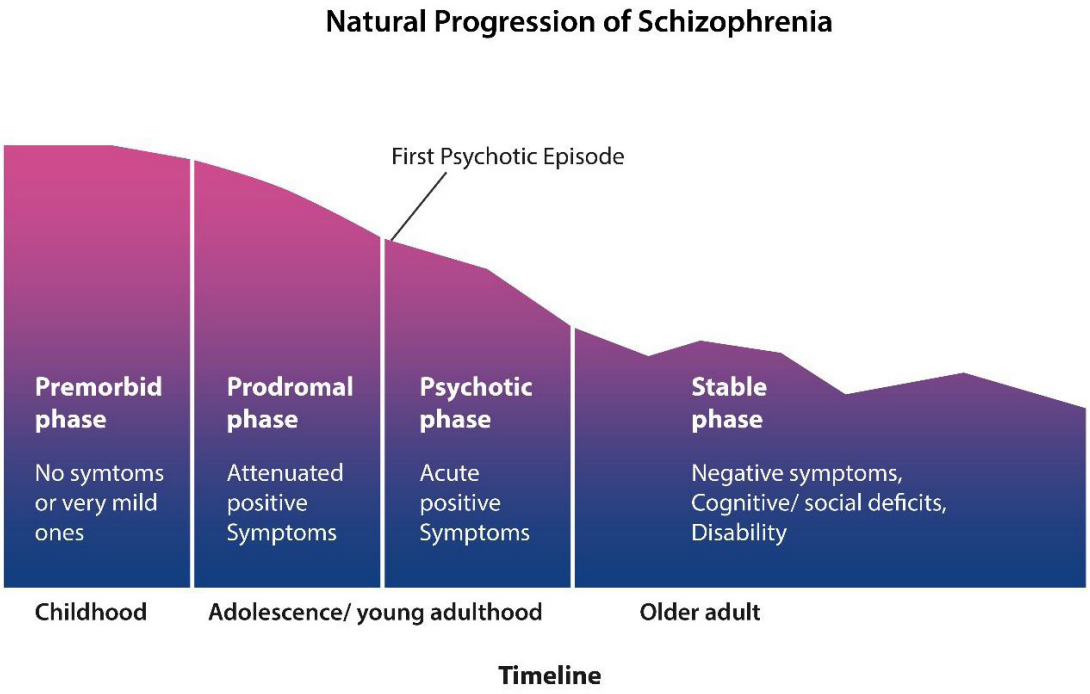


Figure 1: SCZ is believed to be a neurodevelopmental disorder, which starts "in utero". There are usually no symptoms, or very few symptoms in the initial, premorbid phase. The following prodromal phase is marked by behavioral changes but no overt psychosis. The subsequent psychotic phase is characterized by acute positive symptoms, multiple hospitalizations, and medication nonadherence. The last SCZ phase, beginning around the age of 50, is characterized by negative and cognitive symptoms, significant disability, and poor response to medications. As patients get older, cognitive disorders usually begin during this phase.

Under physiological circumstances, SST augments NMDA, while in SCZ, NMDA is hypofunctional, probably reflecting neuronal senescence and loss of this hormone [80]. Therefore, SST augmentation may comprise a strategy for developing etiopathogenetic treatments for the negative and cognitive symptoms of SCZ [72]. Indeed, In neuronal membranes, SST enhances protein kinase B (also called AKT), inhibiting GSK3β, an enzyme suppressed by lithium and several antipsychotic drugs. In addition, SST, activates phosphoinositide 3-kinases (PI3K)/AKT pathway, further suppressing GSK3β [81]. Moreover, AKT upregulation can be accomplished by lowering the neuronal membrane ceramide, highlighting the key role of membrane lipidome in SCZ (see below in Lipid rafts: hubs of cellular senescence).

In IECs, the complex interaction between IGF-1, p53, and npGH, induces premature cellular senescence, disrupting the gut barrier. This facilitates microbial translocation from the GI tract into the host circulation, ultimately reaching the CNS. For example, upon brain entry, microbial LPS was shown to induce neuroinflammation and premature aging, a pathology observed in AD. Indeed, gut microbiota LPS was found postmortem in the brains of AD patients, confirming translocation [82]. Others found, specific microbiota and immunoglobulins in patients with SCZ with negative symptoms, further linking this pathology to microbial migration outside the GI tract [83]. Interestingly, gut microbes, *Bacillus subtilis and Escherichia coli* can synthesize SST, demonstrating a possible feedback mechanism of counteracting excessive npGH [84,85].

It is believed that gray matter loss in SCZ occurs at the expense of neurites and synapses of the inhibitory parvalbumin (PV)-expressing GABAergic interneurons, a subgroup of which release SST. It is noteworthy that neurons secreting vasoactive intestinal polypeptide (VIP) inhibit SST and GABA, disinhibiting the pyramidal cells [86,87] (Figure 3). For this reason, VIP inhibitors should be assessed for negative and cognitive symptoms of SCZ.

During the development and childhood, inhibitory GABAergic interneurons are underdeveloped and appear gradually during adolescence and early adulthood. In contrast, the number of excitatory synapses decreases during this time as the CNS undergoes adolescence-mediated recalibration [5,88]. The loss of gray matter volume and gamma oscillations in SCZ and AD is believed to be the result of excessive microglial "pruning" of neurites and synapses [73,89-91]. However, senescence-depleted SST may lead to the loss of dendritic arborizations, producing the same pathological effect as over-pruning [92].

Cellular senescence is an anticancer program marked by resistance to apoptosis, irreversible proliferation arrest, active metabolism, and a specific secretome, known as the senescence-associated secretory phenotype (SASP) which contains enzymes, cytokines, and npGH [6]. These molecules spread the senescent phenotype to the neighboring healthy cells, promoting inflammation. Upregulated npGH may be the cause of senescent cells' resistance to apoptosis as well as the neuronal reattempts at mitosis. Augmenting gamma oscillatory band may improve insight in

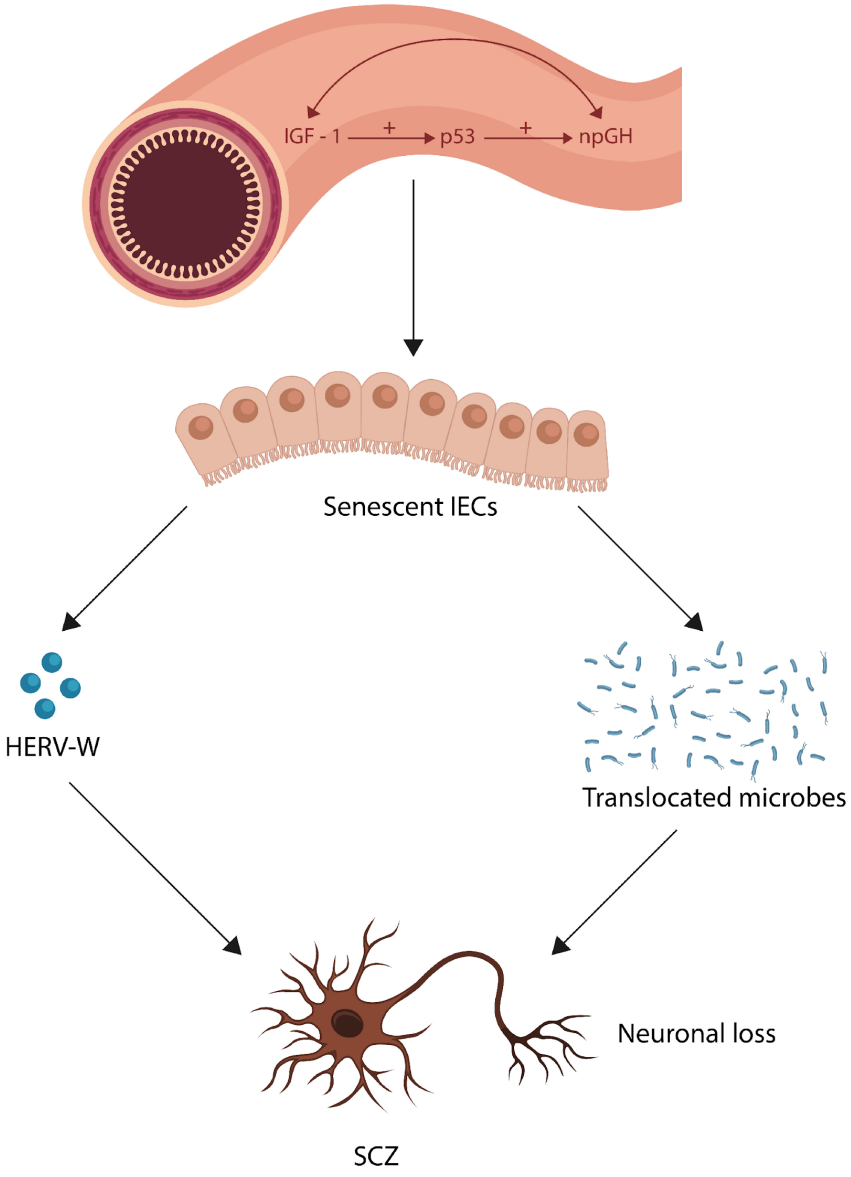


Figure 2: Cellular senescence, an anticancer program, is activated by damaged DNA. The genome guardian, p53 initiates the senescence phenotype and repairs the genome. Senescence lowers SST and increases the levels of npGH which also upregulates IGF-1. In the GI tract, senescent intestinal epithelial cell (IECs) can disrupt the permeability of gut barrier, enabling microbial migration across the lamina propria. Premature neuronal senescence also activates HERVs, viral fossils comprising 8% of the human genome. Translocated bacteria and their molecules can reach the brain, causing neuronal damage by activating microglia.

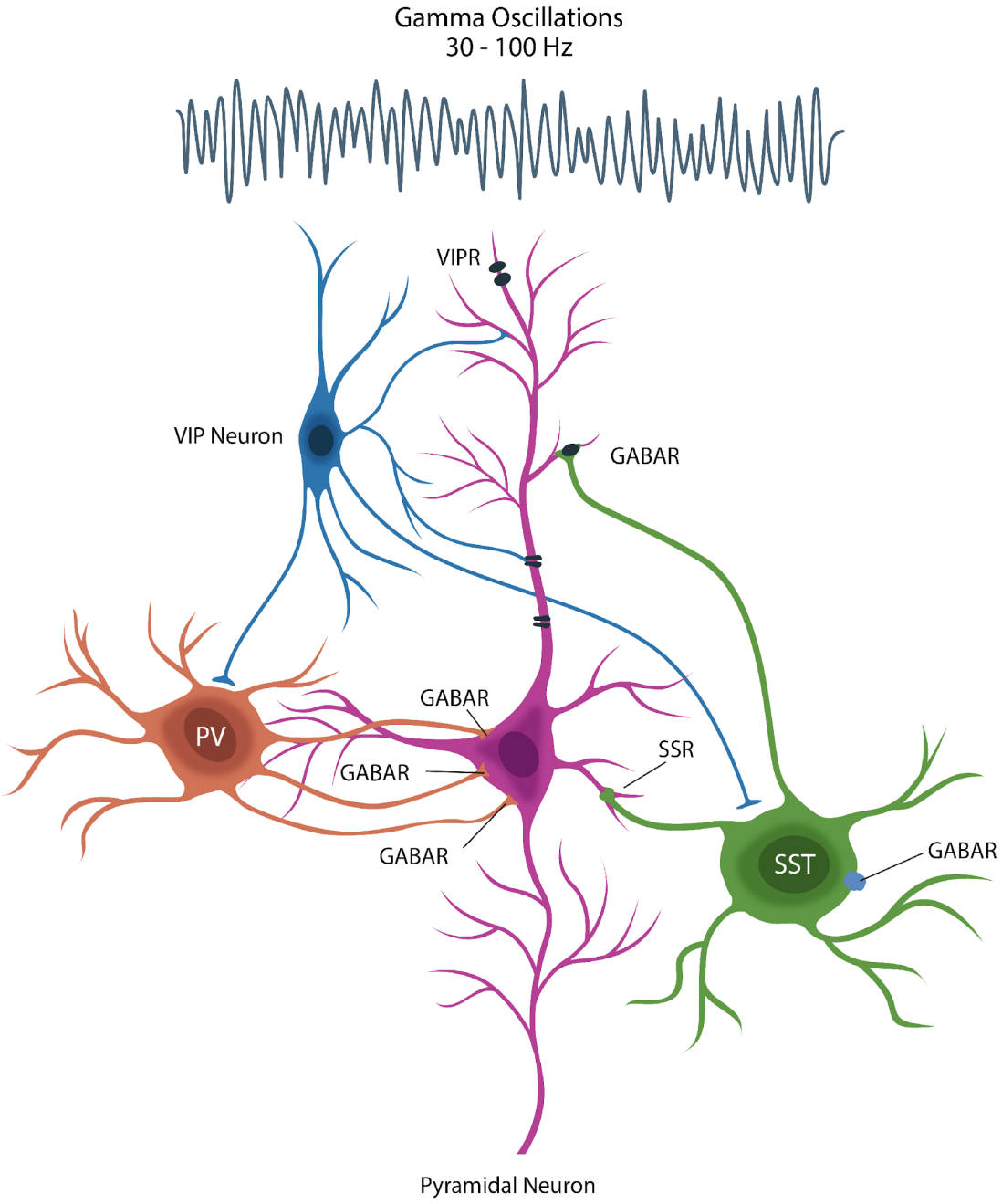


Figure 3: Gamma oscillations comprise a rapid rhythm believed to be generated by the synaptic "chatter" of inhibitory GABAergic interneurons, such as PV-expressing and somatostatin (SST)-expressing cells which interact with GABA receptors. When inhibitory neurons fail to suppress the pyramidal cells, the first psychotic episode may become manifest. In the figure, a VIP neuron inhibits PV and SST cells, disinhibiting the pyramidal neuron.

patients with SCZ, likely by promoting neurite growth, opening novel treatment opportunities [93,94]. For example, several studies have found that 40 Hz intranasal photobiomodulation or transcranial magnetic stimulation (TMS) at 40 Hz were beneficial for negative symptoms and cognition in SCZ [95-99]. Aside from gamma oscillations, anosognosia correlates directly with the loss of both gray matter and SST [100-102]. Can gray matter loss be restored? Studies are contradictory in this area and much more research is needed.

The Good Vibes and The Bad Vibes

Oscillations or vibrations are fundamental properties of all matter, including the living organisms [103,104]. For example, auditory cortex not only responds to the exogenous oscillatory input but also generates its own spontaneous oscillations, likely utilizing these waves as a signaling platform [105]. In addition, pancreatic β-cells utilize electrical and metabolic oscillations to signal with other cells, suggesting that this communication tool is used routinely for intercellular crosstalk [106]. In the CNS, astrocytes communicate via calcium (Ca2+) waves evoked by the GH-activated NMDA channels, implicating this hormone in glial homeostasis [107,108]. This is significant as SCZ, marked by impoverished gamma spectrum, has also been associated with abnormal Ca2+ signaling, further implicating SST in this pathology [109]. Simple organisms, including yeast, were shown to communicate with their counterparts via partially synchronized glycolytic oscillations, indicating that this mechanism is highly conserved in nature [110,111]. Moreover, microbial community in the GI tract was demonstrated to oscillate in synchrony with the metabolism, suggesting that the enteric nervous system (ENS) may sense these signals and relays them to the CNS [104].

Oscillation synchronization via "traveling waves", can transfer information to distant brain regions, likely driving human awareness. In contrast, desynchronization, observed during general anesthesia, induces unconsciousness, emphasizing the role of this signaling platform for the higher order of brain functions [112,113]. Indeed, it is believed that gamma waves, drive both the interoceptive awareness and cognition, contributing to a highly specialized form of information processing [114,115]. Interoceptive awareness refers the individual's ability to direct attention to the endogenous sensory information, discerning visceral cues on well-being, pain, discomfort, or ownership of limbs and body parts. In SCZ, anosognosia was associated with more frequent decompensations, worse psychotic or negative symptoms, and aggressive behavior, emphasizing the importance of insight for the outcome of this illness neuropsychiatric disorders, including SCZ, are often associated with anosognosia, neglect, or unawareness of the illness presence. For example, strokes of the right hemisphere can cause left-sided neglect with denial of left extremities [118]. Another example of anosognosia is failure to acknowledge one's own memory impairment, a phenomenon observed in cognitive disorders as well as in viral infections, including HIV and COVID-19 [119,120]. These findings have rekindled the interest of researchers and clinicians in the mental illness-associated anosognosia. Several neuroimaging studies have linked interoceptive awareness to insight as well as the abundance of GABAergic interneurons in the insular cortex (IC), a brain area associated with insight.

GABAergic interneurons are comprised of PV—expressing neurons, SST-expressing cells and 5-hydroxytryptamine (5HTRs) cells which include VIP-generating neurons (Figure 4). Interestingly, SST interneurons and some VIP neurons express muscarinic receptors, which are currently targeted in SCZ [121]. For example, xanomeline, a muscarinic M1/M4 agonist, exerts antipsychotic properties despite very low affinity for DA receptors, suggesting that non-dopaminergic transmission may be implicated in SCZ [122]. Therefore, enhancing GABAergic signaling to ameliorate anosognosia could likely be accomplished by inhibiting VIP-expressing GABAergic interneurons (Figure 4) [123]. Ameliorating anosognosia may significantly improve the long-term prognosis of SCZ, therefore, searching for therapeutics in this area is of paramount importance [124]. Along this line, a recent preclinical study has identified SST interneurons in anterior insula, suggesting that depletion of this hormone may impair insight by driving neuronal senescence [125].

Taken together, SCZ characteristics, including decreased gray matter volume, anosognosia, and impaired gamma oscillations may mirror the loss of inhibitory SST interneurons. Absent SST, npGH is upregulated, leading to cellular senescence and likely, the negative symptoms of SCZ [126,127].

HERVs, Ancient Viruses Causing Contemporary Illness

DNA damage-associated cellular senescence was shown to activate HERV-W, an ancient retroviral element, associated with SCZ [128-133). HERV-W is encoded in the regulatory region of GABA receptor B1 (GABBR1), linking these pathogens to the inhibitory interneurons. HERV-W encodes for syncytin-1, a placental protein known for fusing individual trophoblasts into the syncytiotrophoblast, enabling placentation. Excessive syncytin-1 may trigger pathology by fusing healthy neurons, a phenomenon observed in neurodegenerative disorders as well as in normal aging [134-136]. Most HERVs are incomplete genes, which are never transcribed, however, some of these elements were "domesticated" in time and had assumed physiological functions. Several studies have shown that HERVs can lay dormant in host DNA until activated by infections, cellular senescence, or placental hormones [137,138]. Upregulated by the damaged DNA, npGH induces cellular senescence and disseminates this phenotype via SASP. Damaged DNA upregulates p53, which in turn, induces further npGH transcription [6]. Recent studies have revealed that p53 can activate HERVs, utilizing them as tools against various cancers, suggesting that these dormant pathogens may destabilize the genome [139-141]. Elevated HERV-W levels were previously documented in SCZ, linking these viral relics to the genetics of SCZ [142].

In our previous work, we have discussed SARS-CoV-2 inhibition

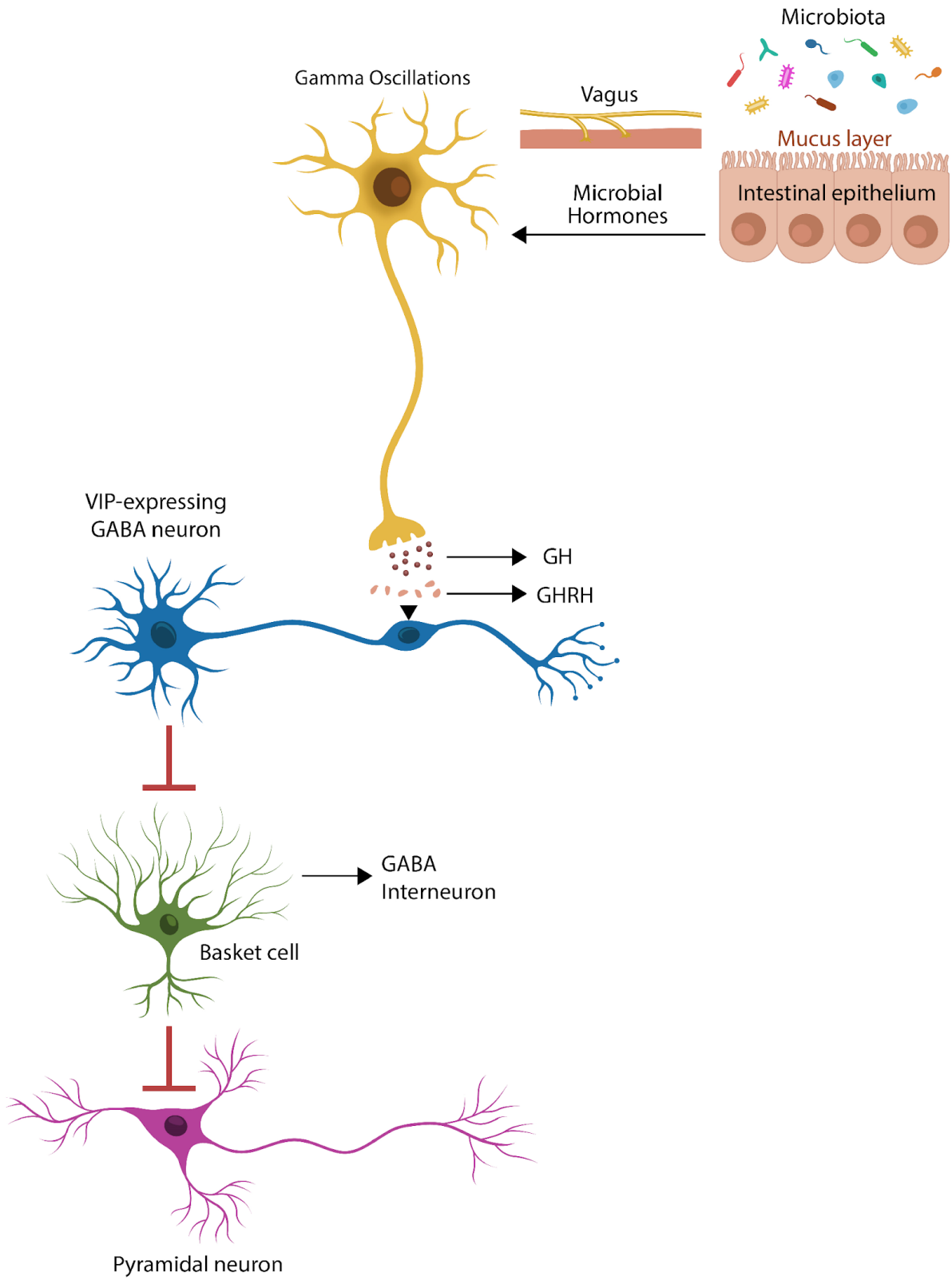


Figure 4: The ENS gastrin neurons sense microbial input from the gut lumen and relay these signals to the CNS via vagal, humoral, and oscillatory pathway. Gastrin neurons secrete GH to activate the VIP-expressing GABA cells. These cells inhibit (the inhibitory) GABA and SST neurons, releasing the pyramidal cells' inhibitory brakes.

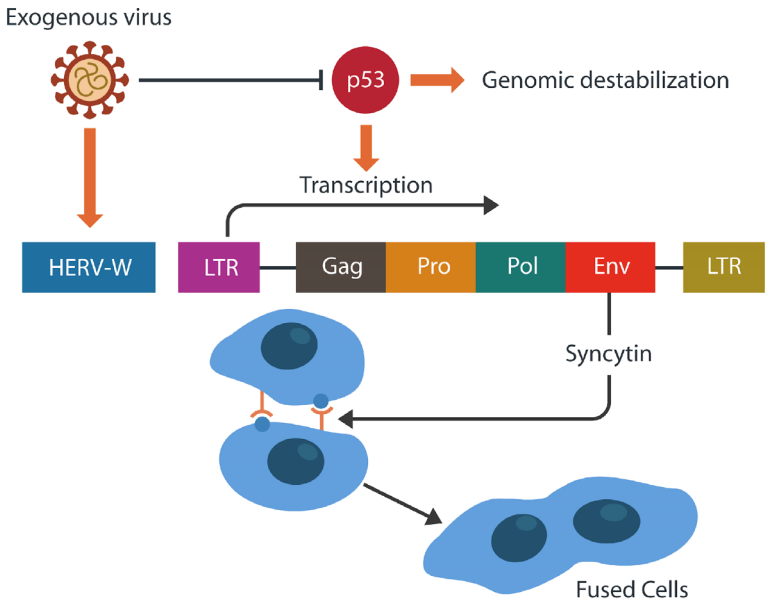


Figure 5: Contemporary viruses, including COVID-19, activate HERV-W gene, while inhibiting p53. Both actions allow for the transcription of HERV envelope (ENV) gene, producing excessive syncyctin-1. This protein drives pathological cell-cell fusion in various organs, including the brain. Fusion of postmitotic neurons may predispose to the development of cognitive or negative symptoms of SCZ.

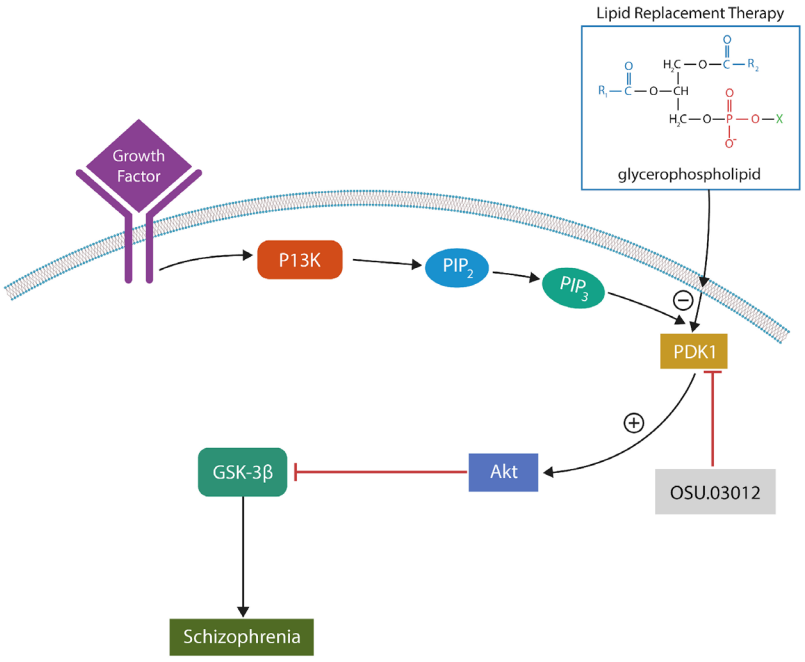


Figure 6: LRT exerts neuroprotective action in SCZ via PDK1/AKT/ GSK3β axis. PS (part of glycerophospholipids) binds PDK1, recruiting this kinase to the cell membrane. Natural or synthetic PDK1 inhibitors, enhance AKT-blockade of GSK3β, ameliorating the negative symptoms of SCZ.

of p53 and HERV-W activation, pathological cell-cell fusion and virus-induced neurocognitive deficits [143] (Figure 5). For this reason, we will not discuss HERVs in more detail here. Taken together, contemporary viruses can activate HERVs to enhance their own infection. Neurocognitive deficits, autoimmune disorders and SCZ were associated with reactivated HERVs.

Novel, Natural Antipsychotic Strategies for Schizophrenia

Membrane and serum lipids are altered in SCZ, suggesting that a better understanding of neurolipidomics, could lead to the development of novel therapies for negative and cognitive symptoms [144]. These include natural lipids with plant-derived PDK1 inhibitors, aiming at replacing the oxidized membrane lipidome with natural phospholipids.

Lipid replacement Therapy (LRT) adapted for schizophrenia (LRT+K)

LRT refers to the oral intake of natural glycerophospholipids to which we added kaempferol (3,4′,5,7-tetrahydroxyflavone), a natural flavonoid. The aim of LRT+K is to gradually replace damaged lipids in neuronal cell membranes with natural glycerides, containing phosphatidylserine (PS) and plant-derived kaempferol.

LRT interacts with a pathway previously implicated in SCZ: PDK1/ AKT/GSK3β (3-phosphoinositide-dependent kinase 1/ protein kinase B/ glycogen synthase kinase 3). PDK1, found upstream of AKT and GSK3β, contains a pleckstrin homology (PH) domain, which binds PS in the cytoplasmic leaflet of cell membranes. PS/PDK1 attachment has two beneficial effects: 1) recruitment of PDK1 at the cell membrane, and 2) maintaining PDK1 in inactive conformation (Figure 6) [145,146]. This modulates the downstream phosphorylome, inhibiting, GSK3β. Uninhibited GSK3β promotes psychosis and several antipsychotic drugs and lithium are inhibitors of this enzyme [147].

AKT also contains a PH domain which binds PS in the lipid rafts. However, unlike PDK1, upon attachment to PS, AKT becomes active (probably via autophosphorylation). Activated AKT suppresses the downstream GSK3β, lowering the risk of psychosis (Figure 6) [145,146]. In contrast, kaempferol inhibits PDK1 (by a non-PH mechanism), probably via regulating the phosphorylation of AKT and GSK3β. Therefore, unlike antipsychotics and lithium, kaempferol, blocks PDK1 in a totally natural manner [148]. In addition, OSU-03012, a synthetic PDK1 inhibitor, is currently being evaluated for anticancer efficacy. OSU-03012 may help LRT by inactivating PDK1 by a mechanism different than PS (Figure 6). Taken together, PS, a component of LRT, inactivates PDK1 by recruiting it to the cell membrane. Conversely, PS attachment, activates AKT effectively suppressing GSK3β and psychosis.

Lipid Rafts: Hubs of Cellular Senescence

Lipids play a key role in the pathogenesis of negative and cognitive symptoms of SCZ not only because of lipid oxidation but also because of decreased membrane cholesterol [149]. For example, a study found that external radiofrequencies-induced cell membrane oscillations depend on the lipid composition (the more cholesterol, the more fluid the membrane) [150]. Cholesterol modulates the bilayer structure of cell membrane by altering not only the fluidity, but also the thickness, compressibility, exocytosis of secretory vesicles, and oscillatory activity. Suggesting that in the absence of this lipid, cell membrane vibrations are attenuated [151]. In this regard, ceramide has a more rigid molecular structure and restrains the oscillatory activity [152].

In senescent neurons, lipid rafts contain a disproportionate amount of ceramide compared to cholesterol, suggesting that old membranes are much less flexible and resistant to synchronization [153,154]. Indeed, earlier studies have implicated ceramide and sphingosine-1-phosphate in SCZ, further linking neuronal senescence to the biophysical properties of cell membranes [155-158]. Interestingly, several antipsychotic drugs intercalate themselves in the lipid bilayer, altering the biophysical properties of cell membranes. This suggests that antipsychotics may exert their actions by dopaminergic and non-dopaminergic mechanisms, the latter, including biophysical [159]. For example, cell membrane sterols were found altered in individuals at ultra-high risk of psychosis (UHR), suggesting that the membrane lipidome may be crucial for the pathogenesis of SCZ [160]. Likewise, in older individuals, the lipid composition of neuronal plasma membrane is altered in favor of ceramide, as cholesterol is replaced with this lipid in older individuals [161-163]. Indeed, loss of cholesterol may reduce gamma frequencies, predisposing to cognitive deficit [164]. Moreover, npGH was demonstrated to upregulate cell membrane ceramides, suggesting that aside from the genome, this hormone may also damage the cell membranes [165]. Taken together, as LRT provides healthy natural lipids to neuronal lipid rafts, this intervention may rehabilitate not only the lipidome but also the gray matter and the oscillatory gamma activity.

Natural and synthetic PDK1 inhibitors

Protein kinases are enzymes that transfer phosphate groups from adenine triphosphate (ATP) to specific proteins. PDK1 inhibitors exert their beneficial effects by inhibiting GSK3β. Natural PDK1 inhibitors are ubiquitous, being present in numerous fruits and vegetables and for this reason, have no known adverse effects (Table 1).

Table 1: Natural flavonoids PDK1 inhibitors.

PDK1 inhibitor	Plant	References
Kaempferol	fruits, vegetables, and herbs	166
Quercetin	Onions, kale, broccoli	167
Myricetin	Oranges, berries, tomatoes, nuts, tea	168
Epigallcatechin-3 gallate	Green tea	169
Lupiwighteone isoflavone	Glycyrrhiza glabra; Lotus pedunculatus	170
Delphinidin	Citrus fruits	171
Honokiol	Cherries, berries, grapes	172
Delphinidin	Cranberries, Concord grapes, Pomegranates	173

Synthetic PDK1 inhibitors

Several synthetic PDK1 inhibitors have been developed, but few can cross the BBB. The exception is OSU-03012, a celecoxib derivative without cyclooxygenase-2 inhibitory activity, which exerts antiviral properties and is currently being evaluated for glioblastoma (Figure 6) [174,175]. OSU-03012 may be a suitable candidate for SCZ with negative and cognitive symptoms. At present, several other PDK1 inhibitors are in clinical trials for in AD.

Conclusions

For the past 70 years, psychiatry has been obsessed with the postsynaptic dopaminergic blockade and paid much less attention to the gray matter loss, enlargement of lateral ventricles, and the paucity of gamma oscillations. Novel SCZ studies have started to emphasize the importance of local hormones, GABAergic interneurons, as well as the lipid composition of neuronal membranes. The therapeutic strategies derived from these models may, for the first time, improve SCZ outcomes. Limiting gray matter loss, restoring the homeostasis of SST interneurons, and npGH inhibition, may address the root cause of SCZ. Biophysical approaches, including TMS or photobiomodulation at 40 Hz, may promote healthy oscillatory activities, restoring the integrity of the connectome and the synchronization of brain areas. Acknowledging brain oscillations as a unique communication platform has the advantage of influencing the connectome in a noninvasive manner. Together, these approaches may address the etiopathogenesis, rather than SCZ symptoms, bringing for the first time, remission instead of symptom reduction.

References

1. El Abdellati K, De Picker L, Morrens M. Antipsychotic Treatment Failure A Systematic Review on Risk Factors and Interventions for Treatment Adherence in Psychosis. Front Neurosci. 2020; 9.
2. Marwaha S, Johnson S. Schizophrenia and employment a review. Soc Psychiatry Psychiatr Epidemiol. 2004; 39: 337-349.
3. Rosenheck R, Leslie D, Keefe R, et al. Barriers to employment for people with schizophrenia. Am J Psychiatry. 2006; 163: 411-417.
4. Salkever DS, Karakus MC, Slade EP, et al. Measures and predictors of community-based employment and earnings of persons with schizophrenia in a multi-site study. Psychiatr Serv. 2007; 58: 315-324.
5. Insel T. Rethinking schizophrenia. Nature. 2010; 468: 187-193.
6. Chesnokova V, Melmed S. Non-pituitary GH regulation of the tissue microenvironment. Endocr Relat Cancer. 2023; 30: e230028.
7. Feng Y, Shen J, He J, et al. Schizophrenia and cell senescence candidate genes screening, machine learning, diagnostic models, and drug prediction. Front Psychiatry. 2023; 14: 1105987.
8. Johansson EM, Bouchet D, Tamouza R, et al. Human endogenous retroviral protein triggers deficit in glutamate synapse maturation and behaviors associated with psychosis. Sci Adv. 2020; 6: eabc0708.
9. Brzezinski-Sinai NA, Brzezinski A. Schizophrenia and Sex Hormones: What Is the Link? Front Psychiatry. 2020; 11: 693.
10. Singh P, Bauernfreund Y, Arya P, et al. Primary hyperparathyroidism presenting as acute psychosis secondary to hypercalcaemia requiring curative parathyroidectomy. J Surg Case Rep. 2018; 2: 023.
11. Heinrich TW, Grahm G. Hypothyroidism Presenting as Psychosis: Myxedema Madness Revisited. Prim Care Companion J Clin Psychiatry. 2003; 6: 260-266.
12. Rutigliano G, Chaumette B, Seeman MV. Editorial Psychoneuroendocrinology of Psychosis Disorders. Front Psychiatry. 2020; 11: 607590.
13. Hussain T, Murtaza G, Kalhoro DH, et al. Relationship between gut microbiota and host-metabolism Emphasis on hormones related to reproductive function. Anim Nutr. 2021; 1: 1-10.
14. Sun LJ, Li JN, Nie YZ. Gut hormones in microbiota-gut-brain cross talk. Chin Med J Engl. 2020; 133: 826-833.
15. Brown JM, Hazen SL. The gut microbial endocrine organ bacterially derived signals driving cardiometabolic diseases. Annu Rev Med. 2015; 66: 343-359.
16. Wang Z, Klipfell E, Bennett BJ, et al. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. Nature. 2011; 472: 57-63.
17. Tang WH, Wang Z, Fan Y, et al. Prognostic value of elevated levels of intestinal microbe-generated metabolite, trimethylamine-N-oxide, in patients with heart failure Refining the gut hypothesis. J Am Coll Cardiol. 2014; 64: 1908-1914.
18. Barandouzi ZA, Lee J, del Carmen Rosas M, et al. Associations of neurotransmitters and the gut microbiome with emotional distress in mixed type of irritable bowel syndrome. Sci Rep. 2022; 12: 1648.
19. Gao J, Xu K, Liu H, et al. Impact of the gut microbiota on intestinal immunity mediated by tryptophan metabolism. Front Cell Infect Microbiol. 2018; 8: 13.
20. Hamamah S, Aghazarian A, Nazaryan A, et al. Role of Microbiota-Gut-Brain Axis in Regulating Dopaminergic Signaling. Biomedicines. 2022; 10: 436.
21. Chen Y, Xu J, Chen Y. Regulation of Neurotransmitters by the Gut Microbiota and Effects on Cognition in Neurological Disorders. Nutrients. 2021; 13: 2099.
22. Markkanen E, Meyer U, Dianov GL. DNA Damage and Repair in Schizophrenia and Autism: Implications for Cancer Comorbidity and Beyond. Int J Mol Sci. 2016; 17: 856.
23. Shishido R, Kunii Y, Hino M, et al. Evidence for increased DNA damage repair in the postmortem brain of the high stress-response group of schizophrenia. Front Psychiatry. 2023; 14: 1183696.

24. Şimşek Ş, Gençoğlan S, Yüksel T, et al. Oxidative Stress and DNA Damage in Untreated First-Episode Psychosis in Adolescents. Neuropsychobiology. 2016; 73: 92-97.
25. Papanastasiou E, Gaughran F, Smith S. Schizophrenia as segmental progeria. J R Soc Med. 2011; 104: 475-484.
26. Murueta-Goyena A, Ortuzar N, Lafuente JV, et al. Enriched Environment Reverts Somatostatin Interneuron Loss in MK-801 Model of Schizophrenia. Mol Neurobiol. 2020; 57: 125-134.
27. Petrie KA, Schmidt D, Bubser M, et al. Neurotensin activates GABAergic interneurons in the prefrontal cortex. J Neurosci. 2005; 25: 1629-1636.
28. Chen CM, Stanford AD, Mao X, et al. GABA level, gamma oscillation, and working memory performance in schizophrenia. Neuroimage Clin. 2014; 4: 531-539.
29. Antonoudiou P, Tan YL, Kontou G, et al. Parvalbumin and Somatostatin Interneurons Contribute to the Generation of Hippocampal Gamma Oscillations. J Neurosci. 2020; 40:7668-7687.
30. Hussain T, Murtaza G, Kalhoro DH, et al. Relationship between gut microbiota and host-metabolism Emphasis on hormones related to reproductive function. Anim Nutr. 2021; 7: 1-10.
31. Martinez-Corral R, Liu J, Prindle A, et al. Metabolic basis of brain-like electrical signalling in bacterial communities. Philos Trans R Soc Lond B Biol Sci. 2019; 374: 20180382.
32. Martinez-Corral R, Liu J, Süel GM, et al. Bistable emergence of oscillations in growing Bacillus subtilis biofilms. Proc Natl Acad Sci U S A. 2018; 115: E8333-E8340.
33. Prindle A, Liu J, Asally M, et al. Ion channels enable electrical communication in bacterial communities. Nature. 2015; 527: 59-63.
34. Liu J, Prindle A, Humphries J, et al. Metabolic co-dependence gives rise to collective oscillations within biofilms. Nature. 2015; 523: 550-554.
35. Lenz P, Søgaard-Andersen L. Temporal and spatial oscillations in bacteria. Nat Rev Microbiol. 2011; 9: 565-577.
36. Erkin Şeker. Bacterial Vibrations. Sci Transl Med. 2013; 5: 196.
37. Raskin DM, de Boer PA. Rapid pole-to-pole oscillation of a protein required for directing division to the middle of Escherichia coli. Proc Natl Acad Sci U S A. 1999; 96: 4971-4976.
38. Rulands S, Lee HJ, Clark SJ, et al. Genome-Scale Oscillations in DNA Methylation during Exit from Pluripotency. Cell Syst. 2018; 7: 63-76.
39. Heltberg MS, Lucchetti A, Hsieh FS, et al. Enhanced DNA repair through droplet formation and p53 oscillations. Cell. 2022; 185: 4394-4408.
40. Wang SW, Tang LH. Emergence of collective oscillations in adaptive cells. Nat Commun. 2019; 10: 5613.
41. Abe H, Terasawa E. Firing pattern and rapid modulation of activity by estrogen in primate luteinizing hormone releasing hormone-1 neurons. Endocrinology. 2005; 146: 4312-4320.
42. Bergsten P, Grapengiesser E, Gylfe E, et al. Synchronous oscillations of cytoplasmic Ca2+ and insulin release in glucose-stimulated pancreatic islets. J Biol Chem. 1994; 269: 8749-8745.
43. Whittington MA, Traub RD, Jefferys JG. Synchronized oscillations in interneuron networks driven by metabotropic glutamate receptor activation. Nature. 1995; 373: 612-615.
44. Agnati LF, Zunarelli E, Genedani S, et al. On the existence of a global molecular network enmeshing the whole central nervous system physiological and pathological implications. Curr Protein Pept Sci. 2006; 7: 3-15.
45. Peyrard M, Bishop AR. Statistical mechanics of a nonlinear model for DNA denaturation. Phys Rev Lett. 1989; 62: 2755-2758.
46. Petoukhov SV. Algebraic harmony and probabilities in genomes. Long-range coherence in quantum code biology. Biosystems. 2021; 209: 104503.
47. Aggarwal A, Brennan C, Shortal B, et al. Coherence of Visual-Evoked Gamma Oscillations Is Disrupted by Propofol but Preserved Under Equipotent Doses of Isoflurane. Front Syst Neurosci. 2019; 13: 19.
48. Vesuna S, Kauvar IV, Richman E, et al. Deep posteromedial cortical rhythm in dissociation. Nature. 2020; 586: 87-94.
49. Zomorrodi R, Loheswaran G, Pushparaj A, et al. Pulsed Near Infrared Transcranial and Intranasal Photobiomodulation Significantly Modulates Neural Oscillations a pilot exploratory study. Sci Rep. 2019; 9: 6309.
50. Liu J, Prindle A, Humphries J, et al. Metabolic co-dependence gives rise to collective oscillations within biofilms. Nature. 2015; 523: 550-554.
51. Koshiyama D, Mariko Tada, Kenji Kirihara, et al. Auditory gamma oscillations predict global symptomatic outcome in the early stages of psychosis a longitudinal investigation. Clin. Neurophysiol. 2018; 129: 2268-2275.
52. Griskova-Bulanova I, Dapsys K, Melynyte S, et al. 40Hz auditory steady-state response in schizophrenia Sensitivity to stimulation type clicks versus flutter amplitude-modulated tones. Neurosci Lett. 2018; 662: 152-157.
53. Zhang Y, Zhang Z, Luo L, et al. 40 Hz Light Flicker Alters Human Brain Electroencephalography Microstates and Complexity Implicated in Brain Diseases. Front Neurosci. 2021; 15: 777183.
54. Chan D, Suk HJ, Jackson BL, et al. Gamma frequency sensory stimulation in mild probable Alzheimer's dementia patients Results of feasibility and pilot studies. PLoS One. 2022; 17: e0278412.
55. Jang HJ, Chung H, Rowland JM, et al. Distinct roles of parvalbumin and somatostatin interneurons in gating the synchronization of spike times in the neocortex. Sci Adv. 2020; 6: eaay5333.

56. Liguz-Lecznar M, Urban-Ciecko J, Kossut M. Somatostatin and Somatostatin-Containing Neurons in Shaping Neuronal Activity and Plasticity. Front Neural Circuits. 2016; 10: 48.
57. Murty DVPS, Manikandan K, Kumar WS, et al. Gamma oscillations weaken with age in healthy elderly in human EEG. Neuroimage. 2020; 215: 116826.
58. Karrasch M, Laine M, Rapinoja P, et al. Effects of normal aging on event-related desynchronization synchronization during a memory task in humans. Neurosci Lett. 2004; 366: 18-23.
59. Chesnokova V, Zonis S, Apostolou A, et al. Local non-pituitary growth hormone is induced with aging and facilitates epithelial damage. Cell Rep. 2021; 37: 110068.
60. Nelson E, Alejandra A, Cristian M, et al. Basal Forebrain Gating by Somatostatin Neurons Drives Prefrontal Cortical Activity. Cerebral Cortex. 2019; 29: 42-53.
61. Kim KS, Seu YB, Baek SH, et al. Induction of cellular senescence by insulin-like growth factor binding protein-5 through a p53-dependent mechanism. Mol Biol Cell. 2007; 18: 4543-4552.
62. Sarubbo F, David Moranta, Silvia Tejada, et al. Impact of Gut Microbiota in Brain Ageing Polyphenols as Beneficial Modulators. Antioxidants. 2023; 12: 812.
63. Liu N, Xiao Y, Zhang W, et al. Characteristics of gray matter alterations in never-treated and treated chronic schizophrenia patients. Transl Psychiatry. 2020; 10: 136.
64. Cahn W, Pol HEH, Lems EBTE, et al. Brain Volume Changes in First-Episode Schizophrenia A 1-Year Follow-up Study. Arch Gen Psychiatry. 2002; 59: 1002-1010.
65. Jääskeläinen E, Juola P, Hirvonen N, et al. A systematic review and meta-analysis of recovery in schizophrenia. Schizophr Bull. 2013; 39: 1296-1306.
66. Zipursky RB. Why are the outcomes in patients with schizophrenia so poor? J Clin Psychiatry. 2014; 2: 20-24.
67. Lai CH, Wu YT, Chen CY, et al. Gray matter increases in fronto-parietal regions of depression patients with aripiprazole monotherapy An exploratory study. Medicine Baltimore. 2016; 95: e4654.
68. Manchia M, Pinna M, Carpiniello B. Haloperidol and loss of gray matter in schizophrenia Reconciling meta-analytical results with molecular pharmacology. Psychiatry Res. 2016; 235: 209-210.
69. Martínez A, Ibarra IA, Vargas R. A quantum chemical approach representing a new perspective concerning agonist and antagonist drugs in the context of schizophrenia and Parkinson's disease. PLoS One. 2019; 14: e0224691.
70. Hudson M, Rind G, O'Brien T, et al. Reversal of evoked gamma oscillation deficits is predictive of antipsychotic activity with a unique profile for clozapine. Transl Psychiatry 2016; 6: e784.
71. Wei Y, Han X, Zhao C. PDK1 regulates the survival of the developing cortical interneurons. Mol Brain. 2020; 13: 65.
72. Alherz F, Alherz M, Almusawi H. NMDAR hypofunction and somatostatin-expressing GABAergic interneurons and receptors A newly identified correlation and its effects in schizophrenia. Schizophr Res Cogn. 2017; 8: 1-6.
73. Perez SM, Boley A, Lodge DJ. Region specific knockdown of Parvalbumin or Somatostatin produces neuronal and behavioral deficits consistent with those observed in schizophrenia. Transl Psychiatry. 2019; 9: 264.
74. Bergé D, Carmona S, Rovira M, et al. Gray matter volume deficits and correlation with insight and negative symptoms in first-psychotic-episode subjects. Acta Psychiatr Scand. 2011; 123: 431-439.
75. Andreasen NC, Olsen SA, Dennert JW, et al. Ventricular enlargement in schizophrenia relationship to positive and negative symptoms. Am J Psychiatry. 1982; 139: 297-302.
76. Horga G, Bernacer J, Dusi N, et al. Correlations between ventricular enlargement and gray and white matter volumes of cortex, thalamus, striatum, and internal capsule in schizophrenia. Eur Arch Psychiatry Clin Neurosci. 2011; 261: 467-476.
77. Chesnokova V, Melmed S. GH and Senescence: A New Understanding of Adult GH Action. J Endocr Soc. 2021; 6: 177.
78. Roy BF, Benkelfat C, Hill JL, et al. Serum antibody for somatostatin-14 and prodynorphin 209-240 in patients with obsessive-compulsive disorder, schizophrenia, Alzheimer's disease, multiple sclerosis, and advanced HIV infection. Biol Psychiatry. 1994; 35: 335-344.
79. Zhou X, Singh M, Sanz Santos G, et al. Pharmacologic Activation of p53 Triggers Viral Mimicry Response Thereby Abolishing Tumor Immune Evasion and Promoting Antitumor Immunity. Cancer Discov. 2021; 11: 3090-3105.
80. Pittaluga A, Bonfanti A, Raiteri M. Somatostatin potentiates NMDA receptor function via activation of InsP(3) receptors and PKC leading to removal of the Mg(2+) block without depolarization. Br J Pharmacol. 2000; 130: 557-566.
81. Aslam M, Idrees H, Ferdinandy P, et al. Somatostatin Primes Endothelial Cells for Agonist-Induced Hyperpermeability and Angiogenesis *In Vitro*. Int J Mol Sci. 2022; 23: 3098.
82. Zhan X, Stamova B, Sharp FR. Lipopolysaccharide Associates with Amyloid Plaques, Neurons and Oligodendrocytes in Alzheimer's Disease Brain A Review. Front Aging Neurosci. 2018; 10: 42.
83. Maes M, Kanchanatawan B, Sirivichayakul S, et al. In Schizophrenia, Increased Plasma IgM/IgA Responses to Gut Commensal Bacteria Are Associated with Negative Symptoms, Neurocognitive Impairments, and the Deficit Phenotype. Neurotox Res. 2019; 35: 684-698.
84. Zhan X, Stamova B, Sharp FR. Lipopolysaccharide Associates with Amyloid Plaques, Neurons and Oligodendrocytes in Alzheimer's Disease Brain A Review. Front Aging Neurosci. 2018; 10: 42.
85. Maes M, Kanchanatawan B, Sirivichayakul S, et al. In Schizophrenia, Increased Plasma IgM/IgA Responses to

Gut Commensal Bacteria Are Associated with Negative Symptoms, Neurocognitive Impairments, and the Deficit Phenotype. Neurotox Res. 2019; 35: 684-698.

86. Jensen EA, Young JA, Mathes SC, et al. Crosstalk between the growth hormone/insulin-like growth factor-1 axis and the gut microbiome A new frontier for microbial endocrinology. Growth Horm IGF Res. 2020; 53-54.
87. Roesler R, Henriques JA, Schwartsmann G. Gastrin-releasing peptide receptor as a molecular target for psychiatric and neurological disorders. CNS Neurol Disord Drug Targets. 2006; 5: 197-204.
88. Iwasawa C, Kuzumaki N, Suda Y, et al. Reduced expression of somatostatin in GABAergic interneurons derived from induced pluripotent stem cells of patients with parkin mutations. Mol Brain. 2019; 12: 5.
89. Iwasaki M, Akiba Y, Kaunitz JD. Recent advances in vasoactive intestinal peptide physiology and pathophysiology focus on the gastrointestinal system. F1000Res. 2019; 8: F1000-F1629.
90. Lim L, Mi D, Llorca A, et al. Development and Functional Diversification of Cortical Interneurons. Neuron. 2018; 100: 294-313.
91. Qvist P, Eskildsen SF, Hansen B, et al. Brain volumetric alterations accompanied with loss of striatal medium-sized spiny neurons and cortical parvalbumin expressing interneurons in Brd1+/− mice. Sci Rep. 2018; 8: 16486.
92. Bulloch AG. Somatostatin enhances neurite outgrowth and electrical coupling of regenerating neurons in Helisoma. Brain Res. 1987; 412: 6-17.
93. Edgar JC, Chen YH, Lanza M, et al. Cortical thickness as a contributor to abnormal oscillations in schizophrenia? Neuroimage Clin. 2013; 4: 122-129.
94. Kaar SJ, Nottage JF, Angelescu I, et al. Gamma Oscillations and Potassium Channel Modulation in Schizophrenia Targeting GABAergic Dysfunction. Clin EEG Neurosci. 2023; 2: 15500594221148643.
95. Sheth BR, Sandkühler S, Bhattacharya J. Posterior Beta and anterior gamma oscillations predict cognitive insight. J Cogn Neurosci. 2009; 21: 1269-1279.
96. Arikan MK, Metin B, Metin SZ, et al. High Frequencies in QEEG Are Related to the Level of Insight in Patients With Schizophrenia. Clin EEG Neurosci. 2018; 49: 316-320.
97. Zomorrodi R, Loheswaran G, Pushparaj A, et al. Pulsed Near Infrared Transcranial and Intranasal Photobiomodulation Significantly Modulates Neural Oscillations a pilot exploratory study. Sci Rep. 2019; 9: 6309.
98. Koshiyama D, Kenji Kirihara, Mariko Tada, et al. Auditory gamma oscillations predict global symptomatic outcome in the early stages of psychosis a longitudinal investigation. Clin Neurophysiol. 2018; 129: 2268-2275.
99. Griskova-Bulanova I, Dapsys K, Melynyte S, et al. 40Hz auditory steady-state response in schizophrenia Sensitivity to stimulation type clicks versus flutter amplitude-modulated tones. Neurosci Lett. 2018; 662: 152-157.
100. Zhang Y, Zhang Z, Luo L, et al. 40 Hz Light Flicker Alters Human Brain Electroencephalography Microstates and Complexity Implicated in Brain Diseases. Front Neurosci. 2021; 15: 777183.
101. Chan D, Suk HJ, Jackson BL, et al. Gamma frequency sensory stimulation in mild probable Alzheimer's dementia patients Results of feasibility and pilot studies. PLoS One. 2022; 17: e0278412.
102. Quigley KS, Kanoski S, Grill WM, et al. Functions of Interoception From Energy Regulation to Experience of the Self. Trends Neurosci. 2021; 44: 29-38.
103. Rose MF, Ahmad KA, Thaller C, et al. Excitatory neurons of the proprioceptive, interoceptive, and arousal hindbrain networks share a developmental requirement for Math1. Proc Natl Acad Sci U S A. 2009; 106: 22462-22467.
104. Fujimoto H, Matsuoka T, Kato Y, et al. Brain regions associated with anosognosia for memory disturbance in Alzheimer's disease a magnetic resonance imaging study. Neuropsychiatr Dis Treat. 2017; 13: 1753-1759.
105. Einstein Albert. Über die von der molekularkinetischen Theorie der Wärme geforderte Bewegung von in ruhenden Flüssigkeiten suspendierten Teilchen On the Movement of Small Particles Suspended in Stationary Liquids Required by the Molecular-Kinetic Theory of Heat PDF. Annalen der Physik. 1905; 322: 549-560.
106. Bi S, Kargeti M, Colin R, et al. Dynamic fluctuations in a bacterial metabolic network. Nat Commun. 2023; 14: 2173.
107. Neymotin SA, Tal I, Barczak A, et al. Detecting Spontaneous Neural Oscillation Events in Primate Auditory Cortex. eNeuro. 2022; 9: 0281-0321.
108. Marinelli I, Fletcher PA, Sherman AS, et al. Symbiosis of Electrical and Metabolic Oscillations in Pancreatic β-Cells. Front Physiol. 2021; 12: 781581.
109. Ramis M, Sarubbo F, Sola J, et al. Cognitive improvement by acute growth hormone is mediated by NMDA and AMPA receptors and MEK pathway. Prog Neuropsychopharmacol Biol Psychiatry. 2013; 45: 11-20.
110. Bazargani N, Attwell D. Astrocyte calcium signaling the third wave. Nat Neurosci. 2016; 19: 182-189.
111. Arjun McKinney A, Petrova R, Panagiotakos G. Calcium and activity-dependent signaling in the developing cerebral cortex. Development. 2022; 149: dev198853.
112. Mojica-Benavides M, van Niekerk DD, Mijalkov M, et al. Intercellular communication induces glycolytic synchronization waves between individually oscillating cells. Proc Natl Acad Sci U S A. 2021; 118: e2010075118.
113. Weber A, Prokazov Y, Zuschratter W, et al. Desynchronisation of glycolytic oscillations in yeast cell populations. PLoS One. 2012; 7: e43276.

114. Besserve M, Lowe SC, Logothetis NK, et al. Shifts of Gamma Phase across Primary Visual Cortical Sites Reflect Dynamic Stimulus-Modulated Information Transfer. PLOS Biology. 2015; 13: e1002257.

115. Davis ZW, Muller L, Martinez-Trujillo J, et al. Spontaneous travelling cortical waves gate perception in behaving primates. Nature. 2020; 587: 432-436.

116. Gallotto S, Sack AT, Schuhmann T, et al. Oscillatory Correlates of Visual Consciousness. Front Psychol. 2017; 8: 1147.

117. Başar E. A review of gamma oscillations in healthy subjects and in cognitive impairment. Int J Psychophysiol. 2013; 90: 99-117.

118. Reddy MS. Insight and Psychosis. Indian J Psychol Med. 2015; 37: 257-260.

119. Woods P, Reed V, Collins M. The relationship between risk and insight in a high-security forensic setting. J Psychiatr Ment Health Nurs. 2003; 10: 510-517.

120. Ten Brink AF, Verwer JH, Biesbroek JM, et al. Differences between left- and right-sided neglect revisited a large cohort study across multiple domains. J Clin Exp Neuropsychol. 2017; 39: 707-723.

121. Juengst S, Skidmore E, Pramuka M, et al. Factors contributing to impaired self-awareness of cognitive functioning in an HIV positive and at-risk population. Disabil Rehabil. 2012; 34: 19-25.

122. Voruz P, Cionca A, Allali G, et al. Functional connectivity underlying cognitive and psychiatric symptoms in post-COVID-19 syndrome is anosognosia a key determinant. Brain Commun. 2022; 4: fcac057.

123. Foster DJ, Bryant ZK, Conn PJ. Targeting muscarinic receptors to treat schizophrenia. Behav Brain Res. 2021; 405: 113201.

124. Andersen M, Fink-Jensen A, Peacock L, et al. The Muscarinic M1/M4 Receptor Agonist Xanomeline Exhibits Antipsychotic-Like Activity in Cebus apella Monkeys. Neuropsychopharmacol 2003; 28: 1168-1175.

125. Lewis DA, Cho RY, Carter CS, et al. Subunit-selective modulation of GABA type a receptor neurotransmission and cognition in schizophrenia. Am J Psychiatry. 2008; 165: 1585-1593.

126. Lysaker PH, Pattison ML, Leonhardt BL, et al. Insight in schizophrenia spectrum disorders relationship with behavior, mood and perceived quality of life, underlying causes and emerging treatments. World Psychiatry. 2018; 17: 12-23.

127. Gould NL, Kolatt Chandran S, Kayyal H, et al. Somatostatin Interneurons of the Insula Mediate QR2-Dependent Novel Taste Memory Enhancement. eNeuro. 2021; 8: 0152-0221.

128. Boskovic M, Vovk T, Kores Plesnicar B, et al. Oxidative stress in schizophrenia. Current neuropharmacology. 2011; 9: 301-312.

129. Zhang XY, Tan YL, Cao LY, et al. Antioxidant enzymes and lipid peroxidation in different forms of schizophrenia treated with typical and atypical antipsychotics. Schizophrenia research. 2006; 81: 291-300.

130. López-Otín C, Pietrocola F, Roiz-Valle D, et al. Meta-hallmarks of aging and cancer. Cell Metab. 2023; 35: 12-35.

131. Yan Q, Wu X, Zhou P, et al. HERV-W Envelope Triggers Abnormal Dopaminergic Neuron Process through DRD2/PP2A/AKT1/GSK3 for Schizophrenia Risk. Viruses. 2022; 14: 145.

132. Ono M, Kawakami M, Ushikubo H. Stimulation of expression of the human endogenous retrovirus genome by female steroid hormones in human breast cancer cell line T47D. J Virol. 1987; 61: 2059-2062.

133. Leboyer M, Tamouza R, Charron D, et al. Human endogenous retrovirus type W (HERV-W) in schizophrenia a new avenue of research at the gene-environment interface. World J Biol Psychiatry. 2013; 14: 80-90.

134. Kwon DN, Lee YK, Greenhalgh DG, et al. Lipopolysaccharide stress induces cell-type specific production of murine leukemia virus type-endogenous retroviral virions in primary lymphoid cells. J Gen Virol. 2011; 92: 292-300.

135. Garcia-Montojo M, Rodriguez-Martin E, Ramos-Mozo P, et al. Syncytin-1/HERV-W envelope is an early activation marker of leukocytes and is upregulated in multiple sclerosis patients. Eur J Immunol. 2020; 50: 685-694.

136. Martínez-Mármol R, Giordano-Santini R, Kaulich E, et al. SA RS-CoV-2 infection and viral fusogens cause neuronal and glial fusion that compromises neuronal activity. Sci Adv. 2023; 9: eadg2248.

137. Martínez-Mármol R, Giordano-Santini R, Kaulich E, et al. SARS-CoV-2 infection and viral fusogens cause neuronal and glial fusion that compromises neuronal activity. Sci Adv. 2023; 9: eadg2248.

138. Wang YN, Ye Y, Zhou D, et al. The Role of Syncytin in Placental Angiogenesis and Fetal Growth. Front Cell Dev Biol. 2022; 10: 852561.

139. Noorali S, Rotar IC, Lewis C, et al. Role of HERV-W syncytin-1 in placentation and maintenance of human pregnancy. Appl Immunohistochem Mol Morphol. 2009; 17: 319-328.

140. Di Giorgio E, Xodo LE. Endogenous Retroviruses ERVs Does RLR RIG-I-Like Receptors-MAVS Pathway Directly Control Senescence and Aging as a Consequence of ERV De-Repression. Front Immunol. 2022; 13: 917998.

141. Zhou X, Singh M, Sanz Santos G, et al. Pharmacologic Activation of p53 Triggers Viral Mimicry Response Thereby Abolishing Tumor Immune Evasion and Promoting Antitumor Immunity. Cancer Discov. 2021; 11: 3090-3105.

142. Zhuo C, Wang D, Zhou C, et al. Double-Edged Sword of Tumour Suppressor Genes in Schizophrenia. Front Mol Neurosci. 2019; 12: 1.

143. Aftab A, Shah AA, Hashmi AM. Pathophysiological Role of HERV-W in Schizophrenia. J Neuropsychiatry Clin Neurosci. 2016; 28: 17-25.

144. Li M, Gao Y, Wang D, et al. Impaired Membrane Lipid Homeostasis in Schizophrenia. Schizophr Bull. 2022; 48: 1125-1135.

145. Heras-Martínez GL, Calleja V, Bailly R, et al. A Complex Interplay of Anionic Phospholipid Binding Regulates 3-Phosphoinositide-Dependent-Kinase-1 Homodimer Activation. Sci Rep. 2019; 9: 14527.

146. Huang BX, Akbar M, Kevala K, et al. Phosphatidylserine is a critical modulator for Akt activation. J Cell Biol. 2011; 192: 979-992.

147. Arcaro A, Aubert M, Espinosa del Hierro ME, et al. Critical role for lipid raft-associated Src kinases in activation of PI3K-Akt signalling. Cell Signal. 2007; 19: 1081-1092.

148. Lucas N, Cho W. Phosphatidylserine binding is essential for plasma membrane recruitment and signaling function of 3-phosphoinositide-dependent kinase-1. J Biol Chem. 2011; 286: 41265-41272.

149. Freyberg Z, Ferrando SJ, Javitch JA. Roles of the Akt/GSK-3 and Wnt signaling pathways in schizophrenia and antipsychotic drug action. Am J Psychiatry. 2010; 167: 388-396.

150. Urs NM, Snyder JC, Jacobsen JP, et al. Deletion of GSK3β in D2R-expressing neurons reveals distinct roles for β-arrestin signaling in antipsychotic and lithium action. Proc Natl Acad Sci USA. 2012; 109: 20732-20737.

151. Maas DA, Martens MB, Priovoulos N, et al. Key role for lipids in cognitive symptoms of schizophrenia. Transl Psychiatry. 2020; 10: 399.

152. Lin L, McCraw MR, Uluutku B, et al. Cell Membrane Oscillations under Radiofrequency Electromagnetic Modulation. Langmuir. 2023; 39: 3320-3331.

153. Yang ST, Kreutzberger AJB, Lee J, et al. The role of cholesterol in membrane fusion. Chem Phys Lipids. 2016; 199: 136-143.

154. Goñi FM, Alonso A. Effects of ceramide and other simple sphingolipids on membrane lateral structure. Biochim Biophys Acta. 2009; 1788: 169-177.

155. Sezgin E, Levental I, Mayor S, et al. The mystery of membrane organization composition, regulation and roles of lipid rafts. Nat Rev Mol Cell Biol. 2017; 18: 361-374.

156. Hamsanathan S, Gurkar AU. Lipids as Regulators of Cellular Senescence. Front Physiol. 2022; 13: 796850.

157. Kayoko Esaki, Shabeesh Balan, Yoshimi Iwayama, et al. Evidence for Altered Metabolism of Sphingosine-1-Phosphate in the Corpus Callosum of Patients with Schizophrenia. Schizophrenia Bulletin. 2020; 5: 1172-1181.

158. Zhuo C, Zhao F, Tian H, et al. Acid sphingomyelinase/ceramide system in schizophrenia implications for therapeutic intervention as a potential novel target. Transl Psychiatry. 2022; 12: 260.

159. Kayoko Esaki, Shabeesh Balan, Yoshimi Iwayama, et al. Evidence for Altered Metabolism of Sphingosine-1-Phosphate in the Corpus Callosum of Patients with Schizophrenia. Schizophrenia Bulletin. 2020; 5: 1172-1181.

160. Zhuo C, Zhao F, Tian H, et al. Acid sphingomyelinase/ceramide system in schizophrenia implications for therapeutic intervention as a potential novel target. Transl Psychiatry. 2022; 12: 260.

161. Alves I, Staneva G, Tessier C, et al. The interaction of antipsychotic drugs with lipids and subsequent lipid reorganization investigated using biophysical methods. Biochim Biophys Acta. 2011; 1808: 2009-2018.

162. Frajerman A, Chaumette B, Farabos D, et al. Membrane Lipids in Ultra-High-Risk Patients Potential Predictive Biomarkers of Conversion to Psychosis. Nutrients. 2023; 15: 2215.

163. Martín MG, Dotti CG. Plasma membrane and brain dysfunction of the old: Do we age from our membranes. Front Cell Dev Biol. 2022; 10: 1031007.

164. Tippetts TS, Holland WL, Summers SA. Cholesterol the devil you know; ceramide the devil you don't. Trends Pharmacol Sci. 2021; 42: 1082-1095.

165. Yu C, Alterman M, Dobrowsky RT. Ceramide displaces cholesterol from lipid rafts and decreases the association of the cholesterol binding protein caveolin-1. J Lipid Res. 2005; 46: 1678-1691.

166. Al-Rekabi Z, Contera S. Multifrequency AFM reveals lipid membrane mechanical properties and the effect of cholesterol in modulating viscoelasticity. Proc Natl Acad Sci USA. 2018; 115: 2658-2663.

167. Tetsuo Negishi, Constance L Chik, Anthony K Ho. Ceramide Enhances Growth Hormone (GH)-Releasing Hormone-Stimulated Cyclic Adenosine 3′,5′-Monophosphate Accumulation but Inhibits GH Release in Rat Anterior Pituitary Cells. Endocrinology. 1999; 140: 5691-5697.

168. Kim J, Kim HS, Choi DH, et al. Kaempferol tetrasaccharides restore skin atrophy via PDK1 inhibition in human skin cells and tissues Bench and clinical studies. Biomed Pharmacother. 2022; 156: 113864.

169. Maurya AK, Vinayak M. PI-103 and Quercetin Attenuate PI3K-AKT Signaling Pathway in T- Cell Lymphoma Exposed to Hydrogen Peroxide. PLoS One. 2016; 11: e0160686.

170. Singh S, Srivastava P. Molecular Docking Studies of Myricetin and Its Analogues against Human PDK-1 Kinase as Candidate Drugs for Cancer. SciRes. 2015; 2: 20-33.

171. Qin J, Fu M, Wang J, et al. PTEN/AKT/mTOR signaling mediates anticancer effects of epigallocatechin-3-gallate in ovarian cancer. Oncol Rep. 2020; 43: 1885-1896.

172. Zughaibi TA, Suhail M, Tarique M, et al. Targeting PI3K/Akt/mTOR Pathway by Different Flavonoids a Cancer Chemopreventive Approach. Int J Mol Sci. 2021; 22: 12455.

173. Liu X, Yao Z. Chronic over-nutrition and dysregulation of GSK3 in diseases. Nutr Metab. 2016; 13: 49.

174. Issinger OG, Guerra B. Phytochemicals in cancer and their effect on the PI3K/AKT-mediated cellular signalling. Biomed Pharmacother. 2021; 139: 111650.

175. Guerra B, Issinger OG. Natural Compounds and Derivatives as Ser/Thr Protein Kinase Modulators and Inhibitors. Pharmaceuticals (Basel). 2019; 12: 4.

176. Ding L, Ren C, Yang L, et al. OSU-03012 Disrupts Akt Signaling and Prevents Endometrial Carcinoma Progression *in vitro* and *in vivo*. Drug Des Devel Ther. 2021; 15: 1797-1810.

177. McCubrey JA, Lahair MM, Franklin RA. OSU-03012 in the treatment of glioblastoma. Mol Pharmacol. 2006; 70: 437-439.