Review Article

New concepts in the development of schizophrenia, autism spectrum disorders, and degenerative brain diseases based on chronic inflammation: A working hypothesis from continued advances in neuroscience research

Russell L. Blaylock[1], Miguel Faria[2]

[1]Theoretical Neuroscience Research, Ridgeland, Mississippi, [2]Clinical Professor of Surgery (Neurosurgery, ret.) and Adjunct Professor of Medical History (ret.), Mercer University School of Medicine, United States.

E-mail: *Russell L. Blaylock - blay6307@gmail.com; Miguel Faria - hfaria@windstream.net

*Corresponding author:
Russell Blaylock,
Theoretical Neuroscience
Research, Ridgeland,
Mississippi, United States.

blay6307@gmail.com

ABSTRACT

This paper was written prompted by a poignant film about adolescent girl with schizophrenia who babysits for a younger girl in an isolated cabin. Schizophrenia is an illness that both authors are fascinated with and that they continue to study and investigate. There is now compelling evidence that schizophrenia is a very complex syndrome that involves numerous neural pathways in the brain, far more than just dopaminergic and serotonergic systems. One of the more popular theories in recent literature is that it represents a hypo glutaminergic deficiency of certain pathways, including thalamic ones. After much review of research and study in this area, we have concluded that most such theories contain a number of shortcomings. Most are based on clinical responses to certain drugs, particularly antipsychotic drugs affecting the dopaminergic neurotransmitters; thus, assuming dopamine release was the central cause of the psychotic symptoms of schizophrenia. The theory was limited in that dopamine excess could only explain the positive symptoms of the disorder. Antipsychotic medications have minimal effectiveness for the negative and cognitive symptoms associated with schizophrenia. It has been estimated that 20–30% of patients show either a partial or no response to antipsychotic medications. In addition, the dopamine hypothesis does not explain the neuroanatomic findings in schizophrenia.

Keywords: Glutamate receptors, Immunoexcitotoxicity, Microglia, Pro-inflammatory cytokines

HISTORICAL BACKGROUND AND CLINICAL PRESENTATION

The following is a short introduction to the historical background of this disease and its clinical symptomatology. Schizophrenia was originally named *dementia praecox for* "premature dementia." In 1893, the German psychiatrist Emil Kraepelin separated the two psychoses with which this disorder had been confused: *dementia praecox* and manic depression. It was renamed schizophrenia by the Swiss psychiatrist Eugen Bleuler in 1908, meaning in Latin "split mind or split personality."[42] It was not until the mid-20th century that true schizophrenia was further separated from split (or multiple) personality hysteria — the latter, subsequently categorized as either a conversion reaction or a dissociative, identity disorder. Hollywood, though, continues

to confuse the two disorders — that is schizophrenia and hysteria — in their films.[41]

As one of us has written elsewhere, the two of the leading lights of psychiatry at the turn of the century, Austrian psychoanalyst Sigmund Freud (1856–1939) and German psychiatrist Emil Kraepelin (1856–1926) had conflicting approaches to mental illness, including schizophrenia. Freud recommended psychotherapy, which was almost always unsuccessful and unfeasible in severely mentally ill patients. Kraepelin, in contrast, preferred more aggressive intervention with electroconvulsive therapy and insulin shock therapy, the former often ineffective, the latter dangerous and no longer used. Thus, psychosurgery came into vogue; fortunately, it was soon supplanted by psychotherapy, which has proven much safer and most efficacious effective in Schizophrenia in at least 75% of patients.[42]

Necessarily in the original descriptions of the disease, the behavioral and sociological aspects of schizophrenia have been emphasized, but not it's anatomic, biochemical, or pathophysiological substrates. For example, schizophrenia has been described as a functional mental illness that begins gradually, occasionally almost suddenly, striking in adolescence or young adulthood. No standard neuroimaging techniques disclosed any definitive pathological abnormalities in these patients. Moreover, there was no objective pathognomonic test that would confirm the illness, which is still diagnosed on the clinical symptomatology and observed behavior.

In his autobiography, Nobel-prize winner Eric R Kandel explains how, as a psychiatrist and research neuroscientist, he had attempted to apply the scientific method to psychiatry as a new "science of the mind." He asserts that the human mind can be studied with biological tools to create this new science. He further asserts that in time all mental disorders, including those categorized as "functional" (or psychological, including schizophrenia by implication), will be found to have a structural, biochemical, and/or molecular basis, and that the old subjective criteria for psychiatric illnesses will completely give way to the new biological and scientific "science of the mind."[58] We do not agree with this viewpoint, rather we agree with Sir John Eccles that the mind is a separate metaphysical entity from the material brain. This does not negate the idea that dysfunction of the brain can result in abnormal behavior and thought patterns of a psychological nature. The analogy of a radio fits here perfectly. The radio represents the brain with its complex of circuits, transistors, and other electronic components, while the mind would represent the invisible radio waves giving activity to the electronic contraption. Any abnormality of the "radio" would be manifested as a garbled radio message or static.

In medical school and in our psychiatry rotations, we learn about the four fundamental symptomatologies of schizophrenia, originally described by Dr. Bleuler as the four as of schizophrenia: (1) looseness of associations, or disordered associations with a loss of contact with reality; (2) autism, a disordered conception of the world with a preference for fantasy rather than reality; (3) a disorder of affect, or an abnormal emotional state or mood; (4) ambivalence, a mixed feeling about a subject matter — one may be unconscious, but the contradictory attitudes may be indirectly expressed. Schizophrenia is also characterized by cognitive impairments, delusions, and hallucinations that are most frequently auditory.[91]

Neurophysiological disorders of the central nervous system neurotransmission and biochemical defects of neurotransmitters production, transport, reuptake, blockage, and degradation have provided the best theories for explaining the good to excellent responses in schizophrenic patients to a variety of neuropharmacological agents. In addition, defects in working memory associated with disconnection of the hippocampal formation with the prefrontal cortex and in neurotransmission in the dorsolateral prefrontal cortex and frontotemporal disconnection have implicated both the frontal and temporal lobes in the neuropathology of schizophrenia.[94,95]

IMMUNOEXCITOTOXICITY IN NEURODEGENERATIVE DISEASES AND SCHIZOPHRENIA

The leading author has written a number of papers on a newer hypothesis of neurodegenerative disease, of which schizophrenia is one.[13-16] This involves what he has described as immunoexcitotoxicity — that is an interaction between immune factors and glutamate receptors that leads to degeneration of specific groups of neurons and neural pathways. Central to this mechanism is prolonged or intermittent activation of the brain's microglia, a major source of immune cytokines, chemokines, and other immune factors as well as the excitotoxins, glutamate, aspartate, and quinolinic acid.[14,15,13,58]

Inflammation in the brain, especially if prolonged, triggers excitotoxicity, which over time destroys, first synaptic connections, axons, and then eventually neuronal cell bodies — something seen in postmortem examinations of autistic brains.[14] Because microglia are the source of both immune cytokines and other mediators as well as excitotoxins one may conclude that inflammation within the brain is always accompanied by excitotoxicity.[14,31] Associated with immunoexcitotoxicity one also witnesses, as an intimate part of the process, high levels of reactive oxygen species (ROS) and reactive nitrogen species and lipid peroxidation products accumulating within these affected brain areas.[81] This has also been confirmed in cases of schizophrenia.[90]

Both postmortem and most *in vivo* positron emission tomography (PET) scanning have demonstrated microglial activation in the affected areas of the brain of schizophrenia patients and autism spectrum disorder (ASD) patients.[47,111] Some PET scans for microglial activation did not show activation in unmedicated schizophrenia patients.[50,112] It has been suggested that in the case of medicated schizophrenic patients this may be because most scanned patients where on antipsychotic medications, but not all, and atypical forms of antipsychotic medications have been shown, in particular, to suppress microglial activation.[11,59]

Interestingly, the areas of the brain most affected in schizophrenia have been shown to have higher densities of microglia than are normally seen in healthy brains (28% higher in frontal cortex and 57% higher in temporal area).[47] The highest concentration of activated microglia occurred in Broadman area 9 an area characteristically affected in schizophrenia. We see this same finding in Parkinson's disease, with the substantia nigra naturally having the highest density of microglia in the brain.[15] In the normal brain, there are relatively high concentrations of microglia in the limbic areas of the brain and prefrontal cortex as well. In this study, the researchers also found that the highest microglial density occurred in the gray matter of the frontal, temporal and cingulate cortex, whereas in the subcortical white matter microglial density was only increased in the frontal and temporal area, concentrated mostly at the junction with the gray matter. No microglial density concentration was seen in the cingulate and corpus collosum subcortical white matter areas. No clustering of the microglia was observed, suggesting a lack of microglial proliferation or recruitment. This would indicate microglial density occurring during early neurodevelopmental stages.

Microglial activation and resulting immunoexcitotoxicity, especially with priming, would explain the dysfunctional behavioral control and cognitive deficiency seen in schizophrenia as this process would alter dendritic and synaptic pruning, and also interfere with later plasticity. The studies of first episode schizophrenia patients have shown extensive network damage in drug treatment naïve patients, which is also seen despite antipsychotic drug treatment.[26]

Microglia priming is also a critical process in this disorder and most neurodegenerative diseases.[9,14,15] Priming is a state where microglia have a dramatic increase in the enzyme systems and cellular signaling responsible for producing the destructive elements released by fully active microglia, such as the excitotoxins and immune mediators (proinflammatory cytokines, interferons and chemokines). Despite priming of the microglia, these destructive elements are not released by the primed microglia at that time. A subsequent immune challenge, either locally or systemically, will initiate full microglial activation and release of much higher levels of destructive elements than with unprimed microglia. Systemic inflammation is a major factor in microglial priming, but a number of environmental factors, both internal and external, can also prime microglia. Aging itself primes microglia.[48,100] Fully activated microglia experience induction of neuronal and inducible nitric oxide synthetase as well as COX-2 production of proinflammatory prostaglandins.[14]

Activation of microglia in schizophrenia was first reported in 1999, where microglial activation was seen in the frontal cortex and hippocampus in 14 patients.[9] Since then, this has been confirmed in a number of studies.[47,50,66] The hypo glutaminergic theory of schizophrenia is based largely on the findings that many of the positive symptoms of schizophrenia improve significantly following stimulation by NMDA receptor agonist and that specific glutamate blocking drugs (phencyclidine [PCP] and ketamine) can induce a schizophrenia-like condition in normal volunteers.[51] Dopamine receptor stimulation does not improve the negative symptoms or cognitive deficits.[46,56] In addition, 20–30% of schizophrenia patients show only partial or no response to antipsychotic treatment.[105]

One of the main problems we find with this theory is that there is compelling evidence that immune/inflammatory events occurring in utero and during early postnatal development can increase the risk of schizophrenia later in life, usually around adolescence.[20,73] Thus, early in the course of the disorder, even before the obvious symptoms develop, one may see subtle psychological changes, indicating that the process begins much earlier and is not fully manifest until a great deal of destructions occurs in brain connectivity and neuronal loss.[12] We hypothesize that early in the course of the disease one witnesses immunoexcitotoxicity, which as the disease progresses we see a progressive loss of neurons and their connections in selected areas of the brain. A loss of these neural pathways leads to further brain dysfunction, especially in memory and behavior. It should be kept in mind that glutamate is the major transmitter for over 50% of the brain and 90% of the cortex.

ASDS AND SCHIZOPHRENIA: A POSSIBLE LINK

It is also important to appreciate that schizophrenia and ASDs share core symptoms and overlap in many ways pathologically, mainly by extensive microglial activation, anatomical changes, and similar behavioral attributes.[25,64,73] Common to both conditions are deficits in social interaction and cognition. In both conditions one sees disruption of cognitive processing, disruption of emotional processing and abnormalities in sensory gating functions of the brain.[64,73] Anatomically, they also share abnormalities

in the cerebellum, insular cortex, right parahippocampus, posterior cingulate, putamen, claustrum, left thalamus, and fusiform gyrus.[16,109] Pinkman *et al.* also noted the two conditions also share a deficit pattern during neuronal activation triggered during social cognition task, specifically within the amygdala, fusiform gyrus, and ventrolateral prefrontal cortex.[87]

In addition, there appears to be a strong genetic link associated with both, and interestingly, a number of these genes have to do with control of microglial function (TREM2, TLRs, TYRO proteins, etc.).[90] Despite the genetic link, an environmental trigger appears to be essential in both disorders.

Research has clearly shown that early life events can have lasting impacts in the brain and behavioral function throughout life.[8,12] The strongest link to schizophrenia has been the observation that prenatal infections increase the risk of both autism and schizophrenia.[32,70] It has been shown that cytokines play an important role in brain development.[10,22] While it was first assumed that the infectious organisms were responsible for the increased incidence of schizophrenia in the offspring, subsequent studies demonstrated that the responsible factors were immune mediators. This was demonstrated by the use of non-infectious immune stimulators such and lipopolysaccharide (LPS) and Poly I: C (double stranded RNA molecule).[62] Both LPS and Poly I: C have been shown to elevate the levels of cytokines in the placenta, amniotic fluid, fetus, and fetal brain.[6]

Of the pro-inflammatory cytokines involved, IL-6 appears to play the major role. The studies have shown that blocking IL-6, using genetic or pharmacologic methods, prevented the long-term anatomical, and behavioral consequences of exposure to Poly I: C.[99]

It has also been shown that animals born to mothers who sustained an immune challenge during gestation demonstrated a specific set of abnormalities in brain function, such as deficits in working memory, abnormal executive function, impaired discrimination, and deficits in both spatial and non-spatial information processing.[32,72,85]

While there are many similarities between autism and schizophrenia, there are also major differences, such as excessive brain growth in the early stages of ASDs. This tends to disappear over time as the disorder progresses. One major difference is that with ASDs is that with ASDs brain inflammation is long-term and continuous, extending into adulthood.[113] One sees a 50-fold increase in TNF-alpha levels in cases of autism, far higher than we see in schizophrenia.[27] Data from autopsy studies and microglial scanning studies suggest that in the schizophrenia the brain inflammation is more intermittent throughout the disease

process. More recent studies suggest that in schizophrenia we are seeing inflammation beginning in prenatal life extending even into adulthood.[18] Despite this, chronic inflammation is less often seen with schizophrenia and IL-6 levels are only modestly elevated, as opposed to what is seen in ASDs.[89] Experimentally, a single dose of Poly I: C only produces acute inflammation in the fetus rather than extending into adulthood.[80,88]

INFLAMMATION AND SCHIZOPHRENIA

The studies have shown that patients with recent onset schizophrenia demonstrate activation of pro-inflammatory networks and inflammatory mediators.[74] Rather than continuous immune activation we may be seeing multiple hits throughout early years of the person's life occurring during development and during the long phase of progression. This would constitute a priming effect. Evidence for a priming effect comes from the observation that early life (prenatal or neonatal) exposure to immune stimulants cause an excessively vigorous immune reaction in the infant when stimulated. For example, we see higher levels of IL-6 and TNF following immune stimulation by phytohemagglutinin and LPS in schizophrenic patients than with normal controls.[79]

It has also been shown that success in treatment parallels lowering of these inflammatory cytokines.[77] Progressive brain atrophy occurs during the course of the disorder associated with either multiple hits or a lower grade, but continuous level of inflammation, less intense than we see with ASDs. Inflammation is also associated with childhood traumas and are associated with a proinflammatory phenotype and a higher incidence of adolescent onset schizophrenia.[36]

We have seen that experimental studies support the link between inflammation, elevated cytokines (especially IL-6) and the development of schizophrenia, including the anatomical and pathological changes seen in the disorder. The source of the pro-inflammatory cytokines appears to be mainly from activated and or primed microglia and invading macrophages, which once in the brain take on the appearance and function of microglia.[14] The question that remains would be—what is the ability of proinflammatory cytokines alone to cause neurodegeneration? For example, it has been shown that TNF-alpha alone in the CNS cannot destroy neurons, despite the presence of very high levels in the extraneuronal space.[83]

THE GLUTAMATE HYPOTHESIS FOR SCHIZOPHRENIA

Stone *et al.* noted that the dopaminergic hypothesis did not adequately explain all the neuroanatomical and clinical

findings in schizophrenia patients.[104] The glutamate hypothesis of schizophrenia causation began with the observation that specific NMDA receptor blockers, such as PCP and ketamine could transiently induce symptoms very similar to schizophrenia.[30] Unlike the antipsychotic medication targeting only the dopamine receptors, which only reduced the positive symptoms, glutamate blockers also improved the negative symptoms of schizophrenia as well as the cogitative problems.[57] Further evidence came from the finding that glutamate antagonists (NMDA receptor blockers) worsened the symptoms in schizophrenic patients.[2,65]

Initially, it was assumed that schizophrenia was a disorder of deficient glutamate receptor function universally. Subsequent studies came to a different conclusion. Most important, it was observed that both phencyclidine and ketamine were selective NMDA receptor blockers. Further studies also demonstrated that rather than low levels of glutamate in the brain, one sees elevated levels, particularly in the striatum and prefrontal cortex (especially anterior cingulate) following NMDA receptor blockade.[23,55,72,75,93] Clearly defined evidence of the effects of ketamine increasing anterior cingulate glutamate levels in humans was demonstrated by Rowland *et al.* in a study using healthy subjects.[93] We see similar elevations in brain glutamate following other agents known to inhibit glutamate release from specific areas of the brain, if confined to the NMDA receptors.[3] 1H-MRS studies have demonstrated increased glutamate brain levels in antipsychotic free and naive subjects during their first episode of psychosis, including subjects with ultra-high risk for psychosis.[34]

Additional evidence comes from treatment studies which have shown that unmedicated schizophrenia patients have elevated brain glutamate levels and that once successfully treated the glutamate levels return to normal. Clinical improvement parallels the fall in striatal glutamate levels.[33] In essence, treatment response seems to follow lowering of the brain glutamate levels in specific brain areas. A recent study found higher glutamate levels in the anterior cingulate cortex in antipsychotic treated patients who were unresponsive to the treatment drugs.[35]

That is, higher glutamate levels were seen in treatment resistant patients than in those who responded well to treatment.

The activated microglia are the main source of elevated glutamate. Inflammatory activation of microglia is accompanied by the release of excitotoxic levels of glutamate and other excitotoxic molecules such as quinolinic acid and aspartate.[14,66,107] Howes and McCutcheon have proposed that microglial activation during neurodevelopment may cause dopamine excess by reducing cortical inhibitory inputs to subcortical dopamine neurons.[52] This would sensitize the dopaminergic neurons to various stresses throughout early life, leading to dopaminergic initiated positive schizophrenic symptoms.[78] It is also known that dopaminergic neurons are influenced by glutamatergic neurons.[43,44] Prenatal activation of microglia has been shown to result in a delayed impairment of glutamatergic synaptic function, which would explain the behavioral and cognitive dysfunction which arises during postnatal development.[92]

HOW NMDA RECEPTOR UNDERACTIVATION RESULTS IN IMMUNOEXCITOTOXICITY AND ELEVATED BRAIN GLUTAMATE LEVELS

Initially, when impaired NMDA receptor function was discovered in schizophrenia, it was assumed that reduced overall glutaminergic function was responsible for the negative symptoms. Recent studies have demonstrated another mechanism. Rather than a general reduction in NMDA receptor function, new studies suggest the thalamus is the main site of NMDA receptor hypofunction.[98] These special NMDA receptor neurons synapse with thalamic GABAergic inter-neurons. A reduction in NMDA receptor function would reduce GABA production, leading to a disinhibition of excitatory downstream neurons. These excitatory neurons synapse with glutaminergic neurons across multiple brain areas known to be hyperactive in schizophrenia.[98,110] Injection of NMDA antagonist into the anterior nucleus of the thalamus results in cortical degeneration, but direct injections of these antagonists into the cortex has no degenerative effects.[98]

The extraneuronal surge of glutamate occurring with NMDA receptor antagonism causes neurodegeneration most likely by acting through AMPA/kainate receptors, in particular, the calcium sensitive GluR2-lacking AMPA receptors.[37,54] Additional evidence comes from the observation that minocycline, by suppressing microglial activation, has been effective in treating the negative symptoms of schizophrenia in antipsychotic refractory cases.[63]

IMMUNOEXCITOTOXIC NEURODEGENERATION IN SCHIZOPHRENIA

A combination of microglial activation and suppression of GABAnergic activity by NMDA receptor suppression, leads to a significant elevation in extraneuronal glutamate levels[34,60] [Figure 1]. Further, the evidence of the critical role being played by associated glutamate elevation was demonstrated in a study using healthy human volunteers in which agents that inhibited glutamate release reversed behavioral and cognitive changes induced by NMDA receptor antagonists.[3]
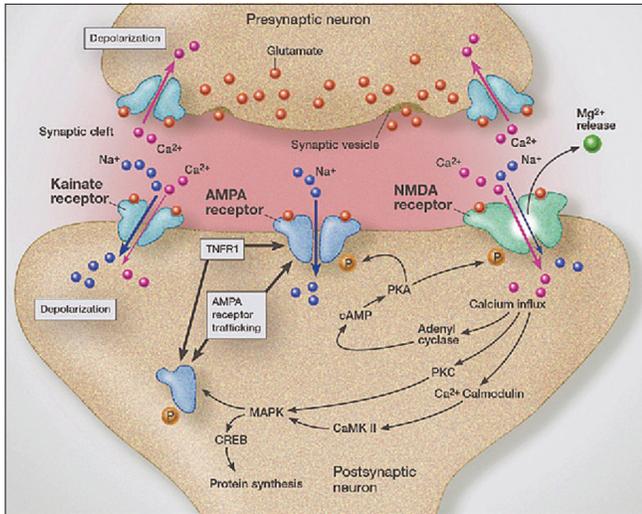
Figure 1: Illustration of pre- and post-synaptic junction demonstrating the neurochemical activity of the three major types of ionotropic glutamate receptors, NMDA, AMPK and Kainate receptors.

It has been hypothesized that the excitotoxicity occurs through excessive activation of AMPA/kainate receptors by the elevated extraneuronal glutamate[1] [Figure 2]. Elevation of quinolinic acid (QUIN) occurs in the face of CNS inflammation as well by shifting the metabolism of tryptophan toward QUIN formation. Elevation of QUIN has been associated with major depression by immune modulation of glutamatergic neurotransmission.[101]

INTERACTION BETWEEN THE IMMUNE SYSTEM AND GLUTAMATE RECEPTORS: MECHANISM OF IMMUNOEXCITOTOXICITY

The earliest reports demonstrating an enhancement of excitotoxicity by TNF-alpha were by Gelbard *et al.* in which they used human neuronal cultures exposed to subtoxic dose of TNF-alpha and AMPA.[45] When exposed individually to these compounds no toxicity was seen but when combined, full excitotoxic neuronal injury was observed. Later this synergistic effect of combining TNF-alpha and an excitotoxic amino acid was shown in an *in vivo* model in which subtoxic doses of either substance alone had no significant toxic effect but when combined produced a large area of tissue necrosis.[49] It was further shown that TNF-alpha, by stimulating TNFR1 pathway, induced excitotoxicity by stimulating the release of high levels of glutamate from the microglia through hemichannels into the extraneuronal space[106] [Figure 3]. It was also shown that stimulation of group 2 metabotropic glutamate receptors (mGluRs) induces TNF-alpha release from microglia. Olmos and Llado proposed that excitotoxicity was enhanced by the ability of
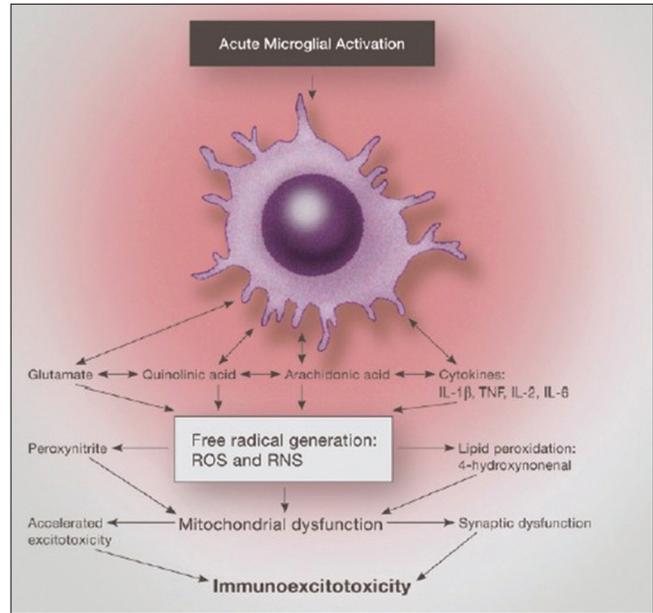
Figure 2: Illustration of the mechanism of immunoexcitotoxicity focusing on a combination of immune activation and excitotoxicity originating from activated microglia. Once fully activated, the microglia releases a combination of immune mediators and excitotoxic compounds with subsequent generation of high levels of reactive oxygen and nitrogen species and lipid peroxidation products. This combination results in mitochondrial dysfunction, further energy deficits, and accelerated excitotoxicity with subsequent neurodegeneration of surrounding structures.

autocrine enhancement of TNF-alpha release from microglia which stimulated inflammatory pathways in the microglia, enhancing the release of glutamate into the extracellular space.[83]

It has also been shown that elevation of proinflammatory cytokines, especially TNF-alpha, inhibits the glutamate reuptake transporters GLAST and GLT-1, which raises extracellular glutamate levels to neurotoxic levels and prevents lowering of extracellular glutamate during activity of the cystine-glutamate antiporter.[19,61,69,108] TNF-alpha also stimulates the up-regulation of glutaminase, the enzyme that converts glutamine to glutamate within astrocytes and microglia.[13,14] Glutamine synthetase, the enzyme responsible for converting glutamate into glutamine, is also suppressed by elevated levels of TNF-alpha.[13,14] TNF-alpha acts through its receptor TNFR1 on microglia to stimulate trafficking of GluR2-lacking AMPA receptors to the neuronal synaptic membrane.[67] These special AMPA receptors, because they are calcium permeable and increaseintraneuronal calcium levels, are more prone to inducing excitotoxicity. In addition, TNF-alpha stimulates internal trafficking of GABA receptors.

Together, these TNF-alpha related effects on glutamate receptors, enzymes and trafficking enhance excitotoxicity

Figure 3: Illustration demonstrating the various ways TNF-alpha enhances excitotoxicity. Other pro-inflammatory cytokines also enhance excitotoxicity, such as IL-1, IL-6, and IL-17, but TNF-alpha is the most prominent player. Excitotoxicity appears to be the final and most destructive event triggered by inflammation and/or microglial priming/activation.

and intimately link inflammatory mediators to excitotoxicity. Because activated microglia are the principal source of both excitotoxins and inflammatory mediators, it becomes difficult to determine exactly how much each contributes to neurodegeneration. My impression is that excitotoxicity is the final common pathway responsible for most of the neurodestruction when microglial are activated.[13,14]

It appears that the neurological damage occurs first either during the third trimester of pregnancy or soon after birth and that until the symptoms of psychosis present themselves. There is a progressive interference with neurodevelopment as well as a process of progressive neurodegeneration of the most involved areas of the brain following birth.[10,12]

NEURODEGENERATION AND SCHIZOPHRENIA

Another important suggestion of excitotoxic neurodegeneration occurs with the widespread loss of neurons and connectivity as the disorder progresses. One sees progressive loss of grey matter volume beginning early in life which continues chronically.[4,53] The greatest grey matter loss occurs in the superior temporal, medial temporal, superior prefrontal, medial prefrontal, thalamus, basal ganglion, and insular regions.[17] Whole brain degeneration also occurs associated with ventricular enlargement and alterations in

white matter.[28,29] NMDA antagonist demonstrate neurotoxic injury and neurodegeneration in specific cells in rats.[39] Yet, there is some evidence that excitotoxicity continues in some brain areas and that mGluR5 is overactive (which is excitotoxic). A more selective suppression of mGluR5 may be beneficial.[90]

Of interest, blocking agonist of metabolic glutamate receptor types 2 and 3 blocks the neurotoxic effects of NMDA antagonists in preclinical models of schizophrenia.[24] These mGluRs negatively modulate glutamate excitotoxicity. These experimental changes are age-dependent just as we see in clinical schizophrenia.[40] As with clinical cases of schizophrenia, experimental models show the greatest neurodegenerative changes beginning with adolescence.[7]

It has been suggested that schizophrenics are generally heavy smokers.[71] It is known that nicotine is a powerful stimulant of the alpha-7 nicotinic acetylcholine receptors, which are suppressors of inflammation and generally responsible for controlling inflammation within the brain—the so-called cholinergic anti-inflammatory system.[86] A loss of nicotinic receptors, which occurs in schizophrenia and ASDs, is thought to enhance brain inflammation.[73] The anti-inflammatory cytokine, TGF-ß1 is also severely lowered in schizophrenia and ASD.[82] Hence, we see a serious imbalance between pro- and anti-inflammatory mechanisms within the schizophrenic brain, with pro-inflammatory predominance.[90]

SCHIZOPHRENIA AND GUT INFLAMMATION

The big question is: What is causing the chronic, low-level inflammation? It has been shown clearly that prenatal infections in the mother can cause postnatal schizophrenia and more recent studies using non-infectious Poly I: C have shown that the mechanism involves cytokine elevations, principally IL-6 and not actual infection.[5,6,76,99] In animal models, blocking IL-6 (IL-8 and IL-1ß) can prevent the schizophrenia/ASD onset postnatally.[21,32,84,90,99]

Another link that has a lot of validity, certainly in some cases of both ASD and schizophrenia, is gut inflammation. Gliadin and gluten have been shown to trigger chronic microglial activation and are linked clinically to a number of cases of schizophrenia.[38,96] Several reports describe significant improvement of cases on assuming a gluten-free diet, while others found little or no improvement.[38,68] There may be an explanation for the failure of improvement on a gluten free diet in these cases.[1] First, it should be appreciated that these gluten-linked cases are associated with a non-celiac gluten sensitivity, which does not show the usual antibody profile of typical celiac disease cases and there is no villus atrophy on duodenal biopsy. This has been called non-celiac gluten sensitivity.[97]

As for why some cases fail to improve, it has been shown that gluten can trigger increased gut permeability, which can persist in some cases after starting a gluten-free diet, as there are often other contributing factors also linked to gut permeability, such as use of nonsteroidal anti-inflammatory drugs. Translocation of other food proteins and colon/intestinal bacteria can trigger continued microglial activation with resulting persistent immunoexcitotoxicity. In addition, gut inflammation can send afferents through the vagus nerve that activate brain microglia.[97] In addition, once the microglia are primed, other environmental factors can precipitate continued microglial activation, such as heavy metals, aluminum, fluoroaluminum, microparticulate fuels, and certain pesticides/herbicides.[103]

CONCLUSION

It is of interest that many of the antipsychotic medications used to treat schizophrenia are known to suppress microglial activation and alter glutamate receptor function.[104] These include risperidone, clozapine, and olanzapine. Some also reduce ROS damage. The studies have shown that drug responses correlate with lowering of S100B levels, a marker for brain inflammation.[90]

As for the neurotransmitters, especially dopamine, it has been shown that treatment resistant forms of schizophrenia (type B patients) were associated with relatively normal levels of dopamine synthesis in the striatum and elevated glutamate levels in the anterior cingulate cortex.[51]

The disruption of several neurotransmitters in schizophrenia is consistent with immunoexcitotoxicity, as a number of neuron types, receptor types and subtypes are affected by high levels of inflammation and excitotoxicity, with associated elevations in reactive oxygen and nitrogen species and lipid peroxidation — that is, these changes are epiphenomenon.

In our opinion, we should be addressing the central mechanism of the problem (immunoexcitotoxicity and microglial activation) rather than attempting to fine tune neurotransmitter disruptions, which can appear in a complex, variable, and often confusing presentation. This also requires attention to gut inflammation and correction of the microbiome.[51] I would refer the reader to my paper in the journal *Surgical Neurology International,* in which i describe in detail how the mechanism of microglial/macrophage-induced immunoexcitotoxicity plays a central mechanism of neurodegeneration in Parkinson's disease.[15]

*An AMPA receptor is the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor is an ionotropic transmembrane receptor for glutamate that mediates fast synaptic transmission in the central nervous system (CNS), and it is considered a non-NMDA receptor

Dr. Russell L. Blaylock is an Associate Editor-in-Chief of the Neuroinflammation and Neuropsychiatry sections and a Consulting Editor in Basic Neuroscience for Surgical Neurology International (SNI).

Dr. Miguel A. Faria is an Associate Editor in Chief in Neuropsychiatry; History of Medicine; and Socioeconomics, Politics, and World Affairs of Surgical Neurology International (SNI).

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

Financial support and sponsorship

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Abbott C, Bustillo J. What have we learned from proton magnetic resonance spectroscopy about schizophrenia? A critical update. Clin Neuropharmacol 2001;24:43-9.
2. Adler CM, Malhotra AK, Elman I, Goldberg T, Egan M, Pickar D, *et al.* Comparison of ketamine-induced thought

disorder in healthy volunteers and thought disorder in schizophrenia. Am J Psychiatry 1999;156:1646-9.

3. Anand A, Charney DS, Oren DA, Berman RM, Hu XS, Cappiello A, et al. Attenuation of the neuropsychiatric effects of ketamine with lamotrigine: Support for hyperglutamatergic effect of N-methyl-D-aspartate receptor antagonists. Arch Gen Psychiatry 2000;57:270-6.

4. Arrango C, Rapado-Castro M, Reig S, Castro-Fornieles J, Gonzales-Pinto A, Ptero S, Baeza I, et al. Progressive brain change in children and adolescent with first-episode psychosis. Arch Gen Psychiatry 2012;69:16-26.

5. Arrode-Bruses G, Bruses JL. Maternal immune activation by poly (I: C) induces expression of cytokines IL-1ß and IL-13, chemokine MCP-1 and colony stimulating factor VEGF in fetal mouse brain. J Neuroinflammation 2012;9:83.

6. Ashdown H, Dumont Y, Ng M, Poole S, Boska P, Luheshi GN. The role of cytokines in mediating effects of prenatal infection in the fetus: Implications for schizophrenics. Mol Psychiatry 2006;11:47-55.

7. Auer RN. Effect of age and sex on N-methyl-D-aspartate antagonists-induced neuronal necrosis in rats. Stroke 1996;27:743-6.

8. Bale TL, Baram TZ, Brown AS, Goldsstein JM, Insel TR, McCarthy MM, et al. Early life programming and neurodevelopmental disorders. Biol Psychiatry 2010;68:314-9.

9. Bayer TA, Buslei R, Havas L, Falkai P. Evidence for activation of microglia in patients with psychiatric illnesses. Neurosci Lett 1999;271:126-8.

10. Benveniste EN. Cytokine actions in the central nervous system. Cytokine Growth Rev 1998;9:259-75.

11. Bian Q, Kato T, Monji A, Hashioka S, Mizoquchi Y, Horikawa H, et al. The effect of atypical antipsychotics, perospirone, zoprasiclone and quetrapine on microglial activation induced by interferon-gamma. Prog Neuropsychopharmacol Biol Psychiatry 2008;32:42-8.

12. Bilbo SD, Schwartz JM. Early-life programming of later-life brain and behavior: A critical role for the immune system. Front Behav Neurosci 2009;3:14.

13. Blaylock RL, Maroon J. Immunoexcitotoxicity as a central mechanism in chronic traumatic encephalopathy-a unifying hypothesis. Surg Neurol Int 2011;2:107.

14. Blaylock RL. Immunology primer for neurosurgeons and neurologists Part 2: Innate brain immunity. Surg Neurol Int 2013;4:118.

15. Blaylock RL. Parkinson's disease: Microglial/macrophage-induced immunoexcitotoxicity as a central mechanism of neurodegeneration. Surg Neurol Int 2017;8:65.

16. Blaylock RL. The Cerebellum in autism spectrum disorders. In: Strunecka A, editor. Cellular and Molecular Biology of Autism Spectrum Disorders. United Arab Emirates: Bentham Books; 2010. p. 17-31.

17. Bora E, Fornito A, Radua J, Walterfang M, Seal M, Wood SJ, et al. Neuroanatomical abnormalities in schizophrenia: A multimodal voxelwise meta-analysis and meta-regression analysis. Schizophr Res 2011;127:46-57.

18. Borrell J, Vela JM, Arevalo-Martin A, Molina-Holgado E, Guaza C. Prenatal immune challenge disrupts sensomotor gating in adult rats, Implications for the etiopathogenesis of schizophrenia. Neuropsychpharmacology 2002;26:204-15.

19. Bridges RJ, Natale NR, Patel SA. System xc-cystine/glutamate antiporter: An update on molecular pharmacology and roles within the CNS. Br J Pharmacol 2012;165:20-34.

20. Brown AS, Derkits EJ. Prenatal infection and schizophrenia: A review of epidemiological and translational studies. Am J Psychiatry 2010;167:261-80.

21. Brown AS, Hooton J, Schaefer CA, Zhang H, Petkova E, Babulas V, et al. Elevated maternal interleukin-8 levels and risk of schizophrenia in adult offspring. Am J Psychiatry 2004;161:889-95.

22. Burns TM, Clough JA, Klein RM, Wood GW, Bergman NE. Developmental regulation of cytokine expression in the mouse brain. Growth Factors 1993;9:253-8.

23. Bustos G, Abarca J, Forray MI, Gysling K, Bradberry CW, Roth RH. Regulation of excitatory amino acid release by N-methyl-D-aspartate receptors in rat striatum: In vivo micro-dialysis studies. Brain Res 1992;585:105-15.

24. Carter K, Dickerson J, Schoepp DD, Reilly M, Herring N, Williams J, et al. The mGlu2/3 receptor agonists LY379268 injected into cortex or thalamus decreases neuronal injury in retrosplenal cortex produced by NMDA receptor antagonist MK-801: Possible implication for psychosis. Neuropharmacology 2004;47:1135-45.

25. Cheng C, Yu K, Fung G, Leung M, Wong C, Li Q, et al. Autistic disorder and schizophrenia: Related ort remote? An anatomical likelihood estimation. PLoS One 2010;5:e12233.

26. Chenz Z, Deng W, Gong Q, Huang C, Jiang L, Li M, et al. Extensive brain structural network anomaly in first-episode treatment-naïve patients with schizophrenia: Morphometrical and covariation study. Psychol Med 2014;44:2489-501.

27. Chez MG, Dowling T, Patel PB, Khanna P, Kominsky M. Elevation of tumor necrosis factor-alpha in cerebrospinal fluid of autistic children. Pediatr Neurol 2007;36:361-5.

28. Colibazzi T, Wexler BE, Bansal R, Hao X, Liu J, Sanchez-Pena J, et al. Anatomical abnormalities in gray and white matter of the cortical surface in persons with schizophrenia. PLoS One 2013;8:e55783.

29. Connor CM, Crawford BC, Akbarian S. White matter neuron alterations in schizophrenia and related disorders. In J Dev Neurosci 2011;29:325-34.

30. Coyle JT, Tsai G, Goff D. Converging evidence of NMDA receptor hypofunction in the pathophysiology of schizophrenia. Ann N Y Acad Sci 2003;1003:318-27.

31. da Cunha A, Nunes FB, Lunardelli A, Pauli V, Amaral RH, de Oliveira LM, et al. Treatment with N-methyl-D-aspartate receptor antagonist (MK-801) protects against oxidative stress in lipopolysaccharide-induced acute lung injury. Int Immunopharmacol 2011;11:706-11.

32. Dammann O, Leviton A. Maternal intrauterine infection, cytokines, and brain damage in the preterm newborn. Pediatr Res 1997;42:1-8.

33. de la Fuente-Sandoval C, Leon-Ortez P, Azacarraga M, Stephano S, Favila R, Diaz-Galvis L, et al. Glutamate levels in the associative striatum before and after 4 weeks of antipsychotic treatment in first episode psychosis: A longitudinal proton magnetic resonance spectroscopy study. JAMA Psychiatry 2013;70:1057-66.

34. de la Funte-Sandoval C, Leon-Ortez P, Favila R, Stephanos S, Mamo D, Ramirez-Bermudez J, *et al*. Higher levels of glutamate in the associative-striatum of subjects with prodromal symptoms of schizophrenia and patients with first episode psychosis. Neuropsychopharmacology 2011;36:1781-91.

35. Demjaha A, Egerton A, Murray RM, Kapur S, Howes OD, Stone JM, *et al*. Antipsychotic treatment resistance in schizophrenia associated with elevated glutamate levels but normal dynamic function. Biol Psychiatry 2014;75:e11-3.

36. Dennison U, McKernan D, Cryan J, Dianan T. Schizophrenia patients with a history of childhood trauma have a pro-inflammatory phenotype. Psychol Med 2012;42:1865-71.

37. Deutsh SI, Rosse RB, Schwartz BL, Mastropaolo JA. A revised excitotoxic hypothesis of schizophrenia: Therapeutic implications. Clin Neuropharmacol 2001;24:43-9.

38. Ergun C, Urhan M, Ayer A. A review on the relationship between gluten and schizophrenia: Is gluten the cause? Nutr Neurosci 2018:21:455-66.

39. Farber NB, Wozniak DF, Price MT, Labruyere J, Huss J, St Peter H, *et al*. Age-specific neurotoxicity in the rat associated with NMDA receptor blockade: Potential relevance to schizophrenia? Biol Psychiatry 1995;38:788-96.

40. Farber NB. The NMDA receptor hypofunction model of psychosis. Ann N Y Acad Sci 2003;1003:119-30.

41. Faria MA. Schizophrenia in the Dramatic Film "Occupied" (2011) and its Critics. United Arab Emirates: Hacienda Publishing; 2018. Available from: https://www.haciendapublishing.com/schizophrenia-in-the-dramatic-film-occupied-2011-and-its-critics-by-miguel-a-faria-md. [Last assecced on 2021 Oct 04].

42. Faria MA. Violence, mental illness, and the brain-a brief history of psychosurgery: Part 1-from trephination to lobotomy. Surg Neurol Int 2013;4:49.

43. Floresco SB, Todd CL, Grace AA. Glutamatergic afferents from the hippocampus to the nucleus accumbens regulate activity of ventral tegmental area dopamine neurons. J Neurosci 2001;21:4915-22.

44. Galtieri DJ, Estep CM, Wokosin DL, Traynelis S, Surmeier DJ. Peduculopontine glutamatergic neurons control spike patterning in substantia nigra dopaminergic neurons. Elife 2017;6:e30352.

45. Gelbard HA, Dzenko KA, DiLoreto D, del Cerro C, del Cerro M, Epstein LG. Neurotoxic effects of tumor necrosis factor alpha in primary human neuronal cultures are mediated by activation of the glutamate AMPA receptor subtype: Implications for AIIDS neuropathogenesis. Dev Neurosci 1994;16:417-22.

46. George M, Amruthesehwar R, Rajkumar RP, Kattimani D, Dkhar SA. Newer antipsychotics and upcoming molecules for schizophrenia. Eur J Clin Pharmacol 2013;69:1497-509.

47. Gober R, Ardalan M, Shiadeh SM, Duque L, Garamsregi SP, Ascona M, *et al*. Microglial activation in postmortem brains with schizophrenia demonstrates distinct morphological changes between brain regions. Brain Path 2021;1:e13003.

48. Godbout JP, Moreau M, Lestage J, Sparkman NL, O'Connor J, Castanon N, *et al*. Aging exacerbates depressive-like behavior in mice in response to activation if the peripheral innate immune system. Neuropsychopharmacology 2007;33:2341-51.

49. Hermann GE, Rogers RC, Bresnahan JC, Beattie MS. Tumor necrosis factor alpha induces cFOS and strongly promotes glutamate-mediated cell death in the rat spinal cord. Neurobiol Dis 2001;8:590-9.

50. Holmes S, Hinz R, Drake R, Gregory C, Conen S, Matthews J, *et al*. *In vivo* imaging of brain microglial activity in antipsychotic-free and medicated schizophrenia: A [^{11}C](R)-PK11195 positron emission tomography study. Mol Psychiatry 2016;21:1672-9.

51. Howes O, McCutcheon R, Stone J. Glutamate and dopamine in schizophrenia: An update for the 21st Century. J Psychopharmacology 2015;29:97-115.

52. Howes OD, McCutcheon R. Inflammation and the neural diathesis-stress hypothesis of schizophrenia: A reconceptualization. Transl Psychiatry 2017;7:e1024.

53. Hutshoff Pol HE, Kahn RS. What happens after the first episode? A review of progressive brain changes in chronically ill patients with schizophrenia. Schizophr Bull 2008;34:354-66.

54. Ikonomidou C, Bosch F, Miksa M, Bittgau P, Vockler J, Dirkranian K, *et al*. Blockade of NMDA receptors and apoptotic neurodegeneration in the developing brain. Science 1999;283:70-4.

55. Iltis I, Koski DM, Eberly LE, Lenson CD, Deelehand DK, Valette J, *et al*. Neurochemical changes in the rat prefrontal cortex following acute phencyclidine treatment: An *in vivo* localized (1)H MRS study. NMR Biomed 2009;22:737-44.

56. Javitt DC, Zukin SR, Heresco-Levy U, Umbricht D. Has an angel shown the way? Etiology and therapeutic implications of the PCP/NMDA model schizophrenia. Schizophr Bull 2012;38:958-66.

57. Javitt DC, Zukin SR. Recent advances in the phencyclidine model of schizophrenia. Am J Psychiatry 1991;148:1301-8.

58. Kandel ER. Search of Memory: The Emergence of a New Science of Mind. New York: WW Norton; 2006. Available from: https://www.surgicalneurologyint.com/wp-content/uploads/2020/08/10205/sni-11-252.pdf. [Last assecced on 2021 Oct 04].

59. Kato T, Monji A, Hashioka S, Kanba S. Risperidone significantly inhibits interferon-gamma induced microglial activation *in vitro*. Schizophr Res 2007;92:108-15.

60. Kegelos LS, Mao X, Stanford AD, Girgis R, Ojeil N, Xu X, *et al*. Elevated prefrontal cortex gamma-aminobutyric acid and glutamate-glutamine levels in schizophrenia measured *in vivo* with proton magnetic resonance spectroscopy. Arch Gen Psychiatry 2012;69:449-59.

61. Kigerl KA, Ankeny DP, Garg SK, Guan Z, Lai W, McTigue DM, *et al*. System X (c) (-) regulates microglia and macrophage glutamate excitotoxicity *in vivo*. Exp Neurol 2012;233:333-41.

62. Kimura M, Toth LA, Agostini H, Cady AB, Majde JA, Kruger JM. Comparison of acute phase responses induced in rabbits by lipopolysaccharide and double-stranded RNA. Am J Physiol 1994;267:R1596-605.

63. Kiss T, Hoffmann WE, Scott L, Kawabe TT, Milici AJ, Nilsen EA, *et al*. Role of thalamic projections in NMDA receptor-induced disruption of cortical slow oscillation and short-term plasticity. Front Psychiatry 2011;2:14.

64. Kolvin I. Studies in the childhood psychoses. I. Diagnostic criteria and classification. Br J Psychiatry 1971;118:381-4.

65. Lahti AC, Koffel B, LaPorte D, Tamminga CA. Subanesthetic doses of ketamine stimulate psychosis in schizophrenia. Neuropsychopharmacology 1995;13:9-19.
66. Laskaris LE, Biase MA, Everall I, Chana G, Christopoulos A, Skafidas E, et al. Microglial activation and progressive brain changes in schizophrenia. Br J Pharmacol 2016;173:666-80.
67. Leonoudakis D, Zhao P, Beattie EC. Rapid tumor necrosis factor alpha-induced exocytosis of glutamate receptor 2-lacking AMPA receptors to extrasynaptic plasma membrane potentiates excitotoxicity. J Neurosci 2008;28:2119-30.
68. Levinta A, Mukovozov I, Tsoutsoulas C. Use of a gluten-free diet in schizophrenia: A systematic review. Adv Nutr 2018;9:824-32.
69. Liao SL, Chen CJ. Differential effects of cytokines and redox potential on glutamate uptake in rat cortical glial cultures. Neurosci Lett 2001;299:113-6.
70. Libby JE, Sweeten TL, McMahon WM, Funjinami RS. Autistic disorder and viral infections. J Neurovirol 2005;11:1-10.
71. Lohr JB, Flynn K. Smoking and schizophrenia. Schizophr Res 1992;8:93-102.
72. Meyer U, Feldon J, Yee BK. A review of the fetal brain cytokine imbalance hypothesis of schizophrenia. Schizophr Bull 2009;35:959-72.
73. Meyer UR, Feldon J, Dammann O. Schizophrenia and autism: Both shared and disorder-specific pathogenesis via perinatal inflammation? Pediatr Res 2011;69:26R-33R.
74. Miller BJ, Buckley P, Seabolt W, Mellor A, Kirkpatrick B. Meta-analysis of cytokine alteration in schizophrenia: Clinical status and antipsychotic effects. Biol Psychiatry 2011;70:663-71.
75. Moghaddam B, Adam B, Verma A, Daly D. Activation of glutamatergic neurotransmission by ketamine: A novel step in the pathway from NMDA receptor blockade to dopaminergic and cognitive disruption associated with the prefrontal cortex. J Neurosci 1997;17:2921-7.
76. Monji A, Kato T, Kanba S. Cytokines and schizophrenia: Microglial hypothesis of schizophrenia. Psychiatry Clin Neurosci 2009;63:257-65.
77. Muller N Inflammation in schizophrenia: Pathogenetic aspects and therapeutic considerations. Schizophr Bull 2018;44:973-82.
78. Muller N, Schwartz MJ. The immunological basis of glutamatergic disturbance in schizophrenia: Towards an integrated view. J Neural Transm Suppl 2007;72:269-80.
79. Nak S, Kim YK. Monocytic, Th1 and Th2 cytokine alterations in the pathophysiology of schizophrenia. Neuropsychobiology 2007;56:55-63.
80. Nyffer M, Meyer U, Yee BK, Feldon J, Knuesel I. Maternal immune activator during pregnancy increases limbic GABAA receptor immunoreactivity in the adult offspring: Implications in schizophrenia. Neuroscience 2006;143:51-62.
81. Nyuygen D, Alvi MV, Kim KY, Kang T, Scott RT, Noh YH, et al. A new vicious cycle involving glutamate excitotoxicity, oxidative stress and mitochondrial dynamics. Cell Death Dis 2011;1:e240.
82. Okada K, Hashimoto K, Iwata Y, Nakamura K, Tsujii M, Tsuchiya KJ, et al. Decreased serum levels of transforming growth factor-ß1 in patients with autism. Prog Neuropsychopharmacol Biol Psychiatry 2007;31:187-90.
83. Olomos G, Llado J. Tumor necrosis factor alpha: A link between neuroinflammation and excitotoxicity. Mediators Inflamm 2014;2014:861231.
84. Parket-Athill EC, Tan J. Maternal activation and autism spectrum disorder: Interleukin-6 signaling as a key mechanistic pathway. Neurosignals 2010;18:113-28.
85. Patterson PH. Immune involvement in schizophrenia and autism: Etiology, pathology, and animal models. Behav Brain Res 2009;205:313-21.
86. Pavlov VA, Wang H, Czura CJ, Friedman SG, Tracy KJ. The cholinergic anti-inflammatory pathway: A missing link in neuroimmunomodulation. Mol Med 2003;9:125-34.
87. Pinkman AE, Hopfinger JB, Pelphrey KA, Piven J, Penn DL. Neural basis for impaired social cognition in schizophrenia and autism spectrum disorders. Schizophr Res 2008;99:164-75.
88. Ponzio NM, Servatius R, Beck K, Marzouk A, Kreider T. Cytokine levels during pregnancy influence immunological profiles and neurobehavioral patterns of the offspiring. Ann N Y Acad Sci 2007;1107:118-28.
89. Potvin S, Stip E, Sepehry AA, Gendron A, Bah R. Kouassi E. Inflammatory cytokine alteration in schizophrenia: A systematic quantitative review. Biol Psychiatry 2008;63:801-8.
90. Prata J, Santos SG, Almeida MI, Coelho R, Barbosa MA. Bridging autism spectrum disorders and schizophrenia through inflammation and biomarkers-pre-clinical and clinical investigations. J Neuroinflammation 2017;14:179.
91. Randel PM, McCurdy L, editors. The Psychiatry Learning System-a Multimedia Self-Instructional Course in Basic Psychiatry. 2nd ed. Charleston, SC: Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina; 1975.
92. Roumier A, Pascual O, Bechade C, Wakselman S, Poncer JC, Real E, et al. Prenatal activation of microglia induces delayed impairment of glutamatergic synaptic function. PLoS One 2008;3:e2595.
93. Rowland LM, Bustillo JR, Mullins PG, Jung RE, Lenroot R, Landgraf E, et al. Effects of ketamine on anterior cingulate glutamate metabolism in healthy humans: A 4-T proton MRS study. Am J Psychiatry 2005;162:394-6.
94. Salloway SP, Malloy PF, Cummings JF. The Neuropsychiatry of Limbic and Subcortical Disorders. Washington, DC: American Psychiatric Publishing, Inc.; 1997. p. 155-66, 187-98.
95. Salloway SP, Malloy PF, Duffy JD. The Frontal Lobes and Neuropsychiatric Illness. Washington, DC: American Psychiatric Publishing, Inc.; 2001. p. 71-82. Available from: https://www.surgicalneurologyint.com/surgicalint-articles/frontal-lobe-syndromes-in-neuropsychiatry-a-book-review. [Last assecced on 2021 Oct 04].
96. Samaroo D, Dickerson F, Kasarda DD, Green PH, Briani C, Yolken RH, et al. Novel immune response to gluten in individuals with schizophrenia. Schizophr Res 2010;118:248-55.
97. Severance EG, Prandovszky E, Castiglione J. Gastroenterology issues in schizophrenia: Why the gut matters. Curr Psychiatry Rep 2015;17:27.
98. Sharp FR, Tomtaka M, Bernaudin M, Tomitaka S. Psychosis: Pathological activation of limbic thalamocortical circuits by psychominetics and schizophrenia? Trends Neurosci

2001;24:330-4.

99.   Smith SE, Li J, Garbett K, Mirnics K, Patterson PH. Maternal immune activation alters fetal brain development through interleukin-6. J Neurosci 2007;27:10695-702.

100. Sparkman NL, Johnson RW. Neuroinflammation associated with aging sensitizes the brain to the effects of infection or stress. Neuroimmunomodulation 2008;15:323-30.

101. Steiner J, Walker M, Gos T, Guillemin GJ, Bernstein HG, Sarnyai Z, et al. Severe depression is associated with increased microglial quinolinic acid in subregions of the anterior cingulate gyrus: Evidence for an immune-modulated glutamatergic neurotransmission? J Neuroinflammation 2011;8:94.

102. Stone JM, Morrison PD, Pilowski LS. Glutamate and dopamine dysregulation in schizophrenia-a synthesis and selective review. J Psychopharmacol 2007;21:440-52.

103. Strunecka A, Blaylock RL, Patocka J, Strunecky O. Immunoexcitotoxicity as the central mechanism of etiopathology and treatment of autism spectrum disorders: A possible role of fluoride and aluminum. Surg Neurol Int 2018;9:74.

104. Sugino H, Futamura T, Mitsumoto Y, Maeda K, Marunaka Y. Atypical antipsychotics suppress production of proinflammatory cytokines and up-regulate interleukin-10 in lipopolysaccharide-treated mice. Prog Neuropsychopharmacol Biol Psychiatry 2009;33:303-7.

105. Suzuki T, Remington G, Mulsant BH, Rajji TK, Uchida H, Gaff-Guerrero A, et al. Treatment resistant schizophrenia and response to antipsychotics: A review. Schizophr Res 2011;133:54-62.

106. Takeuchi H, Jin S, Wang J, Zhang G, Kawanokuchi J, Kuno R, et al. Tumor necrosis factor-alpha induces neurotoxicity via glutamate release from hemichannels of activated microglia in an autocrine manner. J Biol Chem 2006;281:21362-8.

107. Tay TL, Bechade C, D'Andrea I, St-Pierre MK, Henry MS, Roumier A, et al. Microglia gone rogue: Impacts on psychiatric disorders across the lifespan. Front Mol Neurosci 2018;10:421.

108. Tilleux S, Hermans E. Neuroinflammation and regulation of glial glutamate uptake in neurological disorders. J Neurosci Res 2007;85:2059-70.

109. Toal F, Bloemen OJ, Deeley Q, Tunstall N, Daly EM, Page L, et al. Psychosis and autism: Magnetic resonance imaging study if brain anatomy. Br J Psychiatry 2009;194:418-25.

110. Tomitaka S, Tomitaka M, Tolliver BK, Sharp FR. Bilateral blockade of NMDA receptors in anterior thalamus by dizocilpine (MK801) injures pyramidal neurons in rat retrosplenial cirtex. Eur J Neurosci 2000;12:1420-30.

111. van Berckel B, Bossong MG, Boelaard R, Kloet R, Schuitmaker A, Casters E, et al. Microglia activation in recent-onset schizophrenia: A quantitative (R)-[11C] PK$_{11195}$ positron emission tomography study. Biol Psychiatry 2008;64:820-2.

112. van der Doef TF, de Witte LD, Sutterland AL, Jobse E, Yaqub M, Boellaard R, et al. In vivo (R)-[(11)C] PK$_{11195}$ PET imaging of 18kDa translocator protein in recent onset psychosis. NPJ Schizophr 2016;2:16031.

113. Vargas DL, Nascimbene C, Krishnan C, Zimmerman AW, Pardo CA. Neuroglial activation and neuroinflammation in the brain of patients with autism. Ann Neurol 2005;57:67-81.