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Neuroinflammation and Neurotransmission

Mechanisms Involved in Neuropsychiatric Disorders

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Abstract

Some classical psychiatric disorders, such as schizophrenia, autism, major depression, bipolar and obsessive-compulsive disorders, have been related to neuroinflammatory process, immunological abnormalities, and neurotransmission impairment beyond genetic mutations. Neuroinflammation is mostly regulated by glial cells, which respond to physiological and pathological stimuli by anti- and pro-inflammatory cytokine and chemokine signaling; moreover, recent studies have indicated that glial cells also respond to the neurotransmitters. Neurotransmitters regulate many biological processes, such as cell proliferation and synaptogenesis, which contribute to the formation of functional circuits. Alterations in the neurotransmission can lead to many pathological changes that occur in brain disorders. For example, studies have shown that neuroinflammation can alter the metabolism of glutamate as well as the function of its transporters, resulting in cognitive, behavioral, and psychiatric impairments. Cytokines as IL-1 β and IL-6 appear to have an important influence in the dopaminergic and serotonergic neurons. These data together suggest that glial cells via cytokines and abnormal regulation of neurotransmitters can influence psychiatric disorders. The present knowledge about this issue does not allow answering whether neuroinflammation is the cause or the consequence of neurotransmission imbalance and emphasizes the importance to improve in vivo imaging methods and models to elucidate this enigma.

Keywords: neuroinflammation, neurotransmitters, psychiatric disorders

1. Introduction

The processing and the transmission of information by the neurons depend on intracellular and intercellular signaling, which occur, respectively, due to the conduction of an action potential and the neurotransmission across a synapse [1]. The action potential alters the membrane voltage and causes the opening of ion channels and, consequently, the entering of Ca^{2+} inside the neuron. This Ca^{2+} influx leads to neurotransmitters release from the synaptic vesicle into the synaptic space where they can bind to their receptors and activate signaling cascades, be recaptured by presynaptic transporters and astrocytes, or be degraded by specific enzymes that are present in the synaptic space [2]. Neurotransmitters are molecules responsible for the transmission of information from one neuron (presynaptic) to another (postsynaptic) on chemical synapses. There are different kinds of neurotransmitters, which are classified according to their structure and function, and each one has its own mechanism of synthesis and action [2]. In this way, after being released in the synaptic space, they bind to their respective receptors and activate signaling cascades that will result in the clinical effects that are already well known. The neurotransmitters with greater clinical relevance are mainly the acetylcholine, norepinephrine (NE), glutamate (Glu), gamma-amino butyric acid (GABA), dopamine and serotonin (5-HT). Neuroinflammation refers to an inflammatory response that leads to accumulation of glial cells in the central nervous system (CNS) [3], and it is mainly constituted by CNS cells (neuron and glia) together with cytokines, pattern-recognition receptors (PRRs), and peripheral immune cells [4]. The sustained neuroinflammation, for example, is capable of altering membrane expression of neurotransmitter receptors, glutamate and GABA and, consequently, impairing spatial learning, cognitive and motor functions by altering neurotransmission [5]. Therefore, neuroinflammation seems to be involved in different neurodegenerative diseases [4] and psychiatric disorders including autism, schizophrenia, and major depression [6–8]. Also, as will be better explained ahead, altered neurotransmission appears to be related to several neurological diseases such as autism spectrum disorders (ASD), obsessive-compulsive disorder (OCD), bipolar disorder (BD), depression, and schizophrenia, which exhibit alterations of one or more neurotransmitters and either their absence or their excess may result in a pathological situation.

2. Microglia and neurotransmission alterations

Neurotransmission alterations are the etiological hypothesis for many neuropsychiatric diseases, and, in general, the hypotheses are based on the observations of agents that acting on the synaptic concentrations of neurotransmitters can improve the symptoms of the disease [9]. Actually, hypothesis previously postulated has been updated due to the finding of several studies. The monoamine hypothesis, for example, was the first one established to explain the symptoms of depression [9]. According to it, the reduction in the monoamine neurotransmitters, as serotonin and norepinephrine, is the main cause of the depressive symptoms. However, based on more recent data, the etiology of depression can also be related to impairments in the amino neurotransmission, such as glutamate and GABA [9]. Another

example is the dopaminergic hypothesis about schizophrenia, which attributes the main cause of this disease to excessive stimulation of dopamine D2 receptors in the associative striatum and decreased stimulation of dopamine D1 receptors in prefrontal cortex [10]. Indeed, more recent studies have shown that the glutamate and its N-methyl-D-aspartate (NMDA) receptor, as well as the GABAergic, opioid, cholinergic, and serotonergic systems, seem also to be related with etiology of schizophrenia [10]. Alterations in the glutamatergic signaling were also already linked to ASD, a group of neurodevelopmental disorders characterized by neurobehavioral and neurological dysfunctions [11]. Besides genetic propensity, inflammation is another factor that is involved with neurotransmission alterations, as well as neurodegenerative and neuropsychiatric diseases [12, 13]. The acute inflammatory response has the goal to help the organism in the combat of pathogens and repair the damages caused by them. However, when this process remains persistent in time and becomes chronic, it generates a condition of cumulative damage, resulting in neuronal degeneration and in the development of a neurodegenerative disease [4]. According to studies, the use of anti-inflammatory drugs was related to lower incidence of Alzheimer's disease [3]. On the other hand, chronic inflammatory processes such as cancer, infections, and autoimmune syndromes increase the risk of developing neuropsychiatric deviations [14].

For many years, it was assumed that cerebrum was an organ immunologically privileged owed to the existence of the blood-brain barrier (BBB) (reviewed in [15]). However, a number of evidence suggests that peripheral inflammation could generate a brain inflammation by activating microglia and releasing some pro-inflammatory cytokines, as interleukin (IL)-6, IL-1 β , and tumor necrosis factor α (TNF α) [16]. The communication between immune system and brain occurs via cytokines and pathogen-associated molecular patterns (PAMPs) that activate afferent nerves, such as the vagus nerve, or it could access the brain through regions that lack intact BBB, known as circumventricular organs (CVOs), thereby promoting activation of microglia that secretes cytokines and chemokines, leading to the recruitment of cells, such as monocytes and lymphocytes to the brain [17, 18].

In the brain, resident macrophages are known as microglia and comprise approximately 15% of the cells of the CNS, being important in the regulation of inflammatory response, neuronal development, and maintenance of tissue homeostasis [19, 20]. These cells have receptors for serotonin, norepinephrine, GABA, acetylcholine, AMPA, and NMDA glutamate receptor, as well as for group I, II, and III metabotropic glutamate receptors, variations in the concentrations of these mediators could interfere with microglial function and morphology, as well as in the recognition of neuronal activity by the microglia [21, 22]. Glutamate, an important excitatory neurotransmitter of the CNS, acts mostly in the hippocampus, cortex, and caudate nucleus through its metabotropic and ionotropic receptors, NMDA, AMPA, and Kainate and plays an important role in the processes of learning and memory formation, as well as in motor behavior and brain development [23]. The hyperglutamatergic hypothesis of autism is based on studies that showed high levels of glutamate in the serum, lower levels of the enzymes glutamate acid decarboxylase 65 and 67 (GAD65 and GAD67) [24, 25], and the presence of increased gliosis in these patients [11]. Moreover, studies in autism genome found genetic abnormalities in the gene GluR6, which is involved in brain development through the regulation of a member of the ionotropic receptor kainite family [26]. GABA is an important neurotransmitter

in inhibitory synaptic transmissions, which is synthesized from glutamate via the action of enzyme glutamic acid decarboxylase (GAD) [27]. Inflammation induced by lipopolysaccharide (LPS) and polyI:C during the gestational period reduces GABA-producing enzyme, GAD important for development of schizophrenia in animal models [28, 29]. In addition, TNF- α leads to endocytosis of GABA receptors in rat hippocampus while IL-1 and IL-6 reduced GABAergic currents [30–32]. Beyond the decrease in the synaptic availability of monoamines, inflammatory cytokines upregulate the activity of the indoleamine 2,3-dioxygenase (IDO) [14], which alters the neurotransmission by increasing catabolism of tryptophan, the precursor of serotonin, into kynurenine, which can be converted into the metabolite quinolinic acid by activated microglia [33]. Some neurodegenerative and neuropsychiatric disorders [34], as well mood and cognitive impairments [35], present high quantities of kynurenine and its neurotoxic metabolites in the brain or cerebrospinal fluid (CSF). More recently, it has also been shown to influence the neurogenesis in the human hippocampal [36]. Moreover, these cytokines are capable of decreasing the availability of tetrahydrobiopterin (BH4), which is a co-factor to the production of all monoamines [37].

Despite the etiology of all of these neurodegenerative and neuropsychiatric disorders remaining unclear, growing and strong evidence supports the important roles of the neuroinflammation and the neurotransmission alterations in these clinical situations. All these findings and new discoveries allow the improvement of the drug therapy and, consequently, the life of these patients, as well as contribute to the progress in the search for healing.

3. Inflammation: a key factor for mood disorders

Lately, the relationship between inflammation and mood disorders became more evident [38]. In fact, it seems that the immune dysregulation plays an important role in mood disorders during life and is also one of the main factors for the development of the disease. It has been shown that inflammation during prenatal or childhood can trigger the development of mood disorder [39]. A study showed that high levels of IL-6 during childhood can be related to a higher risk of depression during adulthood [40]. The higher levels of IL-6 and IL-1 β can be also an indicative of more susceptibility to commit suicide [41, 42]. Major depressive disorder (MDD) and bipolar disorder (BD) have in common the presence of activated microglia, and hypothalamus-pituitary-adrenal (HPA) axis alterations are highly frequent as well as can modulate synapses and monoaminergic and glutamatergic systems [43].

4. Bipolar disorder (BD)

Bipolar disorder (BD) is a multisystem disorder characterized by depressive phases that alternate with mania or hypomania. However, the presence of some mixed episodes with those two phases is also a possibility. This disorder affects mood, cognition, behavior, and social functioning [44]. BD can be classified in BD-I and BD-II. BD-I is a severe type of BD and the individual usually presents a manic episode for a week or more with an intense mood

disturbance that needs hospitalization or psychotic features. BD-II is classified if the individual had a depressive and a hypomanic episode for at least 4 days with a change in functioning without a manic episode. The prevalence of BD is approximately 1% (BD I and BD II) [45]. This low rate can be explained by the fact that it is hard to diagnose hypomania. BD is also a disabling disease with a high mortality mainly because of comorbid medical conditions [46].

Inflammation is present in BD and is a good parameter to evaluate the prognosis of the impact on social and occupational life of patients and many other comorbidities are associated with higher rates of BD, such as autoimmune disorders, multiple sclerosis (MS), migraine, cardiovascular disorders, obesity, and diabetes which can reduce the life expectancy from 9 to 20 years [47]. There is no consensus whether autoimmune diseases and psychiatric diseases have a common origin pathway; however, it is well known that patients with autoimmune diseases have more often psychiatric symptoms [48]. BD is associated with autoimmune diseases such as Guillain-Barré syndrome (GBS), autoimmune hepatitis, rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, psoriasis, and autoimmune thyroiditis [49].

A chronic low-grade inflammation can disrupt the endothelial barrier permeability and lead to the exposure of bacteria and other compounds to the blood, which could be the first step to the development of autoantibodies that are also described in BD [50]. The presence of anti-NMDA receptor autoantibody has been found in blood and cerebrospinal fluids of patients, which has as main target GluN1 subunit. This autoantibody can impair the receptor dynamics and as a result, synapses can be disrupted, being capable to lead to mood disorders and to cognitive problems that are commonly related to these disorders [51]. During BD phases, pro-inflammatory cytokines in serum can be elevated and levels can be different in each phase and serum cytokines can cross the blood-brain barrier, subsequently causing neuroinflammation [52, 53]. Although it is not yet known if there is causality between CNS and peripheral levels of pro-inflammatory cytokines, the increased levels of these cytokines may be a consequence of rupture of CNS, loss of immune system integrity, and some unsolved inflammatory responses during the development [44].

In animal models, the deleterious effect of TNF- α occurs via excess of glutamate that can cause LTP impairment [54] and the soluble TNF- α receptor type 1 (sTNFR1) is more expressed in serum during euthymia, mania, and depressive episodes in comparison with healthy patients and becomes an important marker for BD [55]. Furthermore, inflammation can also modulate the neurotransmitter levels. For example, IL-2, TNF- α , and IL-6 can decrease 5-HT levels. IL-2 increases the cleavage of tryptophan by modulating indoleamine 2,3-dioxygenase activity, which leads to a decrease in 5-HT levels, while TNF- α and IL-6 increases the metabolization of 5-HT to 5-hydroxyindoleacetic acid (5-HIAA) that also leads to low 5-HT levels. The low availability of 5-HT is also a main characteristic of BD and also MDD [43, 56].

Activated microglia also seems to present a very important feature in BD [57]. Serum TNF- α and IL-1 β can overactivate microglial cells that increase apoptosis, oxidative stress and result in a neuronal dysfunction [58]. In *postmortem* brain of BD patients, the levels of IL-1 β , MyD88 (key factor in TLR4 signaling), NF- κ B subunits (p65 and p50), and activation glial markers were elevated in the prefrontal cortex which is an important region for cognitive control and affective regulation [59]. Some structural brain changes such as the lateral ventricular

enlargement and functional changes in subgenual prefrontal cortex activity and mesolimbic connectivity were also found [60]. BD chronic inflammatory state also activates chronically hypothalamic-pituitary-adrenal (HPA) axis. BD peripheral cortisol levels are increased in patients during the mania/depression episodes and euthymia. Cortisol levels are an indicator of the severity of BD [61]. This increase in cortisol (hypercortisolemia) has also implications in weight gain, insulin resistance, and hypothyroidism [62]. In physiological conditions, the acute glucocorticoid receptor (GR) activation leads to anti-inflammatory effect and in pathological conditions; the chronic activation has the opposite effect by preventing the negative feedback of the immune response which is caused by the modulation of GR. GR expression and sensitivity are decreased in hypothalamus and pituitary which maintain a pro-inflammatory environment that trigger impaired neuroplasticity. All these changes lead to alterations in mood and cognition [63]. Childhood is a critical phase for the development of BD. In this period, the CNS and immune system are not entirely developed and this could be highly affected by psychological stress. Traumatic experiences in childhood increase the chances to develop BD and correlate with earlier onset and severity. It is also related to an inflammatory dysregulation that continues through adulthood which shows that an early trauma can have permanent consequences that could lead to a psychiatric disorder [64]. This intense psychological stress could lead to impairments in GR signaling and in HPA hyperactivity which are associated with the lack of inflammation control [65]. Other factors in trauma also cause immune imbalance such as sleep disturbance, metabolic syndrome, gut microbiota leakage, and drug abuse [49, 66]. The susceptibility to the development of psychiatric disorder is also a result of genetic background together with priming events in early life [67, 68]. BD has a high rate of inheritance that could explain the differences between individuals against the same inflammatory stimulus. So far, the major histocompatibility complex (MHC) was identified in BD as highly polymorphic protein especially in the region of the HLA locus [69].

A correlation between TLR4 and TLR2 with BD has also been shown. Some genotypes of TLR4 and one specific genotype for TLR2 are an indicative of BD's early onset and are associated with a poor inflammatory response. The impairment of important inflammatory response protein shows that inflammatory impairment is an important factor for BD and may somehow lead the individual to be more susceptible to other risk factors like infections and childhood traumas [70, 71]. Studies in BD patients showed that they have more alterations in genes related to IL-6, IL-8, and IFN pathway [72]. The gut microbiota can play an important role in BD because some prebiotics can increase the expression of BDNF and NMDA and also regulate immune system by decreasing hypersensitivity and better immune response [73]. BD patients usually do not practice physical exercises, which are a good tool to improve metabolic parameters that are important characteristics in BD and to have an antidepressant effect [74].

There is still a lot of debate concerning the role of immune dysfunction in the neuropsychiatric disease. However, this immune dysfunction can be an important target in therapeutics and the control of immune system could have a relevant synergic effect during treatment. Many different studies showed the anti-inflammatory concomitant antidepressants, mood stabilizers, and antipsychotics treatment could help the patients. On the other hand, other studies showed that some antipsychotics have pro-inflammatory properties which could help

during the acute state [75]. Even though there is no consensus of the benefits of adjunctive therapy with anti-inflammatory drugs. A study with TNF- α inhibitors in BD patients without any antidepressant therapy showed only effect in patients with high levels of CRP and TNF- α which shows how important is a more effective and individual treatment for BD in following the levels of different cytokines [76].

5. Major depressive disorder (MDD)

Major depressive disorder (MDD) is known as the most relevant disability cause worldwide and is one of the most frequent DSM-IV disorder and the prevalence is of approximately 17% [77]. MDD occurs more in women than in men and its etiology is multifactorial although MDD could be 35% heritable [78]. MDD is characterized by patients having major depressive episodes for at least 2 weeks. The episodes can be recurrent or isolated depending on the intensity and number of symptoms. This could lead to a huge impact on occupational and social life. The long-lasting depressive episodes are followed by anxiety, feelings of guilt, and suicidal thoughts [79]. MDD has a similar profile to BD such as the increase of the risk to develop the disorder is higher if the individual had a trauma during childhood and this could also lead to an increase in the severity and in the lack of response to the treatment [80].

Studies suggest that control of stress-coping is impaired which can be a result of poor communication between a range of brain areas that are related to stress and emotions. It was also found that the volume of basal ganglia, hippocampus, and thalamus are smaller than healthy individuals [81]. In MDD patients, there is a hyper-reactivity of amygdala not only during emotional process but also at resting state. Some important areas of control of amygdala in prefrontal cortex are not able to regulate hyperactivity in amygdala during a negative stimulus in MDD. This hyperactivity is related to a hyperexcitability and enhanced firing rate in stress-response regions [82]. Thus, neurotransmitters regulation in the synaptic cleft plays an important role in MDD.

Monoamine hypothesis is an important mechanism involved in depression where there is a reduced activity of the catecholaminergic and/or serotonergic systems [83]. The dopamine (DA) hypothesis considers the malfunctioning of the system of reward in mesolimbic system by the decrease of dopaminergic transmission that is the result of a decrease in the DA in the synaptic cleft that decreases the dopamine transporter expression and increases the D2 availability in neurons membrane [84]. Noradrenaline (NA) hypothesis shows that noradrenergic neurons control important brain areas such as the medial orbitofrontal cortex that responds to positive stimuli and lateral prefrontal cortex, anterior cingulate, and anterior insula respond to negative stimulus. 5-HT is important for the regulation of emotional behavior. It was previously showed that the decrease of 5-HT in synapse could impact negatively in mood of subjects which have MDD family history [85]. Therapeutic monoamine theory is supported because the drugs available can lead to DA, 5HT, and/or NA increase in synaptic cleft by blocking these monoamines reuptake. These monoamine transporters blockage help several patients; however, in more than 50% patients, they do not show any anti-depressive effect and

also need 3–6 weeks to observe the changes in mood [86]. Although the monoamine theory is well established, it is understandable that this change in neurotransmitters can also lead to changes in other neurotransmitters, for instance, GABA, acetylcholine, histamine, and glutamate [87]. It has been also shown that the levels of glutamate in CSF and blood are increased in MDD patients compared to healthy controls. These higher glutamate levels can be reduced by the use of antidepressants. In postmortem studies, the elevated levels of glutamate in the brain and important alterations in the expression and function of NMDA receptor which is a relevant target for the treatment of MDD. Recently, ketamine, a NMDA inhibitor, could be a promisor treatment for the MDD. Thus, an impairment in glutamate pathway both in the neurotransmitter levels and in its receptor's expression and function is present in MDD [88].

MDD patients presented elevation in serum levels of IL-1 β , IL-6, and TNF- α and an increased microglial activation in some regions of cortex and insula [75, 89]. Although the microglial activation is present, there is also important loss of glia in prefrontal cortex (PFC) and also that chronic stress may lead to MDD by impairing PFC's astrocytes [90]. Almost all the important features observed in BD are also found in MDD, for example, the leaky gut is also seen in MDD which has higher concentrations of IgM and IgA and the presence of high levels of C-reactive protein [91]. MDD is related to neurodegenerative diseases especially because of the presence of neuroinflammation, a common factor between all neurodegenerative diseases. There is a higher probability of Alzheimer's disease (AD) patients developing MDD and vice-versa. Since increased pro-inflammatory cytokines in CSF can lead to depression in AD patients, elevated levels of IL-10 are associated with lower depression scores, showing the relevance of inflammation in the severity of MDD. The A β 40/A β 42 ratio in serum was increased in MDD patients in comparison with healthy controls which show that the A β cleavage control is also impaired. MDD and AD are associated with impaired signaling pathways involving the decrease of BDNF expression, an important growth factor in CNS, and changes in the volume of regions in the brain related to limbic system. However, the exact mechanism involving MDD and AD is still unknown [92–94].

Parkinson's disease (PD) patients present impairment in monoaminergic systems (dopamine, serotonin, and noradrenaline) which can lead to MDD. However, the glutamatergic system is also impaired in PD which could also lead to MDD and cognitive deficits that is also frequently related to MDD [95]. There is also strong evidence suggesting MDD being associated with Huntington's disease (HD), maybe because of high rates of suicide in HD patients compared to the population in general, and that the HD patients can develop MDD during the disease course [96]. Amyotrophic lateral sclerosis as all other neurodegenerative diseases has also an association with MDD. The ALS progression occurs faster if the patients have a high depressive score [97].

Aging can also be an important factor for MDD, because older adults are more vulnerable to MDD. During aging process, there is a reduction in some neurotransmitters such as dopamine and noradrenaline, decrease of BDNF expression, and also increased levels of cortisol due to the imbalance of HPA axis [98]. There is also the involvement of glial activation and expression of pro-inflammatory cytokines that affect the synaptic activity and also are found in MDD patients [99].

6. Obsessive-compulsive disorder

Obsessive-compulsive disorder (OCD) is an anxiety disorder with a prevalence of 2.3% and does not present any correlation between gender [100]. This disorder is characterized by recurrent intrusive thoughts or images that become obsessions and cause a huge distress that lead the individuals to present repetitive behaviors or mental ritual. In OCD, there is an overlap between cortico-striato-thalamic circuits [76]. The repetitive behavior is maybe due to a communication disruption between cortex and dorsal striatum. Studies suggested that the reward system and processing emotional stimuli are impaired in OCD. Thus, the emotional states are dysregulated and the proportion of response is also lost [101]. The precise cause of OCD onset is still not revealed and this disorder can appear during childhood or adulthood. OCD share some features with MDD and BD such as autoimmunity, genetic factors and the comorbid diseases; however some different comorbidities are specific for OCD, such as Tourette's syndrome and eating disorders [102]. The role of microglia in OCD has not been completely elucidated. However, an OCD mouse model called Hoxb8 KO seems to present microglial impairment, but new studies in patients should appear to contribute with this idea. This possible mechanism could be a result of dysregulation of glutamatergic system [103]. OCD has been also related to streptococcal infections in early life [104]. Pro-inflammatory cytokines IL-6, IL-2, IL-4, and TNF- α are increased in plasma of OCD subjects suggesting an important role of inflammation also in OCD [105].

7. Schizophrenia

Schizophrenia comprises a group of closely related chronic psychotic disorders that are characterized by a particular type of disordered thinking, behavior, and in affectionate relationships. The most common abnormalities are a special disorder in the perception of one's self in relation to the external world and hallucinations that differ from delirium and other confusional states, sometimes observed in dementia and depression [106]. Before the onset of schizophrenic disease that usually happens in the end of the childhood or early adulthood or when in remission, the individuals can be considered normal except by their vague and concerned appearance with their own thoughts. There is also a difficulty to fully understand figurative statements or to discern irrelevant to relevant data, to respect the logical limit of time and space and opposite things can be considered as identical as conceptual relationships are distorted. Schizophrenic patients are usually unable to clearly communicate an idea. All these symptoms can be categorized as cognitive symptoms because it directly reflects in executive functions including inability to sustain attention and working memory impairment [57]. Such confused thoughts reflect in the patient's behavior that can manifest as social withdrawal, idleness, aimlessness, aloof, and self-absorption. These are referred to as negative symptoms. Finally, schizophrenic patients can also present auditory and visual hallucinations, bizarre actions, aggression, agitation, delusion, paranoia, and major thought disorders that are symptoms categorized as positive. Cognitive and negative symptoms seem to precede positive symptoms, however, although their distinct clinical manifestations,

it is possible that they usually can co-exist. The prevalence of this syndrome worldwide is about 0.5–1.0% and seems to be related to industrialization, urbanization, and increasing population density [107, 108].

In vivo imaging studies suggest common macroscopic brain abnormalities associated with schizophrenia, also present in drug-naïve patients with first episode psychosis, that include ventricular enlargement, decreased cortical and hippocampal volume, and reduced neuronal size. Furthermore, functional neuroimaging in patients with schizophrenia detected aberrant activity of neuronal circuits in prefrontal cortex, hippocampus, and also some subcortical structures [109]. In accordance with these findings, there was observed a decrease in NMDA receptor expression in postmortem analysis of prefrontal cortex of schizophrenic patients [110], and, in addition, preclinical and clinical data support the theory of stage-specific glutamatergic abnormalities in this illness because analysis of in vivo proton magnetic resonance spectroscopy (1H-MRS) to measure glutamine concentrations in the brain of schizophrenic patients compared to control subjects suggests that early-stage schizophrenia appeared to be associated with abundant glutamatergic activity whereas late-stage schizophrenia showed decreased glutamatergic activity [111].

Furthermore, growing evidence suggests a myelination dysfunction and altered oligodendrocyte number, as well as myelin, N-acetylaspartate (NAA), and fatty-acid biosynthesis dysfunction in prefrontal cortex of postmortem schizophrenia patients, possibly as a mechanism underlying the observed reductions in white matter volume. NAA can also be considered a function neuronal marker because it acts as an osmolyte and donate its acetate group in myelin synthesis [112]. Other metabolites were also analyzed, in vivo, by fractional anisotropy (FA), as myo-inositol, that is associated with aging and neuroinflammation. This metabolite is highly expressed in astrocytes and is also a precursor for the cell signaling phosphatidylinositol and for synthesis phospholipids in cellular membrane. During chronic inflammation and/or slow virus infections of the brain, during glial activation and macrophage infiltration, an increase in myo-inositol is observed. Indeed, myo-inositol increase may contribute to hypomyelination disorders associated with inflammation on white matter microstructure in general [113].

The immune system can contribute to the pathogenic process by generating reactive nitrogen and oxygen species, releasing cytokines via microglia and lymphocytes that promote neuroinflammation. Specifically, the heme oxygenase (HO) system that acts as a sensor for oxidative stress as well as a key modulator of redox homeostasis is composed by two major isoforms, the heme oxygenase 1 (HO-1) that is inducible and the heme oxygenase 2 (HO-2) that is constitutive. Recently, there are some lines of evidence suggesting the involvement of HO-1 in the pathogenesis of schizophrenia [114]. Furthermore, sustained increase of HO-1 in the brain during the pre- or perinatal period could lead to activation of HO-1 in astrocytes prior to the maturation of offspring mesolimbic and nigrostriatal system, what induces changes in DA network structure and function predisposing to neurodevelopmental phenotypes of schizophrenia observed in early adulthood [114]. In the adult, one of the most important and well-established disturbances recognized in schizophrenia is in the dopaminergic neurotransmission, therefore the actual antipsychotics classified as typical and atypical that

are effective in schizophrenic positive symptoms are antidopaminergic drugs, that are not effective on cognitive, negative, and other deficits found in schizophrenic patients [115]. The dopaminergic dysfunction can be a consequence of glutamatergic hypofunction in schizophrenia, being glutamatergic system closely related to the immune system [115].

Some *in vitro* studies proposed that after antipsychotics therapy, some cytokine levels become normalized, such as IFN- γ , that is blunted in the illness, as well as IL-2, ICAM-1, and the ICAM-1 ligand leukocyte function antigen-1, TNF- α , and TNF- α receptors (for more details [119]). Furthermore, medicated schizophrenics patients presented an increase in IL-18 serum levels that play a pivotal role in immunological response type-1 and a decrease in IL-6, one important cytokine of type-2 immune response, suggesting a role for antipsychotics in cytokine levels balance [119]. In schizophrenic patient's blood sample, it is possible to observe the predominance of type-2 immune response due to activated monocytes releasing IL-6, high levels of Th2 type lymphocytes, immunoglobulin E and IL-10 serum levels. In CSF of juvenile schizophrenic patients it was observed an increase in IL-4 levels, one of the most important cytokines in type-2 response indicating that this predominance is not only an exclusive peripheral immune response phenomenon [115].

Science is still far from an effective answer and treatment to offer to schizophrenic patients and, therefore, is still hurried to consider the pro-inflammatory cytokines as a possible target to psychosis treatment. There are many preclinical trials being performed in the world focusing on schizophrenia and major depression treatment with monoclonal antibodies to anti- and pro-inflammatory cytokine (infliximab, tocilizumab) [116], but the Janus face of inflammation mechanisms still needs to be carefully and detailed understood especially in the psychotic brain.

8. Autism spectrum disorders (ASDs)

Disorders on the autism spectrum are classified as neurodevelopmental disorders including childhood disintegrative syndrome, autism itself, pervasive developmental disorder not-otherwise specified (PDD-NOS) and Asperger syndrome, Rett's syndrome [11]. Autism itself is a debilitating neurodevelopmental disorder that starts at early childhood with genetic and environmental causes and immune influence. The ASD symptoms comprise impaired language and communication, impaired social relationship, repetitive behaviors, and a narrow range of interests and many autistics also have intellectual disability [117]. Intellectual disability (ID) comprises significant limitations in both intellectual functioning and adaptive behavior starting in childhood. The stable incidence of ASD in children has been estimated in 0.5–1.0% [117, 11].

In the brain, neuropathologic alterations observed in ASD correlates to cytoarchitecture abnormalities that affect many structures as cortex, limbic system, and cerebellum, leading to hypoplasia of the inferior vermis of the cerebellum with loss of Purkinje cells, asymmetrical enlargement of the amygdala, and increased gliosis (GFAP), whereas biochemical abnormalities include altered energy metabolism, dysregulated amino acid metabolism with increased

aspartate and glutamate serum levels in the amygdala and hippocampus [117]. It is well known that in ASD pathology, abnormalities in genes that regulate the expression of glutamatergic receptors are involved, as mutations in chromosome 6q21, where GluR6 gene is located [26]. The GluR6 genes codify the family of kainite receptors that are ionotropic glutamatergic receptors very important during development [117].

The degree of ASD severity appears to be related to the intensity and period that excitotoxic or immune insult occurs. Woman exposed to ethanol during pregnancy, as well as ketamine, phencyclidine, benzodiazepines, barbiturates, anticonvulsants, or anesthetics can have GluR activity altered. During development, CNS neurons are more susceptible to synaptic environment, and disturbances that increase NMDA receptors activity can easily trigger neurodegeneration due to excitotoxicity [11]. During development of the neural systems, an excess of extraneural glutamate can alter the migratory neuronal pattern, differentiation, and synaptic development, leading to different abnormal brain architecture degrees. A postnatal injury seems to produce lesser ASD syndromes compared to prenatal, as human brain continues to develop during the first 2 years of childhood. In older children, injury due to elevated levels of heavy metals, glutamate, and inflammatory cytokines secondary to microglial activation can affect postnatal brain development [11]. Based on observations made from adult brain exposed to elevated inflammatory cytokines, the capacity of immune system to reestablish a homeostatic state is the major determinant factor as abnormalities of immune system function is always reported in ASD, being overactivation the most commonly seen [11].

According to the literature, immunological abnormalities reported in ASD include a shift in T-helper cells, Th1/Th2, balance, abnormal reactivity of lymphocytes, increased levels of cytokines as IL-1 β and TNF- α , and finally elevated levels of anti-brain antibodies, specifically antibodies against neurotransmitter receptors. In the autistic brain, a considerable loss of Purkinje cells is observed in the cerebellum, the most damaged area, followed by glial activation widespread all over the brain. There is also an increase in macrophage IL-6 and chemoattractant protein-1, which play an important role in the response of innate immune system including monocytes and T-cell activation [11].

Therewithal, there are considerable data proposing that prolonged and excessive microglial activation can impair either neurodevelopment or neurogenesis due to the increase in cytokine release by microglia and excitotoxicity as already observed in CSF, brain tissue, and blood of autistic child with high levels of cytokines and glutamate [118]. The co-localization of NMDA receptors with TNFR was also reported, implicating that GluR can interact with inflammatory cytokine membrane receptors allowing a cross talk that can lead to excitotoxicity especially through TNFR1. Furthermore, TNF can increase the glial release of glutamate by upregulating glutaminase [119].

As in schizophrenia, elevated cytokines during pregnancy have a very important role in ASD as proposed by human studies that found increased levels of INF- γ , IL-4, IL-5, and MCP-1 in mid-gestational mother sera and IL-4 and TNF in amniotic fluid [120]. Elevated levels of inflammatory chemokines such as granulocyte macrophage colony-stimulating factor (GM-CSF) and cytokines as TNF, INF- γ , IL-1 β , IL-4, and IL-6 during mid-gestation have been more

related to ASD subphenotype that presents intellectual disability (ID) than to ASD alone or developmental delay (DD) without autism [121].

Moreover, the production of maternal autoantibodies reactive to seven developmentally regulated proteins in the fetal brain has only been measured in blood of women whose children were later diagnosed with ASD. The seven proteins are Y-box binding protein 1 (YBX1), stress-induced phosphoprotein-1 (STIP1), lactate dehydrogenase A and B (LDH-A and LDH-B), cypin, and collapsing response mediator proteins 1 and 2 (CRMP1 and CRMP2) [120]. However, in order to determine the predictive value of the maternal autoantibodies for autism risk and diagnose, additional studies need to be done, because at this moment it seems to influence, if not define, ASD.

During postnatal period, individuals with ASD could present an increase in endogenous circulating anti-brain auto-immunoglobulins correlating with aberrant behaviors, impaired development and with immune dysregulation (increased IL-6, IL-8, and MCP-1) leading to an increase in the pro-inflammatory Th1/Th2 ratio. Besides the observed increased baseline activity of (natural killer) NK cells, there is a decrease in response to activation suggesting dysfunctional activity and a shift in T-cell population that is decreased [120]. However, the role of IL-17 is still obscure in ASD despite some temptations of explanation in rodent maternal immune activation (MIA) models [122]. The relationship between autoimmune diseases and ASD has long been described. Autism has itself been considered an autoimmune disorder [123, 124] due to the findings that family history of autoimmune disorders is a risk factor for autism and autoantibodies can also be found in multiple sclerosis, systemic lupus erythematosus (SLE), and schizophrenia. These autoantibodies can also cross-react with N-methyl-D-aspartate receptors [124].

9. Schizophrenia and autism spectrum disorders (ASDs), a common source: neurodevelopmental hypothesis of maternal immune activation

There are many evidences linking the etiology and pathophysiology of schizophrenia, with immunological changes especially during prenatal lifetime. During pregnancy, MIA that can be triggered by many common viruses seems to be enough to cause offspring brain function lifelong changes and behavior, in both animal models and humans [125, 126]. In 1964, after rubella pandemic, the incidence of two neurodevelopmental disorders, autism and schizophrenia, increased abruptly from less than 1% to about 13 and 20%, respectively [127]. Subsequent to this first observation, other studies revealed an association with outbreaks of influenza, chicken pox, polio and mumps, and schizophrenia or autism [120, 128, 129] as well as bacterial infections and parasite such as *Toxoplasma gondii* [125, 127]. Furthermore, any environmental insult or genetic predisposition that elevates immune responses above a threshold, like allergies, acute stress, asthma, and exposure to environmental pollutants, have been related to enhanced risk of schizophrenia and autism [125, 126].

According to this theory, during pregnancy, a maternal infection due to viral or bacterial invasion leads to pathogen recognition by peripheral immune cell through the action of the family of toll-like receptors (TLRs), classified as pattern-recognition receptors that is responsible, in peripheral immune system, for the generation and fast release of inflammatory

cytokines, among others. The cytokines can cross the placenta barrier arriving in the fetal blood circulation according to the cytokine structure, gestational stage, and the physiological conditions of both mother and fetus [107]. The placenta from vertebrates is a very complex organ that plays the important role of fetus protection from pathogenic invasion and maintenance of a normal development hormonal environment. In physiological conditions, cytokines are constitutively expressed in placenta and seem to play important roles in the healthy environmental maintenance [130]. The expression of toll-like receptors (TLR) type 2 and 4 on normal human chorionic villi of placenta suggests that placenta can constitute an immunological barrier prepared to sustain and respond a pathogenic attack being also considered a pregnancy-specific component of the innate immune system. However, during maternal infection, a dangerous increase in environmental pro-inflammatory cytokines can strike an increase in placental cytokines that can become threat to the normal development of fetal brain [130]. During the CNS development, different classes of cytokines have different important roles. In the normal development of dopaminergic phenotype, IL-1 β is the cytokine that can induce the mesencephalic progenitor cells conversion, whereas in embryonic hippocampal neural stem cells (NSCs) this cytokine can exert anti-proliferation, anti-neurogenesis, and pro-gliogenesis effects. Furthermore, IL-6 can modulate serotonergic neurons viability, decreasing its survival in fetal brain, in an in vitro model of serotonergic neurons from the rostral raphe embryonic cell culture. During development, TNF- α , in turn, can not only act as a neurotrophic factor in dopaminergic ventral mesencephalic neurons but also it can be neurotoxic at the beginning of brain development [126].

Due to the difficulty of clinical research in identify the molecular pathways downstream of maternal infection, animal models of research became a valuable tool once through this model it become clear the critical roles of cytokines in this process together with oxidative stress, zinc deficiency and hypoferrremia, mediating in prenatal lifetime the neurodevelopmental effects of infection [106, 126]. In animal models, pregnant rodents and non-human primate (NHP) can be exposed to immunological manipulation, and brain structures of offspring can easily be compared to control offspring [131]. The behavior of the offspring can manifest a broad range of schizophrenia and autism-related abnormalities and also decreased ability of the brain to filter out extraneous information, deficits in cognitive flexibility, working memory, and increased anxiety behavior [125, 127, 131]. There are two different protocols that are very well established in MIA models, one that consists in pregnant female exposure to LPS, a bacterial endotoxin (lipopolysaccharide) and other that is based in exposure to polyriboinosinic-polyribocytidilic acid (polyI:C), a synthetic analog of viral double-stranded RNA. Both of them are recognized by toll-like receptors (TLRs), a class of receptors that recognize pathogen, being LPS recognized by TLR4 and polyI:C by TLR3. The female exposure to LPS or polyI:C during pregnancy notably enhances pro-inflammatory cytokine levels in many gestational structures as amniotic fluid and placenta and latter in fetal brain, leading to fetal microglia activation and an increase in transcription factor nuclear factor- κ B (NF- κ B) activity in both fetal and neonatal brains [106, 132] at the same time as white matter injury is observed by evident hypomyelination together with precursor cells of oligodendrocytes death and increased rate of apoptotic neurons during fetal and neonatal brain development. The activation of microglia together with this entire pro-inflammatory scenario is sufficient to induce a delayed increase of AMPA receptor expression and activity in excitatory synapses [132].

When pregnant rodents are exposed to a model of viral infection with poly(I:C) injection, offspring tend to manifest autism spectrum disease behavioral symptoms, as abnormal communication, social interaction, and an increase in repetitive behaviors [126, 131]. When offspring reach adulthood they also exhibit other neuropathologies associated to schizophrenia, as reduced hippocampal volume and cortical thickness as well as and increased ventricular size, deficits in synaptic protein levels, in dendritic spine density, in long-term plasticity and cortical malformation [122, 129], and associated to ASD, aberrant Purkinje cells [125, 127, 129]. Altered serotonergic and dopaminergic signaling was also observed additionally to specific changes in inhibitory neurotransmission and a decrease in several components of the γ -aminobutyric acid (GABA) system, related to both schizophrenia and ASD [125, 126, 129, 131]. Transposed to humans, it seems that most of maternal infections do not lead to ASD or schizophrenia in offspring, but it can act as a disease primer making individual more susceptible to the effects of this maternal infection in the presence of more than one risk factor along adult life, such as familiar historic of schizophrenia or autoimmune diseases [125–127].

Notwithstanding, to bridge the gap between humans and rodents, several groups have established *rhesus* macaque in MIA models to validate remarkably strong finding in rodents. As rodents and humans, these models display behavior symptoms of schizophrenia and ASD that increase in intensity along with age, as repetitive behavior, abnormal communication, and impaired social interactions [129, 131]. Gray and white matter volume is also altered in MIA non-human primate (NHP) models as well as changes in dendritic branching in neonatal offspring [129].

There are some theories made from animal observation suggesting that IL-6 can cross the rodent placental barrier in early and middle gestation but not in the late. It was observed that a maternal viral-like immune activation during the first half of mouse gestation could elevate IL-6 protein levels not followed by an increase in endogenous interleukin production in fetal brain [133] suggesting that IL-6, opposite to IL-1 β and TNF α , can easily cross the placental barrier also in humans. As a matter of fact, to develop and establish a functional immune system, a series of very well-coordinated events during fetal development, that only in late gestational and postnatal stages will achieve the highest functional maturation period, seems to be necessary. In summary, the fetal cytokine reaction observed due to maternal infection is absolutely dependent on the precise gestational stage [107]. However, the mechanism by which this cytokines alter brain development is still unknown. There is an assumption that these cytokines can regulate the expression of immune molecules expressed in neurons, as histocompatibility complex I (MHCI) where it negatively regulates synapse formation, and the synaptic plasticity required for activity-dependent synaptogenesis and dendritic branching [126, 134], that are both altered in neurodevelopmental disorders and are thought to be important in etiology of schizophrenia and ASD [135].

Actually, MIA changes dramatically neuronal levels of MHCI, in brain of neonatal offspring [126], but it is still unknown whether these changes are long-lasting and related to the behavior changes related to disease in later stages of development. Alterations in the MHCI levels may be acute and directly reflecting the nature, intensity and duration of infection, that can

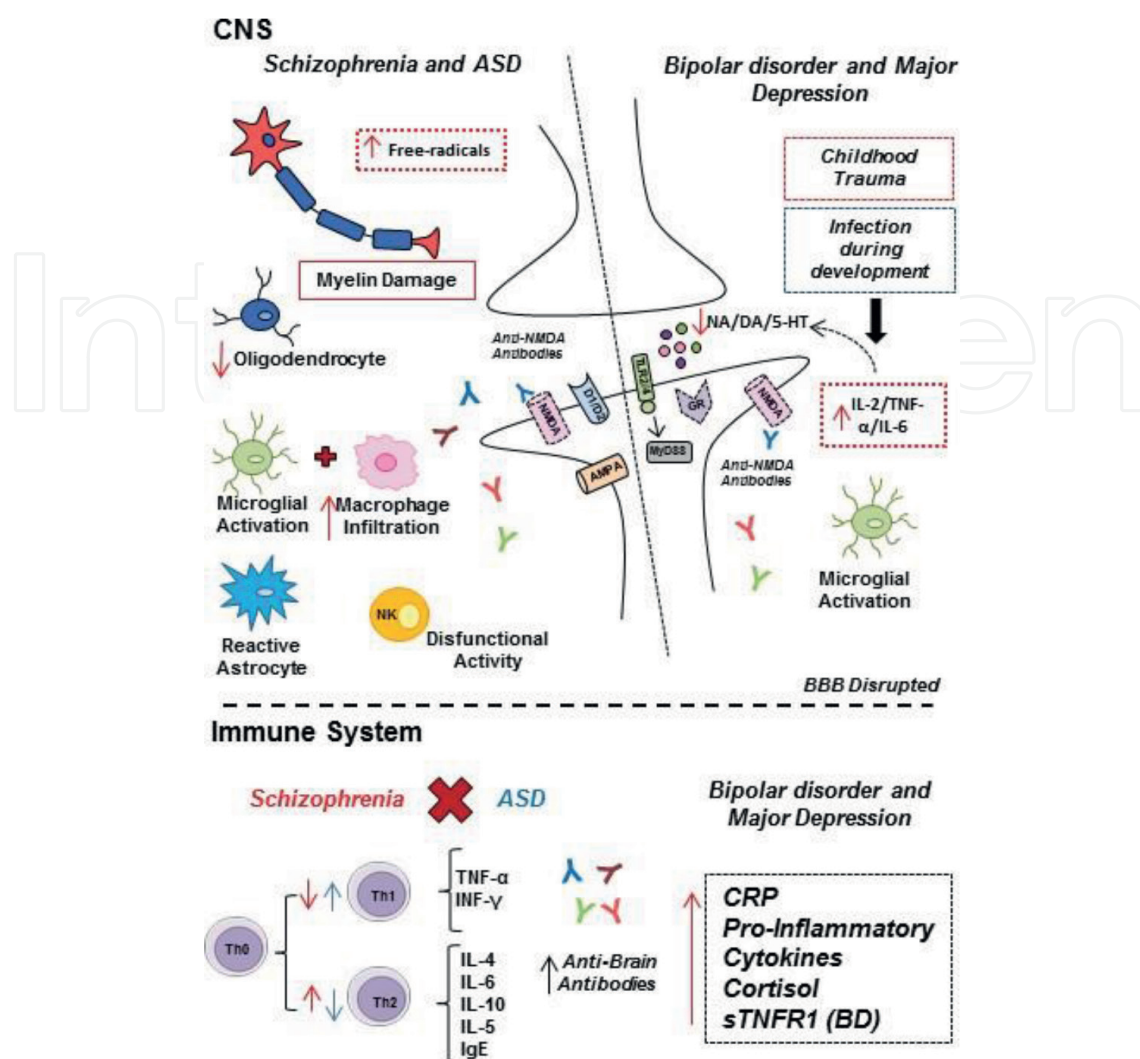


Figure 1. Main changes observed in neuropsychiatric diseases. On left, major immune changes related to schizophrenia and autism spectrum diseases (ASD) observed in central nervous system (CNS). A direct interchange is observed from cellular and molecular components of peripheral system and CNS due to blood brain barrier (BBB) disruption leading to an increase in macrophage infiltration, in microglia activation, and in astrocyte reactivity. There is also an increased inflammatory signaling responsible for higher levels of free radicals that together with decreased oligodendrocyte numbers favors the myelin damage process [112]. An increase in natural killer (NK) cells can be observed; however, its activity is dysfunctional [120]. Altered neurotransmission due to an increased expression of dopaminergic receptors (D1/D2) [111] and a decrease in N-methyl-d-aspartate (NMDA) receptors expression can be found in part as a consequence of the presence of anti-brain antibodies that among other cerebral targets can recognize NMDA receptors [11]. AMPA activity is also disrupted [132]. In peripheral system, a decrease in the shift Th1/Th2 is observed in schizophrenia, whereas an increase in Th1/Th2 relation is observed in autism spectrum disorders (ASDs) [11, 115, 120]. Anti-brain antibodies are also detected in peripheral system. On the right, the main changes in inflammatory response in mood disorders: bipolar disorder (BD) and major depression disorder (MDD) [38]. Most of the changes are consequence of traumas during childhood and/or infections during the development [39]. These diseases have important inflammatory markers such as microglia activation [57, 58], HPA (hypothalamic-pituitary-adrenal) axis impaired [43, 61, 65] and increase in pro-inflammatory cytokines which are related to each other [72, 75, 89]. The increase of C-reactive protein (CRP) and pro-inflammatory cytokines could lead to an increase in cortisol levels and also in the BBB disruption that could also lead to microglia activation. Since TNF- α levels are elevated, there is also a modulation of sTNFR1 in BD [55]. The chronic high levels of cortisol decrease the GR expression, which contributes to the inflammatory imbalance. High levels of cytokines also modulate the amount of neurotransmitters in the synaptic cleft. The levels of noradrenaline (NA), dopamine (DA), and serotonin (5-HT) are downregulated that conducts to the mood changes [85]. The levels of noradrenaline (NA), dopamine (DA), and serotonin (5-HT) are downregulated that conducts to the mood changes [85]. The TLR4 and TLR2 pathways are also changed in BD [70, 71], for instance, the MyD88 is increased [59]. The presence of auto-antibodies is also an important feature in BD and MDD, especially anti-NMDA antibody that impairs glutamatergic pathway and could lead to cognitive impairment [51].

become chronic, due to epigenetic changes that might synergize with other risk factors at different stages of life. Furthermore, as a convergent signaling pathway to cytokines, synaptic scaffolding proteins, and trophic factors, the literature now is trying to understand the role of mammalian target of rapamycin (mTOR) signaling pathway in individuals with schizophrenia, ASD and MIA offspring, as well as schizophrenia-associated DISC-1 mutation in animal models. Changes in physiological mTOR signaling can implicate in neuronal morphology changes, as well as synaptic plasticity and synaptic protein and glutamate receptor synthesis [113].

Several phenotypes related to schizophrenia and ASD, in MIA offspring, can also be prevented with probiotics, environmental enrichment, or maternal supplementation with zinc, several phenotypes related to schizophrenia and ASD, in MIA offspring, can also be prevented with probiotics, environmental enrichment, or maternal supplementation with zinc, specific antibodies to cytokines [122] and later during adolescence MIA rats treated with COX2 inhibitor were protected to develop several schizophrenic behavior aberrations, as well as the treatment with minocycline (a microglia modulator) during a stress condition in adolescence could prevent adult offspring to develop schizophrenic behavior [125, 127]. In particular, autism shares many significant similarities with schizophrenia, including genetic variants and neuroinflammation in early development and chronic inflammatory process affecting especially pregnant woman [111, 120] leading to aberrant neuronal connectivity, synaptic plasticity, and altered neurotransmission in both. Indeed, defects in inhibitory (GABAergic) and excitatory (glutamatergic, dopaminergic) neurotransmission leading to an imbalance of inhibition/excitation can be found in ASD and schizophrenia [111]. A summary of the most relevant similarities between ASD and schizophrenia concerning neuroinflammation in CNS as well as bipolar disorders and major depression are illustrated in **Figure 1**. However, in the immune system some differences can be observed between ASD and schizophrenia.

10. Conclusion

Therefore, a better comprehension about the pathophysiology of inflammation and immune system especially during fetal and neonatal brain development in psychiatric disorders remains an exciting field in science. The hypothesis of finding some answers that lead to a potentially preventable or treatable neurodevelopmental disorders is welcome in a field where current therapeutics are far from an ideal outcome.

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