Neuroscience and Biobehavioral Reviews 55 (2015) 612–626

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

Inflammation in schizophrenia: A question of balance

Juan C. Leza[a,b,d,*], Borja García-Bueno[a,b,d], Miquel Bioque[a,e], Celso Arango[a,c,f], Mara Parellada[a,c,f], Kim Do[g], Patricio O'Donnell[h], Miguel Bernardo[a,e]

[a] Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Complutense University, Madrid, Spain
[b] Department of Pharmacology, Faculty of Medicine, Complutense University, Madrid, Spain
[c] Department of Psychiatry, Faculty of Medicine, Complutense University, Madrid, Spain
[d] Instituto de Investigación Sanitaria (IIS) Hospital 12 de Octubre (i+12), Madrid, Spain
[e] Barcelona Clínic Schizophrenia Unit, Hospital Clínic Barcelona, University of Barcelona, IDIBAPS, Barcelona, Spain
[f] Child and Adolescent Psychiatry Department, IIS Hospital Gregorio Marañón (IISGM), Madrid, Spain
[g] Center for Psychiatric Neuroscience, Department of Psychiatry, Lausanne University Hospital, Lausanne, Switzerland
[h] Pfizer Neuroscience Research Unit, Cambridge, MA, USA

ARTICLE INFO

Article history:
Received 17 December 2014
Received in revised form 22 April 2015
Accepted 18 May 2015
Available online 16 June 2015

Keywords:
Schizophrenia
Psychosis
Inflammation
Oxidative stress
Immune system
Antiinflammatory drugs

ABSTRACT

In the past decade, there has been renewed interest in immune/inflammatory changes and their associated oxidative/nitrosative consequences as key pathophysiological mechanisms in schizophrenia and related disorders. Both brain cell components (microglia, astrocytes, and neurons) and peripheral immune cells have been implicated in inflammation and the resulting oxidative/nitrosative stress (O&NS) in schizophrenia. Furthermore, down-regulation of endogenous antioxidant and anti-inflammatory mechanisms has been identified in biological samples from patients, although the degree and progression of the inflammatory process and the nature of its self-regulatory mechanisms vary from early onset to full-blown disease. This review focuses on the interactions between inflammation and O&NS, their damaging consequences for brain cells in schizophrenia, the possible origins of inflammation and increased O&NS in the disorder, and current pharmacological strategies to deal with these processes (mainly treatments with anti-inflammatory or antioxidant drugs as add-ons to antipsychotics).

Contents

* Corresponding author at: Departamento de Farmacología, Facultad de Medicina, Universidad Complutense, 28040 Madrid, Spain. Tel.: +34 91 394 1478.
E-mail address: jcleza@med.ucm.es (J.C. Leza).

http://dx.doi.org/10.1016/j.neubiorev.2015.05.014
0149-7634/

Schizophrenia (SCHZ) is a heterogeneous syndrome with unclear molecular mechanisms (van Os and Kapur, 2009; Insel, 2010). Forty years ago, it was suggested that inflammatory processes may play a key role in its pathophysiology (Torrey and Peterson, 1973; Horrobin, 1977). These days, there is renewed interest in immune/inflammatory changes and their associated oxidative/nitrosative consequences as key pathophysiological mechanisms (Kirkpatrick and Miller, 2013) at both the peripheral and central nervous system (CNS) level (Meyer et al., 2011). In this review, we will focus on the inflammatory and oxidative/nitrosative mechanisms underlying brain damage in SCHZ and related disorders and the possibility of pharmacological manipulation of these processes in order to improve psychopathology.

1. General aspects of inflammation and oxidative/nitrosative (O&NS) stress of special interest for schizophrenia

Inflammation is a complex biological protective mechanism aimed at removing dangerous elements and initiating healing processes, although it may be "constitutively" present in areas permanently interacting with external pathogens (skin, respiratory, or digestive epithelia). It occurs in parallel (and overlaps) with other local or systemic defense processes: cell recruitment, O&NS, and apoptosis. Usually, it is a stereotyped, non-specific response, considered a mechanism of *innate immunity* (as compared to *adaptive immunity*, specific to each pathogen). It can be considered a protective mechanism, but when excessive in intensity (non-regulated overactivity of mediators) or time (inefficient resolution), it becomes harmful.

The brain has been classically considered an "*immune privileged*" organ (by the presence of the brain–blood barrier, BBB). However, extensive evidence shows that inflammation within the CNS is directly related to many degenerative processes, and there is growing awareness of its role in psychiatric diseases (depression, post-traumatic stress disorder, and SCHZ, among others) (Najjar et al., 2013). Because increased BBB permeability has been described in SCHZ (Hanson and Gottesman, 2005; Uranova et al., 2010), it is plausible that pro/anti-inflammatory mediators may enter from the periphery or may escape from the brain to the systemic circulation in certain neuropathological scenarios.

Microglia, the resident innate immune cells in the CNS, are immediately activated in response to a harmful signal. Astrocytes, the most abundant cells in the brain (involved in maintenance and support of neurons and structural/functional components of the BBB), also become activated after an insult or by signals released by injured neurons or activated microglia. Neurons themselves may "suffer" the consequences of inflammation – and not just passively – as they release inflammatory mediators (Najjar et al., 2013).

Cytokines such as interleukins, interferons, tumor necrosis factor alpha (TNFα), and chemokines are crucial elements of a proper intra- and intercellular inflammatory response, both in the CNS and periphery. Furthermore, cytoplasm–nuclear transcription factors, mainly kappaB (NFκB) and others (AP-1), control the expression of many oxidative and nitrosative mediators through activation of enzymes (i.e., cyclooxygenases —COX— and nitric oxide synthases —NOS—). There are three isoforms of nitric oxide synthase (NOS), two constitutive: neuronal (nNOS or NOS1) and endothelial (eNOS or NOS3), and one inducible: NOS (iNOS or NOS2). iNOS is characterized by its calcium independence to synthesize NO and citrulline from L-arginine and the larger quantities of NO it can generate as compared with the other isoforms after determinate immune stimuli (i.e., infection, stress). In a pathological context, over-activation of iNOS produces high amounts of NO and the superoxide anion (O_2^-) producing enzymes NADPH oxidase and xanthine oxidase. The simultaneous production of NO and O_2^- results in the generation of peroxynitrite ($ONOO^-$), which in turn damages target molecules including proteins, glutathione (GSH), mitochondria, and DNA. This could be considered a protective cytotoxic effect against potential infection agents such as viruses or bacteria. However, iNOS has also been implicated in cell death in many clinical and experimental settings by lipid peroxidation, disruption of the blood–brain barrier, and decreased mitochondrial function. However, there are two major forms of COX enzymes, designated COX-1 and COX-2, in mammalian tissues. COXs isoforms are responsible for the synthesis of endoperoxides, PGG2 and PGH2, which are transformed into specific prostanoids in each tissue by tissue-specific synthase types. Finally, these molecules and their derivatives interact with their specific receptors to modulate cell function (Phillis et al., 2006). COX-1 is constitutively expressed in tissues, including brain tissue, and is responsible for the physiological production of prostaglandins (PGs) (Phillis et al., 2006). Inflammatory mediators such as cytokines, growth factors, and bacterial endotoxins rapidly induce COX-2, which is normally undetectable in healthy tissues, but is constitutively expressed in the kidney, stomach, and brain (Hoffmann, 2000). COX-2 expression could be induced in certain brain regions and it is able to produce peroxides and other free radicals (ROS) and prostanoids such as PGE2 in toxic amounts (10–20 times above the physiological levels produced mainly by COX-1) in pathological processes with a clear inflammatory component (Seibert et al., 1995). Brain COX-2 activity can be also neurotoxic because, during the production of PGE2, ROS are generated and these contribute to the oxidative/nitrosative damage observed (Phillis et al., 2006), and also because PGE2 is able to induce glutamate release by astrocytes generating cellular death by apoptosis (Takadera et al., 2002).

Intracytoplasmatic clusters of molecules called inflammasomes also play a central role in inflammation, mainly by detecting a large range of pathogen-associated molecular patterns and promoting the maturation of cytokines (Latz et al., 2013). All of these molecular signals are activated by cells in order to fight against pathogens and to recruit other CNS and peripheral immune cells for appropriate response.

Such a complex defense mechanism is finely regulated by compensatory anti-inflammatory pathways. One of these mechanisms involves the cyclopentenone prostaglandins (PGs). The most thoroughly studied is 15-deoxy-PGJ_2 (15d-PGJ_2) (Prasad et al., 2008). This is the proposed endogenous ligand for the gamma isoform of peroxisome proliferator-activated nuclear receptors, PPARγ, a transcription factor whose main effect is to mitigate inflammation by repressing the expression of proinflammatory cytokines and of the inducible isoforms of COX and NOS: COX-2 and iNOS (García-Bueno et al., 2008). PPARγ may be pharmacologically activated by a number of synthetic ligands such as the antidiabetic drugs thiazolidinediones, which exert anti-inflammatory, anti-excitotoxic, and proenergetic effects (promote glucose transport and ATP production) in the brain (García-Bueno et al., 2007, 2008, 2010).

Oxidative/nitrosative stress (O&NS) was first described 18 years ago when it was defined as "an imbalance between oxidants and antioxidants in favor of the oxidants, potentially leading to damage" with the ratio of oxidants to antioxidants >1 (Sies, 1997). Thus, O&NS is the result of a lost battle between components necessary to fight against pathogens – but also toxic to healthy cells – and the mechanisms to detoxify them. Some of the by-products of mitochondrial function used to kill pathogens or foreign cells are *radicals* (more precisely, *free radicals*: compounds with unpaired electrons, which make them highly reactive). Most radicals react immediately, looking for stability with other molecules (or even themselves). The majority are oxygen (ROS) or nitrogen species (RNS). At moderate concentrations, free radicals play an important role as regulatory mediators in signaling processes, such as the

Table 1
Who is who in inflammation and oxidative/nitrosative stress.

Inflammatory mediators	Antiinflammatory mediators	O&N stress mediators	Antioxidant mediators
Intercellular	Intercellular	Free radicals	Non-enzymatic
Cytokines	deoxyPGs	$O_2^{-\bullet}$	Glutathione
Chemokines	Antiinflammatory cytokines	$HO^{\bullet}$	Coenzyme Q_{10}
Inflammatory PGs		$NO^{\bullet}$	
Intracellular	Intracellular	Non-free radicals	Enzymatic
NFκB	IκBα	HO_2	Superoxide dismutases catalase
Keap1	PPARγ	H_2O_2	Glutathione reductase
AP1	Nrf2	Singlet O ($^1O_2$)	Glutathione peroxidase
iNOS	deoxyPGsynthases	$ONOO^-$	Glutathione transferases
COX-2			
Inflammasomes			

regulation of vascular tone, platelet adhesion, and oxidative phosphorylation, to produce energy sources (NADPH), monitoring of oxygen tension in the control of ventilation and erythropoietin production, and signal transduction from membrane receptors (Valko et al., 2007).

An excess of O&NS molecules has repercussions on carbohydrates, nucleic acids, and proteins. In lipids, the main reaction of radicals is *lipid peroxidation*. Lipids are major constituents of cell membranes, so peroxidation seriously impairs internal or external membrane structure and/or function (endoplasmic reticulum, mitochondria). Importantly, lipid peroxidation is self-propagating in cell membranes. The products of lipid peroxidation (i.e., malondialdehyde (Halliwell and Chirico, 1993)) are easily detected in plasma and are used as a measure of O&NS. Another new class of lipid mediators called isoprostanes has recently been proposed as reliable peripheral markers of oxidative stress, as they arise from the lipid peroxidation of long-chain unsaturated fatty acids (omega 3 and 6, in particular) (Wu et al., 2013).

This process is also controlled by several mechanisms. The low-molecular-weight thiol, glutathione, and "reactive" protein sulfhydryls (exposed cysteines in many proteins) are primary participants in antioxidant systems. Glutathione is the major soluble antioxidant in cells. Other antioxidants are enzymes. In addition to glutathione peroxidase (GPx) and glutathione reductase, superoxide dismutase (SOD) is present in cytoplasm (Cu/Zn enzyme) and mitochondria (Mn enzyme) (although there is also an extracellular form in plasma, lymph, and synovial fluid). Catalase is a heme protein that catalyzes the reaction in which H_2O_2 is detoxified to water and O_2. Finally, glutathione transferases make glutathione a more reactive nucleophile (molecule capable of donating an electron pair to an electrophile to form a chemical bond), regenerating its antioxidant capacity. Electrophiles are positively charged chemical species (H^+) that are attracted to electrons to form a chemical bond (typically with a nucleophile).

Another antioxidant mediator is the nuclear factor, erythroid-related factor 2 (Nrf2), which binds to the antioxidant response elements within the promoter of antioxidant enzymes, activating their transcription. As with NFκB, inactive Nrf2 is retained in the cytoplasm by association with the protein Keap1. During inflammation or oxidative stress, Nrf2 translocates to the nucleus and transactivates the enzymes (Zenkov et al., 2013). The main participants in inflammation and O&N stress are summarized in Table 1.

Although inflammation and O&NS are interrelated, they are not the same process. O&NS is the main mechanism by which inflammation could generate cell damage and, eventually, death. In a pathogenic scenario, O&NS could be produced by other non-inflammatory-related stimuli (mitochondrial dysfunction, dopamine metabolic pathways, hyperhomocysteinemia, changes in trace elements (manganese, zinc, copper, and iron), smoking, drug treatment, etc.) (Nathan and Cunningham-Bussel, 2013; Bitanihirwe and Woo, 2011).

2. Evidence about oxidative stress and inflammation in schizophrenia

Schizophrenia has also been associated with increased systemic oxidative mediators (e.g., malondialdehyde and thiobarbiturate reactive substances, TBARS) (Zhang et al., 2006; Herken et al., 2011; Emiliani et al., 2014). Another proposed specific and sensitive indicator of oxidative stress status in vivo in SCHZ is increased isoprostanes in plasma and urine (Dietrich-Muszalska and Olas, 2009). In addition, it has also been reported that accumulation of some amino acids (hyperhomocysteinemia) causes O&NS via a number of mechanisms (such as auto-oxidation or increased lipid peroxidation) (Jones et al., 1994), and previous studies have indicated high levels of homocysteine associated with O&NS in SCHZ and first-episode psychosis (FEP) (García-Bueno et al., 2014a,b).

Many studies have shown abnormal antioxidant levels and signs of oxidative stress both in peripheral tissue (Gysin et al., 2011; Flatow et al., 2013; Fournier et al., 2014) and nervous tissue (Do et al., 2000; Prabakaran et al., 2004; Yao and Keshavan, 2011; O'Donnell et al., 2014) of schizophrenic patients, including CNVs and risk genes related directly to antioxidant systems (GCLC: Gysin et al., 2007, GCLM: Tosic et al., 2006, GSTM1: Gravina et al., 2011, GSTM: Kano et al., 2013, GSTT2: Rodríguez-Santiago et al., 2010, MnSOD1: Akyol et al., 2005, NOS1: Reif et al., 2006a, NOS1AP: Brzustowicz, 2004). In a recent meta-analysis focusing on peripheral markers (Flatow et al., 2013), total antioxidant status in the blood was found to be decreased in FEP and increased in longitudinal studies in patients receiving antipsychotic treatment. In red blood cells (RBC), catalase also decreased in FEP and increased in stable outpatients. Superoxide dismutase decreased in acutely relapsed inpatients, FEP, and stable outpatients (Flatow et al., 2013; Coughlin et al., 2013; Fraguas et al., 2012). As a functional and structural correlate of these findings, some of these O&NS parameters have been associated with changes in brain volume (Fraguas et al., 2012) and electrophysiological abnormalities in SCHZ (Ballesteros et al., 2013).

Changes in proteins related to mitochondria and energy metabolism, heat shock proteins, and immune system regulatory molecules, such as CD14 antigen (CD14), chitinase 3-like 1 (CHI3L1), serine–cysteine protease inhibitor A3 (SERPINA3), and paired immunoglobulin-like receptor beta (PILRB) have been found in the brain (Karry et al., 2004; Middleton et al., 2002; Arion et al., 2007). Postmortem studies have reported increased oxidative stress in the prefrontal cortex, anterior cingulate cortex, caudate region, and hippocampus in subtypes of SCHZ (Prabakaran et al., 2004; Gawryluk et al., 2011; Kim et al., 2014; Clark et al., 2006; Wang et al., 2009; Yao et al., 2004, 2006; Nishioka and Arnold, 2004).

It should be born in mind that the majority of the scientific evidence supporting the notion that inflammatory changes may play a significant role in psychotic disorders has been found in chronic

SCHZ. However, the degree and progression of the whole inflammatory process, its consequences, and the nature of its self-regulatory mechanisms may vary during the different stages of psychotic illness (Fineberg and Ellman, 2013). Some studies indicate subtle changes in inflammatory mediators, stress response systems, and O&NS markers at the FEP stage (Borovcanin et al., 2012; Herberth et al., 2013; van Venrooij et al., 2010; O'Donnell, 2012).

Most of the evidence supporting peripheral inflammatory changes in SCHZ involves elevated plasma pro-inflammatory cytokine levels (Miller et al., 2011). Up-regulated inflammation-related genes have also been identified in monocytes (Drexhage et al., 2010a,b). These plasma cytokine abnormalities have also been associated with certain clinical features, such as cognitive impairment and brain volume loss (Fillman et al., 2013; Mondelli et al., 2011) or with negative symptoms (Garcia-Rizo et al., 2012; Kim et al., 2000; Zhang et al., 2008). T-cell dysfunction has been described in patients (Richard and Brahm, 2012), and an imbalance of immune responses in SCHZ toward a major humoral (Th2) response in the plasma and cerebrospinal fluid (CSF) of patients, correlated with worse prognosis, has been suggested (Potvin et al., 2008; Müller et al., 2012a,b, 2013).

Inflammatory evidence is also present in the brain. Abnormal CSF cytokine (McAllister et al., 1995) and leukocyte levels have been identified in brains of SCHZ patients (Nikkila et al., 1999, 2001; Miller et al., 2013a,b). Postmortem evidence for inflammation is growing. Brain microglial activation and abnormal lymphocyte levels have been suggested in postmortem and positron emission tomography studies using (*R*)-[^{11}C]PK11195, a ligand that recognizes the translocator protein (TSPO) (Busse et al., 2012; Doorduin et al., 2009; van Berckel et al., 2008; Steiner et al., 2008). TSPO is a receptor found on activated microglial cells. However, since it has been found in other peripheral cell types, along with the existence in humans of a polymorphism associated with high and low affinity binding site of TSPO ligands, novel highly specific PET ligands for activated microglia are needed. Other postmortem studies have found increased numbers and structural degenerative impairments of HLA-DR$^+$ microglia in SCHZ (Steiner et al., 2006; Wierzba-Bobrowicz et al., 2005; Radewicz et al., 2000).

The possibility has been explored that abnormalities in inflammatory mediators (i.e., PGs and related lipid-derived compounds) in the brain of subjects with SCHZ may affect synaptic monoaminergic neurotransmission, neurocognition, and increased susceptibility to infections (Oresic et al., 2012).

Some authors have suggested that PGE2 is involved in activation of the tryptophan-degrading enzyme indoleamine 2,3-dioxygenase (IDO) that generates potentially neurotoxic kynurenine metabolites, such as kynurenic and quinolinic acids, which could contribute to the pathogenesis of the disease. Thus, changes in kynurenine pathway metabolism have been found in the prefrontal cortex and CSF of subjects with SCHZ (Schwarcz et al., 2001; Nilsson et al., 2005; Sathyasaikumar et al., 2011; Linderholm et al., 2012). Kynurenic acid is an endogenous glutamate NMDA receptor antagonist, and it is also involved in the functioning of mesocorticolimbic DA neurons, linking the dopamine hypothesis of SCHZ with the idea of a deficiency in glutamatergic function (Erhardt et al., 2007).

Increased plasma levels of the inflammatory mediator PGE_2 and increased COX activity have also been reported in FEP (García-Bueno et al., 2014a) and chronic SCHZ (Kaiya et al., 1989; Das and Khan, 1998). In contrast, fewer studies have focused on the role of anti-inflammatory signaling pathways in clinical settings, but there are data showing a clear imbalance in some pro/anti-inflammatory mediators in the blood of patients in initial and chronic phases (García-Bueno et al., 2014a; Martínez-Gras et al., 2011). Some authors have reported an endogenous increase in anti-inflammatory cytokines at different stages of SCHZ as an attempt to counteract (or limit) ongoing pro-inflammatory processes (Borovcanin et al., 2012). Apart from cytokines, classical studies found that PGD_2 (the precursor of 15d-PGJ_2) stimulated the production of cyclic AMP and thereby exerted functional antagonism of dopamine-D2 receptors (Ono et al., 1992). Therefore, PGD_2 and its metabolites could counteract the biochemical and behavioral effects of dopamine, and deficient PGD_2/15d-PGJ_2 signaling in the brain could influence dopamine transmission (Condray and Yao, 2011).

3. Mechanisms whereby O&NS and inflammation lead to brain cell damage and/or neurodegeneration in schizophrenia

Neurodegeneration is characterized by uncontrolled damage to neuronal function and structure, leading to cell death. The major processes by which neurons die are necrosis and apoptosis (programmed cell death). Synergic stimuli that can initiate cell death include O&NS, inflammation, excitotoxicity, mitochondrial dysfunction, and abnormal protein aggregation. Although this is still a matter of debate, in SCHZ, longitudinal imaging studies have detected loss of gray matter in regions of the cerebral cortex (thinning) and ventricular enlargement (Takayanagi et al., 2013). Other signs of cellular damage or abnormal development are also present in the brains of subjects with SCHZ, such as decreased dendritic spine density on cortical pyramidal neurons, volumetric deficits in the hippocampus, and abnormalities in white matter and in structural connectivity of the subcortical tracts, as well as in myelination and oligodendroglia (Arango et al., 2012; Vita et al., 2012; Heckers and Konradi, 2010).

Multiple and interrelated mechanisms have been suggested as possibly involved in brain cell damage or neurodegeneration in SCHZ (Fig. 1). Based on current findings, these possible mechanisms include:

1. Microglial activation or increased microglial cellular density. Although all cell types in the CNS are involved in inflammation, the main mediators of inflammation and enhanced reactive oxygen species and oxidative damage are the activated microglial cells. Some authors have hypothesized that microglia are the main sources of inflammatory mediators and O&NS in SCHZ (Monji et al., 2013). Activated microglia produce prostaglandins, chemokines, cytokines, complement proteins, proteinases, ROS, and RNS, whose sustained production can have a deleterious effect on susceptible cell populations by enhancing oxidative stress and activating cell death pathways through stimulation of kinases and caspase cascades (Monji et al., 2013). There is also some evidence from animal models of SCHZ showing progressive microglial activation, increased iNOS expression, and O&NS markers in the offspring of rats exposed to the viral mimetic polyriboinosinic–polyribocytidylic acid (poly I:C) during pregnancy (Ribeiro et al., 2013). In addition, some antipsychotics inhibit the release of NO from activated microglial cells, possibly through the suppression of $[Ca^{2+}]_i$ elevation in microglial cells (Kato et al., 2008, 2011). However, a role of other cell types in the brain cannot be ruled out: a recent paper indicates neuroinflammation in SCHZ subjects associated with astrogliosis (Catts et al., 2014).
2. Mechanism underlying the interaction between oxidative/nitrosative stress and neuroinflammation. As described above, oxidative stress is closely linked to inflammation. Many inflammatory mediators are activated by oxidative molecules, while activated immune cells such as microglia generate ROS and RNS. The complex interplay between oxidative stress and inflammation is in part governed by the reciprocal interactions between the transcription factors Nrf2 (whose nuclear

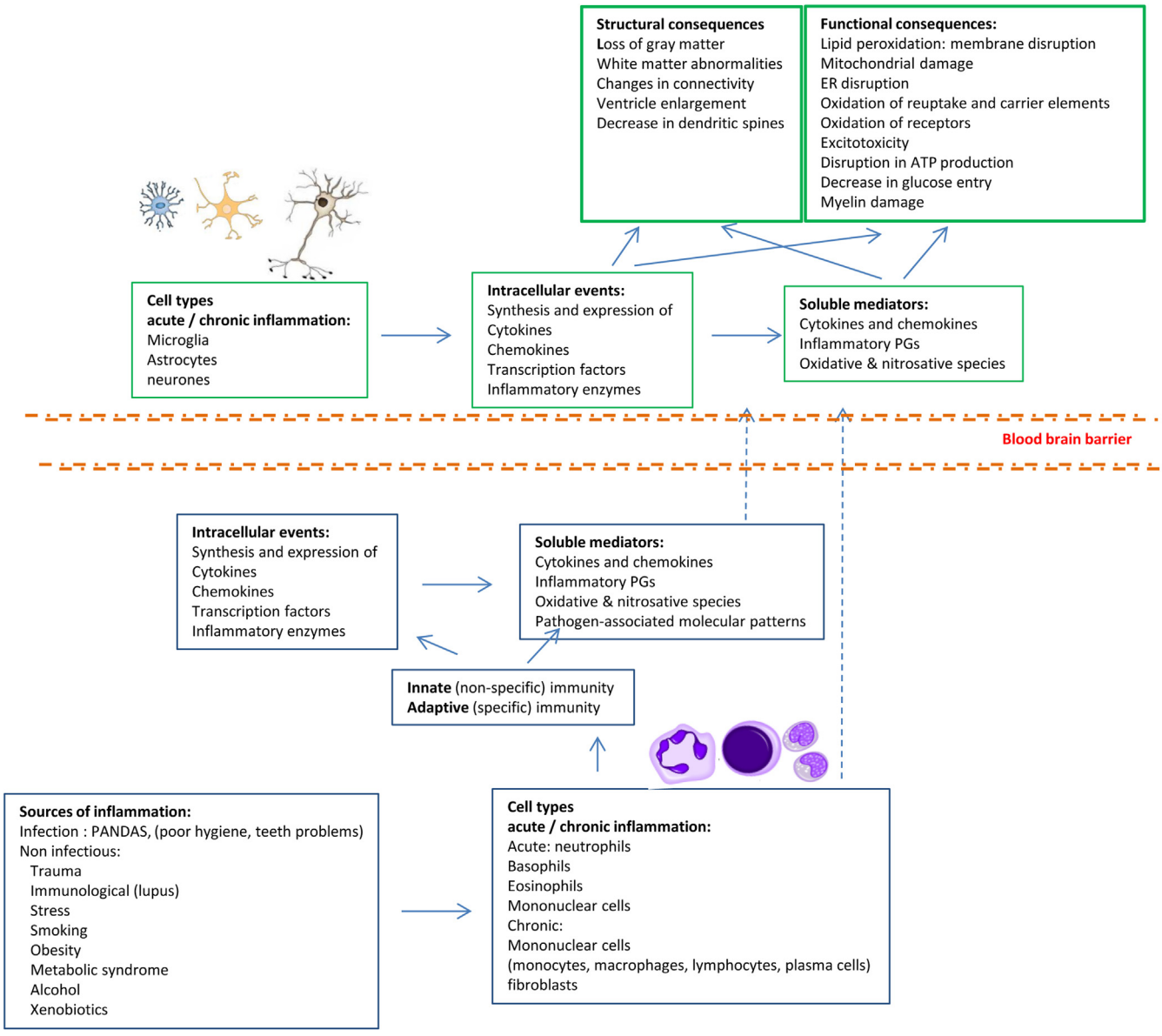

Fig. 1. Mechanisms involved in brain cell damage in schizophrenia.

translocation induces antioxidant phase II gene transcription) and NF-κB (whose translocation to the nucleus promotes transcription of many proinflammatory genes) (Buelna-Chontal and Zazueta, 2013). Converging evidence shows that schizophrenia pathophysiology involves oxidative stress and inflammatory mechanisms, closely interacting and potentiating each other in a damaging positive feed-forward process. The interaction between redox and inflammatory processes occurring at specific or critical time windows during brain development may affect neurons vulnerable to elevated oxidative insults, such as parvalbumin-expressing interneurons (PVI). PVI impairment could account for abnormal circuit synchrony/integration and cognitive deficits (Do et al., 2009; O'Donnell et al., 2014; Steullet et al., 2014). Using a transgenic mouse model with impaired GSH synthesis ($GCLM^{-/-}$) (Steullet et al., 2010), Do et al. showed that, in parallel to oxidative stress, there was an increase of microglia activation more pronounced at peripubertal stage compared to adulthood. This suggests that oxidative stress-induced neuroinflammation was more prominent in the early phases of neurodevelopment. It also argues that the shedding of Receptor for Advanced Glycation End-product (RAGE) induced by matrix metalloproteinases such as MMP9 is a key regulatory mechanism by which oxidative stress interacts with neuroinflammation. This pathological interaction, induced by RAGE, may be a potential trigger of the structural and morphological impairments observed in schizophrenia (Do et al., 2015).

3. Uncontrolled activation of the hypothalamic/pituitary/adrenal axis. As in other psychiatric diseases, the stress response is impaired in SCHZ patients (Walker et al., 2008), who have lower cortisol levels than controls both in anticipation of and after social stress exposure (Ciufolini et al., 2014). However, stress exposure is a crucial factor in the genesis of FEP, and the massive release of glucocorticoids may be directly related to some neurodegenerative fingerprints (e.g., neuronal degeneration, loss of synaptic spines and whole dendrites of pyramidal neurons in the prefrontal cortex, apoptotic cell death, glial cell dysfunction, and decreased neurogenesis in the hippocampus) (Cotter et al., 2001; Arango et al., 2001; Bennett, 2008).
4. Excitotoxicity and disrupted glutamate metabolism. The glutamatergic theory of SCHZ is based on chronic NMDA receptor

hypofunction and an associated net increase of glutamate release in cortical and hippocampal areas, leading to potential excitotoxicity (Stone et al., 2007; Schobel et al., 2013). Most importantly, synaptic NMDA receptor signaling boosts intrinsic antioxidant defenses (Hardingham and Bading, 2010), particularly through direct transcriptional control of the GSH system (Baxter et al., 2015). Thus, NMDA receptor hypofunction leads to deleterious loss of this control and generates oxidative stress. Conversely, oxidative conditions depress NMDA receptor activity (Steullet et al., 2006) through its redox sites (Choi et al., 2001). NMDA receptor hypofunction induced by ketamine consistently leads to IL-6 dependent induction of NADPH oxidase, resulting in overproduction of superoxide and parvalbumin interneuron impairment (Behrens et al., 2007; Belforte et al., 2010).

In addition, defects in the key enzyme of the tryptophan/kynurenine metabolism, indoleamine 2,3-dioxygenase (IDO), resulting in increased production of metabolites such as kynurenic acid or quinolinic acid, have been suggested in psychotic illness (Wonodi et al., 2011; Sathyasaikumar et al., 2011). These metabolites may affect glutamatergic neurotransmission in SCHZ and produce neurodegeneration (Myint and Kim, 2013).

5. Mitochondrial dysfunction and energy deficits (Karry et al., 2004; Andreazza et al., 2010). These could potentially lead to either reduced synaptic plasticity or cell death in SCHZ (Ben-Shachar, 2009).
6. Reduced levels of neurotrophins. Variations in brain-derived neurotrophic factor (BDNF) have been well documented in SCHZ (Nieto et al., 2013). These changes may play a role as part of the impaired neurodevelopment, deficits in neuroplasticity, and dysfunction in synaptic connectivity seen in patients (Durany and Thome, 2004; Shoval and Weizman, 2005; Buckley et al., 2007).
7. Impaired neurogenesis. Abnormal neurogenesis has been found in SCHZ in postmortem studies (Reif et al., 2006b). One of the genes most related to SCHZ is Disrupted-in-SCHZ 1 (DISC-1), which regulates the rate of adult neurogenesis (Zhao et al., 2006). Recently, it has been demonstrated that disruptions of fetal prefrontal cortical neurogenesis related to defects in genes controlling neuronal migration and synaptic transmission are critical in the pathophysiology of SCHZ (Gulsuner et al., 2013).
8. Apoptosis. Differential changes in apoptotic pathways may take place both in early developmental (Gassó et al., 2014) and later progressive phases of SCHZ (Jarskog, 2006), linked to mitochondrial dysfunction and inflammasome activation (Latz et al., 2013).
9. Demyelination. Prolonged microglial activity may lead to oligodendrocyte dysfunction through massive liberation of cytokines and ROS (Li et al., 2005; Schmitz and Chew, 2008). Furthermore, a model of glial–neuronal interactions has been suggested to explain the demyelination identified in brains of patients with SCHZ. According to this model, receptors on astrocytes are not functional in SCHZ, losing their modulator influence on synaptic neurotransmission (Mitterauer and Kofler-Westergren, 2011). Myelin dysfunction in SCHZ may be related to O&NS changes in phospholipid polyunsaturated fatty acids (PUFA) levels in both brain and peripheral membranes (Yao and van Kammen, 2004). More interestingly, redox dysregulation has been shown to impair myelination processes both in preclinical models of oxidative stress and in early psychosis patients with a high risk of glutathione impairment (Monin et al., 2014).
10. Several studies have found that stress exposure excitotoxicity and the resultant O&NS have inhibitory effects on glucose transport and metabolism, through impaired expression, sub-cellular location, and activity of the glucose transporter proteins (De Leon et al., 1997; Mark et al., 1995; Reagan et al., 2000; Lavoie et al., 2011). This reported decrease in glucose uptake leave[?] neurons in an energy-compromised environment, which could detrimentally affect neuronal responsiveness to pathophysiological events. In fact, glucose transport impairment precedes ATP depletion in the brain, increasing neuronal vulnerability to excitotoxicity by compromising the function of ion-motive ATPases (Mark et al., 1995) and glutamate transporters (EAATs) and reducing the ability of neurons to carry out the costly task of managing the consequences of an excitotoxic or metabolic insult (Yusim et al., 2000). This mechanism has been suggested to occur in SCHZ (McDermott and de Silva, 2005) as an early step in the disease prior to neuronal degeneration.

4. Is peripheral inflammation and ox/nox stress related to brain function in schizophrenia?

There is continuous crosstalk between numerous cell types in the CNS (neurons, glia and endothelium-related cells), the BBB, and the periphery (Lampron et al., 2013). These processes are finely regulated by families of mediators (cytokines, chemokines, PGs, trophic factors, glucocorticoids, catecholamines, etc.) that recognize, amplify, or inhibit different signals in both directions. However, in a pathological context, this fine regulation is lost, BBB permeability increases, and a number of brain functions may be affected, including excitatory/inhibitory neurotransmission, stress and alarm phase responses, or synaptic plasticity (Capuron and Miller, 2011). Functional BBB breakdown (elevated CSF:serum albumin ratio; mild pleocytosis or presence of IgG oligoclonal bands) and ultrastructural abnormalities have been identified in patients with SCHZ (Hanson and Gottesman, 2005; Uranova et al., 2010). It has been suggested that increased O&NS may be one of the causes leading to BBB dysfunction. For example, it has been suggested that increased oxidation may contribute to endothelial dysfunction that can be prevented by antipsychotic treatment (Zhang et al., 2003). In this scenario, ROS/NOS species may also cross the BBB, and peripheral ROS/NOS activity could reflect and even affect central ROS/NOS activity. Supporting this idea, some authors have found that decreased production of reactive oxygen species by blood monocytes caused by clozapine correlates with clinical improvement in schizophrenia patients (Gross et al., 2003).

Most neuropathologies manifest interrelated peripheral and central symptomatology and SCHZ is no exception. Determining the peripheral changes in inflammation-related molecules in subjects with a psychotic disorder could be useful not only for diagnosis and monitoring of the natural course of the disease (trait or state biomarkers, risk/protection factors) (Schwarz et al., 2010), but also to reveal possible mechanisms with etiological and pathophysiological relevance. In an interesting approach to solving this issue, one study compared the same inflammatory mediators (i.e., cytokines) in plasma and in postmortem brain tissue from controls and subjects with SCHZ and found the same changes in both compartments, validating the concept that SCHZ can be investigated through systemic biomarkers (Harris et al., 2012). Similarly, a genetic study concluded that a high number of brain transcripts are co-expressed in PBMCs and may represent a pool of genes useful as biomarkers for psychiatric disorders (Rollins et al., 2010). In addition, a recent review suggested a link between peripheral inflammatory/immune processes and MRI-detected anomalies in the brains of individuals with SCHZ (Frodl and Amico, 2014). This relationship has also been demonstrated for other physiological systems strongly related to psychotic illness, such as the endocannabinoid system, and its status in PBMCs is considered a mirror

of what occurs in the CNS in multiple neuropathologies (multiple sclerosis, Huntington's and Parkinson's diseases) (Bioque et al., 2013; Centonze et al., 2008).

Despite these findings, there are still some limitations to establishing a definite relationship between peripheral inflammatory/O&NS mediators and SCHZ neuropathology:

(a) The type and duration of antipsychotic treatment produces changes in several peripheral inflammatory/O&NS mediators (Zhang et al., 2006).
(b) The systemic inflammatory response is highly non-specific and may be activated and/or modified by different stimuli: stress, infections, diet, age, metabolic disorders, alcohol, smoking, abuse of psychotropics, etc. (Kirkpatrick and Miller, 2013).
(c) Complex and continuous dynamic changes in the inflammatory response occur in the natural course of psychosis. This complexity may be one of the causes of controversy regarding the specific role of inflammatory mediators in the pathophysiology of the different psychotic disorders (Meyer et al., 2011).

5. Possible origin of increased O&NS and inflammation in schizophrenia

There are multiple theories dealing with the origin of increased O&NS and inflammation in SCHZ. As a continuum, all of these theories are not mutually exclusive. Five major categories exist:

1. O&NS/inflammatory changes before birth (prenatal or maternal viral, bacterial, and protozoan infections), and obstetric complications (fetal hypoxia, preeclampsia). The common notion is that these factors "prime" an immature fetal immune system that will remain impaired for a lifetime. This permanent deregulation will affect brain development and function and increase the lifetime risk of SCHZ (Brown and Derkits, 2010; Hayes et al., 2014; Miller et al., 2013a,b). It has been proposed that maternal inflammatory response induces oxidative stress in the fetal cells through increased production of inflammatory cytokines (IL-1β, IL-6, and interferon-γ) that cross the placenta (Meyer et al., 2009). Currently, the use of maternal immune activation models in rodents is receiving increasing attention in translational psychiatry (Hida et al., 2013; Giovanoli et al., 2013). These models are relevant because they reproduce in the progeny any[?] cognitive deficits presented in schizophrenia, such as dopaminergic (Ozawa et al., 2006; Vuillermot et al., 2010), serotoninergic (Holloway et al., 2013), glutamatergic (Holloway et al., 2013), GABAergic (Richetto et al., 2014), and metabolic dysregulation (Pacheco-López et al., 2013), synaptic failures (Oh-Nishi et al., 2010), mild neuroinflammation (Garay et al., 2013), oxidative/nitrosative stress (Oskvig et al., 2012), impaired neurogenesis (Liu et al., 2013), and impaired pre-pulse inhibition, reverse learning, and spatial short-term memory, as well as impaired object recognition memory (Hida et al., 2013; Wallace et al., 2014; Richetto et al., 2013; Wolff et al., 2011).
2. O&NS/inflammatory changes in specific phases of brain development and maturation (early adulthood) (Do et al., 2009). During early adulthood, the brain undergoes decisive changes, completing the myelination of axon fibers and synaptic pruning in particular areas. Some immune-related genes are critical for homeostasis and synaptic remodeling. These neurodevelopmental changes coincide with a maturation of dopaminergic neurotransmission in cortical structures. Some of these are at the core of SCHZ pathology and may be crucially affected in adolescence by infections that trigger innate immune responses, microglia activation, and O&NS in the brain (O'Donnell, 2012; Hickie et al., 2009). However, inflammation in SCHZ does not need to be a response to infection. Indeed, it can also be due to deficits in processes controlling cell homeostasis. Immune responses and inflammatory signals are not only driven by pathogens, but are also used as signals maintaining cellular homeostasis in neural tissue. For example, blocking NMDA receptors can cause oxidative stress in parvalbumin interneurons by way of IL-6 (Behrens et al., 2008). Cytokines and MHC molecules are critical for synapse formation and remodeling (Boulanger et al., 2001).
3. O&NS/inflammatory lifetime changes produced by diverse environmental factors, such as episodes of psychosocial stress, infections (viral reactivations, poor hygiene, periodontal problems), dietary deficiencies, alcohol, tobacco, metabolic and autoimmune disorders, medications, etc. The family of Toll-like receptors (TLRs) has emerged as a possible mechanism involved. TLRs are the first line of defense against invading microorganisms and other immune stimuli (in general, PAMPs: pathogen-associated molecular patterns). Their expression is modulated in response to pathogens and other environmental stresses. TLR-4 orchestrates neuroinflammation in animal models and its expression is regulated by stress-induced bacterial translocation of gut microflora (Gárate et al., 2011, 2013). Alterations in peripheral TLR activity have been described in SCHZ (McKernan et al., 2011) and other psychiatric disorders such as depression (Müller et al., 2012a,b).
4. O&NS/inflammatory changes produced as a consequence of genetic susceptibility due to the existence of hypo/hyperpolymorphisms in certain immune/inflammatory-related genes as risk factors for this disorder (Shi et al., 2009; Benros et al., 2011). Genome-wide association studies have identified genes involved in the immune response (MHC, NFκB, IL-6, etc.) that correlate with SCHZ diagnosis (Stefansson et al., 2009; Ripke et al., 2013; Michel et al., 2012; Hashimoto et al., 2011; Sun et al., 2008).
5. Loss or impairment of protective function in at-risk cell types. Parvalbumin-expressing cortical interneurons, a neuronal subtype frequently found to be affected in SCHZ postmortem studies (Lewis et al., 2012), are specifically vulnerable to O&NS because of their high level of activity. In fact, these neurons are also termed "fast-spiking interneurons" and likely require high metabolic activity to sustain such fast firing. They are surrounded by perineuronal nets (PNN), a mesh of glycoproteins that confer protection against O&NS (Lewis et al., 2012). If PNN or other undiscovered protective factors are impaired, this critical cell population may easily express O&NS, leading to impaired parvalbumin interneurons, neural synchronization, and schizophrenia phenotypes (Cabungcal et al., 2013a,b).

Cortical balance between neural excitation and inhibition may be especially affected in peripuberty, as a critical period of high vulnerability for environmental adverse insults (Southwell et al., 2014), in analogy to the known association with childhood trauma in psychotic patients (Kulak et al., 2012).

6. Oxidative stress and inflammation as possible trait/state biomarkers of schizophrenia

Efforts at describing biological markers for SCHZ in pathway-based approaches have been made by psychiatrists as tools for early diagnosis and also for monitoring disease progression and treatment response (Kapur et al., 2012). Several studies have shown that both O&NS and inflammatory markers may vary with the clinical status of patients (Kirkpatrick and Miller, 2013; Coughlin et al., 2013). A recent meta-analysis shows total antioxidant status, RBC catalase, and plasma nitrite as state markers (Coughlin et al., 2013).

In another meta-analysis of inflammatory markers, there appear to be certain state-related markers, including IL 1β, IL-6, and transforming growth factor-beta, as patients with SCHZ have higher concentrations of these cytokines than controls during an exacerbation of symptoms, but no differences during periods of clinical stability (Kirkpatrick and Miller, 2013). C-reactive protein appears to be a proinflammatory state marker (Miller et al., 2013a,b).

In contrast, RBC superoxide dismutase appears to be a trait marker for SCHZ, as levels were found to be significantly decreased in acutely relapsed inpatients, FEP, and stable outpatients (Coughlin et al., 2013). Also, IL-12, interferon-gamma, and TNFα appear to be trait markers (Kirkpatrick and Miller, 2013). In a third meta-analysis in drug-naive FEP, it was suggested that some lymphocyte phenotypes (CD4/CD8) may be state markers for acute exacerbations of psychosis, whereas others (CD56) may be trait markers (Miller et al., 2013a,b). Recently, two studies focused on pro- and anti-inflammatory biomarkers in FEP, showing that increased COX-2 in PBMC and decreased 15d-PGJ_2 plasma levels can be considered trait markers, while plasma levels of NO^-_2 and TBARS are state biomarkers (García-Bueno et al., 2014a,b).

7. The question of non-selectivity of the findings: the broad shadow of stress

As stated above, inflammation is a stereotyped response, in most cases non-specific to a variety of harmful pathogens. Furthermore, inflammation overlaps with other local or systemic processes such as O&NS and apoptosis, and it plays a crucial pathophysiological role in many systemic diseases, e.g., atherosclerosis, obesity, diabetes, metabolic syndrome, etc. Most of the intra- and intercellular factors in inflammation are thus common to these processes, and occur even in non-pathological processes such as aging and stress.

The role of stress (another survival and generalized response) deserves special attention. Stress management is a major contributor to the etiology (as a risk factor) and progression of most of psychiatric disorders including psychotic illness (Beards et al., 2013; Niwa et al., 2013) in its multiple clinical and subclinical manifestations. Notably, patients with SCHZ are more sensitive to stress and frequently report phases of stress in proximity or during transition to full-blown psychosis. In fact, hypercortisolemia is considered a marker of FEP and of acute psychotic episodes (Gallagher et al., 2007). In addition, exposure to physical or psychological stressors may contribute to the pathophysiology of SCHZ due to its effects on the inflammatory response at peripheral and central levels (Bennett, 2008). In recent years, studies conducted with different stress protocols show a pro-inflammatory response in the brain and other systems, characterized mainly by a complex release of several inflammatory mediators such as cytokines, prostanoids, free radicals, and transcription factor activation (García-Bueno et al., 2008). In addition, repeated stress causes an energy-compromised status in the brain, with a decrease in glucose utilization and ATP production, which may account for the excitotoxicity processes seen in this condition (García-Bueno et al., 2007). Stress exposure is present in almost all psychiatric diseases, and its myriad effects on the immune/endocrine system need to be elucidated and controlled. However, as the stress component is inherent to the disease, all therapeutic strategies should be designed to manage its detrimental contribution to the symptomatology of SCHZ.

As in SCHZ, inflammation has increasingly been implicated in a variety of mental disorders, such as mood disorders, attention deficit and hyperactivity disorder, and autism (Uddin and Diwadkar, 2014). Abnormalities in both the immune system and the stress response system have been proposed as mechanisms contributing to pathogenesis in schizophrenia and bipolar disorder (for review see Drexhage et al., 2010a,b; Kupka et al., 2012). Abnormalities of the immune system and glucocorticoid signaling pathway, and interactions between these two systems, may contribute to the common pathophysiology found in major mental illnesses (Fillman et al., 2014). Recent studies demonstrate that some of the heterogeneity in schizophrenia and bipolar disorder may be partially explained by inflammation/stress interactions. It would seem that inflammation has a greater association with schizophrenia while stress signaling has a greater association with bipolar disorder (Fillman et al., 2014). Such environmental factors as maternal infection (leading to developmental or later immune abnormalities) have also been related to the pathogenesis of these two disorders (Yolken and Torrey, 1995; Brown, 2012).

In schizophrenia and bipolar disorder patients, a high inflammatory set point of circulating monocytes at the transcriptome level has been observed, involving various inflammatory transcripts forming distinct fingerprints (the transcriptomic monocyte fingerprint in schizophrenia overlaps with that in bipolar disorder, but also differs with it at points) (Drexhage et al., 2010a,b): there are increased serum levels of compounds of the IL-1, IL-6, and TNF system (albeit modest and inconsistent), and there is also evidence that the IL-2 system is activated in patients with schizophrenia (and perhaps those with mania), although independently of activation of the IL-1, IL-6 and TNF systems, suggesting separate inducing mechanisms for monocyte and T-cell activation (Drexhage et al., 2010a). Recently, an association of serum interleukin 6 and C-reactive protein in childhood with depression and psychosis in young adults has been reported in a population-based longitudinal study (Khandaker et al., 2014). It is also important to take into account that symptoms such as those of depression can play a role in or mediate the immune/inflammatory abnormalities described in early phases of schizophrenia-related disorders (Noto et al., 2015). In bipolar disorder, an elevation of serum IL-6 and TNF have been shown in manic, euthymic, and depressive phases, with IL-2, IL-4, and IL-8, especially elevated in maniac states (Kim et al., 2007; Brietzke et al., 2009).

A recent review has looked at the literature on inflammation in neurodevelopmental disorders or disorders that start in infancy, such as autism spectrum disorders (ASD), finding that ASD are the ones most consistently associated with a systemic proinflammatory status (Mitchell and Goldstein, 2014). In adults, the strongest evidence is for major depressive disorder (Dowlati et al., 2010), and there is very compelling evidence of interferon-induced depression (reviewed in Udina et al., 2012). In addition, an increase in translocator protein density measured by distribution volume (TSPO VT), an indicator of activated microglia and neuroinflammation, has been found in brains of patients during major depressive episodes (Setiawan et al., 2015).

Although the existence of inflammation in different psychiatric disorders seems clear, the direction of the events in the inflammation process with respect to the onset or maintenance of the specific psychiatric disorders is less clear, and it is necessary to take longitudinal approaches in order to disentangle this (García-Bueno et al., 2014b).

8. Antioxidant and anti-inflammatory agents in schizophrenia

Augmentation of antipsychotic therapy with antioxidants may an effective and safe add-on strategy in SCHZ patients. Table 2 summarizes double-blind, randomized, placebo-controlled clinical trials with antioxidant augmentation in SCHZ. Other strategies such as vitamin E (Michael et al., 2002) and lipoic acid (Kim et al., 2008) augmentation have shown encouraging results, but in small samples. Besides clinical assessments, it is also important to identify

Table 2
Double-blind, randomized, placebo-controlled clinical trials with antioxidant augmentation therapy in schizophrenia.

Study	Number of patients	Duration (weeks)	Participants	Intervention	Results (PANSS reduction)
N-Acetylcysteine					
Berk et al. (2008)	140	24	Outpatients w/ SCHZ PANSS > 55	NAC (2 g/d)	NAC > Placebo
Farokhnia et al. (2014)	42	6	Outpatients w/ SCHZ Negative PANSS > 19 + risperidone	NAC (2 g/d)	NAC > Placebo
Vitamin c (L-ascorbic acid)					
Dakhale et al. (2005)	40	8	Outpatients w/ SCHZ	Vitamin C (500 mg/d)	Vitamin C > Placebo[a]
Extract of *Ginkgo biloba*					
Zhang et al. (2001)	109	12	Treatment-resistant inpatients w/ SCHZ + haloperidol	EGB (360 mg/d)	EGB > Placebo[b]
EPA/DHA omega-3 fatty acids augmentation					
Peet et al. (2001)	45	12	Outpatients w/ SCHZ PANSS > 40	EPA (2 g/d)DHA (2 g/d)	EPA > Placebo and EPA > DHA
Peet et al. (2001)	30	12	Inpatients (acute phase) w/ SCHZ (9 PEP + 21 relapses)	EPA (2 g/d)	EPA < Placebo Days without AP treatment: EPA < Placebo
Fenton et al. (2001)	87	16	Outpatients w/ SCHZ or SAD PANSS > 45	EPA (3 g/d)	No differences EPA vs. Placebo
Peet and Horrobin (2002)	122	12	Outpatients w/ SCHZ PANSS > 50	EPA (1 g/d, 2 g/d, 3 g/d)	Clozapine + 2 g/d EPA < Clozapine + Placebo No differences w/ the rest of AP groups
Emsley et al. (2002)	40	12	Outpatients w/ SCHZ PANSS > 50	EPA (3 g/d)	EPA > Placebo
Emsley et al. (2006)	84	12	Outpatients w/ SCHZ or SAD w/ TD	EPA (2 g/d)	No differences EPA vs. Placebo
Berger et al. (2007)	80	12	FEP	EPA (2 g/d)	No differences EPA vs. Placebo

AP: antipsychotic; DHA: docosahexaenoic acid; EGB: extract of *Ginkgo biloba*; EPA: eicosapentaenoic acid; FEP: first episode of psychosis; NAC: N-acetylcysteine; PANSS: positive and negative scale for schizophrenia; SAD: schizoaffective disorder; SCHZ: schizophrenia; TD: tardive dyskinesia.

[a] This study used the Brief Psychiatric Rating Scale (BPRS).

[b] This study used the Scale for the Assessment of Negative Symptoms (SANS) and the Scale for the Assessment of Positive Symptoms (SAPS). No statistically significant differences in BPRS reduction were reported.

objective markers such as EEG findings to monitor the efficacy of the treatment (Lavoie et al., 2008; Carmeli et al., 2012; Ballesteros et al., 2013).

If increased inflammation of the brain contributes to the symptoms of SCHZ, reduction of inflammatory status may improve the clinical picture. A recent update has reviewed the randomized controlled trials on efficacy of anti-inflammatory agents in SCHZ, including aspirin, celecoxib, davunetide, estrogens, and minocycline (Sommer et al., 2011). Table 3 summarizes the main double-blind, randomized, placebo-controlled clinical trials with anti-inflammatory augmentation in SCHZ.

Aspirin showed significant effects on the primary outcome (total PANSS score change), while celecoxib, minocycline, and davunetide showed no significant effect. As some of these studies included a small and heterogeneous number of samples, these results should be interpreted with caution. A recent meta-analysis of these studies showed that NSAID supplementation is not superior to placebo in PANSS total score change from baseline, but suggestive effects were observed in studies on aspirin in inpatients and in FEP (Nitta et al., 2013). However, augmentation with acetylsalicylic acid may have the additional benefit of reducing cardiac and cancer mortality in SCHZ (Sommer et al., 2011). Other ongoing clinical trials (FDA, EMA) include combination therapies (add-on antipsychotics) with salsalate, fluvastatin, simvastatin, methotrexate, resveratrol, hydrocortisone, and ibuprofen.

While the focus has traditionally been on antagonizing the pro-inflammatory pathways, little effort has been made to investigate the anti-inflammatory side of the balance, including stimulation of deoxyPGs or PPARγ activity. Of special interest is the possible use of some thiazolidinediones, potent agonists of PPARγ, widely used as insulin-sensitizing drugs for the treatment of type 2 diabetes (Lehmann et al., 1995). This pharmacological modulation of PPARγ, which may also may directly regulate glutamatergic neurotransmission at the NMDA receptor level (Salehi-Sadaghiani et al., 2012; Almasi-Nasrabadi et al., 2012), has been suggested as a putative treatment for neurocognitive deficits associated with mood and psychotic syndromes (McIntyre et al., 2006), and it can be considered a multi-faceted therapeutic target due to its anti-inflammatory, antioxidant, anti-excitotoxic, and pro-energetic profile (García-Bueno et al., 2010). However, in a recent pilot clinical trial, the PPARγ synthetic ligand rosiglitazone failed to improve cognitive deficits in clozapine-treated patients with SCHZ, so more evidence is needed to design new trials (Yi et al., 2012).

9. Anti-inflammatory effect of antipsychotic agents

In recent years, a growing body of evidence has pointed to an anti-inflammatory effect of antipsychotics as one of the beneficial effects of these drugs in SCHZ patients. The stimulation of anti-inflammatory cytokines such as IL-4, IL-10, and IL-17 seems to be a mechanism elicited by several antipsychotics to regulate uncontrolled and potentially deleterious inflammation in SCHZ (Meyer et al., 2011, Sugino et al., 2009; Maes et al., 1995). It has been shown that risperidone normalizes elevated inflammatory mediators (cytokines and PGs) and restores anti-inflammatory pathways in murine models of neuroinflammation (MacDowell et al., 2013). Chronic administration of others antipsychotics, such as olanzapine or clozapine, also reduce PGE_2 concentration in the rat brain

Table 3
Double-blind, randomized, placebo controlled clinical trials with anti-inflammatory augmentation in schizophrenia.

Study	Number of patients	Duration (weeks)	Participants	Intervention	Results (PANSS reduction)
Aspirin					
Laan et al. (2010)	70	12	Outpatients w/ SCHZ, SAD or SCF PANSS > 60 Duration of illness <10 years	Aspirin (1 g/d)	Aspirin > Placebo
Weiser et al. (2012a)[a]	200	16	SCHZ patients w/ ≥4 (moderate) score on CGI-S and 4 (moderate) score on two of P1, P2, P3, P6 PANSS and/or a total PANSS negative symptoms score ≥18	Aspirin (1 g/d) + pantoprazole (40 mg/d)	Aspirin > Placebo
Celecoxib					
Müller et al. (2002)	50	5	Inpatients (acute phase) w/ SCHZ	Celecoxib (400 mg/d)	Celecoxib > Placebo
Rappard and Mueller (2004)[a]	270	11	Inpatients (acute phase) w/ SCHZ	Celecoxib (400 mg/d)	No differences Celecoxib vs. Placebo
Rapaport et al. (2005)	38	8	Inpatients (acute phase) w/ SCHZ	Celecoxib (400 mg/d)	No differences Celecoxib vs. Placebo
Akhondzadeh et al. (2007)	60		Inpatients (acute phase) w/ SCHZ PANSS > 60	Celecoxib (400 mg/d)	Celecoxib > Placebo
Müller et al. (2010)	50	6	Inpatients (acute phase) w/ SCHZ or SCF Duration of illness <2 years	Celecoxib (400 mg/d)	Celecoxib > Placebo
Davunetide					
Javitt et al. (2012)	42	12	Chronic SCHZ	Davunetide (5 mg/d)	No differences Davunetide vs. Placebo[b] Improved functional capacity
Javitt et al. (2012)	43	12	Chronic SCHZ	Davunetide (30 mg/d)	No differences Davunetide vs. Placebo[b] Improved functional capacity
Minocycline					
Levkovitz et al. (2010)	54	22	Inpatients w/ early SCHZ (<5 years) PANSS > 60	Minocycline 200 mg/d	No differences Minocycline vs. Placebo Improved negative symptoms and executive function
Chaudhry et al. (2012)	140	50	Early SCHZ, SAD, SCF, PNOS (<5 years) PANSS > 60	Minocycline 200 mg/d	No differences Minocycline vs. Placebo Improved negative symptoms
Weiser et al. (2012b)[b]	200	16	SCHZ patients w/ ≥4 (moderate) score on CGI-S and 4 (moderate) score on two of P1, P2, P3, P6 PANSS and/or a total PANSS negative symptoms score ≥18	Minocycline 200 mg/d	No differences Minocycline vs. Placebo

AP: antipsychotic; FEP: first episode of psychosis; PANSS: positive and negative scale for schizophrenia; PNOS: psychosis not otherwise specified; SAD: schizoaffective disorder; SCF: schizophreniform; SCHZ: schizophrenia.
[a] Published only as an abstract.
[b] This study used the Brief Psychiatric Rating Scale (BPRS).

(Cheon et al., 2011). A recent study using an SNP-based analysis of neuroactive pathways implicated PGE_2 as a mediator of the effects of risperidone, olanzapine, and quetiapine (Adkins et al., 2012).

10. Clinical and research implications

We are still far from having ideally effective and safe treatments to offer our patients. There is therefore a need for a change in the drug discovery strategy, mainly based on a better understanding of pathophysiology (Insel, 2010; Lewis and Gonzalez-Burgos, 2006). It is still too soon to consider proinflammatory cytokines and/or their signaling pathways a possible novel strategy to treat psychosis (Potvin et al., 2008), although there are already ongoing trials of adjunctive monoclonal antibody anti/pro-inflammatory cytokine therapy (infliximab, tocilizumab) in major depression and SCHZ, whose results could directly implicate inflammation in the pathophysiology of psychiatric disease (Raison et al., 2013; Miller, 2013). Furthermore, current studies using new anti-inflammatory and antioxidant pharmacological approaches are still in the early stages.

It should be borne in mind that the vast majority of studies reporting inflammatory/immune changes in pro/anti-inflammatory pathways are described in patients with full-blown, chronic SCHZ (Potvin et al., 2008; Das and Khan, 1998; Song et al., 2009; Das et al., 1995; Yokota et al., 2004; Yao et al., 2004). In this

subpopulation, tissue or plasma antioxidant mechanisms may be exhausted (Ghosh et al., 2011). A suggestive hypothesis is that, depending of the course of the disease, there may be compensatory mechanisms or exhaustion. Studies in FEP and prodromal stages are clearly needed.

On the other hand, the inflammatory response is highly non-specific and it is activated in response to multiple endogenous and exogenous factors in the context of psychiatric diseases (Berk et al., 2013). All these parameters need to be controlled and considered before unequivocally implicating particular inflammatory/O&NS mediators in the pathophysiology of SCHZ. Some of the potential confounding factors that contribute to the heterogeneity of the available data are genetic/epigenetic susceptibility, disease state/duration (FEP vs. full-blown schizophrenia), tobacco/cannabis use, body mass index, type and duration of antipsychotic medication, presence of ongoing activity of viruses and other infectious agents, etc.). In addition, the great degree of co-morbidity between psychotic disease and inflammation-related diseases such as depression, obesity, and diabetes, or psychotropic substance abuse, further complicates the scenario (Anderson et al., 2013; Mitchell et al., 2013; Testa et al., 2013).

Despite all the basic and clinical evidence presented to date, three "hot" questions remain to be elucidated in the future:

1. The *unresolved question* of which came first, the chicken or the egg. Efforts should be made to determine if symptomatic onset of the disease occurs in a vulnerable brain (immunologically/inflammatory primed months/years before symptoms manifest), or if a genetically prone subject develops symptoms that will increase the deleterious effects of inflammation and/or infection. Also to be determined is the role of *continuous* inflammation and O&NS throughout the disease (negative symptoms, poor hygiene, increase in BMI and/or obesity, metabolic syndrome, etc.).
2. Is it possible to find an unique *golden marker* for the disease? Great efforts to find biomarkers with broad platforms notwithstanding, a new trend is to study complete and robust pathways with all elements of the intracellular and intercellular pathways, including the elements of balancing mechanisms and their relationship with positive/negative symptomatology and cognition deficits. Inflammation and O&NS pathways are important, as are anti-inflammatory and anti-O&NS pathways. Despite the increasing evidence supporting a role for inflammation and O&NS in the etiology and physiopathology of schizophrenia and other psychotic diseases, the heterogeneity of this complex disorder makes the discovery of a golden marker very difficult. Future translational research should focus on the search for molecular pathways closely related to inflammation and oxidative stress through the use of different approximations and methods, such as fMRI, brain morphometry, postmortem studies, cognitive assessments, peripheral biomarkers, and genetic/epigenetic studies (Kapur et al., 2012; Horváth and Mirnics, 2015).
3. How can the modest clinical effects reported with anti-inflammatory drugs be explained?

First, one limitation of previous clinical trials of adjunctive NSAIDs in SCHZ is the possible inclusion of patients with a mild inflammatory process. Stricter exclusion criteria should be used to avoid this possible confounding factor.

Based on the evidence cited in this review, future studies should have a change of focus. Current studies focus on controlling inflammation via direct anti-inflammatory effects while forgetting the possibilities of pharmacological stimulation of anti-inflammatory pathways. A question for further discussion is whether some aspects of the inflammatory responses in specific phases of SCHZ are an attempt to compensate for or resolve deleterious cellular events. If that is the case, anti-inflammatory agents may prove deleterious themselves. Again, inflammation is a two-faced response whose mechanisms need to be understood in the brain and periphery in SCHZ and carefully manipulated with drugs.

Conflict of interest

Dr. Arango has been a consultant to or has received honoraria or grants from Abbott, Amgen, AstraZeneca, Bristol-Myers Squibb, Janssen Cilag, Lundbeck, Merck, Otsuka, Pfizer, Roche, Servier, Shire, Takeda, and Schering Plough. Dr. Bernardo has been a consultant for, received grant/research support and honoraria from, and been on the speakers/advisory board of ABBiotcs, Adamed, Almirall, Amgen, Eli Lilly, Ferrer, Forum Pharmaceuticals, Gedeon, Hersill, Janssen-Cilag, Lundbeck, Otsuka, Pfizer, Roche, and Servier. Dr. Bioque has been a consultant for, received grant/research support and honoraria from, and been on the speakers/advisory board of Adamed, Ferrer, Janssen-Cilag, Lundbeck, Otsuka, and Pfizer. Dr. O'Donnell is an employee and stockholder of Pfizer. The rest of authors declare no conflicts in relation to the subject of this review, including drugs or products mentioned in the study, payments, or interest by funding agencies.

Acknowledgments

The author's labs & research groups are supported by their home Institutions in Spain: (Univ. Complutense de Madrid and Univ. de Barcelona), Spanish Ministries of Science and Innovation and of Economy and Competitiveness, Health – ISCIII (CIBERSAM, FIS, Instituto de Investigación Sanitaria Imas12), Fondo Europeo de Desarrollo Regional FEDER, Unión Europea, "Un manera de hacer Europa." In the past five years, the labs have also received funding from the Autonomous Governments of Madrid and Catalonia (2014SGR441), Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), 7th Framework Program of the European Union and Foundations (Mutua Madrileña, Alicia Koplowitz, Centre Esther Koplowitz, Caja Navarra). In Switzerland, by the National Center of Competence in Research (NCCR) "SYNAPSY – The Synaptic Bases of Mental Diseases" financed by the Swiss National Science Foundation and the Avina Foundation.

References

Adkins, D.E., et al., 2012. SNP-based analysis of neuroactive ligand–receptor interaction pathways implicates PGE2 as a novel mediator of antipsychotic treatment response: data from the CATIE study. Schizophr. Res. 135 (1–3), 200–201.
Akhondzadeh, S., et al., 2007. Celecoxib as adjunctive therapy in schizophrenia: a double-blind, randomized and placebo-controlled trial. Schizophr. Res. 90 (1–3), 179–185.
Akyol, O., et al., 2005. Association between Ala–^{9}Val polymorphism of Mn-SOD gene and schizophrenia. Prog. Neuropsychopharmacol. Biol. Psychiatry 29, 123–131.
Almasi-Nasrabadi, M., et al., 2012. Involvement of NMDA receptors in the beneficial effects of pioglitazone on scopolamine-induced memory impairment in mice. Behav. Brain Res. 231 (1), 138–145.
Anderson, G., et al., 2013. Schizophrenia is primed for an increased expression of depression through activation of immuno-inflammatory, oxidative and nitrosative stress, and tryptophan catabolite pathways. Prog. Neuropsychopharmacol. Biol. Psychiatry 42, 101–114.
Andreazza, A.C., et al., 2010. Mitochondrial complex I activity and oxidative damage to mitochondrial proteins in the prefrontal cortex of patients with bipolar disorder. Arch. Gen. Psychiatry 67, 360–368.
Arango, C., et al., 2001. At issue: stress, hippocampal neuronal turnover, and neuropsychiatric disorders. Schizophr. Bull. 27 (3), 477–480.
Arango, C., et al., 2012. Progressive brain changes in children and adolescents with first-episode psychosis. Arch. Gen. Psychiatry 69 (1), 16–26.
Arion, D., et al., 2007. Molecular evidence for increased expression of genes related to immune and chaperone function in the prefrontal cortex in schizophrenia. Biol. Psychiatry 62 (7), 711–721.
Ballesteros, A., et al., 2013. Electrophysiological intermediate biomarkers for oxidative stress in schizophrenia. Clin. Neurophysiol. 124 (11), 2209–2215.

Baxter, P.S., et al., 2015. Synaptic NMDA receptor activity is coupled to the transcriptional control of the glutathione system. Nat. Commun. 6, 6761.
Beards, S., et al., 2013. Life events and psychosis: a review and meta-analysis. Schizophr. Bull. 39 (4), 740–747.
Behrens, M.M., et al., 2007. Ketamine-induced loss of phenotype of fast-spiking interneurons is mediated by NADPH-oxidase. Science 318, 1645–1647.
Behrens, M.M., et al., 2008. Interleukin-6 mediates the increase in NADPH-oxidase in the ketamine model of schizophrenia. J. Neurosci. 28 (51), 13957–13966.
Belforte, J.E., et al., 2010. Postnatal NMDA receptor ablation in corticolimbic interneurons confers schizophrenia-like phenotypes. Nat. Neurosci. 13, 76–83.
Bennett, A., 2008. Stress and anxiety in schizophrenia and depression: glucocorticoids, corticotropin-releasing hormone and synapse regression. Aust. N. Z. J. Psychiatry 42 (12), 995–1002.
Benros, M.E., et al., 2011. Autoimmune diseases and severe infections as risk factors for schizophrenia: a 30-year population-based register study. Am. J. Psychiatry 168 (12), 1303–1310.
Ben-Shachar, D., 2009. The interplay between mitochondrial complex I, dopamine and Sp1 in schizophrenia. J. Neural Transm. 116, 1383–1396.
Berger, G.E., et al., 2007. Ethyl-eicosapentaenoic acid in first-episode psychosis: a randomized, placebo-controlled trial. J. Clin. Psychiatry 68 (12), 1867–1875.
Berk, M., et al., 2008. N-acetyl cysteine as a glutathione precursor for schizophrenia – a double-blind, randomized, placebo-controlled trial. Biol. Psychiatry 64 (5), 361–368.
Berk, M., et al., 2013. So depression is an inflammatory disease, but where does the inflammation come from? BMC Med. 11, 200.
Bioque, M., et al., 2013. Peripheral endocannabinoid system dysregulation in first-episode psychosis. Neuropsychopharmacology 38 (13), 2568–2577.
Bitanihirwe, B.K., Woo, T.U., 2011. Oxidative stress in schizophrenia: an integrated approach. Neurosci. Biobehav. Rev. 35 (3), 878–893.
Borovcanin, M., et al., 2012. Elevated serum level of type-2 cytokine and low IL-17 in first episode psychosis and schizophrenia in relapse. J. Psychiatr. Res. 46 (11), 1421–1426.
Boulanger, L.M., et al., 2001. Neuronal plasticity and cellular immunity: shared molecular mechanisms. Curr. Opin. Neurobiol. 11 (5), 568–578.
Brietzke, E.L., et al., 2009. Comparison of cytokine levels in depressed, manic and euthymic patients with bipolar disorder. J. Affect. Disord. 116 (3), 214–217.
Brown, A.S., 2012. Epidemiologic studies of exposure to prenatal infection and risk of schizophrenia and autism. Dev. Neurobiol. 72 (10), 1272–1276.
Brown, A.S., Derkits, E.J., 2010. Prenatal infection and schizophrenia: a review of epidemiologic and translational studies. Am. J. Psychiatry 167 (3), 261–280.
Brzustowicz, L.M., 2004. Linkage disequilibrium mapping of schizophrenia susceptibility to the CAPON region of chromosome 1q22. Am. J. Hum. Genet. 74, 1057–1063.
Buckley, P.F., et al., 2007. Brain derived neurotropic factor in first-episode psychosis. Schizophr. Res. 91 (1–3), 1–5.
Buelna-Chontal, M., Zazueta, C., 2013. Redox activation of Nrf2 & NF-kappaB: a double end sword? Cell Signal. 25, 2548–2557.
Busse, S., et al., 2012. Different distribution patterns of lymphocytes and microglia in the hippocampus of patients with residual versus paranoid schizophrenia: further evidence for disease course-related immune alterations? Brain Behav. Immun. 26 (8), 1273–1279.
Cabungcal, J.H., et al., 2013a. Early-life insults impair parvalbumin interneurons via oxidative stress: reversal by N-acetylcysteine. Biol. Psychiatry 73, 574–582.
Cabungcal, J.H., et al., 2013b. Perineuronal nets protect fast-spiking interneurons against oxidative stress. Proc. Natl. Acad. Sci. U. S. A. 110 (22), 9130–9135.
Capuron, L., Miller, A.H., 2011. Immune system to brain signaling: neuropsychopharmacological implications. Pharmacol. Ther. 130 (2), 226–238.
Carmeli, C., et al., 2012. Glutathione precursor N-acetyl-cysteine modulates EEG synchronization in schizophrenia patients: a double-blind, randomized, placebo-controlled trial. PLoS ONE 7, e29341.
Catts, V.S., et al., 2014. Increased expression of astrocyte markers in schizophrenia: association with neuroinflammation. Aust. N. Z. J. Psychiatry 48, 722–734.
Centonze, D., et al., 2008. The endocannabinoid system in peripheral lymphocytes as a mirror of neuroinflammatory diseases. Curr. Pharm. Des. 14, 2370–2442.
Chaudhry, I.B., et al., 2012. Minocycline benefits negative symptoms in early schizophrenia: a randomised double-blind placebo-controlled clinical trial in patients on standard treatment. J. Psychopharmacol. 26 (9), 1185–1193.
Cheon, Y., et al., 2011. Chronic olanzapine treatment decreases arachidonic acid turnover and prostaglandin E(2) concentration in rat brain. J. Neurochem. 119 (2), 364–376.
Choi, Y., et al., 2001. Three pairs of cysteine residues mediate both redox and Zn^{2+} modulation of the NMDA receptor. J. Neurosci. 21, 392–400.
Ciufolini, S., et al., 2014. HPA axis response to social stress is attenuated in schizophrenia but normal in depression: evidence from a meta-analysis of existing studies. Neurosci. Biobehav. Rev. 47C, 359–368.
Clark, D., et al., 2006. A proteome analysis of the anterior cingulate cortex gray matter in schizophrenia. Mol. Psychiatry 11 (5), 459–470, 423.
Condray, R., Yao, J.K., 2011. Cognition, dopamine and bioactive lipids in schizophrenia. Front. Biosci. 3, 298–330.
Cotter, D.R., et al., 2001. Glial cell abnormalities in major psychiatric disorders: the evidence and implications. Brain Res. Bull. 55 (5), 585–595.
Coughlin, J.M., et al., 2013. Marked reduction of soluble superoxide dismutase-1 (SOD1) in cerebrospinal fluid of patients with recent-onset schizophrenia. Mol. Psychiatry 18 (1), 10–11.
Dakhale, G.N., et al., 2005. Supplementation of vitamin C with atypical antipsychotics reduces oxidative stress and improves the outcome of schizophrenia. Psychopharmacology (Berlin) 182 (4), 494–498.
Das, I., Khan, N.S., 1998. Increased arachidonic acid induced platelet chemiluminescence indicates cyclooxygenase overactivity in schizophrenic subjects. Prostaglandins Leukot. Essent. Fatty Acids 58 (3), 165–168.
Das, I., et al., 1995. Elevated platelet calcium mobilization and nitric oxide synthase activity may reflect abnormalities in schizophrenic brain. Biochem. Biophys. Res. Commun. 212 (2), 375–380.
De Leon, M.J., et al., 1997. Cortisol reduces hippocampal glucose metabolism in normal elderly, but not in Alzheimer's disease. J. Clin. Endocrinol. Metab. 82, 3251–3259.
Dietrich-Muszalska, A., Olas, B., 2009. Isoprostenes as indicators of oxidative stress in schizophrenia. World J. Biol. Psychiatry 10 (1), 27–33.
Do, K.Q., et al., 2000. Schizophrenia: glutathione deficit in cerebrospinal fluid and prefrontal cortex in vivo. Eur. J. Neurosci. 12, 3721–3728.
Do, K.Q., et al., 2009. Redox dysregulation, neurodevelopment, and schizophrenia. Curr. Opin. Neurobiol. 19 (2), 220–230.
Do, K.Q., et al., 2015. Receptor for Advanced Glycation End-product (RAGE) as linking mechanism between neuroinflammation and oxidative stress. Schizophr. Bull. 41, S2–S3.
Doorduin, J., et al., 2009. Neuroinflammation in schizophrenia-related psychosis: a PET study. J. Nucl. Med. 50 (11), 1801–1807.
Dowlati, Y., et al., 2010. A meta-analysis of cytokines in major depression. Biol. Psychiatry 67 (5), 446–457.
Drexhage, R.C., et al., 2010a. The mononuclear phagocyte system and its cytokine inflammatory networks in schizophrenia and bipolar disorder. Expert Rev. Neurother. 10 (1), 59–76.
Drexhage, R.C., et al., 2010b. Inflammatory gene expression in monocytes of patients with schizophrenia: overlap and difference with bipolar disorder. A study in naturalistically treated patients. Int. J. Neuropsychopharmacol. 13 (10), 1369–1381.
Durany, N., Thome, J., 2004. Neurotrophic factors and the pathophysiology of schizophrenic psychoses. Eur. Psychiatry 19 (6), 326–337.
Emiliani, F.E., et al., 2014. Oxidative stress and schizophrenia: recent breakthroughs from an old story. Curr. Opin. Psychiatry 27 (3), 185–190.
Emsley, R., et al., 2002. Randomized, placebo-controlled study of ethyl-eicosapentaenoic acid as supplemental treatment in schizophrenia. Am. J. Psychiatry 159 (9), 1596–1598.
Emsley, R., et al., 2006. The effects of eicosapentaenoic acid in tardive dyskinesia: a randomized, placebo-controlled trial. Schizophr. Res. 84 (1), 112–120.
Erhardt, S., et al., 2007. The kynurenic acid hypothesis of schizophrenia. Physiol. Behav. 92 (1–2), 203–209.
Farokhnia, M., et al., 2014. A double-blind, placebo controlled, randomized trial of riluzole as an adjunct to risperidone for treatment of negative symptoms in patients with chronic schizophrenia. Psychopharmacology (Berlin) 231 (3), 533–542.
Fenton, W.S., et al., 2001. A placebo-controlled trial of omega-3 fatty acid (ethyl eicosapentaenoic acid) supplementation for residual symptoms and cognitive impairment in schizophrenia. Am. J. Psychiatry 158 (12), 2071–2074.
Fillman, S.G., et al., 2013. Markers of inflammation in the prefrontal cortex of individuals with schizophrenia. Mol. Psychiatry 18 (2), 133.
Fillman, S.G., et al., 2014. Markers of inflammation and stress distinguish subsets of individuals with schizophrenia and bipolar disorder. Transl. Psychiatry 4 (2), e365.
Fineberg, A.M., Ellman, L.M., 2013. Inflammatory cytokines and neurological and neurocognitive alterations in the course of schizophrenia. Biol. Psychiatry 73 (10), 951–966.
Flatow, J., et al., 2013. Meta-analysis of oxidative stress in schizophrenia. Biol. Psychiatry 74 (6), 400–409.
Fournier, M., et al., 2014. Impaired metabolic reactivity to oxidative stress in early psychosis patients. Schizophr. Bull. 40, 973–983.
Fraguas, D., et al., 2012. Decreased glutathione levels predict loss of brain volume in children and adolescents with first-episode psychosis in a two-year longitudinal study. Schizophr. Res. 137 (1–3), 58–65.
Frodl, T., Amico, F., 2014. Is there an association between peripheral immune markers and structural/functional neuroimaging findings? Prog. Neuropsychopharmacol. Biol. Psychiatry 48, 295–303.
Gallagher, P., et al., 2007. Plasma cortisol-dehydroepiandrosterone (DHEA) ratios in schizophrenia and bipolar disorder. Schizophr. Res. 90 (1–3), 258–265.
Gárate, I., et al., 2011. Origin and consequences of brain Toll-like receptor 4 pathway stimulation in an experimental model of depression. J. Neuroinflamm. 8, 151.
Gárate, I., et al., 2013. Stress-induced neuroinflammation: role of the Toll-like receptor-4 pathway. Biol. Psychiatry 73 (1), 32–43.
Garay, P.A., et al., 2013. Maternal immune activation causes age- and region-specific changes in brain cytokines in offspring throughout development. Brain Behav. Immun. 31, 54–68.
García-Bueno, B., et al., 2007. Effects of peroxisome proliferator-activated receptor gamma agonists on brain glucose and glutamate transporters after stress in rats. Neuropsychopharmacology 32 (6), 1251–1260.
García-Bueno, B., et al., 2008. Stress as a neuroinflammatory condition in brain: damaging and protective mechanisms. Neurosci. Biobehav. Rev. 32 (6), 1136–1151.
García-Bueno, B., et al., 2010. Is there a role for the nuclear receptor PPARγ in neuropsychiatric diseases? Int. J. Neuropsychopharmacol. 13 (10), 1411–1429.

García-Bueno, B., et al., 2014a. Pro-/anti-inflammatory dysregulation in patients with first episode of psychosis: toward an integrative inflammatory hypothesis of schizophrenia. Schizophr. Bull. 40 (2), 376–387.
García-Bueno, B., et al., 2014b. Pro/anti-inflammatory dysregulation in early psychosis: results from a 6-month follow-up study. Int. J. Neuropsychopharmacol. 18 (2), Oct 31.
Garcia-Rizo, C., et al., 2012. Inflammatory markers in antipsychotic-naive patients with nonaffective psychosis and deficit vs. nondeficit features. Psychiatry Res. 198 (2), 212–215.
Gassó, P., et al., 2014. Increased susceptibility to apoptosis in cultured fibroblasts from antipsychotic-naïve first-episode schizophrenia patients. J. Psychiatr. Res. 48 (1), 94–101.
Gawryluk, J.W., et al., 2011. Decreased levels of glutathione, the major brain antioxidant, in postmortem prefrontal cortex from patients with psychiatric disorders. Int. J. Neuropsychopharmacol. 14 (1), 123–130.
Ghosh, N., et al., 2011. Antioxidant protection: a promising therapeutic intervention in neurodegenerative disease. Free Radic. Res. 45 (8), 888–905.
Giovanoli, S., et al., 2013. Stress in puberty unmasks latent neuropathological consequences of prenatal immune activation in mice. Science 339 (6123), 1095–1099.
Gravina, P., et al., 2011. Genetic polymorphisms of glutathione S-transferases GSTM1, GSTT1, GSTP1 and GSTA1 as risk factors for schizophrenia. Psychiatry Res. 187, 454–456.
Gross, A., et al., 2003. Decreased production of reactive oxygen species by blood monocytes caused by clozapine correlates with EEG slowing in schizophrenic patients. Neuropsychobiology 47 (2), 73–77.
Gulsuner, S., et al., 2013. Spatial and temporal mapping of de novo mutations in schizophrenia to a fetal prefrontal cortical network. Cell 154 (3), 518–529.
Gysin, R., et al., 2007. Impaired glutathione synthesis in schizophrenia: convergent genetic and functional evidence. Proc. Natl. Acad. Sci. U. S. A. 104, 16621–16626.
Gysin, R., et al., 2011. Genetic dysregulation of glutathione synthesis predicts alteration of plasma thiol redox status in schizophrenia. Antioxid. Redox Signal. 15, 2003–2010.
Halliwell, B., Chirico, S., 1993. Lipid peroxidation: its mechanism, measurement, and significance. Am. J. Clin. Nutr. 57 (5 Suppl.), 715S–724S.
Hanson, D.R., Gottesman, I.I., 2005. Theories of schizophrenia: a genetic-inflammatory-vascular synthesis. BMC Med. Genet. 6, 7.
Hardingham, G.E., Bading, H., 2010. Synaptic versus extrasynaptic NMDA receptor signaling: implications for neurodegenerative disorders. Nat. Rev. Neurosci. 11, 682–696.
Harris, L.W., et al., 2012. Comparison of peripheral and central schizophrenia biomarker profiles. PLoS ONE 7 (10), e46368.
Hashimoto, R., et al., 2011. Variants of the RELA gene are associated with schizophrenia and their startle responses. Neuropsychopharmacology 36 (9), 1921–1931.
Hayes, L.N., et al., 2014. Inflammatory molecular signature associated with infectious agents in psychosis. Schizophr. Bull. 40 (5), 963–972.
Heckers, S., Konradi, C., 2010. Hippocampal pathology in schizophrenia. Curr. Top. Behav. Neurosci. 4, 529–553.
Herberth, M., et al., 2013. Identification of a molecular profile associated with immune status in first onset schizophrenia patients. Clin. Schizophr. Relat. Psychoses., 1–14.
Herken, H., et al., 2011. Evidence that the activities of erythrocyte free radical scavenging enzymes and the products of lipid peroxidation are increased in different forms of schizophrenia. Mol. Psychiatry 6, 66–73.
Hickie, I.B., et al., 2009. Are common childhood or adolescent infections risk factors for schizophrenia and other psychotic disorders? Med. J. Aust. 190 (4 Suppl.), S17–S21.
Hida, H., et al., 2013. Behavioral phenotypes in schizophrenic animal models with multiple combinations of genetic and environmental factors. J. Pharmacol. Sci. 121 (3), 185–191.
Hoffmann, C., 2000. COX-2 in brain and spinal cord implications for therapeutic use. Curr. Med. Chem. 7 (11), 1113–1120.
Holloway, T., et al., 2013. Prenatal stress induces schizophrenia-like alterations of serotonin 2A and metabotropic glutamate 2 receptors in the adult offspring: role of maternal immune system. J. Neurosci. 33 (3), 1088–1098.
Horrobin, D.F., 1977. Schizophrenia as a prostaglandin deficiency disease. Lancet 1 (8018), 936–937.
Horváth, S., Mirnics, K., 2015. Schizophrenia as a disorder of molecular pathways. Biol. Psychiatry 77 (1), 22–28.
Insel, T.R., 2010. Rethinking schizophrenia. Nature 468 (7321), 187–193.
Jarskog, L.F., 2006. Apoptosis in schizophrenia: pathophysiologic and therapeutic considerations. Curr. Opin. Psychiatry 19 (3), 307–312.
Javitt, D.C., et al., 2012. Effect of the neuroprotective peptide davunetide (AL-108) on cognition and functional capacity in schizophrenia. Schizophr. Res. 136 (1–3), 25–31.
Jones, B.G., et al., 1994. Lipid peroxidation and homocysteine induced toxicity. Atherosclerosis 105 (2), 165–170.
Kaiya, H., et al., 1989. Elevated plasma prostaglandin E2 levels in schizophrenia. J. Neural Transm. 77 (1), 39–46.
Kano, S., et al., 2013. Genome-wide profiling of multiple histone methylations in olfactory cells: further implications for cellular susceptibility to oxidative stress in schizophrenia. Mol. Psychiatry 18, 740–742.
Kapur, S., et al., 2012. Why has it taken so long for biological psychiatry to develop clinical tests and what to do about it? Mol. Psychiatry 17 (12), 1174–1179.
Karry, R., et al., 2004. Mitochondrial complex I subunits expression is altered in schizophrenia: a postmortem study. Biol. Psychiatry 55 (7), 676–684.
Kato, T.A., et al., 2008. Inhibitory effects of aripiprazole on interferon-gamma-induced microglial activation via intracellular Ca^{2+} regulation in vitro. J. Neurochem. 106 (2), 815–825.
Kato, T.A., et al., 2011. Aripiprazole inhibits superoxide generation from phorbol-myristate-acetate (PMA)-stimulated microglia in vitro: implication for antioxidative psychotropic actions via microglia. Schizophr. Res. 129 (2–3), 172–182.
Khandaker, G.M., et al., 2014. Association of serum interleukin 6 and C-reactive protein in childhood with depression and psychosis in young adult life: a population-based longitudinal study. JAMA Psychiatry 71 (10), 1121–1128.
Kim, Y.K., et al., 2000. Relationships between interleukins, neurotransmitters and psychopathology in drug-free male schizophrenics. Schizophr. Res. 44 (3), 165–175.
Kim, Y.K., et al., 2007. Imbalance between pro-inflammatory and anti-inflammatory cytokines in bipolar disorder. J. Affect. Disord. 104 (1–3), 91–95.
Kim, E., et al., 2008. A preliminary investigation of alpha-lipoic acid treatment of antipsychotic drug-induced weight gain in patients with schizophrenia. J. Clin. Psychopharmacol. 28 (2), 138–146.
Kim, H.K., et al., 2014. Oxidation and nitration in dopaminergic areas of the prefrontal cortex from patients with bipolar disorder and schizophrenia. J. Psychiatry Neurosci. 39 (1), 130155.
Kirkpatrick, B., Miller, B.J., 2013. Inflammation and schizophrenia. Schizophr. Bull. 39 (6), 1174–1179.
Kulak, A., et al., 2012. Behavioral phenotyping of glutathione-deficient mice: relevance to schizophrenia and bipolar disorder. Behav. Brain Res. 226 (2), 563–570.
Kupka, R.W., et al., 2012. Immune activation, steroid resistancy and bipolar disorder. Bipolar Disord. 4 (Suppl. 1), 73–74.
Laan, W., et al., 2010. Adjuvant aspirin therapy reduces symptoms of schizophrenia spectrum disorders: results from a randomized, double-blind, placebo-controlled trial. J. Clin. Psychiatry 71 (5), 520–527.
Lampron, A., et al., 2013. Innate immunity in the CNS: redefining the relationship between the CNS and its environment. Neuron 78 (2), 214–232.
Latz, E., et al., 2013. Activation and regulation of the inflammasomes. Nat. Rev. Immunol. 13 (6), 397–411.
Lavoie, S., et al., 2008. Glutathione precursor, N-acetyl-cysteine, improves mismatch negativity in schizophrenia patients. Neuropsychopharmacology 33, 2187–2199.
Lavoie, S., et al., 2011. Altered glycogen metabolism in cultured astrocytes from mice with chronic glutathione deficit; relevance for neuroenergetics in schizophrenia. PLoS ONE 6, e22875.
Lehmann, J.M., et al., 1995. An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor gamma (PPAR gamma). J. Biol. Chem. 270 (22), 12953–12956.
Levkovitz, Y., et al., 2010. A double-blind, randomized study of minocycline for the treatment of negative and cognitive symptoms in early-phase schizophrenia. J. Clin. Psychiatry 71 (2), 138–149.
Lewis, D.A., Gonzalez-Burgos, G., 2006. Pathophysiologically based treatment interventions in schizophrenia. Nat. Med. 12 (9), 1016–1022.
Lewis, D.A., et al., 2012. Cortical parvalbumin interneurons and cognitive dysfunction in schizophrenia. Trends Neurosci. 35 (1), 57–67.
Li, J., et al., 2005. Peroxynitrite generated by inducible nitric oxide synthase and NADPH oxidase mediates microglial toxicity to oligodendrocytes. Proc. Natl. Acad. Sci. U. S. A. 102, 9936–9941.
Linderholm, K.R., et al., 2012. Increased levels of kynurenine and kynurenic acid in the CSF of patients with schizophrenia. Schizophr. Bull. 38 (3), 426–432.
Liu, Y.H., et al., 2013. Effects of maternal immune activation on adult neurogenesis in the subventricular zone-olfactory bulb pathway and olfactory discrimination. Schizophr. Res. 151 (1–3), 1–11.
MacDowell, K.S., et al., 2013. Risperidone normalizes increased inflammatory parameters and restores anti-inflammatory pathways in a model of neuroinflammation. Int. J. Neuropsychopharmacol. 16 (1), 121–135.
Maes, M., et al., 1995. Interleukin-2 and interleukin-6 in schizophrenia and mania: effects of neuroleptics and mood stabilizers. J. Psychiatr. Res. 29 (2), 141–152.
Mark, R.J., et al., 1995. Amyloid beta-peptide impairs ion-motive ATPase activities: evidence for a role in loss of neuronal Ca^{2+} homeostasis and cell death. J. Neurosci. 15, 6239–6249.
Martínez-Gras, I., et al., 2011. The anti-inflammatory prostaglandin 15d-PGJ2 and its nuclear receptor PPARgamma are decreased in schizophrenia. Schizophr. Res. 128 (1–3), 15–22.
McAllister, C.G., et al., 1995. Increases in CSF levels of interleukin-2 in schizophrenia: effects of recurrence of psychosis and medication status. Am. J. Psychiatry 152 (9), 1291–1297.
McDermott, E., de Silva, P., 2005. Impaired neuronal glucose uptake in pathogenesis of schizophrenia – can GLUT 1 and GLUT-3 deficits explain imaging, postmortem and pharmacological findings? Med. Hypotheses 65, 1076–1081.
McIntyre, R.S., et al., 2006. Managing psychiatric disorders with antidiabetic agents: translational research and treatment opportunities. Expert Opin. Pharmacother. 7 (10), 1305–1321.
McKernan, D.P., et al., 2011. Enhanced peripheral toll-like receptor responses in psychosis: further evidence of a pro-inflammatory phenotype. Transl. Psychiatry 1, e36.
Meyer, U., et al., 2009. A review of the fetal brain cytokine imbalance hypothesis of schizophrenia. Schizophr. Bull. 35, 959–972.
Meyer, U., et al., 2011. Inflammatory processes in schizophrenia: a promising neuroimmunological target for the treatment of negative/cognitive symptoms and beyond. Pharmacol. Ther. 132 (1), 96–110.

Michael, N., et al., 2002. Severe tardive dyskinesia in affective disorders: treatment with vitamin E and C. Neuropsychobiology 46 (Suppl. 1), 28–30.
Michel, M., et al., 2012. Immune system gene dysregulation in autism and schizophrenia. Dev. Neurobiol. 72 (10), 1277–1287.
Middleton, F.A., et al., 2002. Gene expression profiling reveals alterations of specific metabolic pathways in schizophrenia. J. Neurosci. 22 (7), 2718–2729.
Miller, B. An Open-Label Trial of Tocilizumab in Schizophrenia. *Clinicaltrials.gov*: NCT01696929.
Miller, B.J., et al., 2011. Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. Biol. Psychiatry 70 (7), 663–671.
Miller, B.J., et al., 2013a. Prenatal inflammation and neurodevelopment in schizophrenia: a review of human studies. Prog. Neuropsychopharmacol. Biol. Psychiatry 42, 92–100.
Miller, B.J., et al., 2013b. Meta-analysis of lymphocytes in schizophrenia: clinical status and antipsychotic effects. Biol. Psychiatry 73, 993–999.
Mitchell, R.H., Goldstein, B.I., 2014. Inflammation in children and adolescents with neuropsychiatric disorders: a systematic review. J. Am. Acad. Child Adolesc. Psychiatry 53 (3), 274–296.
Mitchell, A.J., et al., 2013. Prevalence of metabolic syndrome and metabolic abnormalities in schizophrenia and related disorders–a systematic review and meta-analysis. Schizophr. Bull. 39 (2), 306–318.
Mitterauer, B.J., Kofler-Westergren, B., 2011. Possible effects of synaptic imbalances on oligodendrocyte–axonic interactions in schizophrenia: a hypothetical model. Front. Psychiatry 2, 15.
Mondelli, V., et al., 2011. Stress and inflammation reduce brain-derived neurotrophic factor expression in first-episode psychosis: a pathway to smaller hippocampal volume. J. Clin. Psychiatry 72 (12), 1677–1684.
Monin, A., et al., 2014. Glutathione deficit impairs myelin maturation: relevance for white matter integrity in schizophrenia patients. Mol. Psychiatry, http://dx.doi.org/10.1038/mp.2014.88 [Epub ahead of print].
Monji, A., et al., 2013. Neuroinflammation in schizophrenia especially focused on the role of microglia. Prog. Neuropsychopharmacol. Biol. Psychiatry 42, 115–121.
Müller, N., et al., 2002. Beneficial antipsychotic effects of celecoxib add-on therapy compared to risperidone alone in schizophrenia. Am. J. Psychiatry 159 (6), 1029–1034.
Müller, N., et al., 2010. Celecoxib treatment in an early stage of schizophrenia: results of a randomized, double-blind, placebo-controlled trial of celecoxib augmentation of amisulpride treatment. Schizophr. Res. 121 (1–3), 118–124.
Müller, N., et al., 2012a. Impaired monocyte activation in schizophrenia. Psychiatry Res. 198 (3), 341–346.
Müller, N., et al., 2012b. Inflammation in schizophrenia. Adv. Protein Chem. Struct. Biol. 88, 49–68.
Müller, N., et al., 2013. Anti-inflammatory treatment in schizophrenia. Prog. Neuropsychopharmacol. Biol. Psychiatry 42, 146–153.
Myint, A.M., Kim, Y.K., 2013. Network beyond IDO in psychiatric disorders: revisiting neurodegeneration hypothesis. Prog. Neuropsychopharmacol. Biol. Psychiatry, pii:S0278-5846(13)00174-7.
Najjar, S., et al., 2013. Neuroinflammation and psychiatric illness. J. Neuroinflamm. 10, 43.
Nathan, C., Cunningham-Bussel, A., 2013. Beyond oxidative stress: an immunologist's guide to reactive oxygen species. Nat. Rev. Immunol. 13 (5), 349–361.
Nieto, R., et al., 2013. BDNF and schizophrenia: from neurodevelopment to neuronal plasticity, learning, and memory. Front. Psychiatry 4, 45.
Nikkila, H.V., et al., 1999. Accumulation of macrophages in the CSF of schizophrenic patients during acute psychotic episodes. Am. J. Psychiatry 156 (11), 1725–1729.
Nikkila, H.V., et al., 2001. Increased frequency of activated lymphocytes in the cerebrospinal fluid of patients with acute schizophrenia. Schizophr. Res. 49 (1–2), 99–105.
Nilsson, L.K., et al., 2005. Elevated levels of kynurenic acid in the cerebrospinal fluid of male patients with schizophrenia. Schizophr. Res. 80 (2–3), 315–322.
Nishioka, N., Arnold, S.E., 2004. Evidence for oxidative DNA damage in the hippocampus of elderly patients with chronic schizophrenia. Am. J. Geriatr. Psychiatry 12 (2), 167–175.
Nitta, M., et al., 2013. Adjunctive use of nonsteroidal anti-inflammatory drugs for schizophrenia: a meta-analytic investigation of randomized controlled trials. Schizophr. Bull. 39 (6), 1230–1241.
Niwa, M., et al., 2013. Adolescent stress-induced epigenetic control of dopaminergic neurons via glucocorticoids. Science 339 (6117), 335–339.
Noto, C., et al., 2015. Effects of depression on the cytokine profile in drug naive first-episode psychosis. Schizophr. Res. [Epub ahead of print].
O'Donnell, P., 2012. Cortical interneurons, immune factors and oxidative stress as early targets for schizophrenia. Eur. J. Neurosci. 35 (12), 1866–1870.
O'Donnell, P., et al., 2014. Oxidative/nitrosative stress in psychiatric disorders: are we there yet? Schizophr. Bull. 40, 960–962.
Oh-Nishi, A., et al., 2010. Maternal immune activation by polyriboinosinic–polyribocytidilic acid injection produces synaptic dysfunction but not neuronal loss in the hippocampus of juvenile rat offspring. Brain Res. 1363, 170–179.
Ono, N., et al., 1992. Influences of cyclooxygenase inhibitors on the cataleptic behavior induced by haloperidol in mice. Prostaglandins Leukot. Essent. Fatty Acids 46 (1), 59–63.
Oresic, M., et al., 2012. Phospholipids and insulin resistance in psychosis: a lipidomics study of twin pairs discordant for schizophrenia. Genome Med. 4 (1), 1.
Oskvig, D.B., et al., 2012. Maternal immune activation by LPS selectively alters specific gene expression profiles of interneuron migration and oxidative stress in the fetus without triggering a fetal immune response. Brain Behav. Immun. 26 (4), 623–634.
Ozawa, K., et al., 2006. Immune activation during pregnancy in mice leads to dopaminergic hyperfunction and cognitive impairment in the offspring: a neurodevelopmental animal model of schizophrenia. Biol. Psychiatry 59 (6), 546–554.
Pacheco-López, G., et al., 2013. Priming of metabolic dysfunctions by prenatal immune activation in mice: relevance to schizophrenia. Schizophr. Bull. 39 (2), 319–329.
Peet, M., Horrobin, D.F., 2002. A dose-ranging exploratory study of the effects of ethyl-eicosapentaenoate in patients with persistent schizophrenic symptoms. J. Psychiatr. Res. 36 (1), 7–18.
Peet, M., et al., 2001. Two double-blind placebo-controlled pilot studies of eicosapentaenoic acid in the treatment of schizophrenia. Schizophr. Res. 49 (3), 243–251.
Phillis, et al., 2006. Cyclooxygenases, lipoxygenases, and epoxygenases in CNS: their role and involvement in neurological disorders. Brain Res. Rev. 52, 201–243.
Potvin, S., et al., 2008. Inflammatory cytokine alterations in schizophrenia: a systematic quantitative review. Biol. Psychiatry 63 (8), 801–808.
Prabakaran, S., et al., 2004. Mitochondrial dysfunction in schizophrenia: evidence for compromised brain metabolism and oxidative stress. Mol. Psychiatry 9 (7), 684–697, 643.
Prasad, R., et al., 2008. 15-deoxy-delta12,14-prostaglandin J2 attenuates endothelial–monocyte interaction: implication for inflammatory diseases. J. Inflamm. (Lond.) 5, 14.
Radewicz, K., et al., 2000. Increase in HLA-DR immunoreactive microglia in frontal and temporal cortex of chronic schizophrenics. J. Neuropathol. Exp. Neurol. 59 (2), 137–150.
Raison, C.L., et al., 2013. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. JAMA Psychiatry 70 (1), 31–41.
Rapaport, M.H., et al., 2005. Celecoxib augmentation of continuously ill patients with schizophrenia. Biol. Psychiatry 57 (12), 1594–1596.
Rappard, F., Mueller, R., 2004. Celecoxib add-on therapy does not have beneficial antipsychotic effects over risperidone alone in schizophrenia. Neuropsychopharmacology 29, S183–S241.
Reagan, L.P., et al., 2000. Oxidative stress and HNE conjugation of GLUT-3 are increased in the hippocampus of diabetic rats subjected to stress. Brain Res. 862, 292–300.
Reif, A., et al., 2006a. Neuronal nitric oxide synthase (NOS-I) haplotype associated with schizophrenia modifies prefrontal cortex function. Mol. Psychiatry 11, 286–300.
Reif, A., et al., 2006b. Neural stem cell proliferation is decreased in schizophrenia, but not in depression. Mol. Psychiatry 11, 514–522.
Ribeiro, B.M., et al., 2013. Evidences for a progressive microglial activation and increase in iNOS expression in rats submitted to a neurodevelopmental model of schizophrenia: reversal by clozapine. Schizophr. Res. 151 (1–3), 12–19.
Richard, M.D., Brahm, N.C., 2012. Schizophrenia and the immune system: pathophysiology, prevention, and treatment. Am. J. Health Syst. Pharm. 69 (9), 757–766.
Richetto, J., et al., 2013. Prenatal versus postnatal maternal factors in the development of infection-induced working memory impairments in mice. Brain Behav. Immun. 33, 190–200.
Richetto, J., et al., 2014. Prenatal immune activation induces maturation-dependent alterations in the prefrontal GABAergic transcriptome. Schizophr. Bull. 40 (2), 351–361.
Ripke, S., et al., 2013. Genome-wide association analysis identifies 13 new risk loci for schizophrenia. Nat. Genet. 45 (10), 1150–1159.
Rodríguez-Santiago, B., et al., 2010. Association of common copy number variants at the glutathione S-transferase genes and rare novel genomic changes with schizophrenia. Mol. Psychiatry 15, 1023–1033.
Rollins, B., et al., 2010. Analysis of whole genome biomarker expression in blood and brain. Am. J. Med. Genet. B 153B, 919–936.
Salehi-Sadaghiani, M., et al., 2012. NMDA receptor involvement in antidepressant-like effect of pioglitazone in the forced swimming test in mice. Psychopharmacology (Berlin) 223 (3), 345–355.
Sathyasaikumar, K.V., et al., 2011. Impaired kynurenine pathway metabolism in the prefrontal cortex of individuals with schizophrenia. Schizophr. Bull. 37, 1147–1156, Schizophr. Res. 2013;151(1–3):1–11.
Schmitz, T., Chew, L.J., 2008. Cytokines and myelination in the central nervous system. Sci. World J. 8, 1119–1147.
Schobel, S.A., et al., 2013. Imaging patients with psychosis and a mouse model establishes a spreading pattern of hippocampal dysfunction and implicates glutamate as a driver. Neuron 78, 81–93.
Schwarcz, R., et al., 2001. Increased cortical kynurenate content in schizophrenia. Biol. Psychiatry 50 (7), 521–530.
Schwarz, E., et al., 2010. Validation of a blood-based laboratory test to aid in the confirmation of a diagnosis of schizophrenia. Biomark. Insights 5, 39–47.
Seibert, K., et al., 1995. Mediation of inflammation by cyclooxygenase-2. Agents Actions Suppl. 46, 41–50.
Setiawan, E., et al., 2015. Role of translocator protein density, a marker of neuroinflammation, in the brain during major depressive episodes. JAMA Psychiatry 72 (3), 268–275.
Shi, J., et al., 2009. Common variants on chromosome 6p22.1 are associated with schizophrenia. Nature 460 (7256), 753–757.
Shoval, G., Weizman, A., 2005. The possible role of neurotrophins in the pathogenesis and therapy of schizophrenia. Eur. Neuropsychopharmacol. 15 (3), 319–329.

Sies, H., 1997. Oxidative stress: oxidants and antioxidants. Exp. Physiol. 82, 291–295.
Sommer, I.E., et al., 2011. Nonsteroidal anti-inflammatory drugs in schizophrenia: ready for practice or a good start? A meta-analysis. J. Clin. Psychiatry 73 (4), 414–419.
Song, X.Q., et al., 2009. The interaction of nuclear factor-kappa B and cytokines is associated with schizophrenia. Biol. Psychiatry 65 (6), 481–488.
Southwell, D.G., et al., 2014. Interneurons from embryonic development to cell-based therapy. Science 344 (6180), 1240622.
Stefansson, H., et al., 2009. Common variants conferring risk of schizophrenia. Nature 460 (7256), 744–747.
Steiner, J., et al., 2006. Distribution of HLA-DR-positive microglia in schizophrenia reflects impaired cerebral lateralization. Acta Neuropathol. 112 (3), 305–316.
Steiner, J., et al., 2008. Immunological aspects in the neurobiology of suicide: elevated microglial density in schizophrenia and depression is associated with suicide. J. Psychiatr. Res. 42 (2), 151–157.
Steullet, P., et al., 2006. Synaptic plasticity impairment and hypofunction of NMDA receptors induced by glutathione deficit: relevance to schizophrenia. Neuroscience 137, 807–819.
Steullet, P., et al., 2010. Chronic redox dysregulation affects the ventral but not dorsal hippocampus: impairment of parvalbumin neurons, gamma oscillations and related behaviors. J. Neurosci. 30, 2547–2558.
Steullet, P., et al., 2014. Redox dysregulation, neuroinflammation, and NMDA receptor hypofunction: a "central hub" in schizophrenia pathophysiology? Schizophr. Res., http://dx.doi.org/10.1016/j.schres.2014.06.021 [Epub ahead of print].
Stone, J.M., et al., 2007. Glutamate and dopamine dysregulation in schizophrenia – a synthesis and selective review. J. Psychopharmacol. 21, 440–452.
Sugino, H., et al., 2009. Atypical antipsychotics suppress production of proinflammatory cytokines and up-regulate interleukin-10 in lipopolysaccharide-treated mice. Prog. Neuropsychopharmacol. Biol. Psychiatry 33 (2), 303–307.
Sun, S., et al., 2008. Association between interleukin-6 receptor polymorphism and patients with schizophrenia. Schizophr. Res. 102 (1–3), 346–347.
Takadera, T., et al., 2002. Prostaglandin E(2) induces caspase-dependent apoptosis in rat cortical cells. Neurosci. Lett. 317 (2), 61–64.
Takayanagi, M., et al., 2013. Reduced anterior cingulate gray matter volume and thickness in subjects with deficit schizophrenia. Schizophr. Res. 150 (2–3), 484–490.
Testa, A., et al., 2013. Psychiatric emergencies (part II): psychiatric disorders coexisting with organic diseases. Eur. Rev. Med. Pharmacol. Sci. 17 (Suppl. 1), 65–85.
Torrey, E.F., Peterson, M.R., 1973. Slow and latent viruses in schizophrenia. Lancet 2 (7819), 22–24.
Tosic, M., et al., 2006. Schizophrenia and oxidative stress: glutamate cysteine ligase modifier as a susceptibility gene. Am. J. Hum. Genet. 79, 586–592.
Udina, M., et al., 2012. Interferon-induced depression in chronic hepatitis C: a systematic review and meta-analysis. J. Clin. Psychiatry 73 (8), 1128–1138.
Uddin, M., Diwadkar, V.A., 2014. Inflammation and psychopathology: what we now know, and what we need to know. Soc. Psychiatry Psychiatr. Epidemiol. 49 (10), 1537–1539.
Uranova, N.A., et al., 2010. Ultrastructural damage of capillaries in the neocortex in schizophrenia. World J. Biol. Psychiatry 11 (3), 567–578.
Valko, M., et al., 2007. Free radicals and antioxidants in normal physiological functions and human disease. Int. J. Biochem. Cell Biol. 39 (1), 44–84.
van Berckel, B.N., et al., 2008. Microglia activation in recent-onset schizophrenia: a quantitative (R)-[11C]PK11195 positron emission tomography study. Biol. Psychiatry 64 (9), 820–822.
van Os, J., Kapur, S., 2009. Schizophr. Lancet 374 (9690), 635–645.
van Venrooij, J.A., et al., 2010. Impaired neuroendocrine and immune response to acute stress in medication-naive patients with a first episode of psychosis. Schizophr. Bull. 38 (2), 272–279.
Vita, A., et al., 2012. Progressive loss of cortical gray matter in schizophrenia: a meta-analysis and meta-regression of longitudinal MRI studies. Transl. Psychiatry 2, e190.
Vuillermot, S., et al., 2010. A longitudinal examination of the neurodevelopmental impact of prenatal immune activation in mice reveals primary defects in dopaminergic development relevant to schizophrenia. J. Neurosci. 30 (4), 1270–1287.
Walker, E., et al., 2008. Stress and the hypothalamic pituitary adrenal axis in the developmental course of schizophrenia. Annu. Rev. Clin. Psychol. 4, 189–216.
Wallace, J., et al., 2014. Evidence that aetiological risk factors for psychiatric disorders cause distinct patterns of cognitive deficits. Eur. Neuropsychopharmacol. 24 (6), 879–889.
Wang, J.F., et al., 2009. Increased oxidative stress in the anterior cingulate cortex of subjects with bipolar disorder and schizophrenia. Bipolar Disord. 11 (5), 523–529.
Weiser, M., et al., 2012a. A randomized trial administering aspirin, minocycline or pramipexole vs placebo as add-on to antipsychotics in patients with schizophrenia or schizoaffecive disorder. Neuropsychopharmacology 38, S314–S446.
Weiser, M., et al., 2012b. A randomized controlled trial of allopurinol vs. placebo added on to antipsychotics in patients with schizophrenia or schizoaffective disorder. Schizophr. Res. 138 (1), 35–38.
Wierzba-Bobrowicz, T., et al., 2005. Quantitative analysis of activated microglia, ramified and damage of processes in the frontal and temporal lobes of chronic schizophrenics. Folia Neuropathol. 43 (2), 81–89.
Wolff, A.R., et al., 2011. Behavioural deficits associated with maternal immune activation in the rat model of schizophrenia. Behav. Brain Res. 225 (1), 382–387.
Wonodi, I., et al., 2011. Downregulated kynurenine 3-monooxygenase gene expression and enzyme activity in schizophrenia and genetic association with schizophrenia endophenotypes. Arch. Gen. Psychiatry 68, 665–674.
Wu, J.Q., et al., 2013. Free radicals, antioxidant defense systems, and schizophrenia. Prog. Neuropsychopharmacol. Biol. Psychiatry 46, 200–206.
Yao, J.K., Keshavan, M.S., 2011. Antioxidants, redox signaling, and pathophysiology in schizophrenia: an integrative view. Antioxid. Redox Signal. 15, 2011–2035.
Yao, J.K., van Kammen, D.P., 2004. Membrane phospholipids and cytokine interaction in schizophrenia. Int. Rev. Neurobiol. 59, 297–326.
Yao, J.K., et al., 2004. Increased nitric oxide radicals in postmortem brain from patients with schizophrenia. Schizophr. Bull. 30 (4), 923–934.
Yao, J.K., et al., 2006. Altered glutathione redox state in schizophrenia. Dis. Markers 22 (1–2), 83–93.
Yi, Z., et al., 2012. Rosiglitazone and cognitive function in clozapine-treated patients with schizophrenia: a pilot study. Psychiatry Res. 200 (2–3), 79–82.
Yokota, O., et al., 2004. Neuronal expression of cyclooxygenase-2, a pro-inflammatory protein, in the hippocampus of patients with schizophrenia. Prog. Neuropsychopharmacol. Biol. Psychiatry 28 (4), 715–721.
Yolken, R.H., Torrey, E.F., 1995. Viruses, schizophrenia, and bipolar disorder. Clin. Microbiol. Rev. 8 (1), 131–145.
Yusim, A., et al., 2000. Glucocorticoids exacerbate the deleterious effects of gp120 in hippocampal and cortical explants. J. Neurochem. 74, 1000–1007.
Zenkov, N.K., et al., 2013. Keap1/Nrf2/ARE redox-sensitive signaling system as a pharmacological target. Biochemistry (Moscow) 78 (1), 19–36.
Zhang, X.Y., et al., 2001. A double-blind, placebo-controlled trial of extract of Ginkgo biloba added to haloperidol in treatment-resistant patients with schizophrenia. J. Clin. Clin. Psychiatry 62 (11), 878–883.
Zhang, X.Y., et al., 2003. The effect of risperidone treatment on superoxide dismutase in schizophrenia. J. Clin. Psychopharmacol. 23 (2), 128–131.
Zhang, X.Y., et al., 2006. Antioxidant enzymes and lipid peroxidation in different forms of schizophrenia treated with typical and atypical antipsychotics. Schizophr. Res. 81 (2–3), 291–300.
Zhang, X.Y., et al., 2008. Lower serum cytokine levels in smokers than nonsmokers with chronic schizophrenia on long-term treatment with antipsychotics. Psychopharmacology (Berlin) 201 (3), 383–389.
Zhao, C., et al., 2006. Distinct morphological stages of dentate granule neuron maturation in the adult mouse hippocampus. J. Neurosci. 26, 3–11.