



Review

# Oxidative Stress and Emergence of Psychosis

Victoria Rambaud <sup>1</sup>, Aude Marzo <sup>1</sup> and Boris Chaumette <sup>1,2,3,\*</sup> <sup>1</sup> Institute of Psychiatry and Neuroscience of Paris, Université Paris Cité, INSERM U1266, 75014 Paris, France<sup>2</sup> GHU-Paris Psychiatrie et Neurosciences, 75014 Paris, France<sup>3</sup> Department of Psychiatry, McGill University, Montreal, QC H3A 1A1, Canada

\* Correspondence: boris.chaumette@inserm.fr

**Abstract:** Treatment and prevention strategies for schizophrenia require knowledge about the mechanisms involved in the psychotic transition. Increasing evidence suggests a redox imbalance in schizophrenia patients. This narrative review presents an overview of the scientific literature regarding blood oxidative stress markers' evolution in the early stages of psychosis and chronic patients. Studies investigating peripheral levels of oxidative stress in schizophrenia patients, first episode of psychosis or UHR individuals were considered. A total of 76 peer-reviewed articles published from 1991 to 2022 on PubMed and EMBASE were included. Schizophrenia patients present with increased levels of oxidative damage to lipids in the blood, and decreased levels of non-enzymatic antioxidants. Genetic studies provide evidence for altered antioxidant functions in patients. Antioxidant blood levels are decreased before psychosis onset and blood levels of oxidative stress correlate with symptoms severity in patients. Finally, adjunct treatment of antipsychotics with the antioxidant N-acetyl cysteine appears to be effective in schizophrenia patients. Further studies are required to assess its efficacy as a prevention strategy. Redox imbalance might contribute to the pathophysiology of emerging psychosis and could serve as a therapeutic target for preventive or adjunctive therapies, as well as biomarkers of disease progression.

**Keywords:** schizophrenia; oxidative stress; ultra-high risk

**Citation:** Rambaud, V.; Marzo, A.; Chaumette, B. Oxidative Stress and Emergence of Psychosis. *Antioxidants* **2022**, *11*, 1870. <https://doi.org/10.3390/antiox11101870>

Academic Editor: Pascal Steullet

Received: 16 August 2022

Accepted: 16 September 2022

Published: 21 September 2022

**Publisher's Note:** MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



**Copyright:** © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

## 1. Introduction

Schizophrenia (SZ) is a complex, multifactorial psychotic disorder, affecting 1% of the population worldwide [1]. The onset of SZ typically occurs between late adolescence and early adulthood and groups together positive, negative and cognitive symptoms. Young individuals at ultra-high risk (UHR) for psychosis can be identified, during the prodromal phase of the disease, based on the presence of attenuated or time-limited psychotic symptoms, or of a familial risk-factor, along with a drop in psychosocial functioning [2]. Despite the well-established clinical criteria required to identify UHR individuals, the risk of conversion to a first episode of psychosis (FEP) in this population reaches 25% after three years of follow-up [3].

Current treatments are mostly effective against the positive symptoms [4], while their resolution does not systematically translate into functional recovery [5]. Indeed, it appears that negative and cognitive symptoms are better predictors of functional recovery [6]. Although increasing effort is being invested in the understanding of negative symptoms, new generations of antipsychotics do not seem to make a difference in the treatment of negative symptoms [7,8]. Moreover, antipsychotics are used to attenuate impairment or suffering in UHR individuals. However, in this group of individuals, treatments with antipsychotics lead to many side effects, and even increase the risk of transitioning in some individuals [9].

Therefore, it appears that the development of more effective treatments for SZ requires a better understanding of the pathophysiology of this multi-factorial disorder. Indeed, early neurobiological changes occurring during the UHR state could play a role as predictors of the transition but also therapeutic targets for prevention strategies. The most promising

window of opportunity for blocking the progression or preventing the onset of SZ, is currently around the UHR state or the FEP [10].

Amongst the multiple molecular mechanisms and neural processes which are altered in psychotic patients, a growing body of evidence suggests that oxidative stress responses are overly active in patients with SZ [11]. Studies have highlighted a dysregulation in redox metabolism during the onset of psychosis and increased oxidative damage is observed in a consistent manner in UHR individuals who subsequently develop psychosis [12]. Oxidative stress results from a shift in redox balance, that is, an accumulation of pro-oxidative factors over the antioxidant defense, leading to damage to lipids, proteins and nuclear and mitochondrial DNA (mtDNA) [13]. Reactive oxygen species (ROS) are produced as a physiological process by mitochondria, immune cells, or as necessary intermediate in enzymatic reactions, and participate in redox signaling and growth regulation [14]. They can also be produced by the brain for redox signaling [15]. The brain is particularly exposed to oxidative stress, due to its intensive neuronal activity which requires high oxygen levels and leads to a higher production of ROS [16]. Moreover, the brain contains high levels of free iron and polyunsaturated fatty acids, which are oxidizing substances and cause the neurons to be particularly vulnerable to oxidative stress [17]. In addition to the oxidative stress markers observed in the blood or brain of patients with SZ, genetic studies reveal that high-risk polymorphisms occur in genes playing a role in redox regulation [18–21].

The oxidative stress theory, as a link between the multiple molecular changes observed in psychosis, can be harnessed to identify oxidative markers of the development of psychosis. Indeed, studies have highlighted a dysregulation in redox metabolism during the onset of psychosis and increased oxidative damage is observed in a consistent manner in UHR individuals who subsequently develop psychosis [12,22].

This review is driven by the present need for understanding the pathophysiological processes involved in SZ in order to improve early treatment strategies. It provides an overview of the experimental and clinical evidence examining oxidative stress in biospecimens, including blood samples and cerebrospinal fluid (CSF), in patients with SZ. More specifically, changes in levels of enzymatic and non-enzymatic antioxidant and oxidative stress markers in the blood and the CNS of patients with SZ and UHR individuals are included.

## 2. Materials and Methods

An initial general search was performed using two databases PubMed and EMBASE. We used the keywords: (“schizophrenia” OR “psychosis”) AND (“antioxidant” OR “oxidative stress”). The initial search screened titles and abstracts only. The limits used were the date of publication (from 1991 to 2022), the species studied (humans) and the language (English). Additional records were identified through other sources.

The inclusion criteria in selecting study were:

- (i) articles published in peer-review journal
- (ii) articles published in English language
- (iii) patients diagnosed with SZ using standard diagnostic methods according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Classification of Disease (ICD) systems
- (iv) studies including both patients and healthy controls cohorts

Figure 1 presents the literature searching stages and the inclusion and exclusion for each stage. Studies that solely focused on a particular oxidative stress biomarker that was not commonly investigated were excluded, along with studies recruiting patients with specific subtypes of SZ only. In addition, due to the contrasting effects that oxidative stress can have on different tissues, studies investigating the levels of oxidative stress in tissues other than the serum, the plasma, or the erythrocytes were excluded. Finally, additional records that were identified from the bibliography of selected articles or from other sources may introduce a bias in the results presented in this narrative review.

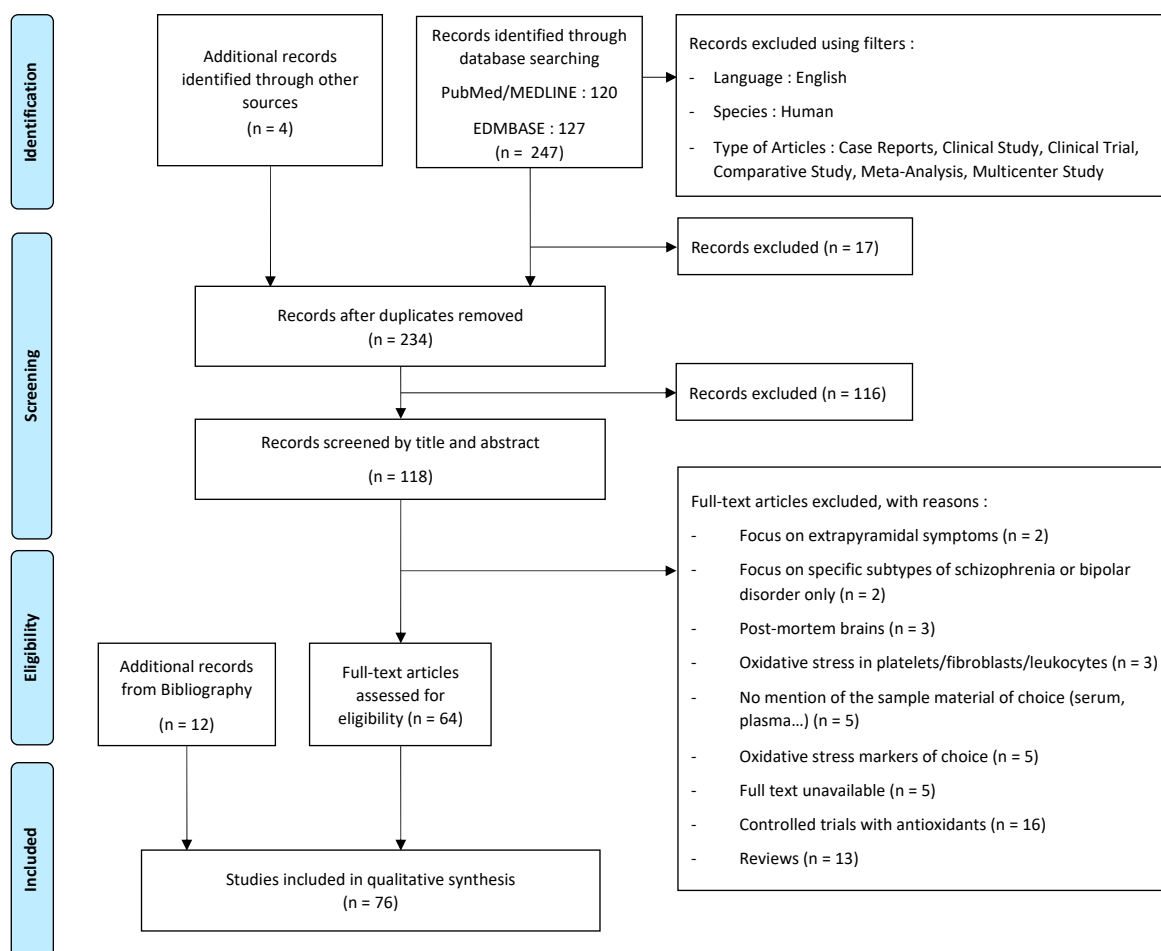


Figure 1. Prisma flowchart.

### 3. Results

A total of 120 papers were identified on PubMed and 127 on EMBASE, of which 64 were relevant research articles according to the criteria mentioned in the Methods section above and Figure 1. In addition, 12 research articles from the literature bibliography were added. The selected articles included comparative studies between healthy individuals and patients with SZ or at risk of developing the disease.

A summary of the core literature used, including 59 research articles, can be found in Tables 1–3. The number of participants in each study can be found in the Supplementary Materials. Articles were grouped according to their results regarding the levels of oxidative stress or antioxidants defense in patients compared to healthy individuals. In addition, the clinical status, including the treatment, of the patients included in each study is mentioned, along with the sample in which biomarkers were measured.

Individuals at risk of developing SZ present decreased antioxidant defenses, except for GPx enzymatic activity (Table 1). On the other hand, amongst FEP patients, more variability is found across findings (Table 2). A larger number of studies found decreased antioxidant defenses and increased oxidative damage products in this group of patients (Table 2). Nonetheless, a study by Li et al., including 354 FEP patients, found decreased oxidative damage to lipids and increased total antioxidant status (TAS) compared to controls [23].

Overall, a large number of results have assessed oxidative stress in patients with SZ, resulting in consistent evidence about a dysfunction in antioxidant defense. Despite the heterogeneity of the findings presented, it is important to note that lipid peroxidation levels are persistently increased in the blood of chronic SZ patients, and that the TAS and the GSH blood levels are decreased (Table 3). In particular, studies with more than 150 participants

recruited, found that the TAS, the GPx and SOD activity were decreased in chronic SZ patients [24–27] (Table 3, Supplementary Table S1).

**Table 1.** Selected peripheral biomarkers of antioxidant status and oxidative damage in unaffected FDR and UHR individuals compared to controls.

Variables	Schizophrenia	Sources	Status
<b>Antioxidant Defense Peripheral Biomarkers</b>			
GPx	↑	Erythrocytes [28]	Unaffected FDR [28]
	↓	Serum [29]	UHR subjects [29]
Catalase	↓	Erythrocytes [28]	Unaffected FDR [28]
SOD	↓	Erythrocytes [28], Serum [29]	Unaffected FDR [28], UHR subjects [29]
TAS	↓	Serum [30], Plasma [31]	Unaffected FDR [30,31]

GPx: Glutathione Peroxidase; SOD: Superoxide Dismutase; TAS: Total Antioxidant Status; UHR: Ultra High Risk; FDR: First-Degree Relatives.

**Table 2.** Selected peripheral biomarkers of antioxidant status and oxidative damage in FEP individuals compared to controls.

Variables	Schizophrenia	Sources	Status
<b>Antioxidant Defense Peripheral Biomarkers</b>			
GPx	↑	Erythrocytes [32,33], Serum [34]	Antipsychotic-naïve [32–34] and antipsychotic-treated [32,34] FEP
	↔	Erythrocytes [23], Serum [35]	Antipsychotic-naïve FEP [23,35]
	↓	Erythrocytes [36], Serum [37], Plasma [38], Whole Blood [39]	Antipsychotic-naïve FEP [36–39]
GR	↔	Erythrocytes [23]	Antipsychotic-naïve FEP [23]
Catalase	↑	Plasma [38]	Antipsychotic-naïve FEP [38]
	↓	Erythrocytes [33,36,40]	Antipsychotic-naïve [33,36] and antipsychotic-treated FEP [40]
GSH	↓	Erythrocytes [41], Serum [34,42], Plasma [32,33,43]	Antipsychotic-naïve [32–34], antipsychotic-free [42,43] and antipsychotic-treated [32,34,41] FEP
SOD	↑	Erythrocytes [39], Serum [44], Plasma [38,45]	Antipsychotic-naïve FEP [38,39,44,45]
	↔	Erythrocytes [33,40,46], Serum [35], Plasma [36,47]	Antipsychotic-naïve [33,35,36] and antipsychotic-treated FEP [40], Antipsychotic-treated patients with SZ [46,47]
TAS	↑	Serum [34], Plasma [38]	Antipsychotic-naïve [38] and antipsychotic-treated [34,38] FEP
	↔	Serum [37,48]	Antipsychotic-naïve FEP [37,48]
	↓	Serum [49], Plasma [32,36,41,50,51]	Antipsychotic-naïve [32,36,49–51] and antipsychotic-treated [32,41] FEP
<b>Oxidative Damage Products</b>			
AGEs	↑	Serum [34]	Antipsychotic-naïve and antipsychotic-treated FEP [34]
Kynurenine	↓	Serum [34]	Antipsychotic-naïve and antipsychotic-treated FEP [34]
MDA/TBARS (Lipid Peroxidation)	↑	Plasma [39,52,53]	Antipsychotic-naïve FEP [39,52,53]
	↔	Plasma [23,36,40,44]	Antipsychotic-naïve [23,36,44], and antipsychotic-treated FEP [40]
	↓	Plasma [38]	Antipsychotic-naïve FEP [38]
LOOH (Lipid Peroxidation)	↑	Plasma [32]	Antipsychotic-naïve and antipsychotic-treated FEP [32]
NO	↑	Serum [42]	Antipsychotic-free FEP [42]

GPx: Glutathione Peroxidase; GR: Glutathione Reductase; GSH: Glutathione; SOD: Superoxide Dismutase; TAS: Total Antioxidant Status; AGEs: Advanced Glycation End-products; MDA: Malondialdehyde; TBARS: Thiobarbituric Acid-Reactive Substances; FEP: First Episode of Psychosis.

**Table 3.** Selected peripheral and brain biomarkers of antioxidant status and oxidative damage in SZ patients compared to controls.

Variables	Schizophrenia	Sources	Status
<b>Antioxidant Defense Biomarkers in the CNS</b>			
GSH	↓	CSF [54], mPFC [54]	Antipsychotic-naïve patients with SZ [54]
SOD	↓	CSF [55]	Antipsychotic-naïve and antipsychotic-treated patients with SZ [55]
<b>Antioxidant Defense Peripheral Biomarkers</b>			
GPx	↑	Erythrocytes [56], Serum [34], Plasma [43]	Antipsychotic-naïve and antipsychotic-treated patients with SZ [34,56], Antipsychotic-free patients with SZ [43]
	↔	Erythrocytes [46,57,58], Serum [37], Plasma [59], Whole Blood [60]	Antipsychotic-naïve [60], antipsychotic-free [46,60] and antipsychotic-treated [37,46,57–60] patients with SZ
	↓	Erythrocytes [28,61–66], Plasma [24–26,67]	Antipsychotic-naïve [63,64], antipsychotic-free [66] and antipsychotic-treated [24–26,28,61–63,65,67] patients with SZ
Catalase	↑	Erythrocytes [61,62,68], Serum [69]	Antipsychotic-treated patients with SZ [61,62,68,69]
	↔	Erythrocytes [46,58,65], Plasma [24–26,43]	Antipsychotic-free [43,46] and antipsychotic-treated [24–26,46,58,65] patients with SZ
	↓	Erythrocytes [28,63,66]	Antipsychotic-naïve [63], antipsychotic-free [66] and antipsychotic-treated [28,63] patients with SZ
GSH	↓	Erythrocytes [61,64,65], Serum [34,70], Plasma [71,72], Whole Blood [73,74]	Antipsychotic-naïve [34,64] and antipsychotic-treated [34,61,65,70–74] patients with SZ
GSSG	↔	Erythrocytes [58]	Antipsychotic-treated patients with SZ [58]
	↑	Whole Blood [74]	Antipsychotic-treated patients with SZ [74]
SOD	↑	Erythrocytes [46,56,61,65,75], Serum [69,76,77], Plasma [45,59]	Antipsychotic-naïve [75,76], antipsychotic-free [46] and antipsychotic-treated [45,56,59,61,65,69,77] patients with SZ
	↔	Erythrocytes [46], Plasma [47]	Antipsychotic-treated patients with SZ [46,47]
	↓	Erythrocytes [28,58,60,63,64,66,78], Serum [73], Plasma [24–26,59,67]	Antipsychotic-naïve [60,66] and antipsychotic-treated [24–26,28,58–60,63,67,73,78] patients with SZ
Ascorbic Acid	↓	Plasma [76,79]	Antipsychotic-naïve [76] and antipsychotic-treated [79] patients with SZ
TAS	↑	Serum [34]	Antipsychotic-naïve and antipsychotic-treated patients with SZ [34]
	↔	Serum [37,60]	Antipsychotic-naïve [60], antipsychotic-free [60] and antipsychotic-treated patients with SZ [37,60]
	↓	Plasma [27,80,81]	Antipsychotic-free [81] and antipsychotic-treated [27,80,81] patients with SZ
<b>ROS-producing enzymes</b>			
XO	↑	Plasma [59]	Antipsychotic-treated patients with SZ [59]
<b>Oxidative Damage Products</b>			
AGEs	↑	Serum [34]	Antipsychotic-naïve and antipsychotic-treated patients with SZ [34]
Kynurenine	↓	Serum [34]	Antipsychotic-naïve and antipsychotic-treated patients with SZ [34]
MDA/TBARS (Lipid Peroxidation)	↑	Erythrocytes [61,62,64,65], Serum [49,69,70,76,77], Plasma [24–26,43,52,56,58–60,67,73],	Antipsychotic-naïve [49,60,64,76], antipsychotic-free [43,60] and antipsychotic-treated [24–26,52,56,58–62,65,67,69,70,73,77] patients with SZ
	↔	Erythrocytes [60,68], Serum [47]	Antipsychotic-treated patients with SZ [47,60,68]
LOOH (Lipid Peroxidation)	↑	Plasma [66]	Antipsychotic-free patients with SZ [66]
NO	↑	Plasma [59,66], Serum [73]	Antipsychotic-free [66] and antipsychotic-treated [59,73] patients with SZ

CSF: Cerebrospinal Fluid; mPFC: medial Prefrontal Cortex; GSH: Glutathione; SOD: Superoxide Dismutase; GPx: Glutathione Peroxidase; GSSG: Glutathione disulfide; TAS: Total Antioxidant Status; ROS: Reactive Oxygen Species; XO: Xanthine Oxidase; AGEs: Advanced Glycation End-products; MDA: Malondialdehyde; TBARS: Thiobarbituric Acid-Reactive Substances; LOOH: Lipid Hydroperoxide; NO: Nitric Oxide; SZ: Schizophrenia.



## 4. Discussion

### 4.1. Evidence of the Involvement of Oxidative Stress in SZ

There is growing evidence for oxidative stress imbalance in SZ, since the early phases of the disorder, but the heterogeneity across studies must be highlighted. Depending on the type of biological factors, both replicated or mixed findings have been reported. Indeed, the blood levels of the antioxidant enzymes GPx, catalase, and SOD are found to be increased by some studies, whereas other studies found it to be unchanged or even decreased. On the other hand, findings about the blood levels of the antioxidant GSH, the TAS, and the levels of several markers of oxidative stress, such as nitric oxide (NO) and malondialdehyde (MDA), are consistent across studies. Blood levels of MDA are commonly determined as thiobarbituric acid reactive substances (TBARS) and are used as a proxy for peroxidation of membrane PUFAs. Indeed, MDA is a product of lipid peroxidation. Multiple studies have demonstrated that patients with SZ have higher blood concentration of MDA [39,69,70,76] and NO, including two meta-analyses [82,83]. One of these studies revealed the good diagnostic performance for serum MDA levels in SZ patients [69]. These findings reveal that a common pathophysiological pathway leads to oxidative stress and membrane lipid damage in patients with SZ. Therefore, the discrepancy observed in the blood levels of the antioxidant enzymes in different studies could be a result of the activation of distinct antioxidant mechanisms in response to increased concentrations of ROS. Indeed, a homeostatic regulation between the GSH and PRX antioxidant systems contributes to the prevention of neuroanatomical defects in psychotic patients exposed to trauma who present with low GPx activity [84]. It seems possible that different compensatory mechanisms activate in response to the failure or the overload of one antioxidant system. Moreover, the levels of GSH and the TAS are consistently decreased in the blood of chronic SZ and FEP patients (Tables 2 and 3). Likewise, a meta-analysis of MRS studies of antioxidant defense in the anterior cingulate cortex (ACC) of SZ patients revealed a reduction of GSH compared to controls [85]. These findings have been replicated in several studies, revealing a strong relationship between peripheral and brain GSH levels [72,86–89]. Although blood levels of oxidative stress are important to determine potential peripheral biomarkers of SZ, levels of these markers in the CNS are necessary to understand the role played by oxidative stress in the pathophysiology of the disease. For instance, low medial prefrontal cortex (mPFC) GSH concentration was shown to correlate with high levels of GPx activity in the blood of patients but not in healthy controls, reflecting a defect in compensatory mechanisms under oxidative conditions in patients with SZ [90].

Moreover, there is genetic evidence supporting the oxidative stress theory of SZ development. Indeed, in this study, the authors showed that low GSH levels in the mPFC correlate with a trinucleotide repeat polymorphism in the gene encoding the catalytic subunit of glutamate-cysteine ligase (GCLC), the rate-limiting enzyme for GSH synthesis [90]. Notably, it was found that individuals carrying the GCLC polymorphism were at higher risk of SZ [19]. Conversely, the effects of GCLC polymorphism on ACC GSH levels were not observed in a more recent study [91]. However, this study investigated SZ patients who were non-responders to treatments and found that a higher proportion of patients with the high-risk GCLC genotype were responders to clozapine [91]. These findings suggest that SZ may arise from different pathophysiological mechanisms, and that oxidative stress is one of the mechanisms at play. Another genetic evidence of reduced antioxidant defense in SZ is the high risk polymorphism in the gene encoding for the glutathione-S-transferase (GSST1) revealed by a meta-analysis [92]. Several other gene mutations associated with the risk of developing SZ, such as *DISC1*, *PROD*, *NRG* and *DTNBP1*, lead to mitochondrial dysfunction and increased oxidative stress [93–96].

Overall, evidence from genetic and biochemical studies of protein contents and activity in SZ suggests that oxidative stress is involved in the pathophysiology of SZ. However, it is important to note that oxidative stress may also be associated with other conditions such as neurodegenerative diseases, or metabolic disorders. Likewise, several limitations to these studies must be acknowledged. First, there are substantial discrepancies across the

findings from these different studies. These may be a result of several factors, including the assessment of indirect markers of oxidative stress and the variability of the sample source (plasma, serum, erythrocytes). In addition, most studies report total GSH levels and do not consider the contribution of the reduced (GSH) and oxidized (GSSG) forms of GSH. Even so, reduced GSH levels are thought to reflect 80-95% of total GSH levels.

The limited replicability of these findings is further demonstrated by the fact that several studies failed to reproduce the association found between peripheral and central GSH levels [97]. However, a proteomics analysis of the changed proteins in post-mortem brains of SZ patients and healthy individuals revealed specific alterations in mitochondrial functions and oxidative stress [98]. Additionally, studies investigating levels of antioxidants in the brain of patients consistently report decreased levels compared to controls [54,55]. Therefore, investigating reliable biomarkers in the CNS would be a relevant strategy to identify individuals at risk of developing SZ in a consistent manner. However, it is an invasive method, highlighting the need for simultaneous analysis of blood and CNS redox biomarkers.

In addition, most studies consider the effects of clinical status on oxidative stress markers. Whereas most studies compare SZ patients with controls, some divide the patients into subgroups according to the duration of the disease [61], gender [67], their smoking status [99], or the subtypes of SZ spectrum disorders [32,41,59,62,67]. These studies found significant differences in antioxidant enzyme activities between males and females [67], smokers and non-smokers [99], and the different subtypes of SZ [32,41,59,62,67]. Finally, the effects of the clinical stage of SZ and antipsychotic treatments on antioxidant systems and oxidation status must be considered carefully.

#### 4.2. Oxidative Stress Biomarkers and Clinical Course of SZ

The previous section reviewed the evidence for oxidative stress in SZ patients. This section will discuss these findings considering the clinical stage of the patients in order to identify pathophysiological mechanisms that may be at play during the evolution of the disease.

Despite there being only two studies investigating individuals at risk of developing psychosis, their findings converge towards increased oxidative stress in this population. In healthy individuals with a family history of psychosis (familial high risk), TAS in the blood is decreased compared to healthy individuals without a family history of psychosis [31]. Interestingly, the authors found that oxidative stress in these healthy individuals was not influenced by negative family environmental factors [31]. In addition, during the preclinical stages of psychosis, UHR individuals present with decreased activity of antioxidant enzymes SOD and GPx compared to healthy individuals [29]. Regarding the early stages of psychosis, there are many studies which focused on FEP patients and found elevated oxidative stress and defects in antioxidant systems prior to the use of antipsychotic treatments [37,53,100,101]. Indeed, one study showed that antipsychotic-naïve FEP patients present with lower blood activity of SOD than chronic SZ patients under antipsychotic treatments [45]. Increased lipid peroxidation, in association with decreased blood levels of catalase, SOD, GPx and GSH in the blood of antipsychotic-naïve FEP patients [101], seem to indicate increased oxidative stress and defects in antioxidant systems. In addition, one meta-analysis reports lower blood TAS and catalase levels in FEP patients, which are then reversed by antipsychotic treatment [13]. In this study, the authors mention that TAS and catalase blood levels could be viewed as state-markers whereas SOD blood levels, which are decreased in both FEP and chronic medicated patients, appear to be trait markers for SZ [13].

It is important to bear in mind the heterogeneity of findings as reported in Table 1. Indeed, amongst the studies reported in this review, many present contradictory results, and one meta-analysis even reports no difference in GSH levels between chronic patients, FEP patients and healthy individuals [102]. In order to understand these discrepancies, it may be recommended to investigate how oxidative stress relates with the patient's symptom profiles. Indeed, higher levels of oxidative stress correlate positively with the severity of symptoms assessed by the Positive and Negative Symptoms Scale (PANSS) [43,66]. On the other hand, lower levels of antioxidants correlate negatively with the severity of

positive and negative symptoms [27,50,51,66,71,81], and correlate positively with global cognitive functioning [41,51]. Interestingly, electrophysiological abnormalities, such as reduced gamma responses, which are frequently observed in SZ patients, correlate with GSH levels in both patients and healthy individuals [74]. Blood GSH levels were also associated with executive functions, as measured by several neuropsychological tests, in both FEP patients and healthy individuals, despite no difference in redox markers between the groups at baseline [36].

Overall, it appears that alterations in antioxidant functions are associated with symptoms severity in patients with SZ. Decreased activity of antioxidant systems has been observed in the prodromal stage of the illness, supporting the hypothesis that oxidative stress might play a causal role in the transition to psychosis [30].

#### 4.3. Link between Oxidative Stress and Current Physiopathological Hypotheses

In order to understand the pathophysiological significance of oxidative stress during the psychotic transition, this section will describe the mechanisms through which oxidative stress might be involved. The different theories of SZ pathophysiology reveal interactions between the mechanisms they describe.

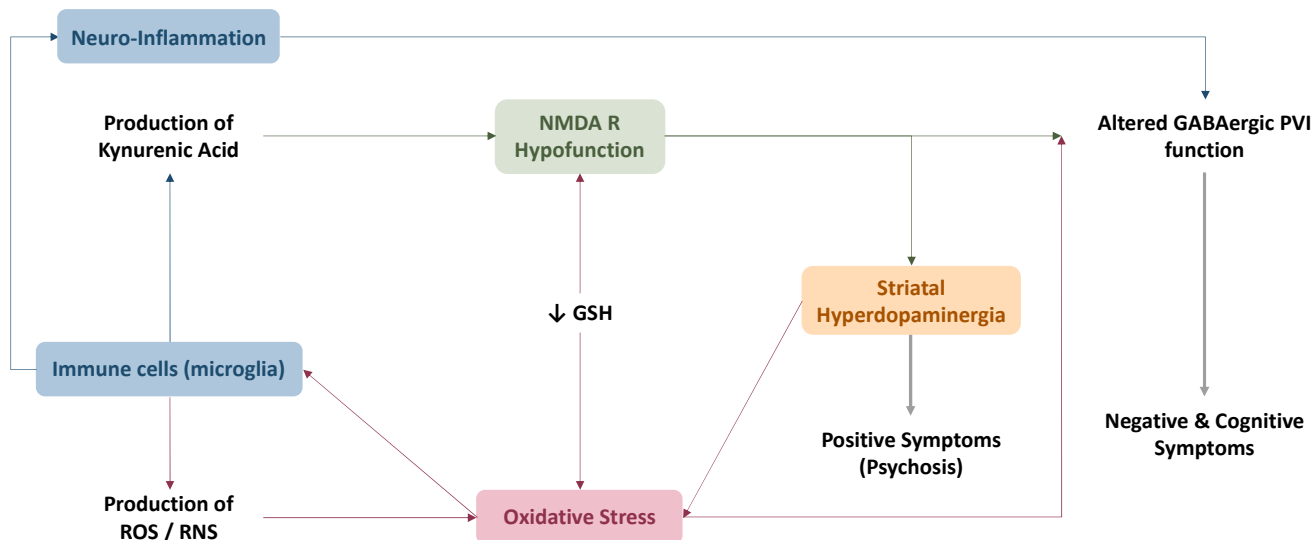
The neurodevelopmental hypothesis of SZ states that interactions between genetic and environmental factors influence brain development in utero, during birth and the first years of life [103]. These neurodevelopmental abnormalities become fully expressed in the mature brain, during early adulthood [103]. According to the oxidative stress hypothesis, damage caused by oxidative stress might be the molecular basis of these changes [104].

A potential source of oxidative stress in the brain comes from auto-oxidation of excess dopamine [105]. Indeed, auto-oxidizable neurotransmitters, like dopamine or epinephrine, are present in excess in the brain, and their metabolism generates large amounts of hydrogen peroxide ( $H_2O_2$ ) [106]. Therefore, of all the brain regions, the basal ganglia, and in particular the striatum, appear to be the most at risk of damage induced by oxidative stress due to high amount of free iron [106,107] and dopamine. Moreover, the dopaminergic theory of SZ proposes that increased dopaminergic activity in the striatum is mainly responsible for the emergence of positive psychotic symptoms [108]. On the other hand, negative symptoms such as a loss of motivation (avolition), or affective flattening, can only be partially explained by hypodopaminergy in the prefrontal cortex (PFC) [108].

Pathological alterations in cortical inhibitory circuits are increasingly studied as therapeutic targets for cognitive and negative symptoms in SZ [109]. In particular, parvalbumin GABAergic interneurons (PVI) and oligodendrocytes have a high susceptibility to oxidative stress [11]. Indeed, PVI are energy demanding for high frequency neuronal synchronization [16]. Therefore, their mitochondria produce ROS at a very high rate, and they require a functional antioxidant system. Oligodendrocytes, on the other hand, have low antioxidant levels despite their high metabolic activity, and thus are also very susceptible to oxidative stress [110]. At the pathophysiological level, PVI and oligodendrocytes' function is altered in SZ. While oligodendrocytes ensure myelination of neurons [111], PVI are required for synchronous firing [112], and both are required for synchronous network dynamics in the brain. Connectivity alterations at the functional and structural levels in SZ have been extensively studied and are present throughout all stages of the illness [113]. There is growing evidence suggesting that PVI impairments constitute a hallmark of SZ [16,114], and are involved in the excitatory/inhibitory neuronal imbalance observed in patients [115]. Altered function of PVI neurons could also be due to *N*-methyl-D-aspartate (NMDA) receptors hypofunction, a key feature of SZ, which forms the basis of the glutamatergic hypothesis of SZ physiopathology [116]. Notably, GSH, which is an essential antioxidant and plays an important role as a scavenger of ROS in brain, is a precursor of glutamate [117]. Indeed, one study found that peripheral low GSH correlates with low glutamate in the ACC [72], therefore it appears the antioxidant activity of GSH in the brain is prioritized over its role as a precursor of glutamate [117].



Eventually, oxidative stress appears to be a convergent ‘hub’ for the different theories explaining SZ pathophysiology, as reviewed by Steullet, Cabungcal [118]. Figure 2 summarizes the interactions between the different theories mentioned.



**Figure 2.** Interaction between the different theories of SZ pathophysiology. Oxidative stress plays a role in the activation of immune cells which in turn lead to more oxidative stress through the production of ROS. Neuroinflammation leads to decreased activity of the GABAergic PVI, which are involved in the emergence of negative and cognitive symptoms. The release of kynurenic acid by the activated microglia acts on the NMDA receptors to decrease their function. Hypofunction of NMDA receptors is also observed when GSH levels are decreased. Overall, it leads to altered function of the GABAergic PVI, as well as increased function of dopaminergic neurons in the striatum. Striatal hyperdopaminergia is thought to contribute to the positive symptoms of SZ.

#### 4.4. Re-Establishing Redox Balance

In addition to the variability observed in SZ patients, but also during pre-clinical stages, patients taking antipsychotic treatments can present with increased or decreased oxidative stress. This section discusses the effects of antipsychotic treatments on oxidative stress, along with the use of antioxidants in clinical trials for SZ patients.

First generation (typical) antipsychotics, such as haloperidol, are thought to induce higher levels of lipid peroxidation in patients than second generation (atypical) antipsychotics, such as clozapine, quetiapine and risperidone [38,70,100,119,120]. Moreover, in drug-naïve FEP patients, atypical antipsychotics reduce the levels of lipid peroxidation after six weeks of treatment [44]. Typical antipsychotics can increase the metabolism of monoamines, thus leading to more ROS being produced [121], whereas atypical antipsychotics seem to demonstrate anti-oxidative and neuroprotective effects [122]. Interestingly, first generation antipsychotics seem to be more frequently associated with side effects such as extrapyramidal symptoms, deemed to be associated with oxidative stress [123,124]. Furthermore, it was found that patients with the high risk GCLC polymorphism were more likely to respond to treatment with clozapine, which suggests that this antipsychotic drug might act on redox pathways [91]. Nonetheless, discrepancies across the findings reveal that the effects of antipsychotic drugs on redox systems are subjected to inter-individual differences. Indeed, one study found that clozapine induced higher levels of lipid peroxidation than haloperidol [77]. Other studies found no effect of antipsychotic treatments on oxidative stress [60,67,81].

Still, a recent meta-analysis revealed promising results from randomized controlled clinical trials using the antioxidant N-Acetyl Cysteine (NAC) as adjunct treatment to antipsychotics in chronic and FEP patients [125]. In particular, adjunct treatment with NAC seems to improve the negative and total PANSS scores in patients [125], along with

cognitive functions such as working memory [126]. More clinical trials using NAC are currently registered, which seems to confirm the importance of this hypothesis in SZ development [127]. Adjunct treatment with the antioxidant vitamin C also proved to reduce lipid peroxidation in patients, and also decreased scores on the Brief Psychiatric Symptoms Scale (BPRS) [120]. Finally, in UHR individuals, omega-3 polyunsaturated fatty acid supplementation had no effect on vitamin E, but decreased total GSH blood levels [128]. The type of antioxidants and their effectiveness at different stages of the illness still require further investigation.

## 5. Conclusions

The scientific literature on blood levels of oxidative stress markers in SZ is marked by a high variability in the findings. Harmonization of assessment and study design should be encouraged to ensure comparability and replicability and to be able to draw definitive conclusions. Indeed, considering the association between brain and blood levels of GSH, which appears to be decreased in the blood of both UHR individuals and FEP patients, it would be an interesting biomarker to consider as part of a diagnosis. However, these findings must be interpreted with caution to prevent the physiopathological mechanisms being directly inferred from dosage. Indeed, reduced antioxidant enzymes activity could indicate a reduced need for these enzymes because of low oxidative stress levels, or a defect in the enzymes leading to high oxidative stress levels. In addition, oxidative stress levels must be assessed while considering important factors such as the gender and smoking status of the patients. Nonetheless, redox mechanisms appear to play a non-negligible role in the early phases of psychosis, and their potential value as biomarkers remains to be explored. Redox mechanisms could also help to better understand the physiopathology of emerging SZ and might serve as therapeutic targets for preventive or adjunctive therapies.

**Supplementary Materials:** The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/antiox11101870/s1>, Table S1: Number of participants included in each study.

**Author Contributions:** B.C. obtained the funding. V.R. reviewed the literature and drafted the manuscript. B.C. and A.M. supervised the study. All authors have read and agreed to the published version of the manuscript.

**Funding:** Boris Chaumette receives funding from the Fondation Bettencourt Schueller. This work has been supported by the French government's "Investissements d'Avenir" program, which is managed by the Agence Nationale de la Recherche (ANR), under the reference PsyCARE ANR-18-RHUS-0014.

**Conflicts of Interest:** Boris Chaumette has received speaking fees from Janssen-Cilag, Lundbeck and Eisai outside this work. The remaining authors declare no conflict of interest.

## References

1. Charlson, F.J.; Ferrari, A.J.; Santomauro, D.F.; Diminic, S.; Stockings, E.; Scott, J.G.; McGrath, J.J.; Whiteford, H.A. Global epidemiology and burden of schizophrenia: Findings from the global burden of disease study 2016. *Schizophr. Bull.* **2018**, *44*, 1195–1203. [[CrossRef](#)] [[PubMed](#)]
2. Yung, A.R.; Nelson, B.; Stanford, C.; Simmons, M.B.; Cosgrave, E.M.; Killackey, E.; Phillips, L.J.; Bechdolf, A.; Buckby, J.; McGorry, P.D. Validation of "prodromal" criteria to detect individuals at ultra high risk of psychosis: 2 year follow-up. *Schizophr. Res.* **2008**, *105*, 10–17. [[CrossRef](#)] [[PubMed](#)]
3. Cannon, T.D.; Cadenhead, K.; Cornblatt, B.; Woods, S.W.; Addington, J.; Walker, E.; Seidman, L.J.; Perkins, D.; Tsuang, M.; McGlashan, T. Prediction of psychosis in youth at high clinical risk: A multisite longitudinal study in North America. *Arch. Gen. Psychiatry* **2008**, *65*, 28–37. [[CrossRef](#)] [[PubMed](#)]
4. Remington, G.; Foussias, G.; Fervaha, G.; Agid, O.; Takeuchi, H.; Lee, J.; Hahn, M. Treating Negative Symptoms in Schizophrenia: An Update. *Curr. Treat. Options Psychiatry* **2016**, *3*, 133–150. [[CrossRef](#)] [[PubMed](#)]
5. Austin, S.F.; Mors, O.; Secher, R.G.; Hjorthøj, C.R.; Albert, N.; Bertelsen, M.; Jensen, H.; Jeppesen, P.; Petersen, L.; Randers, L. Predictors of recovery in first episode psychosis: The OPUS cohort at 10 year follow-up. *Schizophr. Res.* **2013**, *150*, 163–168. [[CrossRef](#)]

6. Meyer, E.C.; Carrión, R.E.; Cornblatt, B.A.; Addington, J.; Cadenhead, K.S.; Cannon, T.D.; McGlashan, T.H.; Perkins, D.O.; Tsuang, M.T.; Walker, E.F. The relationship of neurocognition and negative symptoms to social and role functioning over time in individuals at clinical high risk in the first phase of the North American Prodrome Longitudinal Study. *Schizophr. Bull.* **2014**, *40*, 1452–1461. [[CrossRef](#)]
7. Harvey, R.C.; James, A.C.; Shields, G.E. A systematic review and network meta-analysis to assess the relative efficacy of antipsychotics for the treatment of positive and negative symptoms in early-onset schizophrenia. *CNS Drugs* **2016**, *30*, 27–39. [[CrossRef](#)]
8. Shoja Shafti, S.; Fallah Jahromi, P. A comparative study between olanzapine and risperidone regarding drug-induced electrocardiographic changes. *Cardiovasc. Psychiatry Neurol.* **2014**, *2014*, 37016. [[CrossRef](#)]
9. Raballo, A.; Poletti, M.; Preti, A. Negative Prognostic Effect of Baseline Antipsychotic Exposure in Clinical High Risk for Psychosis (CHR-P): Is Pre-Test Risk Enrichment the Hidden Culprit? *Int. J. Neuropsychopharmacol.* **2021**, *24*, 710–720. [[CrossRef](#)]
10. Millan, M.J.; Andrieux, A.; Bartzokis, G.; Cadenhead, K.; Dazzan, P.; Fusar-Poli, P.; Gallinat, J.; Giedd, J.; Grayson, D.R.; Heinrichs, M.; et al. Altering the course of schizophrenia: Progress and perspectives. *Nat. Rev. Drug Discov.* **2016**, *15*, 485–515. [[CrossRef](#)]
11. Do, K.Q.; Cabungcal, J.H.; Frank, A.; Steullet, P.; Cuenod, M. Redox dysregulation, neurodevelopment, and schizophrenia. *Curr. Opin. Neurobiol.* **2009**, *19*, 220–230. [[CrossRef](#)] [[PubMed](#)]
12. Perkins, D.O.; Jeffries, C.D.; Addington, J.; Bearden, C.E.; Cadenhead, K.S.; Cannon, T.D.; Cornblatt, B.A.; Matheron, D.H.; McGlashan, T.H.; Seidman, L.J. Towards a psychosis risk blood diagnostic for persons experiencing high-risk symptoms: Preliminary results from the NAPLS project. *Schizophr. Bull.* **2015**, *41*, 419–428. [[CrossRef](#)] [[PubMed](#)]
13. Flatow, J.; Buckley, P.; Miller, B.J. Meta-analysis of oxidative stress in schizophrenia. *Biol. Psychiatry* **2013**, *74*, 400–409. [[CrossRef](#)] [[PubMed](#)]
14. Zarkovic, N. Antioxidants and Second Messengers of Free Radicals. *Antioxidants* **2018**, *7*, 158. [[CrossRef](#)]
15. Murphy, M.P.; Holmgren, A.; Larsson, N.-G.; Halliwell, B.; Chang, C.J.; Kalyanaraman, B.; Rhee, S.G.; Thornalley, P.J.; Partridge, L.; Gems, D. Unraveling the biological roles of reactive oxygen species. *Cell Metab.* **2011**, *13*, 361–366. [[CrossRef](#)]
16. Lewis, D.A.; Curley, A.A.; Glausier, J.R.; Volk, D.W. Cortical parvalbumin interneurons and cognitive dysfunction in schizophrenia. *Trends Neurosci.* **2012**, *35*, 57–67. [[CrossRef](#)]
17. Irshad, M.; Chaudhuri, P. *Oxidant-Antioxidant System: Role and Significance in Human Body*; NISCAIR-CSIR: New Delhi, India, 2002.
18. Gravina, P.; Spoletini, I.; Masini, S.; Valentini, A.; Vanni, D.; Paladini, E.; Bossù, P.; Caltagirone, C.; Federici, G.; Spalletta, G. Genetic polymorphisms of glutathione S-transferases GSTM1, GSTT1, GSTP1 and GSTA1 as risk factors for schizophrenia. *Psychiatry Res.* **2011**, *187*, 454–456. [[CrossRef](#)]
19. Gysin, R.; Kraftsik, R.; Sandell, J.; Bovet, P.; Chappuis, C.; Conus, P.; Deppen, P.; Preisig, M.; Ruiz, V.; Steullet, P. Impaired glutathione synthesis in schizophrenia: Convergent genetic and functional evidence. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 16621–16626. [[CrossRef](#)]
20. Rodríguez-Santiago, B.; Brunet, A.; Sobrino, B.; Serra-Juhe, C.; Flores, R.; Armengol, L.; Vilella, E.; Gabau, E.; Guitart, M.; Guillamat, R. Association of common copy number variants at the glutathione S-transferase genes and rare novel genomic changes with schizophrenia. *Mol. Psychiatry* **2010**, *15*, 1023–1033. [[CrossRef](#)]
21. Tomic, M.; Ott, J.; Barral, S.; Bovet, P.; Deppen, P.; Gheorghita, F.; Matthey, M.L.; Parnas, J.; Preisig, M.; Saraga, M.; et al. Schizophrenia and oxidative stress: Glutamate cysteine ligase modifier as a susceptibility gene. *Am. J. Hum. Genet.* **2006**, *79*, 586–592. [[CrossRef](#)]
22. Lavoie, S.; Berger, M.; Schlögelhofer, M.; Schäfer, M.; Rice, S.; Kim, S.; Hesse, J.; McGorry, P.; Smesny, S.; Amminger, G. Erythrocyte glutathione levels as long-term predictor of transition to psychosis. *Transl. Psychiatry* **2017**, *7*, e1064. [[CrossRef](#)] [[PubMed](#)]
23. Langbein, K.; Hesse, J.; Gussew, A.; Milleit, B.; Lavoie, S.; Amminger, G.P.; Gaser, C.; Wagner, G.; Reichenbach, J.R.; Hipler, U.C.; et al. Disturbed glutathione antioxidative defense is associated with structural brain changes in neuroleptic-naïve first-episode psychosis patients. *Prostaglandins Leukot. Essent. Fat. Acids* **2018**, *136*, 103–110. [[CrossRef](#)] [[PubMed](#)]
24. Wei, C.; Sun, Y.; Chen, N.; Chen, S.; Xiu, M.; Zhang, X. Interaction of oxidative stress and BDNF on executive dysfunction in patients with chronic schizophrenia. *Psychoneuroendocrinology* **2020**, *111*, 104473. [[CrossRef](#)]
25. Wu, Z.W.; Yu, H.H.; Wang, X.; Guan, H.Y.; Xiu, M.H.; Zhang, X.Y. Interrelationships between Oxidative Stress, Cytokines, and Psychotic Symptoms and Executive Functions in Patients with Chronic Schizophrenia. *Psychosom. Med.* **2021**, *83*, 485–491. [[CrossRef](#)] [[PubMed](#)]
26. Zhang, X.Y.; Chen, D.C.; Tan, Y.L.; Tan, S.P.; Wang, Z.R.; Yang, F.D.; Okusaga, O.O.; Zunta-Soares, G.B.; Soares, J.C. The interplay between BDNF and oxidative stress in chronic schizophrenia. *Psychoneuroendocrinology* **2015**, *51*, 201–208. [[CrossRef](#)]
27. Zhang, X.Y.; Chen, D.C.; Xiu, M.H.; Tang, W.; Zhang, F.; Liu, L.; Chen, Y.; Liu, J.; Yao, J.K.; Kosten, T.A.; et al. Plasma total antioxidant status and cognitive impairments in schizophrenia. *Schizophr. Res.* **2012**, *139*, 66–72. [[CrossRef](#)]
28. Ben Othmen, L.; Mechri, A.; Fendri, C.; Bost, M.; Chazot, G.; Gaha, L.; Kerkeni, A. Altered antioxidant defense system in clinically stable patients with schizophrenia and their unaffected siblings. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* **2008**, *32*, 155–159. [[CrossRef](#)]
29. Zeni-Graiff, M.; Rios, A.C.; Maurya, P.K.; Rizzo, L.B.; Sethi, S.; Yamagata, A.S.; Mansur, R.B.; Pan, P.M.; Asevedo, E.; Cunha, G.R.; et al. Peripheral levels of superoxide dismutase and glutathione peroxidase in youths in ultra-high risk for psychosis: A pilot study. *CNS Spectr.* **2019**, *24*, 333–337. [[CrossRef](#)]

30. Guler, E.M.; Kurtulmus, A.; Gul, A.Z.; Kocyigit, A.; Kirpinar, I. Oxidative stress and schizophrenia: A comparative cross-sectional study of multiple oxidative markers in patients and their first-degree relatives. *Int. J. Clin. Pract.* **2021**, *75*, e14711. [[CrossRef](#)]
31. Gonzalez-Pinto, A.; Martinez-Cengotitabengoa, M.; Arango, C.; Baeza, I.; Otero-Cuesta, S.; Graell-Berna, M.; Soutullo, C.; Leza, J.C.; Mico, J.A. Antioxidant defense system and family environment in adolescents with family history of psychosis. *BMC Psychiatry* **2012**, *12*, 200. [[CrossRef](#)]
32. Micó, J.A.; Rojas-Corrales, M.O.; Gibert-Rahola, J.; Parellada, M.; Moreno, D.; Fraguas, D.; Graell, M.; Gil, J.; Irazusta, J.; Castro-Fornieles, J.; et al. Reduced antioxidant defense in early onset first-episode psychosis: A case-control study. *BMC Psychiatry* **2011**, *11*, 26. [[CrossRef](#)] [[PubMed](#)]
33. Raffa, M.; Atig, F.; Mhalla, A.; Kerkeni, A.; Mechri, A. Decreased glutathione levels and impaired antioxidant enzyme activities in drug-naive first-episode schizophrenic patients. *BMC Psychiatry* **2011**, *11*, 124. [[CrossRef](#)] [[PubMed](#)]
34. Juchnowicz, D.; Dzikowski, M.; Rog, J.; Waszkiewicz, N.; Zalewska, A.; Maciejczyk, M.; Karakuła-Juchnowicz, H. Oxidative Stress Biomarkers as a Predictor of Stage Illness and Clinical Course of Schizophrenia. *Front. Psychiatry* **2021**, *12*, 728986. [[CrossRef](#)] [[PubMed](#)]
35. Simsek, S.; Gencoglan, S.; Yuksel, T.; Kaplan, I.; Alaca, R.; Aktas, H. Oxidative stress and DNA damage in untreated first-episode psychosis in adolescents. *Neuropsychobiology* **2016**, *73*, 92–97. [[CrossRef](#)]
36. Martínez-Cengotitabengoa, M.; Mac-Dowell, K.S.; Leza, J.C.; Micó, J.A.; Fernandez, M.; Echevarría, E.; Sanjuan, J.; Elorza, J.; González-Pinto, A. Cognitive impairment is related to oxidative stress and chemokine levels in first psychotic episodes. *Schizophr. Res.* **2012**, *137*, 66–72. [[CrossRef](#)]
37. Bai, Z.L.; Li, X.S.; Chen, G.Y.; Du, Y.; Wei, Z.X.; Chen, X.; Zheng, G.E.; Deng, W.; Cheng, Y. Serum Oxidative Stress Marker Levels in Unmedicated and Medicated Patients with Schizophrenia. *J. Mol. Neurosci.* **2018**, *66*, 428–436. [[CrossRef](#)]
38. Li, X.R.; Xiu, M.H.; Guan, X.N.; Wang, Y.C.; Wang, J.; Leung, E.; Zhang, X.Y. Altered Antioxidant Defenses in Drug-Naive First Episode Patients with Schizophrenia Are Associated with Poor Treatment Response to Risperidone: 12-Week Results from a Prospective Longitudinal Study. *Neurotherapeutics* **2021**, *18*, 1316–1324. [[CrossRef](#)]
39. Sarandol, A.; Sarandol, E.; Acikgoz, H.E.; Eker, S.S.; Akkaya, C.; Dirican, M. First-episode psychosis is associated with oxidative stress: Effects of short-term antipsychotic treatment. *Psychiatry Clin. Neurosci.* **2015**, *69*, 699–707. [[CrossRef](#)]
40. Piatoikina, A.S.; Lyakhova, A.A.; Semennov, I.V.; Zhilyaeva, T.V.; Kostina, O.V.; Zhukova, E.S.; Shcherbatyuk, T.G.; Kasyanov, E.D.; Blagonravova, A.S.; Mazo, G.E. Association of antioxidant deficiency and the level of products of protein and lipid peroxidation in patients with the first episode of schizophrenia. *J. Mol. Neurosci.* **2022**, *72*, 217–225. [[CrossRef](#)]
41. Martínez-Cengotitabengoa, M.; Micó, J.A.; Arango, C.; Castro-Fornieles, J.; Graell, M.; Payá, B.; Leza, J.C.; Zorrilla, I.; Parellada, M.; López, M.P. Basal low antioxidant capacity correlates with cognitive deficits in early onset psychosis. A 2-year follow-up study. *Schizophr. Res.* **2014**, *156*, 23–29. [[CrossRef](#)]
42. Zhai, X.; Kang, Y.; Yuan, X.; Wang, Y.; Lu, S.; Lu, Z. Dysfunctional oxidative stress response in first-episode of schizophrenia. *Trop. J. Pharm. Res.* **2021**, *20*, 1251–1259. [[CrossRef](#)]
43. Guidara, W.; Messedi, M.; Naifar, M.; Grayaa, S.; Omri, S.; Ben Thabet, J.; Maalej, M.; Charfi, N.; Ayadi, F. Predictive value of oxidative stress biomarkers in drug-free patients with schizophrenia and schizo-affective disorder. *Psychiatry Res.* **2020**, *293*, 113467. [[CrossRef](#)] [[PubMed](#)]
44. Jordan, W.; Dobrowolny, H.; Bahn, S.; Bernstein, H.G.; Brigadski, T.; Frodl, T.; Isermann, B.; Lessmann, V.; Pilz, J.; Rodenbeck, A.; et al. Oxidative stress in drug-naive first episode patients with schizophrenia and major depression: Effects of disease acuity and potential confounders. *Eur. Arch. Psychiatry Clin. Neurosci.* **2018**, *268*, 129–143. [[CrossRef](#)] [[PubMed](#)]
45. Wu, Z.; Zhang, X.Y.; Wang, H.; Tang, W.; Xia, Y.; Zhang, F.; Liu, J.; Fu, Y.; Hu, J.; Chen, Y.; et al. Elevated plasma superoxide dismutase in first-episode and drug naive patients with schizophrenia: Inverse association with positive symptoms. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2012**, *36*, 34–38. [[CrossRef](#)]
46. Yao, J.K.; Reddy, R.; McElhinny, L.G.; Van Kammen, D.P. Effects of haloperidol on antioxidant defense system enzymes in schizophrenia. *J. Psychiatr. Res.* **1998**, *32*, 385–391. [[CrossRef](#)]
47. Tuncel, O.K.; Sarisoy, G.; Bilgici, B.; Pazvantoglu, O.; Cetin, E.; Unverdi, E.; Avci, B.; Boke, T. Oxidative stress in bipolar and schizophrenia patients. *Psychiatry Res.* **2015**, *228*, 688–694. [[CrossRef](#)]
48. Kriisa, K.; Haring, L.; Vasar, E.; Koido, K.; Janno, S.; Vasar, V.; Zilmer, K.; Zilmer, M. Antipsychotic Treatment Reduces Indices of Oxidative Stress in First-Episode Psychosis Patients. *Oxidative Med. Cell. Longev.* **2016**, *2016*, 9616593. [[CrossRef](#)]
49. Devanarayanan, S.; Nandeesh, H.; Kattimani, S.; Sarkar, S. Relationship between matrix metalloproteinase-9 and oxidative stress in drug-free male schizophrenia: A case control study. *Clin. Chem. Lab. Med.* **2016**, *54*, 447–452. [[CrossRef](#)]
50. Li, X.F.; Zheng, Y.L.; Xiu, M.H.; Chen, D.C.; Kosten, T.R.; Zhang, X.Y. Reduced plasma total antioxidant status in first-episode drug-naive patients with schizophrenia. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* **2011**, *35*, 1064–1067. [[CrossRef](#)]
51. Xie, T.; Li, Q.; Luo, X.; Tian, L.; Wang, Z.; Tan, S.; Chen, S.; Yang, G.; An, H.; Yang, F.; et al. Plasma total antioxidant status and cognitive impairments in first-episode drug-naive patients with schizophrenia. *Cogn. Neurodynamics* **2019**, *13*, 357–365. [[CrossRef](#)]
52. Khan, M.M.; Evans, D.R.; Gunna, V.; Scheffer, R.E.; Parikh, V.V.; Mahadik, S.P. Reduced erythrocyte membrane essential fatty acids and increased lipid peroxides in schizophrenia at the never-medicated first-episode of psychosis and after years of treatment with antipsychotics. *Schizophr. Res.* **2002**, *58*, 1–10. [[CrossRef](#)]
53. Mahadik, S.P.; Mukherjee, S.; Scheffer, R.; Correnti, E.E.; Mahadik, J.S. Elevated plasma lipid peroxides at the onset of nonaffective psychosis. *Biol. Psychiatry* **1998**, *43*, 674–679. [[CrossRef](#)]



54. Do, K.Q.; Trabesinger, A.H.; Kirsten-Krüger, M.; Lauer, C.J.; Dydak, U.; Hell, D.; Holsboer, F.; Boesiger, P.; Cuénod, M. Schizophrenia: Glutathione deficit in cerebrospinal fluid and prefrontal cortex in vivo. *Eur. J. Neurosci.* **2000**, *12*, 3721–3728. [[CrossRef](#)] [[PubMed](#)]
55. Coughlin, J.M.; Hayes, L.N.; Tanaka, T.; Xiao, M.; Yolken, R.H.; Worley, P.; Leweke, F.M.; Sawa, A. Reduced superoxide dismutase-1 (SOD1) in cerebrospinal fluid of patients with early psychosis in association with clinical features. *Schizophr. Res.* **2017**, *183*, 64–69. [[CrossRef](#)]
56. Kuloglu, M.; Ustundag, B.; Atmaca, M.; Canatan, H.; Tezcan, A.E.; Cinkilinc, N. Lipid peroxidation and antioxidant enzyme levels in patients with schizophrenia and bipolar disorder. *Cell Biochem. Funct.* **2002**, *20*, 171–175. [[CrossRef](#)]
57. Reddy, R.; Sahebarao, M.P.; Mukherjee, S.; Murthy, J.N. Enzymes of the antioxidant defense system in chronic schizophrenic patients. *Biol. Psychiatry* **1991**, *30*, 409–412. [[CrossRef](#)]
58. Buosi, P.; Borghi, F.A.; Lopes, A.M.; Facincani, I.D.S.; Fernandes-Ferreira, R.; Oliveira-Brancati, C.I.F.; do Carmo, T.S.; Souza, D.R.S.; da Silva, D.G.H.; de Almeida, E.G.H.; et al. Oxidative stress biomarkers in treatment-responsive and treatment-resistant schizophrenia patients. *Trends Psychiatry Psychother.* **2021**, *43*, 278–285. [[CrossRef](#)]
59. Akyol, Ö.; Herken, H.; Uz, E.; Fadilloğlu, E.; Ünal, S.; Söğüt, S.; Özyurt, H.; Savaş, H.A. The indices of endogenous oxidative and antioxidative processes in plasma from schizophrenic patients: The possible role of oxidant/antioxidant imbalance. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* **2002**, *26*, 995–1005. [[CrossRef](#)]
60. Sarandol, A.; Kirli, S.; Akkaya, C.; Altin, A.; Demirci, M.; Sarandol, E. Oxidative-antioxidative systems and their relation with serum S100 B levels in patients with schizophrenia: Effects of short term antipsychotic treatment. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2007**, *31*, 1164–1169. [[CrossRef](#)]
61. Altuntas, I.; Aksoy, H.; Coskun, I.; Çayköylü, A.; Akçay, F. Erythrocyte Superoxide Dismutase and Glutathione Peroxidase Activities, and Malondialdehyde and Reduced Glutathione Levels in Schizophrenic Patients. *Clin. Chem. Lab. Med. (CCLM)* **2000**, *38*, 1277–1281. [[CrossRef](#)]
62. Herken, H.; Uz, E.; Özyurt, H.; Söğüt, S.; Virit, O.; Akyol, Ö. 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* **2001**, *6*, 66–73. [[CrossRef](#)] [[PubMed](#)]
63. Ranjekar, P.K.; Hinge, A.; Hegde, M.V.; Ghate, M.; Kale, A.; Sitasawad, S.; Wagh, U.V.; Debsikdar, V.B.; Mahadik, S.P. Decreased antioxidant enzymes and membrane essential polyunsaturated fatty acids in schizophrenic and bipolar mood disorder patients. *Psychiatry Res.* **2003**, *121*, 109–122. [[CrossRef](#)]
64. Dadheech, G.; Mishra, S.; Gautam, S.; Sharma, P. Evaluation of antioxidant deficit in schizophrenia. *Indian J. Psychiatry* **2008**, *50*, 16. [[PubMed](#)]
65. Pavlović, D.; Tamburić, V.; Stojanović, I.; Kocić, G.; Jevtović, T.; Đorđević, V. Oxidative stress as marker of positive symptoms in schizophrenia. *Facta Univ.* **2002**, *9*, 157–161.
66. Li, H.C.; Chen, Q.Z.; Ma, Y.; Zhou, J.F. Imbalanced free radicals and antioxidant defense systems in schizophrenia: A comparative study. *J. Zhejiang Univ. Sci. B* **2006**, *7*, 981–986. [[CrossRef](#)] [[PubMed](#)]
67. Zhang, X.Y.; Tan, Y.L.; Cao, L.Y.; Wu, G.Y.; Xu, Q.; Shen, Y.; Zhou, D.F. Antioxidant enzymes and lipid peroxidation in different forms of schizophrenia treated with typical and atypical antipsychotics. *Schizophr. Res.* **2006**, *81*, 291–300. [[CrossRef](#)] [[PubMed](#)]
68. González-Blanco, L.; García-Portilla, M.P.; García-Álvarez, L.; de la Fuente-Tomás, L.; Iglesias García, C.; Sáiz, P.A.; Rodríguez-González, S.; Coto-Montes, A.; Bobes, J. Oxidative stress biomarkers and clinical dimensions in first 10 years of schizophrenia. *Rev. Psiquiatr. Salud Ment. (Engl. Ed.)* **2018**, *11*, 130–140. [[CrossRef](#)]
69. Hursitoglu, O.; Orhan, F.O.; Kurutas, E.B.; Doganer, A.; Durmus, H.T.; Kopar, H. Diagnostic performance of increased malondialdehyde level and oxidative stress in patients with schizophrenia. *Noropsikiyatri Ars.* **2021**, *58*, 184–188. [[CrossRef](#)]
70. Cruz, B.F.; de Campos-Carli, S.M.; de Oliveira, A.M.; de Brito, C.B.; Garcia, Z.M.; Duque do Arifa, R.; de Souza, D.D.G.; Teixeira, A.L.; Salgado, J.V. Investigating potential associations between neurocognition/social cognition and oxidative stress in schizophrenia. *Psychiatry Res.* **2021**, *298*, 113832. [[CrossRef](#)]
71. Nucifora, L.G.; Tanaka, T.; Hayes, L.N.; Kim, M.; Lee, B.J.; Matsuda, T.; Nucifora, F.C., Jr.; Sedlak, T.; Mojtabai, R.; Eaton, W.; et al. Reduction of plasma glutathione in psychosis associated with schizophrenia and bipolar disorder in translational psychiatry. *Transl. Psychiatry* **2017**, *7*, e1215. [[CrossRef](#)]
72. Coughlin, J.M.; Yang, K.; Marsman, A.; Pradhan, S.; Wang, M.; Ward, R.E.; Bonekamp, S.; Ambinder, E.B.; Higgs, C.P.; Kim, P.K.; et al. A multimodal approach to studying the relationship between peripheral glutathione, brain glutamate, and cognition in health and in schizophrenia. *Mol. Psychiatry* **2021**, *26*, 3502–3511. [[CrossRef](#)] [[PubMed](#)]
73. Gonzalez-Liencres, C.; Tas, C.; Brown, E.C.; Erdin, S.; Onur, E.; Cubukoglu, Z.; Aydemir, O.; Esen-Danaci, A.; Brüne, M. Oxidative stress in schizophrenia: A case-control study on the effects on social cognition and neurocognition. *BMC Psychiatry* **2014**, *14*, 268. [[CrossRef](#)] [[PubMed](#)]
74. Ballesteros, A.; Summerfelt, A.; Du, X.; Jiang, P.; Chiappelli, J.; Tagamets, M.; O'Donnell, P.; Kochunov, P.; Hong, L.E. Electrophysiological intermediate biomarkers for oxidative stress in schizophrenia. *Clin. Neurophysiol.* **2013**, *124*, 2209–2215. [[CrossRef](#)] [[PubMed](#)]
75. Khan, N.S.; Das, I. Oxidative stress and superoxide dismutase in schizophrenia. *Biochem. Soc. Trans.* **1997**, *25*, 418S. [[CrossRef](#)]
76. Dakhale, G.; Khanzode, S.; Saoji, A.; Khobragade, L.; Turankar, A. Oxidative damage and schizophrenia: The potential benefit by atypical antipsychotics. *Neuropsychobiology* **2004**, *49*, 205–209. [[CrossRef](#)]



77. Gama, C.S.; Salvador, M.; Andrezza, A.C.; Kapczinski, F.; Silva Belmonte-de-Abreu, P. Elevated serum superoxide dismutase and thiobarbituric acid reactive substances in schizophrenia: A study of patients treated with haloperidol or clozapine. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2006**, *30*, 512–515. [[CrossRef](#)]
78. Mukherjee, S.; Mahadik, S.P.; Scheffer, R.; Correnti, E.E.; Kelkar, H. Impaired antioxidant defense at the onset of psychosis. *Schizophr. Res.* **1996**, *19*, 19–26. [[CrossRef](#)]
79. Subotičanec, K.; Folnegović-Šmalc, V.; Korbar, M.; Meštrović, B.; Buzina, R. Vitamin C status in chronic schizophrenia. *Biol. Psychiatry* **1990**, *28*, 959–966. [[CrossRef](#)]
80. Virit, O.; Altindag, A.; Yumru, M.; Dalkilic, A.; Savas, H.A.; Selek, S.; Erel, O.; Herken, H. A defect in the antioxidant defense system in schizophrenia. *Neuropsychobiology* **2009**, *60*, 87–93. [[CrossRef](#)]
81. Yao, J.K.; Reddy, R.; McElhinny, L.G.; Van Kammen, D.P. Reduced status of plasma total antioxidant capacity in schizophrenia. *Schizophr. Res.* **1998**, *32*, 1–8. [[CrossRef](#)]
82. Goh, X.X.; Tang, P.Y.; Tee, S.F. Blood-based oxidation markers in medicated and unmedicated schizophrenia patients: A meta-analysis. *Asian J. Psychiatr.* **2022**, *67*, 102932. [[CrossRef](#)] [[PubMed](#)]
83. Zhang, M.; Zhao, Z.; He, L.; Wan, C. A meta-analysis of oxidative stress markers in schizophrenia. *Sci. China Life Sci.* **2010**, *53*, 112–124. [[CrossRef](#)] [[PubMed](#)]
84. Alameda, L.; Fournier, M.; Khadimallah, I.; Griffa, A.; Cleusix, M.; Jenni, R.; Ferrari, C.; Klauser, P.; Baumann, P.S.; Cuenod, M.; et al. Redox dysregulation as a link between childhood trauma and psychopathological and neurocognitive profile in patients with early psychosis. *Proc. Natl. Acad. Sci. USA* **2018**, *115*, 12495–12500. [[CrossRef](#)] [[PubMed](#)]
85. Das, T.K.; Javadzadeh, A.; Dey, A.; Sabesan, P.; Théberge, J.; Radua, J.; Palaniyappan, L. Antioxidant defense in schizophrenia and bipolar disorder: A meta-analysis of MRS studies of anterior cingulate glutathione. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2019**, *91*, 94–102. [[CrossRef](#)]
86. Limongi, R.; Jeon, P.; Théberge, J.; Palaniyappan, L. Counteracting Effects of Glutathione on the Glutamate-Driven Excitation/Inhibition Imbalance in First-Episode Schizophrenia: A 7T MRS and Dynamic Causal Modeling Study. *Antioxidants* **2021**, *10*, 75. [[CrossRef](#)]
87. Wang, A.M.; Pradhan, S.; Coughlin, J.M.; Trivedi, A.; DuBois, S.L.; Crawford, J.L.; Sedlak, T.W.; Nucifora, F.C., Jr.; Nestadt, G.; Nucifora, L.G.; et al. Assessing Brain Metabolism with 7-T Proton Magnetic Resonance Spectroscopy in Patients with First-Episode Psychosis. *JAMA Psychiatry* **2019**, *76*, 314–323. [[CrossRef](#)]
88. Kumar, J.; Liddle, E.B.; Fernandes, C.C.; Palaniyappan, L.; Hall, E.L.; Robson, S.E.; Simmonite, M.; Fiesal, J.; Katshu, M.Z.; Qureshi, A.; et al. Glutathione and glutamate in schizophrenia: A 7T MRS study. *Mol. Psychiatry* **2020**, *25*, 873–882. [[CrossRef](#)]
89. Yang, Y.S.; Maddock, R.J.; Lee, J.; Zhang, H.; Hellemann, G.; Narr, K.L.; Marder, S.R.; Green, M.F. Brain glutathione levels and age at onset of illness in chronic schizophrenia. *Acta Neuropsychiatr.* **2019**, *31*, 343–347. [[CrossRef](#)]
90. Xin, L.; Mekle, R.; Fournier, M.; Baumann, P.S.; Ferrari, C.; Alameda, L.; Jenni, R.; Lu, H.; Schaller, B.; Cuenod, M.; et al. Genetic Polymorphism Associated Prefrontal Glutathione and Its Coupling with Brain Glutamate and Peripheral Redox Status in Early Psychosis. *Schizophr. Bull.* **2016**, *42*, 1185–1196. [[CrossRef](#)]
91. Iwata, Y.; Nakajima, S.; Plitman, E.; Truong, P.; Bani-Fatemi, A.; Caravaggio, F.; Kim, J.; Shah, P.; Mar, W.; Chavez, S.; et al. Glutathione Levels and Glutathione-Glutamate Correlation in Patients with Treatment-Resistant Schizophrenia. *Schizophr. Bull. Open* **2021**, *2*, sgab006. [[CrossRef](#)]
92. Kim, S.K.; Kang, S.W.; Chung, J.-H.; Park, H.J.; Cho, K.B.; Park, M.-S. Genetic polymorphisms of glutathione-related enzymes (GSTM1, GSTT1, and GSTP1) and schizophrenia risk: A meta-analysis. *Int. J. Mol. Sci.* **2015**, *16*, 19602–19611. [[CrossRef](#)] [[PubMed](#)]
93. Clay, H.B.; Sullivan, S.; Konradi, C. Mitochondrial dysfunction and pathology in bipolar disorder and schizophrenia. *Int. J. Dev. Neurosci.* **2011**, *29*, 311–324. [[CrossRef](#)] [[PubMed](#)]
94. Park, Y.U.; Jeong, J.; Lee, H.; Mun, J.Y.; Kim, J.H.; Lee, J.S.; Nguyen, M.D.; Han, S.S.; Suh, P.G.; Park, S.K. Disrupted-in-schizophrenia 1 (DISC1) plays essential roles in mitochondria in collaboration with Mitofilin. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 17785–17790. [[CrossRef](#)] [[PubMed](#)]
95. Johnson, A.W.; Jaaro-Peled, H.; Shahani, N.; Sedlak, T.W.; Zoubovsky, S.; Burruss, D.; Emiliani, F.; Sawa, A.; Gallagher, M. Cognitive and motivational deficits together with prefrontal oxidative stress in a mouse model for neuropsychiatric illness. *Proc. Natl. Acad. Sci. USA* **2013**, *110*, 12462–12467. [[CrossRef](#)]
96. Goldshmit, Y.; Erlich, S.; Pinkas-Kramarski, R. Neuregulin rescues PC12-ErbB4 cells from cell death induced by H<sub>2</sub>O<sub>2</sub>. Regulation of reactive oxygen species levels by phosphatidylinositol 3-kinase. *J. Biol. Chem.* **2001**, *276*, 46379–46385. [[CrossRef](#)]
97. Palaniyappan, L.; Park, M.T.M.; Jeon, P.; Limongi, R.; Yang, K.; Sawa, A.; Théberge, J. Is there a glutathione centered redox dysregulation subtype of schizophrenia? *Antioxidants* **2021**, *10*, 1703. [[CrossRef](#)]
98. Prabakaran, S.; Swatton, J.E.; Ryan, M.M.; Huffaker, S.J.; Huang, J.-J.; Griffin, J.L.; Wayland, M.; Freeman, T.; Dudbridge, F.; Lilley, K.S.; et al. Mitochondrial dysfunction in schizophrenia: Evidence for compromised brain metabolism and oxidative stress. *Mol. Psychiatry* **2004**, *9*, 684–697. [[CrossRef](#)]
99. Ustundag, B.; Atmaca, M.; Kirtas, O.; Selek, S.; Metin, K.; Tezcan, E. Total antioxidant response in patients with schizophrenia. *Psychiatry Clin. Neurosci.* **2006**, *60*, 458–464. [[CrossRef](#)]

100. Noto, C.; Ota, V.K.; Gadelha, A.; Noto, M.N.; Barbosa, D.S.; Bonifacio, K.L.; Nunes, S.O.; Cordeiro, Q.; Belangero, S.I.; Bressan, R.A.; et al. Oxidative stress in drug naive first episode psychosis and antioxidant effects of risperidone. *J. Psychiatr. Res.* **2015**, *68*, 210–216. [[CrossRef](#)]
101. Ruiz-Litago, F.; Seco, J.; Echevarria, E.; Martinez-Cengotitabengoa, M.; Gil, J.; Irazusta, J.; Gonzalez-Pinto, A.M. Adaptive response in the antioxidant defence system in the course and outcome in first-episode schizophrenia patients: A 12-months follow-up study. *Psychiatry Res.* **2012**, *200*, 218–222. [[CrossRef](#)]
102. Tsugawa, S.; Noda, Y.; Tarumi, R.; Mimura, Y.; Yoshida, K.; Iwata, Y.; Elsalhy, M.; Kuromiya, M.; Kurose, S.; Masuda, F.; et al. Glutathione levels and activities of glutathione metabolism enzymes in patients with schizophrenia: A systematic review and meta-analysis. *J. Psychopharmacol.* **2019**, *33*, 1199–1214. [[CrossRef](#)] [[PubMed](#)]
103. Weinberger, D.R. Implications of normal brain development for the pathogenesis of schizophrenia. *Arch. Gen. Psychiatry* **1987**, *44*, 660–669. [[CrossRef](#)] [[PubMed](#)]
104. Horrobin, D.F. The membrane phospholipid hypothesis as a biochemical basis for the neurodevelopmental concept of schizophrenia. *Schizophr. Res.* **1998**, *30*, 193–208. [[CrossRef](#)]
105. Weng, M.; Xie, X.; Liu, C.; Lim, K.-L.; Zhang, C.-W.; Li, L. The sources of reactive oxygen species and its possible role in the pathogenesis of Parkinson's disease. *Parkinson's Dis.* **2018**, *2018*, 9163040. [[CrossRef](#)] [[PubMed](#)]
106. Halliwell, B. Oxidative stress and neurodegeneration: Where are we now? *J. Neurochem.* **2006**, *97*, 1634–1658. [[CrossRef](#)]
107. Uttara, B.; Singh, A.V.; Zamboni, P.; Mahajan, R. Oxidative stress and neurodegenerative diseases: A review of upstream and downstream antioxidant therapeutic options. *Curr. Neuropharmacol.* **2009**, *7*, 65–74. [[CrossRef](#)]
108. Davis, K.L.; Kahn, R.S.; Ko, G.; Davidson, M. Dopamine in schizophrenia: A review and reconceptualization. *Am. J. Psychiatry* **1991**, *148*, 1474–1486.
109. Lewis, D.A.; Hashimoto, T.; Volk, D.W. Cortical inhibitory neurons and schizophrenia. *Nat. Rev. Neurosci.* **2005**, *6*, 312–324. [[CrossRef](#)]
110. Back, S.A.; Gan, X.; Li, Y.; Rosenberg, P.A.; Volpe, J.J. Maturation-dependent vulnerability of oligodendrocytes to oxidative stress-induced death caused by glutathione depletion. *J. Neurosci.* **1998**, *18*, 6241–6253. [[CrossRef](#)]
111. Baumann, N.; Pham-Dinh, D. Biology of oligodendrocyte and myelin in the mammalian central nervous system. *Physiol. Rev.* **2001**, *81*. [[CrossRef](#)]
112. Bartos, M.; Vida, I.; Jonas, P. Synaptic mechanisms of synchronized gamma oscillations in inhibitory interneuron networks. *Nat. Rev. Neurosci.* **2007**, *8*, 45–56. [[CrossRef](#)] [[PubMed](#)]
113. Pettersson-Yeo, W.; Allen, P.; Benetti, S.; McGuire, P.; Mechelli, A. Dysconnectivity in schizophrenia: Where are we now? *Neurosci. Biobehav. Rev.* **2011**, *35*, 1110–1124. [[CrossRef](#)] [[PubMed](#)]
114. Zhang, Z.J.; Reynolds, G.P. A selective decrease in the relative density of parvalbumin-immunoreactive neurons in the hippocampus in schizophrenia. *Schizophr. Res.* **2002**, *55*, 1–10. [[CrossRef](#)]
115. Gao, R.; Penzes, P. Common mechanisms of excitatory and inhibitory imbalance in schizophrenia and autism spectrum disorders. *Curr. Mol. Med.* **2015**, *15*, 146–167. [[CrossRef](#)] [[PubMed](#)]
116. Uno, Y.; Coyle, J.T. Glutamate hypothesis in schizophrenia. *Psychiatry Clin. Neurosci.* **2019**, *73*, 204–215. [[CrossRef](#)]
117. Koga, M.; Serritella, A.V.; Messmer, M.M.; Hayashi-Takagi, A.; Hester, L.D.; Snyder, S.H.; Sawa, A.; Sedlak, T.W. Glutathione is a physiologic reservoir of neuronal glutamate. *Biochem. Biophys. Res. Commun.* **2011**, *409*, 596–602. [[CrossRef](#)]
118. Steullet, P.; Cabungcal, J.H.; Monin, A.; Dwir, D.; O'Donnell, P.; Cuenod, M.; Do, K.Q. Redox dysregulation, neuroinflammation, and NMDA receptor hypofunction: A “central hub” in schizophrenia pathophysiology? *Schizophr. Res.* **2016**, *176*, 41–51. [[CrossRef](#)]
119. Dietrich-Muszalska, A.; Kolińska-Lukaszuk, J. Comparative effects of aripiprazole and selected antipsychotic drugs on lipid peroxidation in plasma. *Psychiatry Clin. Neurosci.* **2018**, *72*, 329–336. [[CrossRef](#)]
120. Dakhale, G.N.; Khanzode, S.D.; Khanzode, S.S.; Saoji, A. Supplementation of vitamin C with atypical antipsychotics reduces oxidative stress and improves the outcome of schizophrenia. *Psychopharmacology* **2005**, *182*, 494–498. [[CrossRef](#)]
121. Balijepalli, S.; Kenchappa, R.S.; Boyd, M.R.; Ravindranath, V. Protein thiol oxidation by haloperidol results in inhibition of mitochondrial complex I in brain regions: Comparison with atypical antipsychotics. *Neurochem. Int.* **2001**, *38*, 425–435. [[CrossRef](#)]
122. Miljević, Č.; Nikolić-Kokić, A.; Nikolić, M.; Niketić, V.; Spasić, M.B.; Lečić-Toševski, D.; Blagojević, D. Effect of atypical antipsychotics on antioxidant enzyme activities in human erythrocytes (in vitro study). *Hum. Psychopharmacol. Clin. Exp.* **2013**, *28*, 1–6. [[CrossRef](#)] [[PubMed](#)]
123. Schillevoort, I.; de Boer, A.; Herings, R.M.; Roos, R.A.; Jansen, P.A.; Leufkens, H.G. Risk of extrapyramidal syndromes with haloperidol, risperidone, or olanzapine. *Ann. Pharmacother.* **2001**, *35*, 1517–1522. [[CrossRef](#)]
124. Tollefson, G.D.; Beasley, C.M., Jr.; Tamura, R.N.; Tran, P.V.; Potvin, J.H. Blind, controlled, long-term study of the comparative incidence of treatment-emergent tardive dyskinesia with olanzapine or haloperidol. *Am. J. Psychiatry* **1997**, *154*, 1248–1254.
125. Yolland, C.O.; Hanratty, D.; Neill, E.; Rossell, S.L.; Berk, M.; Dean, O.M.; Castle, D.J.; Tan, E.J.; Phillipou, A.; Harris, A.W.; et al. Meta-analysis of randomised controlled trials with N-acetylcysteine in the treatment of schizophrenia. *Aust. N. Z. J. Psychiatry* **2020**, *54*, 453–466. [[CrossRef](#)] [[PubMed](#)]
126. Pyatoykina, A.S.; Zhilyaeva, T.V.; Semennov, I.V.; Mishanov, G.A.; Blagonravova, A.S.; Mazo, G.E. The double-blind randomized placebo-controlled trial of N-acetylcysteine use in schizophrenia: Preliminary results. *Zhurnal Nevrol. Psikhiatrii Im. SS Korsakova* **2020**, *120*, 66–71. [[CrossRef](#)]

- 
127. Cotton, S.M.; Berk, M.; Watson, A.; Wood, S.; Allott, K.; Bartholomeusz, C.F.; Bortolasci, C.C.; Walder, K.; O'Donoghue, B.; Dean, O.M.; et al. ENACT: A protocol for a randomised placebo-controlled trial investigating the efficacy and mechanisms of action of adjunctive N-acetylcysteine for first-episode psychosis. *Trials* **2019**, *20*, 658. [[CrossRef](#)]
  128. Smesny, S.; Milleit, B.; Schaefer, M.R.; Hipler, U.C.; Milleit, C.; Wiegand, C.; Hesse, J.; Klier, C.M.; Holub, M.; Holzer, I.; et al. Effects of omega-3 PUFA on the vitamin E and glutathione antioxidant defense system in individuals at ultra-high risk of psychosis. *Prostaglandins Leukot. Essent. Fat. Acids* **2015**, *101*, 15–21. [[CrossRef](#)] [[PubMed](#)]