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Implications for reactive oxygen species in schizophrenia pathogenesis

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ABSTRACT

Oxidative stress is a well-recognized participant in the pathophysiology of multiple brain disorders, particularly neurodegenerative conditions such as Alzheimer's and Parkinson's diseases. While not a dementia, a wide body of evidence has also been accumulating for aberrant reactive oxygen species and inflammation in schizophrenia. Here we highlight roles for oxidative stress as a common mechanism by which varied genetic and epidemiologic risk factors impact upon neurodevelopmental processes that underlie the schizophrenia syndrome. While there is longstanding evidence that schizophrenia may not have a single causative lesion, a common pathway involving oxidative stress opens the possibility for intervention at susceptible phases.

1. Introduction

Studies into the etiology and pathogenesis of schizophrenia have implicated a vertiginous array of abnormalities of varied neurotransmitters, cell types, brain regions and epidemiologic associations. One can search the medical literature for most bodily chemicals and find suggestions of tie-ins to schizophrenia. Major lines of research seek to integrate the roles of genetic liability, neurodevelopmental anomalies, aberrant synapse function, and environmental factors such as neonatal infections and substance use, yet the manner in which these distinct factors coalesce into the neurobiology of schizophrenia is largely unknown (Brown, 2011; Keshavan et al., 2011; Tsuang, 2000; van Os et al., 2008). In this review we explore how oxidative stress (and its interrelationship with inflammation) may unify many of these disparate appearing mechanisms. A wide body of evidence finds increased oxidative stress in schizophrenia, including in subjects never previously treated with antipsychotic medication (Emiliani et al., 2014; Yao and Keshavan, 2011). We suggest that many genetic and environmental risk factors for schizophrenia are associated with oxidative stress and inflammation, and outline how these may adversely impact neurodevelopmental and neuromodulatory processes relevant to the neurobiology of schizophrenia.

Eukaryotes generate the bulk of their energy via mitochondria, whose bioenergetic roles include the Krebs cycle, ATP synthesis/oxidative phosphorylation, and oxidation of fatty acids and amino acids. As with most physiologic processes, such metabolism is not 100% efficient and comes with some caveats, particularly the generation of toxic byproducts such as superoxide (O_2^-) and hydroxyl radicals that are prone to damage DNA, enzymes, proteins, lipid, and carbohydrate, among other cellular components. These reactive oxygen species (ROS), broadly referred to as “oxidative stress”, are held in check by families of protective enzymes whose reduction–oxidation (“redox”) reactions convert harmful free radicals into benign, less-reactive molecules. Among these enzymatic families are catalase, the superoxide dismutases, thioredoxins, and over twenty enzymes that utilize glutathione as a cofactor (glutathione peroxidases and glutathione S-transferases). Dysregulation or overwhelming of these protective systems contributes to an increasing number of human diseases in which oxidative stress and inflammation occur, including neurodegenerative disorders such as dementia and amyotrophic lateral sclerosis, and more subtle alterations involved in aging (Haigis and Yankner, 2010; Radak et al., 2011; von Bernhardi and Eugenin, 2012).

Inflammatory processes are exquisitely tied to oxidative stress. The immune system generates lethal quantities of reactive oxygen and nitrogen species to do away with infectious diseases, eliciting inflammation in part via cytokines released by immune cells and microglia. NADPH

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oxidase, for instance, generates superoxide to dispatch with microbes, but at the cost of bystander damage to native tissue (Quinn et al., 2006).

Early development and adolescence are highly dynamic phases of brain development that may be prone to dysfunction that increases the risk of developing schizophrenia (Coyle and Enna, 1976; Crews et al., 2007; Goldman-Rakic and Selemon, 1997; Huttenlocher, 1979; Huttenlocher and de Courten, 1987; Jensen, 2002; Paus et al., 2008; Rakic et al., 1994; Sahara et al., 2012; Tarazi et al., 1998; Thompson and Nelson, 2001; Weinberger, 1987). Myelination, pruning of glutamate synapses, and maturation of interneurons are dynamic processes of this period (Fig. 1). The goal of this review is to highlight how many distinct schizophrenia risk factors converge upon oxidative stress pathways that may perturb neurobiology relevant to schizophrenia.

2. Many schizophrenia risk factors converge upon oxidative stress and inflammation

Environmental influences have long been implicated as schizophrenia risk factors, as identical twins have a 50% concordance rate for schizophrenia and first degree relatives have a 5–10% risk. Important environmental risks include prenatal and birth complications such as hypoxia, neonatal infections, season of birth, drug abuse and autoimmune disease (Brown, 2011). How is it that such vastly different risk factors can increase the risk of schizophrenia? One potential explanation is that these heterogeneous risk factors all are associated with increased in oxidative stress and inflammation. This perturbation of oxidative stress, especially during sensitive stages of brain development, may adversely impact the brain circuitry relevant to development

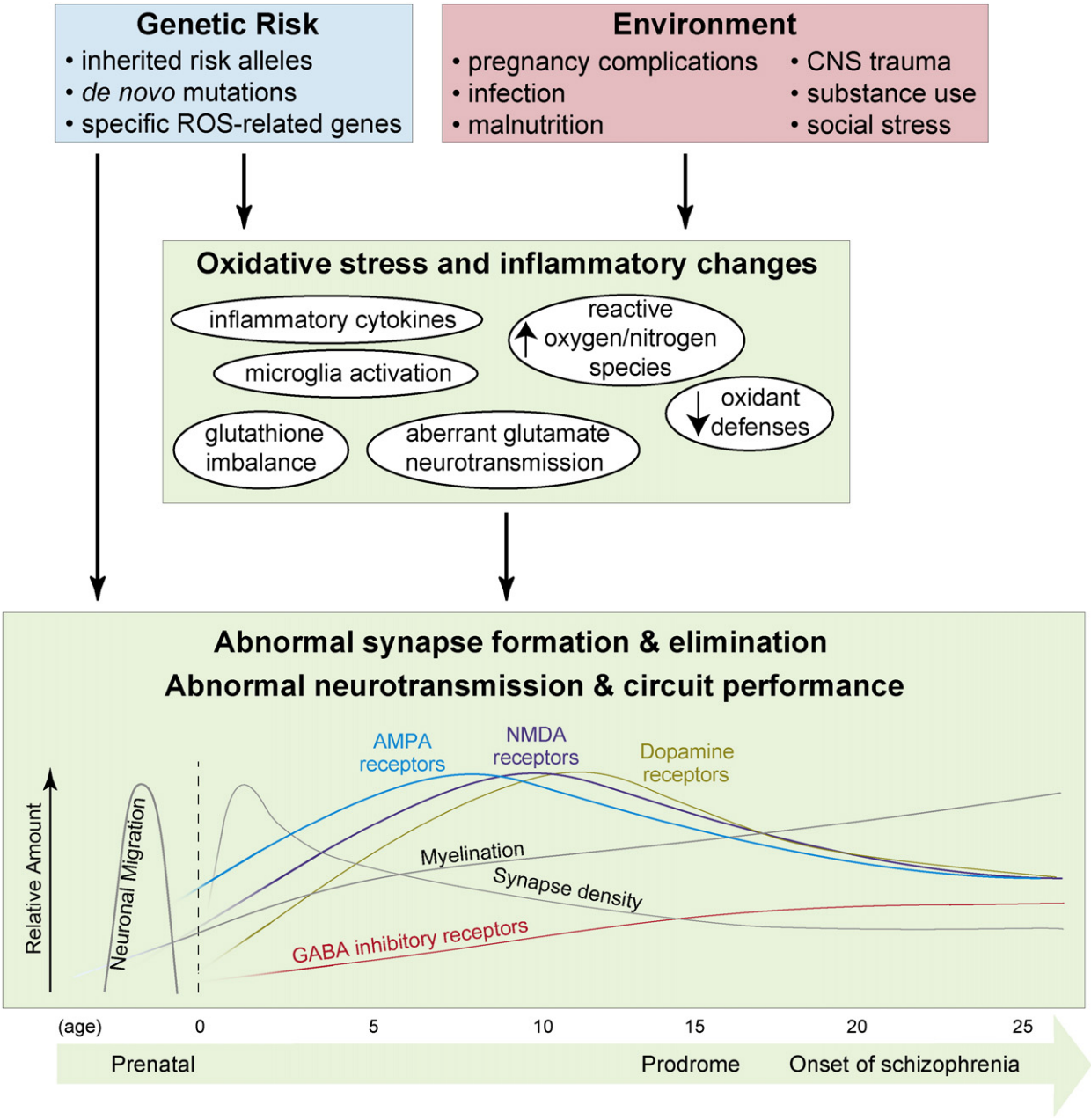

Fig. 1. Redox homeostasis bridges schizophrenia risk factors to brain abnormalities in schizophrenia. Impaired redox homeostasis may be impacted upon by genetic, epigenetic and environmental factors. Such redox abnormalities may impact upon brain abnormalities relevant to schizophrenia, including neurodevelopment, synapse formation, and neurotransmission. The 5:1 ratio of glutamate:GABA neurons is not shown to scale.
Graph compiled from Coyle and Enna (1976), Insel et al. (1990), Tarazi and Baldessarini (2000), Thompson and Nelson (2001), Ewald and Cline (2009), and Huttenlocher (1979).

of schizophrenia (Fig. 1). Inflammatory cytokines elicited by infection, such as TNF-alpha, interleukin-1 (IL-1) and IL-10 utilize NADPH oxidase to generate ROS, activate inflammatory transcription factors such as NF-κB, and produce cellular damage (Ramana and Srivastava, 2010). Inflammatory cytokines appear to be upregulated in postmortem schizophrenia brains (Saetre et al., 2007), and activated microglia can release glutamate and quinolinic acid in quantities sufficient for excitotoxicity and cell death (Smith and Maes, 1995).

Psychosocial stress is increasingly recognized to alter oxidative stress and inflammatory pathways. Socially isolated rat pups develop deficits in prepulse inhibition (PPI), recognition memory, social behavior and anti-inflammatory cytokines, effects which could be reversed by the antipsychotic clozapine and the antioxidant NAC, with less robust effects by either treatment alone (Moller et al., 2013). In mice with deficient NMDA receptors in GABA neurons (a model of schizophrenia-relevant glutamatergic dysfunction), social isolation led to increased ROS and behavioral abnormalities (Jiang et al., 2013). Treatment with apocynin, which neutralizes ROS, improved behavioral phenotypes.

Substance abuse has also been repeatedly implicated as a schizophrenia risk factor (Archer, 2011). Ketamine and PCP have long been invoked as models of pharmacologically induced psychotic symptoms. These agents inhibit the NMDA glutamate receptor and increase reactive nitrogen and oxygen species as part of their mechanism of action (Fantin et al., 2007; Fejgin et al., 2008; Zuo et al., 2007).

In subjects without a family history of schizophrenia, place and season of birth were found to account for quantitatively more cases of schizophrenia in a large Danish study (Cantor-Graae and Pedersen, 2007; Mortensen et al., 1999). Both low and high vitamin D levels are associated with increased risk of schizophrenia, and have been proposed to mediate the season of birth data (McGrath et al., 2003, 2010). In a study of obese children ages 7–14, lower vitamin D levels were associated with increased markers of oxidative stress (Codoner-Franch et al., 2012).

Increased levels of antibody to *Toxoplasma gondii* have been identified in samples obtained from individuals with first-episode schizophrenia (Yolken et al., 2001, 2009). Offspring of mothers with high antibody titers against herpes simplex virus 2 also had an increased risk of psychosis (Buka et al., 2001). Residents of Greater Helsinki, Finland, whose mothers were exposed to the 1957 influenza epidemic, had a significantly elevated risk of developing schizophrenia (Mednick et al., 1988). The maternal influenza association has also been observed in populations in England, Wales (O'Callaghan et al., 1991), and Tokyo (Kunugi et al., 1995). Individuals with autoimmune diseases such as Sjogren's syndrome, celiac disease, iridocyclitis, autoimmune hepatitis, and multiple sclerosis have a higher prevalence of schizophrenia (Benros et al., 2012; Eaton et al., 2006; Jackson et al., 2012).

3. Redox alterations in schizophrenia

Multiple lines of evidence have identified increased oxidative stress in subjects with schizophrenia (Table 1). These studies measure free radicals, oxidative damage to cellular components, or levels of protective antioxidant enzymes and cofactors. A variety of patient samples have been studied, including blood, urine, cerebrospinal fluid (CSF), postmortem brain, and magnetic resonance spectroscopy of live human subjects with and without medications.

3.1. Markers of antioxidant status and oxidative damage

A major approach to characterize oxidative stress is to directly measure the byproducts following free radical damage to cellular components such as proteins, lipids, and DNA. The brain is especially enriched in lipid, which accounts for 40, 60, and 80% of the dry weight of gray matter, white matter, and myelin (O'Brien and Sampson, 1965). Multiple studies have identified increased lipid oxidation products such as malonaldehyde in schizophrenia, as measured by thiobarbituric acid reactive substances (TBARS), in platelets, erythrocytes, urine, and serum/plasma (Table 1). However, others report no change in TBARS in plasma samples (Ranjekar et al., 2003), and decreased TBARS in the CSF of neuroleptic-free patients (Skinner et al., 2005). Increased isoprostanes, byproducts of arachidonic acid oxidation, have been noted in the urine of schizophrenia patients (Dietrich-Muszalska and Olas, 2009a). Increases in the lipid oxidation products, pentane (Phillips et al., 1993) and ethane (Puri et al., 2008), have been reported in patient breath samples. TBARS and protein carbonyls were similarly elevated in younger patients with schizophrenia and patients with longstanding illness (Pedrini et al., 2012). However the analysis used broadly defined terms as early stage as within 10 years of diagnosis and late stage as more than 10 years of illness. Vitamin B6 (pyridoxal), which may have an inhibitory role on protein oxidation, was decreased in schizophrenia relative to controls, and increased with clinical improvement, but failed to do so in treatment nonresponders (Arai et al., 2010; Katsuta et al., 2014). In the same studies, pentosidine, a byproduct of protein oxidation was found to increase in response to association with antipsychotic level in a subset of subjects.

A number of assays (TAC and FRAP) can be utilized to measure nonspecific antioxidant capacity of plasma, with several reports finding decreases in schizophrenia subjects (Chittiprol et al., 2010; Dietrich-Muszalska and Kontek, 2010; Pazvantoglu et al., 2009; Uma Devi et al., 2008; Ustundag et al., 2006; Virit et al., 2009; Yao et al., 1998b; Zhang et al., 2012a), though two identified no differences between patients and controls (Sarandol et al., 2007; Sofic et al., 2002). In a sample from Turkey, deficit syndrome schizophrenia had decreased antioxidant capacity, but not non-deficit cases or controls (Albayrak et al., 2013).

3.2. Glutathione system

Glutathione is the principal cellular antioxidant, its synthesis and metabolism governed by the gamma-glutamyl cycle (Meister and Anderson, 1983). Multiple studies have identified lower glutathione levels in schizophrenia, including decreases of 40% in postmortem caudate nucleus (Yao et al., 2006), 40% in postmortem prefrontal cortex (Gawryluk et al., 2011), 35% in plasma (Dietrich-Muszalska et al., 2009), and 14% in erythrocytes (Altuntas et al., 2000). As glutathione participates in drug metabolism, important confirmatory studies have been performed in medication-naïve schizophrenia subjects, identifying glutathione decreases of 18–26% in erythrocytes (Mico et al., 2011; Raffa et al., 2011) and 28% in plasma (Raffa et al., 2009). Lower glutathione levels also correlated with higher (worse) PANSS symptom scores (Tsai et al., 2013) and worse community functioning (Ballesteros et al., 2013).

Magnetic resonance spectroscopy has been used to quantify in vivo brain glutathione levels in schizophrenia subjects (Rae, 2014). In drug-naïve schizophrenia patients, glutathione levels were decreased by 52% in the prefrontal cortex and 27% in CSF (Do et al., 2000). Under normal circumstances, intracellular levels of glutathione typically exceed extracellular levels by 1000-fold, and this should be taken into consideration when interpreting plasma and CSF measurements. Others found an inverse correlation between negative symptoms of schizophrenia and glutathione levels in the posterior medial frontal cortex—that is, lower levels of glutathione were associated with a greater degree of negative symptoms (Matsuzawa and Hashimoto, 2011). However, this group was unable to find an overall association between glutathione levels and schizophrenia, as was the case for an independent study of glutathione in the anterior cingulate cortex (Terpstra et al., 2005). As magnetic resonance spectroscopy can only sample small areas, additional studies comparing different brain structures are warranted, and would optimally include medication-naive subjects.

Table 1
Studies of the relationship between schizophrenia and oxidative stress.

Gene/molecule of study		Study population	Reference
Measurement of oxidants and antioxidants			
Glutathione	Decreased	Erythrocyte	Altuntas et al. (2000)
	Decreased	Cerebrospinal fluid*	Do et al. (2000)
	Decreased	MRS scanning	Do et al. (2000)
	Decreased	Postmortem brain	Yao et al. (2006)
	Decreased	Plasma*	Raffa et al. (2009)
	Decreased	Plasma	Dietrich-Muszalska et al. (2009)
	Decreased	Plasma	Ruiz-Litago et al. (2012)
	Decreased	Plasma	Raffa et al. (2012a)
	Decreased	Erythrocyte	Mico et al. (2011)
	Decreased	Erythrocyte*	Raffa et al. (2011)
	Decreased	Blood	Gonzalez-Liencres et al. (2014)
	Decreased	Blood	Ballesteros et al. (2013)
	Decreased	Serum	Vidovic et al. (2014b)
	Decreased	Serum	Al-Asmari and Khan (2014)
	Decreased	Serum	Fukushima et al. (2014)
	Decreased, associated with higher PANSS	Serum	Tsai et al. (2013)
	Negative correlation with SANS scores	MRS scanning	Matsuzawa and Hashimoto (2011)
	Increased	MRS scanning	Wood et al. (2009)
	N.S.	MRS scanning	Terpstra et al. (2005)
	N.S.	Cerebrospinal fluid Plasma	Samuelsson et al. (2013)
Superoxide dismutase (SOD)	Decreased expression (SOD1)	Platelet*	Golse et al. (1977)
	Decreased activity	Erythrocyte*	Dadheech et al. (2008)
	Decreased activity	Erythrocyte	Raffa et al. (2012a,b)
	Decreased activity	Plasma	Akyol et al. (2002) and Zhang et al. (2006)
	Decreased activity,	Plasma	Zhang et al. (2013, 2014)
	Decreased activity	Plasma*	Ruiz-Litago et al. (2012)
	Decreased activity	Serum	Gonzalez-Liencres et al. (2014)
	Decreased activity	Serum	Al-Asmari and Khan (2014)
	Decreased activity	Erythrocyte*	Evans et al. (2003) and Mukerjee et al. (1996)
	Decreased activity	Erythrocyte	Ben Othmen et al. (2008), Ranjekar et al. (2003) and Reyazuddin et al. (2014)
	Decreased activity	Platelet	Dietrich-Muszalska et al. (2005)
	Decreased activity	Erythrocyte, Erythrocyte*	Raffa et al. (2009, 2011)
	Decreased expression (SOD1)	Cerebrospinal fluid	Coughlin et al. (2013)
	Increased expression (reversed by risperidone and haloperidol, greater decreases associated with better clinical response)	Blood	Zhang et al. (2012b)
	Increased activity	Blood*	Khan and Das (1997)
	Increased activity	Erythrocyte, Erythrocyte*	Yao et al. (1998a)
	Increased activity	Erythrocyte	Abdalla et al. (1986) Altuntas et al. (2000), Kuloglu et al. (2002), Miljevic et al. (2010b), Reddy et al. (1991) and Zhang et al. (2003)
	Increased activity	Serum	Dakhale et al. (2004)
	Increased expression (Cu–ZnSOD,MnSOD)	Postmortem brain	Michel et al. (2004)
	Increased activity	Serum	Atmaca et al. (2005)
	Increased activity	Serum	Gama et al. (2006)
	Increased activity	Serum	Sarandol et al. (2007)
	Increased activity	Serum	Kunz et al. (2008)
	Increased expression	Serum	Zhang et al. (2009b)
	Increased activity	Plasma	Padurariu et al. (2010)
	N.S. in activity	Polymorphonucleocyte	Srivastava et al. (2001)
Catalase	Decreased activity	Plasma	Ruiz-Litago et al. (2012)
	Decreased activity	Erythrocyte	Ben Othmen et al. (2008) and Ranjekar et al. (2003)
	Decreased activity	Erythrocyte, Erythrocyte*	Raffa et al. (2011) and Raffa et al. (2009)
	Decreased activity	Blood	Raffa et al. (2012a)
	Increased activity	Erythrocyte	Herken et al. (2001b)
	Increased activity	Erythrocyte*	Evans et al. (2003)
	Increased activity	Serum	Atmaca et al. (2005)
	Increased activity	Serum	Al-Asmari and Khan (2014)
	N.S. in activity	Polymorphonucleocyte	Srivastava et al. (2001)
	N.S. in activity	Plasma	Miljevic et al. (2010a)
Glutathione peroxidase	Decreased in activity in only women. N.S. in men.	Erythrocyte*	Abdalla et al. (1986)
	Decreased activity	Plasma	Zhang et al. (2006)
	Decreased activity	Postmortem brain	Yao et al. (2006)
	Decreased activity	Erythrocyte*	Raffa et al. (2009)
	Decreased activity	Erythrocyte	Raffa et al. (2009)
	Decreased activity	Plasma	Miljevic et al. (2010a)
	Decreased activity	Plasma	Boskovic et al. (2013a)
	Decreased activity	Erythrocyte	Herken et al. (2001b) and Padurariu et al. (2010)

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Table 1 (*continued*)

Gene/molecule of study		Study population	Reference
	Decreased activity	Erythrocyte*	Reyazuddin et al. (2014)
	Increased activity	Plasma	Zhang et al. (1998)
	Increased activity	Erythrocyte	Altuntas et al. (2000) and Ranjekar et al. (2003)
	Increased activity	Serum	Atmaca et al. (2005)
	Increased activity	Erythrocyte	Raffa et al. (2011)
	N.S. in activity	Polymorphonucleocyte	Srivastava et al. (2001)
	N.S. in activity	Plasma	Akyol et al. (2002)
Glutathione reductase	Increased	Serum	Al-Asmari and Khan (2014)
GST activity	Increased GST activity	Plasma	Uma Devi et al. (2008)
	N.S. in activity	Plasma	Viinamäki et al. (1994)
Vitamins	Decreased vitamin E	Plasma	Dadheech et al. (2008) and McCreadie et al. (1995)
	Decreased vitamin C	Urine	Suboticanec et al. (1990)
	Decreased vitamin C	Plasma	Dakhale et al. (2004)
	Decreased vitamin C	Plasma	Dadheech et al. (2008), Dakhale et al. (2004) and Suboticanec et al. (1990)
	N.S. in Vitamin E and C	Plasma*	Sarandol et al. (2007)
Uric acid	Decreased	Plasma	Yao et al. (1998c)
	Decreased	Plasma*	Reddy et al. (2003)
Bilirubin	Decreased (bilirubin)	Plasma	Wong et al. (1996) and Yao et al. (1998b)
Biopyrrins	Decreased (bilirubin)	Plasma*	Pae et al. (2004a), Reddy et al. (2003) and Vitek et al. (2010)
	Increased (biopyrrins)	Urine	Miyaoka et al. (2005) and Yasukawa et al. (2007)
	Increased (bilirubins)	Plasma*	Bach et al. (2010), Miyaoka et al. (2000) and Radhakrishnan et al. (2011)
Thioredoxin	Increased	Serum	Zhang et al. (2009a)
	N.S.	Serum	Zhang et al. (2013)
Free thiols	Decreased	Platelet	Dietrich-Muszalska and Olas (2009b)
	Decreased	Serum	Huang et al. (2010)
Total antioxidant capacity (TAC)	Decreased TAC	Plasma, plasma*	Yao et al. (1998b)
The ferric reducing ability of plasma (FRAP)	Decreased TAS	Plasma*	Chittiprol et al. (2010), Pazvantoglu et al. (2009) and Ustundag et al. (2006)
Total antioxidant status (TAS)	Decreased FRAP	Plasma	Uma Devi et al. (2008)
Total antioxidant potential (TAOP)	Decreased TAS	Plasma	Virit et al. (2009)
	Decreased TAC	Plasma	Dietrich-Muszalska and Kontek (2010)
	Decreased TAOP	Serum	Albayrak et al. (2013)
	Increased TAS	Serum	Vidovic et al. (2014b)
	N.S. in TAC	Plasma	Sofic et al. (2002)
	N.S. in TAC	Plasma, plasma*	Sarandol et al. (2007)
Oxidative stress-related molecules			
Fatty acid	Decreased (DHA, DPA)	Red blood cell membrane*	Khan et al. (2002) and Reddy et al. (2004)
	Decreased total PUFA	Red blood cell membrane	Arvindakshan et al. (2003b)
	Decreased (DHA)	Erythrocyte*	Evans et al. (2003)
	Decreased (DHA)	Red blood cell membrane	Peet et al. (2004)
	Decreased total PUFA	Red blood cell membrane	Reddy et al. (2004)
	Decreased (DHA)	Red blood cell membrane*	Kale et al. (2008)
	Increased (arachidonic acid, linoleic acid)	Red blood cell membrane*	Khan et al. (2002)
	Increased (DHA)	Cerebrospinal fluid *	Kale et al. (2008)
	Increase in isoprostanes	Urine	Dietrich-Muszalska and Olas (2009a)
Zinc	Decreased	Plasma*	Nechifor et al. (2004)
	N.S. by medication	Plasma	Nechifor et al. (2004)
	N.S.	Plasma	Yanik et al. (2004)
Products by oxidation			
TBARS (lipid oxidation marker)	Increased (TBARS)	Plasma*	Mahadik et al. (1998)
MDA	Increased (TBARS)	Plasma	Akyol et al. (2002), Ben Othmen et al. (2008), Kuloglu et al. (2002) and Mahadik et al. (2001)
	Increased (TBARS)	Erythrocyte	Altuntas et al. (2000) and Herken et al. (2001b)
	Increased (MDA)	Polymorphonucleocyte	Srivastava et al. (2001)
	Increased (MDA)	Erythrocyte*	Evans et al. (2003)
	Increased (MDA)	Erythrocyte	Reyazuddin et al. (2014)
	Increased (TBARS)	Red blood cell membrane	Arvindakshan et al. (2003a,b)
	Increased (MDA)	Serum*	Dakhale et al. (2004)
	Increased (TBARS)	Blood	Al-Chalabi et al. (2009), Dadheech et al. (2008), Evans et al. (1996), Gama et al. (2006), Guliaeva et al. (1988), Kunz et al. (2008), Olincy et al. (1997), Padurariu et al. (2010), Peet et al. (1993), Prilipko and Lideman (1982) and Zhang et al. (2006)
	Increased (MDA)	Plasma	Zhang et al. (2006)
	Increased (MDA)	Plasma	Sarandol et al. (2007)
	Increased (MDA)	Plasma	Gonzalez-Liencres et al. (2014)
	Increased (MDA)	Plasma	Bulbul et al. (2014)
	Increased (MDA)	Serum	Vidovic et al. (2014b)

Table 1 (*continued*)

Gene/molecule of study		Study population	Reference
	Increased (MDA)	Serum	Al-Asmari and Khan (2014)
	Increased (TBARS)	Platelet	Dietrich-Muszalska and Olas (2009b) and Dietrich-Muszalska et al. (2005)
	Decreased (TBARS)	CSF*	Skinner et al. (2005)
	N.S. (TBARS)	Plasma	Ranjekar et al. (2003)
Lipid peroxidation marker	Increased in pentane	Breath	Kovaleva et al. (1989) and Phillips et al. (1993)
	Increased in ethane	Breath	Puri et al. (2008)
Protein oxidation	Increased 3-nitrotyrosine	Plasma	Dietrich-Muszalska et al. (2009)
	Increased carbonyls	Plasma	Boskovic et al. (2013a)
	Increased carbonyls	Serum	Massuda et al. (2013)
	Increased 3-nitrotyrosine	Platelet	Dietrich-Muszalska and Olas (2009b)
	Increased 4-hydroxynonenal	Postmortem anterior cingulate	Wang et al. (2009)
	Decreased protein nitration	Autopsy, prefrontal cortex	Kim et al. (2014)
NO signaling related molecules	Increased NOS activity	Platelet	Das et al. (1995)
	Increased NOS	Postmortem cerebellar vermis	Karson et al. (1996)
	Increased NO	Erythrocyte	Herken et al. (2001a)
	Increased NO_2–	Plasma	Zoroglu et al. (2002)
	Increased NO	Plasma	Akyol et al. (2002)
	Increased nNOS	Postmortem prefrontal cortex	Baba et al. (2004)
	Increased NO	Serum	Taneli et al. (2004)
	Increased NO	Postmortem caudate	Yao et al. (2004)
	Decreased NO	Polymorphonucleocyte	Srivastava et al. (2001)
	Decreased NOS activity	Postmortem cerebral cortex	Xing et al. (2002)
	Decreased NO_2–	Plasma	Yanik et al. (2003)
	Decreased NO_3–	Plasma	Suzuki et al. (2003)
	Decreased NO_2–, NO_3–	Cerebrospinal fluid	Ramirez et al. (2004)
	Decreased nNOS	Hypothalamus	Bernstein et al. (2005)
	Decreased NO	Plasma	Lee and Kim (2008) and Nakano et al. (2010)
Total ROS	Increased	Neural cells from iPS cells	Paulsen et al. (2012)
Superoxide anions	Increased	Platelets	Dietrich-Muszalska and Kwiatkowska (2014)
DNA oxidation	Increased 8OHdG (oxidative DNA) and 8OHG (oxidative RNA)	Urine	Jorgensen et al. (2013)
	Increased 8OHdG (oxidative DNA)	Postmortem brain (hippocampal neurons)	Nishioka and Arnold (2004)
	Increased 8OHG (oxidative RNA)	Postmortem brain (hippocampal neurons)	Che et al. (2010)
AGEs	Increased autofluorescent	Skin	Kouidrat et al. (2013)
Preclinical study			
Antipsychotics	Olanzapine promoted antioxidant effects	PC12	Wei et al. (2003)
	Antipsychotics increased oxidative stress	Rat	Pillai et al. (2007)
	Clozapine, olanzapine, quetiapine, risperidone decreased oxidative stress	PC12	Wang et al. (2009)
N-acetyl cysteine	Reduced inflammatory cytokine and improved myelination in the developing brain of rats	Rat	Beloosesky et al. (2006) and Lante et al. (2007)
	NAC restored cognitive deficits caused by depletion of glutathione	Rat	Choy et al. (2010)
	NAC administration improves cognitive function and oxidative stress levels in EAAT3-KO mice.	Mouse	Cao et al. (2012)
GCL	Decreased glutathione by BSO caused impaired spatial learning and memory	Rat	Cabungcal et al. (2007)
GCL	Glutathione deficit caused anomalies of the brain neural oscillations and neuronal pathology underlying cerebral integration and cognitive functions	Mouse	Steullet et al. (2010)
GCL	Glucose metabolism and glycogen utilization are dysregulated in astrocytes derived from GCL modifier-KO mouse, which show glutathione deficit. Glutathione deficit may cause dysregulation of brain energy production.	Mouse	Lavoie et al. (2011)
Glutathione	Glutathione metabolism may affect the baseline of glutamate levels in neurons.	PC12, HT22, primary neuron	Koga et al. (2011)
Genetic studies			
GCLC	Significant (GAG repeat in 5′-UTR region)	Caucasian	Gysin et al. (2007)
	N.S. (rs534957, rs2397147, rs502862, rs3799695, s1555906, rs761141, rs553822, rs542914, rs670548)	Japanese	Hanzawa et al. (2011)

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Table 1 (*continued*)

Gene/molecule of study		Study population	Reference
GCLM	Significant (rs2301022, rs3170633)	Caucasian, Chinese Han	Gasso et al. (2010) and Tosic et al. (2006)
	N.S. (rs41303970, rs2301022, rs718875, rs3170633)	Japanese	Kishi et al. (2008)
	N.S. (rs41303970, rs2301022)	Japanese	Matsuzawa et al. (2009)
	N.S. (rs41303970, rs2301022, rs718875, rs7549683)	Japanese	Hanzawa et al. (2011)
GSTM1	Significant (null)	Japanese	Harada et al. (2001)
	Significant (null)	Korean	Pae et al. (2004b)
	Significant (null)	Japanese	Saruwatari et al. (2013)
	Gene × Gene interaction (GSTM1-null/GSTT1)	Italian	Gravina et al. (2011)
	Gene × Gene interaction (GSTM1-null/GSTA1)	Italian	Gravina et al. (2011)
	N.S. (null)	Japanese	Matsuzawa et al. (2009)
GSTT1	Significant (non-deletion)	Iranian	Saadat and Ansari-Lari (2007)
	Significant (non-deletion)	Japanese	Saruwatari et al. (2013)
	N.S. (null)	Japanese	Matsuzawa et al. (2009)
GSTT2	Greater than or equal to 1 (≥) copy of both GSTM1 and GSTT2 associated with schizophrenia	Spanish	Rodriguez-Santiago et al. (2010)
	N.S. (GSTT2-Met139Ile)	Japanese	Matsuzawa et al. (2009)
GSTA1	B polymorphism worse hallucination, increased thalamic DTI diffusivity	Italy	Spalletta et al. (2012)
MnSOD	Significant (Ala9Val)	Turkish	Akyol et al. (2005)
	Ala9Val allele worse cognition on RBANS	Chinese	Zhang et al. (2014)
	N.S. (Ala9Val)	Japanese	Hori et al. (2000)
	N.S. (Ala9Val)	Caucasian	Ventriglia et al. (2006)
	N.S. (Ala9Val)	Korean	Pae et al. (2007)
	N.S. (Val16Ala)	Caucasian	Boskovic et al. (2013b)
NOS1	Significant (rs2682826)	Japanese	Shinkai et al. (2004)
	Significant (rs3782219, rs3782221)	Ashkenazi Jewish	Fallin et al. (2005)
	Significant (rs41279104)	Caucasian	Reif et al. (2006)
	Significant (rs3782206, haplotype rs3782206 + rs3837437)	Chinese Han	Tang et al. (2008)
	N.S. (rs2682826, rs3782206, rs2782219, rs3782221, rs41279104)	Japanese	Okumura et al. (2009)
NOS1AP	Significant (D1S1679)	Spanish	Rosa et al. (2002)
	Significant (rs1415263, rs4145621, rs2661818)	Canadian	Brzustowicz et al. (2004).
	Significant (rs348624)	Chinese Han	Zheng et al. (2005)
GPX1	N.S. (Pro200Leu)	Caucasian	Boskovic et al. (2013b)
CAT	N.S. (262 C>T)	Caucasian	Boskovic et al. (2013b)
TNF	N.S. (308 G>A)	Caucasian	Boskovic et al. (2013b)

* Drug-naïve patients.

Gamma-glutamyl cysteine ligase (GCL) is the rate-limiting enzyme of the glutathione production and is composed of catalytic (GCLC) and modifier (GCLM) subunits, each of which has been investigated as a potential genetic risk factor for schizophrenia. In a Caucasian population, 5′ UTR repeat polymorphisms of *GCLC* were associated with schizophrenia and decreased levels of GCL and glutathione (Gysin et al., 2007). An independent study in a Japanese population examined single nucleotide polymorphisms (SNPs) of *GCLC*, and did not find an association with schizophrenia (Hanzawa et al., 2011), although a different methodology was used that may not have been able to distinguish the 6 different GCLC genotypes (Kulak et al., 2013).

SNPs of the *GCLM* gene have also been associated with schizophrenia in Caucasian (Tosic et al., 2006) and Han Chinese populations (Gasso et al., 2010). Expression levels of the *GCLM* gene were decreased in the fibroblasts of schizophrenia patients who carried the risk allele in a Danish population. The authors suggest that the activity of GCL decreased due to the polymorphisms, consequently leading to decreases in glutathione levels. However, these and several other SNPs of *GCLM* were not associated with schizophrenia in three independent studies of Japanese patients (Hanzawa et al., 2011; Kishi et al., 2008; Matsuzawa et al., 2009). It is possible that the candidate SNPs of Tosic and Ma, rs2301022 and rs3170633, may be population specific, but this will remain unclear until there are additional genotyping studies for the SNPs in this gene in additional populations.

Glutathione peroxidases are an important multigene antioxidant enzyme family that utilizes glutathione to convert hydrogen peroxide into water. Multiple investigators have examined glutathione peroxidase levels in erythrocytes and plasma of schizophrenia subjects, with several studies finding decreased levels (Herken et al., 2001b; Miljevic et al., 2010a; Padurariu et al., 2010; Yao et al., 2006; Zhang et al., 2006) and an additional study finding the decrease only in women (Abdalla et al., 1986). However, the overall pattern has been mixed, with others reporting increases (Altuntas et al., 2000; Atmaca et al., 2005; Raffa et al., 2011; Ranjekar et al., 2003; Zhang et al., 1998) or no change in glutathione peroxidase (Akyol et al., 2002; Srivastava et al., 2001). Glutathione peroxidase activity was decreased in unmedicated schizophrenia patients relative to controls (Raffa et al., 2009). However, the same group found higher activity in first-episode schizophrenia patients (Raffa et al., 2011). Longitudinal studies may clarify whether individual differences explain these changes, or whether there are dynamic changes in cytoprotective enzymes at different stages of the illness. Additional studies are needed for neural tissue and unmedicated subjects, though one report notes decreased glutathione peroxidase in the caudate nucleus of postmortem brain in schizophrenia (Yao et al., 2006).

Glutathione-S-transferases (GSTs) play antioxidant and drug/xenobiotic metabolism roles, utilizing glutathione as a co-factor. This large gene family has over 20 members in humans, divided among multiple isoforms that vary in their expression patterns and substrate specificity

(alpha, kappa, mu, omega, pi, theta, zeta and microsomal). Although no direct measurements of oxidative stress were made, two studies examined the activity of glutathione S-transferase, one finding no change (Viinamäki et al., 1994), and another increased activity (Uma Devi et al., 2008). Genetic association studies suggest there are schizophrenia-associated alleles of *GSTM1* (Harada et al., 2001; Matsuzawa et al., 2009; Pae et al., 2004b) and *GSTT1* (Saadat and Ansari-Lari, 2007). A copy number variation approach found at least 1 copy of both *GSTM1* and *GSTT2* associated with schizophrenia (Rodriguez-Santiago et al., 2010). Another reported association of with specific combinations of GST alleles, such as *GSTM1* null and polymorphisms in *GSTA1* (Gravina et al., 2011). However, a study in a Japanese schizophrenia population could find no association of multiple GST family members (Matsuzawa et al., 2009). Microarray analysis of olfactory neuron progenitors from schizophrenia subjects has also identified increases in *MGST1* expression (Kano et al., 2013). Increased severity of auditory hallucinations has been associated with the GSTA1*B allele (Spalletta et al., 2012) as well as obesity in schizophrenia when GSTM1 null (Saruwatari et al., 2013).

3.3. Catalase

Hydrogen peroxide is prevented from decomposing into harmful radicals through the action of catalase, which converts it into water and oxygen. Catalase levels were decreased in erythrocytes of chronic schizophrenia subjects (Ben Othmen et al., 2008; Ranjekar et al., 2003) as well as recent-onset, unmedicated cases (Raffa et al., 2011). Others report increased catalase in erythrocytes (Herken et al., 2001b), and unchanged levels in neutrophils and plasma (Miljevic et al., 2010a; Srivastava et al., 2001), suggesting that patient erythrocytes are more likely to show decreases, though the reason for this remains unclear.

3.4. Superoxide dismutase

Superoxide dismutase (SOD) is an important neuroprotective enzyme that converts harmful superoxide radicals (O_2^-) to the less toxic, hydrogen peroxide (H_2O_2). Three major SOD forms exist (Fukai and Ushio-Fukai, 2011). Soluble SOD1 (i.e., cytosolic SOD) has a number of mutations associated with amyotrophic lateral sclerosis. SOD2 (manganese-SOD) is localized to mitochondria, and mutations have been linked to cardiomyopathy, motor neuron disease and cancer. An extracellular form, SOD3, is the most abundant form, especially in peripheral tissues, and has been linked to heart and lung disease (Ganguly et al., 2009; van Deel et al., 2008).

Multiple investigators have assessed protein levels and enzymatic activity of superoxide dismutase (SOD) in schizophrenia subjects, however the results have been mixed. Roughly similar numbers of studies find decreased and increased SOD levels or enzymatic function in erythrocytes, neutrophils, and plasma from schizophrenia subjects (Table 1). How can these varying reports be reconciled? While reasonable attempts are often made to control for environmental influences, such as tobacco use, this is not always the case.

One means to potentially disentangle contradictory findings would be for longitudinal studies to determine if antioxidant enzymes are induced or suppressed in different phases of the disease, and to utilize medication free subjects. Erythrocytes from 36 drug-naïve, recent-onset schizophrenia patients had significantly decreased SOD levels compared to controls (Raffa et al., 2011). CSF from recent-onset schizophrenia subjects also demonstrated significantly reduced levels of soluble superoxide dismutase-1 (SOD1) compared to samples from age-matched healthy controls (Coughlin et al., 2013). The iron-binding molecules, ferritin and transferrin, were also significantly decreased in schizophrenia CSF. Iron also holds special relevance in free radical biology as free iron catalyzes the Fenton reaction, which generates highly toxic hydroxyl radicals from hydrogen peroxide. A 12-month study of 49 first episode subjects examined SOD, and multiple other parameters (Ruiz-Litago et al., 2012). 1 and 6 months after the first episode, levels of SOD, glutathione, and total antioxidant decreased further, then recovered by 12 months (the oxidative product TBARS did the reverse, increasing then recovering). Catalase had an initial decrease at 1 month, but recovered at 6 and 12 months. Interestingly, glutathione peroxidase decreased without recovery. Unfortunately, no control subjects participated.

There does not yet appear to be an easy genetic explanation for SOD2 changes in schizophrenia. The Ala9Val polymorphism in SOD2 was associated with schizophrenia in a Turkish population (Akyol et al., 2005), and worse RBANS cognition scores (Zhang et al., 2014). However, Ala9Val and Val16Ala SOD2 alleles were not associated with schizophrenia in Japanese, Korean, or Caucasian groups (Boskovic et al., 2013b; Hori et al., 2000; Pae et al., 2007; Ventriglia et al., 2006).

3.5. Nitric oxide

The free radical, nitric oxide (NO), can act as a neurotransmitter and modulate many processes, including neuronal proliferation, migration, axonal outgrowth, synaptogenesis, synapse plasticity, and formation of neural maps (Contestabile, 2000; Gallo and Iadecola, 2011; Truman et al., 1996). Nitric oxide is synthesized on demand by nitric oxide synthase (NOS) from the amino acid arginine, including after activation of glutamatergic NMDA receptors. NOS and its binding partner, CAPON, have emerged as candidate schizophrenia susceptibility genes (Brzustowicz et al., 2004; Eastwood, 2005; Zoubovsky et al., 2011). Several studies have identified SNPs of neuronal NOS (nNOS or NOS1) associated with risk of schizophrenia (Fallin et al., 2005; Reif et al., 2006; Shinkai et al., 2004; Tang et al., 2008), though one study did not replicate an association in a Japanese population (Okumura et al., 2009).

NOS1 is targeted to synapses by binding to the protein PSD95, an interaction that is regulated by NOS1AP, also known as CAPON (Brzustowicz et al., 2004; Eastwood, 2005; Jaffrey et al., 2002; Zoubovsky et al., 2011). A microsatellite marker located near the NOS1AP locus, D1S1679, was associated with schizophrenia in 8 Spanish nuclear families (Rosa et al., 2002). A Canadian study of 15 SNPs of NOS1AP identified three to be significantly associated with schizophrenia (Brzustowicz et al., 2004). A study in a Chinese Han population identified an additional schizophrenia-associated SNP of NOS1AP, rs348624, that was distinct from the Canadian study finding (Zheng et al., 2005).

The fragile X protein, FMRP, is essential for efficient protein translation of neuronal NOS mRNA and has been found to harbor schizophrenia associated mutations (Fromer et al., 2014; Purcell et al., 2014). Diminished NOS levels may contribute to abnormal circuit formation in neuropsychiatric disorders (Kwan et al., 2012).

In addition to the genetic association of NOS and schizophrenia, NOS levels and NO metabolites, nitrite (NO_2^-) and nitrate (NO_3^-), have also been assessed in patients, although the results have been mixed. A number of reports find decreases in NO-related molecules in schizophrenia. Decreased NOS1 expression was observed in postmortem hypothalamus (Bernstein et al., 2005). Others observed no change in NOS1 and NOS3 expression in prefrontal cortex, though there was an overall decrease in NOS activity (Xing et al., 2002). Decreased NO has been reported in plasma (Lee and Kim, 2008; Nakano et al., 2010) and neutrophils (Srivastava et al., 2001), while decreased NO_2^- & NO_3^- levels were found in patient CSF (Ramirez et al., 2004) and plasma (Suzuki et al., 2003; Yanik et al., 2003). Decreased plasma NO and NO metabolite levels were associated with schizophrenia in a study of 30 schizophrenia subjects and 30 controls. Lower levels were associated with schizophrenia negative symptoms, as measured by PANSS-N, and increased after treatment with the antipsychotic drug, risperidone (Nakano et al., 2010).

By contrast, increased NOS expression levels have been detected in postmortem prefrontal cortex (Baba et al., 2004) and cerebellar vermis of schizophrenia subjects (Karson et al., 1996). NOS activity level was increased in patient platelets (Das et al., 1995). NO and nitrite (NO_2^-) were increased in postmortem caudate nucleus (Yao et al., 2004), and

several blood components including plasma and erythrocytes (Akyol et al., 2002; Herken et al., 2001a; Taneli et al., 2004; Zoroglu et al., 2002). Schizophrenia subjects had increased nitrosative stress damage to plasma proteins (Dietrich-Muszalska et al., 2009) and platelets (Dietrich-Muszalska and Olas, 2009b).

The role of peripheral NO and its metabolites is uncertain. For instance, it is unclear whether peripheral NO has any impact on brain pathways relevant to schizophrenia, especially noting its brief half-life, typically 2–5 seconds. Alternatively one might surmise that any NO imbalance in schizophrenia would be systemic in nature, and not necessarily restricted to the brain. Despite the number of genetic and biochemical reports linking NO to schizophrenia, much remains to be clarified on the association.

3.6. Other metabolites

Multiple additional antioxidant molecules have been assessed in schizophrenia subjects, including vitamin C, vitamin E, bilirubin, albumin, and uric acid, all of which possess antioxidant functions and have been found to be decreased in patient plasma (Table 1). Bilirubin, at physiologic concentrations, is the most potent lipid antioxidant known, and is associated with improved outcomes in cardio- and cerebrovascular disease (Sedlak and Snyder, 2004; Stocker et al., 1987). Decreased bilirubin levels were associated with schizophrenia, including medication naïve subjects (Pae et al., 2004a; Reddy et al., 2003; Vitek et al., 2010). Increases in biopyrrins, an oxidized bilirubin byproduct, have also been reported (Miyaoka et al., 2005; Yasukawa et al., 2007). Others have suggested an association of schizophrenia with Gilbert Syndrome, a condition of benign bilirubin elevation (Bach et al., 2010; Miyaoka et al., 2000; Radhakrishnan et al., 2011), although genetic testing for the syndrome in patients found no such evidence and confirmed decreased bilirubin levels (Vitek et al., 2010).

Poly-unsaturated fatty acids (PUFA) such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) can protect against oxidative stress. Several groups reported decreased DHA in erythrocytes (Evans et al., 2003; Kale et al., 2008; Khan et al., 2002; Peet et al., 2004; Reddy et al., 2004), though the latter found increased levels in CSF. These finding have prompted a number of treatment trials (see Section 6, Potential treatments).

Zinc is an essential catalytic and structural cofactor for many enzymes and other proteins. While it is not directly redox active, under physiologic conditions zinc deficiency is associated with oxidative damage to DNA, protein, and lipids (Eide, 2011). One study found significantly decreased zinc levels in the plasma of 56 drug-naïve schizophrenia subjects (Nechifor et al., 2004), while that and another study found no changes in medicated patients (Yanik et al., 2004).

A meta-analysis assessed TBARS, nitric oxide, catalase, glutathione peroxidase and SOD in schizophrenia. Significantly increased TBARS and nitric oxide were found, with decreases in SOD in disorganized schizophrenia. A high degree of heterogeneity was found across studies (Zhang et al., 2010).

A meta-analysis of 44 studies examined the relation of oxidative stress markers with first episode and established schizophrenia (Flatow et al., 2013). The parameters tested were plasma/serum total antioxidant status, malonaldehyde, TBARS, nitrite, uric acid, and red cell levels of the enzymes SOD, glutathione peroxidase and catalase. The most salient finding was that total antioxidant status (TAS), red cell catalase and plasma nitrite decreased in first episode psychosis, but significantly increased later in the illness: during medicated acute relapses (TAS) and as stable outpatients (catalase & nitrite). Thus these may be "state" markers associated with persistent psychosis, albeit nonspecific in and of themselves. While most of these comparisons were cross sectional studies (e.g., not longitudinal), they did control for tobacco use. Red cell superoxide dismutase were low in first episode psychosis, acute relapse inpatient, and stable outpatients, suggesting this as a candidate stable "trait" marker of schizophrenia. Glutathione peroxidase demonstrated a trajectory of decrease from normal from first episode to treated subjects. The authors only included studies utilizing plasma, serum and red cells, which are all readily obtained but not necessarily the optimal sample regions; there were insufficient numbers of studies to include leukocytes, postmortem brain, MRS or CSF.

4. Neurodevelopment and function of neural pathways relevant to schizophrenia — the impact of ROS

Oxidative stress bridges together multiple risk factors with neurodevelopmental processes relevant to schizophrenia. Differentiation of progenitor stem cells into neurons appears to be regulated by changes in redox molecules. Substrates of proto-oxidative reactions are reported to promote neuronal differentiation, accompanied by metabolic profile shifts towards that of increased oxidative stress and increases in oxidized glutathione (Yanes et al., 2010). Additionally, induced pluripotent stem cells derived from a schizophrenia subjects generated greater ROS levels upon differentiation to neurons (Paulsen et al., 2012) and altered expression patterns of oxidative stress proteins (Brennand et al., 2015).

Evidence of aberrant migration of neuronal progenitors has been described in brain specimens from schizophrenia patients (Arnold et al., 1997; Yang et al., 2011), and by characterization of genetic risk factors for psychosis, such as DISC1 (Kamiya et al., 2005). Non-genetic risk factors might also impact upon neuronal migration by mechanisms that involve oxidative stress. Toxoplasmosis infection of mice harboring a mutant copy of DISC1 has alterations in dendritic spine density among other inflammation-induced neural abnormalities (Abazyan et al., 2010). Maternal immune activation also alters mRNA expression of genes that regulate migration of GABA interneurons from ganglionic eminences to the cortex, including the Distal-less (Dlx) family of transcription factors (Oskvig et al., 2012). Putative biomarkers such as eye tracking abnormalities have been identified in relatives of schizophrenia subjects, and oxidative stress abnormalities may be another such endophenotype, as increased protein carbonyls were also reported in unaffected siblings (Massuda et al., 2013).

Traumatic brain injury (TBI) is associated with an increased risk of schizophrenia. A meta-analysis of 9 studies found a modest odds ratio of 1.65 for increased risk of schizophrenia following TBI, with an odds ratio of 2.8 in those with a family history of schizophrenia (Molloy et al., 2011). Multiple preclinical models implicate oxidative stress and inflammation following TBI (Hicdonmez et al., 2006). TBI results in abnormal migration of neurons, and aberrant axonal and dendritic targeting. These effects may be mediated by altered expression of multiple proteins involved in oxidative stress and inflammation (Kaindl et al., 2007).

4.1. Impact of oxidative stress on neurobiology relevant to schizophrenia

Emerging evidence suggests that ROS, such as superoxide derived from NADPH-oxidase, may serve essential roles in intracellular signaling and neurotransmission (Janssen-Heininger et al., 2008). Hydrogen sulfide, previously thought to be a gaseous toxic byproduct, is also finding expanding signaling roles by direct modification of protein targets in the brain and periphery, directly modifying their sulfhydryl residues (Mustafa et al., 2009; Sen and Snyder, 2010). While redox pathways appear to contribute to normal maintenance of neurotransmission, they may also negatively impact it when unchecked. These aspects may be common principles that bridge oxidative stress disturbances observed in schizophrenia with synapse formation and neurophysiology (Fig. 1).

ROS may also play essential roles in learning and memory processes such as hippocampal long term potentiation (Knapp and Klann, 2002). Mice overexpressing SOD, which removes superoxide, have impaired LTP (Gahtan et al., 1998; Hu et al., 2006; Thiels et al., 2000). While the detailed mechanisms for this pathway are still uncertain, superoxide

does activate a major kinase, ERK, in hippocampal neurons (Kishida et al., 2005). Hydrogen peroxide has also been implicated as a participant in LTP. While high concentrations unsurprisingly lead to impairments in LTP, likely by toxicity, low concentrations may augment NMDA-dependent LTP by a pathway that requires voltage dependent calcium channels (Kamsler and Segal, 2003).

Aberrant glutamate neurotransmission has been implicated in schizophrenia in human and animal models (Javitt, 2007). More recently, exome sequencing of schizophrenia subjects has identified de novo mutations in many genes that affect synaptic function, many of which converge upon glutamate neurotransmission (Fromer et al., 2014; Gulsuner et al., 2013; Purcell et al., 2014). Drugs such as phencyclidine (PCP) and ketamine block NMDA receptors and elicit psychotic symptoms, and postmortem brain samples of schizophrenia patients have decreases of NMDA receptor NR1 subunits and increases in NR2D (Akbarian et al., 1996; Gao et al., 2000; Gordon, 2010). Genetically modified mice with decreased numbers of brain NMDA receptors also demonstrate behavioral alterations relevant to schizophrenia (Belforte et al., 2010; Mohn et al., 1999). PCP decreases glutathione and elicits behavioral abnormalities in mice can also be rescued by treatment with sulforaphane, which induces antioxidant responses (Shirai et al., 2012; Stojkovic et al., 2012). Investigators have sought to mimic diminished NMDA signaling by administering its receptor antagonist MK-801, which increases protein/lipid oxidation and behavior stereotypies, abnormalities that could be improved by treatment with natural antioxidants oleanolic acid and pyrroloquinoline quinone (Ozyurt et al., 2014; Park et al., 2014; Zhou et al., 2014).

Hypofunction of NMDA receptors can be a result of oxidative stress (Do et al., 2009; Keshavan et al., 2011). Pharmacological depletion of glutathione increases oxidation of the NMDA receptor and impairs NMDA-dependent long-term potentiation and paired pulse facilitation (Steullet et al., 2006). Additionally, such NMDA hypofunction can itself lead to increases in oxidative stress, suggesting a bidirectional and possibly feed-forward process (Forder and Tymianski, 2009). Diminished glutathione levels are associated with impaired LTP and paired-pulse facilitation (Almaguer-Melian et al., 2000). One might reason that glutathione deficits simply lead to toxic ROS that impair normal mechanisms of synaptic plasticity. However, as is the case with ROS signaling, glutathione appears to have unexpected roles in regulating neurotransmission. Addition of glutathione can augment NMDA associated depolarization (Janáky et al., 2007; Oja et al., 2000), and even directly elicit neuronal depolarization (Janáky et al., 2007; Varga et al., 1997). There are no known glutathione neurotransmitter receptors and it is not stored in synaptic vesicles. Blockade of NMDA receptors does not affect glutathione neuromodulatory activity, however, glutathione and its metabolites may be candidates to regulate glutamate neurotransmission. Recently, we reported that glutathione can serve as a reservoir of neuronal glutamate, as it is itself, one third glutamate and exists at ~0.2–1 millimolar concentration in the brain (Koga et al., 2011).

The balance between excitatory glutamatergic neurotransmission and inhibitory GABA pathways are an increasingly recognized circuit that may underlie schizophrenia pathophysiology (Lewis et al., 2012; Powell et al., 2012; Yizhar et al., 2011). Loss of the parvalbumin subtype of GABA interneurons (PV-IN) has been found in autopsied brains of schizophrenia patients (Hashimoto et al., 2003). These fast spiking inhibitory interneurons likely play a crucial role in synchronizing gamma rhythms across different brain areas (Cardin et al., 2009; Sohal et al., 2009; Traub et al., 2003). Ketamine appears to reduce expression and staining of the calcium-binding protein parvalbumin in these interneurons, mirroring findings in postmortem schizophrenia brain (Cochran et al., 2003; Keilhoff et al., 2004; Morrow et al., 2007; Rujescu et al., 2006). Additionally, ketamine diminishes the fast-spiking phenotype of these interneurons by generation of superoxide by NADPH oxidase (Behrens et al., 2007). This suggested that oxidative stress, including that generated by ketamine, diminishes parvalbumin expression and the function of this important interneuron family diminished in postmortem schizophrenia brain. The inflammatory cytokine, IL-6, can increase NADPH oxidase activity as well (Behrens et al., 2008). Interneuron population numbers are governed by programmed cell death (apoptosis), a pathway activated by oxidative stress and glutathione depletion (Franco and Cidlowski, 2009; Southwell et al., 2012). Thus, oxidative stress, glutathione, parvalbumin interneurons and cortical EEG synchrony in schizophrenia can be tied together in a single pathway that impacts brain circuitry phenotypes.

PV-IN and other cell types may be a target ripe for clinical intervention, particularly by oxidative stress mechanisms. One animal model that may be useful for dissecting the neurobiology of this pathway involves lesioning the ventral hippocampus of neonatal rodents, which leads to loss of PV-IN in the CA1 pyramidal cell layer and prefrontal cortex 123 days following the lesion (Francois et al., 2009). The glutathione pathway also appears to regulate this pathway. N-acetylcysteine (NAC), which increases glutathione levels, appears to be able to rescue the loss of PV-IN in this model (Cabungcal et al., 2014). Thus NAC had some benefit as a presymptomatic treatment, after the initial lesion but prior to the full onset of symptoms. Knockout mice with a 50% reduction in glutathione exhibit decreased numbers of PV-IN in the ventral hippocampus, accompanied by abnormal gamma-synchrony (Cabungcal et al., 2013; Steullet et al., 2010). In normal human subjects, glutathione levels were associated with mismatch negativity, an electrophysiologic event related potential that is diminished in schizophrenia (Ballesteros et al., 2013). A multivariate statistical analysis suggested interaction of glutathione levels, event related potentials and functional outcomes. Others report that decreased glutathione were associated with decreased 21–40 Hz gamma band power and lower community function in schizophrenia (Ballesteros et al., 2013). The ability of glutathione to function as a glutamate reservoir may also have implications for the interrelations between oxidative stress and event related potentials (Koga et al., 2011).

Another animal model has explored the interaction of oxidative stress/inflammation and psychosocial stress. The former is elicited in juvenile rats by an injection of polyI:C, which elicits a neuroinflammatory response. In adulthood the animals manifested abnormalities in prepulse inhibition (PPI, e.g., a startle response observed in schizophrenia), working memory, and microglia activation, which could be reversed by clozapine treatment (Ribeiro et al., 2013). In a similar approach, neonatal mice received polyI:C, then were exposed to restraint stress at an analogous age to mouse “adolescence”. The two exposures led to impairments in PPI that could be ameliorated by the antioxidant alpha-lipoid acid (Deslauriers et al., 2014).

Roles for astrocytes may also be relevant to oxidative stress and inflammation in schizophrenia. Heme oxygenase is a neuroprotective enzyme that generates the precursor of bilirubin antioxidant, but also prooxidant, iron (Sedlak and Snyder, 2006). Mice overexpressing heme oxygenase-1 in astrocytes had increases in oxidative stress and neuropathologic abnormalities relevant to schizophrenia (Song et al., 2012). The authors identified reductions in *REELIN*, a schizophrenia associated gene, increased dopamine and serotonin in the basal ganglia, reduced dopamine D_1 receptor binding in nucleus accumbens, axodendric pathology, and altered hippocampal cytoarchitecture. The mice also demonstrated attenuated PPI and hyperkinetic behaviors frequently seen in dopamine and glutamate rodent models relevant to schizophrenia.

Following oxidative stress and lipid oxidation, the immune complement system may be triggered to dispose of damaged tissue (Collard et al., 2000). Complement factor H appears to bind the lipid oxidation product, malonaldehyde, where it can attenuate further oxidative stress (Weismann et al., 2011). Intriguingly, a SNP in factor H has been associated with schizophrenia (Boyajyan et al., 2013). Microglia, a macrophage-like brain cell, are activated by complement and this cooperation has participates in synapse elimination and sculpting of brain circuitry (Schafer et al., 2012; Stevens et al., 2007), processes long hypothesized to contribute to schizophrenia pathogenesis. Thus lipid oxidation might provoke excessive complement-mediated synaptic pruning by microglia, a

multistep process that might be therapeutically targets at multiple steps: the oxidative stress, the complement/inflammatory response, and the microglia actions.

4.2. Myelination

White matter deficits have been identified in schizophrenia via neuroimaging modalities (Xu and Li, 2011) and study of post-mortem brain (English et al., 2011). In preclinical models, neonatal infections elicit inflammation and oxidative stress that impairs oligodendrocyte function and myelination (Paintlia et al., 2008; van Os et al., 2008). Treatment with NAC counters the deleterious effects of this inflammation, leading to improved oligodendrocyte functioning, in part through the action of a transcription factor, PPAR (Leisewitz et al., 2008; Paintlia et al., 2008). The PPAR pathway may be an intriguing therapeutic target, as an agonist drug, pioglitazone, has antioxidant and neuroprotective effects on cortical neurons (Gray et al., 2012).

5. Epiphenomena and study heterogeneity

Are changes in ROS causative lesions that contribute to schizophrenia pathogenesis? Preclinical models mentioned above provide a strong foundation for ROS and inflammation adversely impacting brain development and neurotransmission relevant to schizophrenia, though it will take some time to test all of this in humans. Multiple studies cited have included medication-naïve patients, designated with an asterisk (*) in Table 1, and still support roles for oxidative stress in schizophrenia. Questions have been raised as to whether schizophrenia medications generate some of the observed oxidative stress. Some antipsychotic drugs appear to increase oxidative stress, especially haloperidol (Boskovic et al., 2013a; Dietrich-Muszalska et al., 2013), although results have been fairly inconsistent with other antipsychotics, variably increasing or decreasing oxidative stress (Lepping et al., 2011; Reinke et al., 2004).

An unresolved question is whether oxidative stress and inflammation are markers of psychological distress, but not necessarily causative. Massive inflammatory responses occur in many diseases, though only a few are associated with psychosis-like states (vasculitis, toxoplasmosis). The specific locations of oxidative stress may be the means to reconcile these possibilities (e.g., circuitry specifically relating to symptomatology). There is also a good degree of heterogeneity in study findings that may relate to characterization of tissue sources that do not optimally reflect oxidative stress (e.g., plasma vs. tissue samples, peripheral vs. brain tissue). For instance, plasma levels of glutathione are 1000-fold lower than intracellular levels, where the molecule mainly exerts its action. Additionally, different phases of the illness (prodrome, acute, recovery, chronic) may exhibit different patterns of ROS (Ruiz-Litago et al., 2012).

An important consideration for any study of oxidative stress is to control for tobacco use, a behavior known to increase oxidants (Mur et al., 2004) and oxidative stress (Pignatelli et al., 2001; Yamaguchi et al., 2005). Schizophrenia patients have a 2 to 3 fold higher prevalence of tobacco use than the general population (Dervaux and Laqueille, 2008). Future investigations into the links between oxidative stress and schizophrenia need to carefully control for lifestyle risk factors, such as smoking, illicit drug use, and antipsychotic drug treatment. Tobacco use was associated with increased glutathione in control subjects, but not in schizophrenia, suggesting intrinsic glutathione deficits (Ballesteros et al., 2013). The Flatow meta-analysis found that increased malonaldehyde, and decreased in catalase, glutathione peroxidase, SOD and uric acid, remained associated with schizophrenia when smoking was controlled for (Flatow et al., 2013). Other environmental confounders may also have to be considered. Schizophrenic patients residing in urban settings had increased SOD, glutathione peroxidase and the lipid oxidation product malonaldehyde (Reyazuddin et al., 2014).

6. Potential treatments that impact ROS

For 50 years, dopamine antagonist antipsychotic drugs have remained the mainstay of treatment for all stages of the schizophrenia and the mechanism of action has been closely tied to clinically effective doses correlating with dopamine D2 receptor inhibition (Creese et al., 1976; Seeman et al., 1976), and the ability of pro-dopaminergic drugs to elicit psychotic symptoms. There are some provocative studies suggesting that these drugs may have unexpected effects on oxidative stress and inflammation. Activation of dopamine D2 receptors on astrocytes (a type of glia cell) produces an anti-inflammatory effect, and mice with selective knockout of D2 receptors in astrocytes have exaggerated inflammatory responses (Shao et al., 2013). However, the antipsychotic drug clozapine, a D2 blocker, was reported to diminish microglia activation and have neuroprotective effects in neuron–glia cultures (Hu et al., 2012). Thus further study will be needed to clarify the roles of hyperdopaminergic states and antipsychotic drugs on neuron–glia functions and inflammatory response.

Several trials have assessed antioxidant treatment on schizophrenia (Table 2). Vitamin C, added to antipsychotic drug treatment, has been used in several studies at doses ranging from 0.5 to 4 g/day for up to 8 weeks, leading to improvements in MDA levels and mild improvements in BPRS symptom scale scores (Beauclair et al., 1987; Dakhale et al., 2005; Milner, 1963). While these results are intriguing, they must be balanced by a long history of megadose vitamin trials that have not had substantial impact upon schizophrenia treatment (Vaughan and McConaghy, 1999). There may be any number of unexplored explanations for these findings, including that large doses of vitamin C can have pro-oxidant effects, or its major function is not as an antioxidant, but a cofactor for hydroxylation enzymatic reactions (i.e., leading to scurvy in deficiency states).

Vitamin E, 600–1600 IU per day, did not alter BPRS scores in schizophrenia subjects in multiple studies of varying duration, ranging from 2 weeks to 2 years (Adler et al., 1999; Dorfman-Etrog et al., 1999; Lohr and Caligiuri, 1996). Vitamin E also has pro-oxidant effects at higher doses and worsens outcomes in multiple diseases at such doses (Miller et al., 2005; Soni et al., 2010).

In animal models, the antioxidant DL-alpha-lipoic acid can reverse schizophrenia-relevant behaviors elicited by ketamine injection to mice (Vasconcelos et al., 2015) and restore dopamine, norepinephrine and serotonin levels in aged rats (Arivazhagan and Panneerselvam, 2002). However, a 3 month study of alpha-lipoic acid found improvements in oxidative stress parameters in 38 controls, but not in 18 schizophrenia subjects (Vidovic et al., 2014a). An open label study of 12 non-diabetic schizophrenia patients found 1200 mg/day of alpha-lipoic acid was associated with 2.2 kg weight loss over 10 weeks.

Multiple studies report improved symptom severity scores following administration of poly unsaturated fatty acids (PUFA), which include omega-3 (n−3) fatty acids. n−3 and n−6 fatty acids, added to antipsychotic drug treatment, led to improvements in the Positive and Negative Syndrome Scale (PANSS) and the Scale for the Assessment of Negative Symptoms (SANS) (Arvindakshan et al., 2003a; Mellor et al., 1996; Peet, 2008; Peet and Stokes, 2005). EPA and DHA, specific forms of n−3 fatty acids, improved PANSS scores in several studies when given at doses of 1–4 g/day (Emsley et al., 2002; Peet et al., 2001; Peet and Horrobin, 2002). No benefit on symptoms was reported for n−3 fatty acids (Fenton et al., 2001) or PUFA plus vitamin E (Boskovic et al., 2014), though the later increased oxidized (but not total) glutathione. An open label study combined omega-3 fatty acids, vitamin E, finding decreases in BPRS symptom severity and red cell SOD, however the lack of a control group hampers the interpretation of clinical improvement scales (Sivrioglu et al., 2007). A meta-analysis of seven studies, 168 patients receiving EPA, did not find a significant benefit of add on EPA treatment, though the overall trend was to improvement with $p = 0.08$. Similar trends have been noted in trials of PUFA for depression, analysis of which has been complicated by publication bias and a

Table 2
Clinical trials targeting ROS mechanisms in schizophrenia.

Molecule of study	Findings	# Subjects	Reference
Ascorbic acid (vitamin C)	Improved psychotic and mood symptoms in chronic schizophrenia (1 g/day for 3 weeks)	20	Milner (1963)
	Improved BPRS and CGI scores (Increasing doses from 1–8 g/day over 8 weeks)	13	Beauclair et al. (1987)
	Clinical improvement with add-on vitamin C to neuroleptic treatment in 1 patient	1	Sandyk and Kanofsky (1993)
	Improved MDA and ascorbic acid levels; improved BPRS scores (0.5 g/day, 8 weeks)	40	Dakhale et al. (2005)[a]
	N.S. change in Brief Symptom and Behavioral Disturbance Inventories. Five months of variable dosing of vitamins dependent upon blood levels. Average doses — vitamin A (6000 IU), B1 (1345 mg), B3 (3520 mg), B6 (6223 mg), C (2822 mg), E (204 mg), B12 (25 mg) and folate (5.2 mg).	19	Vaughan and McConaghy (1999)[a]
Alpha tocopherol (vitamin E)	N.S. change in BPRS scores (1600 IU/day, 2 months)	158	Lohr and Caligiuri (1996)[a]
	N.S. change in BPRS scores (1600 IU/day, 2 years)	55	Adler et al. (1999)
	N.S. change in BPRS scores (600 IU/day, 2 weeks)	39	Dorfman-Etrog et al. (1999)
Fatty acids	n−3 fatty acids improved positive symptoms (EPA 171 mg/day and DHA 114 mg/day, 6 weeks)	20	Mellor et al. (1996)
	n−3 fatty acids (EPA/DHA 360:240 mg/day) in combination with vitamin C & alpha tocopherol (vitamin C/tocopherol 1 g:800 IU/day, 4 months) improved BPRS and PANSS scores	78	Arvindakshan et al. (2003a)
	n−3 fatty acids (1.2 g/day, 12 weeks) improved PANSS scores.	81	Amminger et al. (2010)[a]
	EPA (3 g/day, 12 weeks) improved PANSS scores.	40	Emsley et al. (2002)[a]
	EPA and DHA (2 g/day each, 3 months) improved PANSS scores. EPA was superior to DHA.	45	Peet et al. (2001)[a]
	EPA (1–4 g/day, 12 weeks) improved PANSS scores. 2 g/day was superior	115	Peet and Horrobin (2002)[a]
	EPA (180 mg/day) and DHA (120 mg/day) with vitamin C (1 g/day) and E (400 IU/day) for 4 month period improved BPRS, SANS, SAS and TBARS	17	Sivrioglu et al. (2007)
	Ethyl EPA (2 g/day, 12 weeks) improved PANSS-negative symptoms and increased glutathione	24	Berger et al. (2008)[a]
	N.S. for effect of ethyl EPA (2d/day, 12 weeks) on BPRS, SANS, CGI, CDSS, GAF, SOFAS, SAS	79	Berger et al. (2007)[a]
	N.S. for effect of ethyl EPA (3 g/day, 16 weeks) on PANSS, M-ADRS, AIMS, S-ARS and CGI	87	Fenton et al. (2001)[a]
	N.S. on symptoms for PUFA + vitamin E		Boskovic et al. (2014)
	N.S. on symptoms for PUFA + alpha lipoic acid (PUFA 3 g/day, alpha lipoic acid 150 mg/day, for	33	Emsley et al. (2014)[a]
	N.S. ($p = 0.08$) for effect of EPA [meta-analysis]	336	Fusar-Poli and Berger (2012)[a]
NAC	Improved mismatch negativity and plasma glutathione levels (2 g/day, 60 days)	11	Lavoie et al. (2008)[a]
	Improved PANSS, CGI, BAS scores (2 g/day, 24 weeks)	140	Berk et al. (2008a)[a]
	Improved PANSS and CGI scores (600 mg/day, 7 days)	1	Bulut et al. (2009)
	Improved multivariate phase EEG synchronization over left parieto-temporal, right temporal, and bilateral prefrontal regions (2 g/day, 60 days)	11	Carmeli et al. (2012)[a]
	Greatest improvement in patients ill 20 years or longer	140	Rapado-Castro et al. (2015)
	improved total and negative symptom PANSS scores, but not positive symptoms scores (NAC 2 g/day for 8 weeks)	42	Farokhnia et al. (2013)[a]
Alpha lipoic acid	Alpha-lipoic acid improved in oxidative stress parameters in 38 controls, but not in 18 schizophrenia subjects (1200 mg/day for 3 months)	56	Vidovic et al. (2014a)
Aspirin	Schizophrenia patients found 4.86 point reduction in PANSS scale scores (1000 mg/day for 3 months)	70	Laan et al. (2010)[a]

[a] Double-blind design.

need for greater numbers of studies using patients with greater severity of symptoms (Bloch and Hannestad, 2012). A double blind randomized trial tested whether antipsychotics could be tapered 2–3 years after a first episode psychosis and replaced with placebo or PUFA plus alpha lipoic acid. No difference was found and the study was terminated early due to the high rate of relapse associated with tapering off the antipsychotic medication (Emsley et al., 2014). However, use of n−3 fatty acids was associated with decreased risk of transition to psychosis in at-risk individuals (Amminger et al., 2010) suggesting need for further exploration in prodromal states.

An emerging treatment avenue for schizophrenia targets pathways involved in oxidative stress and glutamatergic neurotransmission. N-acetylcysteine (NAC) increases levels of brain glutathione by serving as a precursor to cysteine, the rate-limiting resource for glutathione synthesis. Cysteine is also utilized by the glutamate/cysteine (xc-) membrane transporter, increasing the basal or 'ambient' levels of extracellular glutamate (i.e., the baseline quantity of synaptic and extrasynaptic glutamate prior to neurotransmitter release). While these levels of 'ambient' extracellular glutamate (~2 μM) are small relative to the concentrations following glutamate neurotransmitter release (~2000 μM), small changes in their levels can exert significant effects. NAC is proposed to increase extracellular glutamate that stimulates presynaptic metabotropic glutamate receptors (mGluR2/3), leading to an inhibition of excitatory neurotransmission (Kalivas, 2009; Moran et al., 2005). Additionally 'ambient' glutamate can directly stimulate NMDA receptors and also desensitize ionotropic (AMPA & kainate) glutamate receptors (Featherstone and Shippy, 2008; Sah et al., 1989). NAC treatment also impacts animal behavior, reducing cocaine cravings in addiction models (Moran et al., 2005) and reducing inflammatory cytokine after brain infections (Beloosesky et al., 2006; Lante et al., 2007). NAC also recovers cognitive function in rats after glutathione depletion (Choy et al., 2010).

Clinical trials in humans also show promise for NAC. In a study of 140 schizophrenia subjects, 2 g/day of NAC led to improved PANSS scores (Berk et al., 2008a). The strongest effect was in subjects who had been ill 20 years or longer, with positive and functional symptoms showing the greatest benefit (Rapado-Castro et al., 2015). In a double blind, placebo controlled add-on study to risperidone, NAC improved total and negative symptom PANSS scores, but not positive symptoms scores (Farokhnia et al., 2013). NAC also led to improved depression symptoms in 76 subjects with bipolar disorder (Berk et al., 2008b).

Abnormal gamma rhythm synchrony has been found in multiple studies of SZ subjects (Cho et al., 2006; Spencer et al., 2003; Uhlhaas et al., 2006). In a study of 11 SZ subjects, treatment with NAC for 2 months resulted in improved EEG synchrony (Carmeli et al., 2012). Mismatch negativity, a type of auditory evoked potential identified in human schizophrenia subjects, also improved following 60 days of treatment with 2 g/day of NAC (Lavoie et al., 2008).

A double blind placebo controlled study of aspirin (1000 mg/day, 3 months) in 70 schizophrenia patients found 4.86 point reduction in PANSS scale scores (Laan et al., 2010). Given the risk of bleeding from aspirin, additional studies are warranted to confirm this, especially as patients with alterations in immune function had a greater improvement.

7. Conclusions

While ongoing genetic and environmental studies seem to substantiate a long held believe that schizophrenia is not a single disease entity, the question remains as to how so many disparate susceptibilities and mechanisms can elicit a common syndrome. Here we suggest that oxidative stress may be a means to tie together many reproducibly identified risk factors and pathogenic mechanisms. Aberrant neuronal migration, synapse formation, myelination and neurotransmission have all been linked to schizophrenia, and each can be adversely impacted upon by oxidative stress.

Kraepelin considered schizophrenia to have features of an early-onset dementia. It remains an open question as to whether the oxidative stress has a transient impact at crucial developmental stages or has a cumulative effect. However, it does not seem to be of the quantity encountered in Alzheimer's and Parkinson's diseases. Additionally, after the illness reaches a stable phase, schizophrenia symptoms and cognitive impairment do not progressively worsen (Hedman et al., 2012).

ROS may lead to pathophysiological abnormalities by several mechanisms. First, there may be direct damage elicited by inflammation or hypoxia. Second, genetic or environmental influences may deplete antioxidant reserves, leading to ROS susceptibility in the brain, and possibly periphery, where abnormalities may be more easily measured. A "second hit" from additional genetic or environmental influences may impact upon brain development and functioning, crossing a threshold to lead to clinical phenotypes or milder endophenotypes. Finally, ROS signaling, including the NMDA pathway, appears to contribute to normal neurotransmitter signaling that may influence information processing. ROS abnormalities here may also impact upon illness susceptibility and phenotype. Cardiovascular disease remains a major source of morbidity in schizophrenia, and oxidative stress and inflammation markers appear to be associated with its severity (Assies et al., 2014; Vidovic et al., 2014b).

These models have direct relevance for validating novel therapeutic approaches to schizophrenia. The idea that schizophrenia may be a multi-step process that leads to a full blown syndrome is currently not reflected well in schizophrenia treatment. Antipsychotic medication remains the mainstay pharmacotherapy for all stages of the disorder (Fig. 2). This suggests a need for increasing primary prevention efforts for at risk individuals via medication and behavioral intervention. As an analogy, one may consider cardiovascular disease, whose multi-step pathogenesis is fairly well understood and distinct approaches are utilized at different stages of the disorder. For instance, managing cholesterol, HDL/LDL and platelet adhesion are important at all phases, beta blockers and nitrodilators for acute infarction and managing cardiac demand, and diuretics/inotropes for congestive heart failure.

Oxidative stress mechanisms may be ripe for intervention in schizophrenia. Two key phases may be especially relevant. Fetal brain development may be perturbed by oxidative stress from genetic susceptibility or environmental factors such as hypoxia or infection, contributing to schizophrenia risk. Intervention here would be more difficult to broadly implement, but if eventually proven utile, would relate to prenatal care and management of known epidemiologic risk factors of schizophrenia.

A second relevant phase is late adolescence, the age with which schizophrenia onset is most likely to occur. Schizophrenia afflicts 1% of the population and extracts massive tolls via direct costs to the healthcare system, and by an individual becoming ill and frequently unable to work just at the cusp of adulthood (Wu et al., 2005). Considerable brain maturation takes place, including synaptic pruning, myelination and dynamic changes in excitatory glutamatergic and inhibitory GABA synapses (Fig. 1). Modulating oxidative stress pathways here may also offer impact upon onset and severity of the illness. At later, chronic phases of the illness, designer cocktails that target known genetic lesions and specific cognitive/affective deficits would also be feasible targets.

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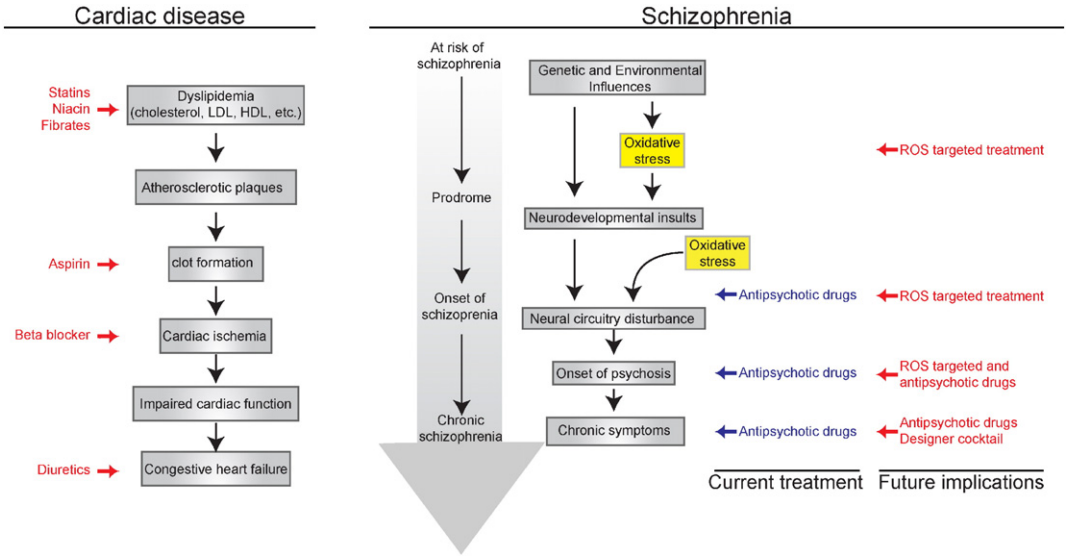

Fig. 2. Current medication treatment paradigms in cardiac disease and schizophrenia. Current pharmacotherapy for schizophrenia primarily utilizes antipsychotic medication at all stages of the illness. By contrast, the rich understanding of the pathogenesis of cardiovascular disease has led to different treatment emphases at different phases. With increasing knowledge of pathogenic mechanisms in schizophrenia, targeting common oxidative stress events and pathways impacted by genetic abnormalities may influence future treatment.

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