CHAPTER

28

Role of Redox Dysregulation in White Matter Anomalies Associated with Schizophrenia

Aline Monin[*,§,#], *Margot Fournier*[*,§,#], *Philipp S. Baumann*[*,§,¶], *Michel Cuénod*[*,§], *Kim Q. Do*[*,§]

[*]Center for Psychiatric Neuroscience, Centre Hospitalier Universitaire Vaudois and University of Lausanne (CHUV-UNIL), Prilly-Lausanne, Switzerland; [§]Department of Psychiatry, Centre Hospitalier Universitaire Vaudois and University of Lausanne (CHUV-UNIL), Prilly-Lausanne, Switzerland; [¶]Service of General Psychiatry, Centre Hospitalier Universitaire Vaudois and University of Lausanne (CHUV-UNIL), Prilly-Lausanne, Switzerland

INTRODUCTION

Schizophrenia is a neurodevelopmental disorder appearing in adolescence or early adulthood resulting from both genetic and environmental risk factors. Despite a high heritability (estimations range between 40% and 60%), monogenic causes cannot account for the cases, leading to the hypothesis of an interaction between genes and environment. Adverse events during prenatal life, perinatal life, childhood, or adolescence have been associated with the illness (Brown, 2011; van Os, Rutten, & Poulton, 2008; Schmitt, Malchow, Hasan, & Falkai, 2014). The delay between occurrence of these events and illness onset has led to the concept of a neurodevelopmental disorder (Catts et al., 2013; Insel, 2010; Weinberger, 1987). Interestingly, schizophrenia coincidentally develops with maturation of the prefrontal cortex (Fuster, 2002; Hoistad et al., 2009): volume of white matter in this region progresses through adolescence to reach a maximal volume in the third decade of life (Bartzokis et al., 2001; Lenroot & Giedd, 2006).

Imaging studies implicated anomalies of the prefrontal cortex in schizophrenia. Clinical manifestations of the illness, including cognitive symptoms, are hypothesized to reflect abnormal brain connectivity. This disconnectivity can result from disturbances of long-range neuronal circuits (i.e., white matter tracts) or of local circuits (i.e., GABAergic and glutamatergic system) (Ruiz, Birbaumer, & Sitaram, 2013; Schmitt, Hasan, Gruber, & Falkai, 2011; Steullet et al., 2014), both of which have been involved in schizophrenia. At the neuropathological level, alterations of oligodendrocytes and myelin appear as clear findings in schizophrenia. Because myelin influences conduction velocity, an impairment of myelination process would disrupt temporal coordination between distant brain regions, affect their synchrony, and thus lead to disconnectivity (Whitford, Ford, Mathalon, Kubicki, & Shenton, 2012).

Current works from our laboratory and others suggest that interactions of genes and environment during neurodevelopment converge to induce redox dysregulation and oxidative stress in schizophrenia (Do, Cabungcal, Frank, Steullet, & Cuenod, 2009; Steullet et al., 2014). In the present review, we will focus on evidences of redox dysregulation and myelin anomalies in patients with schizophrenia as well as in early psychotic patients. Finally, we review data from human studies and rodent models of schizophrenia showing that known genetic and environmental risk factors of schizophrenia induce redox dysregulation/oxidative stress and myelin anomalies. We suggest that oxidative stress during key periods of brain maturation interferes with myelin development thus leading to disconnectivity and schizophrenia symptoms.

[#] Co-first authors.

IMBALANCE OF REDOX HOMEOSTASIS IN SCHIZOPHRENIA

Key Players of Redox Homeostasis

Redox state is a regulatory system of posttranslational modifications that controls cellular signalization in response to oxidants and free radicals. Oxidative stress is defined as an imbalance between prooxidants and antioxidants, which results in macromolecular damages (lipid peroxidation, protein carbonylation, and DNA oxidation) and in dysregulation of the redox system. Major prooxidants are free radicals, that is, reactive oxygen species (ROS; superoxide anion radicals $O_2^{\cdot -}$, hydrogen peroxide H_2O_2, and hydroxyl radicals $OH^{\cdot}$) and reactive nitrogen species (nitric oxide $NO^{\cdot}$ and peroxynitrite $ONOO^-$) (Do, Bovet, et al., 2009; Valko et al., 2007). $NO^{\cdot}$ is produced by the NO synthase in mitochondria and peroxisomes (Szibor, Richter, & Ghafourifar, 2001; Valko et al., 2007). It diffuses through cytoplasm and plasma membranes, and plays signaling roles in various processes such as synaptic plasticity, immune response, or regulation of blood pressure. $NO^{\cdot}$ toxicity is mainly linked to its reaction with $O_2^{\cdot -}$ that forms $ONOO^-$, a strong oxidant inducing lipid oxidation and DNA fragmentation (Figure 1(A)) (Bergendi, Beneš, Ďuračková, & Ferenčik, 1999; Valko et al., 2007). In physiological conditions, $O_2^{\cdot -}$ is produced within the cell by mitochondria and, to a lower extent, by endoplasmic reticulum. $O_2^{\cdot -}$ is reduced by the superoxide dismutase (SOD) into H_2O_2 (Figure 1(A)). Moreover, peroxides are generated at high rates by anabolic and catabolic reactions ongoing in peroxisomes (Schrader & Fahimi, 2006), where catalase catalyzes their decomposition into water. In a reaction catalyzed by iron, peroxides may form $OH^{\cdot}$ radicals, which are highly reactive and thus can lead to lipid peroxidation, protein carbonylation, and DNA oxidation (Figure 1(A)).

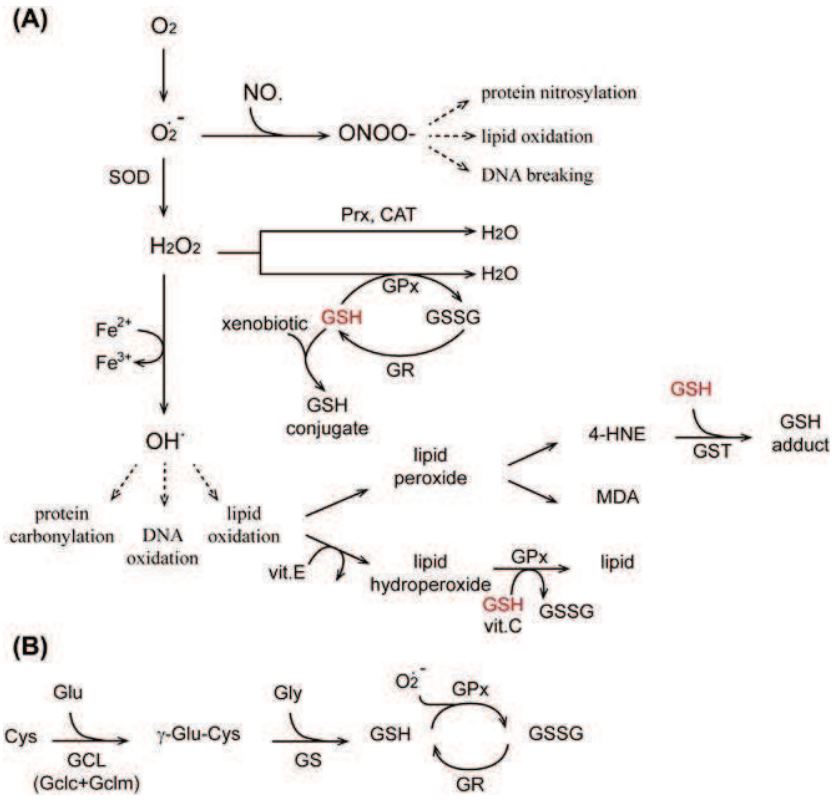

FIGURE 1 Antioxidant system (A) and glutathione (GSH) metabolism (B). (A) Free radicals such as $O_2^{\cdot -}$ are catalyzed to hydrogen peroxide (H_2O_2) through superoxide dismutase (SOD). H_2O_2 can be detoxified to water via peroxiredoxin (Prx) or catalase (CAT). Glutathione peroxidase (GPx) also catalyzes the same reaction, using GSH as a reductant. H_2O_2 can be converted into hydroxyl radical $\cdot OH$ (Fenton reaction), which induces macromolecular damages: protein carbonylation, DNA oxidation, and lipid oxidation. Lipid oxidation generates end products such as 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA), which are indirect oxidative stress markers. Lipids can be restored via vitamin E and GPx reactions using GSH as reductant. GSH acts as reductant to detoxify ROS or lipid via GPx, and is used as substrate by GSH transferase (GST) to detoxify xenobiotics. (B) GSH is synthesized by two consecutive enzymes: glutamine-cysteine ligase (GCL) and glutathione synthetase (GS). GCL has two subunits, the catalytic and the modulatory, coded by GCLC and GCLM. GCL combines cysteine to glutamate to form γ-glutamylcysteine. The second enzyme (GS) catalyzes the final step of GSH synthesis by adding glycine to γ-glutamylcysteine. Reduced GSH can react directly with ROS, generating oxidized GSH (GSSG). Reduced GSH can be recycled via the activity of glutathione reductase (GR).

Recent advances show that redox systems are regulated under dynamic, nonequilibrium conditions. "Redox signaling" is used to describe signaling processes in which a specific oxidative signal is conveyed through a specific redox element to direct a specific cellular response (i.e., Nrf2 redox-signaling pathway). Nrf2, a transcription factor that induces the expression of an array of antioxidant enzymes, is regulated by redox-sensitive proteins. Indeed, in conditions of redox dysregulation, the inhibitor of Nrf2, KEAP1, is oxidized on its cysteine residues, leading to the release of Nrf2 and its translocation to the nucleus (Kensler, Wakabayashi, & Biswal, 2007). Many signaling systems including kinase, phosphatase, and transmembrane ionic signaling (e.g., N-methyl-D-aspartate(NMDA)receptor) can also be regulated by "redox sensing" thiols of critical proteins in the pathways (Jones, 2008). Both redox sensing and redox signaling use thiol switches, especially cysteine residues in proteins which are sensitive to covalent or noncovalent modifications (i.e., reversible oxidation, nitrosylation, and glutathionylation), leading to structural and functional alterations of target protein. This has led to the concept of "orthogonal control of signal transduction systems by redox-sensing mechanisms" (Jones, 2010). Moreover, because redox potentials are differently controlled in subcellular compartments, the same signaling mechanism can be differentially regulated by the local redox environment. At present, there is no methodology to monitor these highly dynamic and unstable dithiol/disulfide switches neither in real-time nor in space (i.e., targeted to specific proteins, cells, and brain regions). Recent proteomics-based approaches are efficient but they assess the endpoint. Indeed, the effects cannot be localized to cell type/structure and artifactual oxidation/reduction can occur during isolation and fixation.

Redox regulators and endogenous antioxidants encompass a variety of enzymatic and nonenzymatic defenses. The nonenzymatic redox regulation is a multipartite system relying mainly on glutathione (GSH), thioredoxin (Trx), and cysteine. The tripeptide GSH is synthesized into two steps, the first and limiting one being catalyzed by the glutamate-cysteine ligase (GCL) (Figure 1(B)) (Lu, 2013). GSH can react with free radicals via a nonenzymatic reaction. This oxidation of GSH generates disulfides (GSSG), which can be restored by GSH reductase (Figure 1(B)). Moreover, many enzymatic reactions use GSH to detoxify ROS or regenerate oxidized molecules. Two main families of enzymes use GSH as a substrate: (1) the GSH peroxidase (GPx), which reduces peroxides or peroxidized lipids, and (2) the GSH transferase (GST), a superfamily of enzymes catalyzing the conjugation of GSH, with mixed functions, such as the detoxification of xenobiotics and the synthesis of steroid hormones (reviewed by Board & Menon, 2013) (Figure 1(A)). In addition, GSH can regenerate other antioxidants such as vitamin C, vitamin E, and glutaredoxin (Grx). Grx, Trx, and peroxiredoxin (Prx) are three families of thiol-dependant antioxidant proteins that can function independently of GSH. Prx catalyze the reduction of peroxides (Figure 1(A)). Grx and Trx reduce protein disulphide and mixed GSH disulphide (in the case of Grx). They are reduced back to their initial state by Trx reductase as well as by GSH in the case of Grx. Both GSH and Trx systems are dependent on reduced nicotinamide adenine dinucleotide phosphate–reducing potential. The very reducing redox state of reduced nicotinamide adenine dinucleotide phosphate/nicotinamide adenine dinucleotide phosphate + makes it the primary source of electrons for redox pathways.

Production of ROS is localized to specific part of the cell and, conversely, redox potential and its regulators are not evenly distributed (Table 1) (Go & Jones, 2008). This distribution has crucial importance in nervous tissues known to present complex compartmentalization. Mitochondria, the main source of $O_2^{\cdot -}$, contain GSH-dependent as well as GSH-independent enzymes (Trx2, TR2 and the manganese SOD, SOD2). In peroxisomes, high producers of H_2O_2, catalase is very active, as well as Prx and GPx (Go & Jones, 2008). GSH and Trx1 both regulate redox potential in the cytoplasm; however, they may vary independently. The nucleus constitutes an isolated environment protecting DNA from chemicals. Few antioxidant proteins are specifically addressed to the nucleus (Table 1), but oxidative stress and a large range of stressors induce translocation of cytoplasmic redox regulators as Trx1 and TR1 (Go & Jones, 2008). The extracellular space has a more oxidized state than the cytoplasm and the major redox couple is cysteine/cystine in contrast with other compartments where GSH/GSSG is main redox regulator (Go & Jones, 2008).

Redox Anomalies in Schizophrenia

Measurements of free radicals and nonradicals oxidants per se remain difficult because of their highly reactive nature. Similarly, redox homeostasis owing to its multipartite nature is not often assessed. Thus, evidences of oxidative stress and redox dysregulation in schizophrenia are mostly based on lowered antioxidant defenses and accumulation of oxidation end products such as 8-oxo-deoxyguanosine (8-oxodG, formed by oxidation of DNA), protein carbonylation, and lipid peroxidation (malondialdehyde, MDA; 4-hydroxynonenal, HNE; thiobarbituric acid reactive substances, TBARS).

Peripheral Marks of Oxidative Stress in Schizophrenia Patients

Marks of oxidative stress have been repeatedly reported in peripheral samples of schizophrenia patients, suggesting a systemic implication of the stress.

TABLE 1 Subcellular Localization of the Major Antioxidant Players According to Gene Ontology Annotations in the Uniprot Database (uniprot.org)

					Glutathione System	
Subcellular Localization	**Major ROS**	**SOD**	**Peroxiredoxin and Catalase**	**Thioredoxin and Glutaredoxin**	**GSH Synthesis and Recycling**	**GPx**	**GST**
Cytoplasm		SOD1	PRX1 PRX2 PRX4 PRX5 PRX6*	TXN TXNRD1 GRX1	GCLC GCLM GSS GR	GPX1 GPX2 GPX4	GSTA1-5 GSTM1-4 GSTO1 GSTP1 GSTT1, 2, 2B
Mitochondria	$O_2\cdot^-$	SOD2	PRX3 PRX5	TXN2 TXNRD2 GRX2 GRX5	GR	GPX4	GSTP1
Peroxisomes	H_2O_2 NO·		PRX5 CAT	GRX5			GSTK1
Nucleus		SOD1		TXN (see note 1) TXNRD1 (see note 2) TXNRD3 (see note 3) GRX2			GSTP1
Secreted		SOD3	PRX4			GPX3 GPX5 GPX6* GPX7*	
Others	H_2O_2: ER		PRX6*: Lysosomes	TXNRD3: Microsome, ER (see note 3)		GPX8*: ER lumen	GSTCD, exosomes

In the Grx family, the protein coded by GRX3 is probably enzymatically inactive and thus was not included. Note 1: The protein Trx1, coded by TXN, is nuclear after ultraviolet irradiation, but is mainly cytoplasmic otherwise. Note 2: Only a splicing variant of TXNRD1 (coding TR1) is reported to be nuclear. Note 3: TXNRD3 (coding TR3) is specifically expressed in testis. ER, endoplasmic reticulum. *: Putative subcellular localization.

In the urine of patients, reports indicate accumulation of 8-oxodG (Jorgensen et al., 2013), lipid peroxides (Anna Dietrich-Muszalska & Olas, 2009), and bilirubin oxidation (Miyaoka et al., 2005).

Increased lipid peroxidation (MDA or TBARS levels) might be the most robust result in blood of patients. Despite some negative studies, plasmatic amounts of MDA are mostly reported to be increased in schizophrenia patients. Consistently, results of two meta-analyses indicate that this increase is present in first episode as well as in chronic patients (Flatow, Buckley, & Miller, 2013; Grignon & Chianetta, 2007). In contrast, some oxidation markers as nitrite are accumulating only in chronic patients (Flatow et al., 2013).

Altogether, these data indicate an ongoing oxidative stress in schizophrenia patients. However, deficiencies of the antioxidant system are more controversial, as detailed in the next section.

Peripheral Levels of Antioxidant Defenses in Schizophrenia Patients

Mirroring the accumulation of oxidation products, the total antioxidant capacity is deficient in blood of schizophrenia patients (Dietrich-Muszalska & Kontek, 2010; Yao, Reddy, McElhinny, & van Kammen, 1998). Although there are negative findings (Sarandol et al., 2007; Sofic, Rustembegovic, Kroyer, & Cao, 2002), it remains significant in a recent meta-analysis (Flatow et al., 2013). The decrease of total antioxidant capacity might be due to lowered levels of GSH in blood, which was reported in schizophrenia patients as early as 1934 (Looney & Childs, 1934) and subsequently in early psychosis patients (Altuntas, Aksoy, Coskun, Caykoylu, & Akcay, 2000; Mico et al., 2011; Raffa et al., 2009).

Data on enzymatic activity are more contrasted, with increase, decrease and no change being reported for SOD, catalase, and GPx. Ruiz-Litago et al. conducted a 1-year follow-up of young drug-naive patients following their hospitalization (mean age at inclusion: 23.1 years) (Ruiz-Litago et al., 2012). They could show the transient nature of some antioxidant defects in plasma: GSH, total antioxidant defenses, as well as SOD and GPx activities were decreased 1 and 6 months after the first episode while TBARS were increased. After 1 year, they were all normalized. Interestingly, a similar study, but with less power, was performed on older patients in acute phase of illness (mean age at inclusion: 36.5 years) (Tsai, Liou, Lin, Lin, & Huang, 2013). This study did not reveal any change for TBARS, SOD, or GPx at 1 month of follow-up, suggesting that the deficits in antioxidant system reported by Ruiz-Litago et al. are specific of disease onset and might be suitable as early prognosis markers in at-risk individuals (Ruiz-Litago et al., 2012). Longitudinal assessment of redox markers on the long term is necessary to characterize their progression and potential phase specific evolution.

Limits and Best Practices for Future Studies

Heterogeneity between studies is concerning, the impact of medication is controversial and the source of variability remains unclear. As suggested by Grignon et al. for MDA levels, heterogeneity of the results might be linked to the variable proportion of drug-free patients (Grignon & Chianetta, 2007). A good example of variability concerns data on SOD activity: the type of sample (plasma, serum, or red blood cells) and smoking status may change the picture completely (Flatow et al., 2013). Moreover, genetic background may account for some differences in the pattern of antioxidant response between individuals. Additional covariates as type of antipsychotic treatment, disease duration, disease phase (acute or not, early or chronic), body mass index, cotinine, glucose levels, and genotyping of key genes of the antioxidant systems are required in future studies. However, recent data noted the absence of exogenous factor contributions (e.g., antipsychotic, diet, and smoke) to blood GSH levels (Ballesteros et al., 2013). In addition, GSH can undergo artifactual oxidation and thus it might be difficult to setup optimal conditions for its measurement in clinical settings.

The complexity of the antioxidant system is also linked to the compartmentalization of the different players. One concern regarding the previously mentioned studies is the lack of discrimination between subcellular compartments. A more detailed characterization of the defects within different organelles and of GSH-independent systems would greatly help to pinpoint the defective systems.

Finally, an important point is also the lack of data to relate anomalies reported in periphery to their potential impact on the central nervous system. Nevertheless, and as detailed later, there are evidences of anomalies in redox homeostasis in the brain of schizophrenia patients.

Evidence for Disrupted Redox Homeostasis in the Brain of Schizophrenia Patients

Postmortem studies revealed increased lipid peroxidation (4-HNE) in the anterior cingulate cortex (Wang, Shao, Sun, & Young, 2009) but TBARS decreased in cerebrospinal fluid. SOD1 (Cu-Zn SOD) is decreased in cerebrospinal fluid of recent-onset schizophrenia patients (Coughlin et al., 2013), but SOD1 and SOD2 (Mn SOD) are increased in chronic patients' brains (Michel et al., 2004). GSH deficits are reported in caudate nucleus and prefrontal cortex of patients (Gawryluk, Wang, Andreazza, Shao, & Young, 2011; Yao, Leonard, & Reddy, 2006). Moreover, GSH levels are found to be reduced by 27% in cerebrospinal fluid of drug-naive chronic patients and by 40% in the prefrontal cortex in a group

of patients as assessed by magnetic resonance spectroscopy (MRS) (Do et al., 2000). Matsuzawa et al. report no change in GSH levels in the posterior medial frontal cortex in chronic patients compared with healthy subjects, although low GSH levels are associated with more severe negative symptoms (Matsuzawa & Hashimoto, 2011). GSH quantification by MRS is a challenging approach and many technical issues may contribute to variability in the results reported previously (Poels et al., 2014). Moreover, recent observations from our group point to a crucial contribution of genotypes to brain GSH levels: indeed, polymorphisms associated with abnormal regulation of GCL and of GSH levels in periphery ("high-risk" genotypes, see Genetic Susceptibility to Oxidative Stress in Schizophrenia Patients Section) predict low GSH levels in prefrontal cortex (Xin et al., 2014). Thus, variability of genotype distribution of this polymorphism in the different relatively small studied samples may explain discrepancies between reports.

Genetic Susceptibility to Oxidative Stress in Schizophrenia Patients

What may cause oxidative stress and redox dysregulation in schizophrenia patients? Genetic factors, as *NRG1*, *PRODH*, and *DISC1*, may lead to oxidative stress via an indirect and yet unclear pathway (see Contribution of Genetic Factors Section). Other rare variants that have been associated with schizophrenia using linkage analysis approaches may directly impact on GSH metabolism. Indeed, copy number variation of genes coding for members of the GST family have been associated with schizophrenia—*GSTT1* (Saadat, Mobayen, & Farrashbandi, 2007), *GSTT2* (Rodriguez-Santiago et al., 2010), and *GSTM1* (Gravina et al., 2011; Harada, Tachikawa, & Kawanishi, 2001)—however, there is one negative report in the Japanese population (*GSTT1*, *GSTT2*, and *GSTM1*) (Matsuzawa et al., 2009). *SOD1* was associated with schizophrenia in a Turkish study (Akyol et al., 2005), but was not replicated (Hori et al., 2000; Pae et al., 2007; Ventriglia et al., 2006). Finally, different polymorphisms of the NOS have been associated with the disease in various ethnic groups (Fallin et al., 2005; Reif et al., 2006; Tang et al., 2008), including in the Japanese population for which there is also one negative report (Okumura et al., 2009). Moreover, polymorphisms in *GCLM* and in the 5′ noncoding region of *GCLC*, which code for the modulatory (GCLM) and catalytic (GCLC) subunit of the rate-limiting enzyme for GSH synthesis (GCL), have been associated with schizophrenia (Gysin et al., 2007; Ma et al., 2010; Tosic et al., 2006). These gene associations were not reproduced in studies of Japanese population (Hanzawa et al., 2011; Kishi et al., 2008; Matsuzawa et al., 2009). However, there are technical issues: *GCLC* polymorphism is a tri-nucleotide repeat of usually seven, eight, or nine repeats. No good surrogate single-nucleotide polymorphism could be identified for any of the repeat lengths (Kulak et al., 2013); therefore, genotypes cannot be derived from available single-nucleotide polymorphisms, for instance, in genome-wide association studies. *GCLC* tri-nucleotide genotypes that are more frequent in patients than control individuals are associated with a decrease in plasma thiol levels (Gysin et al., 2007), impaired regulations of metabolism and of GCL activity following oxidative stress (Fournier et al., 2014; Gysin et al., 2007), and low GSH levels in the anterior cingulate cortex as assessed by MRS (Xin et al., 2014).

Contribution of NMDA Hypofunction and Inflammation to Oxidative Stress

At the molecular level, redox dysregulation may also arise following the impairments of other pathways involved in schizophrenia: NMDA receptor hypofunction and inflammation. Redox pathways present numerous reciprocal interactions with the glutamatergic and immune systems. Indeed, activation of synaptic NMDA receptors strengthens neuronal antioxidant defense mechanisms (Hardingham & Bading, 2010) and NMDA receptor hypofunction increases oxidative stress levels (Jiang, Cowell, & Nakazawa, 2013). In contrast, redox state modulates NMDA receptor function (Aizenman, Lipton, & Loring, 1989; Talukder, Kazi, & Wollmuth, 2011). Likewise, oxidative stress is tightly linked to inflammation. Many inflammatory mediators are activated by oxidative molecules, whereas activated immune cells such as microglia generate ROS/reactive nitrogen species (Buelna-Chontal & Zazueta, 2013; Dwir et al., 2014). These three systems are closely interacting and potentiating each other and a dysregulation within any of these factors can lead to disturbances of the others. It is proposed that dysregulations of redox homeostasis, neuroimmune, and glutamatergic systems induced by interaction between genetic and environmental risk factors during neurodevelopment, constitute one "central hub" contributing to schizophrenia pathophysiology. An imbalance within any of these "hub" systems would affect the excitatory/inhibitory balance of local neuronal circuits (microcircuits) and the connections between distant brain areas (macrocircuits) (Do, Cabungcal, et al., 2009; Kulak et al., 2013; Steullet et al., 2014).

In summary, these data indicate that there are abnormal oxidation levels in the periphery (blood) and in the central nervous system of schizophrenia patients. These redox anomalies are present early in the course of the disease and might be driven by an interaction between genetic and environment risk factors as well as by defects in other molecular pathways involved in schizophrenia (NMDA receptor hypofunction and neuroinflammation). The following sections aim at summarizing the

impact of redox homeostasis imbalance on white matter integrity and connectivity in schizophrenia context.

WHITE MATTER IMPAIRMENTS IN SCHIZOPHRENIA

Connectivity abnormalities have been well-established in schizophrenia. Connectomic studies, mapping neuronal connections based on functional magnetic resonance imaging, revealed abnormal functional connectivity of the prefrontal cortex in first-episode patients. Functional connectivity is enhanced between prefrontal cortex and temporal lobe, and reduced between prefrontal cortex and parietal lobe, posterior cingulate cortex, thalamus, and striatum of patients (Zhou et al., 2007). Hypo- and hyperconnectivity in parietal, occipital lobe, and prominently in frontal and temporal lobe indicate a diffuse functional disconnectivity in schizophrenia (Fornito, Zalesky, Pantelis, & Bullmore, 2012).

Brain regions are wired through white matter tracts, whose development and integrity are essential for the flow of information and synchronization of distant brain regions, and thus for connectivity. Myelination starts before birth, continues through childhood and adolescence and even adulthood for long association tracts (Peters & Karlsgodt, 2014). Neuroimaging and postmortem studies highlighted white matter abnormalities in schizophrenia patients, which may participate to disconnectivity.

Evidences of White Matter Abnormalities in Imaging Studies

The noninvasive properties of magnetic resonance imaging have made it possible to address key questions in regards of timing of brain changes. Diffusion tensor imaging (DTI) is used to probe diffusion of water molecules, and thus reflects the underlying structure of the brain. Fractional anisotropy (FA), a frequently used metric, describes the degree of anisotropy of water diffusion: low FA values are often interpreted as impairment of myelin integrity although it is acknowledged that other factors influence FA as well (fiber coherence and axon diameter for instance) (Beaulieu, 2002).

Despite some discrepancies among studies, low FA has been repeatedly reported in frontal and temporal brain regions of schizophrenia patients (Fitzsimmons, Kubicki, & Shenton, 2013; Kanaan et al., 2005; Kyriakopoulos, Bargiotas, Barker, & Frangou, 2008). Bundle tracts connecting these regions (uncinate fasciculus, cingulum bundle, and arcuate fasciculus) have disrupted integrity, which emphasize frontotemporal circuitry abnormalities in the illness (Takahashi, Sakurai, Davis, & Buxbaum, 2011). To disentangle from other factors the contribution of myelin abnormalities to FA, Du and Ongür propose to combine different imaging methods. Diffusion tensor spectroscopy and magnetization transfer ratio can be used to assess axonal integrity and myelin volume, respectively (Du & Ongur, 2013).

From a functional point of view, there may be a relation between lost white matter integrity and psychopathology. Indeed, more severe cognitive symptoms are associated with greater deficits in the volume of the frontal white matter (Ho, Alicata, et al., 2003; Ren, Wang, & Xiao, 2013).

To summarize, imaging studies indicate disruption of frontotemporal tracts in schizophrenia patients. These anomalies may reflect myelin impairments as suggested by transcriptomics and neurocytochemical findings described in the following section.

Evidences of Oligodendrocyte Disruption in Postmortem Studies

Postmortem studies and histological characterization of patients' brain support the view of altered white matter in schizophrenia patients. Indeed, structural alterations of myelinated fibers are reported in gray and white matter of prefrontal cortex and caudate nucleus of patients (Uranova, Vikhreva, Rachmanova, & Orlovskaya, 2011). Most studies report a decrease in oligodendrocyte density in thalamic nuclei and in prefrontal cortex (Byne et al., 2006; Hof, Haroutunian, Copland, Davis, & Buxbaum, 2002; Uranova, Vostrikov, Orlovskaya, & Rachmanova, 2004; Vostrikov, Uranova, & Orlovskaya, 2007). In prefrontal cortex, the age-related increase in number of mature oligodendrocytes normally observed in control subjects is absent in schizophrenia patients (Vostrikov & Uranova, 2011). Microarray analysis of prefrontal and anterior cingulate cortex of schizophrenia patients indicate a reduced expression of several genes related to myelin and oligodendrocytes (Dracheva et al., 2006; Hakak et al., 2001; Tkachev et al., 2003) and an altered expression of genes coding for cell-cycle maintenance or arrest (Katsel et al., 2008). Altogether, these findings point to impairment of oligodendrocyte maturation and of myelination.

Abnormalities of White Matter at Early Stages of Schizophrenia

Many studies revealed impairment of white matter integrity in tracts connecting frontal and temporal regions already at early stages of schizophrenia (reviewed in Samartzis, Dima, Fusar-Poli, & Kyriakopoulos, 2014), and even at illness onset for the frontal lobe (Hao et al., 2006; Samartzis et al., 2014; Witthaus et al., 2008; Yao et al., 2013). Voxel-based morphometry of structural magnetic images revealed smaller white matter volumes in temporal gyrus, frontal gyrus, and

cingulum of first-episode patients compared with healthy subjects (Witthaus et al., 2008). In addition, early psychosis patients have a reduced progression of frontal white matter volume over time compared with control subjects (Ho, Andreasen, et al., 2003). Based on a recent meta-analysis study, FA values are decreased in two main clusters of the brain in first-episode patients: the right anterior cingulum (uncinate fasciculus and cingulum bundle) and the left temporal deep white matter (longitudinal fasciculus, fornix, fronto-occipital fasciculus, and interhemispheric fibers) (Yao et al., 2013). Furthermore, ultra-high-risk individuals with attenuated positive symptoms (i.e., at risk of developing psychosis) display a reduced volume of white matter in temporal lobe when compared with healthy subjects (Witthaus et al., 2008). Supporting these results, DTI analyses of ultra-high-risk individuals revealed alterations of white matter integrity in various brain regions (Karlsgodt et al., 2008; Peters et al., 2009; Samartzis et al., 2014), the superior and middle frontal lobe as well as the major frontoparietal connecting tract (Carletti et al., 2012). Also in line with these data, ultra-high-risk individuals present abnormal functional connectivity between frontal and temporal regions (Crossley et al., 2009). Interestingly, transition to psychosis in ultra-high-risk subjects is associated with a progressive decrease of white matter integrity in frontal and temporal lobes (Bloemen et al., 2010; Carletti et al., 2012).

In summary, imaging data indicate that white matter deficits are present before onset of illness, at illness onset, and persist in chronic schizophrenia patients. Additional observations suggest that white matter of patients fails to undergo normal myelination. Structural abnormalities in myelin and oligodendrocytes can interfere with long-range neuronal circuitry (Takahashi et al., 2011), and may disrupt synchronization across brain regions (Whitford et al., 2012), leading to complex symptoms in schizophrenia. In the somatosensory system, myelination is an important process to close the critical period of brain plasticity during which the neural circuits are shaped by experiences (Bavelier, Levi, Li, Dan, & Hensch, 2010; Morishita & Hensch, 2008; Takesian & Hensch, 2013). The notion of critical period for brain plasticity could be extended in other systems, including cognition (Barkat, Polley, & Hensch, 2011; Bavelier et al., 2010; Gogolla, Caroni, Luthi, & Herry, 2009). The consequences of delayed myelination on brain maturation remain to be explored in the context of schizophrenia. We will discuss next the evidence in human and animal models suggesting that oxidative stress and redox dysregulation underlie the impaired maturation of white matters and oligodendrocytes in frontal cortex.

ROLE OF REDOX IMBALANCE IN MYELIN IMPAIRMENTS ASSOCIATED WITH SCHIZOPHRENIA

Oligodendrocyte Development and Maturation

To understand how redox dysregulation and oxidative stress affect oligodendrocyte maturation, a description of oligodendrocyte development stages is first needed. Oligodendrocytes undergo a series of maturation stages, which are characterized by the expression of specific cellular surface and myelin component proteins (Figure 2(A)) (Baumann & Pham-Dinh, 2001). Oligodendrocyte progenitor cells (OPC) proliferate in response to growth factors such as platelet-derived growth factors (PDGF) throughout PDGF receptor-signaling pathway. At this stage, OPC present the markers A2B5, NG2, and PDGF receptor. OPC differentiate into preoligodendrocyte cells, which are characterized by multiple processes, a reduced motility, and a decreased sensitivity to growth factors as PDGF. Preoligodendrocytes present typical sulfated glycolipids that are recognized by the O4 antibody. Although preoligodendrocyte branches become more complex throughout development, the transition into immature oligodendrocytes is accompanied by a complete cell-cycle arrest. At this stage, expression of galactocerebroside and 2′,3′-cyclic nucleotide 3′-phosphodiesterase (CNP) begins. After a complete differentiation into mature oligodendrocytes, specific markers such as myelin-associated protein (MAG), myelin oligodendrocyte glycoprotein (MOG), proteolipid protein (PLP), and myelin basic protein (MBP) are present.

Sensitivity of Oligodendrocyte to Redox State

Oligodendrocytes are sensitive to redox dysregulation and oxidative stress because of their intrinsic properties and functions. During myelination process, oligodendrocytes have a high metabolic rate to produce and maintain membranes (Bradl & Lassmann, 2010; Cammer, 1984; El Waly, Macchi, Cayre, & Durbec, 2014). High metabolic activity is known to generate large amount of ROS (Dringen, 2000). Moreover, oligodendrocytes are the predominant iron storing cells in the brain, as it is a required cofactor for myelin synthesis (Thorburne & Juurlink, 1996). Iron catalyzes the formation of oxygen radicals (Figure 1(A)). In addition, myelin sheaths are enriched in polyunsaturated fatty acids (Baumann & Pham-Dinh, 2001), which are vulnerable to radical attacks. Surprisingly, oligodendrocytes display a low activity of GPx and low endogenous GSH levels (Baud et al., 2004; Juurlink, Thorburne, & Hertz, 1998). Data available online indicate that messenger RNA

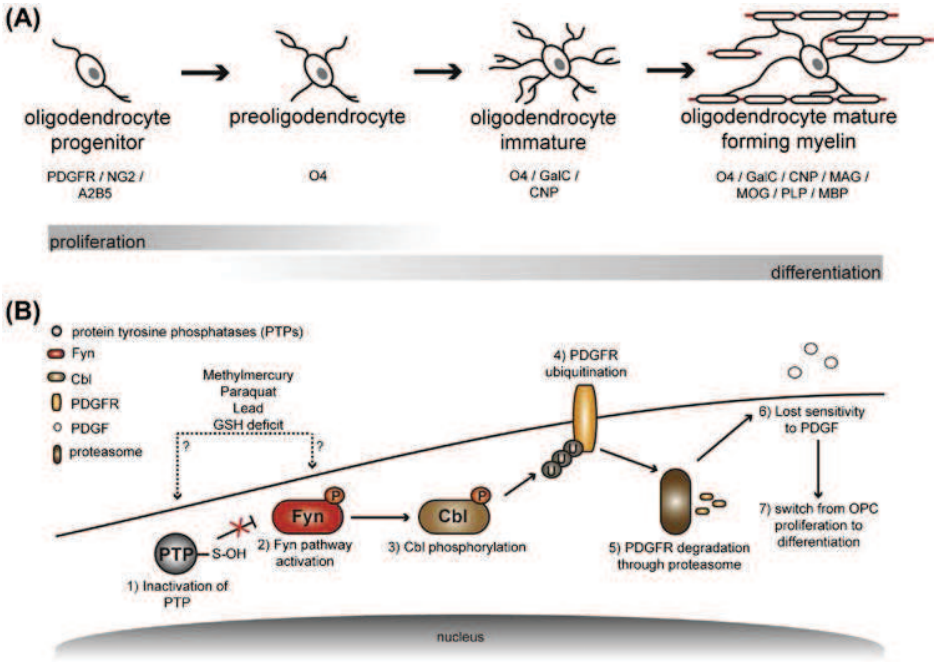

FIGURE 2 Regulation of oligodendrocyte maturation. (A) Oligodendrocyte maturation and markers used to characterize each step of oligodendrocyte development. PDGFR, receptor of platelet-derived growth factors; GalC, galactocerebroside; CNP, 2′,3′-cyclic nucleotide 3′-phosphodiesterase; MAG, myelin associated protein; MOG, myelin oligodendrocyte glycoprotein; PLP, proteolipid protein; MBP, myelin basic protein. (B) Redox state influences the switch between proliferation and differentiation of oligodendrocytes via the modulation of Fyn kinase. (1) In conditions of low GSH levels or oxidative stress, protein tyrosine phosphatases (PTPs) may be oxidized to sulfenic acid (S-OH), inactivating PTPs. (2) Via other signaling pathways or through the inactivation of PTP, Fyn kinase may be activated via autophosphorylation of Fyn activation loop. (3) Fyn kinase phosphorylates Cbl ubiquitin ligase, which (4) ubiquitinylates PDGFR. (5) Tagged PDGFR is targeted and degraded by the proteasome. (6) In response to PDGFR degradation, OPC lost sensitivity to growth factors and (7) switch to early differentiation.

expression of genes related to antioxidant capacity (GCLC) in the prefrontal cortex follow the same expression profile than myelin-related genes (e.g., MAG, PLP, http://braincloud.jhmi.edu/) (Kang et al., 2011). Expression of these genes peaks at late childhood and early adolescence period. Consistently, the most expressed genes in the prefrontal cortex at adolescence are related to myelin, lipid synthesis, the antioxidant system, and energy metabolism (Harris et al., 2009).

In schizophrenia patients, the direct role of redox control for myelin is supported by the positive correlation found between prefrontal cortex GSH levels and FA along the cingulum bundle, which connects the anterior cingulate to limbic structures (Monin et al., 2014). Interestingly, this correlation is present only in individuals younger than age 30 years and is lost when older subjects are included (Monin et al., 2014). The third decade of life corresponds to the final stage of prefrontal cortex maturation and cingulum myelination (Bartzokis et al., 2001; Lebel & Beaulieu, 2011; Lenroot & Giedd, 2006).

The importance of redox control for white matter integrity and oligodendrocyte development is further supported by animal models and in vitro research. Redox state controls oligodendrocyte maturation as well as the switch between proliferation and differentiation (Monin et al., 2014; Noble, Smith, Power, & Mayer-Proschel, 2003). In reduced state, oligodendrocytes proliferate while they differentiate in oxidized state (Noble et al., 2003). Abnormal redox control would interfere with oligodendrocyte development. Consistently, *GCLM*-deficient mice, which present a 70% GSH deficit within the brain and an increase in oxidative stress marks in prefrontal cortex and ventral hippocampus (Cabungcal, Steullet, Kraftsik, Cuenod, & Do, 2013; Steullet et al., 2010), have reduced levels of mature oligodendrocytes and of myelin in the prefrontal cortex at peripubertal period (Monin et al., 2014). Although myelination reaches similar levels in adult *GCLM*-deficient and wild-type mice, DTI study shows persistent impairment of white matter integrity in fornix and anterior commissure (Corcoba et al., 2014). At functional levels, conduction velocity is reduced in both white matter tracts (Corcoba et al., 2014). Therefore, a delay in oligodendrocyte maturation and myelination generated by a redox dysregulation may induce permanent disturbance of FA values. At the cellular level, GSH deficiency in oligodendrocyte progenitors leads to cell-cycle arrest and reduces proliferation

that can be reversed by the antioxidant N-acetylcysteine (Monin et al., 2014; Noble et al., 2003). In presence of growth factors, GSH depletion favors the early differentiation of oligodendrocytes as indicated by the increase of O4 and CNP markers (Monin et al., 2014; Noble et al., 2003) but, in presence of differentiating factor, a deficit in GSH prevents full oligodendrocyte maturation (Monin et al., 2014). Consistently, pharmacological inhibition of GCL decreases the expression of genes that promote oligodendrocyte differentiation and increases expression of those that inhibit differentiation (French, Reid, Mamontov, Simmons, & Grinspan, 2009). At the molecular level, the switch from proliferation to early differentiation is controlled by the PDGFR-Fyn pathway (Figure 2(B)) (Li, Dong, Proschel, & Noble, 2007; Monin et al., 2014). Indeed, redox dysregulation induced by a GSH deficit or oxidative stress generated by toxicants (methylmercury, paraquat, and lead) activates Fyn pathway. Activation of Fyn, a nonreceptor tyrosine kinase, induces phosphorylation of the ubiquitin ligase Cbl known to target PDGFR degradation through proteasome (Figure 2(B)) (Li et al., 2007). The mechanisms underlying the activation of Fyn remain elusive. Phosphorylation and dephosphorylation of Fyn at different tyrosine residues are needed to drive its activity, which could be regulated by protein tyrosine phosphatases (PTPs). PTPs can either negatively or positively modify tyrosine kinases (Ostman & Bohmer, 2001). Although it has been shown that PTPα member activates Fyn (Ponniah, Wang, Lim, & Pallen, 1999), other members of PTPs family could, in contrast, inactivate Fyn. Interestingly, these PTPs have a cysteine residue on their active site, which is sensitive to oxidation (Salmeen & Barford, 2005). In conditions of redox dysregulation or oxidative stress, the inactivation of PTPs via their redox-sensitive site could trigger the activity of tyrosine kinases as Fyn (Figure 2(B)). Interestingly, regulation of Fyn expression is impaired in early psychosis patients associated with a vulnerability to redox dysregulation (Monin et al., 2014). Postmortem studies in prefrontal cortex of schizophrenia patients also reveal abnormal expression of Fyn (Stanley database) (Ohnuma, Kato, Arai, McKenna, & Emson, 2003).

In conclusion, a proper timing of redox regulation is crucial to control the proliferation and differentiation of oligodendrocyte. Oxidative stress or abnormal redox control during the development could therefore contribute to myelin disruptions associated with schizophrenia.

Role of Nonredox Risk Factors in Oxidative Stress and Myelin Impairment

Contribution of Genetic Factors

NRG1

Genetic association studies of schizophrenia identified several alleles of *NRG1* as risk factors for the disease (Mei & Nave, 2014). Specifically, the C allele at rs35753505 and the T allele at rs6994992 were widely associated with the disease (Mei & Nave, 2014). Few studies investigate the relation between NRG1 and oxidative stress in brain. However NRG1 is known to regulate the level of ROS in vitro (Goldshmit, Erlich, & Pinkas-Kramarski, 2001) and several evidences indicate a protective role of NRG1 against oxidative stress by regulating endoplasmic reticulum stress in myocardial cells (Xu et al., 2014).

In schizophrenia patients, carriers of C allele at rs35753505 present a reduction in white matter volume within tracts binding frontal to posterior areas (Cannon et al., 2012). In contrast, T carrier patients have a lower FA in the anterior cingulum (Wang, Jiang, et al., 2009). The relation between *NRG1* risk variants and microstructural integrity was further investigated in healthy subjects to avoid bias because of antipsychotic drugs. White matter integrity in the subcortical white matter of the medial frontal and in the anterior thalamic radiation is reduced in carriers of the schizophrenia risk allele C at rs35753505 (Sprooten et al., 2009; Winterer et al., 2008). In addition, healthy subjects with the risk-associated T variant of *NRG1* at rs6994992 display a decreased FA in thalamic connecting tracts and in the fornix (Douet et al., 2014; McIntosh et al., 2008; Sprooten et al., 2009). Moreover, this T allele is associated with differential developmental trajectories of frontal, temporal, and parietal lobes (Douet et al., 2014). At the molecular level, *NRG1* gene is required to promote specification of oligodendrocyte lineage (Wood, Bonath, Kumar, Ross, & Cunliffe, 2009). *NRG1*-deficient mice are hypomyelinated in the prefrontal cortex (Makinodan, Rosen, Ito, & Corfas, 2012). NRG1, which is axonally bound or secreted, promotes oligodendrocyte survival and modulates myelin thickness through ErbB signaling (Mitew et al., 2013).

DISC1

DISC1 has been associated with various psychiatric conditions, including with schizophrenia (Blackwood et al., 2001; Millar et al., 2000). A missense variant of *DISC1* linked to schizophrenia is associated with low white matter integrity in fiber tracts interconnecting frontal to posterior areas (Sprooten et al., 2011). DISC1 is a multifunctional protein known to be involved in the neurodevelopment, cortical thickness, gray matter, and white matter control (Hikida, Gamo, & Sawa, 2012). DISC1 also plays a role in mitochondria fusion and fission (Park et al., 2010). A reduction in its function impairs mitochondrial dynamic, which leads to enhanced production of ROS and redox dysregulation (Park et al., 2010). In transgenic mice expressing a dominant negative variant of *DISC1*, levels of carbonylated proteins and of 8-oxodG are increased in the prefrontal cortex (Johnson et al., 2013). Moreover, these transgenic mice, which display phenotypes associated with schizophrenia, are characterized by disturbances in oligodendrocyte

differentiation markers (CNP, MAG, PLP, and PDGFR) (Katsel et al., 2011). Indeed, DISC1 is known to be crucial for oligodendrocyte development (Wood et al., 2009). At molecular levels, *DISC1* variant may induce impairment of oligodendrocyte development via NRG1/ErbB signaling pathway (Katsel et al., 2011). These data also suggest a relationship between DISC1 and NRG1 for oligodendrocyte function.

Together, these data support the notion that schizophrenia involves several genetic loci that are indirectly associated with both disruption of oxidative stress and oligodendrocyte maturation.

Contribution of Environmental Factors

Environmental factors may also lead to redox dysregulation, oxidative stress, and myelination defect. To date, few studies have focused on the relation between early-life adversity and the impairment of white matter integrity in schizophrenia patients. However, several evidences in healthy subjects and other myelin-associated disorders suggest that environmental stress or childhood trauma alter white matter tracts.

Inflammation

Inflammation and oxidative stress widely influence each other (Bitanihirwe & Woo, 2011; Kirkpatrick & Miller, 2013; Steullet et al., 2014). Infection induces the formation of cytokines, inflammatory agents associated with free radical production that in turn promote inflammation. Little is known about the impact of pre- or postnatal inflammation on white matter in schizophrenia patients, but diseases with a prominent inflammatory component (such as multiple sclerosis and periventricular leukomalacia) are accompanied with disruption of white matter and marks of oxidative stress (Ferreira et al., 2013; Gironi et al., 2014; Haynes, Folkerth, Trachtenberg, Volpe, & Kinney, 2009). Multiple sclerosis is an autoimmune disease with abnormal integrity of white matter and demyelinating lesions mainly in the spinal cord, in addition to immune cell infiltration (El Waly et al., 2014; Roosendaal et al., 2009). Patients also display increased lipid peroxidation and impairment of GSH and of antioxidant enzymatic defenses (Ferreira et al., 2013; Pasichna, Morozova, Donchenko, Vinychuk, & Kopchak, 2007; Seven, Aslan, Incir, & Altintas, 2013). Interestingly, recent data strongly associate infectious agents such as Epstein-Barr virus and human herpes virus 6A to multiple sclerosis (El Waly et al., 2014).

In rodent, prenatal immune challenge with synthetic analog of double-stranded RNA (polyriboinosinic-polyribocytidilic acid (poly I:C)) has been used to mimic viral infection. Injected in dams, this inflammatory agent generates behavioral deficits reminiscent of schizophrenia in the offsprings (Bitanihirwe, Peleg-Raibstein, Mouttet, Feldon, & Meyer, 2010; Meyer & Feldon, 2012). Moreover, poly I:C prenatal administration decreases GSH levels in the whole brain (Makinodan et al., 2009) and induces a delay in myelination (Makinodan et al., 2008). Indeed, myelin thickness and myelin protein levels such as MBP are reduced in 14-day-old mice but not in adult animals (Makinodan et al., 2008). Myelin impairments were specifically reported within the hippocampus and absent for the prefrontal cortex. In culture, poly I:C treatment promotes oligodendrocyte apoptosis and drastically reduces the number of the mature oligodendrocytes (Bsibsi, Nomden, van Noort, & Baron, 2012; Steelman & Li, 2011).

Obstetric Complications

Oxidative stress may play a role in obstetric complications such as preeclampsia and preterm birth because these events are associated with inflammation and marks of oxidation in the placenta. Moreover, hypoxia and hyperoxia are reported in preterm infants (Burton & Jauniaux, 2011). Premature babies present reduced volumes of white matter compared with term children (Back & Rosenberg, 2014; Salmaso, Jablonska, Scafidi, Vaccarino, & Gallo, 2014) and abnormal white matter integrity persists in adulthood (Eikenes, Lohaugen, Brubakk, Skranes, & Haberg, 2011). White matter injury, including the periventricular leukomalacia, is the major cause of brain injury in preterm birth (Back & Rosenberg, 2014; Chew, Fusar-Poli, & Schmitz, 2013). This disease with problems of motor control is characterized by periventricular white matter injuries and periventricular necrosis (Haynes et al., 2003). Interestingly, lipid peroxidation and nitrosative stress marks are present in oligodendrocytes of patients (Haynes et al., 2003).

In rodents, hypoxia or hyperoxia exposure, which are used to model the consequences of preterm birth, induce aberrant myelination process. Mice exposed to chronic hypoxia specifically present a delay in oligodendrocyte differentiation leading to abnormal myelin structure as demonstrated by electron microscopy (Jablonska et al., 2012). Consistently, hyperoxia exposure between 6 and 8 postnatal days generates ROS and triggers a delay in white matter and oligodendrocyte maturation in the corpus callosum (Gerstner et al., 2008; Schmitz et al., 2011). Interestingly, the number of oligodendrocyte labeled with CC1 marker returns to normal levels by 15 days (Schmitz et al., 2011). Hyperoxia exposure transiently disrupts development of myelin and generates persistent impairment in white matter integrity along corpus callosum as indicated by a low FA value in young adult rodents (Ritter et al., 2013; Schmitz et al., 2011).

Early-Life Trauma

Clinical evidences associate early trauma such as emotional abuse to schizophrenia. Emotional abuses encompass several forms, including physical and sexual abuse, verbal aggression, and social neglect. Early-life adversity deregulates the control of reaction

to stress by the hypothalamic-pituitary-adrenal (HPA) axis and therefore may contribute to oxidative stress (Schiavone, Jaquet, Trabace, & Krause, 2013). Indeed, several evidences showed a role of the oxidative stress in the control of HPA axis. After psychosocial stress conditions, reduced nicotinamide adenine dinucleotide phosphate oxidase, which generates ROS, is increased in the hypothalamus and consequently disturbs HPA axis (Colaianna et al., 2013). In addition, oxidative stress reduces glucocorticoids negative feedback loop through nuclear translocation of glucocorticoid receptors (Asaba et al., 2004). Moreover, in the serum, oversecretion of glucocorticoids induces ROS (Sato, Takahashi, Sumitani, Takatsu, & Urano, 2010). In the brain, glucocorticoids also reduce the activities of antioxidant defenses (SOD, catalase, and GST) and the level of GSH (Zafir & Banu, 2009). Thus, oxidative stress affects HPA axis that further induces redox dysregulation and oxidative stress.

Posttraumatic stress disorder (PTSD) is commonly reported in maltreated children who suffered of emotional abuse. Maltreated children and adolescents diagnosed with PTSD present a reduction of the white matter volume in the superior temporal gyrus and the prefrontal cortex compared with nonmaltreated control subjects (De Bellis, Keshavan, Frustaci, et al., 2002; De Bellis, Keshavan, Shifflett, et al., 2002). Interestingly, brain volume negatively correlates with the duration of abuse (De Bellis, Keshavan, Shifflett, et al., 2002). Because these studies do not include subjects with maltreatments and without PTSD, consequences of maltreatment and/or the presence of PTSD on white matter cannot be distinguished. In young adults without PTSD, DTI analysis reveals a negative correlation between FA value within the inferior fronto-occipital fasciculus and early-life adversity (Frodl et al., 2012). Individuals exposed to early traumatic experiences also present a reduction in white matter integrity in the corpus callosum compared with nonexposed group (Lu et al., 2013; Paul et al., 2008). In young adults, subjects exposed to parental verbal abuse display reduced microstructural integrity in the arcuate fasciculus, and around the cingulum bundle and the fornix (Choi, Jeong, Rohan, Polcari, & Teicher, 2009). Consequently, parental verbal abuse is associated with alteration of the white matter integrity in tracts connecting parts of the limbic systems, including the prefrontal cortex (Choi et al., 2009). Early neglect is one type of trauma that has been considerably studied in the past few decades (Eluvathingal et al., 2006; Govindan, Behen, Helder, Makki, & Chugani, 2010; Hanson et al., 2013). Children who experienced early neglect in orphanage have a decrease volume of total white matter (Hanson et al., 2013). Despite a greater FA in the anterior thalamic radiation and the forceps minor, lower FA in early-deprived children has been underlined in a number of white matter tracts connecting the temporal lobe to the prefrontal cortex (Hanson et al., 2013). In addition, adopted children present a decreased FA in pathways of the limbic system, including the uncinate fasciculus (Eluvathingal et al., 2006; Govindan et al., 2010). Such disruption of the structural integrity was negatively associated with the duration of stay in the orphanage (Govindan et al., 2010).

In adult rodents, social isolation compromises the activity of GSH-related antioxidant defenses in blood and liver, and increases oxidation marks such as lipid peroxidation (Djordjevic, Djordjevic, Adzic, & Radojcic, 2010; Goncalves, Dafre, Carobrez, & Gasparotto, 2008). Social isolation of adult mice reduces myelin thickness in the prefrontal cortex (Liu et al., 2012). Early social isolation endured during juvenile and early adolescent periods specifically impairs oligodendrocyte maturation and myelination in the prefrontal cortex (Makinodan et al., 2012). Indeed, levels of MBP and MAG messenger RNA expression are reduced in socially deprived animals (Makinodan et al., 2012). In contrast, social deprivation endured after adolescent period, when oligodendrocyte development is completed, does not alter myelin contents. At the molecular level, the NRG1/ErbB signaling pathway has been proposed to contribute to such oligodendrocyte maturation impairments (Makinodan et al., 2012).

Altogether, these data suggest that oligodendrocyte maturation and myelination are particularly sensitive to oxidative stress generated by trauma endured during childhood or adolescence, and may lead to white matter anomalies in adulthood.

CONCLUSIONS AND PERSPECTIVES

Marks of oxidation and lowered antioxidant defenses are repeatedly associated with schizophrenia, thus tightening the link between redox dysfunction and illness physiopathology. We suggest that redox imbalance in tight interaction with NMDA receptor hypofunction and neuroinflammation constitutes a hub on which converge genetic and environmental risk factors, leading to brain disconnectivity (Figure 3(A)). Evidence from the literature indicates that risk factors for schizophrenia are associated with both oxidative stress and myelin defects in human. The sensitivity of oligodendrocytes to redox changes is well-demonstrated in vitro because dysregulation of redox homeostasis affects the balance between proliferation and differentiation of precursor cells. Therefore, a proper redox control is essential during periods of myelination that close window of plasticity in brain development. Because dynamics of maturation vary across brain regions, we propose that environmental

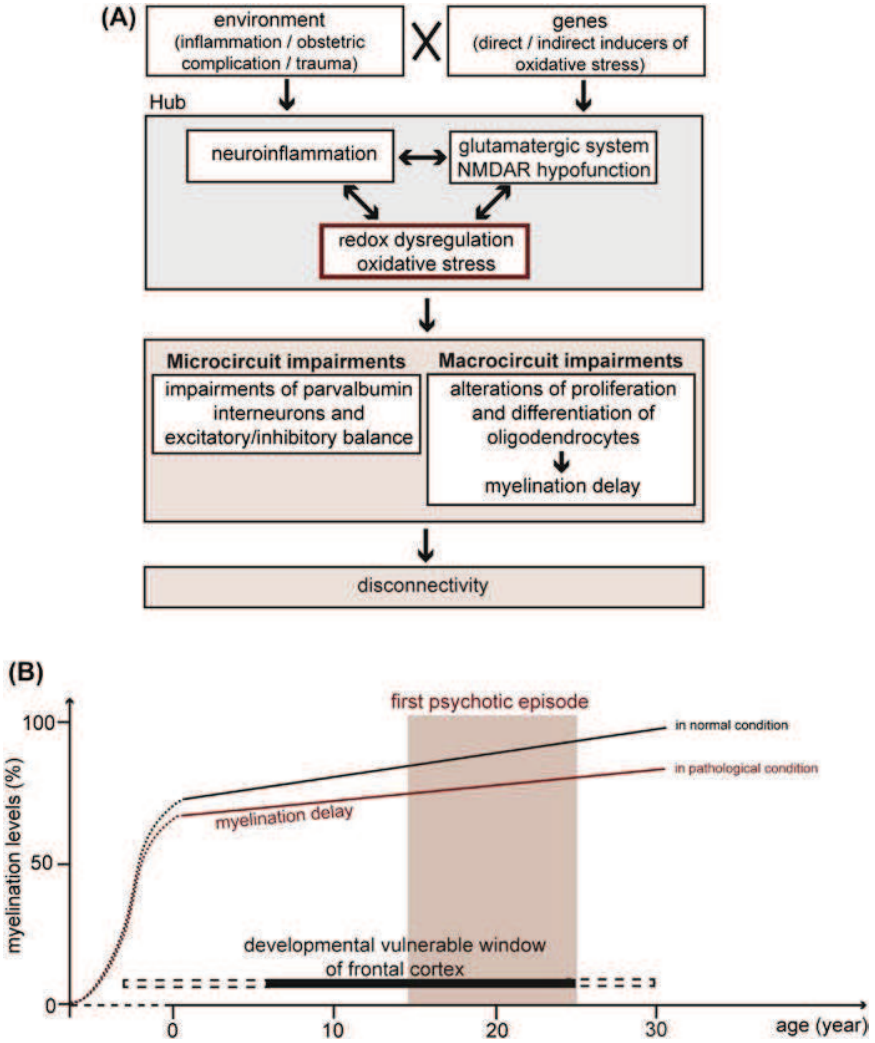

FIGURE 3 Potential mechanism underlying macrocircuit impairments in schizophrenia. (A) Redox dysregulation and oxidative stress, neuroinflammation, and glutamatergic system constitute one hub on which converge environmental and genetic factors. Redox dysregulation and oxidative stress are known to impair parvalbumin interneurons and excitatory/inhibitory balance of local neuronal circuits, and alter proliferation and differentiation of oligodendrocytes. Together, they may lead to microcircuit and macrocircuit disconnectivity. (B) The sensitivity of oligodendrocytes to redox dysregulation is specific to their maturation stage. The coincidence of schizophrenia onset with late prefrontal cortex development and the several evidences of structural abnormalities in prefrontal cortex support the hypothesis of a vulnerability window, during which stress would induce a myelination delay.

insults would preferentially impair myelin within maturing regions rather than in those fully developed. Different timing of environmental insults could thus lead to clinically heterogeneous symptoms. This model raises the hypothesis of a time window during which individuals with predisposition for redox dysfunction would be primed to develop schizophrenia by environmental factors that occurred during key periods of brain development (Figure 3(B)).

This model highlights the need for early interventions that prevent or limit the disruption of white matter integrity. Fyn, which participates to the switch of oligodendrocyte precursor proliferation to differentiation (Monin et al., 2014), is an interesting drug target. Broader antioxidants are already tested in clinical trials: some studies report positive effects of vitamins C and E, omega-3 fatty acid, and N-acetylcysteine on schizophrenia symptoms and even on psychosis prevention. Exploring the effect of these add-on therapies on white matter parameters and on disconnectivity in early stages of the disease should clarify their mode of action and, in the long term, help avoiding transition to psychosis and reducing the disabilities associated with the illness chronicity.

References

Aizenman, E., Lipton, S. A., & Loring, R. H. (1989). Selective modulation of NMDA responses by reduction and oxidation. *Neuron*, *2*(3), 1257–1263.

Akyol, O., Yanik, M., Elyas, H., Namli, M., Canatan, H., Akin, H., et al. (2005). Association between Ala-9Val polymorphism of Mn-SOD gene and schizophrenia. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *29*(1), 123–131. http://dx.doi.org/10.1016/j.pnpbp.2004.10.014.

Altuntas, I., Aksoy, H., Coskun, I., Caykoylu, A., & Akcay, F. (2000). Erythrocyte superoxide dismutase and glutathione peroxidase activities, and malondialdehyde and reduced glutathione levels in schizophrenic patients. *Clinical Chemistry and Laboratory Medicine*, *38*(12), 1277–1281. http://dx.doi.org/10.1515/CCLM.2000.201.

Asaba, K., Iwasaki, Y., Yoshida, M., Asai, M., Oiso, Y., Murohara, T., et al. (2004). Attenuation by reactive oxygen species of glucocorticoid suppression on proopiomelanocortin gene expression in pituitary corticotroph cells. *Endocrinology*, *145*(1), 39–42. http://dx.doi.org/10.1210/en.2003-0375.

Back, S. A., & Rosenberg, P. A. (2014). Pathophysiology of glia in perinatal white matter injury. *Glia*. http://dx.doi.org/10.1002/glia.22658.

Ballesteros, A., Jiang, P., Summerfelt, A., Du, X., Chiappelli, J., O'Donnell, P., et al. (2013). No evidence of exogenous origin for the abnormal glutathione redox state in schizophrenia. *Schizophrenia Research*, *146*(1–3), 184–189. http://dx.doi.org/10.1016/j.schres.2013.02.001.

Barkat, T. R., Polley, D. B., & Hensch, T. K. (2011). A critical period for auditory thalamocortical connectivity. *Nature Neuroscience*, *14*(9), 1189–1194. http://dx.doi.org/10.1038/nn.2882.

Bartzokis, G., Beckson, M., Lu, P. H., Nuechterlein, K. H., Edwards, N., & Mintz, J. (2001). Age-related changes in frontal and temporal lobe volumes in men: a magnetic resonance imaging study. *Archives of General Psychiatry*, *58*(5), 461–465.

Baud, O., Greene, A. E., Li, J., Wang, H., Volpe, J. J., & Rosenberg, P. A. (2004). Glutathione peroxidase-catalase cooperativity is required for resistance to hydrogen peroxide by mature rat oligodendrocytes. *Journal of Neuroscience*, *24*(7), 1531–1540. http://dx.doi.org/10.1523/JNEUROSCI.3989-03.2004.

Baumann, N., & Pham-Dinh, D. (2001). Biology of oligodendrocyte and myelin in the mammalian central nervous system. *Physiological Reviews*, *81*(2), 871–927.

Bavelier, D., Levi, D. M., Li, R. W., Dan, Y., & Hensch, T. K. (2010). Removing brakes on adult brain plasticity: from molecular to behavioral interventions. *Journal of Neuroscience*, *30*(45), 14964–14971. http://dx.doi.org/10.1523/JNEUROSCI.4812-10.2010.

Beaulieu, C. (2002). The basis of anisotropic water diffusion in the nervous system – a technical review. *NMR in Biomedicine*, *15*(7–8), 435–455. http://dx.doi.org/10.1002/nbm.782.

Bergendi, L., Beneš, L., Ďuračková, Z., & Ferenčik, M. (1999). Chemistry, physiology and pathology of free radicals. *Life Sciences*, *65*(18–19), 1865–1874. http://dx.doi.org/10.1016/S0024-3205(99)00439-7.

Bitanihirwe, B. K., Peleg-Raibstein, D., Mouttet, F., Feldon, J., & Meyer, U. (2010). Late prenatal immune activation in mice leads to behavioral and neurochemical abnormalities relevant to the negative symptoms of schizophrenia. *Neuropsychopharmacology*, *35*(12), 2462–2478. http://dx.doi.org/10.1038/npp.2010.129.

Bitanihirwe, B. K., & Woo, T. U. (2011). Oxidative stress in schizophrenia: an integrated approach. *Neuroscience & Biobehavioral Reviews*, *35*(3), 878–893. http://dx.doi.org/10.1016/j.neubiorev.2010.10.008.

Blackwood, D. H., Fordyce, A., Walker, M. T., St Clair, D. M., Porteous, D. J., & Muir, W. J. (2001). Schizophrenia and affective disorders–cosegregation with a translocation at chromosome 1q42 that directly disrupts brain-expressed genes: clinical and P300 findings in a family. *American Journal of Human Genetics*, *69*(2), 428–433.

Bloemen, O. J., de Koning, M. B., Schmitz, N., Nieman, D. H., Becker, H. E., de Haan, L., et al. (2010). White-matter markers for psychosis in a prospective ultra-high-risk cohort. *Psychological Medicine*, *40*(8), 1297–1304. http://dx.doi.org/10.1017/S0033291709991711.

Board, P. G., & Menon, D. (2013). Glutathione transferases, regulators of cellular metabolism and physiology. *Biochimica et Biophysica Acta (BBA) – General Subjects*, *1830*(5), 3267–3288. http://dx.doi.org/10.1016/j.bbagen.2012.11.019.

Bradl, M., & Lassmann, H. (2010). Oligodendrocytes: biology and pathology. *Acta Neuropathologica*, *119*(1), 37–53. http://dx.doi.org/10.1007/s00401-009-0601-5.

Brown, A. S. (2011). The environment and susceptibility to schizophrenia. *Progress in Neurobiology*, *93*(1), 23–58. http://dx.doi.org/10.1016/j.pneurobio.2010.09.003.

Bsibsi, M., Nomden, A., van Noort, J. M., & Baron, W. (2012). Toll-like receptors 2 and 3 agonists differentially affect oligodendrocyte survival, differentiation, and myelin membrane formation. *Journal of Neuroscience Research*, *90*(2), 388–398. http://dx.doi.org/10.1002/jnr.22767.

Buelna-Chontal, M., & Zazueta, C. (2013). Redox activation of Nrf2 & NF-kappaB: a double end sword? *Cell Signal*, *25*(12), 2548–2557. http://dx.doi.org/10.1016/j.cellsig.2013.08.007.

Burton, G. J., & Jauniaux, E. (2011). Oxidative stress. *Best Practice & Research Clinical Obstetrics & Gynaecology*, *25*(3), 287–299. http://dx.doi.org/10.1016/j.bpobgyn.2010.10.016.

Byne, W., Kidkardnee, S., Tatusov, A., Yiannoulos, G., Buchsbaum, M. S., & Haroutunian, V. (2006). Schizophrenia-associated reduction of neuronal and oligodendrocyte numbers in the anterior principal thalamic nucleus. *Schizophrenia Research*, *85*(1–3), 245–253. http://dx.doi.org/10.1016/j.schres.2006.03.029.

Cabungcal, J. H., Steullet, P., Kraftsik, R., Cuenod, M., & Do, K. Q. (2013). Early-life insults impair parvalbumin interneurons via oxidative stress: reversal by N-acetylcysteine. *Biological Psychiatry*, *73*(6), 574–582. http://dx.doi.org/10.1016/j.biopsych.2012.09.020.

Cammer, W. (1984). Carbonic anhydrase in oligodendrocytes and myelin in the central nervous system. *Annals of the New York Academy of Sciences*, *429*, 494–497.

Cannon, D. M., Walshe, M., Dempster, E., Collier, D. A., Marshall, N., Bramon, E., et al. (2012). The association of white matter volume in psychotic disorders with genotypic variation in NRG1, MOG and CNP: a voxel-based analysis in affected individuals and their unaffected relatives. *Translational Psychiatry*, *2*, e167. http://dx.doi.org/10.1038/tp.2012.82.

Carletti, F., Woolley, J. B., Bhattacharyya, S., Perez-Iglesias, R., Fusar Poli, P., Valmaggia, L., et al. (2012). Alterations in white matter evident before the onset of psychosis. *Schizophrenia Bulletin*, *38*(6), 1170–1179. http://dx.doi.org/10.1093/schbul/sbs053.

Catts, V. S., Fung, S. J., Long, L. E., Joshi, D., Vercammen, A., Allen, K. M., et al. (2013). Rethinking schizophrenia in the context of normal neurodevelopment. *Frontiers in Cellular Neuroscience*, *7*, 60. http://dx.doi.org/10.3389/fncel.2013.00060.

Chew, L. J., Fusar-Poli, P., & Schmitz, T. (2013). Oligodendroglial alterations and the role of microglia in white matter injury: relevance to schizophrenia. *Developmental Neuroscience*, *35*(2–3), 102–129. http://dx.doi.org/10.1159/000346157.

Choi, J., Jeong, B., Rohan, M. L., Polcari, A. M., & Teicher, M. H. (2009). Preliminary evidence for white matter tract abnormalities in young adults exposed to parental verbal abuse. *Biological Psychiatry*, *65*(3), 227–234. http://dx.doi.org/10.1016/j.biopsych.2008.06.022.

Colaianna, M., Schiavone, S., Zotti, M., Tucci, P., Morgese, M. G., Backdahl, L., et al. (2013). Neuroendocrine profile in a rat model of psychosocial stress: relation to oxidative stress. *Antioxidants & Redox Signaling*, *18*(12), 1385–1399. http://dx.doi.org/10.1089/ars.2012.4569.

Corcoba, A., Steullet, P., Duarte, J. M., van de Looij, Y., Gruetter, R., & Do, K. Q. (2014). Impaired white matter integrity in fornix and anterior commissure in a schizophrenia mouse model of redox dysregulation. *Biological Psychiatry*, *75*(9S), 175S.

Coughlin, J. M., Ishizuka, K., Kano, S. I., Edwards, J. A., Seifuddin, F. T., Shimano, M. A., et al. (2013). Marked reduction of soluble superoxide dismutase-1 (SOD1) in cerebrospinal fluid of patients with recent-onset schizophrenia. *Molecular Psychiatry*, *18*(1), 10–11. http://dx.doi.org/10.1038/mp.2012.6.

Crossley, N. A., Mechelli, A., Fusar-Poli, P., Broome, M. R., Matthiasson, P., Johns, L. C., et al. (2009). Superior temporal lobe dysfunction and frontotemporal dysconnectivity in subjects at risk of psychosis and in first-episode psychosis. *Human Brain Mapping*, *30*(12), 4129–4137. http://dx.doi.org/10.1002/hbm.20834.

De Bellis, M. D., Keshavan, M. S., Frustaci, K., Shifflett, H., Iyengar, S., Beers, S. R., et al. (2002). Superior temporal gyrus volumes in maltreated children and adolescents with PTSD. *Biological Psychiatry*, *51*(7), 544–552.

De Bellis, M. D., Keshavan, M. S., Shifflett, H., Iyengar, S., Beers, S. R., Hall, J., et al. (2002). Brain structures in pediatric maltreatment-related posttraumatic stress disorder: a sociodemographically matched study. *Biological Psychiatry*, *52*(11), 1066–1078.

Dietrich-Muszalska, A., & Kontek, B. (2010). Lipid peroxidation in patients with schizophrenia. *Psychiatry and Clinical Neurosciences*, *64*(5), 469–475. http://dx.doi.org/10.1111/j.1440-1819.2010.02132.x.

Dietrich-Muszalska, A., & Olas, B. (2009). Isoprostenes as indicators of oxidative stress in schizophrenia. *The World Journal of Biological Psychiatry*, *10*(1), 27–33. http://dx.doi.org/10.1080/15622970701361263.

Djordjevic, J., Djordjevic, A., Adzic, M., & Radojcic, M. B. (2010). Chronic social isolation compromises the activity of both glutathione peroxidase and catalase in hippocampus of male wistar rats. *Cellular and Molecular Neurobiology*, *30*(5), 693–700. http://dx.doi.org/10.1007/s10571-009-9493-0.

Do, K. Q., Bovet, P., Cabungcal, J. H., Conus, P., Gysin, R., Lavoie, S., et al. (2009). Redox dysregulation in schizophrenia: genetic susceptibility and pathophysiological mechanisms. In (3rd ed.) *Handbook of neurochemistry and molecular neurobiology* (vol. 2) (p. 27).

Do, K. Q., Cabungcal, J. H., Frank, A., Steullet, P., & Cuenod, M. (2009). Redox dysregulation, neurodevelopment, and schizophrenia. *Current Opinion in Neurobiology*, *19*(2), 220–230. http://dx.doi.org/10.1016/j.conb.2009.05.001.

Do, K. Q., Trabesinger, A. H., Kirsten-Kruger, M., Lauer, C. J., Dydak, U., Hell, D., et al. (2000). Schizophrenia: glutathione deficit in cerebrospinal fluid and prefrontal cortex in vivo. *European Journal of Neuroscience*, *12*(10), 3721–3728.

Douet, V., Chang, L., Pritchett, A., Lee, K., Keating, B., Bartsch, H., et al. (2014). Schizophrenia-risk variant rs6994992 in the neuregulin-1 gene on brain developmental trajectories in typically developing children. *Translational Psychiatry*, *4*, e392. http://dx.doi.org/10.1038/tp.2014.41.

Dracheva, S., Davis, K. L., Chin, B., Woo, D. A., Schmeidler, J., & Haroutunian, V. (2006). Myelin-associated mRNA and protein expression deficits in the anterior cingulate cortex and hippocampus in elderly schizophrenia patients. *Neurobiology of Disease*, *21*(3), 531–540. http://dx.doi.org/10.1016/j.nbd.2005.08.012.

Dringen, R. (2000). Metabolism and functions of glutathione in brain. *Progress in Neurobiology*, *62*(6), 649–671.

Du, F., & Ongur, D. (2013). Probing myelin and axon abnormalities separately in psychiatric disorders using MRI techniques. *Frontiers in Integrative Neuroscience*, *7*, 24. http://dx.doi.org/10.3389/fnint.2013.00024.

Dwir, D., Cabungcal, J.-H., Steullet, P., Fournier, M., Tirouvanziam, R., & Do, K. Q. (2014). Involvement of the receptor for advanced glycation end-product (RAGE) in redox dysregulation and neuroinflammation in an animal model of schizophrenia. *Biological Psychiatry*, *75*(9).

Eikenes, L., Lohaugen, G. C., Brubakk, A. M., Skranes, J., & Haberg, A. K. (2011). Young adults born preterm with very low birth weight demonstrate widespread white matter alterations on brain DTI. *NeuroImage*, *54*(3), 1774–1785. http://dx.doi.org/10.1016/j.neuroimage.2010.10.037.

El Waly, B., Macchi, M., Cayre, M., & Durbec, P. (2014). Oligodendrogenesis in the normal and pathological central nervous system. *Frontiers in Neuroscience*, *8*, 145. http://dx.doi.org/10.3389/fnins.2014.00145.

Eluvathingal, T. J., Chugani, H. T., Behen, M. E., Juhasz, C., Muzik, O., Maqbool, M., et al. (2006). Abnormal brain connectivity in children after early severe socioemotional deprivation: a diffusion tensor imaging study. *Pediatrics*, *117*(6), 2093–2100. http://dx.doi.org/10.1542/peds.2005-1727.

Fallin, M. D., Lasseter, V. K., Avramopoulos, D., Nicodemus, K. K., Wolyniec, P. S., McGrath, J. A., et al. (2005). Bipolar I disorder and schizophrenia: a 440-single-nucleotide polymorphism screen of 64 candidate genes among Ashkenazi Jewish case-parent trios. *American Journal of Human Genetics*, *77*(6), 918–936. http://dx.doi.org/10.1086/497703.

Ferreira, B., Mendes, F., Osorio, N., Caseiro, A., Gabriel, A., & Valado, A. (2013). Glutathione in multiple sclerosis. *British Journal of Biomedical Science*, *70*(2), 75–79.

Fitzsimmons, J., Kubicki, M., & Shenton, M. E. (2013). Review of functional and anatomical brain connectivity findings in schizophrenia. *Current Opinion in Psychiatry*, *26*(2), 172–187. http://dx.doi.org/10.1097/YCO.0b013e32835d9e6a.

Flatow, J., Buckley, P., & Miller, B. J. (2013). Meta-analysis of oxidative stress in schizophrenia. *Biological Psychiatry*, *74*(6), 400–409. http://dx.doi.org/10.1016/j.biopsych.2013.03.018.

Fornito, A., Zalesky, A., Pantelis, C., & Bullmore, E. T. (2012). Schizophrenia, neuroimaging and connectomics. *NeuroImage*, *62*(4), 2296–2314. http://dx.doi.org/10.1016/j.neuroimage.2011.12.090.

Fournier, M., Ferrari, C., Baumann, P. S., Polari, A., Monin, A., Bellier-Teichmann, T., et al. (2014). Impaired metabolic reactivity to oxidative stress in early psychosis patients. *Schizophrenia Bulletin*. http://dx.doi.org/10.1093/schbul/sbu053.

French, H. M., Reid, M., Mamontov, P., Simmons, R. A., & Grinspan, J. B. (2009). Oxidative stress disrupts oligodendrocyte maturation. *Journal of Neuroscience Research*, *87*(14), 3076–3087. http://dx.doi.org/10.1002/jnr.22139.

Frodl, T., Carballedo, A., Fagan, A. J., Lisiecka, D., Ferguson, Y., & Meaney, J. F. (2012). Effects of early-life adversity on white matter diffusivity changes in patients at risk for major depression. *Journal of Psychiatry Neuroscience*, *37*(1), 37–45. http://dx.doi.org/10.1503/jpn.110028.

Fuster, J. M. (2002). Frontal lobe and cognitive development. *Journal of Neurocytology*, *31*(3–5), 373–385.

Gawryluk, J. W., Wang, J. F., Andreazza, A. C., Shao, L., & Young, L. T. (2011). Decreased levels of glutathione, the major brain antioxidant, in post-mortem prefrontal cortex from patients with psychiatric disorders. *International Journal of Neuropsychopharmacology*, *14*(1), 123–130. http://dx.doi.org/10.1017/S1461145710000805.

Gerstner, B., DeSilva, T. M., Genz, K., Armstrong, A., Brehmer, F., Neve, R. L., et al. (2008). Hyperoxia causes maturation-dependent cell death in the developing white matter. *Journal of Neuroscience*, *28*(5), 1236–1245. http://dx.doi.org/10.1523/JNEUROSCI.3213-07.2008.

Gironi, M., Borgiani, B., Mariani, E., Cursano, C., Mendozzi, L., Cavarretta, R., et al. (2014). Oxidative stress is differentially present in multiple sclerosis courses, early evident, and unrelated to treatment. *Journal of Immunology Research*, *2014*, 961863. http://dx.doi.org/10.1155/2014/961863.

Go, Y. M., & Jones, D. P. (2008). Redox compartmentalization in eukaryotic cells. *Biochimica et Biophysica Acta*, *1780*(11), 1273–1290. http://dx.doi.org/10.1016/j.bbagen.2008.01.011.

Gogolla, N., Caroni, P., Luthi, A., & Herry, C. (2009). Perineuronal nets protect fear memories from erasure. *Science*, *325*(5945), 1258–1261. http://dx.doi.org/10.1126/science.1174146.

Goldshmit, Y., Erlich, S., & Pinkas-Kramarski, R. (2001). Neuregulin rescues PC12-ErbB4 cells from cell death induced by H(2)O(2). Regulation of reactive oxygen species levels by phosphatidylinositol 3-kinase. *Journal of Biological Chemistry*, *276*(49), 46379–46385. http://dx.doi.org/10.1074/jbc.M105637200.

Goncalves, L., Dafre, A. L., Carobrez, S. G., & Gasparotto, O. C. (2008). A temporal analysis of the relationships between social stress, humoral immune response and glutathione-related antioxidant defenses. *Behavioural Brain Research*, *192*(2), 226–231. http://dx.doi.org/10.1016/j.bbr.2008.04.010.

Govindan, R. M., Behen, M. E., Helder, E., Makki, M. I., & Chugani, H. T. (2010). Altered water diffusivity in cortical association tracts in children with early deprivation identified with Tract-Based Spatial Statistics (TBSS). *Cerebral Cortex*, *20*(3), 561–569. http://dx.doi.org/10.1093/cercor/bhp122.

Gravina, P., Spoletini, I., Masini, S., Valentini, A., Vanni, D., Paladini, E., et al. (2011). Genetic polymorphisms of glutathione S-transferases GSTM1, GSTT1, GSTP1 and GSTA1 as risk factors for schizophrenia. *Psychiatry Research*, *187*(3), 454–456. http://dx.doi.org/10.1016/j.psychres.2010.10.008.

Grignon, S., & Chianetta, J. M. (2007). Assessment of malondialdehyde levels in schizophrenia: a meta-analysis and some methodological considerations. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *31*(2), 365–369. http://dx.doi.org/10.1016/j.pnpbp.2006.09.012.

Gysin, R., Kraftsik, R., Sandell, J., Bovet, P., Chappuis, C., Conus, P., et al. (2007). Impaired glutathione synthesis in schizophrenia: convergent genetic and functional evidence. *Proceedings of the National Academy of Sciences of the United States of America*, *104*(42), 16621–16626. http://dx.doi.org/10.1073/pnas.0706778104.

Hakak, Y., Walker, J. R., Li, C., Wong, W. H., Davis, K. L., Buxbaum, J. D., et al. (2001). Genome-wide expression analysis reveals dysregulation of myelination-related genes in chronic schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America*, *98*(8), 4746–4751. http://dx.doi.org/10.1073/pnas.081071198.

Hanson, J. L., Adluru, N., Chung, M. K., Alexander, A. L., Davidson, R. J., & Pollak, S. D. (2013). Early neglect is associated with alterations in white matter integrity and cognitive functioning. *Child Development*, *84*(5), 1566–1578. http://dx.doi.org/10.1111/cdev.12069.

Hanzawa, R., Ohnuma, T., Nagai, Y., Shibata, N., Maeshima, H., Baba, H., et al. (2011). No association between glutathione-synthesis-related genes and Japanese schizophrenia. *Psychiatry and Clinical Neurosciences*, *65*(1), 39–46. http://dx.doi.org/10.1111/j.1440-1819.2010.02157.x.

Hao, Y., Liu, Z., Jiang, T., Gong, G., Liu, H., Tan, L., et al. (2006). White matter integrity of the whole brain is disrupted in first-episode schizophrenia. *NeuroReport*, *17*(1), 23–26.

Harada, S., Tachikawa, H., & Kawanishi, Y. (2001). Glutathione S-transferase M1 gene deletion may be associated with susceptibility to certain forms of schizophrenia. *Biochemical and Biophysical Research Communications*, *281*(2), 267–271. http://dx.doi.org/10.1006/bbrc.2001.4347.

Hardingham, G. E., & Bading, H. (2010). Synaptic versus extrasynaptic NMDA receptor signalling: implications for neurodegenerative disorders. *Nature Reviews Neuroscience*, *11*(10), 682–696. http://dx.doi.org/10.1038/nrn2911.

Harris, L. W., Lockstone, H. E., Khaitovich, P., Weickert, C. S., Webster, M. J., & Bahn, S. (2009). Gene expression in the prefrontal cortex during adolescence: implications for the onset of schizophrenia. *BMC Medical Genomics*, *2*, 28. http://dx.doi.org/10.1186/1755-8794-2-28.

Haynes, R. L., Folkerth, R. D., Keefe, R. J., Sung, I., Swzeda, L. I., Rosenberg, P. A., et al. (2003). Nitrosative and oxidative injury to premyelinating oligodendrocytes in periventricular leukomalacia. *Journal of Neuropathology & Experimental Neurology*, *62*(5), 441–450.

Haynes, R. L., Folkerth, R. D., Trachtenberg, F. L., Volpe, J. J., & Kinney, H. C. (2009). Nitrosative stress and inducible nitric oxide synthase expression in periventricular leukomalacia. *Acta Neuropathologica*, *118*(3), 391–399. http://dx.doi.org/10.1007/s00401-009-0540-1.

Hikida, T., Gamo, N. J., & Sawa, A. (2012). DISC1 as a therapeutic target for mental illnesses. *Expert Opinion on Therapeutic Targets*, *16*(12), 1151–1160. http://dx.doi.org/10.1517/14728222.2012.719879.

Ho, B. C., Alicata, D., Ward, J., Moser, D. J., O'Leary, D. S., Arndt, S., et al. (2003). Untreated initial psychosis: relation to cognitive deficits and brain morphology in first-episode schizophrenia. *American Journal of Psychiatry*, *160*(1), 142–148.

Ho, B. C., Andreasen, N. C., Nopoulos, P., Arndt, S., Magnotta, V., & Flaum, M. (2003). Progressive structural brain abnormalities and their relationship to clinical outcome: a longitudinal magnetic resonance imaging study early in schizophrenia. *Archives of General Psychiatry*, *60*(6), 585–594. http://dx.doi.org/10.1001/archpsyc.60.6.585.

Hof, P. R., Haroutunian, V., Copland, C., Davis, K. L., & Buxbaum, J. D. (2002). Molecular and cellular evidence for an oligodendrocyte abnormality in schizophrenia. *Neurochemical Research*, *27*(10), 1193–1200.

Hoistad, M., Segal, D., Takahashi, N., Sakurai, T., Buxbaum, J. D., & Hof, P. R. (2009). Linking white and grey matter in schizophrenia: oligodendrocyte and neuron pathology in the prefrontal cortex. *Frontiers in Neuroanatomy*, *3*, 9. http://dx.doi.org/10.3389/neuro.05.009.2009.

Hori, H., Ohmori, O., Shinkai, T., Kojima, H., Okano, C., Suzuki, T., et al. (2000). Manganese superoxide dismutase gene polymorphism and schizophrenia: relation to tardive dyskinesia. *Neuropsychopharmacology*, *23*(2), 170–177. http://dx.doi.org/10.1016/S0893-133X(99)00156-6.

Insel, T. R. (2010). Rethinking schizophrenia. *Nature*, *468*(7321), 187–193. http://dx.doi.org/10.1038/nature09552.

Jablonska, B., Scafidi, J., Aguirre, A., Vaccarino, F., Nguyen, V., Borok, E., et al. (2012). Oligodendrocyte regeneration after neonatal hypoxia requires FoxO1-mediated p27Kip1 expression. *Journal of Neuroscience*, *32*(42), 14775–14793. http://dx.doi.org/10.1523/JNEUROSCI.2060-12.2012.

Jiang, Z., Cowell, R. M., & Nakazawa, K. (2013). Convergence of genetic and environmental factors on parvalbumin-positive interneurons in schizophrenia. *Frontiers in Behavioral Neuroscience*, *7*, 116. http://dx.doi.org/10.3389/fnbeh.2013.00116.

Johnson, A. W., Jaaro-Peled, H., Shahani, N., Sedlak, T. W., Zoubovsky, S., Burruss, D., et al. (2013). Cognitive and motivational deficits together with prefrontal oxidative stress in a mouse model for neuropsychiatric illness. *Proceedings of the National Academy of Sciences of the United States of America*, *110*(30), 12462–12467. http://dx.doi.org/10.1073/pnas.1307925110.

Jones, D. P. (2008). Radical-free biology of oxidative stress. *American Journal of Physiology Cell Physiology*, *295*(4), C849–C868. http://dx.doi.org/10.1152/ajpcell.00283.2008.

Jones, D. P. (2010). Redox sensing: orthogonal control in cell cycle and apoptosis signalling. *Journal of Internal Medicine*, *268*(5), 432–448. http://dx.doi.org/10.1111/j.1365-2796.2010.02268.x.

Jorgensen, A., Broedbaek, K., Fink-Jensen, A., Knorr, U., Greisen Soendergaard, M., Henriksen, T., et al. (2013). Increased systemic oxidatively generated DNA and RNA damage in schizophrenia. *Psychiatry Research*, *209*(3), 417–423. http://dx.doi.org/10.1016/j.psychres.2013.01.033.

Juurlink, B. H., Thorburne, S. K., & Hertz, L. (1998). Peroxide-scavenging deficit underlies oligodendrocyte susceptibility to oxidative stress. *Glia*, *22*(4), 371–378.

Kanaan, R. A., Kim, J. S., Kaufmann, W. E., Pearlson, G. D., Barker, G. J., & McGuire, P. K. (2005). Diffusion tensor imaging in schizophrenia. *Biological Psychiatry*, *58*(12), 921–929. http://dx.doi.org/10.1016/j.biopsych.2005.05.015.

Kang, H. J., Kawasawa, Y. I., Cheng, F., Zhu, Y., Xu, X., Li, M., et al. (2011). Spatio-temporal transcriptome of the human brain. *Nature*, *478*(7370), 483–489. http://www.nature.com/nature/journal/v478/n7370/abs/nature10523.html#supplementary-information.

Karlsgodt, K. H., van Erp, T. G., Poldrack, R. A., Bearden, C. E., Nuechterlein, K. H., & Cannon, T. D. (2008). Diffusion tensor imaging of the superior longitudinal fasciculus and working memory in recent-onset schizophrenia. *Biological Psychiatry*, *63*(5), 512–518. http://dx.doi.org/10.1016/j.biopsych.2007.06.017.

Katsel, P., Davis, K. L., Li, C., Tan, W., Greenstein, E., Kleiner Hoffman, L. B., et al. (2008). Abnormal indices of cell cycle activity in schizophrenia and their potential association with oligodendrocytes. *Neuropsychopharmacology*, *33*(12), 2993–3009. http://dx.doi.org/10.1038/npp.2008.19.

Katsel, P., Tan, W., Abazyan, B., Davis, K. L., Ross, C., Pletnikov, M. V., et al. (2011). Expression of mutant human DISC1 in mice supports abnormalities in differentiation of oligodendrocytes. *Schizophrenia Research*, *130*(1–3), 238–249. http://dx.doi.org/10.1016/j.schres.2011.04.021.

Kensler, T. W., Wakabayashi, N., & Biswal, S. (2007). Cell survival responses to environmental stresses via the Keap1-Nrf2-ARE pathway. *Annual Review of Pharmacology and Toxicology*, *47*(1), 89–116. http://dx.doi.org/10.1146/annurev.pharmtox.46.120604.141046.

Kirkpatrick, B., & Miller, B. J. (2013). Inflammation and schizophrenia. *Schizophrenia Bulletin*, *39*(6), 1174–1179. http://dx.doi.org/10.1093/schbul/sbt141.

Kishi, T., Ikeda, M., Kitajima, T., Yamanouchi, Y., Kinoshita, Y., Kawashima, K., et al. (2008). Glutamate cysteine ligase modifier (GCLM) subunit gene is not associated with methamphetamine-use disorder or schizophrenia in the Japanese population. *Annals of the New York Academy of Sciences*, *1139*, 63–69. http://dx.doi.org/10.1196/annals.1432.022.

Kulak, A., Steullet, P., Cabungcal, J. H., Werge, T., Ingason, A., Cuenod, M., et al. (2013). Redox dysregulation in the pathophysiology of schizophrenia and bipolar disorder: insights from animal models. *Antioxidants & Redox Signaling*, *18*(12), 1428–1443. http://dx.doi.org/10.1089/ars.2012.4858.

Kyriakopoulos, M., Bargiotas, T., Barker, G. J., & Frangou, S. (2008). Diffusion tensor imaging in schizophrenia. *European Psychiatry*, *23*(4), 255–273. http://dx.doi.org/10.1016/j.eurpsy.2007.12.004.

Lebel, C., & Beaulieu, C. (2011). Longitudinal development of human brain wiring continues from childhood into adulthood. *Journal of Neuroscience*, *31*(30), 10937–10947. http://dx.doi.org/10.1523/JNEUROSCI.5302-10.2011.

Lenroot, R. K., & Giedd, J. N. (2006). Brain development in children and adolescents: insights from anatomical magnetic resonance imaging. *Neuroscience & Biobehavioral Reviews*, *30*(6), 718–729. http://dx.doi.org/10.1016/j.neubiorev.2006.06.001.

Li, Z., Dong, T., Proschel, C., & Noble, M. (2007). Chemically diverse toxicants converge on Fyn and c-Cbl to disrupt precursor cell function. *PLoS Biology*, *5*(2), e35. http://dx.doi.org/10.1371/journal.pbio.0050035.

Liu, J., Dietz, K., DeLoyht, J. M., Pedre, X., Kelkar, D., Kaur, J., et al. (2012). Impaired adult myelination in the prefrontal cortex of socially isolated mice. *Nature Neuroscience*, *15*(12), 1621–1623. http://dx.doi.org/10.1038/nn.3263.

Looney, J. M., & Childs, H. M. (1934). The lactic acid and glutathione content of the blood of schizophrenic patients. *Journal of Clinical Investigation*, *13*(6), 963–968. http://dx.doi.org/10.1172/JCI100639.

Lu, S., Wei, Z., Gao, W., Wu, W., Liao, M., Zhang, Y., et al. (2013). White matter integrity alterations in young healthy adults reporting childhood trauma: a diffusion tensor imaging study. *Australian & New Zealand Journal of Psychiatry*, *47*(12), 1183–1190. http://dx.doi.org/10.1177/0004867413508454.

Lu, S. C. (2013). Glutathione synthesis. *Biochimica et Biophysica Acta (BBA) – General Subjects*, *1830*(5), 3143–3153. http://dx.doi.org/10.1016/j.bbagen.2012.09.008.

Ma, J., Li, D. M., Zhang, R., Yang, X. D., Gao, C. G., Lu, S. M., et al. (2010). Genetic analysis of glutamate cysteine ligase modifier (GCLM) gene and schizophrenia in Han Chinese. *Schizophrenia Research*, *119*(1–3), 273–274. http://dx.doi.org/10.1016/j.schres.2009.12.017.

Makinodan, M., Rosen, K. M., Ito, S., & Corfas, G. (2012). A critical period for social experience-dependent oligodendrocyte maturation and myelination. *Science*, *337*(6100), 1357–1360. http://dx.doi.org/10.1126/science.1220845.

Makinodan, M., Tatsumi, K., Manabe, T., Yamauchi, T., Makinodan, E., Matsuyoshi, H., et al. (2008). Maternal immune activation in mice delays myelination and axonal development in the hippocampus of the offspring. *Journal of Neuroscience Research*, *86*(10), 2190–2200. http://dx.doi.org/10.1002/jnr.21673.

Makinodan, M., Yamauchi, T., Tatsumi, K., Okuda, H., Noriyama, Y., Sadamatsu, M., et al. (2009). Yi-gan san restores behavioral alterations and a decrease of brain glutathione level in a mouse model of schizophrenia. *Journal of Brain Disease*, *1*, 1–6.

Matsuzawa, D., & Hashimoto, K. (2011). Magnetic resonance spectroscopy study of the antioxidant defense system in schizophrenia. *Antioxidants & Redox Signaling*, *15*(7), 2057–2065. http://dx.doi.org/10.1089/ars.2010.3453.

Matsuzawa, D., Hashimoto, K., Hashimoto, T., Shimizu, E., Watanabe, H., Fujita, Y., et al. (2009). Association study between the genetic polymorphisms of glutathione-related enzymes and schizophrenia in a Japanese population. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *150B*(1), 86–94. http://dx.doi.org/10.1002/ajmg.b.30776.

McIntosh, A. M., Moorhead, T. W., Job, D., Lymer, G. K., Munoz Maniega, S., McKirdy, J., et al. (2008). The effects of a neuregulin 1 variant on white matter density and integrity. *Molecular Psychiatry*, *13*(11), 1054–1059. http://dx.doi.org/10.1038/sj.mp.4002103.

Mei, L., & Nave, K. A. (2014). Neuregulin-ERBB signaling in the nervous system and neuropsychiatric diseases. *Neuron*, *83*(1), 27–49. http://dx.doi.org/10.1016/j.neuron.2014.06.007.

Meyer, U., & Feldon, J. (2012). To poly(I: C) or not to poly(I: C): advancing preclinical schizophrenia research through the use of prenatal immune activation models. *Neuropharmacology*, *62*(3), 1308–1321. http://dx.doi.org/10.1016/j.neuropharm.2011.01.009.

Michel, T. M., Thome, J., Martin, D., Nara, K., Zwerina, S., Tatschner, T., et al. (2004). Cu, Zn- and Mn-superoxide dismutase levels in brains of patients with schizophrenic psychosis. *Journal of Neural Transmission*, *111*(9), 1191–1201. http://dx.doi.org/10.1007/s00702-004-0160-9.

Mico, J. A., Rojas-Corrales, M. O., Gibert-Rahola, J., Parellada, M., Moreno, D., Fraguas, D., et al. (2011). Reduced antioxidant defense in early onset first-episode psychosis: a case-control study. *BMC Psychiatry*, *11*, 26. http://dx.doi.org/10.1186/1471-244X-11-26.

Millar, J. K., Wilson-Annan, J. C., Anderson, S., Christie, S., Taylor, M. S., Semple, C. A., et al. (2000). Disruption of two novel genes by a translocation co-segregating with schizophrenia. *Human Molecular Genetics*, *9*(9), 1415–1423.

Mitew, S., Hay, C. M., Peckham, H., Xiao, J., Koenning, M., & Emery, B. (2013). Mechanisms regulating the development of oligodendrocytes and central nervous system myelin. *Neuroscience*. http://dx.doi.org/10.1016/j.neuroscience.2013.11.029.

Miyaoka, T., Yasukawa, R., Yasuda, H., Shimizu, M., Mizuno, S., Sukegawa, T., et al. (2005). Urinary excretion of biopyrrins, oxidative metabolites of bilirubin, increases in patients with psychiatric disorders. *European Neuropsychopharmacology*, *15*(3), 249–252. http://dx.doi.org/10.1016/j.euroneuro.2004.11.002.

Monin, A., Baumann, P. S., Griffa, A., Xin, L., Mekle, R., Fournier, M., et al. (2014). Glutathione deficit impairs myelin maturation: relevance for white matter integrity in schizophrenia patients. *Molecular Psychiatry*. http://dx.doi.org/10.1038/mp.2014.88.

Morishita, H., & Hensch, T. K. (2008). Critical period revisited: impact on vision. *Current Opinion in Neurobiology*, *18*(1), 101–107. http://dx.doi.org/10.1016/j.conb.2008.05.009.

Noble, M., Smith, J., Power, J., & Mayer-Proschel, M. (2003). Redox state as a central modulator of precursor cell function. *Annals of the New York Academy of Sciences*, *991*, 251–271.

Ohnuma, T., Kato, H., Arai, H., McKenna, P. J., & Emson, P. C. (2003). Expression of Fyn, a non-receptor tyrosine kinase in prefrontal cortex from patients with schizophrenia and its correlation with clinical onset. *Brain Research. Molecular Brain Research*, *112*(1–2), 90–94.

Okumura, T., Okochi, T., Kishi, T., Ikeda, M., Kitajima, T., Yamanouchi, Y., et al. (2009). No association between polymorphisms of neuronal oxide synthase 1 gene (NOS1) and schizophrenia in a Japanese population. *NeuroMolecular Medicine*, *11*(2), 123–127. http://dx.doi.org/10.1007/s12017-009-8068-z.

van Os, J., Rutten, B. P., & Poulton, R. (2008). Gene-environment interactions in schizophrenia: review of epidemiological findings and future directions. *Schizophrenia Bulletin*, *34*(6), 1066–1082. http://dx.doi.org/10.1093/schbul/sbn117.

Ostman, A., & Bohmer, F. D. (2001). Regulation of receptor tyrosine kinase signaling by protein tyrosine phosphatases. *Trends in Cell Biology*, *11*(6), 258–266.

Pae, C. U., Kim, T. S., Patkar, A. A., Kim, J. J., Lee, C. U., Lee, S. J., et al. (2007). Manganese superoxide dismutase (MnSOD: Ala-9Val) gene polymorphism may not be associated with schizophrenia and tardive dyskinesia. *Psychiatry Research*, *153*(1), 77–81. http://dx.doi.org/10.1016/j.psychres.2006.04.011.

Park, Y. U., Jeong, J., Lee, H., Mun, J. Y., Kim, J. H., Lee, J. S., et al. (2010). Disrupted-in-schizophrenia 1 (DISC1) plays essential roles in mitochondria in collaboration with Mitofilin. *Proceedings of the National Academy of Sciences of the United States of America*, *107*(41), 17785–17790. http://dx.doi.org/10.1073/pnas.1004361107.

Pasichna, E. P., Morozova, R. P., Donchenko, H. V., Vinychuk, S. M., & Kopchak, O. O. (2007). Lipid peroxidation and antioxidant defence enzyme activity in multiple sclerosis. *Ukrainskiĭ Biokhimicheskiĭ Zhurnal*, *79*(5), 165–174.

Paul, R., Henry, L., Grieve, S. M., Guilmette, T. J., Niaura, R., Bryant, R., et al. (2008). The relationship between early life stress and microstructural integrity of the corpus callosum in a non-clinical population. *Neuropsychiatric Disease and Treatment*, *4*(1), 193–201.

Peters, B. D., & Karlsgodt, K. H. (2014). White matter development in the early stages of psychosis. *Schizophrenia Research*. http://dx.doi.org/10.1016/j.schres.2014.05.021.

Peters, B. D., Schmitz, N., Dingemans, P. M., van Amelsvoort, T. A., Linszen, D. H., de Haan, L., et al. (2009). Preliminary evidence for reduced frontal white matter integrity in subjects at ultra-high-risk for psychosis. *Schizophrenia Research*, *111*(1–3), 192–193. http://dx.doi.org/10.1016/j.schres.2009.03.018.

Poels, E. M., Kegeles, L. S., Kantrowitz, J. T., Slifstein, M., Javitt, D. C., Lieberman, J. A., et al. (2014). Imaging glutamate in schizophrenia: review of findings and implications for drug discovery. *Molecular Psychiatry*, *19*(1), 20–29. http://dx.doi.org/10.1038/mp.2013.136.

Ponniah, S., Wang, D. Z., Lim, K. L., & Pallen, C. J. (1999). Targeted disruption of the tyrosine phosphatase PTPalpha leads to constitutive downregulation of the kinases Src and Fyn. *Current Biology*, *9*(10), 535–538.

Raffa, M., Mechri, A., Othman, L. B., Fendri, C., Gaha, L., & Kerkeni, A. (2009). Decreased glutathione levels and antioxidant enzyme activities in untreated and treated schizophrenic patients. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *33*(7), 1178–1183. http://dx.doi.org/10.1016/j.pnpbp.2009.06.018.

Reif, A., Herterich, S., Strobel, A., Ehlis, A. C., Saur, D., Jacob, C. P., et al. (2006). A neuronal nitric oxide synthase (NOS-I) haplotype associated with schizophrenia modifies prefrontal cortex function. *Molecular Psychiatry*, *11*(3), 286–300. http://dx.doi.org/10.1038/sj.mp.4001779.

Ren, Y., Wang, H., & Xiao, L. (2013). Improving myelin/oligodendrocyte-related dysfunction: a new mechanism of antipsychotics in the treatment of schizophrenia? *International Journal of Neuropsychopharmacology*, *16*(3), 691–700. http://dx.doi.org/10.1017/S1461145712001095.

Ritter, J., Schmitz, T., Chew, L. J., Buhrer, C., Mobius, W., Zonouzi, M., et al. (2013). Neonatal hyperoxia exposure disrupts axon-oligodendrocyte integrity in the subcortical white matter. *Journal of Neuroscience*, *33*(21), 8990–9002. http://dx.doi.org/10.1523/JNEUROSCI.5528-12.2013.

Rodriguez-Santiago, B., Brunet, A., Sobrino, B., Serra-Juhe, C., Flores, R., Armengol, L., et al. (2010). Association of common copy number variants at the glutathione S-transferase genes and rare novel genomic changes with schizophrenia. *Molecular Psychiatry*, *15*(10), 1023–1033. http://dx.doi.org/10.1038/mp.2009.53.

Roosendaal, S. D., Geurts, J. J., Vrenken, H., Hulst, H. E., Cover, K. S., Castelijns, J. A., et al. (2009). Regional DTI differences in multiple sclerosis patients. *NeuroImage*, *44*(4), 1397–1403. http://dx.doi.org/10.1016/j.neuroimage.2008.10.026.

Ruiz, S., Birbaumer, N., & Sitaram, R. (2013). Abnormal neural connectivity in schizophrenia and fMRI-brain-computer interface as a potential therapeutic approach. *Frontiers in Psychiatry*, *4*, 17. http://dx.doi.org/10.3389/fpsyt.2013.00017.

Ruiz-Litago, F., Seco, J., Echevarria, E., Martinez-Cengotitabengoa, M., Gil, J., Irazusta, J., et al. (2012). Adaptive response in the antioxidant defence system in the course and outcome in first-episode schizophrenia patients: a 12-months follow-up study. *Psychiatry Research*, *200*(2–3), 218–222. http://dx.doi.org/10.1016/j.psychres.2012.07.024.

Saadat, M., Mobayen, F., & Farrashbandi, H. (2007). Genetic polymorphism of glutathione S-transferase T1: a candidate genetic modifier of individual susceptibility to schizophrenia. *Psychiatry Research*, *153*(1), 87–91. http://dx.doi.org/10.1016/j.psychres.2006.03.024.

Salmaso, N., Jablonska, B., Scafidi, J., Vaccarino, F. M., & Gallo, V. (2014). Neurobiology of premature brain injury. *Nature Neuroscience*, *17*(3), 341–346. http://dx.doi.org/10.1038/nn.3604.

Salmeen, A., & Barford, D. (2005). Functions and mechanisms of redox regulation of cysteine-based phosphatases. *Antioxidants & Redox Signaling*, *7*(5–6), 560–577. http://dx.doi.org/10.1089/ars.2005.7.560.

Samartzis, L., Dima, D., Fusar-Poli, P., & Kyriakopoulos, M. (2014). White matter alterations in early stages of schizophrenia: a systematic review of diffusion tensor imaging studies. *Journal of Neuroimaging*, *24*(2), 101–110. http://dx.doi.org/10.1111/j.1552-6569.2012.00779.x.

Sarandol, A., Kirli, S., Akkaya, C., Altin, A., Demirci, M., & Sarandol, E. (2007). Oxidative-antioxidative systems and their relation with serum S100 B levels in patients with schizophrenia: effects of short term antipsychotic treatment. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *31*(6), 1164–1169. http://dx.doi.org/10.1016/j.pnpbp.2007.03.008.

Sato, H., Takahashi, T., Sumitani, K., Takatsu, H., & Urano, S. (2010). Glucocorticoid generates ROS to induce oxidative injury in the Hippocampus, leading to impairment of cognitive function of rats. *Journal of Clinical Biochemistry and Nutrition*, *47*(3), 224–232. http://dx.doi.org/10.3164/jcbn.10-58.

Schiavone, S., Jaquet, V., Trabace, L., & Krause, K. H. (2013). Severe life stress and oxidative stress in the brain: from animal models to human pathology. *Antioxidants & Redox Signaling*, *18*(12), 1475–1490. http://dx.doi.org/10.1089/ars.2012.4720.

Schmitt, A., Hasan, A., Gruber, O., & Falkai, P. (2011). Schizophrenia as a disorder of disconnectivity. *European Archives of Psychiatry and Clinical Neurosciences*, *261*(Suppl. 2), S150–S154. http://dx.doi.org/10.1007/s00406-011-0242-2.

Schmitt, A., Malchow, B., Hasan, A., & Falkai, P. (2014). The impact of environmental factors in severe psychiatric disorders. *Frontiers in Neuroscience*, *8*, 19. http://dx.doi.org/10.3389/fnins.2014.00019.

Schmitz, T., Ritter, J., Mueller, S., Felderhoff-Mueser, U., Chew, L. J., & Gallo, V. (2011). Cellular changes underlying hyperoxia-induced delay of white matter development. *Journal of Neuroscience*, *31*(11), 4327–4344. http://dx.doi.org/10.1523/JNEUROSCI.3942-10.2011.

Schrader, M., & Fahimi, H. D. (2006). Peroxisomes and oxidative stress. *Biochimica et Biophysica Acta*, *1763*(12), 1755–1766. http://dx.doi.org/10.1016/j.bbamcr.2006.09.006.

Seven, A., Aslan, M., Incir, S., & Altintas, A. (2013). Evaluation of oxidative and nitrosative stress in relapsing remitting multiple sclerosis: effect of corticosteroid therapy. *Folia Neuropathologica*, *51*(1), 58–64.

Sofic, E., Rustembegovic, A., Kroyer, G., & Cao, G. (2002). Serum antioxidant capacity in neurological, psychiatric, renal diseases and cardiomyopathy. *Journal of Neural Transmission*, *109*(5–6), 711–719. http://dx.doi.org/10.1007/s007020200059.

Sprooten, E., Lymer, G. K., Munoz Maniega, S., McKirdy, J., Clayden, J. D., Bastin, M. E., et al. (2009). The relationship of anterior thalamic radiation integrity to psychosis risk associated neuregulin-1 variants. *Molecular Psychiatry*, *14*(3), 237–238. http://dx.doi.org/10.1038/mp.2008.136 233.

Sprooten, E., Sussmann, J. E., Moorhead, T. W., Whalley, H. C., Ffrench-Constant, C., Blumberg, H. P., et al. (2011). Association of white matter integrity with genetic variation in an exonic DISC1 SNP. *Molecular Psychiatry*, *16(7)*(685), 688–689. http://dx.doi.org/10.1038/mp.2011.15.

Steelman, A. J., & Li, J. (2011). Poly(I: C) promotes TNFalpha/TNFR1-dependent oligodendrocyte death in mixed glial cultures. *Journal of Neuroinflammation*, *8*, 89. http://dx.doi.org/10.1186/1742-2094-8-89.

Steullet, P., Cabungcal, J. H., Kulak, A., Kraftsik, R., Chen, Y., Dalton, T. P., et al. (2010). Redox dysregulation affects the ventral but not dorsal hippocampus: impairment of parvalbumin neurons, gamma oscillations, and related behaviors. *Journal of Neuroscience*, *30*(7), 2547–2558. http://dx.doi.org/10.1523/JNEUROSCI.3857-09.2010.

Steullet, P., Cabungcal, J. H., Monin, A., Dwir, D., O'Donnell, P., Cuenod, M., et al. (2014). Redox dysregulation, neuroinflammation, and NMDA receptor hypofunction: a "central hub" in schizophrenia pathophysiology? *Schizophrenia Research*. http://dx.doi.org/10.1016/j.schres.2014.06.021.

Szibor, M., Richter, C., & Ghafourifar, P. (2001). Redox control of mitochondrial functions. *Antioxidants & Redox Signaling*, *3*(3), 515–523. http://dx.doi.org/10.1089/15230860152409149.

Takahashi, N., Sakurai, T., Davis, K. L., & Buxbaum, J. D. (2011). Linking oligodendrocyte and myelin dysfunction to neurocircuitry abnormalities in schizophrenia. *Progress in Neurobiology*, *93*(1), 13–24. http://dx.doi.org/10.1016/j.pneurobio.2010.09.004.

Takesian, A. E., & Hensch, T. K. (2013). Balancing plasticity/stability across brain development. *Progress in Brain Research*, *207*, 3–34. http://dx.doi.org/10.1016/B978-0-444-63327-9.00001-1.

Talukder, I., Kazi, R., & Wollmuth, L. P. (2011). GluN1-specific redox effects on the kinetic mechanism of NMDA receptor activation. *Biophysical Journal*, *101*(10), 2389–2398. http://dx.doi.org/10.1016/j.bpj.2011.10.015.

Tang, W., Huang, K., Tang, R., Zhou, G., Fang, C., Zhang, J., et al. (2008). Evidence for association between the 5′ flank of the NOS1 gene and schizophrenia in the Chinese population. *International Journal of Neuropsychopharmacology*, *11*(08), 1063–1071. http://dx.doi.org/10.1017/S1461145708008924.

Thorburne, S. K., & Juurlink, B. H. (1996). Low glutathione and high iron govern the susceptibility of oligodendroglial precursors to oxidative stress. *Journal of Neurochemistry*, *67*(3), 1014–1022.

Tkachev, D., Mimmack, M. L., Ryan, M. M., Wayland, M., Freeman, T., Jones, P. B., et al. (2003). Oligodendrocyte dysfunction in schizophrenia and bipolar disorder. *Lancet*, *362*(9386), 798–805. http://dx.doi.org/10.1016/S0140-6736(03)14289-4.

Tosic, M., Ott, J., Barral, S., Bovet, P., Deppen, P., Gheorghita, F., et al. (2006). Schizophrenia and oxidative stress: glutamate cysteine ligase modifier as a susceptibility gene. *American Journal of Human Genetics*, *79*(3), 586–592. http://dx.doi.org/10.1086/507566.

Tsai, M. C., Liou, C. W., Lin, T. K., Lin, I. M., & Huang, T. L. (2013). Changes in oxidative stress markers in patients with schizophrenia: the effect of antipsychotic drugs. *Psychiatry Research*, *209*(3), 284–290. http://dx.doi.org/10.1016/j.psychres.2013.01.023.

Uranova, N. A., Vikhreva, O. V., Rachmanova, V. I., & Orlovskaya, D. D. (2011). Ultrastructural alterations of myelinated fibers and oligodendrocytes in the prefrontal cortex in schizophrenia: a postmortem morphometric study. *Schizophrenia Research and Treatment*, *2011*, 325789. http://dx.doi.org/10.1155/2011/325789.

Uranova, N. A., Vostrikov, V. M., Orlovskaya, D. D., & Rachmanova, V. I. (2004). Oligodendroglial density in the prefrontal cortex in schizophrenia and mood disorders: a study from the Stanley Neuropathology Consortium. *Schizophrenia Research*, *67*(2–3), 269–275. http://dx.doi.org/10.1016/S0920-9964(03)00181-6.

Valko, M., Leibfritz, D., Moncol, J., Cronin, M. T., Mazur, M., & Telser, J. (2007). Free radicals and antioxidants in normal physiological functions and human disease. *International Journal of Biochemistry & Cell Biology*, *39*(1), 44–84. http://dx.doi.org/10.1016/j.biocel.2006.07.001.

Ventriglia, M., Scassellati, C., Bonvicini, C., Squitti, R., Bevacqua, M. G., Foresti, G., et al. (2006). No association between Ala9Val functional polymorphism of MnSOD gene and schizophrenia in a representative Italian sample. *Neuroscience Letters*, *410*(3), 208–211. http://dx.doi.org/10.1016/j.neulet.2006.10.009.

Vostrikov, V., & Uranova, N. (2011). Age-related increase in the number of oligodendrocytes is dysregulated in schizophrenia and mood disorders. *Schizophrenia Research and Treatment*, *2011*, 174689. http://dx.doi.org/10.1155/2011/174689.

Vostrikov, V. M., Uranova, N. A., & Orlovskaya, D. D. (2007). Deficit of perineuronal oligodendrocytes in the prefrontal cortex in schizophrenia and mood disorders. *Schizophrenia Research*, *94*(1–3), 273–280. http://dx.doi.org/10.1016/j.schres.2007.04.014.

Wang, F., Jiang, T., Sun, Z., Teng, S. L., Luo, X., Zhu, Z., et al. (2009). Neuregulin 1 genetic variation and anterior cingulum integrity in patients with schizophrenia and healthy controls. *Journal of Psychiatry & Neuroscience*, *34*(3), 181–186.

Wang, J. F., Shao, L., Sun, X., & Young, L. T. (2009). Increased oxidative stress in the anterior cingulate cortex of subjects with bipolar disorder and schizophrenia. *Bipolar Disorder*, *11*(5), 523–529. http://dx.doi.org/10.1111/j.1399-5618.2009.00717.x.

Weinberger, D. R. (1987). Implications of normal brain development for the pathogenesis of schizophrenia. *Archives of General Psychiatry*, *44*(7), 660–669.

Whitford, T. J., Ford, J. M., Mathalon, D. H., Kubicki, M., & Shenton, M. E. (2012). Schizophrenia, myelination, and delayed corollary discharges: a hypothesis. *Schizophrenia Bulletin*, *38*(3), 486–494. http://dx.doi.org/10.1093/schbul/sbq105.

Winterer, G., Konrad, A., Vucurevic, G., Musso, F., Stoeter, P., & Dahmen, N. (2008). Association of 5′ end neuregulin-1 (NRG1) gene variation with subcortical medial frontal microstructure in humans. *NeuroImage*, *40*(2), 712–718. http://dx.doi.org/10.1016/j.neuroimage.2007.12.041.

Witthaus, H., Brune, M., Kaufmann, C., Bohner, G., Ozgurdal, S., Gudlowski, Y., et al. (2008). White matter abnormalities in subjects at ultra high-risk for schizophrenia and first-episode schizophrenic patients. *Schizophrenia Research*, *102*(1–3), 141–149. http://dx.doi.org/10.1016/j.schres.2008.03.022.

Wood, J. D., Bonath, F., Kumar, S., Ross, C. A., & Cunliffe, V. T. (2009). Disrupted-in-schizophrenia 1 and neuregulin 1 are required for the specification of oligodendrocytes and neurones in the zebrafish brain. *Human Molecular Genetics*, *18*(3), 391–404. http://dx.doi.org/10.1093/hmg/ddn361.

Xin, L., Mekle, R., Ferrari, C., Baumann, P. S., Alameda, L., Moser, H., et al. (2014). Genetic association with prefrontal glutathione deficit: a 3T 1H MRS study in early psychosis. *Biological Psychiatry*, *75*(9), 108S.

Xu, M., Wu, X., Jie, B., Zhang, X., Zhang, J., Xin, Y., et al. (2014). Neuregulin-1 protects myocardial cells against H_2O_2-induced apoptosis by regulating endoplasmic reticulum stress. *Cell Biochemistry and Function*, *32*(5), 464–469. http://dx.doi.org/10.1002/cbf.3038.

Yao, J. K., Leonard, S., & Reddy, R. (2006). Altered glutathione redox state in schizophrenia. *Disease Markers*, *22*(1–2), 83–93.

Yao, J. K., Reddy, R., McElhinny, L. G., & van Kammen, D. P. (1998). Reduced status of plasma total antioxidant capacity in schizophrenia. *Schizophrenia Research*, *32*(1), 1–8.

Yao, L., Lui, S., Liao, Y., Du, M. Y., Hu, N., Thomas, J. A., et al. (2013). White matter deficits in first episode schizophrenia: an activation likelihood estimation meta-analysis. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *45*, 100–106. http://dx.doi.org/10.1016/j.pnpbp.2013.04.019.

Zafir, A., & Banu, N. (2009). Modulation of in vivo oxidative status by exogenous corticosterone and restraint stress in rats. *Stress*, *12*(2), 167–177. http://dx.doi.org/10.1080/10253890802234168.

Zhou, Y., Liang, M., Jiang, T., Tian, L., Liu, Y., Liu, Z., et al. (2007). Functional dysconnectivity of the dorsolateral prefrontal cortex in first-episode schizophrenia using resting-state fMRI. *Neuroscience Letters*, *417*(3), 297–302. http://dx.doi.org/10.1016/j.neulet.2007.02.081.