Available online at www.sciencedirect.com
ScienceDirect
Current Opinion in Neurobiology

Redox dysregulation, neurodevelopment, and schizophrenia

Kim Q Do, Jan H Cabungcal, Anita Frank, Pascal Steullet and Michel Cuenod

In schizophrenia, a developmental redox dysregulation constitutes one 'hub' on which converge genetic impairments of glutathione synthesis and environmental vulnerability factors generating oxidative stress. Their timing at critical periods of neurodevelopment could play a decisive role in inducing impairment of neural connectivity and synchronization as observed in schizophrenia. In experimental models, such redox dysregulation induces anomalies strikingly similar to those observed in patients. This is mediated by hypoactive NMDA receptors, impairment of fast-spiking parvalbumin GABA interneurons and deficit in myelination. A treatment restoring the redox balance without side effects yields improvements of negative symptoms in chronic patients. Novel interventions based on these mechanisms if applied in early phases of the disease hold great therapeutic promise.

Addresses
Center for Psychiatric Neuroscience, Department of Psychiatry, Lausanne University Hospital, Site de Cery, CH-1008 Prilly-Lausanne, Switzerland

Corresponding author: Do, Kim Q (kim.do@chuv.ch), Cabungcal, Jan H (JanHarry.Cabungcal@unil.ch), Frank, Anita (anita.frank@chuv.ch), Steullet, Pascal (pascal.steullet@chuv.ch) and Cuenod, Michel (michel.cuenod@hospvd.ch)

Current Opinion in Neurobiology 2009, **19**:1–11

This review comes from a themed issue on Development
Edited by Takao Hensch and Andrea Brand

0959-4388/$ – see front matter
Published by Elsevier Ltd.

DOI 10.1016/j.conb.2009.05.001

Introduction

Schizophrenia is a chronic, devastating, and costly mental illness affecting about 1% of the world population. It develops progressively, often undetected during childhood and adolescence in a premorbid phase, leading to the onset of psychosis at early adulthood. While present antipsychotic treatments are effective against positive symptoms (delusions, hallucinations, and thought disorder), they have significant side effects and are almost ineffectual for negative (deficits in social abilities and speech, affective flattening) and cognitive symptoms (attention, memory, and executive functions) and perceptual instability (basic symptoms).

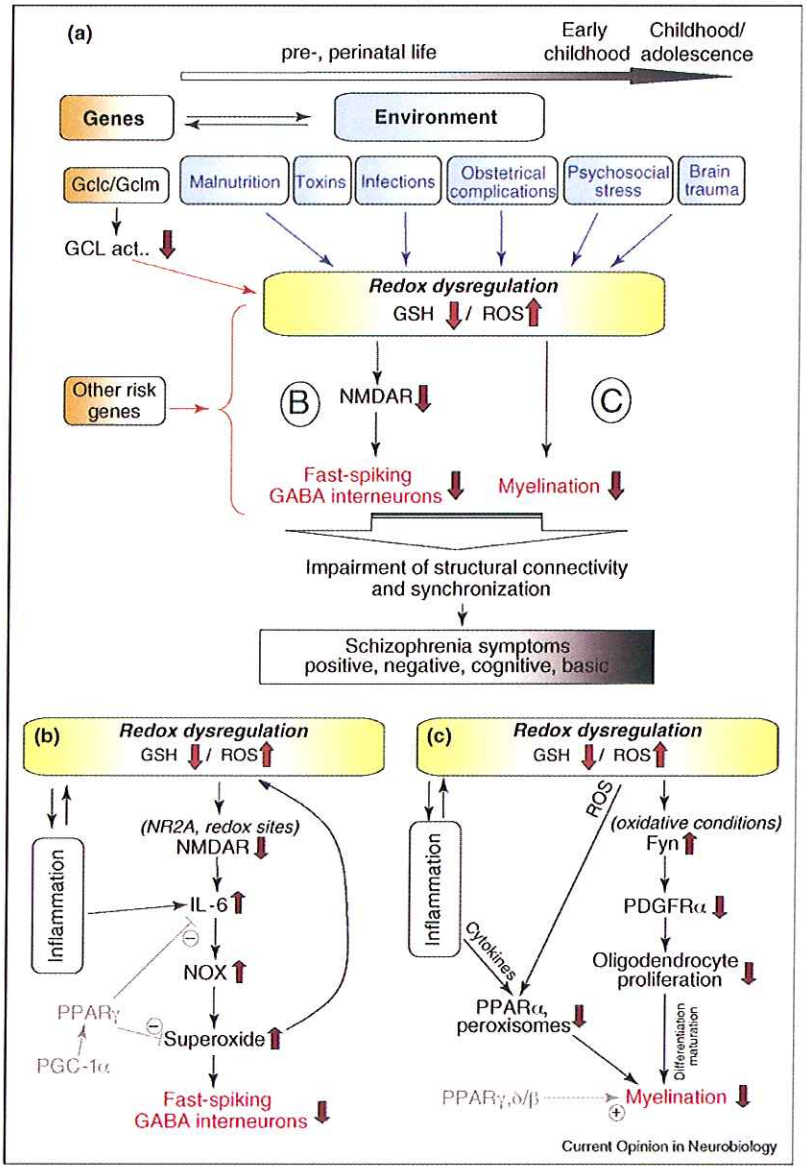
Converging evidence suggests that schizophrenia is a developmental syndrome involving faulty connectivity deriving from multiple genetic and environmental factors [1,2•] that set off a cascade of events extending into adulthood [3,4]. Anatomical findings point to a highly distributed underlying neuropathology. It is necessary to identify 'hubs' or 'final common pathways' leading to various phenotypes [2•]. The present review focus on glutathione (GSH) deficit/redox dysregulation/oxidative stress being such 'hub' candidate, not excluding other potential hubs.

Oxidative and nitrosative stress result from an imbalance between overproduction of reactive oxygen species (ROS), and reactive nitrogen species (RNS) on one side and deficiency of enzymatic and nonenzymatic antioxidants on the other side. This leads to deleterious (per)-oxidations of lipids, proteins, and DNAs [5•]. ROS include superoxide ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2), hydroxyl radical ($^{\bullet}OH$), and peroxyl radical ($ROO^{\bullet}$), while RNS include nitric oxide ($NO^{\bullet}$) and the highly toxic peroxynitrite ($ONOO^-$). The defense systems against oxidative and nitrosative stress consist of enzymes such as superoxide dismutase, glutathione peroxidases, catalase and of nonenzymatic antioxidants which include GSH, ascorbic acid (vitamin C), α-tocopherol (vitamin E), carotenoids, and flavonoids. The brain is particularly vulnerable to oxidative damage because of its high oxygen utilization, its high content of oxidizable polyunsaturated fatty acids and the presence of redox-active metals (Cu and Fe).

The tripeptide GSH (γ-glutamyl-cysteine-glycine), abundant in the cytosol (1–11 mM), nuclei (3–15 mM), and mitochondria (5–11 mM), is the major thiol antioxidant and redox buffer of the cell. GSH maintains the redox state of critical protein sulfydryls that are necessary for redox-sensitive processes [6••] such as cell cycle regulation and cell differentiation [7], receptor activation (e.g. NMDA receptor [8]), signal transduction, and transcription factor (e.g. Nrf-2 and NF-κB). The main protective roles of GSH against oxidative stress are: firstly, GSH is a cofactor of several detoxifying enzymes against oxidative stress, for example glutathione peroxidase, glutathione transferase, and others [9•]; secondly, GSH scavenges hydroxyl radical and singlet oxygen directly, detoxifying hydrogen peroxide and lipid peroxides by the catalytic action of glutathione peroxidase; thirdly, GSH is able to regenerate the most important antioxidants, vitamins C and E, back to their active forms. This capacity is

Please cite this article in press as: Do KQ, et al. Redox dysregulation, neurodevelopment, and schizophrenia, Curr Opin Neurobiol (2009), doi:10.1016/j.conb.2009.05.001

Figure 1



Convergence of genetic and environmental factors on redox system in schizophrenia pathophysiology. **(a)** Environmental risk factors for schizophrenia can cause transient or even long-term redox dysregulation in the brain and peripheral tissues (see Supplementary table 1A). Such environmentally induced redox dysregulation when combined with a genetic susceptibility (e.g. 'high-risk' polymorphism of GCLC, the gene coding for the catalytic subunit of glutamate cysteine ligase (GCL)) could lead to the disruption of normal brain development and maturation. For instance, redox dysregulation can impair the development of parvalbumin-immunoreactive (PV-IR) interneurons and oligodendrocytes. The resulting decrease in number of functional fast-spiking interneurons and myelination would affect the structural and functional connectivity in the brain and contribute to the development of schizophrenia-related symptoms. **(b)** Redox dysregulation affects fast-spiking interneurons. A decrease in GSH levels and/or increase in ROS lead(s) to NMDAR hypofunction [39]. The NR2A subunit is particularly sensitive to the thiol redox status [38] and plays a pivotal role in the maintenance of the function of PV interneurons [48•]. In addition, NMDAR hypofunction has been recently shown to increase levels of interleukin-6 (IL-6), followed by an increase in NADPH oxidase (NOX) activity and superoxide production that ultimately affects normal expression of PV [49••,50•]. The production of superoxide might further enhance the oxidative stress, particularly in subjects with a genetic susceptibility associated with antioxidant systems. The high expression of PGC-1α, a coactivator of peroxisome proliferator activated receptors γ (PPARγ), in GABAergic interneurons during postnatal development and adulthood [51] suggests that PPARγ could help counteract this mechanism via inhibition of IL-6 and superoxide scavenging by upregulation of superoxide dismutase. **(c)** Redox dysregulation affects myelination. Oxidative conditions have been shown to increase Fyn activity leading to a decrease in platelet-derived growth factor receptor-α (PDGFR-α)-mediated signaling and a decrease in proliferation of oligodendrocyte precursors [31••]. In addition, ROS and cytokines inhibit PPARα-dependent peroxisome function known to be essential for oligodendrocyte maturation and myelination [27•]. PPARγ, β/δ-dependent pathways that are implicated in the oligodendrocyte differentiation and myelination could also protect against excessive oxidative stress via

Please cite this article in press as: Do KQ, et al. Redox dysregulation, neurodevelopment, and schizophrenia, Curr Opin Neurobiol (2009), doi:10.1016/j.conb.2009.05.001

linked with the redox state of the glutathione disulfide–glutathione couple (GSSG/2GSH). Thus GSH deficiency induces oxidative stress, leading to deleterious (per)oxidations of lipids, proteins, and DNAs, altering lipid metabolism and affecting mitochondrial function.

In schizophrenia, we propose that developmental dysregulation of GSH synthesis of genetic origin, when combined with environmental risk factors generating oxidative stress, can play a critical role in inducing deficits in neural connectivity and synchronization observed in the disease (Figure 1a). This would be mediated by hypoactive NMDA receptors (NMDA-Rs), developmental impairment of fast-spiking parvalbumin (PV) GABA interneurons (Figure 1b), and anomalies in myelination (Figure 1c).

Causes of redox dysregulation and oxidative stress

Genetic impairment of GSH synthesis

In schizophrenia, impaired antioxidant defense systems and increased lipid peroxidation have been reported in peripheral tissues and postmortem brain of schizophrenia patients [10–13]. However the variability in these results highlights the contribution of diverse genotypes and tissues studied [14•]. It remains unclear whether this oxidative stress is due to excess of ROS or to deficit in antioxidant mechanisms or a combination of both. We propose here that a primary genetic defect of GSH synthesis is at the origin of the failure of antioxidant defenses in schizophrenia. This implies the involvement of a critical neurodevelopmental component in schizophrenia when compared with neurodegenerative disorders. Indeed there is also increasing evidence for the involvement of oxidative stress induced cellular damage in the pathogenesis of various neurodegenerative diseases such as Parkinson's (PD), Alzheimer's (ALZ), and Huntington's (HD) diseases. However in these cases, ROS/RNS increase and GSH depletion appear to be downstream consequences of other primary causes (such as i.e. mitochondrial complex I dysfunction in PD, amyloid-β peptide toxicity in ALZ, and huntingtin-related mitochondrial dysfunction in HD) [5•].

A genetic origin for redox dysregulation was first demonstrated through the association of schizophrenia with various polymorphisms in the key genes for GSH synthesis, namely the rate limiting enzyme glutamate cysteine ligase (GCL) composed of two subunits: catalytic (GCLC, 73 kDa) and modulatory (GCLM, 30 kDa). Two single nucleotide polymorphisms (SNPs) of GCLM [15] and a GAG-trinucleotid repeat (GAG-TNR) of GCLC genes [16•], were associated with schizophrenia (Figure 2b,c). In two case–control studies, totalizing now 570 patients and 797 controls, the GCLC genotypes 7/7 and 7/9 TNR are more frequent in controls ('low-risk' genotypes), while 8/7, 8/8, 8/9, and 9/9 are more frequent in patients (high-risk). The 'high-risk' genotypes are present in 35–40% of patients. In skin fibroblast cultures under oxidative stress conditions, 'high-risk' compared to 'low-risk' subjects have lower GCLC gene and protein expression, GCL activity, and GSH levels, demonstrating that GAG-TNR variants are associated with dysfunctional regulatory mechanisms [16•] (Figure 2d). This is consistent with the decreased GSH levels in CSF and in medial prefrontal cortex (PFC) *in vivo* [17] (see also [18•], Figure 2a), as well as in postmortem striatum [11]. Furthermore, 'high-risk' genotype patients have lower plasma GSH levels and higher oxidized cysteine levels than 'low-risk' ones (unpublished data), pointing to generalized oxidative systemic conditions [13].

Furthermore, other susceptibility genes also induce an oxidative state: a positive association with schizophrenia has been found for SNPs in *PRODH* which increases the proline oxidase activity [19], promoting ROS generation [20].

Finally, we propose that redox dysregulation could also affect *epigenetic* processes [21] through dysregulation of *DNA methylation* via methionine and the *trans*-methylation pathway. Indeed, under oxidative stress conditions, methionine synthase is inactivated, allowing homocysteine to be shunted into the *trans*-sulfuration pathway favoring GSH synthesis [22]. However, in case of impaired GSH synthesis in 'high-risk' genotypes, both *trans*-methylation and *trans*-sulfuration pathways could be depressed [14•], leading to perturbations of the DNA methylation process and increase in homocysteine levels as often observed in schizophrenia [23].

Taken together, these results provide evidence that polymorphisms in the key GSH synthesizing genes associated with schizophrenia lead to redox dysregulation favoring deleterious consequences of oxidative and nitrosative stress.

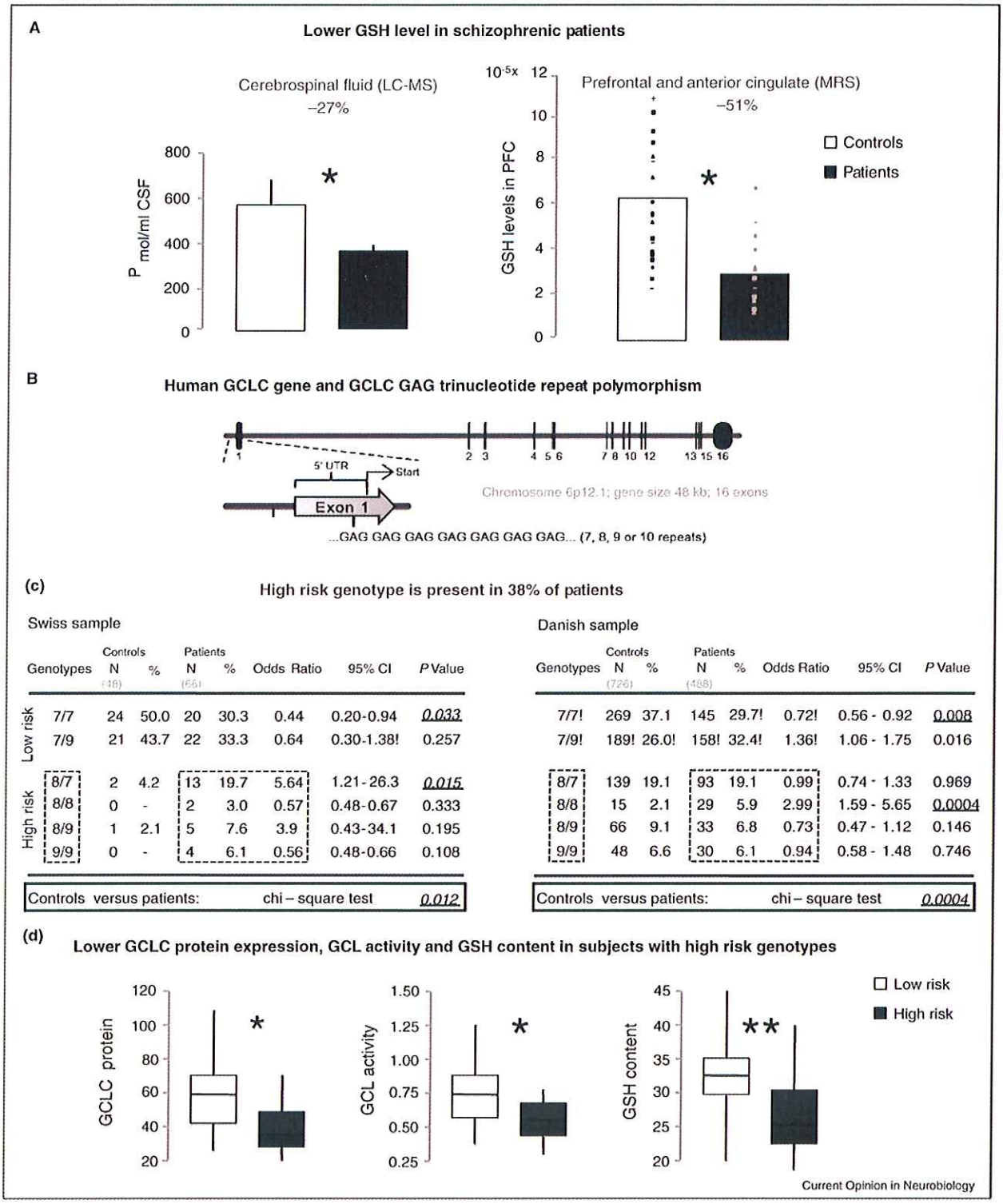
Environmental factors generating oxidative stress

Various established environmental risk factors [2•] are known to induce oxidative stress (Supplementary Table 1). These would be particularly damaging when combined with a genetically deficient regulation of redox system. Impacts during early development may become apparent only in adulthood.

(Figure 1 Legend Continued) upregulation of superoxide dismutase [66•]. The proposed mechanisms for the redox dysregulation-induced decrease in functional fast-spiking interneurons and in myelination involve inflammation-related signaling. In addition, many environmental risk factors (infections, obstetrical complications such as hypoxia, psychological stress, and brain trauma) induce redox dysregulation and inflammatory processes, suggesting that both processes are tightly linked and together can impair normal brain development.

Please cite this article in press as: Do KQ, et al. Redox dysregulation, neurodevelopment, and schizophrenia, Curr Opin Neurobiol (2009), doi:10.1016/j.conb.2009.05.001

Figure 2



Clinical studies indicate involvement of glutathione (GSH) dysregulation in schizophrenia. **(a)** GSH levels are lower in schizophrenia patients (*filled bars*) than in controls (*open bars*), measured in cerebrospinal fluid by liquid chromatography–mass spectrometry (LC–MS) (*left panel*) and in medial prefrontal cortex by magnetic resonance spectrometry (MRS) (*right panel*) (adapted from [17]). *Left panel*: mean ± SE; *right panel*: mean and individual data (symbols).

Please cite this article in press as: Do KQ, et al. Redox dysregulation, neurodevelopment, and schizophrenia, Curr Opin Neurobiol (2009), doi:10.1016/j.conb.2009.05.001

Early insults include malnutrition, exposure to toxins, maternal infection, obstetrical complications (pre-eclampsia and hypoxia), and maternal or early-life stress [24,25]. Globally, in both human and animal models, they lead to increase in ROS generation, lipid, protein, and DNA (per)oxidation, and decrease in GSH and antioxidant defense system (Supplementary Table 1A). They also lead to increased inflammation [26,27•], emphasizing the tight link between inflammation and oxidative stress. Emerging evidence suggests that the precise timing of prenatal infection may influence the specificity of its structural and functional delayed consequences: infection occurring in early/middle pregnancy leads to reduced prefrontal D1 receptors, deficit in spatial exploration, sensorimotor gating, and selective associative learning, while immune challenge at late gestation leads to reduced hippocampal NMDA-R subunits and impairment in reversal learning and spatial working memory [28,29]. Interestingly, the antioxidant *N*-acetyl cysteine (NAC) prevents the deleterious delayed consequences of a prenatal inflammation [27•,30]. Environmental toxins such as methyl mercury, lead, and paraquat (herbicides) increase oxidative status and disrupt mitogenic signaling of oligodendrocyte precursors [31••].

Late environmental factors that dysregulate the redox system include malnutrition, brain trauma, and stress during childhood, adolescence, and adulthood. Although evidence in humans is still sparse, psycho-social stresses lead to GSH deficiency and lipid, protein, and mitochondria damage as demonstrated in restraint stress rodents [32]. Redox dysregulation induced by numerous environmental factors or manipulation of redox systems also lead to diverse behavioral alterations at adulthood, including cognitive, social, and emotional impairments (Supplementary Table 1B).

Any of those environmental insults could worsen a fragile redox equilibrium and, depending on the phase of brain development when they occur, could prevent normal maturation processes, resulting in defective connectivity between various brain regions, including the midbrain, nucleus accumbens, thalamus, temporo-limbic, and PFCs, all involved in schizophrenia [33]. GSH deficiency thus appears to be a key element in the 'redox dysregulation hub' on which various genetic and environmental risk factors converge to perturb brain maturation with delayed functional consequences in early adulthood.

Consequences of redox dysregulation and oxidative stress

Exposure to oxidative stress at various developmental stages affects at least two essential cerebral processes that are dysfunctional in schizophrenia (Figures 1 and 3): firstly, NMDA-R hypofunction, mediating impairment of PV fast-spiking GABAergic interneurons (FSGIs), crucial for synchronization activity and secondly, deficient myelination. The interaction with dopaminergic systems is discussed in Figure 3d [34•].

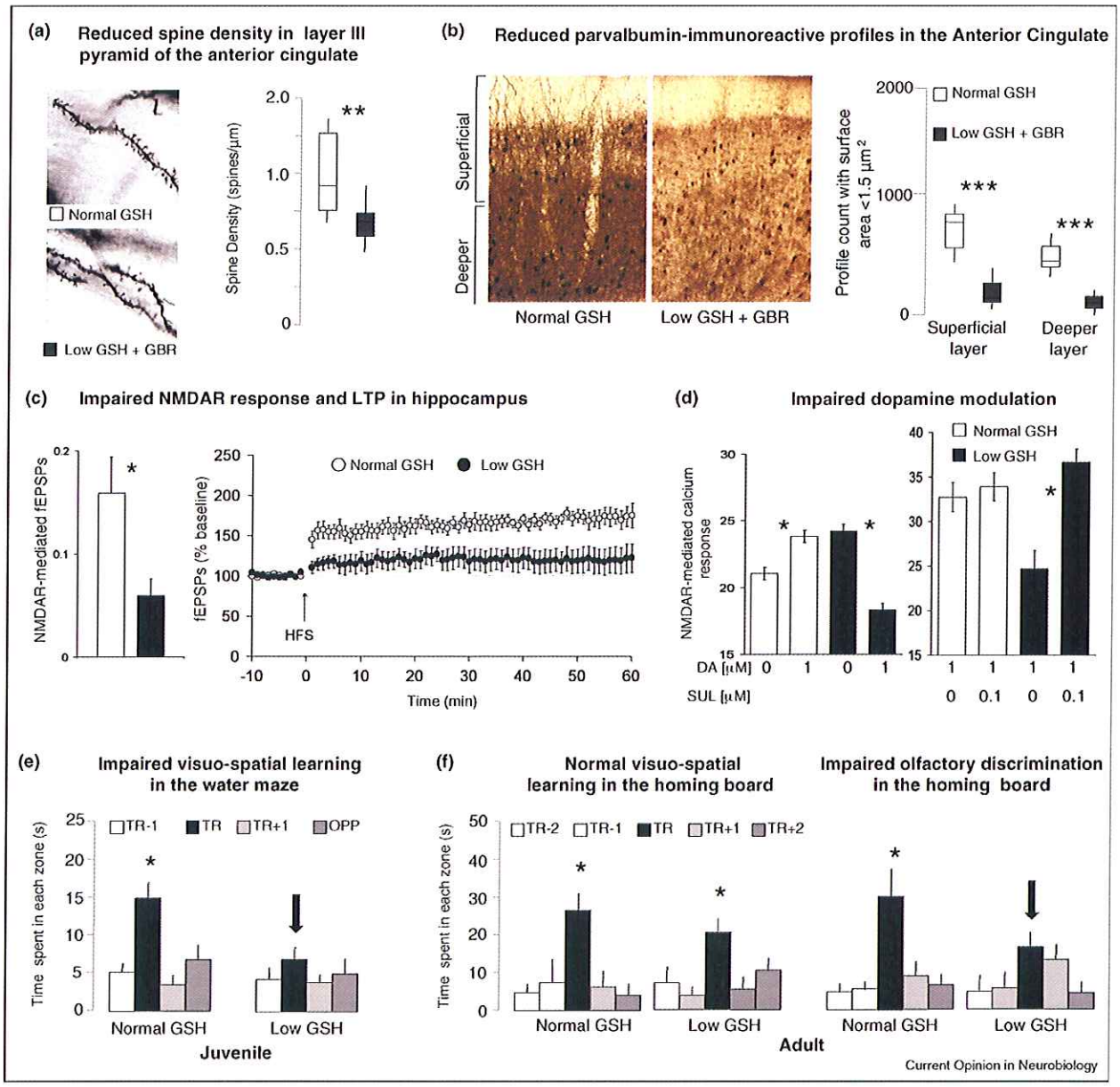
Converging evidence points to *NMDA-R hypofunction* in schizophrenia [35–37]. NMDA-Rs, through redox-sensitive active sites, are depressed under oxidizing conditions [8,38]. GSH deficit leads to decreased NMDA-R response and LTP [39] (Figure 3c). In addition, the intrasynaptic activation of NMDA-R upregulates various antioxidant systems, including thioredoxin–peroxiredoxin systems [40••] suggesting that NMDA-R hypofunction might further contribute to cellular oxidative stress. Indeed NMDA-R antagonists induce a rapid increase in ROS [41].

In patients postmortem tissues, PV immunoreactivity (PV-IR) of FSGI is decreased in layers III–IV of PFC, anterior cingulate cortex, and hippocampus [42,43]. Immunoreactivity of GABA, its synthesizing enzyme GAD67 and its transporter GAT are also decreased, leading to excitatory–inhibitory imbalance [44]. Similar alterations were observed following application of NMDA-R antagonists [45,46]. We observed decreased PV-IR in anterior cingulate but not somatosensory cortex of rodents with transitory GSH deficit from postnatal day 5 to 16 [47•] (Figure 3b). It thus appears that redox dysregulation induces impairment in FSGI, particularly during brain development. The NMDA-R hypofunction-induced FSGI defect is mediated by IL6, which in turn activates NAPDH oxidase (NOX) (Figure 1b) [48•,49••,50•]. The latter produces ROS, which should be particularly toxic when combined with a GSH deficit of genetic origin. PGC-1α, a coactivator of peroxisome proliferator activated receptors γ (PPARγ), is also involved via its influence on GABAergic signaling and survival, and antioxidant defense mechanisms [51], (EK Lucas, abstract in *Soc Neurosci Abstr 2008*, 747.7). Indeed, the high expression of PGC-1α in GABAergic interneurons during postnatal development and adulthood [51] suggests that PPARγ could help counteract this mechanism via inhibition of IL-6 and superoxide scaven-

(Figure 2 Legend Continued) $^{*}P < 0.05$. **(b)** Schematic representation of the GCLC gene. Vertical black bars represent the exons. Position of the 5′-UTR GAG-TNR polymorphism is upstream of the start codon (bowed arrow). **(c)** GCLC GAG-TNR polymorphism in both Swiss (*left panel*) and Danish (*right panel*) samples shows a significant difference between the genotype distribution of controls and patients [X^2-test with a 2 × 6 contingency table (controls and patients × genotypes 7/7, 7/9, 8/7, 8/8, 8/9, and 9/9)]. 'High-risk' genotypes (8/7, 8/8, 8/9, and 9/9; gray dotted box) are present in about 38% of patients. For each genotype, number of individuals (*N*), % and statistical comparison between controls and patients [with odd ratio (OR), 95% confidence interval (CI), and *P*-values] are given (adapted from updated [16•]). **(d)** Functional relevance of the GCLC GAG-TNR polymorphism in the Swiss sample. In fibroblasts, GCLC protein expression (*left panel*), GCL activity (*middle panel*), and GSH content (*right panel*) are lower in 'high-risk' (8/7, 8/8, 8/9, and 9/9; dark box) than 'low-risk' genotypes (7/7 and 7/9; light box). Each box plot depicts 25%, 75%, and median values. The error bars show values in the 1.5 box lengths range. $^{*}P < 0.05$ and $^{**}P < 0.01$ (adapted from [16•]).

Please cite this article in press as: Do KQ, et al. Redox dysregulation, neurodevelopment, and schizophrenia, Curr Opin Neurobiol (2009), doi:10.1016/j.conb.2009.05.001

Figure 3



In experimental models, low GSH induces structural, physiological, and behavioral anomalies. **(a)** The density of spines on the apical dendrites of layer III pyramids in the anterior cingulate (AC) is reduced in low GSH + GBR rats (treated with BSO, a GSH synthesis inhibitor, and GBR, a DA reuptake inhibitor which increases local DA levels, mimicking the impact of environmental stress) compared to normal GSH rats (PBS 'control' treated). Rats were treated between postnatal days P5 and P24 and spines quantified at P24. In the box plot, filled bars represent low GSH rats, open bars represent normal GSH rats. Each bar depicts 25 and 75% values; the horizontal line shows the median. $^{**}P < 0.01$. Photomicrographs illustrate Golgi stained layer III dendrite of a pyramid in the AC of normal GSH (*upper panel*) and low GSH rats (*lower panel*) (F Gheorghita, *in preparation*). **(b)** The number of parvalbumin-immunoreactive (PV-IR) profiles in AC is reduced in low GSH rats (treated with BSO and GBR) compared to normal GSH rats (PBS 'control' treated). Rats are treated between postnatal days P5 and P16 and PV-IR quantified at P16. In the box plot, filled bars represent low GSH rats, open bars represent normal GSH rats. $^{***}P < 0.001$. Photomicrographs illustrate PV-IR profiles in the AC from rats with normal GSH (left panel) and low GSH (right panel) (adapted from [47•]). **(c)** Low GSH levels cause NMDAR hypofunction (left panel) and a concomitant impairment of high frequency stimulation-induced long-term potentiation in hippocampus (*right panel*) (adapted from [39]). **(d)** Low intracellular GSH levels alter dopamine (DA) modulation of NMDA-mediated calcium response in cortical neurons. DA decreases NMDA response in low GSH, while the same DA concentration (1 µM) enhances NMDA response in neurons with normal GSH (left panel). Blocking D2-type receptors with sulpiride (SUL) prevents DA-induced decrease of NMDA in low GSH neurons (right panel). This suggests that antipsychotics, as D2 antagonists, might prevent such negative modulation of the NMDA responses. The effect of a GSH deficit on DA modulation of calcium response was due to an alteration of DA modulation of L-type-calcium

Please cite this article in press as: Do KQ, et al. Redox dysregulation, neurodevelopment, and schizophrenia, Curr Opin Neurobiol (2009), doi:10.1016/j.conb.2009.05.001

ging by upregulation of superoxide dismutase. Thus converging findings point to a key role of redox dysregulation in anomalies of FSGI, particularly in anterior cortical areas. We also observed spine density decreases in the latter's layer III pyramidal cells (Figure 3a), possibly related to the rich innervation by DA whose metabolism generates ROS, thus further contributing to oxidative damage [52].

There is increasing evidence that schizophrenia is associated with abnormalities in local-range and long-range *synchronization activity in the beta (13–30 Hz) and gamma (30–80 Hz) frequency* ranges [53,54]. This induces functional disconnectivity in cortical networks during *perceptual and cognitive processes* [55,56]. FSGI exert powerful, long-lasting, and locally spreading inhibition and thus are critically involved in the functional cortical circuitry responsible for gamma band synchronization and EEG oscillations during sensory integration and cognitive tasks [44,57,58••]. Interestingly, we observed reduced number of PV-IR interneurons and decreased kainate-induced γ-oscillations in the hippocampus of *gclm−/−* mice that have a 70% decrease in brain GSH (P Steullet *et al.*, abstract in *Soc Neurosci Abstr 2008*, 657.4). These mice also display hyperactivity, stronger response to acute stress, alterations in social behavior, and deficiency in object memory (A Frank *et al.*, abstract in *Soc Neurosci Abstr 2008*, 657.7; see also [59,60,61]). Overall, FSGI impairments induced by redox dysregulation may play an important role in the decreased γ-oscillations power leading to various schizophrenia phenotypes, depending on the specific neural circuitries impaired.

Recent evidence from gene expression profiling, neurocytochemical, and neuroimaging studies points to the impairment of *oligodendroglia-mediated myelination* in schizophrenia [62,63]. This process is particularly affected by redox regulation [64]. Oligodendrocytes and their progenitor cells are also highly sensitive to oxidative stress [65]. Oxidative conditions decrease cell proliferation through the disruption of mitogenic signaling involving Fyn1 and PDGFRα, leading to oligodendrocyte deficits and myelination anomalies [31••]. PPARs-mediated pathways might be protective through their antioxidative actions and their role in oligodendrocyte maturation [27•,66•] (Figure 1c). A deficit in myelination would influence axonal conduction velocity and thus disrupt precise synchronization. It would also impact on pathways essential for intermodal sensory integration and 'binding' processes, underlying the cognitive and negative symptoms [56]. As cortical myelination continues through late adolescence for the temporal and prefrontal regions, its deficit could be related to the delayed onset of the disease to early adulthood. Interestingly, the myelin marker MBP (myelin basic protein) is also decreased in gclm−/− mice (JH Cabungcal *et al.*, abstract in *Soc Neurosci Abstr 2008*, 657.14).

In view of the role played by FSGI and myelination impairments in schizophrenia, it is tempting to speculate in analogy to the visual system that similar *critical period* in cortical areas of the anterior forebrain and their corresponding functions might be perturbed by redox dysregulation. Indeed, in the monocular deprivation model of the visual system, the critical period for plasticity relies on both PV FSGI maturation for its initiation and on myelin-derived Nogo receptor signaling for its termination [67,68••,69], (H Morishita *et al.*, abstract in *Soc Neurosci Abstr 2008*, 28.5). Interestingly, the antidepressant fluoxetine, efficient in the functional recovery of acuity [70], has been shown to upregulate the antioxidant system [71]. Also efficient is the treatment with chondroitinase ABC [72] which degrades the extracellular matrix structures called perineuronal nets (PNNs). The latter enwrap PV cells, the maturation of which triggers the endogenous critical period. We observed in gclm−/− mice that GSH deficit led to a delayed appearance of both PV and PNN immunoreactivity in PFC (JH Cabungcal *et al.*, abstract in *Soc Neurosci Abstr 2008*, 657.14). In this context, in analogy to amblyopia pathophysiology, schizophrenia could be related to a delay/deficiency in initiation and closure of specific critical period. Moreover, as the subtype specification of cortical interneurons depends on both the spatial and temporal origin of their precursors in the developing telencephalic eminences [73], the timing of various environmental insults during development (early, middle, end of pregnancy, or postnatal) may lead to distinct impact on different interneuron subtypes. Investigation on experimental models with genetic redox

(Figure 3 Legend Continued) channels [34•]. Because calcium signaling via NMDAR [44] and L-type calcium channels [79] and dopamine signaling mostly via D2R [80] promote PV maturation, it is tempting to speculate that a deficit in GSH might also affect PV maturation via alteration of DA modulation of calcium signaling. In addition, the postpubertal emergence of DA-induced excitability of PFC interneurons via D2R [81] might be also compromised by a redox dysregulation affecting DA-modulation of L-type calcium channels. Finally, an enhanced discharge of hippocampal pyramidal neurons, because of FSGI impairments, could overstimulate ventral tegmental DA neurons, inducing an increased cortical DA liberation [44]. Data are presented as the mean ± SE, $^*P < 0.05$ (adapted from [34•]). **(e)** A transitory GSH deficit during early brain development (postnatal days P5–P16) impairs visuo-spatial learning of *juvenile rats* in the water maze. Mean (±SE) time spent swimming in four equivalent zones (training zone: Tr; other zones: Tr − 1, Tr + 1, Opp) during three 60-s probe trials of place and cue condition in normal GSH (PBS-treated, *left panel*) and low GSH rats (BSO-treated, *right panel*). The arrow indicates the nonsignificant difference time spent in the training zone versus the other zones. $^*P < 0.05$ (adapted from [59]). **(f)** A transitory GSH deficit during early brain development does not affect visuo-spatial learning in the homing board in *adult rats* (*left panels*), but significantly impairs olfactory discrimination (*right panels*) when the homing table is baited with five olfactory cues placed in five different zones. Mean (±SE) time spent in five equivalent zones (Tr: trained zone; other zones: Tr + 1, Tr + 2 Tr − 2, Tr − 1) during the 120-s probe trial. The arrow indicates the nonsignificant difference time spent in the training zone versus the other zones. $^*P < 0.05$ (adapted from [59]).

Please cite this article in press as: Do KQ, et al. Redox dysregulation, neurodevelopment, and schizophrenia, Curr Opin Neurobiol (2009), doi:10.1016/j.conb.2009.05.001

dysregulation combined with environmental stressors applied at various development stages should contribute to test this hypothesis.

Therapeutic perspectives

A proof-of-concept has been provided by a clinical trial with the GSH precursor NAC [74]. NAC, given as add-on treatment to antipsychotics in a double-blind placebo-controlled study, increased GSH plasma levels, improved negative symptoms, and reduced side effects (akathisia) in chronic patients [75]. NAC was also effective in improving mismatch negativity (MMN) [76], an auditory-related, NMDA-dependent evoked potential typically impaired in schizophrenia [77]. This is encouraging since present antipsychotic treatments are rather ineffective against cognitive and negative symptoms and have no effect on MMN, a preattentional component that is proposed to gate some cognitive and functional modules [78].

Conclusion

Redox dysregulation may constitute a 'hub' where genetic and environmental vulnerability factors converge and their timing during neurodevelopment could play a decisive role on some schizophrenia phenotypes. In experimental models, such redox dysregulation induces anomalies strikingly similar to those observed in patients. A treatment restoring redox balance, deprived of side effects, yields improvements in chronic patients. Its application during early psychosis and prodromal phase, intended to halt pathological developmental processes is promising. The proposed mechanisms should provide biomarkers for an early detection, paving the way for prevention perspectives.

Acknowledgements

We thank all patients and controls who participated in the studies, Sidney Wiener for reading the manuscript, P Magistretti for his support and all collaborators involved, including: R Gysin, C Butticaz, P Conus, A Cottier, F Gheorghita, JP Hornung, S Lavoie, H Moser, A Polari, M Preisig, D Preissmann, F Schenk, T Teichmann. Work supported by Swiss National Foundation 310000–116689, 'Loterie Romande', NARSAD, Alamaya Foundation.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.conb.2009.05.001.

References and recommended reading

Papers of particular interest published within the period of review have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Tandon R, Keshavan MS, Nasrallah HA: **Schizophrenia, "just the facts" what we know in 2008. 2. Epidemiology and etiology**. *Schizophr Res* 2008, **102**:1-18.

2. • Van OJ, Rutten BP, Poulton R: **Gene–environment interactions in schizophrenia: review of epidemiological findings and future directions**. *Schizophr Bull* 2008, **34**:1066-1082.
This is an excellent review on the gene–environment interactions in the etiology of schizophrenia, with an emphasis on major environmental factors.

3. Lewis DA, Levitt P: **Schizophrenia as a disorder of neurodevelopment**. *Annu Rev Neurosci* 2002, **25**:409-432.

4. Rapoport JL, Addington AM, Frangou S, Psych MR: **The neurodevelopmental model of schizophrenia: update 2005**. *Mol Psychiatry* 2005, **10**:434-449.

5. • Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, Telser J: **Free radicals and antioxidants in normal physiological functions and human disease**. *Int J Biochem Cell Biol* 2007, **39**:44-84.
This is an excellent review on reactive oxygen species (ROS) and reactive nitrogen species (RNS, e.g. nitric oxide, NO•) and their dual role as both deleterious and beneficial species. ROS and RNS are normally generated by tightly regulated enzymes, such as NO synthase (NOS) and NAD(P)H oxidase isoforms, respectively. Overproduction of ROS results in oxidative stress, a deleterious process and important mediator of damage to cell structures, including lipids and membranes, proteins, and DNA. At low/moderate concentrations, beneficial effects of ROS/RNS involve physiological roles in cellular responses to noxia, as for example in defense against infectious agents, in the function of a number of cellular signaling pathways, and the induction of a mitogenic response. Various ROS-mediated actions in fact protect cells against ROS-induced oxidative stress and re-establish or maintain 'redox balance' termed also 'redox homeostasis'.

6. •• Jones DP: **Radical-free biology of oxidative stress**. *Am J Physiol Cell Physiol* 2008, **295**:C849-C868.
Besides free radical-induced macromolecular damage that has been studied extensively as a mechanism of oxidative stress, this timely review focuses on the involvement of redox dysregulation that can occur without free radical generation. Oxidative stress can also occur as a consequence of the disruption of thiol redox circuits, which normally function in cell signaling and physiological regulation. The redox states of thiol systems are sensitive to two electron oxidants and controlled by the thioredoxins (Trx), GSH, and cysteine. Trx and GSH systems are maintained under stable, but nonequilibrium conditions, because of the continuous oxidation of cell thiols at a rate of about 0.5% of the total thiol pool per minute. Redox-sensitive thiols are critical for signal transduction (e.g. H-Ras and PTP-1B), transcription factor binding to DNA (e.g. Nrf-2, nuclear factor-κB), receptor activation (e.g. NMDA receptor), and other processes. Nonradical oxidants, including peroxides, quinones are generated enzymatically from both endogenous (e.g. dopamine) and exogenous precursors and do not require free radicals as intermediates to oxidize or modify these thiols and disrupt function.

7. Shi ZZ, Osei-Frimpong J, Kala G, Kala SV, Barrios RJ, Habib GM, Lukin DJ, Danney CM, Matzuk MM, Lieberman MW: **Glutathione synthesis is essential for mouse development but not for cell growth in culture**. *Proc Natl Acad Sci U S A* 2000, **97**:5101-5106.

8. Lipton SA, Choi YB, Takahashi H, Zhang D, Li W, Godzik A, Bankston LA: **Cysteine regulation of protein function — as exemplified by NMDA-receptor modulation**. *Trends Neurosci* 2002, **25**:474-480.

9. • Lu SC: **Regulation of glutathione synthesis**. *Mol Aspects Med* 2009, **30**:42-59.
This is an extensive review on the biological functions of GSH, its synthesis and metabolism and on transcription factors controlling its regulation. This is a brief survey of its perturbation in various pathologies.

10. Khan MM, Evans DR, Gunna V, Scheffer RE, Parikh VV, Mahadik SP: **Reduced erythrocyte membrane essential fatty acids and increased lipid peroxides in schizophrenia at the never-medicated first-episode of psychosis and after years of treatment with antipsychotics**. *Schizophr Res* 2002, **58**:1-10.

11. Yao JK, Leonard S, Reddy R: **Altered glutathione redox state in schizophrenia**. *Dis Markers* 2006, **22**:83-93.

12. Herken H, Uz E, Ozyurt H, Sogut S, Virit O, Akyol O: **Evidence that the activities of erythrocyte free radical scavenging enzymes and the products of lipid peroxidation are increased in different forms of schizophrenia**. *Mol Psychiatry* 2001, **6**:66-73.

13. Prabakaran S, Swatton JE, Ryan MM, Huffaker SJ, Huang JT, Griffin JL, Wayland M, Freeman T, Dudbridge F, Lilley KS *et al.*: **Mitochondrial dysfunction in schizophrenia: evidence for compromised brain metabolism and oxidative stress**. *Mol Psychiatry* 2004, **9**:684-697 643.

14. • Do KQ, Bovet P, Cabungcal JH, Conus P, Gysin R, Lavoie S, Steullet P, Cuenod M: **Redox dysregulation in schizophrenia:**

Please cite this article in press as: Do KQ, et al. Redox dysregulation, neurodevelopment, and schizophrenia, Curr Opin Neurobiol (2009), doi:10.1016/j.conb.2009.05.001

genetic susceptibility and pathophysiological mechanisms. In *Handbook of Neurochemistry and Molecular Neurobiology*, vol 27. Edited by Lajtha A. New York: Springer; 2009.

This is a review covering in detail some topics of the present paper.

15. Tosic M, Ott J, Barral S, Bovet P, Deppen P, Gheorghita F, Matthey ML, Parnas J, Preisig M, Saraga M *et al.*: **Schizophrenia and oxidative stress: glutamate cysteine ligase modifier as a susceptibility gene.** *Am J Hum Genet* 2006, **79**:586-592.

16. • Gysin R, Kraftsik R, Sandell J, Bovet P, Chappuis C, Conus P, Deppen P, Preisig M, Ruiz V, Steullet P *et al.*: **Impaired glutathione synthesis in schizophrenia: convergent genetic and functional evidence.** *Proc Natl Acad Sci U S A* 2007, **104**:16621-16626.

This paper presents the trinucleotid polymorphism associated with schizophrenia in the gene of the GSH synthesizing enzyme and its functional consequences in fibroblasts challenged by an oxidative stress, revealing dysregulation of the redox homeostasis.

17. Do KQ, Trabesinger AH, Kirsten-Kruger M, Lauer CJ, Dydak U, Hell D, Holsboer F, Boesiger P, Cuenod M: **Schizophrenia: glutathione deficit in cerebrospinal fluid and prefrontal cortex in vivo.** *Eur J Neurosci* 2000, **12**:3721-3728.

18. • Matsuzawa D, Obata T, Shirayama Y, Nonaka H, Kanazawa Y, Yoshitome E, Takanashi J, Matsuda T, Shimizu E, Ikehira H *et al.*: **Negative correlation between brain glutathione level and negative symptoms in schizophrenia: a 3T 1H-MRS study.** *PLoS ONE* 2008, **3**:e1944.

GSH levels measured by MRS in posterior medial frontal cortex of 20 schizophrenia patients were negatively correlated with negative symptoms. There was no significant changes in GSH levels when compared with normal controls, probably because of genotypes heterogeneity.

19. Kempf L, Nicodemus KK, Kolachana B, Vakkalanka R, Verchinski BA, Egan MF, Straub RE, Mattay VA, Callicott JH, Weinberger DR, Meyer-Lindenberg A: **Functional polymorphisms in PRODH are associated with risk and protection for schizophrenia and fronto-striatal structure and function.** *PLoS Genet* 2008, **4**:e1000252.

20. Phang JM, Donald SP, Pandhare J, Liu Y: **The metabolism of proline, a stress substrate, modulates carcinogenic pathways.** *Amino Acids* 2008, **35**:681-690.

21. Akbarian S, Huang HS: **Epigenetic regulation in human brain-focus on histone lysine methylation.** *Biol Psychiatry* 2009, **65**:198-203.

22. Deth R, Muratore C, Benzecry J, Power-Charnitsky VA, Waly M: **How environmental and genetic factors combine to cause autism: a redox/methylation hypothesis.** *Neurotoxicology* 2008, **29**:190-201.

23. Brown AS, Bottiglieri T, Schaefer CA, Quesenberry CP Jr, Liu L, Bresnahan M, Susser ES: **Elevated prenatal homocysteine levels as a risk factor for schizophrenia.** *Arch Gen Psychiatry* 2007, **64**:31-39.

24. Mittal VA, Ellman LM, Cannon TD: **Gene-environment interaction and covariation in schizophrenia: the role of obstetric complications.** *Schizophr Bull* 2008, **34**:1083-1094.

25. Brown AS, Susser ES: **Prenatal nutritional deficiency and risk of adult schizophrenia.** *Schizophr Bull* 2008, **34**:1054-1063.

26. Garcia-Bueno B, Madrigal JL, Lizasoain I, Moro MA, Lorenzo P, Leza JC: **Peroxisome proliferator-activated receptor gamma activation decreases neuroinflammation in brain after stress in rats.** *Biol Psychiatry* 2005, **57**:885-894.

27. • Paintlia MK, Paintlia AS, Khan M, Singh I, Singh AK: **Modulation of peroxisome proliferator-activated receptor-alpha activity by *N*-acetyl cysteine attenuates inhibition of oligodendrocyte development in lipopolysaccharide stimulated mixed glial cultures.** *J Neurochem* 2008, **105**:956-970.

Prenatal inflammation (via LPS) induces selective depletion of developing oligodendrocytes and hypomyelination via a decrease in GSH, increase in ROS, and dysfunction of peroxisomes. *N*-Acetylcysteine prevents LPS-induced redox dysregulation and attenuates hypomyelination via a PPAR-α-dependent mechanism.

28. Meyer U, Nyffeler M, Yee BK, Knuesel I, Feldon J: **Adult brain and behavioral pathological markers of prenatal immune challenge during early/middle and late fetal development in mice.** *Brain Behav Immun* 2008, **22**:469-486.

29. Meyer U, Nyffeler M, Engler A, Urwyler A, Schedlowski M, Knuesel I, Yee BK, Feldon J: **The time of prenatal immune challenge determines the specificity of inflammation-mediated brain and behavioral pathology.** *J Neurosci* 2006, **26**:4752-4762.

30. Lante F, Meunier J, Guiramand J, Maurice T, Cavalier M, de Jesus Ferreira MC, Aimar R, Cohen-Solal C, Vignes M, Barbanel G: **Neurodevelopmental damage after prenatal infection: role of oxidative stress in the fetal brain.** *Free Radic Biol Med* 2007, **42**:1231-1245.

31. •• Li Z, Dong T, Proschel C, Noble M: **Chemically diverse toxicants converge on Fyn and c-Cbl to disrupt precursor cell function.** *PLoS Biol* 2007, **5**:e35.

In previous study [64], the authors showed that the redox status induced by various growth factors determine the fate of oligodendrocyte precursors, with oxidizing factors favoring differentiation while reducing status promote precursor proliferation. Here they show that exposure of mercury and other pro-oxidant toxins lead to more oxidized conditions in oligodendrocyte precursors and suppress their division via the down-regulation of PDGFR-α. This downregulation is due to enhanced degradation of PDGFR-α through activation of Fyn and c-CBl. The antioxidant *N*-acetylcysteine prevents this deleterious effect of the pro-oxidant toxins.

32. Chakraborti A, Gulati K, Banerjee BD, Ray A: **Possible involvement of free radicals in the differential neurobehavioral responses to stress in male and female rats.** *Behav Brain Res* 2007, **179**:321-325.

33. Lewis DA, Lieberman JA: **Catching up on schizophrenia: natural history and neurobiology.** *Neuron* 2000, **28**:325-334.

34. • Steullet P, Lavoie S, Kraftsik R, Guidi R, Gysin R, Cuenod M, Do KQ: **A glutathione deficit alters dopamine modulation of L-type calcium channels via D2 and ryanodine receptors in neurons.** *Free Radic Biol Med* 2008, **44**:1042-1054.

This paper describes a mechanism by which dopamine signaling can be affected in conditions of impaired GSH synthesis. In cultured cortical neurons, a GSH deficit changes the dopamine modulation of NMDA-mediated calcium responses, from enhanced responses in control neurons to decreased responses in low GSH neurons. This is due to a change in dopamine modulation of L-type calcium channels which is dependent on redox-sensitive ryanodine receptors (RyRs), whose function is enhanced in low GSH neurons. Blocking D2R receptors prevents the alteration of dopamine modulation induced by a GSH deficit. Data suggest that enhanced RyRs in low GSH neurons strengthens intracellular calcium-dependent pathways following activation of D2-type receptors and causes a decrease in function of L-type channels.

35. Javitt DC, Zukin SR: **Recent advances in the phencyclidine model of schizophrenia.** *Am J Psychiatry* 1991, **148**: 1301-1308.

36. Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, Bremner JD, Heninger GR, Bowers MB Jr, Charney DS: **Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses.** *Arch Gen Psychiatry* 1994, **51**:199-214.

37. Coyle JT: **Glutamate and schizophrenia: beyond the dopamine hypothesis.** *Cell Mol Neurobiol* 2006, **26**:365-384.

38. Kohr G, Eckardt S, Luddens H, Monyer H, Seeburg PH: **NMDA receptor channels: subunit-specific potentiation by reducing agents.** *Neuron* 1994, **12**:1031-1040.

39. Steullet P, Neijt HC, Cuenod M, Do KQ: **Synaptic plasticity impairment and hypofunction of NMDA receptors induced by glutathione deficit: relevance to schizophrenia.** *Neuroscience* 2006, **137**:807-819.

40. •• Papadia S, Soriano FX, Leveille F, Martel MA, Dakin KA, Hansen HH, Kaindl A, Sifringer M, Fowler J, Stefovska V *et al.*: **Synaptic NMDA receptor activity boosts intrinsic antioxidant defenses.** *Nat Neurosci* 2008, **11**:476-487.

This is an elegant piece of work that has identified a new NMDAR-mediated, synaptic (but not extrasynaptic) activity-dependent web of coordinated transcriptional changes that lead to enhanced neuronal antioxidant defenses, particularly relevant in diseases associated with

Please cite this article in press as: Do KQ, et al. Redox dysregulation, neurodevelopment, and schizophrenia, Curr Opin Neurobiol (2009), doi:10.1016/j.conb.2009.05.001

oxidative damage. Thus the toxicity of NMDAR antagonists such as MK-801 on neonatal neurons may be due from their blockade of synaptic activity, and therefore the antioxidant pathways.

41. Zuo DY, Wu YL, Yao WX, Cao Y, Wu CF, Tanaka M: **Effect of MK-801 and ketamine on hydroxyl radical generation in the posterior cingulate and retrosplenial cortex of free-moving mice, as determined by in vivo microdialysis.** *Pharmacol Biochem Behav* 2007, **86**:1-7.

42. Benes FM, Berretta S: **GABAergic interneurons: implications for understanding schizophrenia and bipolar disorder.** *Neuropsychopharmacology* 2001, **25**:1-27.

43. Lewis DA, Hashimoto T, Volk DW: **Cortical inhibitory neurons and schizophrenia.** *Nat Rev Neurosci* 2005, **6**:312-324.

44. Lisman JE, Coyle JT, Green RW, Javitt DC, Benes FM, Heckers S, Grace AA: **Circuit-based framework for understanding neurotransmitter and risk gene interactions in schizophrenia.** *Trends Neurosci* 2008, **31**:234-242.

45. Braun I, Genius J, Grunze H, Bender A, Moller HJ, Rujescu D: **Alterations of hippocampal and prefrontal GABAergic interneurons in an animal model of psychosis induced by NMDA receptor antagonism.** *Schizophr Res* 2007, **97**:254-263.

46. Abekawa T, Ito K, Nakagawa S, Koyama T: **Prenatal exposure to an NMDA receptor antagonist, MK-801 reduces density of parvalbumin-immunoreactive GABAergic neurons in the medial prefrontal cortex and enhances phencyclidine-induced hyperlocomotion but not behavioral sensitization to methamphetamine in postpubertal rats.** *Psychopharmacology (Berl)* 2007, **192**:303-316.

47. • Cabungcal JH, Nicolas D, Kraftsik R, Cuenod M, Do KQ, Hornung JP: **Glutathione deficit during development induces anomalies in the rat anterior cingulate GABAergic neurons: relevance to schizophrenia.** *Neurobiol Dis* 2006, **22**:624-637.

This study is the first to show that a low glutathione during early brain development leads to a specific impairment of parvalbumin-immunoreactive (fast-spiking GABAergic interneuron) profiles in anterior cingulate cortex of a rat.

48. • Kinney JW, Davis CN, Tabarean I, Conti B, Bartfai T, Behrens MM: **A specific role for NR2A-containing NMDA receptors in the maintenance of parvalbumin and GAD67 immunoreactivity in cultured interneurons.** *J Neurosci* 2006, **26**:1604-1615.

PV interneurons have a five times higher NR2A/NR2B ratio than pyramidal neurons and NR2A-selective, but not NR2B-selective antagonist reduces PV-IR: this indicates a role of NR2A-containing NMDAR in the maintenance of functional fast-spiking PV interneurons.

49. •• Behrens MM, Ali SS, Dao DN, Lucero J, Shekhtman G, Quick KL, Dugan LL: **Ketamine-induced loss of phenotype of fast-spiking interneurons is mediated by NADPH-oxidase.** *Science* 2007, **318**:1645-1647.

Ketamine-induced decrease in GAD67 and PV expression is due to the production of superoxide via NADPH-oxidase activity. This deleterious effect on fast-spiking PV interneurons is prevented by apocinin, an inhibitor of NADPH-oxidase, or a SOD-mimetic compound.

50. • Behrens MM, Ali SS, Dugan LL: **Interleukin-6 mediates the increase in NADPH-oxidase in the ketamine model of schizophrenia.** *J Neurosci* 2008, **28**:13957-13966.

Neuronal production of interleukin-6 is necessary and sufficient for ketamine-mediated activation of NADPH-oxidase leading to dysfunction of fast-spiking PV interneurons.

51. Cowell RM, Blake KR, Russell JW: **Localization of the transcriptional coactivator PGC-1alpha to GABAergic neurons during maturation of the rat brain.** *J Comp Neurol* 2007, **502**:1-18.

52. Grima G, Benz B, Parpura V, Cuenod M, Do KQ: **Dopamine-induced oxidative stress in neurons with glutathione deficit: implication for schizophrenia.** *Schizophr Res* 2003, **62**: 213-224.

53. Spencer KM, Nestor PG, Niznikiewicz MA, Salisbury DF, Shenton ME, McCarley RW: **Abnormal neural synchrony in schizophrenia.** *J Neurosci* 2003, **23**:7407-7411.

54. Uhlhaas PJ, Linden DE, Singer W, Haenschel C, Lindner M, Maurer K, Rodriguez E: **Dysfunctional long-range coordination of neural activity during Gestalt perception in schizophrenia.** *J Neurosci* 2006, **26**:8168-8175.

55. Tallon-Baudry C, Bertrand O, Delpuech C, Permier J: **Oscillatory gamma-band (30–70 Hz) activity induced by a visual search task in humans.** *J Neurosci* 1997, **17**:722-734.

56. Uhlhaas PJ, Singer W: **Neural synchrony in brain disorders: relevance for cognitive dysfunctions and pathophysiology.** *Neuron* 2006, **52**:155-168.

57. Traub RD, Whittington MA, Stanford IM, Jefferys JG: **A mechanism for generation of long-range synchronous fast oscillations in the cortex.** *Nature* 1996, **383**:621-624.

58. •• Sohal VS, Zhang F, Yizhar O, Deisseroth K: **Parvalbumin neurons and gamma rhythms enhance cortical circuit performance.** *Nature* 2009, (online 26 April 2009) doi:10.1038/nature07991 Letter.

This elegant study uses a panel of optogenetic technologies to show that parvalbumin interneurons are sufficient and necessary to generate emergent gamma-frequency rythmicity in the cortex in-vivo. In addition, gamma-frequency modulation of excitatory inputs enhances signal transmission in neocortex by reducing circuit noise and amplifying circuit signals.

59. Cabungcal JH, Preissmann D, Delseth C, Cuenod M, Do KQ, Schenk F: **Transitory glutathione deficit during brain development induces cognitive impairment in juvenile and adult rats: relevance to schizophrenia.** *Neurobiol Dis* 2007, **26**:634-645.

60. Castagne V, Rougemont M, Cuenod M, Do KQ: **Low brain glutathione and ascorbic acid associated with dopamine uptake inhibition during rat's development induce long-term cognitive deficit: relevance to schizophrenia.** *Neurobiol Dis* 2004, **15**:93-105.

61. Castagne V, Cuenod M, Do KQ: **An animal model with relevance to schizophrenia: sex-dependent cognitive deficits in osteogenic disorder-Shionogi rats induced by glutathione synthesis and dopamine uptake inhibition during development.** *Neuroscience* 2004, **123**:821-834.

62. Tkachev D, Mimmack ML, Ryan MM, Wayland M, Freeman T, Jones PB, Starkey M, Webster MJ, Yolken RH, Bahn S: **Oligodendrocyte dysfunction in schizophrenia and bipolar disorder.** *Lancet* 2003, **362**:798-805.

63. Dracheva S, Davis KL, Chin B, Woo DA, Schmeidler J, Haroutunian V: **Myelin-associated mRNA and protein expression deficits in the anterior cingulate cortex and hippocampus in elderly schizophrenia patients.** *Neurobiol Dis* 2006, **21**:531-540.

64. Smith J, Ladi E, Mayer-Proschel M, Noble M: **Redox state is a central modulator of the balance between self-renewal and differentiation in a dividing glial precursor cell.** *Proc Natl Acad Sci U S A* 2000, **97**:10032-10037.

65. Back SA, Gan X, Li Y, Rosenberg PA, Volpe JJ: **Maturation-dependent vulnerability of oligodendrocytes to oxidative stress-induced death caused by glutathione depletion.** *J Neurosci* 1998, **18**:6241-6253.

66. • Leisewitz AV, Urrutia CR, Martinez GR, Loyola G, Bronfman M: **A PPARs cross-talk concertedly commits C6 glioma cells to oligodendrocytes and induces enzymes involved in myelin synthesis.** *J Cell Physiol* 2008, **217**:367-376.

This study shows respective involvement of PPARs α, β/δ, and γ in oligodendrocyte differentiation and myelin synthesis.

67. Hensch TK: **Critical period plasticity in local cortical circuits.** *Nat Rev Neurosci* 2005, **6**:877-888.

68. •• Morishita H, Hensch TK: **Critical period revisited: impact on vision.** *Curr Opin Neurobiol* 2008, **18**:101-107.

This excellent review and the previous one [70] highlight the impact of critical period on visual acuity and the involvement of PV GABAergic interneurons. This critical period can be manipulated in animal models by resetting excitatory–inhibitory balance or removal of molecular 'brakes' on structural plasticity.

69. McGee AW, Yang Y, Fischer QS, Daw NW, Strittmatter SM: **Experience-driven plasticity of visual cortex limited by myelin and Nogo receptor.** *Science* 2005, **309**:2222-2226.

Please cite this article in press as: Do KQ, et al. Redox dysregulation, neurodevelopment, and schizophrenia, Curr Opin Neurobiol (2009), doi:10.1016/j.conb.2009.05.001

70. Maya Vetencourt JF, Sale A, Viegi A, Baroncelli L, De PR, O'Leary OF, Castren E, Maffei L: **The antidepressant fluoxetine restores plasticity in the adult visual cortex**. *Science* 2008, **320**:385-388.

71. Zafir A, Banu N: **Antioxidant potential of fluoxetine in comparison to Curcuma longa in restraint-stressed rats**. *Eur J Pharmacol* 2007, **572**:23-31.

72. Pizzorusso T, Medini P, Landi S, Baldini S, Berardi N, Maffei L: **Structural and functional recovery from early monocular deprivation in adult rats**. *Proc Natl Acad Sci U S A* 2006, **103**:8517-8522.

73. Butt SJ, Fuccillo M, Nery S, Noctor S, Kriegstein A, Corbin JG, Fishell G: **The temporal and spatial origins of cortical interneurons predict their physiological subtype**. *Neuron* 2005, **48**:591-604.

74. Atkuri KR, Mantovani JJ, Herzenberg LA, Herzenberg LA: ***N*-Acetylcysteine — a safe antidote for cysteine/glutathione deficiency**. *Curr Opin Pharmacol* 2007, **7**:355-359.

75. Berk M, Copolov D, Dean O, Lu K, Jeavons S, Schapkaitz I, nderson-Hunt M, Judd F, Katz F, Katz P *et al.*: ***N*-Acetyl cysteine as a glutathione precursor for schizophrenia — a double-blind, randomized, placebo-controlled trial**. *Biol Psychiatry* 2008, **64**:361-368.

76. Lavoie S, Murray MM, Deppen P, Knyazeva MG, Berk M, Boulat O, Bovet P, Bush AI, Conus P, Copolov D *et al.*: **Glutathione precursor, *N*-acetyl-cysteine, improves mismatch negativity in schizophrenia patients**. *Neuropsychopharmacology* 2008, **33**:2187-2199.

77. Umbricht D, Schmid L, Koller R, Vollenweider FX, Hell D, Javitt DC: **Ketamine-induced deficits in auditory and visual context-dependent processing in healthy volunteers: implications for models of cognitive deficits in schizophrenia**. *Arch Gen Psychiatry* 2000, **57**:1139-1147.

78. Light GA, Braff DL: **Stability of mismatch negativity deficits and their relationship to functional impairments in chronic schizophrenia**. *Am J Psychiatry* 2005, **162**:1741-1743.

79. Jiang M, Swann JW: **A role for L-type calcium channels in the maturation of parvalbumin-containing hippocampal interneurons**. *Neuroscience* 2005, **135**:839-850.

80. Porter LL, Rizzo E, Hornung JP: **Dopamine affects parvalbumin expression during cortical development in vitro**. *J Neurosci* 1999, **19**:8990-9003.

81. Tseng KY, O'Donnell P: **Dopamine modulation of prefrontal cortical interneurons changes during adolescence**. *Cereb Cortex* 2007, **17**:1235-1240.

Please cite this article in press as: Do KQ, et al. Redox dysregulation, neurodevelopment, and schizophrenia, Curr Opin Neurobiol (2009), doi:10.1016/j.conb.2009.05.001

Supplementary material

Table 1

A	Insult	Time of insult	Tissue	GSH and AOX	Oxidative stress	Recovery	References
Fetal and early postnatal life	**Inflammation** LPS	E10.5	BR *4 months*	GSH ↓ AOX altered	ROS ↑		[1]
		E18-19	BR, LI *E19-20*	GSH ↓ (normal at PD2)	ROS ↑ Peroxisome ↓	N-acetyl cysteine	[2-4]
	Hypoxia	PD7	BR *PD8,14*	GSH ↓ Protein thiol ↓	ROS ↑	GPX ↑ Edaravone	[5-8]
		Pregnancy 26–41 wks	BL, CF	GSH ↓ AOX altered	ROS ↑		[9, 10]
	Preeclampsia	Pregnancy 38 wks-birth	BL, PLAC	GSH → AOX altered, selenium ↓	ROS ↑		[11-13]
	Maternal diabetes STZ-induced	Pregnancy At day 1	BR, LI *PD1*	GSH ↑ (LI), GSH ↓ (BR) AOX altered	ROS ↑		[14]
	Malnutrition undernutrition	Gestation and pre-weaning	BR *PD21,62*	GSH → AOX altered	ROS → at PD21 ROS ↑ at PD62		[15]
	low protein diet	Gestation and pre-weaning	BR *PD2,15*	GSH ↓ (normal at PD60) AOX altered	ROS ↑		[16, 17]
	Toxins mercury	Pregnancy	BR *PD21*	GSH ↓ AOX altered	ROS ↑		[18]
	lead	Prenatal + PD1-21	BR	GSH ↓ AOX altered	ROS ↑	Epigallocatechin-gallate	[19, 20]
	lead	Infant 4-12 yrs	BL	GSH ↓ correlate with lead ↑	ROS ↑ correlate with lead ↑		[21]
	pyrethroid	Prenatal + PD1-30	BR *PD31*	GSH ↓ AOX altered	ROS ↑		[22]
	Psychosocial stress restraint	E7-13 or E14-20	BR *PD30*		ROS ↑		[23]
	maternal separation	PD2-14	BL		ROS ↑		[24]
Adolescence - Adulthood	**Psychosocial stress** examination	Students	BL	AOX altered	ROS ↑		[25]
	restraint	Young adult	BR	GSH ↓ AOX altered	ROS ↑	N-acetyl cysteine α-tocopherol	[26]
	restraint / cold	Adult	BR, LI, KI, HE	GSH ↓ AOX altered	ROS ↑	NO inhibitors COX-2 inhibitors	[27-29]
	Brain trauma	Adult	BR *4 days posttrauma*	GSH ↓ AOX altered	ROS ↑		[30]

Table 1. (A) Effects of environmental risk factors on GSH levels, antioxidant systems and oxidative stress. Exposure to toxins, malnutrition, obstetrical complications such as hypoxia-ischemia and preeclampsia, and psychosocial stress imposed during pregnancy, childhood and adulthood can perturb the redox systems in brain and peripheral tissues (i.e., decrease GSH levels and/or alter enzymatic antioxidant systems, and/or increase oxidative stress). Some of these alterations in the brain prevail days or even months after the end of the insult (orange cells). Light blue sections correspond to data collected in humans, while other sections relate to rodents. Tissue abbreviations: BL = blood or plasma; BR = brain; CF = cerebrospinal fluid; HE = heart; KI = kidney; LI = liver; PLAC = placenta. Measurements were done immediately after the insult unless mentioned. Embryonic day and postnatal day are abbreviated respectively, E and PD. Other abbreviations: AOX: antioxidant systems including activity of glutathione peroxidases (GPX), glutathione reductase, catalase and superoxide dismutases; ROS: oxidative stress estimated by measuring either directly ROS levels, lipid peroxidation (LPO), protein oxidation, or DNA oxidation.

Table 1

B	Factor	Manipulation	Behavior(s) changed	Recovery	References
Fetal to early postnatal life	GSH synthesis down-regulation	BSO + Vitamin C ↓ (+ DA ↑)	Working memory (-) Spatial learning / memory (-) Object recognition memory (-)		[31-33]
	Inflammation	LPS	Spatial learning / memory (-) Sensory motor gating (-)	N-acetyl cysteine	[4, 34]
		PolyI:C	Object recognition memory (-) Sensory motor gating (-) Stimulant-induced activity (+) Exploratory behavior (-) (*) Associative learning (-)	Fluoxetine	[35-38]
	Hypoxia	Hypoxia	Spatial learning / memory (-) Sensory motor gating (-) Exploratory behavior (-) (*) Social behavior (-)	Melatonin	[39-42]
	Toxins	Lead	Spatial learning / memory (-) Social behavior (-) Anxiety (+)		[43, 44]
		Pyrethroid	Emotionally driven memory (-)		[22]
	Brain trauma	Brain contusion Excitotoxic lesion	Exploratory behavior (-) Object recognition memory (-) Emotionally driven memory (-)	Resveratrol Melatonin	[45, 46]
Adulthood	GSH synthesis down-regulation	BSO (+ DA ↑) CHX	Working memory (-) Spatial learning / memory (-) Object recognition memory (-) Stimulant-induced activity (-) Exploratory behavior (-) (*) Anxiety (+)	Ferulic acid Apocinin Bay 60-7550	[47-51]
	Elevation of oxidative stress	D-galactose quinolinic acid Vitamin A	Spatial learning / memory (-) Emotionally driven memory (-) Exploratory behavior (-) Anxiety (+)	Lipoic acid Tolmetin Sulindac	[52-55]
	GSH-related	GR ↑	Anxiety (+)	Inhibition of glyoxalase 1	[56]
		PCP+ xCT manipulation	Working memory (-) Social behavior (-)	N-acetyl cysteine	[57]
	Psychosocial Stress	1-6h restrain 72h sleep deprivation	Spatial learning / memory (-) Exploratory activity (-) Anxiety (+)	N-acetyl cysteine Curcumin Quercetin COX-2 inhibitors	[26, 29, 57-59]
	Brain trauma	Brain contusion	Spatial learning / memory (-)	OPC-14117 SOD ↑	[60, 61]

Table 1. (B) Effects of environmental insults or redox dysregulation on adult rodent behavior. Redox dysregulation induced by environmental factors or manipulation of redox systems leads to diverse behavioral alterations in adulthood, including cognitive, social and emotional impairments. Note that behavioral changes listed for each factor were not necessarily observed in all studies. Symbols: (*) the behavior remained unaltered in one or more studies; (+) enhanced or increased; (-) impaired or reduced. Abbreviations: BSO (buthionine sulfoximine); CHX (2-cyclohexene-1-one); COX (cyclooxygenase); DA (dopamine); GR (glutathione reductase); LPS (lipopolysaccharide); PCP (phencyclidine); PolyI:C (polyriboinosinic-polyribocytidilic acid); SOD (superoxide dismutases); xCT (cystine-glutamate antiporter).

REFERENCES

1. Zhu Y, Carvey PM, Ling Z: **Altered glutathione homeostasis in animals prenatally exposed to lipopolysaccharide**. *Neurochem Int* 2007, **50**:671-680.

2. Paintlia MK, Paintlia AS, Contreras MA, Singh I, Singh AK: **Lipopolysaccharide-induced peroxisomal dysfunction exacerbates cerebral white matter injury: attenuation by N-acetyl cysteine**. *Exp Neurol* 2008, **210**:560-576.

3. Buhimschi IA, Buhimschi CS, Weiner CP: **Protective effect of N-acetylcysteine against fetal death and preterm labor induced by maternal inflammation**. *Am J Obstet Gynecol* 2003, **188:**203-208.

4. Lante F, Meunier J, Guiramand J, de Jesus Ferreira MC, Cambonie G, Aimar R, Cohen-Solal C, Maurice T, Vignes M, Barbanel G: **Late N-acetylcysteine treatment prevents the deficits induced in the offspring of dams exposed to an immune stress during gestation**. *Hippocampus* 2008, **18:**602-609.

5. Sheldon RA, Christen S, Ferriero DM: **Genetic and pharmacologic manipulation of oxidative stress after neonatal hypoxia-ischemia**. *Int J Dev Neurosci* 2008, **26:**87-92.

6. Payton KS, Sheldon RA, Mack DW, Zhu C, Blomgren K, Ferriero DM, Northington FJ: **Antioxidant status alters levels of Fas-associated death domain-like IL-1B-converting enzyme inhibitory protein following neonatal hypoxia-ischemia**. *Dev Neurosci* 2007, **29:**403-411.

7. Noor JI, Ikeda T, Ueda Y, Ikenoue T: **A free radical scavenger, edaravone, inhibits lipid peroxidation and the production of nitric oxide in hypoxic-ischemic brain damage of neonatal rats**. *Am J Obstet Gynecol* 2005, **193:**1703-1708.

8. Dafre AL, Arteni NS, Siqueira IR, Netto CA: **Perturbations in the thiol homeostasis following neonatal cerebral hypoxia-ischemia in rats**. *Neurosci Lett* 2003, **345:**65-68.

9. Schmidt H, Grune T, Muller R, Siems WG, Wauer RR: **Increased levels of lipid peroxidation products malondialdehyde and 4-hydroxynonenal after perinatal hypoxia**. *Pediatr Res* 1996, **40:**15-20.

10. Gulcan H, Ozturk IC, Arslan S: **Alterations in antioxidant enzyme activities in cerebrospinal fluid related with severity of hypoxic ischemic encephalopathy in newborns**. *Biol Neonate* 2005, **88:**87-91.

11. Kaur G, Mishra S, Sehgal A, Prasad R: **Alterations in lipid peroxidation and antioxidant status in pregnancy with preeclampsia**. *Mol Cell Biochem* 2008, **313:**37-44.

12. Dordevic NZ, Babic GM, Markovic SD, Ognjanovic BI, Stajn AS, Zikic RV, Saicic ZS: **Oxidative stress and changes in antioxidative defense system in erythrocytes of preeclampsia in women**. *Reprod Toxicol* 2008, **25:**213-218.

13. Mistry HD, Wilson V, Ramsay MM, Symonds ME, Broughton PF: **Reduced selenium concentrations and glutathione peroxidase activity in preeclamptic pregnancies**. *Hypertension* 2008, **52:**881-888.

14. Raza H, John A: **Glutathione metabolism and oxidative stress in neonatal rat tissues from streptozotocin-induced diabetic mothers**. *Diabetes Metab Res Rev* 2004, **20:**72-78.

15. Partadiredja G, Worrall S, Simpson R, Bedi KS: **Pre-weaning undernutrition alters the expression levels of reactive oxygen species enzymes but not their activity levels or lipid peroxidation in the rat brain**. *Brain Res* 2008, **1222:**69-78.

16. Feoli AM, Siqueira I, Almeida LM, Tramontina AC, Battu C, Wofchuk ST, Gottfried C, Perry ML, Goncalves CA: **Brain glutathione content and glutamate uptake are reduced in rats exposed to pre- and postnatal protein malnutrition**. *J Nutr* 2006, **136:**2357-2361.

17. Feoli AM, Siqueira IR, Almeida L, Tramontina AC, Vanzella C, Sbaraini S, Schweigert ID, Netto CA, Perry ML, Goncalves CA: **Effects of protein malnutrition on oxidative status in rat brain**. *Nutrition* 2006, **22:**160-165.

18. Stringari J, Nunes AK, Franco JL, Bohrer D, Garcia SC, Dafre AL, Milatovic D, Souza DO, Rocha JB, Aschner M, Farina M: **Prenatal methylmercury exposure hampers glutathione antioxidant system ontogenesis and causes long-lasting oxidative stress in the mouse brain**. *Toxicol Appl Pharmacol* 2008, **227:**147-154.

19. Babu MS, Gopal NV, Reddy KP: **Post natal antioxidant enzyme activity of rat brain regions during developmental lead exposure**. *J Environ Biol* 2007, **28:**21-27.

20. Yin ST, Tang ML, Su L, Chen L, Hu P, Wang HL, Wang M, Ruan DY: **Effects of Epigallocatechin-3-gallate on lead-induced oxidative damage**. *Toxicology* 2008, **249:**45-54.

21. Ahamed M, Verma S, Kumar A, Siddiqui MK: **Environmental exposure to lead and its correlation with biochemical indices in children**. *Sci Total Environ* 2005, **346:**48-55.

22. Sinha C, Seth K, Islam F, Chaturvedi RK, Shukla S, Mathur N, Srivastava N, Agrawal AK: **Behavioral and neurochemical effects induced by pyrethroid-based mosquito repellent exposure in rat offsprings during prenatal and early postnatal period**. *Neurotoxicol Teratol* 2006, **28:**472-481.

23. Song L, Zheng J, Li H, Jia N, Suo Z, Cai Q, Bai Z, Cheng D, Zhu Z: **Prenatal Stress Causes Oxidative Damage to Mitochondrial DNA in Hippocampus of Offspring Rats**. *Neurochem Res* 2008.

24. Marais L, van Rensburg SJ, van Zyl JM, Stein DJ, Daniels WM: **Maternal separation of rat pups increases the risk of developing depressive-like behavior after subsequent chronic stress by altering corticosterone and neurotrophin levels in the hippocampus**. *Neurosci Res* 2008, **61:**106-112.

25. Sivonova M, Zitnanova I, Hlincikova L, Skodacek I, Trebaticka J, Durackova Z: **Oxidative stress in university students during examinations**. *Stress* 2004, **7:**183-188.

26. Chakraborti A, Gulati K, Banerjee BD, Ray A: **Possible involvement of free radicals in the differential neurobehavioral responses to stress in male and female rats**. *Behav.Brain Res.* 2007, **179:**321-325.

27. Madrigal JL, Olivenza R, Moro MA, Lizasoain I, Lorenzo P, Rodrigo J, Leza JC: **Glutathione depletion, lipid peroxidation and mitochondrial dysfunction are induced by chronic stress in rat brain**. *Neuropsychopharmacology* 2001, **24:**420-429.

28. Sahin E, Gumuslu S: **Immobilization stress in rat tissues: alterations in protein oxidation, lipid peroxidation and antioxidant defense system**. *Comp Biochem Physiol C Toxicol Pharmacol* 2007, **144:**342-347.

29. Kumari B, Kumar A, Dhir A: **Protective effect of non-selective and selective COX-2-inhibitors in acute immobilization stress-induced behavioral and biochemical alterations**. *Pharmacol Rep* 2007, **59:**699-707.

30. Ansari MA, Roberts KN, Scheff SW: **Oxidative stress and modification of synaptic proteins in hippocampus after traumatic brain injury**. *Free Radic Biol Med* 2008, **45:**443-452.

31. Cabungcal JH, Preissmann D, Delseth C, Cuenod M, Do KQ, Schenk F: **Transitory glutathione deficit during brain development induces cognitive impairment in juvenile and adult rats: relevance to schizophrenia**. *Neurobiol.Dis.* 2007, **26:**634-645.

32. Castagne V, Rougemont M, Cuenod M, Do KQ: **Low brain glutathione and ascorbic acid associated with dopamine uptake inhibition during rat's development induce long-term cognitive deficit: relevance to schizophrenia**. *Neurobiol.Dis.* 2004, **15:**93-105.

33. Castagne V, Cuenod M, Do KQ: **An animal model with relevance to schizophrenia: sex-dependent cognitive deficits in osteogenic disorder-Shionogi rats induced by glutathione synthesis and dopamine uptake inhibition during development**. *Neuroscience* 2004, **123:**821-834.

34. Fortier ME, Luheshi GN, Boksa P: **Effects of prenatal infection on prepulse inhibition in the rat depend on the nature of the infectious agent and the stage of pregnancy**. *Behav Brain Res* 2007, **181:**270-277.

35. Zuckerman L, Weiner I: **Maternal immune activation leads to behavioral and pharmacological changes in the adult offspring**. *J Psychiatr Res* 2005, **39:**311-323.

36. Wolff AR, Bilkey DK: **Immune activation during mid-gestation disrupts sensorimotor gating in rat offspring**. *Behav Brain Res* 2008, **190:**156-159.

37. Ozawa K, Hashimoto K, Kishimoto T, Shimizu E, Ishikura H, Iyo M: **Immune activation during pregnancy in mice leads to dopaminergic hyperfunction and cognitive impairment in the offspring: a neurodevelopmental animal model of schizophrenia**. *Biol Psychiatry* 2006, **59:**546-554.

38. Meyer U, Nyffeler M, Yee BK, Knuesel I, Feldon J: **Adult brain and behavioral pathological markers of prenatal immune challenge during early/middle and late fetal development in mice**. *Brain Behav Immun* 2008, **22:**469-486.

39. Carloni S, Perrone S, Buonocore G, Longini M, Proietti F, Balduini W: **Melatonin protects from the long-term consequences of a neonatal hypoxic-ischemic brain injury in rats**. *J Pineal Res* 2008, **44:**157-164.

40. Rogalska J, Caputa M, Wentowska K, Nowakowska A: **Stress-induced behaviour in adult and old rats: effects of neonatal asphyxia, body temperature and chelation of iron**. *J Physiol Pharmacol* 2006, **57 Suppl 8:**17-34.

41. Tejkalova H, Kaiser M, Klaschka J, Stastny F: **Does neonatal brain ischemia induce schizophrenia-like behavior in young adult rats?** *Physiol Res* 2007, **56:**815-823.

42. Adriani W, Giannakopoulou D, Bokulic Z, Jernej B, Alleva E, Laviola G: **Response to novelty, social and self-control behaviors, in rats exposed to neonatal anoxia: modulatory effects of an enriched environment**. *Psychopharmacology (Berl)* 2006, **184:**155-165.

43. Soodi M, Sharifzadeh M, Naghdi N, Ostad N, Abdollahi M, Roghani A: **Systemic and developmental exposure to lead causes spatial memory deficits and a reduction in COX-2 immunoreactivity in the hippocampus of male rats**. *J Neurosci Res* 2007, **85:**3183-3192.

44. Moreira EG, Vassilieff I, Vassilieff VS: **Developmental lead exposure: behavioral alterations in the short and long term**. *Neurotoxicol Teratol* 2001, **23:**489-495.

45. Sonmez U, Sonmez A, Erbil G, Tekmen I, Baykara B: **Neuroprotective effects of resveratrol against traumatic brain injury in immature rats**. *Neurosci Lett* 2007, **420:**133-137.

46. Bouslama M, Renaud J, Olivier P, Fontaine RH, Matrot B, Gressens P, Gallego J: **Melatonin prevents learning disorders in brain-lesioned newborn mice**. *Neuroscience* 2007, **150:**712-719.

47. Shukitt-Hale B, Erat SA, Joseph JA: **Spatial learning and memory deficits induced by dopamine administration with decreased glutathione**. *Free Radic.Biol.Med.* 1998, **24:**1149-1158.

48. Mamiya T, Kise M, Morikawa K: **Ferulic acid attenuated cognitive deficits and increase in carbonyl proteins induced by buthionine-sulfoximine in mice**. *Neurosci Lett* 2008, **430:**115-118.

49. Jacobsen JP, Rodriguiz RM, Mork A, Wetsel WC: **Monoaminergic dysregulation in glutathione-deficient mice: Possible relevance to schizophrenia?** *Neuroscience* 2005, **132:**1055-1072.

50. Masood A, Nadeem A, Mustafa SJ, O'Donnell JM: **Reversal of oxidative stress-induced anxiety by inhibition of phosphodiesterase-2 in mice**. *J Pharmacol Exp Ther* 2008, **326:**369-379.

51. Dean O, Bush AI, Berk M, Copolov DL, van den Buuse M: **Glutathione depletion in the brain disrupts short-term spatial memory in the Y-maze in rats and mice**. *Behav Brain Res* 2009, **198:**258-262.

52. Zhang XL, Jiang B, Li ZB, Hao S, An LJ: **Catalpol ameliorates cognition deficits and attenuates oxidative damage in the brain of senescent mice induced by D-galactose**. *Pharmacol Biochem Behav* 2007, **88:**64-72.

53. Cui X, Zuo P, Zhang Q, Li X, Hu Y, Long J, Packer L, Liu J: **Chronic systemic D-galactose exposure induces memory loss, neurodegeneration, and oxidative damage in mice: protective effects of R-alpha-lipoic acid**. *J Neurosci Res* 2006, **84:**647-654.

54. Dairam A, Muller AC, Daya S: **Non-steroidal anti-inflammatory agents, tolmetin and sulindac attenuate quinolinic acid (QA)-induced oxidative stress in primary hippocampal neurons and reduce QA-induced spatial reference memory deficits in male Wistar rats**. *Life Sci* 2007, **80:**1431-1438.

55. de Oliveira MR, Silvestrin RB, Mello E Souza, Moreira JC: **Oxidative stress in the hippocampus, anxiety-like behavior and decreased locomotory and exploratory activity of adult rats: effects of sub acute vitamin A supplementation at therapeutic doses**. *Neurotoxicology* 2007, **28:**1191-1199.

56. Hovatta I, Tennant RS, Helton R, Marr RA, Singer O, Redwine JM, Ellison JA, Schadt EE, Verma IM, Lockhart DJ, Barlow C: **Glyoxalase 1 and glutathione reductase 1 regulate anxiety in mice**. *Nature* 2005, **438:**662-666.

57. Baker DA, Madayag A, Kristiansen LV, Meador-Woodruff JH, Haroutunian V, Raju I: **Contribution of cystine-glutamate antiporters to the psychotomimetic effects of phencyclidine**. *Neuropsychopharmacology* 2008, **33:**1760-1772.

58. Kumar A, Goyal R: **Quercetin protects against acute immobilization stress-induced behaviors and biochemical alterations in mice**. *J Med Food* 2008, **11:**469-473.

59. Singh A, Kumar A: **Protective effect of alprazolam against sleep deprivation-induced behavior alterations and oxidative damage in mice**. *Neurosci Res* 2008, **60:**372-379.

60. Aoyama N, Katayama Y, Kawamata T, Maeda T, Mori T, Yamamoto T, Kikuchi T, Uwahodo Y: **Effects of antioxidant, OPC-14117, on secondary cellular damage and behavioral deficits following cortical contusion in the rat**. *Brain Res* 2002, **934:**117-124.

61. Pineda JA, Aono M, Sheng H, Lynch J, Wellons JC, Laskowitz DT, Pearlstein RD, Bowler R, Crapo J, Warner DS: **Extracellular superoxide dismutase overexpression improves behavioral outcome from closed head injury in the mouse**. *J Neurotrauma* 2001, **18:**625-634.