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Review

Redox dysregulation, neuroinflammation, and NMDA receptor hypofunction: A “central hub” in schizophrenia pathophysiology?

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ABSTRACT

Accumulating evidence points to altered GABAergic parvalbumin-expressing interneurons and impaired myelin/axonal integrity in schizophrenia. Both findings could be due to abnormal neurodevelopmental trajectories, affecting local neuronal networks and long-range synchrony and leading to cognitive deficits. In this review, we present data from animal models demonstrating that redox dysregulation, neuroinflammation and/or NMDAR hypofunction (as observed in patients) impairs the normal development of both parvalbumin interneurons and oligodendrocytes. These observations suggest that a dysregulation of the redox, neuroimmune, and glutamatergic systems due to genetic and early-life environmental risk factors could contribute to the anomalies of parvalbumin interneurons and white matter in schizophrenia, ultimately impacting cognition, social competence, and affective behavior via abnormal function of micro- and macrocircuits. Moreover, we propose that the redox, neuroimmune, and glutamatergic systems form a “central hub” where an imbalance within any of these “hub” systems leads to similar anomalies of parvalbumin interneurons and oligodendrocytes due to the tight and reciprocal interactions that exist among these systems. A combination of vulnerabilities for a dysregulation within more than one of these systems may be particularly deleterious. For these reasons, molecules, such as N-acetylcysteine, that possess antioxidant and anti-inflammatory properties and can also regulate glutamatergic transmission are promising tools for prevention in ultra-high risk patients or for early intervention therapy during the first stages of the disease.

1. Introduction

Schizophrenia is considered a disorder with an important neurodevelopmental component. Various genetic and environmental risk factors can affect brain developmental processes including maturation of interneurons and oligodendrocytes, which could eventually contribute to the emergence of the symptoms during adolescence and early adulthood (Insel, 2010). Our current understanding of the neurobiological processes involved in schizophrenia remains, however, limited. Many hypotheses have been proposed, but a consensus among the research community is lacking. Prominent hypotheses include disturbance of glutamatergic neurotransmission in the form of hypofunction of NMDA receptors (NMDARs) (Krystal et al., 1994; Coyle et al., 2012; Kantrowitz and Javitt, 2012; Steiner et al., 2013), neuroinflammation (Saetre et al., 2007; Potvin et al., 2008; van Berckel et al., 2008; Meyer, 2013), and redox dysregulation (Do et al., 2009a,b; Clay et al., 2011; Gysin et al., 2011; Martins-de-Souza et al., 2011; Yao and Keshavan, 2011). We propose that dysregulation of redox homeostasis, neuroimmune, and glutamatergic systems induced by different etiological factors constitute, via their reciprocal interactions, one “central hub” as a common final pathway contributing to this disorder (Fig. 1). Here, we review the effect of dysregulation of each of these systems and their interactions on excitatory/inhibitory balance of local neuronal circuits (microcircuits), as well as the connections between distant brain areas (macrocircuits). In particular, we propose that dysfunction in these systems has deleterious effects on normal development of cortical and hippocampal parvalbumin-expressing interneurons (PVIs), which are essential for fast local neuronal synchronization, and on oligodendrocytes, which form myelin sheets around axons providing fast signal conduction between the brain regions. Anomalies of PVIs and oligodendrocytes are indeed widely recognized in schizophrenia and considered to contribute to abnormal brain connectivity leading to cognitive, affective, and social deficits.

2. A “hub” formed by the redox, glutamatergic, and neuroimmune systems

A dysregulation of the redox, glutamatergic, and neuroimmune systems has all been reported in schizophrenia. Genetic and/or

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Abbreviations: NAC, N-acetylcysteine; PN, pyramidal neuron; PNN, perineuronal net; PVIs, parvalbumin interneurons; RNS, reactive nitrogen species; ROS, reactive oxygen species.

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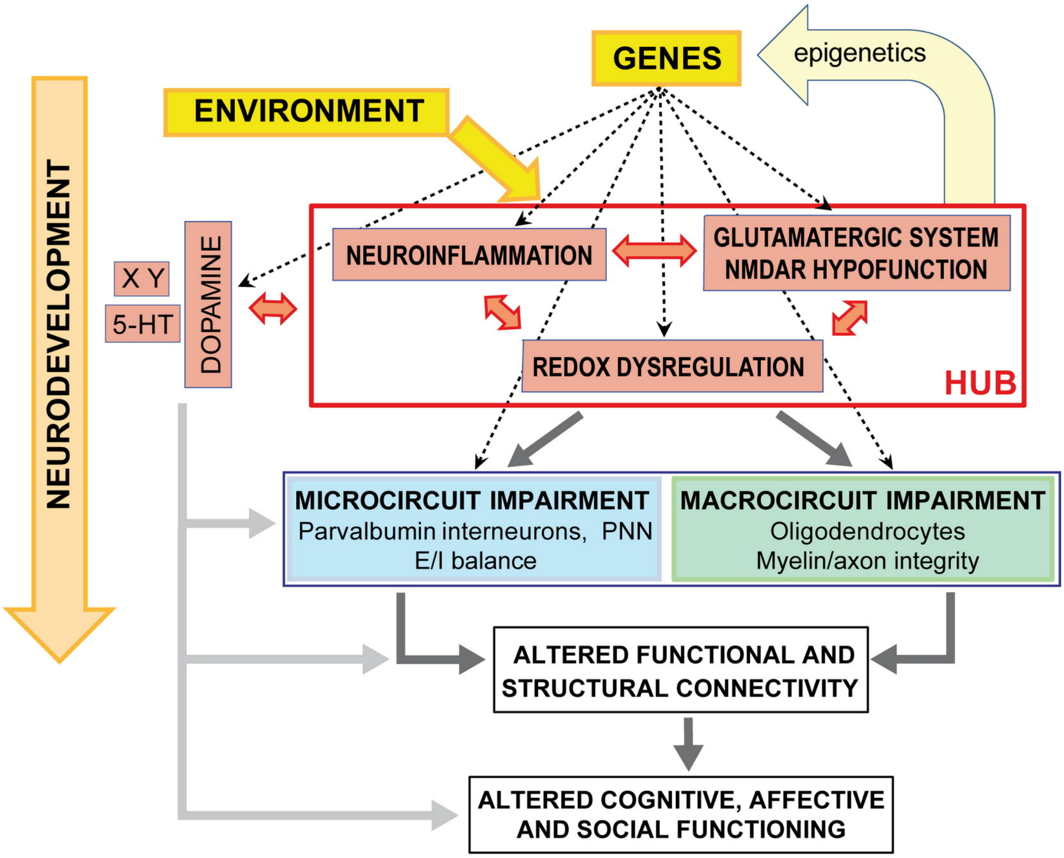

Fig. 1. Proposed "hub" formed of the redox, neuroimmune, and glutamatergic systems whose dysregulation during development could disrupt maturation of parvalbumin interneurons (PVIs) and oligodendrocytes, two cell types affected in schizophrenia and critical for short- and long-range neuronal network synchronization. This could impact structural and functional connectivity circuits affecting diverse aspects of cognitive, affective and social functioning (Buckholtz and Meyer-Lindenberg, 2012). Genetic risk factors combined with environmental insults can affect the homeostasis of one or several of the "hub" systems which in turn could impact the others through reciprocal interactions (*reciprocal arrows*). Genetic vulnerability to redox dysregulation in schizophrenia is supported by polymorphisms and copy number variations in genes related to the GSH metabolism (Tosic et al., 2006; Gysin et al., 2007; Rodriguez-Santiago et al., 2010; Gravina et al., 2011; Mehta et al., 2013). In addition, impaired function of proteins coded by other plausible risk genes, including *DISC1*, *PROD*, *G72*, *NRG*, *DTNBP1*, indirectly leads to oxidative stress often via mitochondrial dysfunction (Goldshmit et al., 2001; Krishnan et al., 2008; Park et al., 2010; Clay et al., 2011; Gokhale et al., 2012; Johnson et al., 2013). Genes related to the immune system have also been identified as potent risk genes for schizophrenia, in particular the major histocompatibility complex (*MHC*) genes, one of the most replicated genetic risk factors for schizophrenia disorder (Stefansson et al., 2009; Smyth and Lawrie, 2013). Finally, genetic vulnerability for NMDAR hypofunction seems to be more associated with potent risk genes encoding proteins that indirectly influence the function of this receptor; this includes D-amino acid oxidase, G72, dysbindin, and neuregulin (see Coyle et al., 2012), mGluR5 and proteins belonging to the postsynaptic NMDAR complex (Kirov et al., 2012; Timms et al., 2013; Fromer et al., 2014; Purcell et al., 2014). Developmental insults that are known to increase the risk for schizophrenia cause redox dysregulation/oxidative stress (Walter et al., 2002; Do et al., 2009b) and/or neuroinflammation (Schiavone et al., 2009; Brenhouse and Andersen, 2011; Garate et al., 2013; Kaur et al., 2013). Note that the dopaminergic or serotoninergic (5-HT) systems (and others = X Y) modulated by risk-factor genes and environment could also impact micro- and macrocircuits either directly or indirectly via interactions with the above "hub". *Dotted arrows* depict impact of genetic risk factors. E/I balance: excitatory/inhibitory balance; PNN: perineuronal net surrounding PVIs.

environmental risk factors can contribute to disturbances within each of these tightly interdependent systems (see Fig. 1 and its legend for more details). In particular, redox pathways represent a central node via their numerous reciprocal interactions with the glutamatergic and immune systems. Oxidative stress is defined as an imbalance between antioxidants and pro-oxidants (reactive oxygen species (ROS) and reactive nitrogen species (RNS)), resulting in macromolecular damage. In addition, redox signaling plays a key regulating role in many cellular and physiological processes (Jones, 2008). A redox dysregulation can affect cell proliferation/differentiation, energy metabolism, and neurotransmission via an alteration of redox-sensitive protein function, redox-dependent gene expression, and epigenetic mechanisms (Valko et al., 2007; Cyr and Domann, 2011; Ray et al., 2012). Several proteins related to glutamatergic neurotransmission contain modulatory redox sites, including glutamine synthase (Mustafa et al., 2007), serine racemase (responsible for synthesis of glycine, a NMDAR co-agonist (Pinteaux et al., 1996)), and NMDARs (Choi et al., 2001). While redox state modulates NMDAR function, activation of synaptic NMDARs strengthens neuronal antioxidant defense mechanisms (Hardingham and Bading, 2010). Moreover, glutathione (GSH), the main antioxidant and redox regulator, constitutes a neuronal reservoir of glutamate (Koga et al., 2011). These observations indicate that redox and glutamatergic systems are intimately dependent. Likewise, oxidative stress is tightly linked to inflammation. Many inflammatory mediators are activated by oxidative molecules, while activated immune cells such as microglia generate ROS and RNS. The complex interplay between oxidative stress and inflammation is in part governed by the reciprocal interactions between the transcription factors Nrf2 (whose nuclear translocation induces antioxidant phase II gene transcription) and NF-κB (whose translocation to the nucleus promotes transcription of many pro-inflammatory genes) (Buelna-Chontal and Zazueta, 2013). Finally, an imbalance of the immune system may also affect NMDAR function. Human subjects with anti-NMDAR encephalitis develop psychosis (Dalmau et al., 2011) and antibodies against NMDAR have been reported in patients diagnosed with schizophrenia (Steiner et al., 2013). Moreover, inflammatory processes cause increased production of kynurenic acid, an endogenous NMDAR antagonist, via dysregulation of tryptophan/kynurenine metabolism (Muller et al., 2011). Thus, redox, immune, and glutamatergic systems form a triad in which each of its elements can influence the others. Diverse genetic vulnerabilities and environmental risk factors may affect one element of this triad, impacting in turn the other systems. Because of the complex interactions between

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each element of this triad, it is difficult to untangle the respective contribution of each system in the pathophysiology. To our view, the primary effector may depend on the specific combination of the genetic vulnerability and environmental insults. Therefore, the redox, immune, and glutamatergic systems may be considered together as one "central hub" in which a dysregulation in any of them can lead to a common pathophysiological condition, such as dysconnectivity via impairment of PVIs and oligodendrocytes.

3. Parvalbumin interneurons

PVIs are GABAergic neurons that form inhibitory synapses onto either the cell body (for parvalbumin-expressing basket cells) or the axon initial segment (for parvalbumin-expressing chandelier cells) of pyramidal neurons (PNs). Basket cells control inputs reaching the soma of PNs, while chandelier cells control PN output. PVIs, which are interconnected via gap junctions (Fukuda et al., 2006) and reciprocal GABAergic synapses, constitute a cellular network able to synchronize the excitatory state of large numbers of PNs (Bartos et al., 2007). By way of feedback and feedforward inhibition, fast-spiking interneurons exert precise temporal control on information that can flow through PNs. These interneurons favor summation and transmission of converging inputs arriving synchronously onto a PN. By controlling synchronized excitability state of a network of PNs, PVIs also allow the binding of information that reach these different PNs during a defined and narrow time window (Fries et al., 2007). Therefore, PVIs strongly influence local neuron-network dynamic. They are critical for high-frequency neuronal synchrony, reflected in gamma band oscillations (30–80 Hz) (Fuchs et al., 2007; Cardin et al., 2009; Sohal et al., 2009; Gulyas et al., 2010; Massi et al., 2012), but can also modulate neuronal activity in the theta band (4–8 Hz), as well as theta–gamma coupling (Wulff et al., 2009; Korotkova et al., 2010). The maturation of PVIs and their associated extracellular matrix defines a critical period of cortical network plasticity during postnatal development (Morishita and Hensch, 2008). Moreover, plasticity within the basket-cell network contributes to memory learning, consolidation and retrieval (Donato et al., 2013) and PVIs promote neuronal progeny survival and development in the hippocampus (Song et al., 2013). Furthermore, in prefrontal cortical regions, heavily implicated in schizophrenia pathophysiology, PVIs mature during adolescence (Tseng and O'Donnell, 2007; O'Donnell, 2011) and is therefore a neural population with a protracted developmental trajectory that could explain the peri-adolescent onset of schizophrenia symptoms.

3.1. Evidence for abnormal PVI in schizophrenia

Compelling evidence suggests an imbalance between glutamatergic excitation and GABAergic inhibition in schizophrenia (Lisman et al., 2008; O'Donnell, 2011). Anomalies associated with PVIs constitute a hallmark of the disease, including reduced density of parvalbumin-immunoreactive cells in the hippocampal formation (Zhang and Reynolds, 2002; Wang et al., 2011) and alterations at the level of basket and chandelier cells in the dorsolateral prefrontal cortex (DLPFC) of postmortem brains (Lewis et al., 2012). These alterations include reduced expression of parvalbumin and GAD67 (isoform of glutamic acid decarboxylase, the GABA synthesizing enzyme), changes in their pre and postsynaptic terminals (Lewis et al., 2012), and reduced expression of Kv3.1-containing $K+$ channels, which play a critical role in their fast-spiking properties (Yanagi et al., 2014). Moreover, the extracellular matrix (perineuronal net: PNN) that surrounds many PVIs is reduced in DLPFC (Mauney et al., 2013), entorhinal cortex, and amygdala of schizophrenia patients (Pantazopoulos et al., 2010). Current data suggest an impaired maturation of PVIs rather than a deficit due to the chronicity of the illness. The DLPFC of young patients already has low expression levels of parvalbumin and GAD67 (Hoftman et al., 2013), and gene expression pattern in PVIs of schizophrenia individuals resembles that of non-mature cells (Gandal et al., 2012). Therefore, dysfunction of the PVI-associated network may lead to abnormal neuronal activity in patients, including oscillatory activity within theta, beta and gamma ranges (Uhlhaas and Singer, 2010, 2012; McNally et al., 2013). Ultimately, interneuron dysfunction could contribute to altered sensory perception (Atallah et al., 2012), deficits in working memory (Korotkova et al., 2010; Roux et al., 2012), attention (Rouhinen et al., 2013), and learning (Carlen et al., 2012).

3.2. Mechanisms underlying abnormal PVIs

Recent studies have revealed anomalies in hippocampal and/or prefrontal PVIs in many preclinical animal models aiming to reproduce genetic vulnerabilities (Hikida et al., 2007; Fazzari et al., 2010; Wen et al., 2010; Carlson et al., 2011) or environmental risk factors (Brown, 2011) such as prenatal maternal stress (Stevens et al., 2013), maternal and perinatal immune challenge (Meyer et al., 2008; Jenkins et al., 2009), hypoxia (Dell'Anna et al., 1996; Komitova et al., 2013), early-life iron deficiency (Callahan et al., 2013), maternal separation (Brenhouse and Andersen, 2011) and social isolation (Harte et al., 2007; Schiavone et al., 2009). These developmental insults cause oxidative stress (Walter et al., 2002; Do et al., 2009b) and/or neuroinflammation (Brenhouse and Andersen, 2011; Garate et al., 2013; Kaur et al., 2013). Furthermore, non-genetic developmental models also result in altered prefrontal PVIs (Tseng et al., 2008; Lodge et al., 2009). In rats with a neonatal ventral hippocampal lesion, the normal peri-adolescent maturation of PVIs is impaired (Tseng et al., 2008), and in this model PVIs show evidence of oxidative stress prior to the onset of behavioral deficits (O'Donnell et al., 2011). Below, we present evidence that PVIs are particularly affected during their development by oxidative stress, neuroinflammation, and NMDAR hypofunction.

3.2.1. Vulnerability to redox dysregulation/oxidative stress

To support high-frequency neuronal synchronization, fast-spiking PVIs are energy demanding. This requires optimal mitochondrial performance (Kann et al., 2011) with enhanced metabolic activity and oxidative phosphorylation (Harris et al., 2012) leading to elevated mitochondria-generated ROS. Consequently, PVIs need well-regulated antioxidant systems to neutralize ROS and maintain proper redox state. Interestingly, the power of β/γ neuronal activity is positively correlated with blood GSH levels in patients (Ballesteros et al., 2013). These cells are vulnerable to redox dysregulation, whether induced by a compromised antioxidant system or ROS overproduction. In an animal model with low GSH content, as reported in the brain of some schizophrenia patients (Do et al., 2000; Yao et al., 2006; Gawryluk et al., 2011), there is a deficit in prefrontal and hippocampal PVIs, impairing high-frequency neuronal synchronization (Steullet et al., 2010; Cabungcal et al., 2013a,b). Interestingly, an inhibition of GSH synthesis restricted to PVIs is sufficient to affect these interneurons (Cabungcal et al., 2013b) and oxidative stress precedes the PVI deficit (Steullet et al., 2010). PVIs can also be affected when antioxidant systems other than GSH are compromised. A reduced number of parvalbumin-immunoreactive cells is observed in mice with a deletion for the selenoprotein P, a glycoprotein with antioxidant properties (Pitts et al., 2012) or for PGC-1α, a transcription factor regulating mitochondria function and ROS metabolism (Lucas et al., 2010). Furthermore, superoxide overproduction by NADPH oxidase (NOX) is also deleterious to PVIs (Behrens et al., 2007), and NOX inhibition prevents the PVI impairment induced by social isolation (Schiavone et al., 2009).

Most importantly, prefrontal cortical PVIs are more vulnerable to a redox dysregulation during postnatal development than later in life. A pharmacologically induced transient postnatal deficit in GSH causes both immediate and long-term decreased densities of parvalbumin-immunoreactive cells in the anterior cingulate cortex (ACC) (Cabungcal et al., 2006; Steullet et al., 2011; Kulak et al., 2013). In mice with a chronic GSH deficit (*Gclm* KO mice, Kulak et al., 2012), administration of a dopamine re-uptake inhibitor (GBR-12909), which partially mimics dopamine release during psychosocial stress (Lataster et al., 2011) and produces

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ROS via the catabolism of dopamine (Cadet and Brannock, 1998; Rabinovic and Hastings, 1998), decreases permanently the density of parvalbumin-immunoreactive cells in the ACC when applied during postnatal development, but not adulthood (Cabungcal et al., 2013a). Thus, immature PVIs may have a less robust antioxidant defense system than mature cells. Alternatively, molecular mechanisms underlying PVI maturation are highly sensitive to a redox imbalance. Interestingly, the vulnerability of prefrontal immature PVIs is associated with the absence of fully mature PNN, which protects these cells against oxidative stress (Cabungcal et al., 2013b). However, excess of oxidative stress also affects PNN (Cabungcal et al., 2013b), which can in turn impact PVIs. Indeed, the maturation and phenotypic maintenance of PVIs require incorporation of a non-cell autonomous homeobox protein, Otx2, through its affinity with PNN (Beurdeley et al., 2012; Miyata et al., 2012).

The implication of redox dysregulation/oxidative stress for the developmental impairment of PVIs has been further substantiated by recent studies on experimental neurodevelopmental models that do not directly manipulate the redox system. First, the widely studied neonatal ventral hippocampal lesion model also displays oxidative stress and PVI defect, both of which are prevented by a juvenile and adolescence treatment with the antioxidant and GSH precursor, N-acetylcysteine (NAC) (O'Donnell et al., 2011; Sullivan and O'Donnell, 2012). Second, a single injection of the DNA-alkylating agent methylazoxymethanol acetate (MAM) during pregnancy, which also causes schizophrenia phenotypes in adult rats, leads to anomalies in PVIs and neuronal synchronization (Penschuck et al., 2006; Lodge et al., 2009). MAM-treated rats have also decreased brain GSH levels (Cleland et al., 2013). Collectively, these studies demonstrate that a redox dysregulation during a critical developmental period can disrupt normal maturation of PVIs.

3.2.2. Vulnerability to NMDAR hypofunction

Numerous studies show that NMDAR blockade in adults disrupts excitatory/inhibitory balance in cortical circuits, affecting PVIs (Behrens et al., 2007) and neuronal network activity (Homayoun and Moghaddam, 2007; Korotkova et al., 2010; Lazarewicz et al., 2010; Carlen et al., 2012; Kocsis et al., 2013). However, PVIs are especially vulnerable to NMDAR hypofunction during development (Abekawa et al., 2007; Wang et al., 2008, 2013; Powell et al., 2012). Inhibition of NMDARs during early life causes a persistent decrease in the number of parvalbumin-immunoreactive cells without cell death (Powell et al., 2012), suggesting that disruption of NMDAR-mediated signaling impairs maturation of these cells. Indeed, the maturation of PVIs is activity-dependent (Chattopadhyaya et al., 2004; Patz et al., 2004). Calcium entrance is necessary for the maturation of PNN (Dityatev et al., 2007) and PVIs (Jiang and Swann, 2005; Kinney et al., 2006), and activation of NR2A-containing NMDARs contributes to the molecular signaling that leads to the maturation of these cells (Kinney et al., 2006; Zhang and Sun, 2011).

3.2.3. Interactions between NMDAR hypofunction and redox dysregulation

It is intriguing that NMDAR hypofunction and redox dysregulation impair PVI maturation in similar ways. This raises the possibility that both mechanisms interfere with the maturation of PVIs via related molecular mechanisms. Interestingly, synaptic NMDAR activation boosts GSH, thioredoxin, and peroxiredoxin systems via calcium-mediated signaling involving activation of CREB and inhibition of FOXO (Papadia et al., 2008; Hardingham and Bading, 2010). The work from Nakazawa and colleagues indicates that impaired maturation of PVIs induced by NMDAR hypofunction is due to a redox dysregulation. When applied during postnatal development, a deletion of the NR1 subunit of NMDARs in a subpopulation of interneurons (including most PVIs) leads to parvalbumin and GAD67 expression deficit along with oxidative stress in PVIs (Belforte et al., 2010; Jiang et al., 2013). In these mice, social isolation exacerbates oxidative stress and PVI deficits, both of which are prevented by a NOX inhibitor (Jiang et al., 2013). In NOX-2 knockout mice, PVIs are protected from a postnatal ketamine treatment, indicating a crucial role of NOX in the PVI impairment following early-life blockade of NMDAR (Powell et al., 2012). However, the lack of NMDAR-mediated signaling also causes a reduction in PGC-1α levels and expression of several antioxidant enzymes (Jiang et al., 2013), and decreases GSH levels (Stojkovic et al., 2012). These observations suggest that NMDAR hypofunction can weaken antioxidant defenses, contributing to a redox dysregulation and affecting cell maturation. The downregulation of antioxidant systems by NMDAR blockade may be particularly significant in PVIs of young individuals, since NMDAR-mediated postsynaptic responses are stronger in immature compared to mature PVIs (Wang and Gao, 2009, 2010; Rotaru et al., 2011). However, a redox dysregulation can also downregulate NMDAR function on its own. Functional downregulation of NMDARs by oxidative conditions can occur via either extracellular redox-sensitive sites located on NR1 and NR2A subunits (Kohr et al., 1994; Choi et al., 2001) or by Ca^{2+}/calmodulin-dependent protein kinase II (Bodhinathan et al., 2010). A transient postnatal GSH deficit results in NMDAR hypofunction (Steullet et al., 2006) and impairs PVIs (Cabungcal et al., 2006). Therefore, redox dysregulation and NMDA receptor hypofunction during postnatal development can interact synergistically, creating a vicious circle that is particularly detrimental for PVIs.

3.2.4. Vulnerability to neuroinflammation

Because of the tight link between oxidative stress and inflammation, it is not surprising that pro-inflammatory molecules affect PVIs. Interleukin-6 mediates ketamine-induced NOX upregulation and subsequently PVI deficits (Behrens et al., 2008). A genome-wide profiling and immunohistological study revealed that reduced PVI density in schizophrenia patients is associated with two modules of genes differentially expressed in patients compared to healthy subjects, among which are many immune/inflammation-related genes (Hwang et al., 2013). Early-life pro-inflammatory conditions, such as maternal and neonatal immune challenges, cause a persistent decrease in the number of prefrontal and/or hippocampal parvalbumin-immunoreactive interneurons (Meyer et al., 2008; Jenkins et al., 2009). This deleterious effect could result from a redox dysregulation as maternal immune challenge transiently decreases GSH and vitamin E levels and increase oxidative stress in the hippocampus (Lante et al., 2007). A reduced number of hippocampal and prefrontal parvalbumin-immunoreactive interneurons are also observed in Schnurri-2 KO mice, a genetic model for enhanced neuroinflammation via increased NF-κB-dependent gene expression (Takao et al., 2013). These mice show increased expression of inflammation-related genes and NOX, which affects PVIs. The PVI impairment following maternal separation can be prevented by non-steroidal anti-inflammatory drugs (Brenhouse and Andersen, 2011). Nevertheless, the possibility that a ROS scavenger can also protect PVIs against the effect of maternal separation cannot be excluded. These data clearly show that neuroinflammation impacts PVIs, but the specific role of pro-inflammatory molecules and oxidative stress remains to be established. A combination of vulnerability for pro-inflammatory conditions and redox dysregulation due to environmental and genetic factors may be particularly deleterious for PVIs. This combination has been demonstrated in transgenic mice expressing a putative dominant-negative disrupted in schizophrenia 1 (DN-DISC1), which display enhanced prefrontal oxidative stress (Johnson et al., 2013) and shows stronger PVI deficits following a postnatal immune challenge (Ibi et al., 2010).

To conclude, PVIs are particularly vulnerable to redox dysregulation/oxidative stress, NMDAR hypofunction, and neuroinflammation during early development. Genetic vulnerabilities and environmental insults that would affect homeostasis of either redox, or glutamatergic, or neuroimmune system could affect the other systems with amplified negative consequences on PVI maturation and subsequently on neuronal network synchronization and information processing.

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4. Oligodendrocytes/myelination

4.1. Evidence for impaired oligodendrocytes/myelination in schizophrenia

Oligodendrocytes and myelination are clearly impaired in schizophrenia (Davis et al., 2003; Takahashi et al., 2011; Chew et al., 2013). The observations supporting this claim include decreased expression of oligodendrocyte-related genes (Hakak et al., 2001; Tkachev et al., 2003; Katsel et al., 2005), impairment of oligodendrocyte maturation (Kerns et al., 2010), reduced number and/or density of oligodendrocytes in gray and white matter (Hof et al., 2003; Uranova et al., 2004; Byne et al., 2008), apoptotic oligodendrocytes and ultrastructural alterations in myelinated fibers (Uranova et al., 2001). The anomalies at the level of myelin/axonal integrity increase with illness duration (Uranova et al., 2011). Studies using magnetic resonance techniques such as diffusion tensor imaging (DTI) also suggest abnormal white matter along different fiber tracts, including within and between frontal and temporal areas (Fitzsimmons et al., 2013). Although less consistent than in chronic patients, white matter anomalies are observed in ultra high-risk subjects and first-episode patients (Kyriakopoulos and Frangou, 2009; Fitzsimmons et al., 2013), suggesting a neurodevelopmental component for this impairment. Oligodendrocytic and myelination anomalies in schizophrenia could affect axonal integrity and conduction velocity (Whitford et al., 2011), with the consequence of disrupting temporal control of long-range brain synchronization.

4.2. Mechanisms underlying impaired oligodendrocytes/myelination

Genes related to oligodendrocytes and myelination have been associated with schizophrenia (Takahashi et al., 2011), suggesting that white matter anomalies in this disorder could have a direct genetic origin. However, other mechanisms could also impact white matter integrity. Perinatal insults and psychosocial stress during childhood and adolescence are correlated with structural changes in white matter (Eluvathingal et al., 2006; Huang et al., 2012; Chew et al., 2013). In rodents, early-life insults, most of which cause PVI impairment, also affect oligodendrocytes and myelination. These insults include maternal and early postnatal immune challenge (Fan et al., 2005; Paintlia et al., 2008), perinatal hypoxia (Oorschot et al., 2013), hypoxia-ischemic insults (Robinson et al., 2005), and social isolation (Liu et al., 2012; Makinodan et al., 2012). These observations suggest that some of the biological causes for the developmental PVI and white matter anomalies could be similar.

4.2.1. Vulnerability to redox dysregulation/oxidative stress

In vitro studies show that oligodendrocytes are susceptible to oxidative stress due to their high metabolic activity and iron content combined with low antioxidant levels (Back et al., 1998; Baud et al., 2004; Fragoso et al., 2004). Furthermore, the intracellular redox state controls the proliferation and differentiation of oligodendrocytes (Smith et al., 2000; Li et al., 2007; Do et al., 2012), and low GSH levels affect oligodendrocyte maturation (French et al., 2009). Peripubertal *Gclm* KO mice (which have low brain GSH content) present a deficit in myelin-associated proteins and mature oligodendrocytes in the ACC (Monin et al., 2014). This deficit, which recovers in adulthood, is accompanied by an increase in prefrontal N-acetylaspartate (das Neves Duarte et al., 2012), suggesting an impaired myelin lipid synthesis during prefrontal cortical maturation (Kulak et al., 2013). Interestingly during this period, genes associated with myelin and lipid synthesis, antioxidant response systems, mitochondria function and glycolysis are highly expressed (Harris et al., 2009). Therefore, a proper redox state controlled by GSH may be critical for adequate myelination in prefrontal gray matter during this period of high metabolic activity. In addition, a decrease in fractional anisotropy is observed along a few fiber tracts in *Gclm* KO mice, also suggesting white matter anomalies (Corcoba et al., 2014). Interestingly, we found a positive correlation between GSH content in the ACC and fractional anisotropy along the cingulum bundle in young adult human subjects (Monin et al., 2014). Taken together, these findings indicate that a redox dysregulation can cause oligodendrocytic developmental anomalies and/or delay in gray and white matter which may eventually contribute to abnormal myelin sheath and axonal integrity.

4.2.2. Vulnerability to NMDAR dysfunction

Postnatal inhibition of NMDARs causes deficit not only in PVIs, but also in myelination (Zhang et al., 2012). It is, however, unclear whether the myelination impairment results from the redox dysregulation also observed with this manipulation (Stojkovic et al., 2012) or from the loss of NMDAR signaling in oligodendrocytes. NMDARs are indeed expressed in immature and mature oligodendrocytes. Activation of these receptors in oligodendrocytes modulates their metabolism, promotes their differentiation from immature into mature stage, and favors myelination around axons (Cao and Yao, 2013; Li et al., 2013). Interestingly, NMDAR activation promotes the differentiation of cultured oligodendrocytes via NOX-mediated ROS (Cavaliere et al., 2012). A combination of redox dysregulation and NMDAR hypofunction could be therefore deleterious for oligodendrocyte differentiation and myelination.

4.2.3. Vulnerability to neuroinflammation

Oligodendrocytes, like PVIs, are also vulnerable to early-life neuroinflammation (Chew et al., 2013). Neonatal administration of inflammatory cytokines such as Il-1β reduces the number of developing oligodendrocytes (Cai et al., 2004; Fan et al., 2009). Maternal and early postnatal immune challenges impair myelination (Fan et al., 2005; Makinodan et al., 2008; Paintlia et al., 2008) and long-range synchronization (Dickerson et al., 2010). As microglial cells and cytokines participate in normal brain development (Bilbo and Schwarz, 2012; Kettenmann et al., 2013), a dysregulation of cytokine-mediated pathways could disrupt normal developmental processes. However, current data indicate that redox dysregulation contributes to myelination impairment due to early-life inflammation. Alpha-phenyl-n-tert-butylnitrone (PBN), a free radical scavenger, protects oligodendrocytes and myelination against neonatal immune challenge (Fan et al., 2008). Likewise, NAC prevents this deficit by attenuating the dysfunction of peroxisomes, organelles important for ROS detoxification and myelin-lipid metabolism (Paintlia et al., 2008). Moreover, the decreased expression of myelin-related genes induced by cytokines (Il-1β and TNF-α) in human primary oligodendrocytes is blocked by NAC (Jana and Pahan, 2005), suggesting that these inflammatory molecules act through redox dysregulation. Finally, the tetracycline antibiotic, minocycline, prevents hypomyelination induced by immune challenge, and its protective effect is associated with decreased microglial activation, cytokine levels, and oxidative stress (Fan et al., 2005). In a genetic model of enhanced pro-inflammation (Schnurri-2 KO mice), the expression of myelin-associated proteins is reduced, which could be due to a NOX upregulation (Takao et al., 2013). These data show that the impact of early-life neuroinflammation on oligodendrocytes and myelination is in part due to the generation of ROS/RNS. Thus as for PVIs, a vulnerability to redox dysregulation may further exacerbate the deleterious effect of pro-inflammatory conditions on myelin integrity.

Taken together, it is remarkable that PVIs and oligodendrocytes are affected by similar early-life insults and by the disruption of redox, neuroimmune and glutamatergic systems. One reason for this shared vulnerability could be related to the high metabolic requirement of these two cell types. The data compiled in the present review strongly suggest that genetic and environmental risk factors, which lead to dysregulation of the "hub" comprised of redox, neuroimmune and glutamatergic systems, would invariably affect PVIs and white matter, and consequently impair long- and short-range neuronal network connectivity. Given the pivotal role of PVIs, PNN, and myelin in regulating brain plasticity dynamics and active epochs (McGee et al., 2005; Morishita and Hensch, 2008; Miyata et al., 2012), the dysregulation

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of this “hub” could yield the slow emergence of clinical symptoms by altering the timing of key windows of critical period of brain plasticity (Morishita et al., 2010). Because of the complex interplay between redox, immune, and glutamatergic systems, we propose that combinations of genetic and environmental risk factors could generate a vicious circle of dysregulation within all these systems, ultimately giving rise to abnormal functional and structural connectivity deficits, as observed in schizophrenia. We have however to acknowledge that this hypothesis is based mostly on observations and experiments in rodent models and postulates that the mechanisms are similar in humans. Moreover, we have to emphasize that other systems such as the dopamine system known to be implicated in schizophrenia and their reciprocal interactions with the proposed “hub” (see: Avshalumov et al., 2007; Baker et al., 2002; Kulak et al., 2013; Lodge and Grace, 2011; Meiser et al., 2013; Meyer and Feldon, 2009; Moller et al., 2013; Steullet et al., 2008) certainly participate in the pathology. Increasing evidence points to altered stress-reactivity as a vulnerability marker for psychosis (Myin-Germeys et al., 2003; Lataster et al., 2013). The biological mechanism underlying psychotic reactivity to stress could be related to hyper-reactivity of dopamine neurons to environmental stimuli and stress (Myin-Germeys et al., 2005; Lataster et al., 2011; Mizrahi et al., 2012). As dopamine catabolism is known to generate ROS, its excess would induce an oxidative stress. Metabolomic approach in cells derived from patients and controls highlights the possibility of using metabolic signatures of reactivity to oxidative stress as biomarkers for early psychosis (Fournier et al., 2014).

5. N-acetylcysteine, a potential therapeutic or prevention drug

Novel strategies aiming to regulate redox, immune, and glutamatergic systems could therefore be potentially useful to prevent or attenuate developmental anomalies yielding schizophrenia pathophysiology. To date, clinical trials using molecules targeting either the glutamatergic system (mGluR5, mGluR2/3, glycine site of NMDARs) (Javitt, 2012; Kantrowitz and Javitt, 2012; Poels et al., 2014; Vinson and Conn, 2012), the immune (Muller et al., 2013; Leza et al., in press), or antioxidant systems (Reddy and Reddy, 2011; Leza et al., in press) have produced mixed results, some encouraging and others inconclusive. Several promising clinical phase III trials aiming to act on the glutamatergic system proved inconclusive, but other relatively small scale clinical studies targeting the glycine site of NMDAR using D-serine indicate positive effects (Kantrowitz and Javitt, 2012). The efficacy of such molecules may however depend on the disease stages but also on patient subgroups. Future trials should focus on unmedicated patients in the early phase of the disease and target not only clinical but also biological measures such as mismatch negativity as readouts.

Several antioxidants have been tested in relatively small clinical trials as add-on to antipsychotics; this includes vitamin C, vitamin E, and N-acetylcysteine (NAC) (see for reviews: Leza et al., in press; Reddy and Reddy, 2011). Vitamins C and E are non-enzymatic antioxidants that scavenge free radicals in the cytosol and at the level of cell membranes, respectively. GSH is required for the recycling of oxidized vitamin C into its active form, while vitamin C is itself needed to reactivate oxidized vitamin E. Therefore, the efficacy of these vitamins may greatly depend on the integrity of the GSH system and the intrinsic redox status. This might explain the limited or the lack of efficacy of these compounds. However, these vitamins have also been given with some success together with 3-omega fatty acids which are key components of membrane phospholipids and have anti-inflammatory properties among others (see reviews: Leza et al., in press; Muller et al., 2013; Sinn et al., 2010). Interestingly, Bentsen et al. (2013) found that vitamins and 3-omega fatty acids, when given separately, can be deleterious in a subgroup of patients. In the present review, we will however focus on NAC because it has antioxidant and anti-inflammatory properties, and can regulate glutamatergic neurotransmission. NAC is already used as antioxidant and GSH precursor to treat GSH deficiency in a wide range of infections, genetic defects, and metabolic disorder (Zafarullah et al., 2003; Atkuri et al., 2007). Therefore, it represents a safe and potential compound for the prevention or treatment of schizophrenia and other psychiatric disorders (Berk et al., 2013). NAC is deacetylated to form cysteine, the rate-limiting precursor of GSH, and therefore yields upregulation of GSH synthesis when cells face an excess of ROS production. NAC also participates in the control of the intracellular redox state by supplying cysteine into the cystine/cysteine redox couple (Mandal et al., 2010). In addition, NAC has anti-inflammatory effects, likely via its antioxidant properties. Finally, NAC upregulates the activity of the astrocytic cystine/glutamate antiporter, leading to cellular entry of cystine (which can be reduced to cysteine and incorporated into GSH) and extracellular release of glutamate (Bridges et al., 2012). This antiporter plays an important role in the regulation of extrasynaptic glutamate levels, which in turn regulate synaptic glutamate release via presynaptic mGluR2/3 (Baker et al., 2002). Thus, NAC could be useful to reduce synaptic glutamate release and to indirectly enhance NMDAR function via its antioxidant and redox regulator properties. Studies on several preclinical models and a few clinical trials on schizophrenia patients have recently provided a proof of concept that NAC could be a useful therapeutic tool.

5.1. NAC in preclinical models

In mice with a weakened GSH synthesis (*Gclm* KO mice), NAC prevents PVI and PNN deficits induced by an oxidative insult during postnatal development (Cabungcal et al., 2013a), although it does not increase GSH levels because of the *Gclm* deletion (das Neves Duarte et al., 2012). Furthermore, in young *Gclm* KO mice, NAC normalizes most of the neurochemical profiles, including the glutamine/glutamate ratio known to be altered in a similar way in first-episode schizophrenia patients (das Neves Duarte et al., 2012). Likewise, NAC reduces oxidative stress, protects prefrontal PVIs, and prevents deficits in mismatch negativity and prepulse inhibition in the neonatal ventral hippocampal lesion rat model (O'Donnell et al., 2011; Sullivan and O'Donnell, 2012). NAC also prevents myelin impairment following a maternal immune challenge (Paintlia et al., 2008), re-establishes normal function of the cystine/glutamate antiporter and GSH levels in MAM-injected rats (Cleland et al. 2013), normalizes extracellular glutamate levels and attenuates behavioral anomalies in phencyclidine-treated rats (Lutgen et al., 2013), reduces oxidative stress and rescues abnormal behavioral phenotype in G72/G30 transgenic mice (Otte et al., 2011), and reverses the social isolation-induced changes in corticostriatal monoamine levels (Moller et al., 2013). Thus, NAC has beneficial effects on very diverse animal models relevant to schizophrenia.

5.2. NAC in clinical trials

Although beneficial effects of a compound in rodent models do not necessarily translate into an efficient therapeutic drug in humans, the few published clinical studies using NAC show some promises. In a first randomized double-blind placebo-controlled trial, an add-on treatment of NAC in chronic patients diminished negative symptoms and improved global functioning (Berk et al., 2008). Two additional studies also demonstrated that chronic patients improved with add-on NAC, particularly in their negative symptoms (Bulut et al., 2009; Farokhnia et al., 2013). In addition, NAC normalized neuronal activity and connectivity and improved mismatch-negativity (Lavoie et al., 2008), an auditory-related, NMDA-dependent evoked potential typically impaired in schizophrenia (Umbricht et al., 2000). NAC also increased phase synchronization of neuronal activity over the left parieto-temporal, the right temporal, and the bilateral prefrontal regions (Carmeli et al., 2012). However, the beneficial effect of NAC has to be taken with caution since the current data is based on only a few studies

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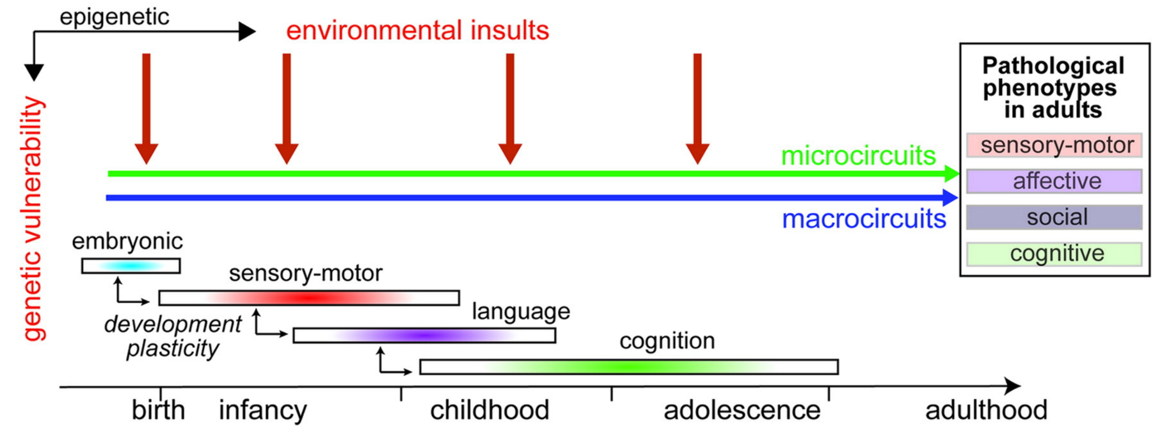

Fig. 2. The timing of environmental insults levied upon an individual (at risk) during his development, may determine which brain region microcircuits and which macrocircuits connecting distant brain areas are structurally and functionally affected. The period(s) of vulnerability of a micro- or macrocircuit may vary according to the genetic risk factors and the nature of the environmental stress and may be influenced by the developmental trajectory of other brain areas. In addition, microcircuits might be particularly susceptible prior to their final maturation during the period of enhanced plasticity. Therefore, the timing of environmental insults during development combined with specific genetic vulnerability could differentially affect circuit connectivity associated with sensory–motor function, social competence, affective behavior, and cognition leading to heterogeneous clinical phenotypes. An early insult could lead to more severe and wide-spectrum clinical phenotypes than a later insult.

showing relatively moderate clinical improvement in chronic schizophrenia patients, possibly due to the low bioavailability and membrane permeability of NAC which enters the brain at a very modest rate (Farr et al., 2003). The development of other molecules with better bioavailability and blood–brain barrier permeability is therefore needed. As vitamins C and E or 3-omega fatty acids are detrimental for a subgroup of patients (Bentsen et al., 2013), it would be also advisable using biomarkers to identify patients that would most benefit from an antioxidant treatment. Moreover, NAC or other molecules that target redox, immune, and glutamatergic systems may be more beneficial for young subjects at risk than for chronic patients because the defects in PVIs and oligodendrocytes/myelination may precede illness onset. Finally, it would be also worth investigating compounds such as sulforaphane (Shirai et al., 2012) that upregulate Nrf2-dependent phase II detoxification enzymes and antioxidant proteins which include the cystine/glutamate antiporter and enzymes of the GSH system (Lavoie et al., 2009).

6. Concluding remarks

Brain development is dependent upon sequences of events: proliferation, differentiation, migration, formation, and maturation of neuronal circuitry. The pace of development varies among brain structures, with the prefrontal cortex being the last to mature. Brain maturation mechanisms are under genetic control and influenced by environmental insults, suggesting that different brain regions could be vulnerable to a dysregulation of the "hub" during specific developmental periods. For instance, under a GSH deficit, the most susceptible periods for oxidative stress differ in the ACC, the ventral and dorsal hippocampi (Steullet et al., 2010; Cabungcal et al., 2013a). Moreover, inflammation induced at different prenatal periods can lead to distinct adult phenotypes (Meyer et al., 2008). Therefore, the timing of environmental insults during development combined with specific genetic vulnerability could differentially affect circuit connectivity and cognition, social competence, and affective behavior, leading to heterogeneous clinical phenotypes (Fig. 2).

The body of knowledge reviewed above suggests that it would be worth to intervene early during brain development on all three elements of the proposed "hub". The genetic vulnerability factors, although important as potential biomarkers for high-risk individuals, may not lend themselves to therapeutic interventions. In contrast, we propose that targeting neuroinflammation, oxidative stress, and NMDAR hypofunction at critical developmental periods and early in the disease may reduce neuropathological anomalies and alleviate the risk of emergence of clinical manifestations.

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Conflict of interest

P. O. is an employee and stockholder of Pfizer, Inc. All other authors declare no conflict of interest.

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