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Targeting Oxidative Stress and Aberrant Critical Period Plasticity in the Developmental Trajectory to Schizophrenia

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Schizophrenia is a neurodevelopmental disorder reflecting a convergence of genetic risk and early life stress. The slow progression to first psychotic episode represents both a window of vulnerability as well as opportunity for therapeutic intervention. Here, we consider recent neurobiological insight into the cellular and molecular components of developmental critical periods and their vulnerability to redox dysregulation. In particular, the consistent loss of parvalbumin-positive interneuron (PVI) function and their surrounding perineuronal nets (PNNs) as well as myelination in patient brains is consistent with a delayed or extended period of circuit instability. This linkage to critical period triggers (PVI) and brakes (PNN, myelin) implicates mistimed trajectories of brain development in mental illness. Strategically introduced antioxidant treatment or later reinforcement of molecular brakes may then offer a novel prophylactic psychiatry.

Key words: oxidative stress/GABA/parvalbumin/perineuronal net/myelin/oligodendrocyte/NAC

Introduction

The protracted progression to psychosis[1] represents both a window of vulnerability and opportunity for therapeutic intervention. In a general sense, many manifestations of the disease are thoughts, feelings or actions that are normal in childhood or early adolescence which become inadequate in adulthood. This supports a view that neural processes which are normally shaped during various critical periods (CPs) in development fail to stabilize. Various basic affective, intellectual, and social cognitions, which should be consolidated during brain development, thus seem to remain open to fluctuations in adult patients.

In healthy development, convergent multisensory inputs are progressively selected in order to filter the salient ones and focus attention. This process is fundamental to establish "common sense" knowledge and "natural self-evidence" notions (eg, "the sky is blue and above the earth" or "young people will become old") which are typically settled and confirmed during development. Their deficits lead to basic symptoms[2] and disorders of the self believed to be central to the phenomenology of schizophrenia (SZ; see reviews by Parnas[3,4]). They affect the core of subjective experience constituting the permanent flow of consciousness.

One important aspect of such anomalies concerns agency and ownership, most likely involving mistimed impulse conduction of corollary discharge in central motor-sensory fibers, due to delays in myelination (as documented below). Indeed, the perception of self is in part the result of differences in response to stimuli evoked from external sources and those generated by the subject—differences which are blurred if corollary discharges are deficient.[5,6] If a CP were to remain open, perceptual incoherence and instabilities in basic knowledge would lead to symptoms such as loss of common sense. At a more complex level, ambivalence extending toward indecision about actions and unresolved contradictory ideas (frequently observed in patients) may further reflect the failure to develop clear polarities between positive or negative affect evoked by interpersonal relationships.

Poorly filtered, multiple sensory inputs can become overwhelming and stress inducing. Impaired convergence of interoceptive and exteroceptive sensory inputs may lead to a loose perception of "self" as observed in patients. At the same time, patients make strikingly original connections between images, words, or ideas typical of poetic creativity seen in young people, who also tend

to make loose associations between unrelated sensory information, leading to unsuspected phantasmal production. As Baudelaire once wrote, "genius is nothing more nor less than childhood recovered at will." We propose that prolonged windows of plasticity manifest by incomplete CP closure may instead contribute to mental illness.

Here, we consider a modern neurobiological understanding of the cellular and molecular determinants of developmental CP as they relate to the pathophysiology of SZ. A pivotal role for parvalbumin-positive interneuron (PVI) maturation in both CP opening and closure (by their surrounding perineuronal net [PNN] and myelination) on the one hand, and their impairment in SZ patients and animal models on the other, suggest various CP aspects could be perturbed in the disease. The issue is complicated in that synaptic plasticity itself is likely disrupted for genetic reasons[7] and that myelin and long-range connectivity fail to develop normally. Redox dysregulation/oxidative stress reflecting complex interaction between genetic and environmental risk factors in the developmental impairment of PVI/PNN and of myelination will be highlighted. A consideration of SZ symptoms from the perspective of impaired developmental trajectory may suggest optimal timing for preventive treatment with redox regulators/antioxidants, thus offering potentially novel strategies for preventive therapies.

Mechanisms of CP Brain Development

Perhaps the best-studied CP model is the enduring loss of responsiveness in primary visual (V1) cortex to a "lazy" or otherwise deprived eye. The behavioral consequence, amblyopia (poor visual acuity), afflicts 2%–5% of the human population and remains without a known cure in adulthood. From the initial discovery by Hubel and Wiesel over 50 years ago, a biological picture has emerged wherein axons serving the two eyes compete with each other upon first converging onto individual neurons in V1. Molecular tools have now begun to unravel the cellular mechanisms which control the onset and closure of such windows for cortical plasticity.[8] Overall, three key concepts have emerged (figure 1):

1. Excitatory-inhibitory (E-I) circuit balance is a trigger. Specific gamma-aminobutyric acid (GABA) circuit maturation underlies the onset timing of plasticity and is shifted across brain regions consistent with the hierarchical, cascading nature of development.[9] Thus, premature gain-of-function by pharmacological agents (benzodiazepines) can trigger precocious onset, whereas genetic (GAD65 deletion) or environmental disruption of GABA circuit function (dark rearing, hearing loss) leads to a delayed plasticity. These manipulations are so powerful that they can determine whether an animal is before, at the peak, or past a plastic window regardless of chronological age. In other words, CP timing per se is plastic.

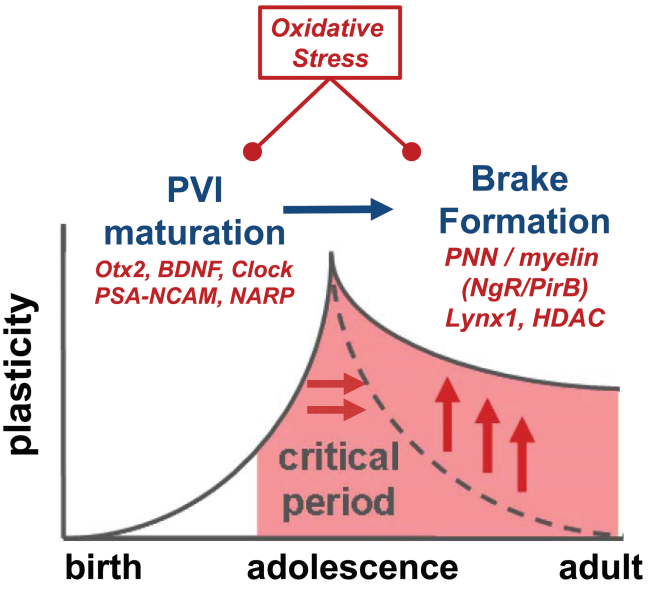

Fig. 1. Prolonged critical period plasticity as endophenotype. Schizophrenia symptoms may reflect delayed plasticity due to a failure of critical period onset/closure. Our hypothesis is that disease etiologies may dysregulate the expression of molecular brakes which normally follow parvalbumin-positive interneuron (PVI) maturation and extend developmental plasticity. Ultimately, this would destabilize circuit function in the face of undesirable information, as seen in mental illness. A common mechanism impacting PVI/perineuronal nets/myelin is redox dysregulation, which represents a novel target for preventive neurodevelopmental intervention. Alternatively, once PVI functional impairment is detected (eg, mismatch negativity [MMN], γ-oscillations), a supplemental reinforcement of molecular brakes on plasticity may be considered.

Among the diversity of inhibitory cell types, it is the PVI large basket cell which serves as the pivotal plasticity switch.[9] PVI mature at different rates across brain regions, contributing to the sequential timing of CP. They are dependent upon a variety of extrinsic factors for their health and maintenance, such as brain-derived neurotrophic factor (BDNF), polysialylated-neural cell adhesion molecule (PSA-NCAM), or Otx2 homeoprotein, which appear just ahead of CP onset.[8] Notably, PVI networks are interconnected via gap junctions[10] and reciprocal GABAergic synapses, capable of synchronizing the excitatory state of large numbers of pyramidal neurons.[11] By way of feedback and feed-forward inhibition, these fast-spiking interneurons exert precise temporal control on information flow, favoring summation and transmission of synchronously arriving, convergent input. As such, they allow the binding of information that reaches different pyramidal neurons during a defined and narrow time window,[12] as reflected in γ-band oscillations (30–80 Hz)[13–17] but can also modulate neuronal activity in the θ-band (4–8 Hz), as well as θ-γ coupling[18,19] (figure 2). The maturation of neural synchrony has been suggestively linked to the development of cortical networks.[20]

2. Synaptic pruning and homeostasis mediate plasticity. Once PVI enter an optimal state, local circuit rewiring

in response to sensory experience is enabled. PVI are the first responders to discordant sensory input, shifting their visual response rapidly.[8] Subsequently, a biochemical sequence of synaptic pruning and homeostasis is triggered in pyramidal cells[8,9]: initially freeing synaptic space through the action of secreted proteases (tissue-type plasminogen activator, tPA) to cleave cell adhesion molecules, synapses, and axons, prior to sprouting new connections through homeostatic growth processes involving tumor necrosis factor alpha (TNFα) and protein synthesis.

3. Molecular "brakes" limit adult plasticity to stabilize neural networks initially sculpted by experience. As PVI mature, they gradually acquire an extracellular coating, called the PNN, which tightly encapsulates the PVI cell body and proximal neurites. In other words, CP closure may reflect an active process on top of the long-held view of declining plasticity factors. A growing number of late-expressing, brake-like factors act to limit excessive circuit rewiring in adulthood. These include structural obstacles which physically prevent neurite pruning and outgrowth, such as PNN or myelin in the extracellular matrix.[8,21] Both chondroitin sulfate proteoglycans in the PNN and inhibitory myelin molecules bind to the Nogo receptor (NgR),[22] which acts in a complex with immune genes such as PirB to restrict CP plasticity.[23,24] In addition, functional brakes (eg, Lynx1)[25] can dampen neuromodulatory systems (eg, acetylcholine, serotonin) which endogenously regulate E-I circuit balance.

Windows of plasticity, therefore, arise between the maturation of an optimal E-I balance controlling the machinery of synaptic pruning and a later emerging consolidating set of brake-like factors, which can be reversed (figure 1). Notably, the same principles are repeatedly being observed across brain regions. Adult spatial learning and object recognition reflect bistable PVI states in hippocampal area CA3[26], focally recapitulating basic CP mechanism throughout life. Adult prefrontal cortex (PFC) encodes acoustic (music) preferences established during a CP early in life and is rendered malleable again later by histone deacetylase (HDAC) inhibitors.[27] Interestingly, lifting this epigenetic brake (with valproate) in mice renews prefrontal neuron recruitment and has been successfully applied to healthy human adults learning absolute pitch discrimination.[28] The basic cellular principles defined in mouse brain may, therefore, translate to humans.

Relevance of CP Mechanism for SZ

PVI/PNN Impairment

Compelling evidence suggests an imbalance between glutamatergic excitation and GABAergic inhibition in SZ.[29,30] Anomalies associated with PVI are a hallmark of the disease, including their reduced density in the hippocampal formation[31,32] and alterations at the level of basket and chandelier cells in the dorsolateral prefrontal cortex (DLPFC) of postmortem brains.[33] Moreover, the extracellular matrix (PNN) that surrounds most PVI is weakened in the DLPFC,[34] entorhinal cortex, and amygdala of SZ patients.[35] Current data suggest an impaired PVI maturation rather than a deficit due to the chronic nature of the illness. Therefore, dysfunction of the PVI network may lead to abnormal neuronal activity in patients, including oscillatory activity within θ, β, and γ ranges.[36–38] Ultimately, interneuron dysfunction could contribute to altered sensory perception,[39] deficits in working memory,[18,40] attention,[41] and learning.[42]

Recent studies have revealed anomalies in hippocampal and/or prefrontal PVI in many preclinical animal models aiming to reproduce genetic vulnerabilities[43–46] or environmental risk factors[47] such as prenatal maternal stress,[48] maternal and perinatal immune challenge,[49,50] hypoxia,[51,52] early-life iron deficiency,[53] maternal separation,[54] and social isolation.[55,56] Similarly, nongenetic developmental models also result in altered prefrontal PVI.[57,58]

Oligodendrocyte/Myelination Impairment

Convergent evidence points to oligodendrocytes and myelination defects in SZ[59–61] both at the neurocytochemical and transcriptomic, as well as neuroimaging levels. Structural alterations of myelinated fibers are reported in gray and white matter of PFC and caudate nucleus of patients.[62] Most studies find a decrease in oligodendrocyte density in thalamic nuclei and PFC.[63–66] In the latter, an age-related increase in number of mature oligodendrocytes normally observed in control subjects is absent in SZ patients.[67] Microarray analysis of patients' prefrontal and anterior cingulate cortices reveal a reduced expression of several genes related to myelin and oligodendrocytes[68–70] and an altered expression of genes coding for cell-cycle maintenance or arrest.[71] Altogether, these findings point to impaired oligodendrocyte maturation and myelination.

Such anomalies in SZ could affect axonal integrity and conduction velocity[72] with a consequence of disrupting temporal control over long-range brain synchronization. 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 in SZ.[73–75] Although less consistent than in chronic patients, white matter anomalies are also observed in first-episode patients and ultra high-risk subjects.[73,75,76] In summary, imaging data indicate that white matter deficits are present before/at illness onset and persist in chronic SZ patients, suggesting a neurodevelopmental component to this impairment.

Vulnerability to Redox Dysregulation/Oxidative Stress

Oxidative stress is defined as an imbalance between prooxidants and antioxidants, resulting in macromolecular

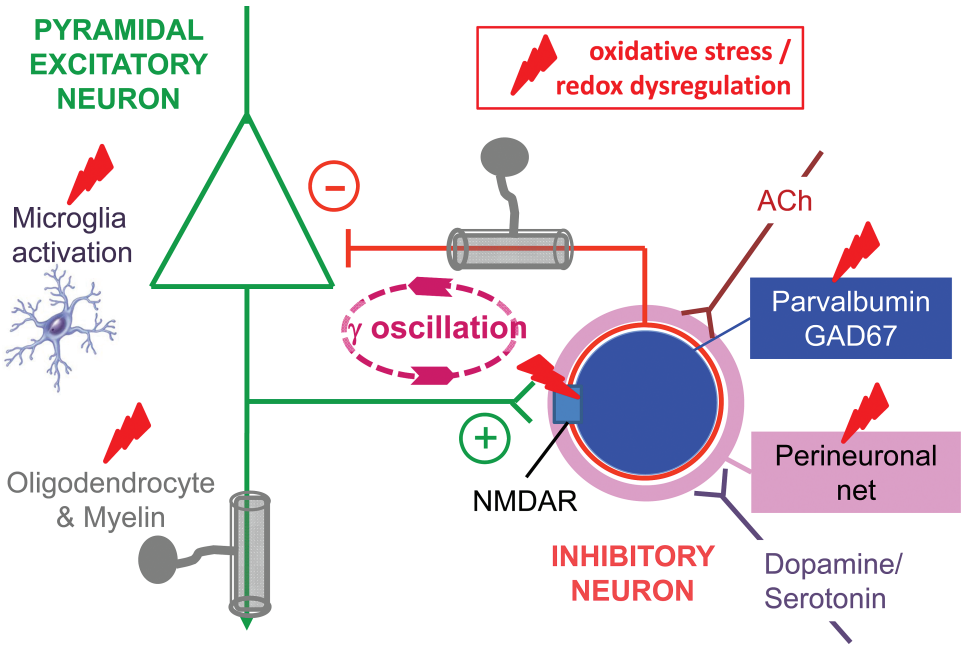

Fig. 2. Impact of oxidative stress/redox dysregulation on microcircuits. Schematic representation of the impact of oxidative stress/redox dysregulation on cortical microcircuits, including excitatory pyramidal and inhibitory parvalbumin-positive interneuron (PVI) connected reciprocally and supporting γ-oscillations. Oxidative stress/redox dysregulation interacts with inflammatory microglial cells, activating them, and with the *N*-methyl-D-aspartate receptors, reducing their activity, in both cases leading to a damaging potentiating effect. As a consequence, PVI surrounded by their perineuronal nets and myelin-forming oligodendrocytes are impaired, as manifested by alterations of local oscillations and distant synchronization. These cellular and molecular changes are known to alter critical periods timing. Likewise, microcircuits are affected by cholinergic and by catecholaminergic inputs.

damage and disruption of redox signaling and control. Recent advances in redox biology show that thiol/disulfide redox systems are regulated under dynamic, nonequilibrium conditions, with distinct redox potentials among subcellular compartments. Apart from traditional "redox signaling" used to describe processes in which a specific oxidative signal is conveyed through a specific redox element to direct a particular cellular response (eg, NF-E2-related factor-2 [Nrf-2] pathway), many general signaling systems including kinases and transmembrane ionopores (eg, N-methyl-D-Aspartate-receptor [NMDA-R]) can be regulated by "redox-sensing" thiols of critical proteins in the pathway.[77]

Both redox sensing and redox signaling use thiol switches, especially cysteine (Cys) residues in proteins which are sensitive to covalent or noncovalent modification (ie, reversible oxidation, nitrosylation, glutathionylation), leading to structural and functional alteration of target proteins. This has led to the emerging concept of "orthogonal control of signal transduction systems by redox-sensing mechanisms."[78] Moreover, because redox potentials are controlled differently in subcellular compartments, the same signaling mechanism can be differentially controlled by the prevailing local redox environment. This thiol-based redox regulation has crucial importance in nervous tissues known to present complex compartmentalization.

PVI/PNN Vulnerability

To support high-frequency neuronal synchronization, fast-spiking PVI are energy demanding. This requires optimal mitochondrial performance[79] with enhanced metabolic activity and oxidative phosphorylation[80] leading to elevated mitochondria-generated reactive oxygen species (ROS).[81] Consequently, PVI need well-regulated antioxidant systems to neutralize ROS and maintain proper redox state. These cells are vulnerable to redox dysregulation, whether induced by a compromised antioxidant system or ROS overproduction (figure 2).

In a transgenic mouse model (*Gclm* KO) carrying low levels of the main nonprotein cellular redox regulator and antioxidant, glutathione (GSH), similar to some SZ patients,[82–84] a deficit in prefrontal and hippocampal PVI is observed, impairing high-frequency neuronal synchronization.[85–87] Compromised GSH synthesis restricted only to PVI is sufficient to affect these cells[86] and oxidative stress precedes the PVI deficit.[87] Under these conditions of PVI-specific redox dysregulation, CP plasticity (as measured in V1) is notably prolonged concomitant with their loss of PNN.[88]

PVI can also be affected when antioxidant systems other than GSH are compromised. A reduced number of PVI is observed in mice bearing a deletion of selenoprotein P, a glycoprotein with antioxidant properties[89] or for PGC-1α, a transcription factor regulating mitochondria function and ROS metabolism.[90] Furthermore, superoxide

overproduction by nicotinamide adenine dinucleotide phosphate reduced form (NADPH) oxidase (NOX) is also deleterious to PVI,[91] and NOX inhibition prevents the PVI impairment induced by social isolation.[56]

Most importantly, prefrontal cortical PVI are more vulnerable to a redox dysregulation during postnatal development than later in life. A pharmacologically induced transient postnatal deficit in GSH yields both immediate and long-term decreased PVI density in anterior cingulate cortex (ACC).[92–94] In *Gclm*-KO mice,[95] administration of a dopamine reuptake inhibitor (GBR-12909), which partially mimics dopamine release during psychosocial stress[96] and produces ROS via the catabolism of dopamine,[97,98] permanently decreases PVI density in the ACC when applied during postnatal development, but not in adulthood.[85] Thus, immature PVI may have a less robust antioxidant defense system than mature cells.

Alternatively, molecular mechanisms underlying PVI maturation may be highly sensitive to a redox imbalance. Interestingly, the vulnerability of prefrontal immature PVI is associated with the absence of fully mature PNN, which protects these cells against oxidative stress.[86] In turn, excess oxidative stress also affects PNN,[86] which reciprocally impact PVI. Indeed, the maturation and phenotypic maintenance of PVI requires translocation of a noncell autonomous homeobox protein, Otx2, through its affinity with PNN.[99,100]

One interesting example of relevance to SZ is the role of *Clock* genes in the neocortex. Circadian rhythms have been shown to regulate redox homeostasis in the brain, and disruption of circadian genes causes neuronal oxidative damage.[101] Aberrant circadian rhythmicity has long been linked to mental illness, and very recent work identifies a postnatal emergence of rhythmic gene expression outside the suprachiasmatic nucleus.[102] Maturation of PVI is particularly sensitive to *Clock*/*Bmal* gene deletion with the consequence of protracted CP timing into adulthood. Cell-specific transcriptome profiling of PVI by FACS reveals altered expression of genes downstream of CLOCK related to the respiratory chain (eg, *Cox* and *Nduf* family genes) and redox regulation (eg, *Gpx4*). Thus, circadian clock genes may preserve PVI integrity and prevent the manic behaviors observed when they are disrupted.

A role for redox dysregulation/oxidative stress in the developmental impairment of PVI 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 defects, both of which are prevented by juvenile and adolescent treatment with the antioxidant and GSH precursor, *N*-acetylcysteine (NAC).[103] Second, a single injection of the DNA-alkylating agent methylazoxymethanol acetate (MAM) during pregnancy, which also causes SZ phenotypes in adult rats, leads to anomalies in PVI and neuronal synchronization.[57,104] MAM-treated rats show decreased brain GSH levels[105] and increased oxidative stress (A. A. Grace and K. Q. Do, unpublished results, 2014).

In the MAM model, a reduction in ventral hippocampal PV expression is sufficient to induce an augmented dopaminergic system function and behavioral hyperresponsivity to amphetamine.[106] Moreover, evidence in patients[33] and in MAM rats suggest that in the PFC there is a general decrease in PV levels rather than PVI loss, whereas in hippocampus it appears that neuronal loss occurs.[107] Third, genetic models (eg, DISC1, PRODH, G71) all exhibit elevated oxidative stress consistent with their PVI abnormalities. In addition, preliminary results in collaboration with the Coyle and La Mantia labs, respectively, reveal oxidative stress-induced PVI/PNN loss in D-serine racemase KO and 22q11 mouse models (K. Q. Do, 44th US Soc for Neuroscience, 2014). Together, these studies demonstrate that redox dysregulation during a critical developmental period can disrupt normal PVI maturation representing one core pathophysiological mechanism in SZ.

Oligodendrocyte Sensitivity to Redox State

Oligodendrocytes are sensitive to redox dysregulation and oxidative stress due to their intrinsic properties and functions. During the myelination process, they have a high metabolic rate to produce and maintain membranes.[108–110] High metabolic activity is known to generate copious amounts of ROS,[111] whereas oligodendrocytes display surprisingly low GPx activity and intrinsically low GSH levels.[112,113]

In SZ patients, a direct role for redox control of myelin is seen in the positive correlation between prefrontal GSH levels and functional anisotropy along the cingulum bundle, which connects the ACC to limbic structures.[114] The importance of redox control for white matter integrity and oligodendrocyte development is further supported by animal models and in vitro research. Redox state controls oligodendrocyte maturation as well as the switch between proliferation (reduced state) and differentiation (oxidized state).[114,115]

Abnormal redox control would interfere with oligodendrocyte development. Consistent with this, *Gclm*-KO mice bearing a 70% GSH deficit within brain and increased oxidative stress marks in the PFC and ventral hippocampus[85,87] have lower levels of mature oligodendrocytes and myelin in the peripubertal period[114] (figure 2). Although myelination reaches similar levels in adult *Gclm*-KO and wild-type mice, DTI reveals persistent impairment of white matter integrity and reduced conduction velocity in the fornix and anterior commissure.[116]

At the cellular level, GSH deficiency in oligodendrocyte progenitors leads to cell-cycle arrest and reduces proliferation which can be reversed by the antioxidant NAC.[114,115]

At a molecular level, the switch from proliferation to early differentiation is controlled by the platelet-derived growth factor receptor (PDGFR-Fyn) pathway.[114,117] Nonreceptor tyrosine kinase, Fyn, is activated by redox dysregulation,[117] and interestingly, is impaired in early psychosis patients associated with a vulnerability to redox dysregulation.[114] Postmortem studies in the PFC of SZ patients also reveal abnormal Fyn expression (Stanley database).[118] Oxidative stress/abnormal redox control during development could therefore contribute to myelin disruptions associated with SZ.

Anomalies of Plasticity in SZ

Pathophysiological changes in SZ are thus consistent with a removal of "brakes" on plasticity, such as the PNN loss, altered E-I balance, or myelin deficits. All these factors are induced by redox dysregulation/oxidative stress among others, which may then yield prolonged network instability.[88] Thus, mistimed developmental trajectories of brain plasticity may underlie in part the pathogenesis of SZ. Although limited to date, there is emergent evidence recently reporting dysfunctional plasticity in SZ.[119–122] Deficits in long-term potentiation-like plasticity in SZ patients probed by transcranial direct current stimulation are notably restricted to chronic patients, whereas first onset patients do not differ significantly from healthy controls with a trend toward increased plasticity.[123] Excessive plastic states likely precede the progressive degenerative process as in other animal models and brain disorders.[25,124]

Outlook for Preventive Developmental Therapies

Early detection and early intervention in psychotic disorders has become a major focus both in clinical and translational research in psychiatry. The considerations discussed above strongly support this strategy. They highlight mechanisms and drug targets which might modify disease progression or even contribute to prevention, and pave the way for biomarkers needed for early detection and use as efficacy endpoints (apart from clinical symptoms) in clinical trials.

Two noninvasive biomarkers might be worth exploring: (1) anomalies of γ-oscillations as a robust marker of the PVI microcircuit and (2) anomalies of fiber tract connectivity as measured by DTI. As discussed above, oxidative stress or redox dysregulation contribute crucially to PVI and myelin impairment in SZ. Moreover, as reviewed in Steullet et al,[125] dysregulation of redox homeostasis is fully reciprocal to neuroinflammation and NMDA-R hypofunction (figure 2). This triad constitutes one central pathophysiological "hub" upon which various genetic and environmental risk factors converge during neurodevelopment, leading to structural and functional connectivity impairments. Drugs targeting the triadic hub of oxidative stress, neuroinflammation, or NMDA-R hypofunction[125] would be promising candidates to prevent deleterious effects on cortical and hippocampal PVI and oligodendrocytes/myelin. As such treatments (eg, omega-3, sulforaphane, NAC) should be applied in early phases of the illness, they should be devoid of serious side-effects. Adolescent treatment with atypical antipsychotics (risperidone, clozapine) in the prenatal immune activation model can also prevent hippocampal volume loss and lateral ventricle enlargement as well as behavioral abnormalities.[126] However, whether this is mediated through PVI/myelin and CP plasticity is unknown and their serious side effects would temper their use from a preventive perspective.

Converging evidence also points to membrane phospholipid and polyunsaturated fatty acid (PUFA) defects in early course and chronic SZ.[127] As membrane PUFAs are highly susceptible to free radical insults, increased oxidative stress may be one of the mechanisms responsible for membrane PUFA reduction. Indeed, oxidative stress in first-episode SZ is associated with decreased PUFA content and increased breakdown products of membrane lipids,[128] possibly with a familial basis.[129,130] In particular, decreased membrane PUFA levels are associated with increased levels of total lipid peroxides, decreased levels of vitamin E, and increased severity of negative symptoms.[131,132] The use of PUFA, particularly omega-3, is a potential alternative and adjunct to current antipsychotics treatments. Omega-3 fatty acids are effective in reducing oxidative stress in preclinical models[133,134] and dietary supplementation may be beneficial in psychiatric conditions.[135] Omega-3 might be most promising in preventing the transition to psychosis for at-risk mental state subjects.[136]

Sulforaphane is a dietary isothiocyanate found in broccoli sprouts and has gained attention as a natural, and safe, anticancer compound.[137–140] Evidence suggests that sulforaphane is able to reduce oxidative stress by activating the Nrf-2 antioxidant response element pathway, upregulating phase II detoxification enzymes and antioxidant proteins.[141] Sulforaphane was shown to protect against antipsychotic-induced oxidative stress in dopaminergic neuroblastoma cells by increasing GSH and quinone oxidoreductase (NQO1) activity.[142] In mice injected with phencyclidine, sulforaphane attenuated prepulse inhibition (PPI) deficits in a dose-dependent manner, as well as reducing hyperlocomotion at higher doses.[143]

NAC, known as a GSH precursor, also has antioxidant and anti-inflammatory properties per se and can regulate glutamatergic neurotransmission. It represents a safe and potential compound for the prevention or treatment of SZ and other psychiatric disorders.[144] 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 to the control of the intracellular redox

state by supplying cysteine into the cystine/cysteine redox couple.[145]

In *Gclm*-KO mice, NAC prevents PVI and PNN deficits induced by an oxidative insult during postnatal development[85] and normalizes most of the neurochemical profiles, including the glutamine/glutamate ratio known to be altered in a similar way in first-episode SZ patients.[146] Likewise, NAC reduces oxidative stress, protects prefrontal PVI, and prevents deficits in MMN and PPI in the developing rat neonatal ventral hippocampal lesion model which is independent of redox manipulation and shows E-I imbalance.[103]

NAC also prevents myelin impairment following a maternal immune challenge,[147] reestablishes normal function of the cystine/glutamate antiporter and GSH levels in MAM-injected rats,[148] normalizes extracellular glutamate levels, and attenuates behavioral anomalies in phencyclidine-treated rats.[149] It reduces oxidative stress, rescues abnormal behavioral phenotype in G72/G30 transgenic mice,[150] and reverses the social isolation-induced changes in corticostriatal monoamine levels.[151] Thus, NAC has beneficial effects across a very diverse panel of animal models relevant to SZ.

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.[152] Two additional studies also demonstrate that chronic patients improved with supplemental NAC, particularly in their negative symptoms.[153,154] Moreover, NAC normalized neuronal activity and connectivity and improved MMN,[155] an auditory-related, NMDA-dependent evoked potential typically impaired in SZ.[156] Although not performed during development, these studies can be considered as a proof-of-concept, pointing to the efficacy of an antioxidant and possibly favoring the closure of a pathological CP.

NAC also increased phase synchronization of neuronal activity over the left parieto-temporal, the right temporal, and the bilateral prefrontal regions.[157] However, the beneficial effect of NAC has to be taken with caution because the current data are based on only a few studies showing relatively moderate clinical improvement in chronic SZ patients, probably due to the low bioavailability and membrane permeability of NAC which enters the brain at a very modest rate.[158] The development of other molecules with better bioavailability and blood-brain barrier permeability is therefore needed.

Interestingly, Du and Grace[159] have reported that peripubertal administration of diazepam prevents the increase in dopamine neuron activity and blunts the behavioural hyper-responsivity to amphetamine in the developmental MAM rats. This effect of diazepam may be mediated by normalizing PVI/CP plasticity because CP delay in the GAD65 deletion model can be rescued by enhancing GABA transmission directly with diazepam.[160]

Because the disruption of PVI maturation and myelination would combine to delay or prolong CP plasticity (figure 1), it may also be useful to strategically introduce well-timed brakes on plasticity or to lift them as needed (as in amblyopia recovery[21]). Several candidate factors have recently been identified,[8] including PNN-promoting transcription factors (Otx2),[94] modulators of cholinergic transmission (Lynx1),[25] or epigenetic regulators (HDAC).[161] An intriguing target may be the NgR/PirB signalling complex which interacts with both chondroitin sulfate proteoglycans in the PNN as well as myelin molecules.[22,23] Notably, the plasticity modulating effect of NgR deletion has recently been traced to PVI circuits specifically.[162] Further methods to modulate PVI maturational state, ideally from the blood periphery are desirable as therapeutic agents. The peculiar localization of noncell autonomous factors, such as Otx2 synthesis within the accessible choroid plexus,[163] is particularly appealing.

Conclusions

Commonly observed abnormalities in the PVI and myelin of SZ patients or associated animal models would predict altered levels of brain plasticity, such as greater perceptual learning in SZ patients.[164] Proper timing of redox regulation is crucial to control the proliferation and differentiation of PVI and oligodendrocytes, which in turn contribute to CP timing. Therapeutic approaches aimed at thwarting the emerging redox imbalance may efficiently prevent the impairment of these CP triggers and brakes underlying developmental trajectories of cognitive function. Such approaches, including antioxidants/redox modulators, cognitive interventions in childhood and adolescence, or enhancement of molecular brakes thereafter might become viable strategies toward prophylactic psychiatry.[165]

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