REVIEW

Oxidative stress, prefrontal cortex hypomyelination and cognitive symptoms in schizophrenia

DA Maas1,2, A Vallès1,3 and GJM Martens1

Schizophrenia (SZ) is a neurodevelopmental disorder with a broad symptomatology, including cognitive symptoms that are thought to arise from the prefrontal cortex (PFC). The neurobiological aetiology of these symptoms remains elusive, yet both impaired redox control and PFC dysconnectivity have been recently implicated. PFC dysconnectivity has been linked to white matter, oligodendrocyte (OL) and myelin abnormalities in SZ patients. Myelin is produced by mature OLs, and OL precursor cells (OPCs) are exceptionally susceptible to oxidative stress. Here we propose a hypothesis for the aetiology of cognitive symptomatology in SZ: the redox-induced prefrontal OPC-dysfunctioning hypothesis. We pose that the combination of genetic and environmental factors causes oxidative stress marked by a build-up of reactive oxygen species that, during late adolescence, impair OPC signal transduction processes that are necessary for OPC proliferation and differentiation, and involve AMP-activated protein kinase, Akt-mTOR-P70S6K and peroxisome proliferator receptor alpha signalling. OPC dysfunction coincides with the relatively late onset of PFC myelination, causing hypomyelination and disruption of connectivity in this brain area. The resulting cognitive deficits arise in parallel with SZ onset. Hence, our hypothesis provides a novel neurobiological framework for the aetiology of SZ cognitive symptoms. Future research addressing our hypothesis could have important implications for the development of new (combined) antioxidant- and promyelination-based strategies to treat the cognitive symptoms in SZ.

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INTRODUCTION

Schizophrenia (SZ) is a neurodevelopmental disorder with positive, negative and cognitive symptoms. Current treatments only target positive symptoms, therefore identifying new treatment strategies that aim at negative and cognitive symptoms is of crucial importance. To achieve this, the elucidation of the neurobiological correlates underlying these symptoms is a necessary first step. Cognitive symptoms of SZ, the focus of this review, include poor executive functioning and are thought to arise from the prefrontal cortex (PFC).1,2 Both redox imbalance and PFC dysconnectivity have been implicated in the aetiology of these symptoms.

SZ IS ASSOCIATED WITH REDOX IMBALANCE

Redox imbalance is a state of high oxidative stress caused by an imbalance between the production of reactive oxygen species (ROS) and antioxidants that reduce ROS. A continuous balance between ROS production and reduction is crucial to maintain ROS-dependent cellular processes as well as to prevent ROS-induced cell damage.

Environmental insults that are associated with SZ cause oxidative stress

One of the most important risk factors for the development of SZ is the activation of the maternal immune system.3,4 The mechanism by which maternal immune activation affects brain development likely involves oxidative stress.5 For example, lipopolysaccharide (LPS) exposure during pregnancy induces the release of pro-inflammatory cytokines that induce ROS generation and peroxisomal dysfunction, whereas antioxidants such as N-acetyl cysteine can reverse the negative effects of LPS exposure on brain development.6 Other environmental factors associated with redox imbalance and SZ are prenatal malnutrition and maternal stress during pregnancy.7–12 For example, low protein intake during pregnancy has been shown to induce mitochondrial dysfunction and a decrease in endogenous antioxidants, resulting in higher ROS production.13 In addition, obstetric events, such as hypoxia, and environmental insults later in life, such as social stress, are associated with oxidative stress and represent risk factors for SZ.14–20

Redox imbalance in SZ patients

Genetic studies have shown associations between oxidative stress gene polymorphisms and SZ,21,22 including genetic variations in glutathione cysteine ligase (GCL) and several glutathione-S-transferases,23–25 both involved in the synthesis of the endogenous antioxidant glutathione. Fibroblasts of patients carrying genetic variations in GCL display lower glutathione and GCL protein expression, and thus redox imbalance.25 Unlike genetic association studies, the available genome-wide association studies (GWASs) have not provided convincing evidence for oxidative stress-related genetic predisposition in SZ, and therefore additional GWASs with larger sample sizes may be necessary.
In addition, both downregulation of components of the antioxidant synthesis pathway and increases in ROS levels have been observed in SZ patients. For instance, total antioxidant and glutathione plasma levels are lower in non-medicated, medicated, first-episode as well as chronic SZ patients, in line with the reduced glutathione levels found in the PFC and cerebral spinal fluid of SZ patients and in post mortem SZ brains, in which abnormal redox-related protein expression has also been found. Furthermore, peripheral levels of ROS are increased, and those of glutathione peroxidase and superoxide dismutase are decreased in SZ patients, independent of drug use or disease stage. Hence, both lower levels of antioxidants and higher levels of ROS are core features of the disorder and are not influenced by disease progression or medication use, indicating that redox imbalance is a primary characteristic of the disorder. Interestingly, in SZ patients, deficits in executive functioning are correlated with higher ROS levels and lower antioxidant-related protein levels, directly linking redox imbalance to cognitive dysfunction.

Redox imbalance in SZ rodent models

The N-methyl-D-aspartate-antagonist MK-801-induced rat model for SZ shows increased oxidative stress specifically in the PFC, although higher levels of brain mitochondrial ROS have been found in a ketamine-induced rat model. Inversely, glutathione depletion in rats leads to SZ-like phenotypes. In addition, knockout mice that lack a crucial subunit of the GCL enzyme show significant reduction of glutathione levels in the anterior cortex, especially during the prepuperal period, which is followed by SZ-like behaviour in the time frame of disease onset and SZ-like neural changes in the hippocampus (HIP) of the adult knockout mice, including an increase in oxidative stress and a decrease in the number of parvalbumin (PV) interneurons. Therefore, redox imbalance may represent the main trigger for brain alterations before disease onset, which negatively influence cognition later on.

PREFRONTAL DYSCONNECTIVITY IS ASSOCIATED WITH COGNITIVE SYMPTOMS OF SZ

Diffusion magnetic resonance imaging reveals alterations in white matter (WM) integrity, that is, lower fractional anisotropy (FA; for a review, see Wheeler and Vojnoskos), in both medicated and non-medicated SZ subjects. Importantly, even before SZ disease onset, a reduced WM integrity occurs in frontal areas and advances in further stages of the disorder to more caudal and posterior regions.

WM abnormalities in SZ are associated with cognitive symptomatology

Correlations between cognition and frontal WM integrity have been reported in healthy individuals. In chronic SZ, abnormalities in cognitive processing speed are associated with WM disruptions in, among others, frontal areas, and in first-episode SZ patients a lower frontal WM integrity is correlated with more severe cognitive symptoms. Interestingly, deficit SZ (that is, SZ with strong cognitive impairment) is associated with severe WM abnormalities. Furthermore, cognitive symptomatology of SZ patients worsens as the disease progresses, in line with the ongoing WM alterations.

Origin of lower FA in SZ PFC

A low FA value in diffusion magnetic resonance imaging is indicative of alterations in WM that can be attributed to several cellular factors, including reduced myelination and aberrant axonal properties. Diffusion tensor as well as kurtosis imaging reveal a lower FA and increased radial diffusivity in combination with no changes in axial diffusivity in the frontal lobe of SZ patients. This indicates that myelin rather than axonal abnormalities form the neurobiological basis of the diffusion magnetic resonance imaging aberrations in SZ. Other diffusion studies show similar results. Direct evidence for axonal degeneration in SZ is indeed lacking. Furthermore, magnetisation transfer ratio, a more specific imaging measure for myelin, shows lower myelin levels in, among others, the PFC of SZ patients compared with controls. These low myelin levels predict impaired processing speed in SZ and link decreased myelination to cognitive symptoms of the disorder.

SZ IS ASSOCIATED WITH OLIGODENDROCYTE ABNORMALITIES AND DECREASED MYELINATION

Myelin is produced by oligodendrocytes (OLs) that are derived from OL precursor cells (OPCs) in the developing as well as the adult brain. Plasticity in the formation and retraction of myelin sheaths by OLs also occurs from early childhood to adulthood. Neuronal activity can instruct OPCs to divide and mature, and can stimulate myelin sheath production by OLs, leading to increased myelination and improved behavioural performance. Conversely, reduced neuronal stimulation by social isolation impairs myelination, which correlates with behavioural and cognitive dysfunction. Altered myelination dynamics may have a major role in cognition as well as in psychiatric disorders like SZ.

Evidence from human post mortem studies

In the PFC of SZ patients, lower OL size and regional-specific differences in OL density alongside higher levels of OL apoptosis and necrosis have been observed, accompanied by lower levels of myelin. Evidence from rodent models that range from pharmacological and transgenic to neurodevelopmental models. For example, administration of the NMDA receptor antagonist MK-801 in adulthood is used as a model for SZ (for a review see Neill et al.) and alters brain expression of, among others, platelet-derived growth factor (PDGF), proteolipid protein, myelin basic protein and 2′,3′-Cyclic-nucleotide 3′-phosphodiesterase, and decreases WM volume, together with myelin sheath degeneration. Furthermore, mice transgenic for SZ-associated locus G72/G30 show SZ-like behavioural traits and myelin-related protein expression changes. In addition, severe hypomyelination has been observed in mice mutant for the myelination-associated gene quaking (a gene downregulated in SZ) alongside structural abnormalities of myelin sheath thickness and composition. Moreover, rodent models for demyelination display SZ-like behavioural abnormalities, for example, cuprizone demyelination leads to reduced expression of several OL-related transcripts and diminished ability to perform a SZ-relevant cognitive flexibility task.

Genetic evidence

OL-related gene variants correlate with reduced WM integrity and cognitive performance. Nevertheless, candidate gene association studies and a large meta-analysis of genetic risk for SZ have shown that myelin- and OL-related genes are not
Reduced myelin basic protein expression and OL number in the rat 20-fold higher free-iron levels than astrocytes, 106,107 probably times as much), three times lower glutathione concentration and OPcs and OLs contain exceptionally high amounts of ROS (six
DEFICIT
REDOX IMBALANCE CAN CAUSE AN OPC MATURATION
SECONDARY PHENOTYPE WITH AN INDIRECT, NON-GENETIC CAUSE.

cases the myelin pathology observed in SZ likely reflects a secondary phenotype with an indirect, non-genetic cause.

REDOX IMBALANCE CAN CAUSE AN OPC MATURATION
DEFICIT
OPCs and OLs contain exceptionally high amounts of ROS (six times as much), three times lower glutathione concentration and 20-fold higher free-iron levels than astrocytes,106,107 probably because their myelin synthesis entails a high metabolic rate.108 This means that OPcs and OLs are constantly under a high degree of oxidative stress to which the cells are already more susceptible. In fact, redox changes of only 15–20% can already influence signal transduction pathways such as PDGFα stimulation of OPC proliferation and maturation.109 The susceptibility of OPcs and OLs to oxidative stress has serious implications for the process of myelination. For instance, oxidative stress leads to downregulation of myelin-related gene expression in human OLs in vitro,110 and reduced myelin basic protein expression and OL number in the rat brain.111–113 Hence, the myelination abnormalities observed in SZ may well be due to oxidative stress-related OPC dysfunctioning.

HYPOTHESIS OF REDOX-INDUCED PREFRONTAL OPC
DYSFUNCTIONING
On the basis of the above, we here propose the redox-induced prefrontal OPC-dysfunctioning hypothesis. Environmental and genetic factors lead to a faulty antioxidant system, as well as redox imbalance resulting in OPC/OL proliferation and maturation arrest during adolescence, causing hypomyelination of the PFC, insufficient PFC functioning and subsequently the cognitive symptoms observed in SZ. OL; oligodendrocyte; OPC, OL precursor cell; PFC, prefrontal cortex; SZ, schizophrenia.

significantly associated with the disorder.101–105 Therefore, in most cases the myelin pathology observed in SZ likely reflects a secondary phenotype with an indirect, non-genetic cause.

ROS CAN CAUSE OPC DYSFUNCTIONING
Baseline levels of oxidative stress in OPcs are high. In SZ, oxidative stress levels in OPcs are even higher because of extra ROS production by environmental factors as well as intracellular abnormalities that lead to extra ROS production and less ROS clearance (see above). The cause of OPC dysfunction in SZ may be explained by two different, but related, cellular pathways described below. In both pathways, ROS inactivates protein synthesis that is necessary for OPC proliferation and differentiation via the mammalian target of rapamycin (mTOR)-P70S6K pathway. The inactivation of the latter pathway leads to OPC proliferation arrest, apoptosis and hypomyelination.114

ROS CAN CAUSE OPC DYSFUNCTIONING
The relatively active metabolism in OPC mitochondria leads to the production of ROS as a by-product of the respiratory chain (Figure 2). The elevated ROS levels cannot be effectively reduced by glutathione because in OPcs glutathione levels are low. Excess ROS leads to an overstimulation of AMP-activated protein kinase (AMPK), which activates the tuberous sclerosis 1/2 complex. This complex prevents the activation of the mTOR-P70S6K pathway through inhibition of ras homologue enriched in brain (RHEB).115 Moreover, RHEB mediation of mTOR activity is necessary for OPC differentiation into myelinating OLs.116 In addition, AMPK stimulation causes enhanced biosynthesis of mitochondria via peroxisome proliferator-activated receptor gamma coactivator-1 alpha as well as the upregulation of glutathione and other antioxidants. However, these antioxidant levels are not sufficient to rescue the redox imbalance in SZ OPcs.117 Proliferator-activated receptor gamma coactivator-1 alpha transactivation of peroxisome proliferator receptor alpha inhibits transcriptional nuclear factor kappa-light-chain-enhancer of activated B cells,118 preventing efficient transcriptional activation of its target genes, thus contributing to OPC dysfunctioning.119–120 In addition, environmental factors implicated in SZ (for example, prenatal stress and malnutrition) may cause the production of cytokines such as tumour necrosis factor alpha.121,122 This cytokine can activate AMPK, but also directly leads to both the mitochondrial uptake of calcium that might trigger apoptosis and to the additional activation of complex I of the respiratory chain, followed by an increase in ROS production.115

The other cellular pathway that can give rise to reduced activity of the mTOR-P70S6K pathway includes signalling via PDGFαR. As stated above, activation of this receptor is necessary for proliferation and maturation of OPcs. The increased levels of ROS in SZ OPcs cause stimulation of Fyn kinase, which in turn activates C-Casitas B-lineage Lymphoma.109,123 This overactivation of C-Casitas B-lineage Lymphoma has been shown to decrease PDGFα receptor numbers on the OPC cell membrane, reduce mTOR-P70S6K pathway activation and lower protein synthesis rate for proliferation and differentiation, disrupting OPC cell

Figure 1. Flowchart of the redox-induced prefrontal OPC-dysfunctioning hypothesis. Environmental and genetic factors lead to a faulty antioxidant system, as well as redox imbalance resulting in OPC/OL proliferation and maturation arrest during adolescence, causing hypomyelination of the PFC, insufficient PFC functioning and subsequently the cognitive symptoms observed in SZ, OL, oligodendrocyte; OPC, OL precursor cell; PFC, prefrontal cortex; SZ, schizophrenia.
Interestingly, glutathione depletion, both in vivo and in vitro, inhibits Fyn-dependent maturation of OPCs, accompanied by reduced myelination.\(^{126}\)

Proof of concept for the hypothesis that hypoactivation of the mTOR-P70S6K pathway leads to inhibition of OPC proliferation and maturation, and subsequently hypomyelination is provided by the fact that conditional mTOR knockout in mouse OPCs leads to various myelination defects.\(^{127}\) Furthermore, a number of studies have demonstrated that ERK1/2 signalling (which inhibits the tuberous sclerosis 1/2 complex and, therefore, increases mTOR-P70S6K signalling) can enhance myelination. For example, ERK1/2 signalling is implicated in the mechanism of action of diosgenin, a drug that enhances OPC differentiation and myelination,\(^{128}\) and of miconazole, which promotes remyelination in vitro and in animal models of multiple sclerosis (MS).\(^{129}\)

In sum, a correct regulation of the AMPK, mTOR-P70S6K and ERK1/2 pathways is essential for OPC functioning and myelination. In SZ, these pathways are affected by increased oxidative stress, leading to OPC dysfunctioning and subsequently hypomyelination.

**REDOX IMBALANCE, ABERRANT MYELINATION AND COGNITIVE FUNCTIONING ARE DIRECTLY RELATED**

Evidence from SZ patients and rodent models Low glutathione levels are correlated with reduced WM integrity in the medial PFC of SZ patients and in PFC myelin of GCL knockout mice and mature OL numbers are decreased.\(^{126}\)

Environmental risk factors for SZ that are related to oxidative stress are also linked to myelination abnormalities. For example, prenatal stress leads to myelination and WM abnormalities,\(^{130,131}\) and prenatal infection causes effects on myelination and WM.\(^{132,133}\) The effects of prenatal infection on oxidative stress in adulthood are largely unknown, whereas in young animals the glutathione metabolism is affected.\(^{134,135}\) Although a link between prenatal infection and both myelination deficits and redox imbalance has thus been observed, it is not clear whether the infection-induced effects on myelination are directly mediated by the redox imbalance. An interesting recent investigation studying the relationship between redox imbalance, reduced myelination and cognition has shown that in vitro hypoxia leads to oxidative stress that causes OPC maturation defects, which can be rescued by free-radical scavengers.\(^{136}\) Likewise, under in vivo hypoxic circumstances ROS levels are higher, OPC maturation does not take place, myelination is decreased, mice show cognitive impairments and when free-radical scavengers are provided the cellular as well as behavioural abnormalities are rescued.\(^{136}\) Hence, redox imbalance causes hypomyelination and cognitive decline.

Redox-related demyelination leads to cognitive defects in MS The connection between oxidative stress and myelination defects, as observed in SZ, has also been found in MS, a disease associated...
with major demyelination. For example, in active demyelinating lesions of post mortem MS brains high levels of oxidised lipids and DNA are present, and apoptotic OLs contain oxidised DNA.\(^{137,138}\) It is thought that in MS the elevated oxidative stress is caused by inflammation and leads to the progressive demyelination that characterises this neurodegenerative disease.\(^{139}\) The fact that MS patients show cognitive symptoms similar to those observed in SZ (for reviews, see Korakas \(^{140}\) and Cardoso et al.\(^{141}\)) together with the observation that MS is associated with oxidative stress, decreased myelination and cognitive decline strengthens our hypothesis that an interaction between these factors exists in SZ.

IS HYPOMYELINATION DURING SZ DISEASE ONSET PFC-SPECIFIC?
Frontal WM development coincides with the prodromal SZ phase/onset of psychosis

WM maturation commences in central and extends to more lateral brain regions over time,\(^{142,143}\) and WM volume peaks during early adolescence.\(^{144}\) From this period onwards, the PFC white/grey matter ratio rises with increasing age.\(^{145}\) In frontal areas, WM and connectivity maturation occurs during late adolescence. In addition, the superior longitudinal fasciculus shows increasing connectivity during adolescence\(^{146}\) and corticosomal WM tracts reach peaks of maturation between the ages of 23 and 39.\(^{147}\) These findings indicate that WM maturation in frontal areas is ongoing during SZ disease onset.

High-risk individuals have a lower FA than controls,\(^{51}\) and prodromal patients (at-risk individuals who proceed to psychosis) show a progressive reduction in WM integrity in frontal regions over time,\(^{53}\) In contrast to the increase in integrity leading to the WM maturation peak observed in controls,\(^{148-150}\) WM tracts of other association areas (for example, the uncinate and arcuate fasciculi, the anterior and dorsal cingulate and parts of the corpus callosum) are not different in high-risk versus prodromal individuals.\(^{151}\) Moreover, in prodromal SZ patients WM integrity reductions are observed only in frontal areas, whereas in first-episode patients decreases in WM are found in frontal as well as more caudal regions, including the inferior longitudinal fasciculus and the internal capsule.\(^{51-53}\) In chronic SZ, lower FA is found in frontal, caudal and more posterior regions, including the corpus callosum, minor and major forceps, inferior fronto-occipital fasciculus and the splenium.\(^{50,54,55}\) Thus, even before SZ disease onset a reduced WM integrity occurs in frontal areas that advances in further stages of the disorder, proceeding from frontal towards more caudal and posterior brain regions.

Myelination of most brain regions is completed within the first year of life, whereas the myelination of association areas is ongoing until the thirties, after which myelin levels stabilise and finally decline from the late fifties onwards.\(^{152,153}\) The extent of cortical myelination is positively correlated with cognitive performance throughout life.\(^{153}\) PFC myelination, which occurs during late adolescence, displays a time frame similar to that of PFC WM development.\(^{154}\) In addition, human PFC myelin-related mRNA expression peaks during late adolescence.\(^{155}\) Thus, the prodromal phase/onset of SZ coincides with the time frame of PFC myelination, and during this stage frontal WM is affected.\(^{149}\) Furthermore, adult SZ dorsolateral and medial PFC mRNA expression patterns of OL-related genes are similar to those in the juvenile healthy developing brain.\(^{156}\) Therefore, it seems that myelin does not reach the mature state in the SZ PFC during adolescence, as it does in healthy brain development.

Cognitive symptomatology in SZ is associated with age-related decline in WM integrity

It is important to note that cognitive symptoms of SZ are observed already during the prodromal phase and worsen when psychosis starts. As such, these symptoms follow a developmental pattern that is similar to the decline in WM integrity in SZ. WM maturation and the cognitive functioning of inhibitory control are indeed correlated.\(^{157}\) In addition, the poor working memory of SZ patients correlates with a low WM integrity in the superior longitudinal fasciculus, a frontal structure that matures during adolescence.\(^{157}\)

The role of OPCs in the PFC and other brain areas during adolescence

In the adult brain, OPCs are necessary for myelin repair following damage.\(^{158}\) However, as OPCs make up to 4% of the adult brain\(^{159}\) and appear to be evenly distributed throughout the brain, it seems unlikely that they would be involved in only myelin repair. It has been hypothesised that following the major myelination event during the first year of life a subset of OPCs change into a subtype with a morphology and function different from those of precursor cells of OLs.\(^{160,161}\) This second type of OPC may have a role in the monitoring of neuronal activity and the immune response.\(^{160,162}\) Recently, a brain region-dependent variation in the distribution of various subtypes of OPCs has been shown, which differs between young and adult animals.\(^{163}\) For example, adult monkey motor cortex OPCs mainly give rise to perivascular cells, not OLs.\(^{164}\) Likewise, during adolescence, readily myelinated brain areas may well have a set of OPCs that is functionally different from the set of OPCs in brain areas in which myelination is ongoing, such as the PFC that is likely to have OPCs programmed to become OLs.

Oxidative stress may cause apoptosis of pre-OLs in the SZ PFC

The cells that are in transition from OPC to OL are called pre-OLs. The detrimental effects of ROS are the largest in this subtype of OLs.\(^{165,166}\) The excessive build-up of ROS in pre-OLs during SZ adolescence may lead to apoptosis or a cell cycle arrest followed by an inability to sufficiently produce myelin. In the SZ PFC, a lower number of cells expressing OLG1G2 (a marker for all cells of the OL lineage) is observed, with no changes in the number of OPCs, suggesting that indeed PFC OPC maturation impairment in SZ is a likely cause of the lack of myelination in this brain area.\(^{167}\)

In addition to the PFC, demyelination and a decreased WM integrity have also been observed in the HIP of SZ brains.\(^{168-171}\) However, HIP WM defects become apparent during first-episode SZ and are fully evident only during the chronic state of SZ,\(^{171-173}\) and as such their development follows a different time course than the PFC WM defects that occur already in the prodromal phase. Nevertheless, the neurobiological mechanisms causing OL and myelin defects may be similar in the PFC, HIP and other brain areas of SZ patients. Differentiating OPCs are most vulnerable to oxidative stress; therefore, PFC myelination that is dependent on these cells is harmed during early stages of SZ (as discussed above). Oxidative stress levels increase over time and may reach a level at which mature myelinating OLs are also damaged, and thus regions like the HIP and other brain areas, that depend on mature OLs to maintain proper myelination, will be affected during later stages of SZ. Furthermore, oxidative stress may cause perturbation of de novo myelination in the HIP and other brain areas, a possibility that requires further investigation.

NEUROBIOLOGICAL LINK BETWEEN HYPOMYELINATION AND INTERNEURON ABNORMALITIES

A significant body of evidence suggests that interneuron abnormalities in both the PFC and HIP have an important role in SZ pathology.\(^{174-179}\) Interneurons in the PFC mature during adolescence.\(^{179}\) Apart from OLs and OPCs, interneurons are also relatively vulnerable to the effects of oxidative stress because of their high mitochondrial demand.\(^{180}\) Interestingly, oxidative stress-based animal models for SZ display both myelin...
Abnormalities and interneuron defects. Oxidative stress in PV interneurons has been proposed as a cause of SZ and PV interneuron densities are reduced in, among other brain regions, SZ PFC and Hip. Impaired myelination of the PV interneurons may render them more susceptible to degeneration in late adolescence, contributing to the reduced PV interneuron densities. Thus, the combination of aberrant myelination and reduction in the number of PV interneurons in the PFC and Hip, both caused by oxidative stress, may well lead to an inefficient neuronal network and eventually to SZ-like symptoms (for review, see Steuelt et al.).

PV interneurons are responsible for the cortical high-frequency gamma-band oscillations that are involved in cognitive functioning and disrupted in SZ. The degree of myelination is dependent on neuronal activity, and PV cells are the most active of all interneurons and the only interneuron subtype to be myelinated. Interestingly, a recent review states that the ineffective myelination of specifically PV interneurons, according to our hypothesis caused by high oxidative stress levels, would generate altered gamma-band oscillations and cognitive deficits in SZ.

**THERAPEUTIC IMPLICATIONS**

The redox-induced prefrontal OPC-dysfunctioning hypothesis of the cognitive symptoms in SZ may have important implications for novel treatment strategies.

**Pharmacological manipulations**

On the basis of the molecular map of the relationship between oxidative stress and OPC functioning (Figure 2), new preventive strategies for individuals at high risk for SZ could include antioxidant treatment. In this regard, antioxidant treatment is effective in rodent models, and decreases symptom severity in SZ patients. Therefore, the use of antioxidants, or compounds that generate an increased production of endogenous antioxidants, may be attractive for SZ therapy.

New potential therapeutic targets include components of the mTOR-P70S6K or ERK1/2 pathway (to be activated) and/or AMPK signalling (to be downregulated) in OPCs, and upregulation of the number of PDGFRA receptors in the cell membrane of OPCs. In this respect, increasing mTOR signalling by inducing the upregulation of brain-derived neurotrophic factor (for example, through 1-amino-1,3-dicarboxycyclopentane) may be considered, and the drugs diosgenin and miconazole could be used to boost ERK1/2 signalling. Moreover, drugs that are known to increase and cognitive functioning and disrupted in SZ. Furthermore, meltation transfer ratio and diffusion magnetic resonance imaging may be used to study PFC myelination over time of individuals at high risk to develop SZ, together with PFC-relevant cognitive assessment. Such studies would establish a relationship between SZ risk, SZ development, PFC WM integrity, myelin levels and cognitive (dys)functioning. In addition, the studies would give insight into whether PFC WM and myelin deficits are indeed caused by a deficiency in prefrontal myelination within the window of SZ disease onset, and whether these shortcomings correlate with cognitive dysfunction in SZ. If confirmed, our hypothesis may significantly contribute to the development of novel antioxidant- and promyelination-based strategies to treat the cognitive symptomatology of this devastating disorder.

**CONFLICT OF INTEREST**

The authors declare no conflict of interest.

**REFERENCES**

1. Orellana G, Slachevsky A. Executive functioning in schizophrenia. Front Psychiatry 2013; 4: 35.
2. Senkowski D, Gallinat J. Dysfunctional prefrontal gamma-band oscillations reflect working memory and other cognitive deficits in schizophrenia. Biol Psychiatry 2015; 77: 1010–1019.
3. Zuckerman L, Rehavi M, Nachman R, Weiner I. Immune activation during pregnancy in rats leads to a postpubertal emergence of disrupted latent inhibition, dopaminergic hyperfunction, and altered limbic morphology in the offspring: a novel neurodevelopmental model of schizophrenia. Neuropsychopharmacology 2003; 28: 1778–1789.
4. Brown AS, Patterson PH. Maternal infection and schizophrenia: implications for prevention. Schizophr Bull 2011; 37: 284–290.
5. Osuigwe DB, Elkahalou AG, Johnson KR, Phillips TM, Herkenham M. Maternal immune activation by LPS selectively alters gene expression profiles of interneuron migration and oxidative stress in the fetus without triggering a fetal immune response. Brain Behav Immun 2012; 26: 623–634.
6. Painitia MK, Painitia 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.
7. Cillia JD, Read LL, Droet V, Kao A, Kelly A, Duff KE et al. Vitamin D insufficiency and schizophrenia risk: evaluation of hyperprolinemia as a mediator of association. Schizophr Res 2014; 156: 15–22.
8. Crews M, Lally J, Gardner-Sood P, Howes O, Bonaccorso S, Smith S et al. Vitamin D deficiency in first episode psychosis: a case-control study. Schizophr Res 2013; 150: 533–537.
9. McGrath J, Eyles DW, Pedersen CB, Anderson C, Ko P, Burke TH et al. Neonatal vitamin D status and risk of schizophrenia: a population-based case-control study. Arch Gen Psychiatry 2010; 67: 889–894.
10. Eyles D, Almeras L, Benech P, Patatian A, Mackay-Sim A, McGrath J et al. Developmental vitamin D deficiency alters the expression of genes encoding mitochondrial, cytoskeletal and synaptic proteins in the adult rat brain. J Steroid Biochem Mol Biol 2007; 103: 538–545.
76 Kubicki M, Park H, Westin CF, Nestor PG, Mulkern RV, Maier SE. Myelination abnormalities and cognitive impairment in early-onset schizophrenia-spectrum disorders. J Am Acad Child Adolesc Psychiatry 2014; 53: 362–372, e361-362.

74 Scheel M, Prokscha T, Bayerl M, Gallinat J, Montag C. Myelination dehypomelination in brain research: a review. Clin Psychopharmacol Neurosci 2012; 10: 13–24.

78 Lang DJ, Yip E, MacKay AL, Thornton AE, Vila-Rodriguez F, MacEwan GW. Reduced white matter integrity from the Stanley Neuropathology Consortium. Schizophr Res 2004; 67: 269–275.

77 Neill JC, Barnes S, Cook S, Grayson B, Idris NF, McLean SL et al. Animal models of cognitive dysfunction and negative symptoms of schizophrenia: focus on NMDA receptor antagonists. Pharmacol Ther 2010; 128: 419–432.

75 Prata DP, Kanaan RA, Barker GJ, Sherrill S, Woolley J, Georgieva L et al. Risk variant of oligodendrocyte lineage transcription factor 2 is associated with reduced white matter integrity. Hum Brain Mapp 2013; 34: 2025–2031.

84 Zai C, Chakravarty MM et al. Oligodendrocyte genes, white matter tract integrity, and cognition in schizophrenia. Cereb Cortex 2013; 23: 2044–2057.

86 Uranova NA, Vostrikov VM, Orlovskaya DD, Rachmanova VI. Oligodendroglial density in the prefrontal cortex in schizophrenia and mood disorders: a study from the Stanley Neuropathology Consortium. Schizophr Res 2004; 67: 151–163.

87 Vostrikov VM, Urana NO, Rachmanova VI, Orlovskaya DD. Lowered oligodendrocyte cell density in the prefrontal cortex in schizophrenia. Zh Nevrol Psikhiatr Im Korshakova 2004; 104: 47–51.

88 Hof PR, Haroutunian V, Friedman JL, Buxton C, Perl DP et al. Loss and altered spatial distribution of oligodendrocytes in the superior frontal gyrus in schizophrenia. Biol Psychiatry 2003; 53: 1075–1085.

89 Stark AK, Uylings HB, Sanz-Arigita E, Pakkenberg B. Gial cell loss in the anterior cingulate cortex, a subregion of the prefrontal cortex, in subjects with schizophrenia. Am J Psychiatry 2004; 161: 882–888.

90 Flynn SW, Lang DJ, Mackay AL, Gogarhi V, Vavasour IM, Whittall KP et al. Abnormalities of myelination in schizophrenia detected in vivo with MRI, and post-mortem with analysis of oligodendrocyte proteins. Mol Psychiatry 2003; 8: 811–820.

91 Hakak Y, Walker JR, Li C, Wong WH, Davis KL, Buxbaum JD et al. Genome-wide expression analysis reveals dysregulation of myelination-related genes in chronic schizophrenia. Proc Natl Acad Sci USA 2008; 105: 4746–4751.

92 Neill JC, Barnes S, Cook S, Grayson B, Idris NF, McLean SL et al. PDGFRA/NG2 and PDGFbeta receptor antagonism. Neuropsychopharmacology 2010; 35: 612–628.

93 light in the anterior cingulate cortex, a subregion of the prefrontal cortex, in subjects with schizophrenia. Am J Psychiatry 2004; 161: 882–888.

94 Xiu Y, Kong XR, Zhang L, Qiu X, Chao FL, Peng C et al. White matter abnormalities in schizophrenia detected with DTI and MTR from the Stanley Neuropathology Consortium. Schizophr Res 2004; 67: 269–275.
Cytokine expression in the fetal brain. Free Radical Biol Med 2007; 42: 1231–1245.

154 Miyamoto HN, Maki T, Pham LD, Hayakawa K, Seo JH, Mandeville ET et al. Oxidative stress interferes with white matter renewal after prolonged cerebral hypoperfusion in mice. Stroke 2013; 44: 3516–3521.

155 Haidler F, Fischer MT, Frischer JM, Bauer J, Hoffberger R, Botond G et al. Oxidative damage in multiple sclerosis lesions. Brain 2011; 134(Pt 7): 1914–1924.

156 Schub C, Wimmer L, Hametner S, Haidler L, Van Dam AM, Liblau RS et al. Oxidative tissue injury in multiple sclerosis is only partly reflected in experimental disease models. Acta Neuropathol 2014; 128: 247–266.

157 Lassmann H, von Horsens J, Mahd D. Progressive multiple sclerosis: pathology and pathogenesis. Nat Rev Neurology 2010; 2: 647–656.

158 Korakas N, Tolasaki M. Cognitive impairment in multiple sclerosis: a review of neuropsychological assessments. Cogn Behav Neurol 2016; 29: 55–67.

159 Cardoso M, Olmo NF, Frasquier YD. Systematic review of cognitive dysfunction in pediatric and juvenile multiple sclerosis. Pediatr Neurol 2015; 53: 287–292.

160 Cancelliere A, Mangano FT, Air EL, Jones BV, Altaye M, Rajagopal A et al. DTI values in key white matter tracts from infancy through adolescence. AJNR Am J Neuroradiol 2013; 34: 1443–1449.

161 Yap QJ, Teh I, Fusari-Poli P, Sum MY, Kuswanto C, Sim K. Tracking cerebral white matter changes across the lifespan: insights from diffusion tensor imaging studies. J Neurotransm 2013; 120: 1369–1395.

162 Pfefferbaum A, Woolley JB, Bhattacharyya S, Perez-Iglesias R, Fusari Poli P, Valmaglia L et al. Alterations in white matter evident before the onset of psychosis. Schizophr Bull 2012; 38: 1308–1317.

163 Kochunov P, Williamson DE, Lancaster J, Fox P, Cornell J, Blangero J et al. Fractional anisotropy of water diffusion in cerebral white matter across the lifespan. Neurobiol Aging 2012; 33: 9–20.

164 Carletti F, Woolley JB, Bhattacharyya S, Perez-Iglesias R, Fusari Poli P, Valmaglia L et al. Alterations in white matter evident before the onset of psychosis. Schizophr Bull 2012; 38: 1170–1179.

165 Karlsgodt KH, Jacobson SC, Seal M, Jernigan TL. Development of cortical and subcortical brain structures in childhood and adolescence: a structural MRI study. Dev Med Child Neurol 2002; 44: 4–16.

166 Peters BD, Szpak SR, Prada J, Ruta T, Gruner P, DeRosse P et al. White matter development in adolescence: diffusion tensor imaging and meta-analytic results. Schizophr Bull 2012; 38: 1308–1317.

167 Kochunov P, Williamson DE, Lancaster J, Fox P, Cornell J, Blangero J et al. Fractional anisotropy of water diffusion in cerebral white matter across the lifespan. Neurobiol Aging 2012; 33: 9–20.

168 Karlsgodt KH, Niendam TA, Bearden CE, Cannon TD. White matter integrity and psychosis in ultra-high-risk subjects: a diffusion tensor imaging study. Front Neurosci 2010; 4: 242–243.

169 Karlsgodt KH, Niendam TA, Bearden CE, Cannon TD. White matter integrity and psychosis in ultra-high-risk subjects: a diffusion tensor imaging study. Front Neurosci 2010; 4: 242–243.

170 Karlsgodt KH, Jacobson SC, Seal M, Fusari-Poli P. The relationship of developmental and adult changes in white matter to the onset of psychosis. Curr Pharm Des 2012; 18: 422–433.

171 Lassmann H, van Horssen J, Mahd D. Progressive multiple sclerosis: pathology and pathogenesis. Nat Rev Neurology 2010; 2: 647–656.

172 Korakas N, Tolasaki M. Cognitive impairment in multiple sclerosis: a review of neuropsychological assessments. Cogn Behav Neurol 2016; 29: 55–67.

173 Cardoso M, Olmo NF, Frasquier YD. Systematic review of cognitive dysfunction in pediatric and juvenile multiple sclerosis. Pediatr Neurol 2015; 53: 287–292.

174 Cancelliere A, Mangano FT, Air EL, Jones BV, Altaye M, Rajagopal A et al. DTI values in key white matter tracts from infancy through adolescence. AJNR Am J Neuroradiol 2013; 34: 1443–1449.

175 Yap QJ, Teh I, Fusari-Poli P, Sum MY, Kuswanto C, Sim K. Tracking cerebral white matter changes across the lifespan: insights from diffusion tensor imaging studies. J Neurotransm 2013; 120: 1369–1395.

176 Pfefferbaum A, Woolley JB, Bhattacharyya S, Perez-Iglesias R, Fusari Poli P, Valmaglia L et al. Alterations in white matter evident before the onset of psychosis. Schizophr Bull 2012; 38: 1308–1317.

177 Kochunov P, Williamson DE, Lancaster J, Fox P, Cornell J, Blangero J et al. Fractional anisotropy of water diffusion in cerebral white matter across the lifespan. Neurobiol Aging 2012; 33: 9–20.

178 Karlsgodt KH, Jacobson SC, Seal M, Fusari-Poli P. The relationship of developmental and adult changes in white matter to the onset of psychosis. Curr Pharm Des 2012; 18: 422–433.

179 Karlsgodt KH, Niendam TA, Bearden CE, Cannon TD. White matter integrity and psychosis in ultra-high-risk subjects: a diffusion tensor imaging study. Front Neurosci 2010; 4: 242–243.

180 Karlsgodt KH, Jacobson SC, Seal M, Fusari-Poli P. The relationship of developmental and adult changes in white matter to the onset of psychosis. Curr Pharm Des 2012; 18: 422–433.

181 Lassmann H, van Horssen J, Mahd D. Progressive multiple sclerosis: pathology and pathogenesis. Nat Rev Neurology 2010; 2: 647–656.
181 Wischhof L, Irrsack E, Diorio C, Koch M. Prenatal LPS-exposure – a neurodevel-
ompmental rat model of schizophrenia – differentially affects cognitive functions,
myelination and parvalbumin expression in male and female offspring. Progr
Neuropsychopharmacol Biol Psychiatry 2015; 57: 17–30.

182 Behrens MM, Sejnowski TJ. Does schizophrenia arise from oxidative dysregula-
tion of parvalbumin-interneurons in the developing cortex? Neuropsychophar-
aacology 2009; 57: 193–200.

183 Beasley CL, Zhang ZJ, Patten I, Reynolds GP. Selective deficits in prefrontal
cortical GABAergic neurons in schizophrenia defined by the presence of
calcium-binding proteins. Biol Psychiatry 2002; 52: 708–715.

184 Zhang Z, Sun J, Reynolds GP. A selective reduction in the relative density of
parvalbumin-immunoreactive neurons in the hippocampus in schizophrenia pa-
ients. Chin Med J 2002; 115: 819–823.

185 Steplett P, Cabungcal JH, Monin A, Dwir D, O’Donnell P, Cuenod M et al. Redox
dysregulation, neurotransfination, and NMDA receptor hypofunction: a "central
hub" in schizophrenia pathophysiology. Schizophr Res 2016; 176: 41–51.

186 Lewis DA, Curley AA, Gliausier JR, Volk DW. Cortical parvalbumin interneurons
and cognitive dysfunction in schizophrenia. Trends Neurosci 2012; 35: 57–67.

187 Kim T, Thanksahan S, McKenna JT, McNally JM, Yang C. Choo JH et al. Cortically
projecting basal forebrain parvalbumin neurons regulate cortical gamma band
oscillations. Proc Natl Acad Sci USA 2015; 112: 3535–3540.

188 Stedehouder J, Kushner SA. Myelination of parvalbumin interneurons: a parsi-
monious locus of pathophysiological schizophrenia in schizophrenia. Mol
Psychiatry 2017; 22: 4–12.

189 Cabungcal JH, Coudotte DS, Lewis EM, Tejeda HA, Piantadosi P, Pollock C et al.
Juvenile antioxidant treatment prevents adult deficits in a developmental model of
schizophrenia. Neuron 2014; 83: 1073–1084.

190 Arvidskahan M, Ghate M, Ranjekar PK, Evans DR, Mahadik SP. Supplementation
with a combination of omega-3 fatty acids and antioxidants (vitamins E and C)
improves the outcome of schizophrenia. Schizophr Res 2003; 62: 195–204.

191 Fulmer CG, VonDran MW, Stillman AA, Huang Y, Hempstead BL, Dreyfus CF.
Astrocyte-derived BDNF supports myelin protein synthesis after cuprizone-
duced demyelination. J Neurosci 2014; 34: 8186–8196.

192 Deshmukh VA, Tardif V, Lyssiotis CA, Green CC, Kerman B, Kim HJ et al. A regenerative
approach to the treatment of multiple sclerosis. Nature 2013; 502:
327–332.

193 Landza T, Mueser KT, Wyka KE, Shreck E, Jespersen R, Jacobs MA et al. Devel-
opment of a group and family-based cognitive behavioural therapy program for
young at risk for psychosis. Early Int Psychiatry 2015; 10: 511–521.

194 Weisbrod M, Aschenbrenner S, Pflueger U, Kaiser S, Roesch-Ely D. [Rehabilitation
in persons with schizophrenic spectrum disorders: the impact of cognition and
cognitive remediation therapy]. Fortschr Neurol Psychiatr 2014; 82:
128–134.

195 Morrison AP, Turkington D, Pyle M, Spencer H, Brabban A, Dunn G et al. Cog-
nitive therapy for people with schizophrenia spectrum disorders not taking
antipsychotic drugs: a single-blind randomised controlled trial. Lancet 2014;
383: 1395–1403.

196 Lam KC, Ho CP, Wa JC, Chan SM, Yam KK, Yeung OS et al. Metacognitive training
(MCT) for schizophrenia improves cognitive insight: a randomized controlled
trial in a Chinese sample with schizophrenia spectrum disorders. Behav Res Ther
2013; 51: 124–132.

197 Bennett JJ, Madden DJ. Disconnected aging: cerebral white matter integrity and
age-related differences in cognition. Neuroscience 2013; 276: 187–205.

198 Karbasforoushan H, Duffy B, Blackford JJ, Woodward ND. Processing speed
impairment in schizophrenia is mediated by white matter integrity. Psychol Med
2015; 45: 109–120.