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## REVIEW

# Oxidative stress, prefrontal cortex hypomyelination and cognitive symptoms in schizophrenia

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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 dysfunctioning 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).<sup>1,2</sup> 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.<sup>3,4</sup> The mechanism by which maternal immune activation affects brain

development likely involves oxidative stress.<sup>5</sup> 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.<sup>6</sup> Other environmental factors associated with redox imbalance and SZ are prenatal malnutrition and maternal stress during pregnancy.<sup>7–12</sup> 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.<sup>13</sup> 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.<sup>14–20</sup>

## Redox imbalance in SZ patients

Genetic studies have shown associations between oxidative stress gene polymorphisms and SZ,<sup>21,22</sup> including genetic variations in glutathione cysteine ligase (GCL) and several glutathione-S-transferases,<sup>23–25</sup> 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.<sup>25</sup> 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.

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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,<sup>26–29</sup> in line with the reduced glutathione levels found in the PFC and cerebral spinal fluid of SZ patients<sup>30,31</sup> and in *post mortem* SZ brains,<sup>32</sup> in which abnormal redox-related protein expression has also been found.<sup>33</sup> Furthermore, peripheral levels of ROS are increased, and those of glutathione peroxidase and superoxide dismutase are decreased in SZ patients,<sup>34–39</sup> 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,<sup>38</sup> directly linking redox imbalance to cognitive dysfunction.<sup>35</sup>

#### 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,<sup>40</sup> although higher levels of brain mitochondrial ROS have been found in a ketamine-induced rat model.<sup>41</sup> Inversely, glutathione depletion in rats leads to SZ-like phenotypes.<sup>42–44</sup> In addition, knockout mice that lack a crucial subunit of the GCL enzyme show significant reduction of glutathione levels in the anterior cortex,<sup>45</sup> especially during the prepubertal period, which is followed by SZ-like behaviour in the time frame of disease onset<sup>46</sup> 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.<sup>47</sup> 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 Voineskos<sup>48</sup>), in both medicated and non-medicated SZ subjects.<sup>49,50</sup> 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.<sup>50–55</sup>

#### WM abnormalities in SZ are associated with cognitive symptomatology

Correlations between cognition and frontal WM integrity have been reported in healthy individuals.<sup>56,57</sup> In chronic SZ, abnormalities in cognitive processing speed are associated with WM disruptions in, among others, frontal areas,<sup>58–60</sup> and in first-episode SZ patients a lower frontal WM integrity is correlated with more severe cognitive symptoms.<sup>61,62</sup> Interestingly, deficit SZ (that is, SZ with strong cognitive impairment<sup>63,64</sup>) is associated with severe WM abnormalities.<sup>65–68</sup> Furthermore, cognitive symptomatology of SZ patients worsens as the disease progresses, in line with the ongoing WM alterations.<sup>69,70</sup>

#### 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.<sup>71</sup> 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.<sup>72</sup> 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.<sup>73,74</sup> 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.<sup>75,76</sup> These low myelin levels predict impaired processing speed in SZ and link decreased myelination to cognitive symptoms of the disorder.<sup>77,78</sup>

#### 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.<sup>79–81</sup> Plasticity in the formation and retraction of myelin sheaths by OLs also occurs from early childhood to adulthood.<sup>80,81</sup> Neuronal activity can instruct OPCs to divide and mature, and can stimulate myelin sheath production by OLs,<sup>82</sup> leading to increased myelination and improved behavioural performance.<sup>83</sup> Conversely, reduced neuronal stimulation by social isolation impairs myelination, which correlates with behavioural and cognitive dysfunction.<sup>84,85</sup> Accordingly, altered myelination dynamics may have a major role in cognition as well as in psychiatric disorders like SZ.

#### Evidence from human *post mortem* studies

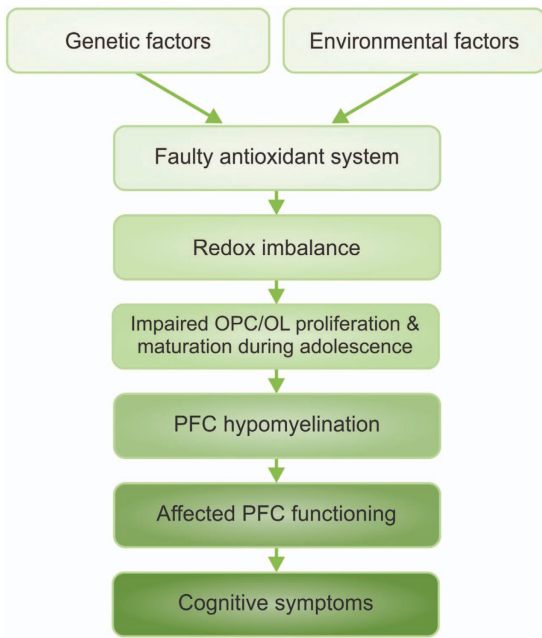
In the PFC of SZ patients, lower OL size and regional-specific differences in OL density alongside higher levels of OL apoptosis and necrosis have been observed, accompanied by lower levels of myelin.<sup>86–90</sup> Furthermore, expression of the myelin-associated proteins 2',3'-Cyclic-nucleotide 3'-phosphodiesterase and myelin-associated glycoprotein is significantly lower in SZ anterior frontal cortex,<sup>90</sup> and differential mRNA expression of these two and other myelin-related genes has been observed in SZ dorsolateral PFC.<sup>91</sup> Overall, there is abundant evidence for an OL as well as a myelin deficit in the PFC of *post mortem* brain.

#### Evidence from rodent models

Evidence for a myelin deficit in SZ is also provided by studies on rodent models that range from pharmacological and transgenic to neurodevelopmental models. For example, administration of the MK-801 in adulthood is used as a model for SZ (for a review see Neill *et al.*<sup>92</sup>) and alters brain expression of, among others, platelet-derived growth factor (PDGF), proteolipid protein, myelin basic protein and 2',3'-Cyclic-nucleotide 3'-phosphodiesterase,<sup>93</sup> and decreases WM volume, together with myelin sheath degeneration.<sup>94</sup> Furthermore, mice transgenic for SZ-associated locus G72/G30 show SZ-like behavioural traits and myelin-related protein expression changes.<sup>95</sup> 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.<sup>96,97</sup> 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.<sup>98</sup>

#### Genetic evidence

OL-related gene variants correlate with reduced WM integrity and cognitive performance.<sup>99,100</sup> 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



**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.

significantly associated with the disorder.<sup>101–105</sup> Therefore, in most 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,<sup>106,107</sup> probably because their myelin synthesis entails a high metabolic rate.<sup>108</sup> 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 PDGF $\alpha$  stimulation of OPC proliferation and maturation.<sup>109</sup> 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*,<sup>110</sup> and reduced myelin basic protein expression and OL number in the rat brain.<sup>111–113</sup> 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 of cognitive symptomatology in SZ. This hypothesis states that in SZ the combination of environmental factors and genetic predisposition causes oxidative stress, marked by a build-up of ROS in OPCs (Figure 1). During late adolescence, the high ROS levels impair OPC signal transduction processes that are necessary for their proliferation

and differentiation. OPC dysfunctioning coincides with the relatively late onset of PFC myelination, and causes hypomyelination and disruption of connectivity in this brain area. The resulting cognitive symptoms coincide with SZ onset.

In the next sections, evidence for this hypothesis will be presented. First, the relationship between redox imbalance, hypomyelination and cognitive functioning in the PFC will be highlighted. Second, the molecular mechanisms underlying the impairment of OPC functioning by ROS will be discussed. Third, we will consider the critical developmental time period of PFC myelination and, in particular, of PFC hypomyelination in SZ.

#### 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.<sup>114</sup>

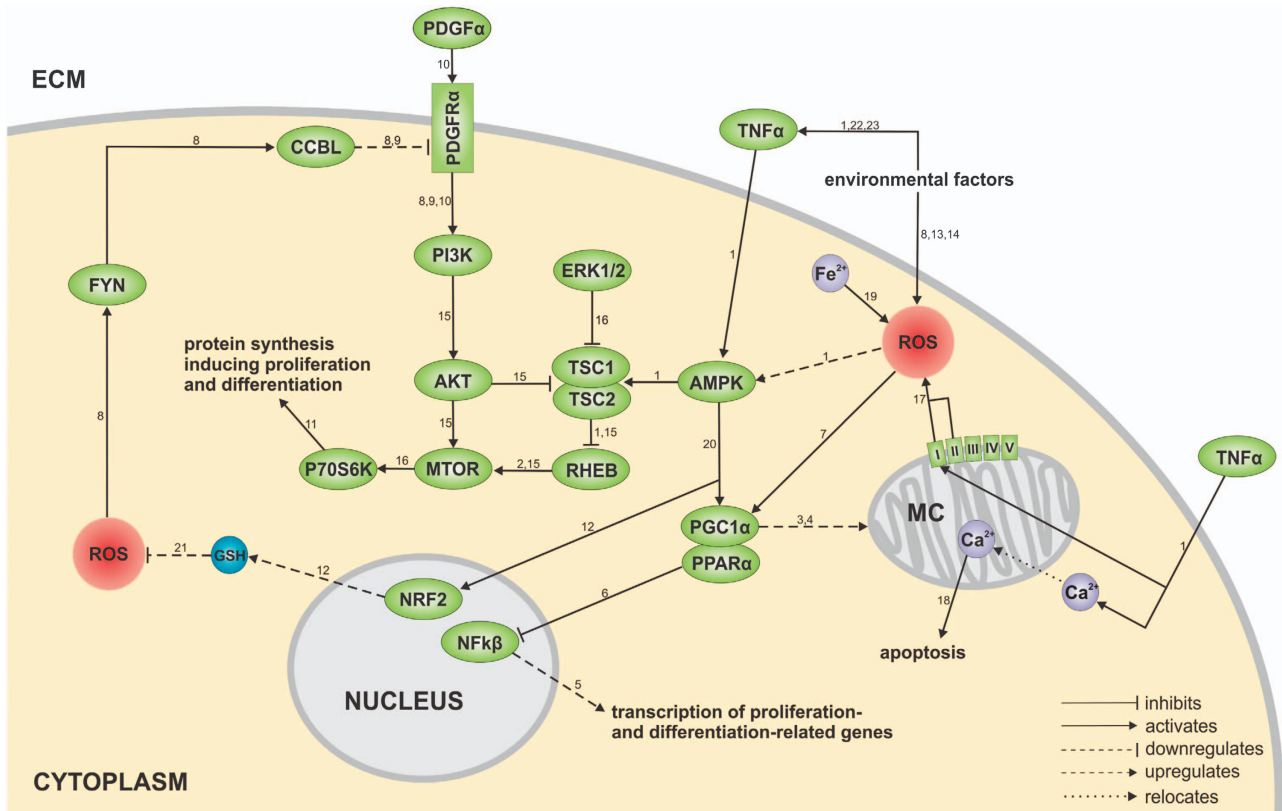
Figure 2 presents a molecular map that is based on the literature described below and depicts the interactions among various molecules inactivating the mTOR-P70S6K pathway in SZ OPCs.

#### Inactivation of the mTOR-P70S6 pathway in SZ OPCs

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).<sup>115</sup> Moreover, RHEB mediation of mTOR activity is necessary for OPC differentiation into myelinating OLs.<sup>116</sup> 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.<sup>117</sup> 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,<sup>118</sup> preventing efficient transcriptional activation of its target genes, thus contributing to OPC dysfunctioning.<sup>118–120</sup> 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.<sup>121,122</sup> 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.<sup>115</sup>

The other cellular pathway that can give rise to reduced activity of the mTOR-P70S6K pathway includes signalling via PDGFR $\alpha$ . 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.<sup>109,123</sup> This overactivation of C-Casitas B-lineage Lymphoma has been shown to decrease PDGFR $\alpha$  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 2.** Molecular map of pathways that lead ROS to cause OPC dysfunctioning in SZ. A molecular map is essential to elucidate the neurobiological mechanisms underlying the impairment of OPC functioning by ROS in the SZ PFC. The map shows that two cellular pathways result in a reduced activation of the mTOR-P70S6K pathway under conditions of increased ROS production and decreased antioxidant levels. The first pathway involves ROS-induced downregulation of PDGFR $\alpha$ , leading to sub-activation of the mTOR-P70S6K pathway. The second AMPK-related pathway leads to inhibition of the mTOR-P70S6K signalling cascade, as well as to downregulation of the transcription of proliferation- and differentiation-related genes. Inactivation of mTOR-P70S6K causes decreased protein synthesis for proliferation and differentiation, and consequently leads to OPC dysfunctioning. See section 'ROS can cause OPC dysfunctioning - Inactivation of the mTOR-P70S6K pathway in SZ OPCs' for a description, Supplementary Table 1 for the pertinent references and the list of abbreviations for full names of all components of the molecular map. AMPK, AMP-activated protein kinase; mTOR, mammalian target of rapamycin; OPC, oligodendrocyte precursor cell; PDGF, platelet-derived growth factor; PFC, prefrontal cortex; ROS, reactive oxygen species; SZ, schizophrenia.

function.<sup>109,124,125</sup> Interestingly, glutathione depletion, both *in vivo* and *in vitro*, inhibits Fyn-dependent maturation of OPCs, accompanied by reduced myelination.<sup>126</sup>

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.<sup>127</sup> 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,<sup>128</sup> and of miconazole, which promotes remyelination *in vitro* and in animal models of multiple sclerosis (MS).<sup>129</sup>

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.<sup>126</sup> 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,<sup>130,131</sup> and prenatal infection causes effects on myelination and WM.<sup>132,133</sup> The effects of prenatal infection on oxidative stress in adulthood are largely unknown, whereas in young animals the glutathione metabolism is affected.<sup>134,135</sup> 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.<sup>136</sup> 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.<sup>136</sup> 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.<sup>137,138</sup> 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.<sup>139</sup> The fact that MS patients show cognitive symptoms similar to those observed in SZ (for reviews, see Korakas *et al.*<sup>140</sup> and Cardoso *et al.*<sup>141</sup>) 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,<sup>142,143</sup> and WM volume peaks during early adolescence.<sup>144</sup> From this period onwards, the PFC white/grey matter ratio rises with increasing age.<sup>145</sup> In frontal areas, WM and connectivity maturation occurs during late adolescence. In addition, the superior longitudinal fasciculus shows increasing connectivity during adolescence<sup>146</sup> and corticocortical WM tracts reach peaks of maturation between the ages of 23 and 39.<sup>147</sup> These findings indicate that WM maturation in frontal areas is ongoing during SZ disease onset.

High-risk individuals have a lower FA than controls,<sup>51</sup> and prodromal patients (at-risk individuals who proceed to psychosis) show a progressive reduction in WM integrity in frontal regions over time,<sup>51</sup> in contrast to the increase in integrity leading to the WM maturation peak observed in controls.<sup>148–150</sup> 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.<sup>151</sup> 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.<sup>51–53</sup> 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.<sup>50,54,55</sup> 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.<sup>152,153</sup> The extent of cortical myelination is positively correlated with cognitive performance throughout life.<sup>153</sup> PFC myelination, which occurs during late adolescence, displays a time frame similar to that of PFC WM development.<sup>154</sup> In addition, human PFC myelin-related mRNA expression peaks during late adolescence.<sup>155</sup> Thus, the prodromal phase/onset of SZ coincides with the time frame of PFC myelination, and during this stage frontal WM is affected.<sup>149</sup> Furthermore, adult SZ dorsolateral and medial PFC mRNA expression patterns of OL-related genes are similar to those in the juvenile healthy developing brain.<sup>156</sup> 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.<sup>157</sup> 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.<sup>157</sup>

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.<sup>158</sup> However, as OPCs make up to 4% of the adult brain<sup>159</sup> 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.<sup>160,161</sup> This second type of OPC may have a role in the monitoring of neuronal activity and the immune response.<sup>160,162</sup> Recently, a brain region-dependent variation in the distribution of various subtypes of OPCs has been shown, which differs between young and adult animals.<sup>163</sup> For example, adult monkey motor cortex OPCs mainly give rise to perivascular cells, not OLs.<sup>164</sup> 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.<sup>165,166</sup> 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 OLIG2 (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.<sup>167</sup>

In addition to the PFC, demyelination and a decreased WM integrity have also been observed in the HIP of SZ brains.<sup>168–171</sup> However, HIP WM defects become apparent during first-episode SZ and are fully evident only during the chronic state of SZ,<sup>171–173</sup> 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.<sup>174–179</sup> Interneurons in the PFC mature during adolescence.<sup>179</sup> Apart from OLs and OPCs, interneurons are also relatively vulnerable to the effects of oxidative stress because of their high mitochondrial demand.<sup>180</sup> Interestingly, oxidative stress-based animal models for SZ display both myelin

abnormalities and interneuron defects.<sup>181</sup> Oxidative stress in PV interneurons has been proposed as a cause of SZ<sup>182</sup> and PV interneuron densities are reduced in, among other brain regions, SZ PFC<sup>183</sup> and HIP.<sup>184</sup> 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 Steullet *et al.*<sup>185</sup>).

PV interneurons are responsible for the cortical high-frequency gamma-band oscillations that are involved in cognitive functioning and disrupted in SZ.<sup>186,187</sup> The degree of myelination is dependent on neuronal activity,<sup>83</sup> and PV cells are the most active of all interneurons and the only interneuron subtype to be myelinated.<sup>188</sup> Interestingly, a recent review states that the inefficient 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.<sup>188</sup>

### 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,<sup>189</sup> and decreases symptom severity in SZ patients.<sup>180,190</sup> 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 PDGFR $\alpha$  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.<sup>128,129,191</sup> Moreover, drugs that are known to increase myelination by mature OLs and that are tested in the MS field (for example, benzotropine<sup>192</sup>) may prove useful for the treatment of cognitive symptoms in SZ as well.

#### Cognitive behavioural therapy

Cognitive behavioural therapy specific for cognitive deficits in SZ reduces symptom severity and improves cognitive performance.<sup>193–196</sup> As learning and neuronal activation upregulate myelin levels in cortical regions, and WM integrity in SZ is directly linked to cognitive functioning, beneficial cognitive and other neuronal activity-dependent therapies may be, at least in part, mediated by an experience-dependent increase of PFC myelination.<sup>83,197–201</sup>

### CONCLUSIONS

Here we propose the redox-induced prefrontal OPC-dysfunctioning hypothesis for the aetiology of cognitive symptoms in SZ (Figure 1). This hypothesis states that in SZ a combination of increased ROS levels caused by genetic and/or environmental factors and a decreased ROS clearance caused by a

faulty antioxidant system leads to a build-up of ROS in OPCs. ROS may result in the dysfunctioning of OPCs through a number of cellular pathways, including the ERK1/2 and AMPK signalling cascades that cause an inactivation of the mTOR-P70S6K pathway, and hence negatively influence proliferation and differentiation of this cell type (Figure 2). OPC dysfunctioning occurs in late adolescence, during the critical period of PFC myelination. Therefore, in SZ patients the PFC is hypomyelinated, leading to dysconnectivity and the cognitive symptoms of SZ.

A next step would be the testing of the hypothesis proposed here, in both animal models and SZ patients. For instance, animal models for SZ that show both high oxidative stress levels and PFC hypomyelination (such as the APO-SUS rats, and the rodent prenatal infection and hypoxia models) may be treated with antioxidants from a young age onwards to assess whether lowering oxidative stress can (partially) rescue myelination deficits in the PFC, together with PFC-dependent cognitive functioning, and evaluate the width of the therapeutic window. Furthermore, magnetisation 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.

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