Myelin and oligodendrocyte lineage cell dysfunctions: New players in the etiology and treatment of depression and stress-related disorders

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Abstract

Depressive disorders are complex, multifactorial disorders that have been traditionally attributed exclusively to neuronal abnormalities. However, recent studies have increased our understanding of the contribution of glial cells – and particularly of oligodendroglia – to the pathogenesis and treatment outcome of depression and stress-related disorders. This review scrutinizes recent studies focusing on the neurosupportive functions exerted by myelin and oligodendrocyte lineage cells and their disruption in depression and stress-related disorders. It also illustrates how myelin and oligodendroglia respond to antidepressants and non-pharmacological treatment alternatives, and proposes oligodendroglia-directed approaches as novel therapeutic options for depressive disorders.

Depressive disorders are a major contributor to the overall global burden of disease (Ferrari et al., 2013), with more than 300 million people affected by major depressive disorder (MDD) worldwide (World Health Organization, 2018). Therapeutic options, including psychological treatments and antidepressant drugs, are available. However, antidepressants currently in use have significant time lag, numerous side effects and are not effective on a large fraction of patients (Trivedi et al., 2006; Cipriani et al., 2009; Bauer et al., 2017). Our incomplete knowledge of the biological mechanisms underlying the development and onset of depressive disorders limits our understanding of how drugs and other types of intervention operate at the cellular/molecular level and constitutes a major obstacle in the development of novel therapies. In this frame, an additional element of complexity resides in the heterogeneity of depressive disorder clinical manifestations (Nandi et al., 2009) and in the reported sexual dimorphism, with a two-fold higher rate of depression, greater illness severity and different treatment outcomes in women compared to men (Kornstein et al., 2000a,b; Scheibe et al., 2003; Labonté et al., 2017). This suggests that the cellular and molecular mechanisms leading to depressive disorders may differ in distinct individuals and by sex.

Depression is thought to be a multifactorial disease, resulting from the interaction of genetic and environmental factors, including exposure to physical, social and psychological stressors during early and adult life (Halldorsdottir, and Binder, 2017; Bleys et al., 2018; Zhao et al., 2018). Nevertheless, the identity of the genetic determinants of susceptibility and their relationship with the other proposed contributing factors remain by and large elusive (Flint and Kendler 2014; Sullivan et al., 2018; Culverhouse et al., 2018). Similar to most psychiatric disorders, depression has long been interpreted as the exclusive consequence of abnormalities in neurons. Deficits in monoaminergic neurotransmission (Meyer et al., 2006; Belmaker et al., 2008; Booij et al., 2015) along with structural, functional, and neurochemical defects in GABAergic and glutamatergic neurons

in cortical and limbic regions (Duman et al., 2019 and references therein) have been proposed as the neurobiological substrates of the anatomical and functional alterations observed in the brain of depressed patients and animal models of depression (Drevets 2000). Such cellular/molecular alterations are thought to emerge as a consequence of the disruption of neurodevelopmental events and/or of the activation of regressive phenomena (Ansorge et al., 2007; Bennett, 2011). In this context, stress-dependent activation of the hypothalamic-pituitary adrenocortical (HPA) system and sustained elevated levels of plasma corticosterone appear to play an important role in the emergence of neurotransmission alterations and in the onset of depressive symptoms (Karten et al., 1999; McEwen and Morrison, 2013; Duman et al., 2019). Further, detection of increased inflammatory markers and activation of peripheral and resident (i.e. microglia) immune system cells in depressed individuals triggered the hypothesis of a neuroimmune etiology in at least a subgroup of patients (Mechawar and Savitz, 2016). Importantly, this lead to the recognition of the contribution of non-neuronal central nervous system (CNS) cells in the pathogenesis of depressive disorders (Sild et al., 2017). In this frame, increasing knowledge on glial cell functions together with evidence of their alterations in depression and stress-related disorders suggest now a conceptual shift toward a glial-inclusive viewpoint. Clinical and preclinical studies show that, along with microglia and astrocytes, oligodendrocyte lineage cells and myelin are remarkably affected. These alterations may be interpreted as the mere consequence of the disruption of oligodendroglia cross-talk with neurons and other CNS/peripheral cells. Nevertheless, accumulating evidence strongly suggests that they can be causally upstream of neuronal dysfunction in the pathogenesis of depressive disorders and participate in treatment outcome.

In this review, I summarize the advancements achieved over recent years toward the understanding of oligodendroglia neurosupportive functions and their disruption in depression and stress-related disorders. I also discuss how myelin and oligodendrocyte

lineage cells respond to antidepressant treatments and how experimental strategies aimed at correcting oligodendroglia defects impact on depressive symptoms in preclinical models, in view of proposing the combination of neuronal- and oligodendroglia-directed approaches as a novel therapeutic option for depressive disorders. Note that, in accordance with the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5), that distinguishes depressive disorders from bipolar disorder (BD), this review does not cover clinical studies focusing on BD patients.

Neurosupportive and neuromodulatory functions of myelin and oligodendrocyte lineage cells

Myelin and mature oligodendrocytes

By assuring a high speed action potential (AP) conduction along neuronal axons, myelination is one of the major contributors to the evolutionary success of vertebrates, being uniquely expanded in the human brain and essential for CNS development and functions (Tomassy et al., 2015). During CNS ontogenesis, myelin is produced by the spiral wrapping of mature oligodendrocyte (OL) plasma membrane extensions around discrete axon segments, called internodes (Snaidero et al., 2014). Here, current loss is prevented by the electrical insulation provided by tightly packed myelin sheaths, whereas the regeneration of neuronal AP occurs at the level of non-myelinated axonal tracts, termed nodes of Ranvier, where voltage-sensitive sodium (Na_v) channels – responsible for AP genesis - are clustered in close proximity to paranodal fast potassium (K^+) channels required for AP repolarization. Such organization allows the so-called saltatory conduction of neuronal impulses. Recent studies showed that myelin forms onto both excitatory (Tomassy et al., 2014) and inhibitory (Micheva et al., 2016; Stedehouder et al., 2017) neurons, where conduction velocity can reach up to 150 m/s (Rasminsky and Sears, 1972). Of note, OLs also increase AP conduction speed by mechanisms additional to

115 saltatory conduction. Dual whole-cell recordings demonstrated that OL depolarization, that
116 can be induced by activation of neurotransmitter receptors including glutamatergic (AMPA,
117 NMDA, and kainate) and GABAergic (GABAA) receptors (Karadottir and Attwell., 2007),
118 reduces the AP latency (Yamazaki et al., 2007). Further, OLs/myelin promote the spatial
119 segregation of nodal proteins and the achievement/maintenance of a critical axonal
120 diameter (Hamada and Kole, 2015; Freeman et al., 2016; Kaplan et al., 2000; Smith et al.,
121 2013). Consistently, dys-/de-myelination eventually result in a slow and continuous AP
122 propagation along axons (Hamada et al., 2017) and in the loss of impulse discharge
123 synchrony among neurons (Freeman et al., 2016; Maheras et al., 2018). Notably,
124 synchronous discharge is thought to be the way by which neuronal networks encode
125 information about the relatedness of responses and is critical for the development and
126 execution of motor/perceptual/cognitive functions (Singer 1999; James et al., 2008). In
127 addition to the above mentioned functions, OLs have been shown to play also a crucial
128 role in supporting axonal integrity and long-term survival of axons and neurons. OL/myelin
129 loss or dysfunctions result in axonal alterations – including axonal transport defects,
130 altered cytoskeletal stability and axon swelling – that can eventually lead to axon and
131 neuronal degeneration. Notably, there is no simple correlation between the degree of
132 demyelination and axonal defects, suggesting that the absence of myelin wrapping *per se*
133 is not the primary cause of neurodegeneration (Nave et al., 2010). Rather, OL axo-/neuro-
134 supportive actions are attributed to the metabolic and trophic support – including the
135 release of lactate, brain derived neurotrophic factor (BDNF), glial-cell line derived
136 neurotrophic factor (GDNF), and insulin-like growth factor-1 (IGF-1) (Philips and Rothstein,
137 2017; Saab et al., 2016; Lee at al., 2012; Bankston et al., 2013; Wilkins et al., 2003;
138 Dougherty et al., 2000; Jang et al., 2019) and to the regulation of axonal excitability
139 through K^+ buffering (Schirmer et al., 2018; Larson et al., 2018). Finally, recent findings

show that OLs and myelin can influence neurotransmitter release in a region- and neurotransmitter-specific manner (Maheras et al., 2018; Roy et al., 2007).

In humans, the acquisition of OL mature functional features – including myelination and the above mentioned neurosupportive/neuromodulatory functions – is a multi-step process that peaks during childhood and, in the limbic system and prefrontal cortex (PFC), continues during adulthood (Nickel and Gu, 2018; Fig.1). Both a cell-intrinsic developmental program and environmental factors participate in the regulation of the sequence of events that transform oligodendrocyte precursor cells (OPCs) into mature and myelinating OLs (Tomassy et al., 2015). Being a relatively late and mostly postnatal ontogenic process (Fig.1), OL maturation and myelination are particularly prone to be affected by the early individual's experience, including sensory experience, social interaction, and different types of stress (Toritsuka et al., 2015; Vargas et al., 2014; Mount and Monje 2017). At the cellular/molecular level, the effect of such external factors are mediated by changes in the oligodendroglia crosstalk with neurons, microglia, and astrocytes (Tomassy et al., 2015; Clemente et al., 2013). Adaptive myelination (i.e. experience-dependent de-novo myelin deposition and remodeling of already formed myelin internodes) continues also during the adult life (Hughes et al., 2018; Hill et al., 2018; Mount and Monje 2017) and is thought to influence neurological functions.

Oligodendrocyte precursor cells

After the completion of myelination, a large reservoir of OPCs – also named neuron-glia antigen 2 (NG2)-expressing glia - persist in the adult CNS parenchyma (Boda and Buffo 2010), where they sustain oligodendrogenesis in health (Boda et al., 2015; Hill et al., 2014; Xiao et al., 2016) and disease (Assinck et al., 2017; Baxi et al., 2017). Of note, OPCs establish intimate physical and functional interactions with neurons, that allow them to operate as sensors of the neuronal activity. Namely, OPCs establish physical contacts with

functionally relevant neuronal domains, including dendrites, somata, nodes of Ranvier and synaptic cleft (Parolisi and Boda, 2018 and references therein). Further, unique among glial cells, OPCs are directly connected with neurons through glutamatergic and GABAergic neuron-to-OPC synapses. These contacts form in parallel with neuronal synaptogenesis and are lost during OPC maturation (Maldonado and Angulo, 2015). Further, during CNS maturation, the frequency and amplitude of glutamatergic inputs onto OPCs increase (Mangin et al., 2008), whereas GABAergic neuron-to-OPCs synaptic transmission is restricted to developmental stages (Orduz et al., 2015, Balia et al., 2015). Notably, similar to mature OLs, OPCs express a repertoire of ion channels and neurotransmitter receptors apt to monitor the activity of the surrounding neurons (Larson et al., 2016). Further, they have features that are expected for active modulators of the neuronal activity (Boda and Buffo, 2014; Pepper et al., 2018), including the expression and release of a complex array of neuromodulatory and neuroprotective factors, such as neurotrophins, growth factors, cell adhesion and extracellular matrix (ECM) molecules, matrix metalloproteases and metalloprotease inhibitors, inflammatory cytokines/immunomodulatory factors, morphogens (reviewed in Parolisi and Boda, 2018). In this context, the release of the ectodomain of the NG2 protein from OPC surface was shown to critically regulate neuronal synaptic activity and AP conduction, by influencing AMPA receptor currents and NMDAR-dependent long-term potentiation (LTP) in cortical pyramidal neurons (Sakry et al., 2014). Consistent with these data, the selective ablation of about 50% of OPCs in adult mice results in deficits in the glutamatergic neurotransmission in PFC pyramidal neurons (Birey et al., 2015).

Taken together these findings show that myelin and oligodendrocyte lineage cells – including both mature OLs and OPCs - exert an active role in regulating neuronal physiology and neural circuit computation that extends far beyond providing electrical

191 insulation (as summarized in Fig. 2). Disruption of myelin deposition/plasticity and OPC/OL
192 dysfunctions can thus profoundly impact on neuronal function and connectivity.
193
194 **Myelin and oligodendroglia alterations in depression and stress-related disorders**
195 In vivo neuroimaging and postmortem histopathological studies have repeatedly
196 documented compromised white matter (WM)/myelin integrity (Tham et al., 2011) and
197 oligodendroglia abnormalities (i.e. reduction of OL/OPC numbers and altered OL
198 morphology) in the brain of MDD and stressed patients (as summarized in Table 1 and
199 Fig.3). Molecular studies have also reported altered levels of mRNAs and proteins critically
200 involved in OL differentiation and myelination in different cortical areas (Table1),
201 suggesting a dysfunctional OL maturation in MDD and stress-related disorders. Consistent
202 with this interpretation, the levels of N-acetylaspartate (NAA), that supports the energetic
203 demands of myelination (Francis et al., 2016), were reduced in the dorsolateral prefrontal
204 WM in treatment-naive MDD patients, as detected by proton magnetic resonance
205 spectroscopy (Wang et al.,2012). Notably, changes in oligodendroglia-related gene
206 expression differed in temporal and prefrontal cortical areas (Aston et al., 2005; Rajkowska
207 et al., 2015; Lutz et al., 2017), while no significant alteration of these genes could be
208 detected in most subcortical regions (Barley et al., 2009), indicating a region-specific
209 dysfunction possibly mirroring a susceptibility heterogeneity in subsets of oligodendroglia
210 (Crawford et al., 2016). Interestingly, MDD women and men showed opposite changes of
211 oligodendroglia-related genes (i.e. decreased in women, increased in men) in MDD-
212 relevant brain areas, such as the dorsolateral PFC, anterior cingulate cortex and amygdala
213 (Seney et al., 2018), suggesting a role for OL dysfunction in determining MDD sexual
214 dimorphisms.
215 Consistent with these findings, preclinical studies have shown prominent myelin and
216 oligodendroglia defects, that paralleled the emergence of depressive-like behaviors in

mice exposed to stress during the early/juvenile and adult life (Fig.3). Namely, neonatal maternal separation was associated with impaired PFC myelination (Yang et al., 2017). OLs with a simpler morphology and shorter branching, decreased expression of myelin genes and reduced myelin thickness were reported in the PFC of mice that experienced protracted social isolation during their juvenile or adult life (Makinodan et al., 2012; Liu et al., 2012). Notably, social re-integration was able to rescue such abnormalities when isolation occurred during adulthood (Liu et al., 2012), but not when it occurred early in life (Makinodan et al., 2012), suggesting the existence of a critical period for social experience-dependent OL maturation and myelination. Reduction of mature OL density, severe hypomyelination and selective downregulation of transcripts enriched in OL lineage cells were also found in the PFC of adult mice chronically exposed to other types of stressors (i.e. social defeat, forced swimming, restraint or unpredictable chronic stress; Banasr et al., 2007; Surget et al., 2008; Young et al., 2016; Liu et al., 2018). Mouse PFC OPCs also displayed a remarkable vulnerability to chronic stress in the adult life, showing atrophic processes (Young et al., 2016), reduced density and proliferation (Czeh et al., 2007; Banasr et al., 2007; Birey et al., 2015) and suppressed secretion of fibroblast growth factor 2 (FGF2; Birey et al., 2015). Notably, reduced OPC density could be detected only in the mouse cohort that responded to stress with depression-like behavioural alterations, while no alteration was found in stress-resilient subjects, suggesting that oligodendroglia defects can be implicated in inter-individual differences in stress vulnerability (Birey et al., 2015).

Proposed mechanisms underlying oligodendroglia defects in depression and stress-related disorders

Several models have been proposed to explain oligodendroglial cell loss/dysfunction in MDD or following stress. Since both OPCs and differentiating OLs express dopamine D3

243 receptors, the first candidate mechanism was the disruption of the dopaminergic
244 neurotransmission (Nestler and Carlezon, 2000). Yet, treatment with quinpirole, a selective
245 D2 and D3 receptor agonist, was shown to inhibit oligodendroglia maturation, whereas the
246 dopamine antagonist haloperidol had the opposite effect (Bongarzone et al., 1998). Thus,
247 it is unlikely that a diminished dopaminergic neurotransmission could be at the base of
248 oligodendroglia maturation defects.
249 Increased levels of circulating corticosterone due to the overactivation of HPA axis in
250 stress conditions could be potentially upstream of oligodendroglia loss/dysfunction. Both
251 OPCs and OLs express glucocorticoid receptors (Cheng and deVellis, 2000; Matsusue et
252 al., 2014), whose activation induces downstream intracellular pathways that eventually
253 affect their morphology and proliferation rates (Alonso, 2000; Wennstrom et al., 2006;
254 Miyata et al., 2011).
255 Pro-inflammatory cytokines and reactive oxygen species (ROS) released by activated
256 microglia, detected in MDD and after stress (Zhang et al., 2018), have been also proposed
257 to cause OL damage and atrophy, and to reduce OPC proliferation (di Penta et al., 2013:
258 Wennstrom et al., 2014; Domingues et al., 2016). Notably, OLs from MDD patients
259 showed reduced oxidative stress defences (i.e. expression of mRNAs coding for
260 superoxide dismutases (SOD) 1 and 2, catalase (CAT) and glutathione peroxidase1
261 (GPX1) (Szebeni et al., 2014), and increased DNA oxidation markers and DNA damage
262 repair enzymes (Szebeni et al., 2017), compared to those of control subjects. This
263 triggered the hypothesis that in MDD OLs may undergo an “accelerated aging”, also
264 corroborated by the observation of shorter telomeres in MDD OLs (Szebeni et al., 2014).
265 Whether such reduced ability to cope with oxidative stress is innate (i.e. cell-intrinsic and
266 determined by genetic factors), or emerges as a consequence of oligodendroglia exposure
267 to extrinsic factors (including altered levels of neurotransmitters, hormones or pro-
268 inflammatory cytokines/ROS) is still obscure.

Finally, it has been recently hypothesized that epigenetic factors (including histone/DNA modifications and microRNAs) exert a prominent role in determining oligodendroglia gene expression abnormalities in MDD and stress-related disorders (Lutz et al., 2017; Miguel-Hidalgo et al., 2017; Yang et al., 2017). Altered levels of histone deacetylases (HDACs) have been reported in peripheral white blood cells of MDD patients, suggesting a disturbed chromatin regulation leading to gene expression alterations (Hobara et al., 2010). Consistently, in rodents, early life adverse experience, such as neonatal maternal deprivation, was associated with changes in expression/activity of HDACs in specific brain regions (Yang et al., 2017; Reus et al., 2013). Of note, HDAC activity is essential for OL differentiation (Marin-Husstege et al. 2002; Ye et al. 2009). In line with the idea of a HDAC-dependent alteration of OL physiology, after social isolation, adult mouse oligodendroglia displayed increased histone acetylation and increased euchromatin, indicative of a less differentiated state (Liu et al., 2012). Further, a genome-wide screening of DNA methylation showed that early adversity (i.e. child abuse) abuse was associated with changes in DNA methylation of oligodendrocyte genes (Lutz et al., 2017)

Oligodendroglia response to antidepressants, lifestyle factors and other treatment options for MDD

In agreement with the idea of a prominent contribution of oligodendroglia defects in the emergence of depression-associated symptoms, several studies have reported that antidepressants counteracted MDD/stress associated oligodendroglia loss and rescued oligodendrogenesis and oligodendroglia-related gene expression defects. Namely, selective serotonin reuptake inhibitors (SSRIs) and serotonin/norepinephrine reuptake inhibitor (SNRI) have been reported to normalize WM volume in MDD patients (Zeng et al., 2012). Clinical studies also showed that the SSRI fluoxetine increased cerebral WM NAA content (Mostert et al., 2006). In rodents, treatment with the SSRI fluoxetine or

fluvoxamine promoted OL survival upon injury (Lee et al., 2015; Ghareghani et al., 2017), and rescued chronic stress-induced reduction of PFC OPC proliferation (Kodama et al.,2004; Czeh et al., 2007; Elsayed et al., 2012) and corticolimbic OL transcriptome changes (Surget et al., 2009; Sibille et al., 2009). Nevertheless, fluoxetine did not appear to restore WM/myelin integrity in a rat model of chronic stress (Gao et al., 2009), suggesting that its antidepressant effects may be, at least in part, mediated by OL/OPC – dependent, but myelin-independent mechanisms. In mice, the SNRI desvenlafaxine prevented stress-induced reduction of OL/OPC markers and alterations in cholesterol biosynthesis proteins, while alleviating depression-like phenotypes (Wang et al., 2014). Consistently, the SNRI venlafaxine reduced myelin/OL loss and alleviated depression-like behaviors in a rodent model of cuprizone-induced demyelination (Zhang et al., 2019; see also below). Further, since OPCs and OLs express NMDAR (Karadottir and Attwell, 2007), they are expected to be target for new rapid-acting agents such as ketamine (Duman et al., 2019). These findings suggest that the antidepressant effect of these drugs may be exerted via the restoration of myelin/oligodendroglia defects. This idea is corroborated by the observation of poor responses to antidepressant treatments in patients with severe WM alteration (Peng et al., 2013; Serafini et al., 2015).

Along this line, emerging evidence suggests that myelin and oligodendrocyte lineage cells mediate the effects of therapeutic alternatives for drug treatment-resistant depression, such as psychotherapy, electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS) and deep brain stimulation (DBS) (Minichino et al., 2012; Drobisz and Damborská, 2019). Early-stage psychotherapy was shown to restore frontal WM integrity in MDD patients (Wang et al., 2013). Other clinical studies reported that ECT reduced WM structural abnormalities in MDD patients, as assessed by increased WM fractional anisotropy in frontal brain regions (Nobuhara et al., 2004; Anderson et al., 2016). In addition, in rodents, ECT stimulated OPC proliferation in PFC, hippocampus and

amygdala of stressed and non-stressed subjects (Wennström et al., 2003, 2004, 2006; Madsen et al., 2005; Öngür et al., 2007). Moreover, low intensity rTMS administered as an intermittent theta burst stimulation increased newborn OL numbers, OL survival and myelination in the adult mouse cortex (Cullen et al. 2019), while DBS in Parkinson Disease patients was associated with increased proliferation of parenchymal progenitors (Vedami-Mai et al., 2014).

Finally, lifestyle factors found to have antidepressant effects, such as exercise and environmental enrichment (EE) (Blumenthal et al., 2007; SIGN, 2010; Grippo et al., 2014), reportedly increased OPC proliferation in depression relevant brain regions (Mandyam et al., 2007; Ehninger et al., 2011), and preserved OL density and myelin integrity in rodent models of depression (Xiao et al., 2018; Tang et al., 2019).

Taken together, these findings show that myelin and oligodendroglia respond to a variety of antidepressant treatment options, further suggesting their critical contribution to the etiology and treatment outcome of depression and stress-related disorders.

Can myelin/oligodendrocyte lineage cell alterations cause depression?

Disruption of myelin/OL/OPC multifaceted neurosupportive/neuromodulatory functions could be at the base, or at least largely contribute, to most CNS anatomical, functional and cellular/molecular defects reported MDD and stress-related disorder, including reduced/altered brain connectivity, decreased glutamatergic neurotransmission, increased risk for excitoxicity (Duman et al., 2019), altered organization of nodes of Ranvier and paranodes (Miyata et al., 2016), and decreased expression/misregulation of endogenous antidepressant factors, such as BDNF, GDNF, IGF1 and FGF2 (Castren and Kojima, 2016; Polyakova et al., 2015; Satomura et al., 2011; Turner et al., 2012; Evans et al., 2004; Duman and Monteggia 2006; Sharma et al., 2015).

The idea that loss of myelin and oligodendroglia dysfunctions can be causally involved in the pathogenesis of depressive disorders is corroborated by co-morbidity of demyelinating disorders and depression in humans and rodents (Arnett et al., 2008; Yang et al., 2017; Zhang et al., 2019). A more direct evidence of the primary role of oligodendroglia loss/abnormalities in the development of depression has been provided by the observation that the genetic ablation of adult mouse OPCs resulted in depressive-like behaviors , that can be rescued by OPC repopulation (Birey et al., 2015). Emergence of such depressive phenotype has been attributed to the reduction of OPC-released FGF2, since they could be recapitulated by the selective knock-down of FGF2 in OPCs (Birey et al., 2015). Accordingly, mice in which erbB signaling, an important player in OL maturation, is selectively blocked in oligodendroglia, showed reduced myelination, alterated dopaminergic system and depression-relevant behaviors (Roy et al., 2007). Thus, at least in animal models, selective OPC/OL dysfunctions were shown to be upstream to the emergence of depressive-like behaviors. This suggests that oligodendroglia-directed therapeutic approaches may be effective (co-)treatments in depression and stress-related disorders. In line with this view, clemastine, a pro-remyelinating antimuscarinic drug, remarkably rescued depression-relevant behaviors in socially isolated mice (Liu et al., 2016).

Concluding Remarks and Open Issues

Depressive disorders are complex, multifactorial disorders that have been traditionally attributed exclusively to neuronal abnormalities. Recent studies have increased our understanding of neurosupportive/neuromodulatory functions exerted by myelin and oligodendrocyte lineage cells and provided evidence of their contribution to the pathogenesis and treatment outcome of MDD and stress-related disorders. Compromised WM integrity, microstructural myelin alterations, OL/OPC dysfunction and loss, and altered

oligodendroglia-related gene expression have been consistently reported, whereas SSRIs/SNRIs and other treatment options/lifestyle factors have been proposed to operate via the restoration of myelin/oligodendroglia functions. Remarkably, cell type –specific genetic manipulations have shown that selective OPC/OL dysfunctions can be upstream to the emergence of depressive-like behaviors in rodents. Accordingly, oligodendroglia-directed therapeutic approaches were effective in reversing depressive-like behaviors in an animal model of chronic stress. Thus, myelin/oligodendrocyte lineage cells appear now as novel promising targets for the treatment for depressive disorders. Yet, neuropathological postmortem studies reporting oligodendroglia phenotypes (i.e. myelin microstructural abnormalities, altered OL/OPC number, distribution or morphology) in human patients are still relatively few and mostly focused on myelin and mature OLs. OPCs were very rarely investigated (see also Table1). The characterization of these aspects is desirable, also in view of obtaining a better understanding of how myelin/oligodendrocyte lineage cell states correlate with illness severity and duration as well as with different treatment options and outcomes.

Interestingly, oligodendroglia and myelin vulnerability is also shared by other serious mental illnesses, such as schizophrenia (SZ) and BD. Such commonality have been attributed to the late and protracted myelination of human frontal and temporal lobes (Fig. 1), and to its vulnerability to inflammation and other insults (Haroutunian et al., 2014). Although the pattern of WM abnormalities and the underlying mechanisms are likely different in the MDD vs. SZ and BD, such shared pathological aspect may suggest a common responsiveness to drugs. This may open underexplored ways to treat MDD and stress-related disorders. In line with this idea, the mood stabilizers lithium and valproate, have promyelinating effects and were effective in treating depressed patients not responding to antidepressants (Bschor, 2014; Vigo & Baldessarini, 2009). However, the envision of more defined therapeutic strategies for MDD and stress-related disorders

requires further investigative efforts not only to gain a deeper knowledge of the timing/persistence of myelin/oligodendroglia dysfunctions, but also to unveil the underlying specific molecular substrates.

Figure legends

Figure 1. Progression of myelination in the human brain

Timing of myelination events in the main WM tracts and intracortical fibers, based on (Volpe et al., 2018). Note that myelination of intracortical fibers and associative areas is late and protracted up to adult stages, while adaptive myelination continues throughout life. Myelination of the temporal and frontal lobe follows that of caudal regions and progress from the central sulcus to the poles. ON, optic nerve; CC, corpus callosum.

Figure 2. Properties and functions of oligodendrocyte lineage cells

(A,B) Microphotographs of OPCs in the adult mouse cortex. OPCs are identified based on NG2 positivity (A) or YFP-positivity in NG2CreER^{TM};R26^{YFP} mice 1 week after tamoxifen injection (B). (C,D) Microphotographs of mature OLs in the adult mouse corpus callosum. Mature OLs are identified based on GSTπ positivity (C) or YFP-positivity in NG2CreER^{TM};R26^{YFP} mice 4 weeks after tamoxifen injection (D). Note OL processes aligned to axons in (D). DAPI counterstains cell nuclei. Scale bars: 20µm. AP, action potential; ECM, extracellular matrix; OPC, oligodendrocyte precursor cell; OL, oligodendrocyte.

Figure 3. Schematic representation of myelin and oligodendroglia alterations reported in MDD patients and animal models of depression.

Orange boxes (above) include the proposed underlying mechanisms. Green boxes (below) include antidepressant drugs and interventions having positive effects on myelin and OL/OPC alterations. DBS, deep brain stimulation; ECT, electroconvulsive therapy ; EE, enriched environment; FGF2, fibroblast growth factors, MDD, Major Depressive Disorder; OPC, oligodendrocyte precursor cell; OL, oligodendrocyte; ROS, reactive oxygen species;

rTMS, repetitive transcranial magnetic stimulation; SNRIs, serotonin/norepinephrine reuptake inhibitor; SSRIs, selective serotonin reuptake inhibitors.

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Competing Interests

The author declares no conflict of interest.

Data availability statement

Supporting data are entirely available within the article. Further information will be provided upon request.

Abbreviation list

AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AP, action potential; BD, bipolar disorder; BDNF, brain-derived neurotrophic factor; CAT, catalase; DBS, deep brain stimulation; DSM-5, Diagnostic and Statistical Manual of Mental Disorders-5; ECM, extracellular matrix; ECT, electroconvulsive therapy ; EE, enriched environment; FGF2, fibroblast growth factors; GABA, γ-aminobutyric acid; GDNF, glial-cell line derived neurotrophic factor; GPX1, glutathione peroxidase1; HDAC, histon deacetylase; HPA, hypothalamic-pituitary adrenocortical; IGF-1, insulin-like growth factor-1; K^+, potassium; LTP, long-term potentiation; MDD, Major Depressive Disorder; NAA, N-acetylaspartate; Na_V, voltage-sensitive sodium channels; NG2, neuron-glia antigen 2; NMDA, N-methyl-D-aspartate; OPC, oligodendrocyte precursor cell; OL, oligodendrocyte; ROS, reactive oxygen species; rTMS, repetitive transcranial magnetic stimulation; SNRIs,

455 serotonin/norepinephrine reuptake inhibitor; SOD superoxide dismutase; SSRIs, selective

456 serotonin reuptake inhibitors; SZ, schizophrenia; WM, white matter.

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1 **Table 1. WM/myelin and oligodendroglia abnormalities in MDD and stress-related disorders**

Type of disorder	WM/myelin state	OL number and morphology	OPC number and morphology	Oligodendroglia-related gene expression
MDD	**<u>In vivo neuroimaging:</u>** **DTI** Reduction of WM FA, indicative of WM hypoplasia and microstructural abnormalities, in the CC, DL-PFC, ACC, right parietal WM, hippocampus, thalamus and specific thalamic tracts (Alexopoulos et al., 2002; Taylor et al., 2004; Nobuhara et a., 2004; Bae et al., 2006; Nobuhara et al., 2006; Ma et al., 2007; Taylor et al., 2008; Cardoso de Almeida and Phillips, 2013; Osoba et al.,2013; de Diego-Adeliño et al.,2014; Yamada et al., 2015; Miyata et al., 2016; Smagula and Aizenstein, 2016; Jiang et al., 2017; Matsuoka et al., 2017; Jiang et al., 2018; Wu et al., 2018) **MRI:** Increased WMH, indicative of WM lesion, in the periventricular and deep WM (Pompili et al.,2008; Grangeon et al., 2010; Tully et al., 2017). **qMRI:** Lower R1, indicative of a reduced myelin content at the whole-brain level, LPFC and NAcc (Sacchet and Gotlib 2017) **MTI:** Decreased MTR, indicative of reduced myelin integrity in left hemisphere frontostriatal, limbic areas, occipital WM, in the genu and splenium of the CC (Kumar et al., 2004; Spilt et al., 2006; Gunning-Dixon et al., 2008; Jia et al., 2017). **<u>Postmortem histopathological analyses:</u>** Reduction of myelin Kluver–Barrera staining in the deep WM in the DLPFC (Regenold et al., 2007)	Reduced glial cell number, numerically likely to be OLs, in subgenual PFC BA24 of familial MDD patients (Ongür et al., 1998) Reduced OL density in layer VI of the DLPFC BA9 (Uranova et al., 2004). Reduced OL density in the amygdala (Hamidi et al., 2004). Reduced density of perineuronal OLs in layer III of the DLPFC BA9 (Vostrikov et al., 2007) Reduced oligodendrocyte lineage cells (i.e. Olig2+) density in the aPFC BA10 (Hayashi et al., 2011). Decreased OL soma size in the VPFC WM (Rajkowska et al., 2015).	Reduced OPC density in the frontal cortex (Birey et al., 2015)	Reduction of MBP protein in the aPFC of depressed individuals who died by suicide (Honer et al., 1999) Decreased expression of genes encoding for transcription factors (i.e. OLIG2, SOX10) and molecules critically involved in OL differentiation (i.e. ERBB3) and myelin synthesis (ASPA, UGT8, ENPP2, EDG2, KLK6), structural myelin components (i.e. CNP, MAG, MAL, MOG, MOBP, PMP22, PLLP, PLP1) in the temporal cortex (Aston et al., 2005). Reduction of NOGO-B mRNA in the frontal cortex (Novak et al., 2006). Reduced expression of CNP mRNA and protein, and of MBP, PLLP, MOBP, GPR37, ENPP2 mRNAs in the amygdala (Sibille et al., 2009). Reduction of QKI protein in the cortex, hippocampus and amygdala (Klempan et al., 2009). Reduction of MOG, OMG and PLP1 mRNAs in DLPFC BA9 (Kim and Webster 2010). Reduced expression of PLP1 mRNA, increased expression of CNP, MOG and OLIG1 mRNAs, decreased expression of CNPase protein in the WM of the VPFC (Rajkowska et al., 2015). Decreased expression of genes enriched in oligodendrocyte lineage cells in the DLPFC, ACC, and basolateral amygdala of MDD women, increased expression in MDD men (Seney et al., 2018). Reduction of MBP protein in the VMPFC WM (Tanti et al., 2018).

	Increased myelin thickness along axons in the genu of the CC (high resolution light microscopy; Williams et al., 2015) Decreased intracortical myelin in the DLPFC (Luxol Fast Blue; Lake et al., 2017) Decreased myelin in the splenium of CC (high resolution light microscopy; Williams et al., 2019)			
Child abuse/ trauma/ neglect	**<u>In vivo neuroimaging:</u>** **DTI:** Reduced FA values, indicative of WM structural abnormalities, in the genu and body of the CC, fornix crus, cingulum, corona radiata and external capsule of adults (Lu et al., 2013; Bick et al., 2015) **Postmortem histopathological analyses:** Reduction in the thickness of myelin sheaths around small-diameter axons in the ACC of adult subjects (Lutz et al., 2017)	Reduced OL density in the ACC of adult subjects (Lutz et al., 2017)	No change in OPC density in the ACC of adult subjects (Lutz et al., 2017)	Global impairment of the myelin-related transcriptional program in the ACC of adult subjects (Lutz et al., 2017)

Abbreviations: ACC, anterior cingulate cortex; aPFC, anterior prefrontal cortex; ASPA, Aspartoacylase; BA9, Brodmann area 9; BA10, Brodmann area 10; CC, corpus callosum; CNP, 2',3'-Cyclic Nucleotide 3' Phosphodiesterase; DLPFC, dorsolateral prefrontal cortex; DTI, Diffusion Tensor Imaging; EDG2, Endothelial Differentiation, Lysophosphatidic Acid G-Protein-Coupled Receptor, 2; ENPP2, Ectonucleotide Pyrophosphatase/Phosphodiesterase 2; ERBB3, Erb-B2 Receptor Tyrosine Kinase 3; FA, fractional anisotropy; GPR37, G Protein-Coupled Receptor 37; KLK6, Kallikrein Related Peptidase 6; LPFC, lateral prefrontal cortex; MAG, Myelin Associated Glycoprotein; MAL, Mal, T Cell Differentiation Protein; MOBP, Myelin Associated Oligodendrocyte Basic Protein; MOG, myelin oligodendrocyte glycoprotein; MRI, Magnetic Resonance Imaging; MTR, magnetization transfer ratio; MTI, Magnetization Transfer Imaging; NAcc, nucleus accumbens; NOGO, Reticulon 4; OLIG1, Oligodendrocyte Transcription Factor 1; OLIG2, Oligodendrocyte Transcription Factor 2; OMG, oligodendrocyte myelin glycoprotein; PLLP, Plasmolipin; PLP1, proteolipid protein 1; PMP22, Peripheral Myelin Protein 22; QKI, Quaking; qMRI, quantitative magnetic resonance imaging; SOX10, SRY-related HMG-box 10; UGT8, UDP Glycosyltransferase 8; VMPFC, ventromedial prefrontal cortex; VPFC, ventral prefrontal cortex; WM, white matter; WMH, White Matter Hyperintensities.

In-utero

1st year

Infancy

Adulthood

Adolescence

Medial lemniscus

Cerebellar peduncles

ON

Striatum

Pyramidal tracts

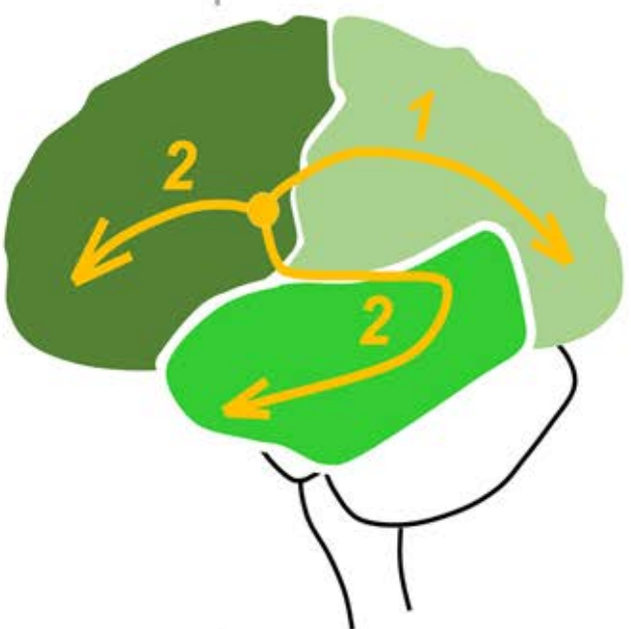
Fornix

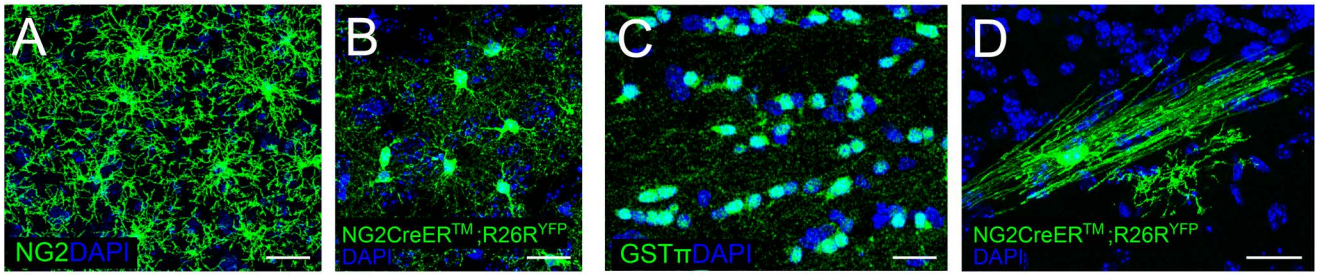
CC, cereb. commissures

Cingulum

Intracortical fibers, Associative areas

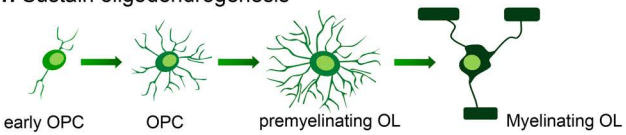
Adaptive myelination



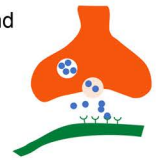


Properties & functions of OPCs

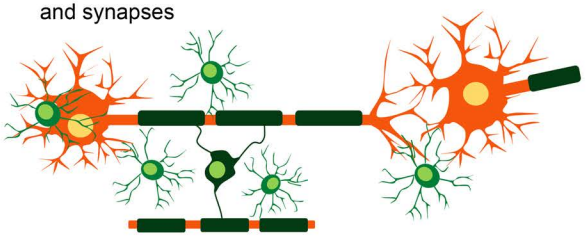
1. Sustain oligodendrogenesis



2. Receive neuronal synapses and respond to neurotransmitters

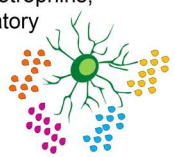


3. Contact neuronal somata, dendrites, nodes of Ranvier and synapses



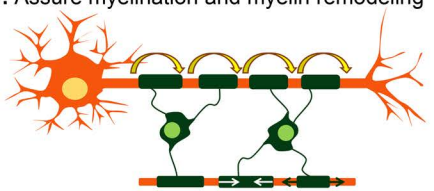
4. Regulate glutamatergic synapse activity

5. Produce and release growth factors, neurotrophins, morphogens, ECM components, inflammatory cytokines and immunomodulatory factors



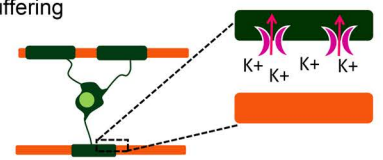
Properties & functions of mature OLS

1. Assure myelination and myelin remodeling

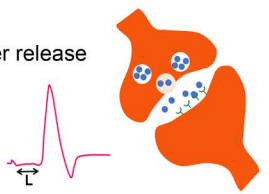


2. Promote the maturation of axons and nodes of Ranvier

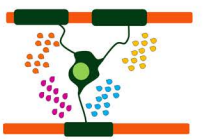
3. Regulate neuronal excitability through K^+ buffering

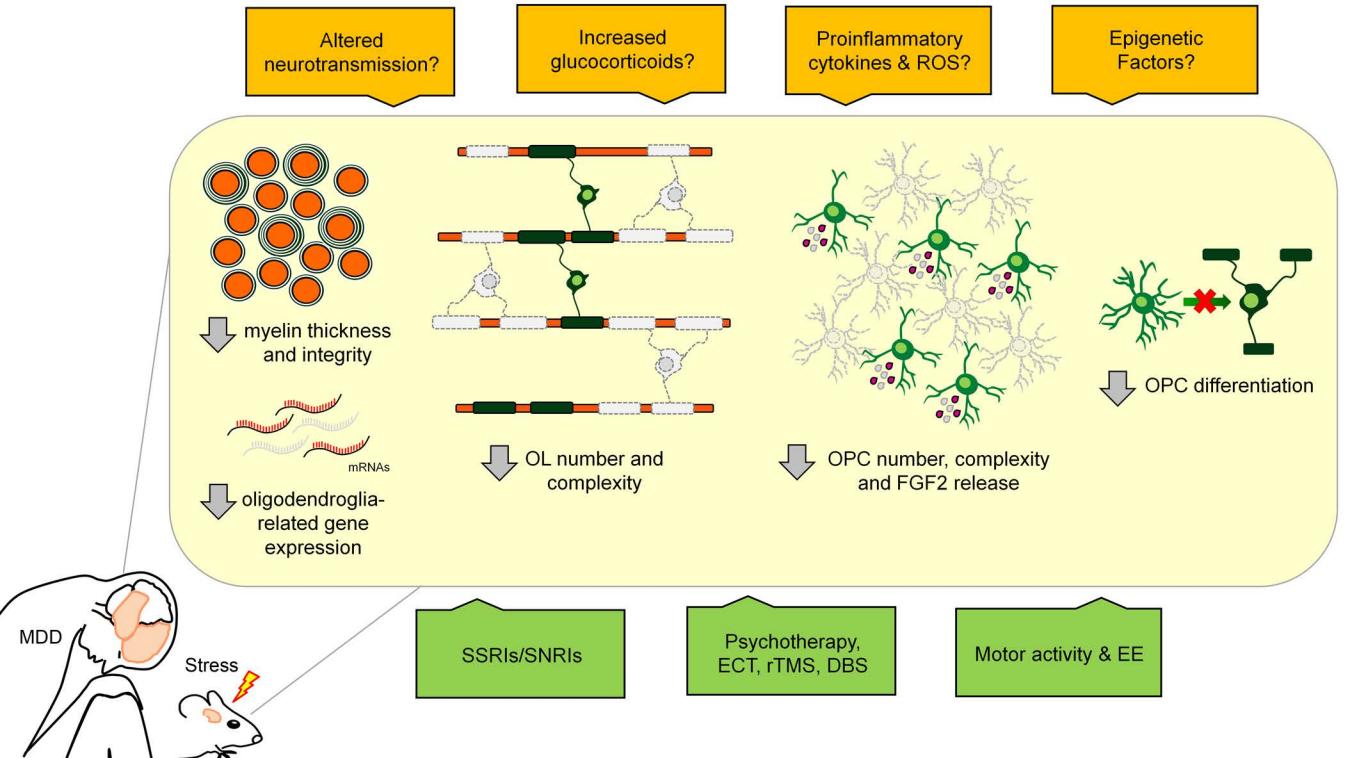


4. Influence neurotransmitter release and reduce AP latency



5. Metabolic and trophic support (lactate, growth factors and neurotrophic factors)




Altered neurotransmission?
Increased glucocorticoids?
Proinflammatory cytokines & ROS?
Epigenetic Factors?
myelin thickness and integrity
mRNAs
oligodendroglia-related gene expression
OL number and complexity
OPC number, complexity and FGF2 release
OPC differentiation
MDD
Stress
SSRIs/SNRIs
Psychotherapy, ECT, rTMS, DBS
Motor activity & EE