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1 **Myelin and oligodendrocyte lineage cell dysfunctions: new players in the etiology**
2 **and treatment of depression and stress-related disorders**

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18

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27 **Abstract**

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

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

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

63 in cortical and limbic regions (Duman et al., 2019 and references therein) have been
64 proposed as the neurobiological substrates of the anatomical and functional alterations
65 observed in the brain of depressed patients and animal models of depression (Drevets
66 2000). Such cellular/molecular alterations are thought to emerge as a consequence of the
67 disruption of neurodevelopmental events and/or of the activation of regressive phenomena
68 (Ansorge et al., 2007; Bennett, 2011). In this context, stress-dependent activation of the
69 hypothalamic-pituitary adrenocortical (HPA) system and sustained elevated levels of
70 plasma corticosterone appear to play an important role in the emergence of
71 neurotransmission alterations and in the onset of depressive symptoms (Karten et al.,
72 1999; McEwen and Morrison, 2013; Duman et al., 2019). Further, detection of increased
73 inflammatory markers and activation of peripheral and resident (i.e. microglia) immune
74 system cells in depressed individuals triggered the hypothesis of a neuroimmune etiology
75 in at least a subgroup of patients (Mechawar and Savitz, 2016). Importantly, this lead to
76 the recognition of the contribution of non-neuronal central nervous system (CNS) cells in
77 the pathogenesis of depressive disorders (Sild et al., 2017). In this frame, increasing
78 knowledge on glial cell functions together with evidence of their alterations in depression
79 and stress-related disorders suggest now a conceptual shift toward a glial-inclusive
80 viewpoint. Clinical and preclinical studies show that, along with microglia and astrocytes,
81 oligodendrocyte lineage cells and myelin are remarkably affected. These alterations may
82 be interpreted as the mere consequence of the disruption of oligodendroglia cross-talk with
83 neurons and other CNS/peripheral cells. Nevertheless, accumulating evidence strongly
84 suggests that they can be causally upstream of neuronal dysfunction in the pathogenesis
85 of depressive disorders and participate in treatment outcome.

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

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

96

97 **Neurosupportive and neuromodulatory functions of myelin and oligodendrocyte** 98 **lineage cells**

99 *Myelin and mature oligodendrocytes*

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

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

142 In humans, the acquisition of OL mature functional features – including myelination and
143 the above mentioned neurosupportive/neuromodulatory functions – is a multi-step process
144 that peaks during childhood and, in the limbic system and prefrontal cortex (PFC),
145 continues during adulthood (Nickel and Gu, 2018; Fig.1). Both a cell-intrinsic
146 developmental program and environmental factors participate in the regulation of the
147 sequence of events that transform oligodendrocyte precursor cells (OPCs) into mature and
148 myelinating OLs (Tomassy et al., 2015). Being a relatively late and mostly postnatal
149 ontogenic process (Fig.1), OL maturation and myelination are particularly prone to be
150 affected by the early individual's experience, including sensory experience, social
151 interaction, and different types of stress (Toritsuka et al., 2015; Vargas et al., 2014; Mount
152 and Monje 2017). At the cellular/molecular level, the effect of such external factors are
153 mediated by changes in the oligodendroglia crosstalk with neurons, microglia, and
154 astrocytes (Tomassy et al., 2015; Clemente et al., 2013). Adaptive myelination (i.e.
155 experience-dependent de-novo myelin deposition and remodeling of already formed
156 myelin internodes) continues also during the adult life (Hughes et al., 2018; Hill et al.,
157 2018; Mount and Monje 2017) and is thought to influence neurological functions.

158

159 *Oligodendrocyte precursor cells*

160 After the completion of myelination, a large reservoir of OPCs – also named neuron-glia
161 antigen 2 (NG2)-expressing glia - persist in the adult CNS parenchyma (Boda and Buffo
162 2010), where they sustain oligodendrogenesis in health (Boda et al., 2015; Hill et al., 2014;
163 Xiao et al., 2016) and disease (Assinck et al., 2017; Baxi et al., 2017). Of note, OPCs
164 establish intimate physical and functional interactions with neurons, that allow them to
165 operate as sensors of the neuronal activity. Namely, OPCs establish physical contacts with

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

188 Taken together these findings show that myelin and oligodendrocyte lineage cells –
189 including both mature OLs and OPCs - exert an active role in regulating neuronal
190 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

217 mice exposed to stress during the early/juvenile and adult life (Fig.3). Namely, neonatal
218 maternal separation was associated with impaired PFC myelination (Yang et al., 2017).
219 OLs with a simpler morphology and shorter branching, decreased expression of myelin
220 genes and reduced myelin thickness were reported in the PFC of mice that experienced
221 protracted social isolation during their juvenile or adult life (Makinodan et al., 2012; Liu et
222 al., 2012). Notably, social re-integration was able to rescue such abnormalities when
223 isolation occurred during adulthood (Liu et al., 2012), but not when it occurred early in life
224 (Makinodan et al., 2012), suggesting the existence of a critical period for social
225 experience-dependent OL maturation and myelination. Reduction of mature OL density,
226 severe hypomyelination and selective downregulation of transcripts enriched in OL lineage
227 cells were also found in the PFC of adult mice chronically exposed to other types of
228 stressors (i.e. social defeat, forced swimming, restraint or unpredictable chronic stress;
229 Banasr et al., 2007; Surget et al., 2008; Young et al., 2016; Liu et al., 2018). Mouse PFC
230 OPCs also displayed a remarkable vulnerability to chronic stress in the adult life, showing
231 atrophic processes (Young et al., 2016), reduced density and proliferation (Czeh et al.,
232 2007; Banasr et al., 2007; Birey et al., 2015) and suppressed secretion of fibroblast growth
233 factor 2 (FGF2; Birey et al., 2015). Notably, reduced OPC density could be detected only
234 in the mouse cohort that responded to stress with depression-like behavioural alterations,
235 while no alteration was found in stress-resilient subjects, suggesting that oligodendroglia
236 defects can be implicated in inter-individual differences in stress vulnerability (Birey et al.,
237 2015).

238

239 **Proposed mechanisms underlying oligodendroglia defects in depression and** 240 **stress-related disorders**

241 Several models have been proposed to explain oligodendroglial cell loss/dysfunction in
242 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.

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

284

285 **Oligodendroglia response to antidepressants, lifestyle factors and other treatment** 286 **options for MDD**

287 In agreement with the idea of a prominent contribution of oligodendroglia defects in the
288 emergence of depression-associated symptoms, several studies have reported that
289 antidepressants counteracted MDD/stress associated oligodendroglia loss and rescued
290 oligodendrogenesis and oligodendroglia-related gene expression defects. Namely,
291 selective serotonin reuptake inhibitors (SSRIs) and serotonin/norepinephrine reuptake
292 inhibitor (SNRI) have been reported to normalize WM volume in MDD patients (Zeng et al.,
293 2012). Clinical studies also showed that the SSRI fluoxetine increased cerebral WM NAA
294 content (Mostert et al., 2006). In rodents, treatment with the SSRI fluoxetine or

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

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

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

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

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

335

336 **Can myelin/oligodendrocyte lineage cell alterations cause depression?**

337 Disruption of myelin/OL/OPC multifaceted neurosupportive/neuromodulatory functions
338 could be at the base, or at least largely contribute, to most CNS anatomical, functional and
339 cellular/molecular defects reported MDD and stress-related disorder, including
340 reduced/altered brain connectivity, decreased glutamatergic neurotransmission, increased
341 risk for excitotoxicity (Duman et al., 2019), altered organization of nodes of Ranvier and
342 paranodes (Miyata et al., 2016), and decreased expression/misregulation of endogenous
343 antidepressant factors, such as BDNF, GDNF, IGF1 and FGF2 (Castren and Kojima,
344 2016; Polyakova et al., 2015; Satomura et al., 2011; Turner et al., 2012; Evans et al.,
345 2004; Duman and Monteggia 2006; Sharma et al., 2015).

346 The idea that loss of myelin and oligodendroglia dysfunctions can be causally involved in
347 the pathogenesis of depressive disorders is corroborated by co-morbidity of demyelinating
348 disorders and depression in humans and rodents (Arnett et al., 2008; Yang et al., 2017;
349 Zhang et al., 2019). A more direct evidence of the primary role of oligodendroglia
350 loss/abnormalities in the development of depression has been provided by the observation
351 that the genetic ablation of adult mouse OPCs resulted in depressive-like behaviors , that
352 can be rescued by OPC repopulation (Birey et al., 2015). Emergence of such depressive
353 phenotype has been attributed to the reduction of OPC-released FGF2, since they could
354 be recapitulated by the selective knock-down of FGF2 in OPCs (Birey et al., 2015).
355 Accordingly, mice in which erbB signaling, an important player in OL maturation, is
356 selectively blocked in oligodendroglia, showed reduced myelination, altered
357 dopaminergic system and depression-relevant behaviors (Roy et al., 2007). Thus, at least
358 in animal models, selective OPC/OL dysfunctions were shown to be upstream to the
359 emergence of depressive-like behaviors. This suggests that oligodendroglia-directed
360 therapeutic approaches may be effective (co-)treatments in depression and stress-related
361 disorders. In line with this view, clemastine, a pro-remyelinating antimuscarinic drug,
362 remarkably rescued depression-relevant behaviors in socially isolated mice (Liu et al.,
363 2016).

364

365 **Concluding Remarks and Open Issues**

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

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

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

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

401 **Figure legends**

402

403 **Figure 1. Progression of myelination in the human brain**

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

409

410 **Figure 2. Properties and functions of oligodendrocyte lineage cells**

411 (A,B) Microphotographs of OPCs in the adult mouse cortex. OPCs are identified based on
412 NG2 positivity (A) or YFP-positivity in NG2CreERTM;R26^{YFP} mice 1 week after tamoxifen
413 injection (B). (C,D) Microphotographs of mature OLs in the adult mouse corpus callosum.
414 Mature OLs are identified based on GST π positivity (C) or YFP-positivity in
415 NG2CreERTM;R26^{YFP} mice 4 weeks after tamoxifen injection (D). Note OL processes
416 aligned to axons in (D). DAPI counterstains cell nuclei. Scale bars: 20 μ m. AP, action
417 potential; ECM, extracellular matrix; OPC, oligodendrocyte precursor cell; OL,
418 oligodendrocyte.

419

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

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

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

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435

436 **Competing Interests**

437 The author declares no conflict of interest.

438

439 **Data availability statement**

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

442

443 **Abbreviation list**

444 AMPA, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AP, action potential; BD,
445 bipolar disorder; BDNF, brain-derived neurotrophic factor; CAT, catalase; DBS, deep brain
446 stimulation; DSM-5, Diagnostic and Statistical Manual of Mental Disorders-5; ECM,
447 extracellular matrix; ECT, electroconvulsive therapy ; EE, enriched environment; FGF2,
448 fibroblast growth factors; GABA, γ -aminobutyric acid; GDNF, glial-cell line derived
449 neurotrophic factor; GPX1, glutathione peroxidase1; HDAC, histon deacetylase; HPA,
450 hypothalamic-pituitary adrenocortical; IGF-1, insulin-like growth factor-1; K⁺, potassium;
451 LTP, long-term potentiation; MDD, Major Depressive Disorder; NAA, N-acetylaspartate;
452 Nav, voltage-sensitive sodium channels; NG2, neuron-glia antigen 2; NMDA, N-methyl-D-
453 aspartate; OPC, oligodendrocyte precursor cell; OL, oligodendrocyte; ROS, reactive
454 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	<p><u>In vivo neuroimaging:</u></p> <p>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 al., 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-Adelino 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)</p> <p>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).</p> <p>qMRI: Lower R1, indicative of a reduced myelin content at the whole-brain level, LPFC and NAcc (Sacchet and Gotlib 2017)</p> <p>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).</p> <p><u>Postmortem histopathological analyses:</u></p> <p>Reduction of myelin Kluver–Barrera staining in the deep WM in the DLPFC (Regenold et al., 2007)</p>	<p>Reduced glial cell number, numerically likely to be OLs, in subgenual PFC BA24 of familial MDD patients (Ongür et al., 1998)</p> <p>Reduced OL density in layer VI of the DLPFC BA9 (Uranova et al., 2004).</p> <p>Reduced OL density in the amygdala (Hamidi et al., 2004).</p> <p>Reduced density of perineuronal OLs in layer III of the DLPFC BA9 (Vostrikov et al., 2007)</p> <p>Reduced oligodendrocyte lineage cells (i.e. Olig2+) density in the aPFC BA10 (Hayashi et al., 2011).</p> <p>Decreased OL soma size in the VPFC WM (Rajkowska et al., 2015).</p>	<p>Reduced OPC density in the frontal cortex (Birey et al., 2015)</p>	<p>Reduction of MBP protein in the aPFC of depressed individuals who died by suicide (Honer et al., 1999)</p> <p>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).</p> <p>Reduction of NOGO-B mRNA in the frontal cortex (Novak et al., 2006).</p> <p>Reduced expression of CNP mRNA and protein, and of MBP, PLLP, MOBP, GPR37, ENPP2 mRNAs in the amygdala (Sibille et al., 2009).</p> <p>Reduction of QKI protein in the cortex, hippocampus and amygdala (Klempan et al., 2009).</p> <p>Reduction of MOG, OMG and PLP1 mRNAs in DLPFC BA9 (Kim and Webster 2010).</p> <p>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).</p> <p>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).</p> <p>Reduction of MBP protein in the VMPFC WM (Tanti et al., 2018).</p>

	<p>Increased myelin thickness along axons in the genu of the CC (high resolution light microscopy; Williams et al., 2015)</p> <p>Decreased intracortical myelin in the DLPFC (Luxol Fast Blue; Lake et al., 2017)</p> <p>Decreased myelin in the splenium of CC (high resolution light microscopy; Williams et al., 2019)</p>			
<p>Child abuse/trauma/neglect</p>	<p><u>In vivo neuroimaging:</u></p> <p>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)</p> <p>Postmortem histopathological analyses: Reduction in the thickness of myelin sheaths around small-diameter axons in the ACC of adult subjects (Lutz et al., 2017)</p>	<p>Reduced OL density in the ACC of adult subjects (Lutz et al., 2017)</p>	<p>No change in OPC density in the ACC of adult subjects (Lutz et al., 2017)</p>	<p>Global impairment of the myelin-related transcriptional program in the ACC of adult subjects (Lutz et al., 2017)</p>

2

3 **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.

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In-utero



1st year

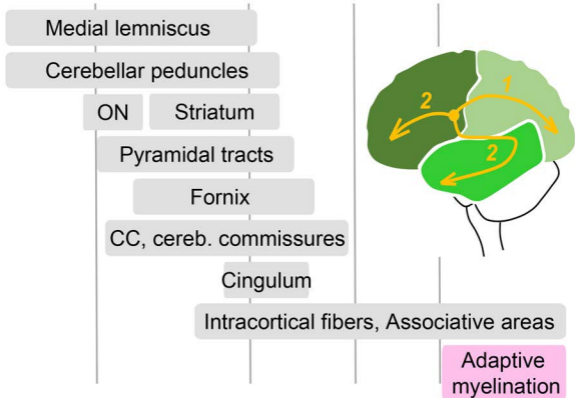


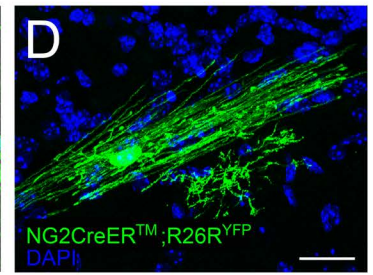
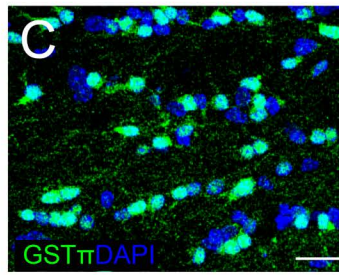
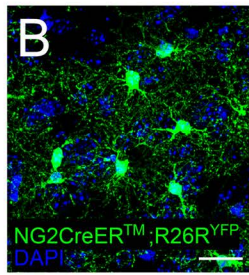
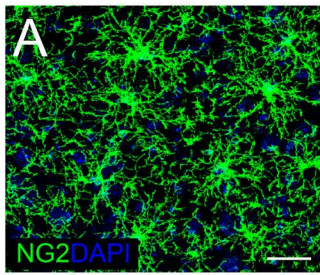
Infancy



Adulthood

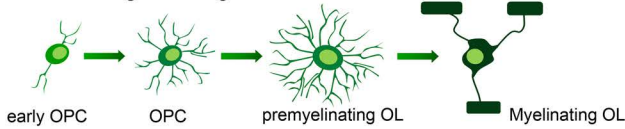
Adolescence



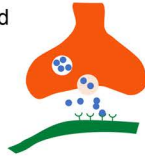


Properties & functions of OPCs

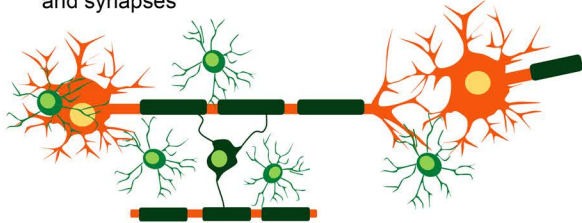
1. Sustain oligodendrogenesis



2. Receive neuronal synapses and respond to neurotransmitters



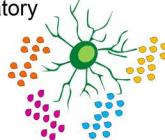
3. Contact neuronal somata, dendrites, nodes of Ranvier and synapses



4. Regulate glutamatergic synapse activity

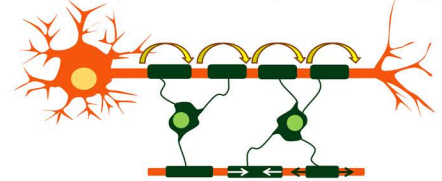


5. Produce and release growth factors, neurotrophins, morphogens, ECM components, inflammatory cytokines and immunomodulatory factors



Properties & functions of mature OLS

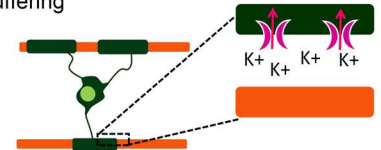
1. Assure myelination and myelin remodeling



2. Promote the maturation of axons and nodes of Ranvier



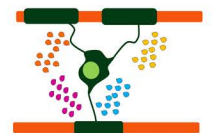
3. Regulate neuronal excitability through K⁺ buffering



4. Influence neurotransmitter release and reduce AP latency



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

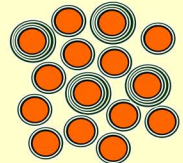


Altered neurotransmission?

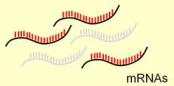
Increased glucocorticoids?

Proinflammatory cytokines & ROS?

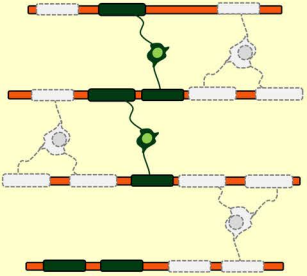
Epigenetic Factors?



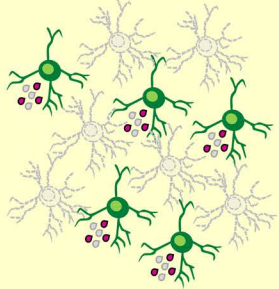
↓ myelin thickness and integrity



↓ oligodendroglia-related gene expression



↓ OL number and complexity



↓ OPC number, complexity and FGF2 release



↓ OPC differentiation



SSRIs/SNRIs

Psychotherapy, ECT, rTMS, DBS

Motor activity & EE