

Oligodendrocyte lineage cells dysfunction in depression: early life stress, adolescent vulnerability and the emerging role of lipid metabolism

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Chenyu Gao, Mengyu Liu, Jude Uzoechina & Zhijun Zhang

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1 **Oligodendrocyte lineage cells dysfunction in depression: early life
2 stress, adolescent vulnerability and the emerging role of lipid
3 metabolism**

4 Chenyu Gao, M.M.^{1,2}, Mengyu Liu, M.Sc.¹, Jude Uzoechina, B.Sc.^{2,3,4}, Zhijun Zhang,
5 M.D., Ph.D.^{1,2,3*}

6

7 1 Department of Neurology in Affiliated Zhongda Hospital and Jiangsu Provincial
8 Medical Key Discipline, School of Medicine, Institute of Neuropsychiatry, Key
9 Laboratory of Developmental Genes and Human Disease, Southeast University,
10 Nanjing, China

11 2 Shenzhen Key Laboratory of Precision Diagnosis and Treatment of Depression,
12 Department of Mental Health and Public Health, Faculty of Life and Health Sciences
13 of Shenzhen University of Advanced Technology, Shenzhen, China

14 3 The Brain Cognition and Brain Disease institute, Shenzhen Institutes of Advanced
15 Technology, Chinese Academy of Sciences, Shenzhen, China

16 4 University of Chinese Academy of Sciences, Beijing, China

17

18 *Corresponding author

19 Zhijun Zhang

20 Department of Neurology in Affiliated Zhongda Hospital and Jiangsu Provincial
21 Medical Key Discipline, School of Medicine, Institute of Neuropsychiatry, Key
22 Laboratory of Developmental Genes and Human Disease, Southeast University, 87
23 Dingjiaqiao Road, Nanjing 210009, China

24 E-mail:janemengzhang@vip.163.com

25 **Abstract**

26 Depression, as a serious global public health issue, is exhibiting an increasing incidence
27 among younger populations, particularly adolescents, who face unique diagnostic
28 challenges and poorer prognoses. Despite extensive studies on monoaminergic
29 dysfunction, neuroinflammation, and synaptic deficits, its pathophysiological
30 mechanisms remain incompletely understood, particularly in relation to developmental
31 stage-specific vulnerabilities. Oligodendrocyte (OL) lineage cells have recently
32 emerged as potential contributors to depression pathology, not only through their
33 myelinating roles but also via non-myelinating functions, such as metabolic support,
34 neuroimmune interaction, and circuit modulation. Early life represents a critical
35 development window characterized by rapid proliferation, differentiation, and lipid
36 synthesis of oligodendrocyte precursor cells, during which these cells are highly
37 susceptible to environmental stressors. Such developmental susceptibility may underlie
38 the long-lasting impact of early life stress (ELS) contribute to depression risk across
39 the lifespan. This review summarizes recent advances in understanding the myelinating
40 and non-myelinating functions of OL lineage cells related to depression pathology, with
41 particular emphasis on their developmental vulnerability to ELS and potential
42 contribution of lipid metabolic dysregulation. We further review emerging
43 pharmacological and non-pharmacological strategies targeting OL lineage cells as
44 potential therapeutic methods.

45 **Key words:** depression, oligodendrocyte lineage cells, early life stress, adolescent
46 vulnerability

47 **Introduction**

48 According to the latest World Health Organization report, approximately 280 million
49 individuals worldwide are affected by depression, with rising incidence and a trend
50 toward younger onset^{1,2}. Adolescents represent one of the fastest-growing depression
51 populations, demonstrating significantly higher suicide risks compared to adult
52 patients^{2–5}. While core symptoms of depression include low mood, diminished interest,
53 and anhedonia, adolescent patients more often present with irritability and frequent
54 somatic complaints (headache, abdominal pain, etc.)^{3,6}. These atypical presentations
55 leads to misdiagnosis and worse prognosis^{6,7}.

56 The pathogenesis of depression remains incompletely understood. Multiple hypotheses
57 have been proposed and extensively investigated, including the monoamine hypothesis,
58 impaired synaptic plasticity, chronic low-grade inflammation causing peripheral-to-
59 central inflammatory cascades, hypothalamic-pituitary-adrenal axis hyperactivation,
60 and microglia-driven neuroinflammation^{8–11}. While these hypotheses provide valuable
61 insights into depression pathology, most derive from adult animal models and thus
62 overlook the unique vulnerabilities of the developing brain.

63 Oligodendrocyte (OL) lineage cells, from oligodendrocyte precursor cells (OPCs) to
64 immature oligodendrocytes (OLs) and mature OLs, are essential for brain function.
65 Mature OLs are well known for their role in myelin sheath formation and metabolic
66 support of axons^{12,13}, while OPCs also regulate neural development, angiogenesis, and
67 neural circuit plasticity, as well as influencing inflammation¹⁴. During early life period,
68 rapid proliferation and differentiation make these cells highly plastic yet vulnerable to

69 stress¹⁵, which can produce amplified and long-lasting effects on neural circuit
70 maturation and brain function.

71 Emerging evidences have linked OL lineage cells dysfunction not only to white matter
72 abnormalities but also to disruptions in metabolic support, immune crosstalk, and
73 neuroplasticity network regulation that were relevant to depression^{14,16–18}. Recent
74 single-nucleus transcriptomic profiling revealed substantial transcriptional
75 dysregulation in OPCs in the dorsolateral prefrontal cortex of male individuals with
76 depression¹⁹, further implicating OL lineage cells as molecular contributors. Although
77 most mechanistic insights come from adults, these findings nonetheless provide a
78 valuable framework for exploring similar effects during sensitive developmental
79 periods.

80 Myelin is composed of over 70% lipids, making lipid metabolism critical for OLs
81 function and myelin maintenance²⁰. Recent researches have highlighted altered lipid
82 metabolism in depression^{21–27}, however, direct evidence linking OLs lipid dysfunction
83 to pathology of depression remains limited. Given the critical role of lipid homeostasis
84 in OLs biology and myelin integrity, lipid metabolism dysregulation represents a
85 promising, yet underexplored, pathway through which OL lineage cells may contribute
86 to the pathology of depression.

87 This review summarizes current evidence on myelinating and non-myelinating
88 functions of OL lineage cells and their involvement in lipid metabolic dysregulation,
89 with a focus on how early life stress (ELS) may confer heightened vulnerability to
90 depression. We also discuss therapeutic strategies targeting OL lineage cells.

91 2 The developmental origins and functions of OL lineage cells

92 Understanding the developmental origins of OL lineage cells is essential for
93 contextualizing their functional vulnerabilities in neuropsychiatric disorders. The
94 spatial-temporal pattern of the generation of OPCs shapes cellular heterogeneity and
95 region-specific myelination programs, potentially influencing the susceptibility of
96 myelinated circuits in both white and gray matter to early life or adolescent insults.

97 The developmental origins of the OL lineage cells have been well characterized in
98 rodents in previous reviews^{28–31}. In rodents, OL lineage cells arise in temporally
99 staggered waves from ventral forebrain source (medial ganglionic eminence [MGE] /
100 anterior entopeduncular area, ~E12.5; lateral ganglionic eminence [LGE] / the caudal
101 ganglionic eminence [CGE], ~E15.5) and from dorsal cortex postnatally, with newer
102 lineage analyses indicating that MGE-derived cells persist into adulthood whereas
103 LGE/CGE contributions to adult cortex were limited^{32–38}. In humans development
104 occurs within an expanded outer subventricular zone rich in outer radial glia (oRG)^{39–}
105 ⁴³; although early study suggested that oRG could directly generate EGFR⁺ pre-OPCs⁴⁴,
106 more recent single-cell and lineage-tracing data indicated that OPCs were primarily
107 derived from EGFR⁺ basal multipotent intermediate progenitor cells produced by
108 truncated radial glia in the ventricular zone rather than from oRG⁴⁵. These conserved
109 and primate-specific ontogenetic routes establish the initial distribution and molecular
110 diversity of OL lineage cells. Although the majority of OPCs are specified during
111 embryonic development, they retain a remarkable capacity for proliferation and
112 differentiation throughout life^{15,46–48}. This lifelong plasticity peaks during adolescence,

113 when myelination programs are still expanding and neural circuits remain highly
114 malleable^{46,49}.

115 Across the lifespan, OL lineage cells fulfill distinct stage-specific functions.

116 Specifically, mature OLs primarily form and maintain compact myelin sheaths around

117 axons⁵⁰. Parinode, specialized structures adjacent to nodes of Ranvier, anchor myelin

118 lamellae via cell adhesion molecule networks to ensure the precision of saltatory

119 conduction⁵¹. Beyond this myelinating role, mature OLs contribute to axonal support

120 and neural circuit stability through multiple non-myelinating functions, including

121 metabolic and alternative energy support via monocarboxylic acid transporters (MCTs)-

122 mediated lactate/pyruvate shuttling during glucose deprivation^{13,52,53}, lipid metabolism

123 for membrane integrity^{54,55}, and secretion of neurotrophic factors such as brain-derived

124 neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF) to

125 promote synaptic stability, neuronal survival, and axonal growth^{56–58}(Figure 1). OPCs

126 retain life-long proliferation and differentiation capacity to generate new OLs, rapidly

127 responding to neuronal activity to support adaptive myelination and maintain the

128 plasticity of learning and emotion related circuits¹². Beyond this myelinating potential,

129 OPCs participate in diverse non-myelinating functions, including direct process-somata

130 contacts (PSCs) with neurons to modulate lysosomal activity and metabolism in activity

131 dependent manner¹⁷, forming synapse-like structures with interneurons to release γ-

132 aminobutyric acid (GABA) and regulate the excitation-inhibition balance⁵⁹, and

133 engaging in axon engulfment and synaptic pruning to refine neural circuits^{60–62}(Figure

134 1).

135 These developmental and functional attributes, particularly the extended plasticity of
136 OPCs and the structural specialization of mature OLs, make OL lineage cells
137 indispensable for circuit maturation while also rendering them sensitive to perturbations
138 during adolescence, when myelination trajectories and stress responsiveness converge,
139 creating a heightened window of vulnerability for neural network stability.

140 **3 OL lineage cells dysfunction in depression pathology**

141 A growing body of evidence has indicated that OL lineage cells are actively involved
142 in the pathology of depression⁶³. Structural and molecular disruptions in mature OLs,
143 affecting myelin architecture, and in OPCs, affecting supportive and regulatory
144 functions, have been consistently linked to reduced neural network efficiency and
145 altered stress responsivity^{64–68}. Cross-species and multi-scale investigations, including
146 in vivo neuroimaging, human postmortem analyses, animal model pathology, and
147 multi-omics profiling, have converged on a central theme: white matter microstructural
148 abnormalities, myelin impairment, and oligodendrocyte lineage dysfunction are
149 recurrent features of depression^{64,66,69–74}.

150 **3.1 OLs pathology in depression**

151 Multimodal neuroimaging, postmortem, and mechanistic studies have indicated that
152 mature OLs are disrupted in depression, with distinct signatures in adolescent versus
153 adult cases (**Figure 1**). In adolescents, diffusion tensor imaging (DTI) studies have
154 consistently revealed altered white matter microstructure in emotion-regulatory tracts,
155 including reduced fractional anisotropy (FA) and increased radial diffusivity (RD) in

156 the uncinate fasciculus (UF), corpus callosum genu, corona radiata, and dorsal
157 cingulum bundle, reflecting delayed or dysregulated myelination and disrupted
158 connectivity in emotion regulatory networks^{70,75–79}. Ho et al.⁷⁰ further indicated sex-
159 specific differences, with female adolescent patients showing increased R1, a myelin
160 content proxy, in the UF and callosal genu; higher R1 in the left UF was also positively
161 associated with current depression severity. This suggests that experience-driven
162 increases in myelination may occur during episodes of depression in female adolescents,
163 which could, when occurring during sensitive developmental periods, contribute to
164 heightened vulnerability. In line with this, longitudinal and familial-risk studies have
165 shown that trajectories of myelin maturation and white matter microstructure interact
166 with psychosocial stressors, jointly shaping resilience or susceptibility to depression
167 during adolescence^{80–82}.

168 In adults, depression is more often associated with loss or degeneration of previously
169 established myelin. Multimodal imaging studies using DTI and myelin-sensitive
170 quantitative MRI studies have consistently shown reduced white matter integrity in key
171 tracts and regions, including the fornix, thalamus, inferior fronto-occipital fasciculus,
172 uncinate fasciculus, orbitofrontal cortex, and anterior cingulate cortex (ACC), with the
173 severity of structural impairment correlating with clinical symptom intensity^{67,71,83–89}.

174 Notably, patients with early-onset depression (defined variably as ≤ 25 or ≤ 30 years)
175 showed increased FA value and mean RD value according to the DTI study along with
176 an increased peripheral blood myelin oligodendrocyte glycoprotein (MOG) level, in
177 contrast to the reduction observed in late-onset cases^{75,84}. Such findings point toward

178 potential pathological heterogeneity across onset-age subtypes of depression and
179 highlight the need for longitudinal and biomarker-based studies to clarify OL-related
180 mechanisms in younger patients. Postmortem histopathology studies confirmed
181 reduced OLs density and compact myelin integrity in the prefrontal cortex (PFC) and
182 ACC, often accompanied by compensatory OPCs proliferation^{64,66}. Besides, a genome-
183 wide study identified genetic variants in *TNFRSF21* (involved in OLs maturation) and
184 *ARFGEF1* (involved in myelination) that were associated with cognitive deficits in
185 depression⁷³. Consistently, cross-species transcriptomic analysis identified conserved
186 OLs dysregulation across diverse stress paradigms and in patients with depression,
187 further consolidating OLs dysfunction as a core pathological feature⁷⁴. Chronic stress
188 paradigms in adult rodents recapitulated these changes, producing shortened and
189 thinned myelin sheaths in hippocampal and cortical regions such as medial prefrontal
190 cortex (mPFC), as well as functional deficits in mature OLs^{90,72}; however, only reduced
191 myelin protein concentration were observed in the nucleus accumbens (NAc),
192 highlighting region-specific vulnerability⁶⁹. Notably, chronic stress led to disrupted
193 nodes of Ranvier, altered Caspr and Kv1.1 distribution, and reduced cAMP and
194 membrane potential via OL-specific SGK1-mGluR signaling, impairing axonal
195 conduction and associated behaviors⁹⁰. Although astrocyte-derived lactate has been
196 linked to neuronal excitability and depressive-like behaviors in rodents⁹¹, there is
197 currently no direct evidence that lactate derived from OL lineage cells modulates mood-
198 related circuit. Nonetheless, OL lineage cells displayed metabolic heterogeneity, where
199 OPCs and immature OLs produce lactate via higher lactate dehydrogenase (LDH)

200 expression, while mature OLs mainly deliver pyruvate⁹². Whether developmental shifts
201 in OL metabolic support contribute to adolescent vulnerability to depression remains
202 unclear, and may warrant future investigation.

203 Beyond energy metabolism, OL-specific disruption of iron homeostasis was shown to
204 trigger oxidative stress, neuroinflammation, and impaired synaptogenesis in PFC and
205 hippocampus, driving depressive-like behavior in mice⁹³. It underscored iron regulation
206 as an additional non-myelinating vulnerability of OLs in depression beyond energy
207 metabolism.

208 Together, these findings show that adolescent depression involves disrupted myelin
209 maturation, whereas adult depression is marked by degeneration and functional
210 impairment of mature OLs. Such distinctions have implications for timing and targeting
211 of myelin-protective interventions.

212 3.2 OPCs pathology in depression

213 Chronic stress consistently induces dynamic responses in OPCs, although the direction
214 and magnitude of these changes vary across brain regions, stress paradigms, and
215 developmental stages. In adult rodents, chronic social stress decreased proliferative
216 OPCs in the mPFC while simultaneously increasing mature OLs in the amygdala,
217 highlighting brain region-specific remodeling⁹⁴. Similarly, chronic social defeat stress
218 (CSDS) in susceptible mice elevated OPCs density yet reduced mature OLs in the
219 mPFC, without altering total OPCs density, suggesting impaired differentiation rather
220 than cell loss⁶⁹. Genetic ablation of NG2⁺ OPC in the mPFC induced depressive like
221 behavior, further implicating OPCs involved in depression through mechanisms such

222 as reduced secretion of FGF2⁶⁵. Chronic stress paradigms, including CSDS or circadian
223 misalignment, induced hypomyelination in the prefrontal cortex accompanied by OPCs
224 morphological deficits, aberrant differentiation, and emergence of immune-like OLs
225 (Im-OLs), which might integrate stress responses with myelin disruption^{68,95}. In
226 adolescent mice, OPC-specific perturbations such as OL *ITPR2* deletion interrupted
227 calcium homeostasis, suppressed proliferation, and reduced mature OLs, leading to
228 depressive- and anxiety-like behaviors⁹⁶. In humans, OPC-like progenitors from the
229 olfactory epithelium correlated with cognitive performance and showed plastic
230 responses to antidepressant treatment, suggesting peripheral OPCs populations may
231 reflect or contribute to CNS mood-related processes⁹⁷. Despite variations in
232 proliferation and differentiation patterns, a common theme across these studies is that
233 OPCs respond to stressors with lineage disruption, which contributes to depression
234 pathology. The observed heterogeneity underscores the need for further investigation
235 of brain region-, age-, and stress paradigm-specific OPCs alternations, particularly in
236 adolescence, a period of heightened vulnerability.

237 Beyond their roles as progenitors, OPCs exerted direct regulatory functions on neuronal
238 circuits that may contribute to depression pathology^{59,98,99,17}(Figure 1). At the cellular
239 level, OPCs could form bona fide synapses with glutamatergic and GABAergic neurons,
240 dynamically modulating excitatory-inhibitory balance via activity-dependent calcium
241 signaling and receptor expression, with disruptions linked to maladaptive circuit
242 remodeling under stress^{100–102,98}. In addition to serving as recipients of neuronal input,
243 OPCs could actively release neurotransmitters: selective photoactivation of NG2⁺ glia

244 was shown to drive GABA release onto interneurons, enhancing inhibitory transmission
245 and triggering anxiety-like behaviors that contribute to chronic social defeat stress
246 phenotypes⁵⁹. Moreover, it has been reported that OPCs are involved in synaptic
247 pruning and axon engulfment, disturbing circuit refinement during critical
248 developmental windows and promoting network rigidity^{103,61,62,60}. To date, there has
249 been no direct evidence showing that chronic stress disrupts OPC-mediated synaptic
250 pruning or axon engulfment. However, parallel evidence in microglia, where chronic
251 social defeat stress drove complement-dependent excessive synaptic pruning and
252 connectivity loss in the mPFC, suggesting that glia-mediated synaptic remodeling
253 contributed to stress-related behavioral abnormalities^{104,105}. Given OPCs' capacity for
254 synaptic interactions and axonal remodeling, their potential involvement in stress-
255 induced circuit rigidity remains an important and understudied field.

256 Together, these findings have suggested that OPCs dysfunction extends beyond lineage
257 arrest to mechanistic bridge between stress, circuit dysregulation, and the emergence of
258 depressive-like behaviors.

259 **4 Effects of ELS on OL lineage cells and myelin plasticity**

260 The differentiation of OPCs into myelinating mature OLs persists throughout lifespan,
261 with peak differentiation activity occurring during early childhood and stabilizing in
262 adolescence^{15,49}. Beyond the congenital developmental program, myelin also undergoes
263 experience-dependent and activity-driven adaptive development¹⁰⁶. Current researches
264 have demonstrated that newly generated mature OLs can participate in highly dynamic

adaptive myelination processes not only in adulthood but also during early developmental stage^{107,108}. This process exhibited high sensitivity to external stimuli inputs, providing structural foundations for early-stage neural plasticity while simultaneously creating potential susceptibility for adolescent depression^{15,109}.

269 **4.1 Early life stage: a critical window for OL lineage cells development**

270 During early life stage, the peak periods of OPCs differentiation and myelination coincide with windows of neuron plasticity, suggesting potential contributions of 272 developing OL-neuron crosstalk to depression pathology^{110,111}. During development, 273 neurons dynamically communicated with OLs through synapse-like structures to 274 precisely regulate myelination and its plasticity^{17,62,112}. In adolescent mice, monocular 275 visual deprivation delayed OPCs differentiation and maturation in the visual cortex; 276 correspondingly, blocking OPCs differentiation reduced dendritic spine density, 277 weakened inhibitory synaptic transmission, and induced enhanced plasticity in 278 adulthood¹¹³. This indicates that early-life OPCs maturation critically stabilizes neural 279 circuits and constrains neural plasticity during adulthood. Moreover, it has been 280 reported that OPCs have similar synaptic pruning function as microglia during 281 development stage, further demonstrating the importance of OLs in the regulation of 282 neural plasticity during developmental stage^{60–62}. The dynamics of lipid metabolism in 283 OLs during early life stage is a central driver of myelin formation. OLs ensured efficient 284 myelin formation and dynamic remodeling by precisely regulating the synthesis, 285 storage, and reuse of cholesterol and sphingolipids¹¹⁴. In the brain, cholesterol synthesis 286 peaks during adolescence and then enters a steady state, which is one of the phases of

287 rapid myelin formation¹¹⁵. These collectively suggest that early life stage is a critical
288 window for OL lineage cells development and function.

289 **4.2 Long-term effects of ELS**

290 Accumulating evidences have indicated that ELS disrupted OLs development and
291 myelination through multiple ways¹¹⁶ (**Table 1**). A prospective cohort study of over
292 2,000 adolescents demonstrated that family-environment stress (e.g., harsh parenting
293 and domestic conflict) significantly impair cortical myelination in the ACC¹¹⁷; while a
294 longitudinal neuroimaging finding revealed that childhood socioeconomic deprivation
295 broadly decelerates myelination across cortical, subcortical, and core white matter
296 regions¹¹⁸. Postmortem studies further identified OLs homeostasis disruption in the
297 ACC and ventromedial prefrontal cortex white matter of depression patients with
298 childhood maltreatment histories, potentially linked to persistent myelination deficits
299 mediated by epigenetic reprogramming^{119,120}. Consistently, a lipidomic postmortem
300 analysis reported dysregulated fatty acid composition in the ACC myelin phospholipid
301 pool of depressed suicides with child abuse histories, pointing to metabolic
302 vulnerability of myelin membranes under ELS¹²¹. Another postmortem study of abused
303 children showed upregulated expression of perineuronal nets (PNNs)-related genes
304 (e.g., *VCAN*, *PTPRZ1*, *TNR*) in OPCs concomitant with increased cortical PNNs density,
305 suggesting ELS may drive persistent affective disorders through OPCs-mediated PNNs
306 malformation and subsequent neural plasticity impairment¹²². More recently, these
307 findings have been extended to the basolateral amygdala (BLA) in another human
308 postmortem study, where a novel nuclei-sorting method revealed reduced expression of

309 the myelin-associated gene *MOBP* in OLs from depression patients with childhood
310 maltreatment histories¹²³. Notably, OPCs/OLs densities and myelin coverage were
311 preserved, pointing instead to transcriptional dysregulation of OL lineage cells in limbic
312 circuits as a potential mechanism linking ELS to depression¹²³. A recent study using a
313 neonatal hippocampus subfield MRI framework revealed delayed hippocampus
314 myelination in preterm infants, with persistent deficit up to term-equivalent age despite
315 preserved hippocampus volume¹²⁴. This impairment showed regional specificity, being
316 more pronounced in the CA1 region and less affected in the CA2 region, potentially
317 underlying the elevated long-term risk of depression¹²⁴.

318 Various animal studies have progressively elucidated ELS-induced OL lineage cells
319 impairments. DTI studies in adult rhesus macaques depressive-like behavior models
320 exposed to variable foraging demand stress (VFD) during early life have shown that
321 such ELS selectively impairs prefrontal-limbic white matter integrity, manifesting as
322 desynchronization of white matter maturation in anterior brain regions and aberrant
323 compensatory coordination in posterior regions^{125,126}. A meta-analysis by Orso et al.¹²⁷
324 demonstrated that ELS or prenatal stress (PNS) exposure increased microglial density
325 with somatic hypertrophy while reducing OLs density in rodent brains. Teissier et al.¹²⁸
326 revealed that maternal separation (MS) drove premature differentiation of OPCs in
327 PFC of mice, resulting in OPCs pool depletion, myelination deficits, and subsequent
328 depressive-like behaviors in adulthood. This process was mediated by abnormalities in
329 neuron-glia interactions driven by inhibition of neuron activity in PFC¹²⁸. In contrast,
330 ELS-exposed rat models exhibited distinct OL lineage cells dysfunction characterized

331 by impaired OPCs differentiation capacity, reduced mature OLs numbers, and enhanced
332 apoptosis – all paralleled by elevated oxidative stress and persistent anxiety/depressive-
333 like behavior¹²⁹. Notably, the effect of ELS has been demonstrated spatiotemporal
334 specificity: adolescent chronic stress selectively suppresses OPCs
335 proliferation/differentiation in the PFC and lateral habenula (LHb), but spares the
336 amygdala and medial habenula (MHb)¹³⁰. Chronic social isolation lasting the entire
337 adolescent period (postnatal days 21-65, P21-P65) induced simpler OLs morphology
338 without any change of OLs density in the mPFC of mice¹³¹. Crucially, even short-term
339 isolation during early adolescence (P21-P35) sufficed to induce similar pathological
340 alterations, whereas identical stress exposure after P35 (approximately mid-to-late
341 adolescent) produced no significant effects¹³¹. Mechanistic investigation revealed that
342 juvenile social experience regulates the "critical time window" for maturation of OLs
343 in the PFC through the ErbB3 signaling pathway, demonstrating precise spatiotemporal
344 specificity - an effect absent in the motor cortex¹³¹. These findings collectively suggest
345 that OL lineage cells developmental impairment exhibits strict spatial (brain-region-
346 dependent) and temporal (developmental-stage-specific) constraints. Furthermore, MS
347 was shown to reduce OPCs population in the hippocampus, inhibit Wnt7b paracrine
348 signaling, thereby suppressing Wnt/β-catenin pathway-dependent astrocyte
349 development, ultimately leading to depressive-like behaviors in mice¹³². An update
350 study further demonstrated that MS activated peripheral CD4⁺ T cells and elevated
351 xanthine levels, which inhibited the adenosine A1 receptor (A1R) signaling pathway of
352 OPCs in the PFC, resulting in myelin damage and anxiety/depressive-like

353 phenotypes¹³³, suggesting OPCs might serve as key mediators of peripheral immune-
354 central nervous system crosstalk in depression pathogenesis. A single acute juvenile
355 traumatic stress exposure induced sex-specific long-term alterations in gray matter
356 myelination within PFC, amygdala and hippocampus in adulthood, with female rats
357 exhibiting widespread myelin reduction whereas males showed no persistent effects¹³⁴.
358 In contrast, this stress increases gray matter myelination in the amygdala and
359 hippocampus of adolescent male rats, while reduced the number of OLs in the PFC of
360 adolescent female rats in the short term¹³⁴. This indicated potential sexual heterogeneity
361 in ELS-induced long-term and short-term consequences.
362 As an important part of early life stress, the influence of PNS on the development of
363 OLs in offspring should not be ignored. A high-fat diet during pregnancy inhibited OLs
364 maturation and suppressed myelination-related gene/protein expression in the PFC of
365 the offspring, thereby inducing depressive-like behaviors that persist into adulthood¹³⁵.
366 Notably, this study specifically identified male-biased myelination-related protein
367 deficits¹³⁵, which paradoxically contrasted with the female-specific myelination
368 impairment caused by acute juvenile stress mentioned below¹³⁴. This discrepancy
369 suggests a stress-type-dependent sexual dimorphism in the regulation of OL lineage
370 cells. Similarly, maternal exposure to a cafeteria diet during pregnancy and lactation
371 primed depressive-like behavior in offspring, accompanied by reduced volume in
372 the PFC, hippocampus, and NAc, as well as synaptic deficits and decreased myelination
373 in the dentate gyrus¹³⁶. Consistently, expression of myelination-related genes (e.g., *Mag*,
374 *Mbp*) was reduced in the BLA of offspring whose mother experienced ELS, concurrent

375 with DNA methylation elevated¹³⁷. Critically, this effect demonstrated dynamic
376 interactions with perinatal selective serotonin reuptake inhibitors (SSRIs) exposure, with
377 male offspring exhibiting heightened sensitivity to such combined stressors¹³⁷.
378 Furthermore, in a maternal immune activation (MIA) non-human primate model,
379 prenatal exposure to the viral mimetic poly(I:C) induced hippocampus-specific OL
380 lineage cells abnormality in adolescent offsprings (developmentally equivalent to
381 humans aged 14-16 years)¹³⁸. The abnormality featured upregulated myelination-
382 related genes (*OLIG2, SOX10, MYRF, MBP, CNP, MOG, MAG*) and downregulated
383 OPCs marker gene *PDGFRA*, accompanied by increased social deficits and stereotypic
384 behaviors¹³⁸. It has also been reported that paternal early social isolation epigenetically
385 elevates sperm miR-124, impairing maturation of OLs and myelination in the mPFC of
386 offsprings, thereby disrupting social behavior across generations¹³⁹. Collectively, these
387 findings indicate that prenatal environmental stress reshape OL lineage cells
388 developmental trajectories, thereby exerting transgenerational effects on offspring
389 neural circuit function.

390 Taken together, evidence from human postmortem, neuroimaging, and animal models
391 indicates that ELS persistent and multifaceted impacts on OL lineage cells development
392 and myelination through transcriptional, epigenetic, immune, and neuronal activity-
393 dependent regulation. Future work is needed to disentangle these interacting pathways
394 and identify therapeutic windows for intervention.

395 **5 Dysregulation of lipid metabolism in OLs**

396 OLs are highly active in lipid metabolism, which is indispensable for both myelination
397 and broader central nervous system homeostasis. Myelin membranes are composed of
398 over 70% lipids, with cholesterol and sphingolipids constituting the major fraction²⁰.
399 Beyond myelin synthesis, OLs dynamically exchange fatty acids and cholesterol with
400 neurons and astrocytes to support energy metabolism, oxidative protection, and
401 synaptic plasticity^{140,55,141,20}. Multiple clinical studies have demonstrated that lipid
402 metabolism dysregulation was prevalent in both adult and adolescent depression^{23,142,26},
403 which has strong correlations with depression severity, cognitive deficits, and
404 prognosis^{25,27,143}. Thus, disruption of OLs lipid homeostasis probably represent a
405 crucial nexus linking stress exposure to myelin deficits and depression.

406 **5.1 Dysregulation of cholesterol metabolism**

407 During myelination, OLs synthesize cholesterol for membrane construction, and this
408 biosynthetic activity persists in adulthood to maintain myelin stability and axonal
409 support¹¹⁴. Chronic stress has been shown to impair this process by suppressing
410 phosphorylation of 3-hydroxy-3-methylglutaryl-CoA synthase (HMGCR), a rate-
411 limiting enzyme in cholesterol biosynthesis, leading to reductions in myelin proteins
412 such as MBP and MOG and consequent white matter disruption²². Single-nucleus RNA
413 sequencing further demonstrated persistent downregulation of cholesterol transporters
414 genes (e.g., *Apoe*, *Apod*) and regulatory factors genes (e.g., *Dhcr24*, *Srebf2*) in OLs in
415 the hypothalamus of mice after chronic stress, resulting in abnormal cholesterol
416 accumulation, altered OLs developmental trajectories, and depressive-like behaviors²⁴.

417 In patients with depression, downregulation of the myelin-related
418 gene *CNP* exacerbates cholesterol metabolic dysfunction, which results in axonal
419 metabolic support failure and synaptic plasticity impairment¹⁴⁴. Such dysregulation
420 interacts with chronic stress-induced neuroinflammation, forming a vicious cycle: pro-
421 inflammatory factors (e.g., IL-1 β , TNF- α) suppress cholesterol synthase expression,
422 while abnormal cholesterol metabolites amplify microglia activation, collectively
423 aggravating inflammation-mediated OPCs differentiation defects and myelin
424 damage^{145–147}. Significantly, the antidepressant venlafaxine could restore HMGCR
425 activity to ameliorate cholesterol metabolism, suggesting therapeutic potential²².

426 **5.2 Dysregulation of sphingolipid metabolism**

427 Sphingolipids serve as essential lipids for OLs to maintain myelin structure and
428 signaling functions, constituting 30-40% of myelin lipids²⁰. Their metabolites, such as
429 ceramides, act as bioactive mediators of inflammation responses under stress or injury
430 conditions²⁰. Accumulating evidence underscored the indispensable role of central
431 sphingolipid metabolic dysregulation in depression pathology^{21,23,148}. In animal models,
432 stress exposure enhanced sphingomyelinase/ceramidase activity in emotion-related
433 regions (e.g., hippocampus and PFC), correlating with depressive-like behaviors and
434 impaired myelin integrity^{148–150}. Direct evidence linking shingolipid metabolism to
435 adolescent oligodendrocyte dysfunction in depression is currently lacking, representing
436 an important knowledge gap for future research.

437 Together, these findings underscored OLs lipid homeostasis as an emerging mechanistic
438 link between stress, myelination deficits, and depression. A recent study demonstrated

439 that ELS induced widespread lipid metabolism dysregulation in the depressed rat
440 brain¹⁵¹, supporting the notion that ELS broadly perturbs lipid homeostasis, although
441 direct evidence linking these alternations to OL lineage cells remains limited. While
442 most evidence centers on cholesterol pathways, and much of the current data treats lipid
443 metabolism as a largely parallel pathway, this emerging evidence suggests that lipid
444 dysregulation could represent a convergent mechanism mediating the effects of ELS on
445 OL lineage cells development and myelination. Future studies, particularly in
446 adolescent models, are needed to clarify whether and how dysregulation of OL lipid
447 homeostasis contributes to ELS-induced OL dysfunction, and whether therapeutic
448 modulation of these pathways can restore myelin integrity and resilience against
449 depression.

450 **6 Therapeutic strategies targeting OL lineage cells**

451 In recent years, diverse interventions, ranging from small-molecule drugs to lifestyle
452 modifications, have been shown to ameliorate or prevent depression-associated myelin
453 damage through multiple mechanisms: promoting OPCs differentiation, enhancing
454 myelin repair, remodeling lipid/energy metabolism, and alleviating inflammatory
455 responses (**Figure 2**). These findings provide a wealth of candidates for developing
456 novel antidepressant strategies centered on OLs regulation.

457 **6.1 Pharmacological interventions**

458 Clemastine, a classical antihistamine, has been demonstrated in vitro and in vivo to
459 promote OPCs differentiation into mature OLs and accelerate remyelination in

lysolecithin-induced demyelination models^{152–154}. Its efficacy has been validated in a randomized, controlled, double-blind crossover clinical trial for multiple sclerosis¹⁵⁵. Preclinical studies (including in adolescent social isolation models and CSDS models) have further revealed its capacity to rescue stress-induced depressive-like behaviors through enhanced OPCs differentiation, myelin repair, and neuroinflammatory modulation^{156–160}. However, emerging evidence suggested that clemastine's impact may be age- and context- dependent: in developmental models, clemastine increased OPCs differentiation but paradoxically impaired myelin formation and conduction velocity, potentially via disruption of microglia-OL crosstalk¹⁶¹. These findings highlight the need for caution when considering clemastine in pediatric or adolescent populations, and underscore the importance of microglia-OL interactions in mediating promyelinating therapies. Fingolimod (FTY720), a non-selective sphingosine-1-phosphate G protein-coupled receptor modulator, not only enhanced OPCs survival and migration but also accelerated myelin regeneration in chemical-induced demyelination models, concomitant with improved cognitive and emotional behaviors^{162–165}. The classic SSRIs paroxetine was reported to exhibit antidepressant effects partially through promoting OPCs proliferation/differentiation and subsequent myelin repairment^{166,167}. Ketamine, a rapid-acting antidepressant drug, was recently shown to repair CSDS-induced myelin damage via α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor-mediated OPCs differentiation; suppression of myelin oligodendrocyte basic protein expression abolishes its sustained antidepressant effects¹⁶⁸. Quetiapine, an atypical antipsychotic with established adjunctive efficacy in depression^{169,170},

482 enhanced oligodendrocyte differentiation and myelination through dual mechanisms:
483 downregulating Cdkn1a expression in OPCs/neurons and increasing nuclear-to-
484 cytoplasmic translocation of Olig1 transcription factor^{169,171}. Plant-derived bioactive
485 compounds have demonstrated significant therapeutic potential in various
486 neuropsychiatric disorders, with growing recognition of its antidepressant properties.
487 Recent research revealed that total flavonoids from Astragalus (a primary active
488 constituent of Astragalus root) exerted antidepressant effects by enhancing
489 hippocampus myelination in chronic unpredictable mild stress models¹⁷². This process
490 is mediated through upregulation of OLs transcription factors Olig2/Sox10 and
491 concurrent suppression of the Wnt/β-catenin signaling pathway¹⁷². *Hypericum*
492 *perforatum* (St. John's Wort), a well-established botanical antidepressant, showed
493 emerging potential in adolescent depression management¹⁷³. Its bioactive constituent,
494 hyperforin, not only promoted OPCs differentiation but also enhanced mitochondrial
495 function, while concurrently protecting against mitochondrial toxicity-induced
496 damage¹⁷⁴. These findings suggest a candidate mechanism through which *Hypericum*
497 *perforatum* may exert antidepressant effects, at least in part, by supporting OL lineage
498 cell function.

499 In summary, pharmacological strategies targeting OL lineage cells, including classical
500 antidepressants and antipsychotics, remyelination-promoting agents, and plant-derived
501 bioactive compounds, have demonstrated multifaceted therapeutic potential. These
502 drugs exert their effects through promoting OPCs proliferation and differentiation,
503 enhancing myelin repair, and modulating neuroinflammatory responses. Nevertheless,

504 most of these pharmacological data originate from adult or preclinical studies, and their
505 safety profiles in adolescent populations remain largely uncharacterized. Age-related
506 differences in pharmacokinetics, off-target neurodevelopmental effects, and potential
507 interference with ongoing myelination could pose additional risks. Recent studies in
508 adolescents (e.g., Ketamine¹⁷⁵ and deep transcranial magnetic stimulation [TMS]¹⁷⁶)
509 have shown acceptable safety and tolerability, but long-term data on OL/myelin
510 outcomes are still lacking. Thus, rigorous age-specific safety evaluations will be crucial
511 before clinical translation of OL-targeting interventions in youth.

512 **6.2 Non-pharmacological interventions**

513 Non-pharmacological antidepressant strategies targeting OL lineage cells are becoming
514 a research hotspot. Electroconvulsive therapy (ECT) counteracts glucocorticoid-
515 induced inhibition of OLs generation by restoring the proliferation of OPCs and
516 promoting their differentiation in the amygdala and hippocampus^{177,178}. In terms of
517 neuromodulation, 5 Hz repetitive TMS (rTMS) improved chronic stress-induced
518 myelin damage and depressive-like behaviors by increasing the number of Olig2⁺ OLs
519 in the PFC and hippocampus¹⁷⁹. This effect was independent of the neurogenesis-
520 promotion function of fluoxetine and showed synergistic effects in combination
521 therapy¹⁷⁹.

522 Metabolic interventions based on gut-brain axis shows unique potential. Enterococcus
523 faecalis EF-2001 reversed depressive-like behaviors in olfactory bulbectomy mice
524 model by activating the neuronal CREB/BDNF and astrocyte-based LIF/STAT3
525 signaling pathways to promote OPCs differentiation and myelination in the PFC¹⁸⁰.

526 Dietary metabolic studies reveal that a high-fat diet rich in palmitic acid can partially
527 compensate for fatty acid synthesis defects in OLs, improving developmental myelin
528 sheath growth, suggesting the potential value of dietary lipid intake for myelin
529 repairment¹⁸¹. Additionally, the ketogenic diet (KD), as a non-pharmacological
530 treatment for pediatric refractory epilepsy, has demonstrated myelin repairment effects
531 in numerous preclinical and clinical studies related to multiple sclerosis, with increasing
532 evidence supporting its antidepressant potential^{182–186}. Leclercq S et al.¹⁸⁷ showed that
533 gut microbiota dysbiosis-induced inhibition of β-hydroxybutyrate synthesis was
534 associated with social impairment, depression, and white matter alterations in alcohol
535 use disorder, implying that the KD may exert antidepressant effects through OLs-
536 targeted mechanisms. Omega-3 fatty acids (ω-3), particularly eicosapentaenoic acid
537 and docosahexaenoic acid, showed adjuvant antidepressant efficacy by reducing sleep
538 deprivation-induced myelin damage and OLs lipid peroxidation^{188,189}. It also rescued
539 offspring from depressive behaviors caused by maternal high-fat diet during gestation
540 and lactation period via improving the suppression of MOG and myelin and lymphocyte
541 protein expression, restoring the reduced number of OPCs and mature OLs in the PFC
542 and cingulate cortex¹⁹⁰. Notably, there was sex-specific heterogeneity of effect of ω-3
543 on depression: significant in male offspring but not in female rats¹⁹⁰.

544 Exercise-induced antidepressant effects are also related to OL lineage cells function and
545 myelin remodeling. A DTI study found that mice exhibited increased hippocampus
546 volume, with FA values positively correlated with exercise intensity, along with an
547 increased number of OPCs in the corpus callosum¹⁹¹. Consistently, running exercise

548 protected white matter integrity in CUMS-induced depression rats by restoring
549 myelinated fiber length, myelin sheath volume and thickness, thereby rescuing
550 behavioral deficits¹⁹². In a chronic stress model, running exercise (but not fluoxetine)
551 specifically increased the number of mature OLs (CC1⁺/Olig2⁺) and MBP levels in the
552 CA1 region, while promoting OPCs proliferation in the PFC¹⁹³. Further evidence
553 revealed that treadmill running alleviated depressive-like behaviors while increasing
554 the number of CNPase⁺ mature OLs in hippocampal CA3 and dentate gyrus,
555 highlighting a regional heterogeneity of exercise-induced OLs protection¹⁹⁴. This effect
556 showed developmental stage dependency: adolescent exercise increased the number of
557 mature OLs in the PFC, whereas young adult exercise had more significant effects on
558 inducing OPCs differentiation¹⁹⁵. Long-term exercise promoted increased MCT1 in the
559 PFC, suggesting that exercise might exert antidepressant effects by rescuing neuronal
560 energy deficits through OLs-mediated lactate shuttle¹⁹⁵.

561 In summary, non-pharmacological strategies targeting OL lineage cells (physical
562 intervention, metabolic intervention, and lifestyle improvement) provide a
563 multidimensional intervention for the treatment of depression by regulating
564 myelination, OPCs proliferation, and OL-neuronal interactions. Collectively, these
565 findings highlight OL lineage cells as promising therapeutic targets, while future studies
566 should clarify the translational efficacy, developmental stage specificity, and long-term
567 safety of these pharmacological and non-pharmacological interventions in depression.

568 **7 Conclusions**

569 The pathogenesis of depression remains incompletely understood. Compared to adult
570 depression, adolescent depression has a more insidious onset, complicating diagnosis
571 and limiting treatment options - implying a potentially distinct underlying pathology.
572 OLs, once considered merely as myelin-producing cells, are now recognized for their
573 non-myelinating roles, including energy provision, metabolic regulation, immune
574 response, and modulation of synaptic plasticity. Notably, emerging evidence shows that
575 OPCs interact with neurons via synaptic contacts and participate in synapse modulation
576 during development, a process further shaped by microglia^{17,61}. These findings suggest
577 that OL lineage cells may contribute to neuro-immune-metabolic interactions and their
578 potential involvement in the pathology of adolescent depression. However, most studies
579 still focus on myelin function, with limited exploration of OL lineage cells' non-
580 canonical roles. Moreover, findings on the spatial, temporal, and sex-specific
581 heterogeneity of OL lineage cells in depression remain inconsistent. Current research
582 is largely based on adult models, lacking dynamic developmental-stage tracking, which
583 restricts our understanding of adolescent-specific pathology. Additionally, validated
584 biomarkers associated with OL lineage cells along with non-invasive tools for *in vivo*
585 assessment of OL-specific pathology are still lacking, limiting the translational
586 potential of OL-targeted research. Advances in neuroimaging techniques, such as high-
587 resolution magnetic resonance spectroscopy and positron emission tomography (PET)
588 molecular probes, have shown promise in tracking neurotransmission in clinical
589 depression cohorts^{196–198}. However, most of these approaches are not designed to

590 specifically capture oligodendrocyte dynamics, especially in developmental
591 populations.

592 To address these challenges, future research can be expanded in the following directions.

593 First, studies based on single-cell spatial omics could uncover transcriptional, lipid
594 metabolic, and epigenetic characteristics of OL lineage cells across brain regions,

595 identifying potential pathological subtypes and key regulatory molecules. Second,
596 studies should focus on the developmental time windows and causality validation,

597 especially regarding OPCs-neuron communication, to dissect how OL lineage cells
598 regulate neural plasticity through metabolic coupling and immune crosstalk with

599 neurons, microglia, and astrocytes. Third, based on the evidence that ELS exerts
600 persistent and multifaceted impacts on OL lineage cells, future studies should also aim

601 to disentangle how ELS-induced alterations in OPC differentiation, myelination
602 dynamics, and metabolic programming affect the maturation of neural circuits and

603 constrain synaptic plasticity, thereby heightening vulnerability to adolescent depression.

604 Longitudinal studies integrating developmental tracking with mechanistic validation in
605 both animal models and human cohorts are needed to identify critical windows of

606 susceptibility and clarify the causal pathways. Given the emerging evidence linking
607 lipid metabolism to oligodendrocyte development, myelin integrity, and neural

608 plasticity, future studies should systematically explore lipid-derived biomarkers and
609 lipid-targeted interventions. Finally, future translational research should prioritize the

610 development of OL-targeted imaging probes (e.g., PET ligands for myelin-associated
611 proteins or lipid metabolism markers). Efforts should be directed toward identifying

612 adolescent-relevant OL lineage cells derived biomarkers, developing precise
613 interventions based on mechanistic insights, and evaluating the developmental-stage-
614 specific efficacy of existing treatments, including small molecule antidepressants,
615 metabolic modulators, and physical therapies, to advance precision treatment of
616 adolescent depression.

617 **Ethics approval and consent to participate**

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619 **Competing interests**

620 The authors declare that they have no competing interests.

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628 **Author contributions**

629 **CG** designed the conceptual framework and structure of the review, conducted the
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1255 **Figure 1. An overview of OL lineage cells dysfunction in depression**
1256 **pathology.** OL lineage cells exhibits both myelinating functions and non-myelinating
1257 functions, and their pathological alternations contribute to depression. In adolescents,
1258 pathology includes dysregulated myelination, network-level dysfunctions, and sex-
1259 specific vulnerabilities, whereas adult pathology features progressive myelin loss,
1260 impaired remyelination, and molecular risk signatures (e.g., MBP, MOG, *TNFRSF21*,
1261 *ARFGEF1*). Beyond myelination, mature OLs provide metabolic support to axons by
1262 shuttling glycolysis-derived lactate/pyruvate and engaging lipids β -oxidation (β -OX)
1263 under low glucose condition, while secreting neurotrophic factors (BDNF, GDNF).
1264 OPCs interact with neurons via PSCs, modulate synaptic activity, and refine circuits.
1265 Non-myelinating pathology in depression includes secretory and immune-like changes,
1266 circuit dysfunction, energy dyshomeostasis, and lipid metabolism disturbance.
1267 Abbreviation: TCA, tricarboxylic acid cycle.

1268 **Figure 2. Therapeutic strategies targeting OL lineage cells in**
1269 **depression.** Both pharmacological and non-pharmacological interventions have
1270 demonstrated potential in improving depression-related OL lineage cells dysfunction
1271 through multiple mechanisms. Small-molecule drugs such as clementine, fingolimod,
1272 paroxetine, ketamine, and quetiapine promote OPCs differentiation and enhance myelin
1273 repair. Plant compounds exert antidepressant effects by upregulating OL-specific
1274 transcription factors and improving mitochondrial and myelin function. Non-
1275 pharmacological interventions - including physical interventions, metabolic therapies,
1276 and lifestyle interventions - promote myelin plasticity, enhance glia-neuron crosstalk
1277 and metabolic coupling.

1278

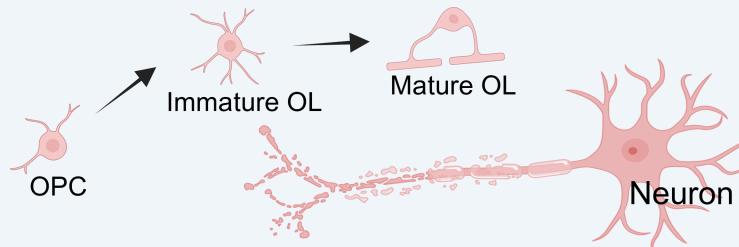
1279 **Table.1 Long-term effects of ELS on OL lineage cells development and function**

Research type	Stress paradigm	Stress period	Assessment age	Core brain regions	OL lineage cells-associated changes	Ref
Prospective cohort study	Family-environment stress	Before 6 years of age	8-14 years of age	ACC	Myelin deficit	¹¹⁷
Human neuroimaging study	Childhood socioeconomic deprivation	Mostly before 12 years of age	Median age 18.7 years	Cortical, subcortical, and core white matter regions	Myelin deficit	¹¹⁸
Human neuroimaging study	Premature labor	Gestational age between 23- and 44-weeks	0.9-8.6 weeks after birth	Hippocampus	Delayed myelination	¹²⁴
Postmortem study	Child abuse	Before 15 years of age	Mostly adult	ACC	OLs genes DNA methylation alternation Myelin deficit MBP ↓ Mature OLs ↑	¹¹⁹
Postmortem study	Child abuse	Before 15 years of age	Adult	vmPFC	MAS1 ↑ Immature OLs ↓	¹²⁰
Postmortem study	Child abuse	Before 15 years of age	Adult	vmPFC	OPCs-mediated PNNs formation ↓	¹²²
Postmortem study	Child abuse	N/A	N/A	BLA	<i>MOBP</i> ↓ in OLs	¹²³

Postmortem study	Child abuse	Before 15 years of age	Adult	ACC	Delayed myelination, arachidonic acid synthesis dysregulation <i>OLIG2, SOX10, MYRF, MBP, CNP, MOG, MAG ↑ PDGFRA ↓</i>	121
Non-human primate study	MIA	1 st and 2 nd trimester	3.5–4 years of age	Hippocampus	<i>OLIG2, SOX10, MYRF, MBP, CNP, MOG, MAG ↑ PDGFRA ↓</i>	138
Non-human primate study	VFD	2-6 months of age	Around 5 years of age	Prefrontal limbic white matter region	Myelin deficit	126
Non-human primate study	VFD	2-6 months of age	Around 5 years of age	Anterior limb white matter region	Myelin deficit	125
Rodent study	MS	P2-14	P15 and adult	PFC	OPCs differentiation ↑ Myelin deficits	128
Rodent study	ELS (foot shock)	P21-26	P75-82	Hippocampus	OPCs differentiation ↓	129
Rodent study	CSDS	P28-37	P40	PFC, LHb	OPCs proliferation/differentiation ↓ OPCs	130
Rodent study	CSDS	P28-37	P40	Amygdala, MHb	OPCs proliferation/differentiation ↑ Myelin deficit	130
Rodent study	Chronic social isolation	P21-65/ P21-35	P65	PFC	OLs↓ MBP↓	131
Rodent study	MS	P2-12	P23	Hippocampus	OPCs ↓	132
Rodent study	MS	P2-21	P42	mPFC	A1R signaling pathway ↓ OPCs and OLs ↓	133

Rodent study	Acute juvenile traumatic stress	P28	P40 and P95	PFC, hippocampus, amygdala	Myelination alternations depend on sex	134
Rodent study	HFD for dams	Pregnancy and lactation 9 weeks (pre-pregnancy, pregnancy, and lactation)	Adolescent and adult	PFC	MOG, MAL, CNPase ↓ OLs ↓	135
Rodent study	Cafeteria diet for dams	P60	NAc, hippocampus, PFC	Decreased myelination	136	
Rodent study	ELS of dams	P2-15	P21	BLA	<i>Mag, Mbp</i> ↓	137
Rodent study	Early social isolation of sires and offspring	P21-41 (sires); P21-34 (offspring)	P34	mPFC	MBP ↓ hypomyelination	139

Myelinating Functions & Pathology



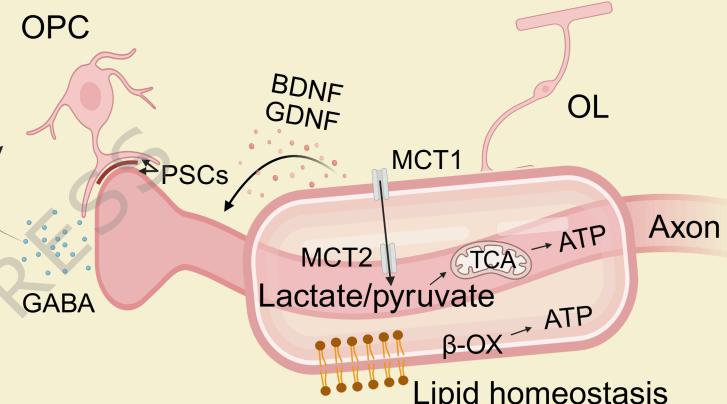
Adolescent depression

- Dysregulated myelination
- Gender differences
- Network-level dysfunction
- Risk: accelerated OLs maturation
- Resilience: preserved OL maturation

Adult depression

- Myelin loss/degeneration
- Onset heterogeneity
- Dysregulated remyelination
- Risk molecules: MBP, MOG, *TNFRSF21*, *ARFGEF1*

Non-myelinating Functions & Pathology



Biological Functions

Mature OLs:

- Metabolic support
- Lipid metabolism
- Neurotrophic support

OPCs:

- Direct neuronal interactions
- Synaptic modulation
- Circuit refinement

Depression Pathology

- Secretory & immune-like changes
- Circuit dysfunction
- Energy dysregulation
- Lipid metabolism disturbance

