—Review—

Impact of Sex Differences in Oligodendrocytes and Their Progenitor Cells on the Pathophysiology of Neuropsychiatric Disorders

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Neuropsychiatric disorders such as multiple sclerosis, Alzheimer's disease, and autism spectrum disorder exhibit significant sex differences in prevalence, progression, and response to treatment. Emerging evidence suggests that oligodendrocytes (OLs) and oligodendrocyte precursor cells (OPCs) play pivotal roles in these pathologies via mechanisms involving neuroinflammation, energy metabolism, and hormonal modulation, resulting in distinct functional outcomes. Specifically, female OPCs display higher proliferative and migratory capacities, whereas male OPCs are more prone to differentiation and myelination, thus contributing to robust myelin integrity. Dysregulation of these cells disrupts myelination and exacerbates disease progression. Addressing sex-specific gene expression in OPCs and OLs is therefore considered crucial for the development of targeted therapeutic strategies. This review highlights the significance of sex differences in the proliferation and differentiation of OPCs, as well as gene expression changes in OPCs and OLs, and emphasizes their contribution to the pathophysiology of neuropsychiatric disorders. Improved understanding of these differences is vital for advancing personalized sex-specific treatments and improving the clinical outcomes of neuropsychiatric disorders.

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Key words: oligodendrocyte, oligodendrocyte progenitor cell, neuropsychiatric disorders, sex differences

Introduction

Elucidating the pathophysiology of neuropsychiatric disorders is crucial in the development of effective treatment and prevention strategies. Glial cells, traditionally considered as supportive cells for neurons, actively regulate neural functions[1] and are directly linked to pathogenesis[2]. Among glial cells, microglia and astrocytes have been widely studied in relation to neuropsychiatric disorders[3,4]. However, recent spatial transcriptomic and single-cell analyses have shown that oligodendrocytes (OLs) and oligodendrocyte precursor cells (OPCs) are also involved in disease pathology[5,6], that OLs are notably vulnerable to amyloid plaques in Alzheimer's disease (AD)[5], and that the white matter, which is composed of axons enveloped by myelin sheaths produced by these cells, is impaired before the onset of dementia symptoms[7]. Furthermore, genetic or pharmacological disruption of OPC and OL homeostasis affects microglial phagocytic activity and amyloid production, resulting in amyloid plaque accumulation[8]. These findings highlight the importance of OPCs and OLs in the pathology of neuropsychiatric diseases.

The pathology, prevalence, and treatment effects of neuropsychiatric disorders differ by sex. Autism spectrum disorder (ASD)[9] and Parkinson's disease (PD)[10] both have a higher incidence in males, whereas AD[11] and multiple sclerosis (MS)[12] have a higher prevalence[11] and relapse rate[12], respectively, in females. The efficacy of therapies for these diseases is limited in part by insufficient consideration of sex differences. Therefore, the present review outlines the current knowledge regarding sex differences in OPCs and OLs to understand the pathophysiology of neuropsychiatric disorders and inform the development of sex-specific therapeutic strategies.

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Proliferation of OPCs, Differentiation into OLs, and Subsequent Myelination

In the central nervous system (CNS), OPCs proliferate and differentiate into OLs during embryonic development. Myelination begins with interactions between axons and OLs[13]. Fate mapping experiments using OPCs expressing specific antigens such as NG2 and platelet-derived growth factor receptor alpha (PDGFR*a*) subunit[14] have shown that OPCs originate from distinct precursors at different developmental stages: during mid-gestation from Nkx2.1-expressing precursors in the ventral germinal zones of medial ganglionic eminences, and during late gestation from Gsh2 expression in the lateral ganglionic eminence. From late gestation to the early postnatal stages, OPCs are generated from the dorsal ventricular zone expressing Emx1, and later from the subventricular zone. The adult CNS harbors OPC populations capable of differentiating into OLs[15], the development of which is regulated by key signaling pathways and transcription factors. For example, sonic hedgehog signaling promotes differentiation via expression of Nkx6.1 and Nkx6.2[16], inducing expression of Olig1 and Olig2, which are necessary for OPC differentiation[17]. Sox family transcription factors such as Sox9 and Sox10 are crucial for OPC survival and myelin-related gene expression[18]. OPCs start differentiating into OLs at approximately embryonic day 18.5, a process that continues into adulthood. This process involves epigenetic mechanisms[19] and hormonal factors[20], including sex hormones, triiodothyronine, and insulin. OPCs further promote lipid synthesis, including essential components, such as O4 and galactosylceramide, which are critical for myelin formation, leading to OL maturation[21] (**Fig. 1**).

Neural Activity-Dependent Proliferation and Differentiation of OPCs and Myelination Regulate Conduction Velocity, Ultimately Contributing to Control of Cognitive Functions

OLs support myelin remodeling and repair in the CNS; however, adult OPCs have a limited capacity to generate new OLs[15]. Indeed, most human OLs are formed by age 5 years, and the annual replacement rate is low[22]. In mice, OLs have a long lifespan: 90% of those in the corpus callosum at age 2 months persist for at least 8 months[23]. Although pathological conditions, such as MS, can promote differentiation of OPCs into OLs, ^{14}C analysis has shown that OPCs rarely proliferate and differentiate into mature OLs[24]. These findings suggest that OPCs and OLs exhibit limited changes in adults, indicating a minor role in cognitive functions, such as learning and memory. However, *in vivo* imaging using two-photon microscopy has shown ongoing OL generation and myelin remodeling throughout life[25].

OPCs and OLs exhibit neural activity-dependent plasticity that affects cognitive functions[1]. Indeed, magnetic resonance imaging (MRI) studies in humans indicate that learning and training in skills such as juggling induces structural changes in the white matter[26]. Motor learning and fear memory induce proliferation and maturation of OPCs into OLs, thereby promoting myelination and regulating conduction velocity[27,28], which is crucial for learning and spatial memory[27–29]. This process involves neurotransmitter receptors on OL-lineage cells, including receptors for glutamate, GABA, and ATP, which mediate calcium signaling and affect cell proliferation, differentiation, and neural circuitry activity[30] (**Fig. 1**). A recent *in vivo* two-photon imaging study showed that AD model mice exhibit dysregulation of neural activity-dependent calcium responses and ATP-dependent abnormal calcium responses, which suggests these factors contribute to disease pathology[31]. This indicates that disruption of OPC proliferation, differentiation into OLs, and myelination may all contribute to neuropsychiatric disorders. Furthermore, sex-based differences in these mechanisms may play a role in the pathogenesis of these disorders. The next section highlights the evidence for sex differences in OPCs and OLs.

Sex Differences in OPCs and OLs under Normal Conditions

Gene expression during OPC proliferation and differentiation into OLs is influenced by several factors and exhibits significant sex differences. RNA and proteomic analyses of rat-derived OPCs showed that female OPCs exhibit higher proliferation and migration abilities, increased energy metabolism (ATP levels), and elevated proliferation-associated gene expression of *Olig1*, *Olig2*, *NF1*, and *Pdgfa*[32]. Additionally, genes related to blood-brain barrier regulation (e.g., *Tgfβ1*, *Igf1*), which are associated with neuropsychiatric disorders, are upregulated in females[32]. Conversely, male OPCs show enhanced differentiation and myelination capabilities, with higher expression of myelin-related genes such as *myelin basic protein* (*Mbp*), *myelin-associated glycoprotein* (*Mag*), *2′,3′-cyclic nucleotide phosphodiesterase* (*Cnp*), and *myelin regulatory factor* (*Myrf*)[32]. One study using high-dimensional single-cell transcriptomic analyses of over 2.3 million cells across 17 tissues, including brain obtained from mice, found that

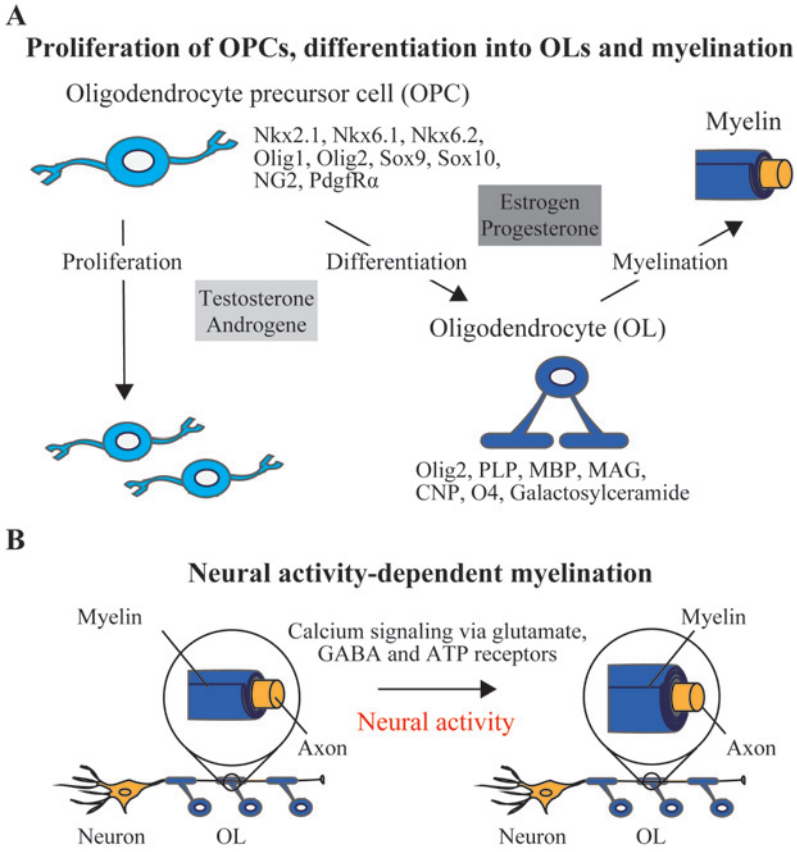

Fig. 1 Overview of proliferation and differentiation of OPCs and activity-dependent myelination
(**A**) The transcription factors and cell identity markers associated with proliferation and differentiation of OPCs and OLs are presented. Additionally, the sex hormones that facilitate proliferation and differentiation of OPCs and myelination are shown.
(**B**) Calcium signaling through neurotransmitter receptors is essential for activity-dependent myelination, such as the enhancement of myelin thickness.

genes involved in cholesterol and fatty acid metabolism [*3-hydroxy-3-methylglutaryl-CoA synthase 1* (*Hmgcs1*) and *fatty acid binding protein 5* (*Fabp5*)] were elevated in female OLs[33], potentially contributing to sex differences in myelination. Furthermore, a study involving the single-nucleus RNA sequencing of postmortem human brain samples of 20 donors (equally divided into two age groups: 10 young adults aged 30-45 years and 10 older adults aged 60-75 years, representing both sexes) revealed that OPCs and OLs both exhibit region-specific gene expression. Females displayed increased expression of *neurexin 1* (*NRXN1*, associated with AD and MS) and *hypoxia inducible factor 3 subunit alpha* (*HIF3A*, related to oxidative stress), while males exhibited elevated expression of *heat shock protein family A (Hsp70) member 1A* (*HSPA1A*) in OPCs, OLs, astrocytes, and microglia, indicating potential sex-specific stress responses[34]. These findings underscore the importance of considering sex differences in the OPC and OL populations to understand CNS pathology and develop targeted therapies.

Sex hormones play a significant role in these differences by broadly regulating glial cell activity and immune responses[35]. Estrogen and progesterone enhance OL differentiation and myelination, whereas testosterone and androgen promote OPC proliferation and differentiation. These processes are mediated by the expression of multiple genes related to oligodendrogenesis, including Olig1 and Olig2, and myelogenesis, including MBP and PLP, all driven by sex hormones[20]. Studies of rodents have shown that males have more OLs in the corpus callosum and fornix, with higher mRNA expression of proteolipid protein (PLP)/DM20 and carbonic anhydrase-II, and increased expression of MBP and CNP. In contrast, females have higher levels of cleaved caspase-3 and μ-calpain, re-

Table 1 Summary of Sex Differences in OPCs and OLs under Normal and Pathological Conditions

	Normal conditions		MS		AD	
	Male	Female	Male	Female	Male	Female
Clinical features	Not applicable	Not applicable	Rapid progression of symptoms	High susceptibility	Not applicable	High incidence rate
Structural, histological, and biochemical changes	Increase in OL numbers Increase in PLP, MBP, CNP expression	Increase in cleaved caspase-3 High OL turnover rate	Lateral ventricle enlargement, decreased grey matter volume	Androgen receptors in microglial promote remyelination	Not applicable	AD-pathology-associated subpopulations were enriched
Gene expression	Rat culture: Myelination (MBP, MAG, CNP, Myrf) ↑ Human brain: HSPA1A ↑	Rat culture: Proliferation (Olig1, Olig2, NF1, Pdgfα) ↑ Blood brain barrier regulation (Tgfβ1, Igf1) ↑ Mouse brain: Hmgcs1 and Fabp5 ↑ Human brain: NRXN1 and HIF3A ↑	Not applicable	Human brain: Myelination (GPNMB, PARD3, QKI, TNR) ↑ Axon-myelin contact and adhesion molecules (NCAM2, NLGN1, CADM2, CLDN11, ANK3, IL1RAPL1, CTNND2, LPHN3) ↑	Not applicable	Human brain: AD-pathology-associated genes (CADM2, NLGN1, QDPR and CRYAB) ↑
	PD		ASD		Aging	
	Male	Female	Male	Female	Male	Female
Clinical features	High incidence rate and more severe symptoms	Not applicable	High incidence rate	Not applicable	Not applicable	Not applicable
Structural, histological, and biochemical changes	Decrease in OL numbers	Not applicable	Increase in OL numbers Decrease in OPC numbers	Not applicable	Not applicable	Estrogen may delay brain aging
Gene expression	Not applicable	Human brain: Long non-coding RNA (Gm42418) ↑	Not applicable	Human brain: Actin filament depolymerization enzyme (MICAL3) ↑	Not applicable	Not applicable

sulting in increased turnover of OLs and myelination[36,37]. These sex differences, which emerge during the first 10 days postnatally and are influenced by androgen receptors[38], may affect the white matter tracts of the human brain[39], potentially resulting in sex differences in neuropsychiatric disorders (**Table 1**).

Sex Differences in OPCs and OLs in Neuropsychiatric Disorders and Aging

MS is an autoimmune disease characterized by chronic inflammation and demyelinating lesions due to impacts on the myelin sheath produced by OLs. While females are more susceptible to developing MS, male patients generally experience more rapidly progressive neurological deficits and cognitive decline. MRI scans and pathological studies have revealed that this progression in males is associated with lateral ventricle enlargement, decreased grey matter volume[40], and chronic immune activation[12]. One meta-analysis of transcriptomic data revealed sex differences in immune responses. In female patients with MS, factors related to the myeloid lineage and pro-inflammatory environment are influenced by changes in interleukin (e.g., IL-1 and IL-6 levels). In contrast, male patients with MS exhibit changes in factors related to the lymphoid lineage that influence the activation of T and natural killer cells[41]. These differences are believed to contribute to the variations observed in brain lesions. Sex hormones also play a significant role in these differences. For example, androgen exerts neuroprotective, anti-inflammatory, and remyelinating effects in de-

myelinated model male mice and in men with MS. However, its effects in females with low androgen levels remain poorly understood. Further, androgen induces microglial responses towards remyelination through androgen receptors expressed in microglia in lesions from demyelinated female mice and in women with MS, thereby promoting remyelination[42]. This highlights the crucial link between immune cells and remyelination. Moreover, recent single-cell RNA sequencing analyses of human samples showed that, in females, OPCs exhibited increased expression of myelin-related genes and genes involved in the differentiation of OLs and myelin repair processes (GPNMB, PARD3, QKI, and TNR). Additionally, the genes associated with axonal-myelin contact and neuronal adhesion molecules (NCAM2, NLGN1, CADM2, CLDN11, ANK3, IL1RAPL1, CTNND2, and LPHN3) were upregulated in OLs, indicating a greater propensity for remyelination in females than in males. This has also been elucidated at the cellular level, thereby emphasizing the importance of considering sex differences in understanding MS pathology and developing targeted therapies[43].

AD is characterized by amyloid plaque accumulation, neurofibrillary tangle burden, and neuronal loss, resulting in cognitive decline. AD is more prevalent in women, particularly postmenopausal women, who represent approximately two-thirds of all cases. Various studies have highlighted the role of sex hormones in neuroinflammation and bioenergetic metabolism[6,44] in these sex differences. Single-cell RNA sequencing of postmortem prefrontal cortex samples has further revealed disease-associated and sex-specific gene expression changes in cellular brain populations, including OPCs and OLs[6]. This analysis identified cellular subpopulations that were associated with AD pathology (amyloid plaques, neurofibrillary tangles, etc.) and those that were not, including specific types of neurons, microglia, astrocytes, OPCs, and OLs. OLs in AD pathology-associated subpopulations expressed markers such as *CADM2*, *NLGN1*, *QDPR*, and *CRYAB*, the latter of which is an anti-apoptotic and neuroprotective chaperone whose dysfunction may worsen inflammation and demyelination. Furthermore, AD pathology-associated subpopulations were enriched in female cells, whereas non-pathological subpopulations were predominantly male. In males, global transcriptional activation in OLs positively correlated with pathological changes, while no such shift was observed in females. Unlike male OPCs, female OPCs exhibit downregulation of gene expression in response to pathology. There is also a significant association between white matter lesion volume and cognitive decline in females, indicating a reduced transcriptional response to AD pathology in female OPCs and OLs[6]. Understanding these sex differences in OPCs and OLs is crucial in understanding the complex progression of AD and developing new targeted therapies.

Although PD is characterized by the accumulation of α-synuclein within neurons and the subsequent loss of dopaminergic cells, OPCs and OLs may play a crucial role in its pathogenesis. Single-cell RNA sequencing analysis of the human substantia nigra revealed that, unlike AD, PD is associated with dopaminergic neurons, OPCs, and OLs, rather than with microglia and astrocytes. This association was further found to be linked to genes enriched in metabolic processes and gene regulation[45]. Similar findings were observed in mouse single-cell transcriptomic data[46]. Notably, clinical sex differences in the incidence and progression of PD have also been found, with males typically having a higher incidence and more severe symptoms[47]. Sex differences in myelin, detected using MRI, are associated with tremor and asymmetry in motor symptoms. Furthermore, recent single-cell RNA sequencing analyses have shown that the reduction in the expression of long non-coding RNAs (e.g., *Gm42418*) implicated in PD pathology was greater in male OLs than in female OLs[33]. These findings indicate that understanding sex differences in OPC and OL in PD could help clarify the molecular mechanisms underlying the disease, particularly those related to sex-specific differences.

In addition to neurological disorders, sex differences in OPCs and OLs can affect the pathogenesis of psychiatric disorders and aging. ASD is also more prevalent in males, likely owing to genetic and hormonal factors. A recent review highlighted the pivotal role of OLs and myelination in ASD, focusing on how specific brain regions exhibiting hypomyelination or hypermyelination are linked to ASD symptoms. These discrepancies can affect neural connectivity and brain areas associated with social interaction and communication, indicating that OPC and OL dysfunction may play a role in ASD pathophysiology[48]. Analysis of sex-specific cellular and molecular differences in mice exposed to prenatal valproic acid showed increased OL numbers and decreased OPC proportions in males[49]. Moreover, transcriptomic analysis of the amygdala in ASD model mice revealed sex differences in the gene expression and methylation patterns of OLs and microglia[50]. Furthermore, recent single-nucleus

RNA sequencing profiles indicated sex differences in gene expression in OPCs and OLs within the developing human cortex and highlighted the higher expression of the actin filament depolymerization enzyme MICAL3 in females[51]. MICAL3, which is highly expressed in OLs after spinal cord injury, may further contribute to axonal regeneration[52]. These observations indicate that sex differences may contribute to ASD phenotypes and serve as targets for therapeutic interventions.

Finally, recent research has shown that OLs accumulate somatic single-nucleotide variations 81% faster than neurons, with mutations occurring predominantly in inactive genomic regions[53]. OPCs and OLs are central to myelination and maintenance, and age-related functional changes due to aging affect cognitive and motor functions. In aged mice, OPCs exhibit reduced proliferation and impaired differentiation[54], leading to decreased myelin production and maintenance, which contributes to cognitive decline and progression of neurodegenerative diseases such as AD[55]. Moreover, age-related pathologies in OPCs and OLs exhibit sex differences that are significantly influenced by sex hormones. Estrogen, which is known for its neuroprotective properties, may also delay brain aging in females[35]. These findings suggest that degeneration of OPCs and OLs could contribute to sex-related differences in age-related diseases (**Table 1**).

Conclusions

Research on sex-related differences in glial cell functionality is advancing rapidly[35], and there is growing interest in sex-specific therapies that can preserve and enhance the functions of OPCs and OLs. Understanding the myelination mechanisms and gene expression changes in OPCs and OLs will improve our knowledge of disease mechanisms, thereby promoting development of new treatments that consider sex differences.

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