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REVIEW

White matter and neurological disorders

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Abstract The central nervous system is simply divided into two distinct anatomical regions based on the color of tissues, i.e. the gray and white matter. The gray matter is composed of neuronal cell bodies, glial cells, dendrites, immune cells, and the vascular system, while the white matter is composed of concentrated myelinated axonal fibers extending from neuronal soma and glial cells, such as oligodendrocyte precursor cells (OPCs), oligodendrocytes, astrocytes, and microglia. As neuronal cell bodies are located in the gray matter, great attention has been focused mainly on the gray matter regarding the understanding of the functions of the brain throughout the neurophysiological areas, leading to a scenario in which the function of the white matter is relatively underestimated or has not received much attention. However, increasing evidence shows that the white matter plays highly significant and pivotal functions in the brain based on the fact that its abnormalities are associated with numerous neurological diseases. In this review, we will broadly discuss the pathways and functions of myelination, which is one of the main processes that modulate the functions of the white matter, as well as the manner in which its abnormalities are related to neurological disorders.

Keywords White matter · Myelination · Neurological disorders · Alzheimer's disease · Huntington's disease · Multiple sclerosis

Introduction

The central nervous system (CNS) consists of multiple types of cells, such as neurons, vascular cells, and glial cells. In particular, glial cells, which are also known as supporting cells, are mainly divided into astrocytes, microglia, and oligodendrocytes based on their functions. Astrocytes play pivotal functions in the brain by aiding the blood–brain barrier (BBB) (Michinaga and Koyama 2019), supplying nutrients to neurons (Tang et al. 2014), regulating ion concentrations in the extracellular space (Walz 2000), filling up the space to form a glial scar (Yang et al. 2020), serving as intermediaries in the myelinating activity of oligodendrocytes (Kıray et al. 2016), and fulfilling synaptic functions (Santello et al. 2019). Microglia are known as neuronal macrophages and fulfill a variety of tasks associated with immune defenses and the maintenance of homeostasis in the CNS. Microglia constantly scavenge the CNS to engulf unnecessary or damaged cells, by invading pathogens and debris (Neumann et al. 2009; Lloyd and Miron 2019), promoting inflammation, and repairing infected and damaged tissues (Jeong et al. 2013; Voet et al. 2019). Microglia also participate in synaptic pruning during development (Lui et al. 2016; Lehrman et al. 2018). The main role of oligodendrocytes is the formation of the myelin sheath, which insulates axonal fibers and regulates conduction speed via saltatory conduction. Besides, these glial cells closely

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communicate with neurons via various mechanisms such as neurotransmitters, calcium response, protein interaction, etc. (Fields and Stevens-Graham 2002). Especially, the interaction between myelinating oligodendoryctes and neurons plays a very pivotal role in forming a proper nodal structure including channel localization, and consequently neuronal activities (Fields and Stevens-Graham 2002).

Given the important functions of myelin in the brain, the main topic of this review, abnormal myelination is related to numerous neurological diseases, including multiple sclerosis, Huntington's disease, and Alzheimer's disease, and even to metabolic diseases, such as obesity. We will also review the relationship between white matter abnormalities and neurological diseases (Fig. 1).

Myelination and oligodendrocytes

Myelin is a multilamellar lipid membrane complex that tightly wraps axonal fibers, forming nodes of Ranvier, paranodes, juxtaparanodes, and internodes (Fig. 2). Myelin is constructed by oligodendrocytes in the CNS or by Schwann cells in the peripheral nervous system. Oligodendrocytes differentiate from oligodendrocyte precursor cells (OPCs), which express neural/glial antigen 2 (NG2) and the platelet-derived growth factor receptor alpha (PDGFRα). The activation of PDGFRα in OPCs by its ligand, the platelet-derived growth factor A (PFGFA), promotes cell proliferation (van Heyningen et al. 2001), migration (Baroti et al. 2016), and viability (Watzlawik et al. 2013). OPCs play several roles in the brain. Principally, they serve as precursors of oligodendrocytes by providing myelin formation. In addition to their major functions regarding myelination, OPCs play a regulatory role in leptin signaling in the hypothalamus (Djogo et al. 2016), in the neuro-immunological response (Nakano et al. 2017), in maintaining the homeostatic status of microglia (Liu and Aguzzi 2019), and possibly in angiogenesis (Kishida et al. 2019). OPCs are firstly produced from neural progenitors in the ventral-most precursor in the medial ganglionic eminence at embryonic stage 12.5 (E12.5), although the production of OPCs also occurs in the lateral and caudal ganglionic eminences as the embryonic development progresses (after E18; Richardson et al. 2006). The OPCs generated from precursors are self-proliferative (Clarke et al. 2012) and can differentiate into different types of cells in the presence of specific environments and signals. Their destination varies according to the developmental stage. Perinatal OPCs can differentiate into oligodendrocytes or astrocytes, whereas postnatal OPCs are only differentiated to oligodendrocytes (Zhu et al. 2011), except for those residing in the piriform cortex, where they possibly differentiate to neurons (Guo et al. 2010).

Various factors induce the differentiation of OPCs to oligodendrocytes (Fig. 3). OPCs receive synaptic input

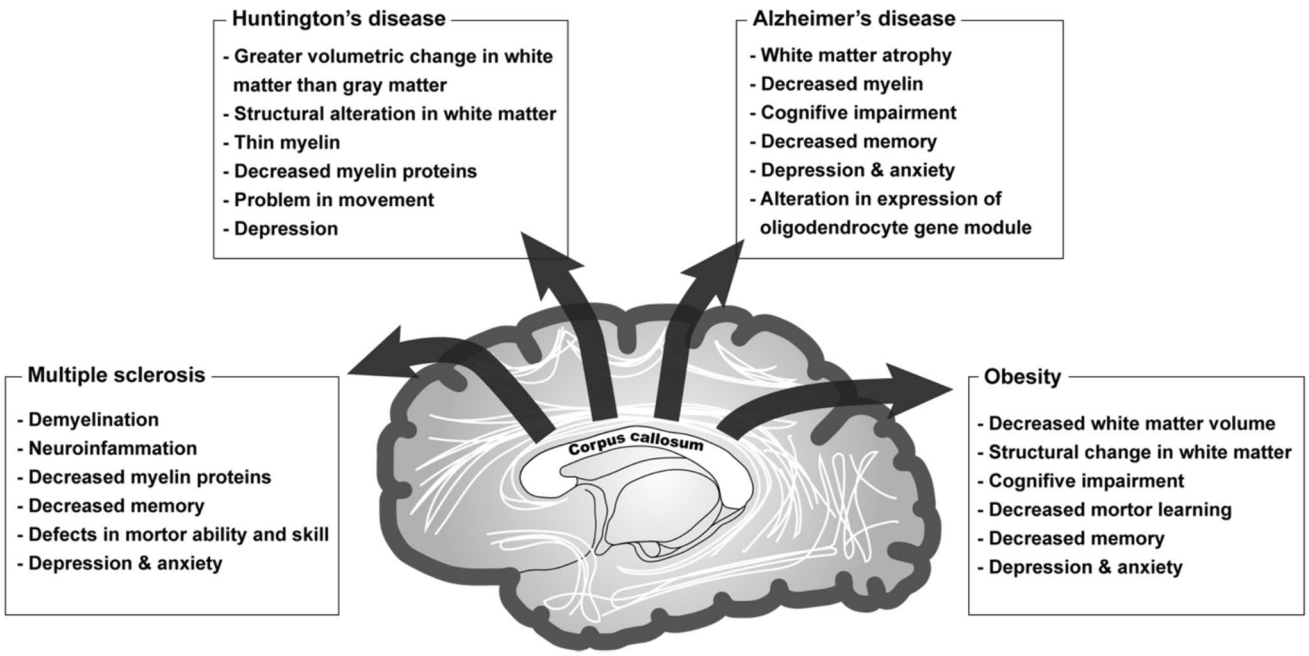

Fig. 1 Neurological disorders associated with an abnormal white matter. Increasing evidence has shown that white matter abnormalities are related to several neurological disorders, including multiple sclerosis, Huntington's disease, and Alzheimer's disease, and even to obesity. White matter alterations regarding volume or structure are commonly observed in those disorders. Furthermore, cognitive impairment, memory decline, decreased motor skills, and mood disorders (such as depression and anxiety) have been observed in those diseases

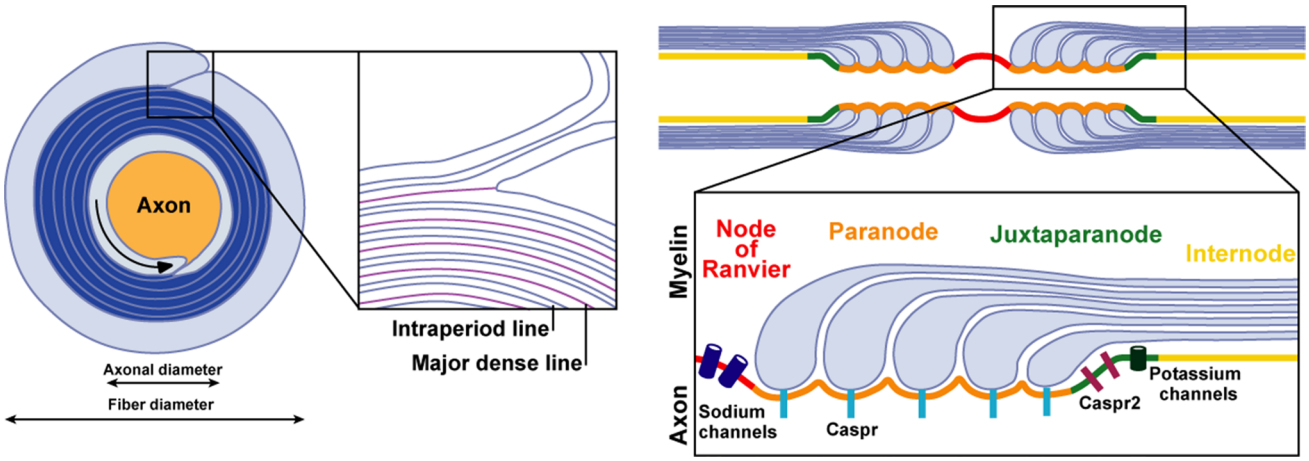

Fig. 2 Myelin structure. Myelin is a multilamellar membranous structure that wraps axons. The process of myelination forms four nodal structures in axons: nodes of Ranvier, paranodes, juxtaparanodes, and internodes. The sodium and potassium channels needed for axonal action potential are highly concentrated in the nodes of Ranvier and juxtaparanodes, respectively. The Caspr and Caspr2 proteins of the Neurexin family are localized in paranodes and juxtaparanodes, respectively, and establish adhesions between axons and myelin

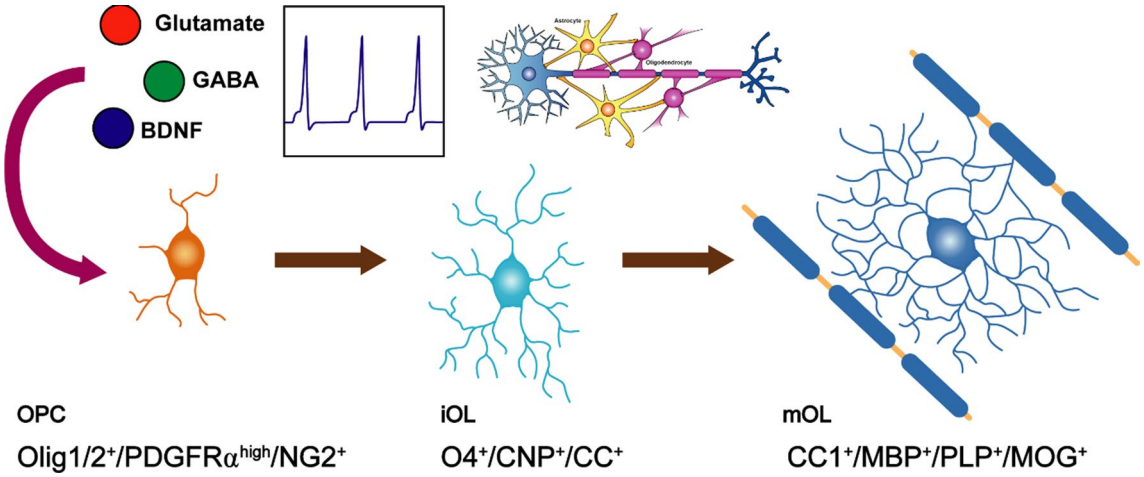

Fig. 3 Oligodendrocyte differentiation. Myelination is thought to be dependent on neuronal activity. In support of this contention, neurotransmitters, such as glutamate and GABA, have been shown to induce the differentiation of oligodendrocyte precursor cells to oligodendrocytes (OLs). Furthermore, a recent study reported that the brain-derived neurotrophic factor (BDNF), which is released from neurons, can induce this differentiation process. The differentiation of OPCs into OL shows a drastic change in gene expression patterns. The representative genes for each stage include Olig1/2/PDGFRα/NG2 for OPCs, O4/CNP/CC for immature oligodendrocytes (iOLs), and CC/MBP/PLP/MOG for mature oligodendrocytes (mOLs)

from unmyelinated glutamatergic and GABAergic neurons (Kukley et al. 2010; Boulanger and Messier 2017), which can affect OPC migration and differentiation (Tong et al. 2009; Li et al. 2010). A study demonstrated that stimulations on axons induced OPC proliferation and differentiation while they blocked action potentials from axon delayed myelination (Mensch et al. 2015). Glutamate was shown to promote the translation of myelin-associated proteins at axon–oligodendrocyte contacts (Wake et al. 2011). In addition, the brain-derived neurotrophic factor (BDNF) was also demonstrated to promote myelination (Xiao et al. 2010). In addition to physiological factors, a biophysical factor, i.e., the diameter of axons, is associated with myelination (Mayoral et al. 2018).

Modulation of axonal conduction speed

The main function of myelin is the insulation of axonal fibers, which increases the speed of signal propagation by enabling saltatory conduction. The speed of conduction is one of the most important factors in the phenomenon of

spiking-time-dependent plasticity (STDP) which is suggested by Dan and Poo (2004). The STDP is the neural synaptic plasticity that is controlled by spiking time in both pre- and postsynaptic regions. The postsynaptic activation immediately before presynaptic activation depresses the synaptic strength (timing-dependent long-term depression, t-LTD). Conversely, postsynaptic activation immediately after presynaptic activation enhances the synaptic strength (timing-dependent long-term potentiation, t-LTP). The weight of the synaptic strength controlled by STDP is dependent on the time interval between pre- and postsynaptic activation, with a shorter time interval inducing a greater weight of t-LTP and t-LTD (Zhang et al. 1998; Dan and Poo 2004; Brzosko et al. 2019). Given this mechanism, the conduction speed plays a pivotal role in synaptic plasticity and eventually in brain functions. In fact, the neuronal synchronization between brain regions has been suggested as a fundamental mechanism in brain functions such as memory formation (Jutras and Buffalo 2010), and more recent research demonstrated the importance of proper myelination manipulating conduction speed to synchronize neural activity in motor learning (Kato et al. 2020).

Several factors associated with both myelin and neurons regulate the conduction speed in the axonal fiber tract. The first factor is the axonal diameter. Because the spreading of an electrical signal in a neuron is mediated by the flow of ions at the intracellular and extracellular regions, the basic properties of neuronal signal propagation follow cable theory (Rall 2011). In electrodynamics, thicker cables exhibit a smaller resistance and faster conduction. This correlation can also be applied to axonal fibers. The axonal diameter is positively correlated with the conduction velocity, although the correlation patterns vary between myelinated and unmyelinated axons regarding the increased slope (Wen and Chklovskii 2010). The second factor is the myelin thickness (Waxman 1980; Lazari et al. 2018). The thickening of myelin around axons affords tighter insulation and prevents the electrical conduction from spreading in the radial direction, thereby enhancing its speed (Waxman 1980). However, the myelin thickness may not be sufficient to explain the increase in conduction speed, considering that the in-compactness of myelination can also increase the thickness of myelin, possibly weakening the insulation, which will be discussed in detail later. The last factor is the average size of the nodes of Ranvier and the axonal internode length; of note, this subject remains quite controversial among researchers in this field. Recent research suggested that the length of the nodes of Ranvier might be another factor affecting the conduction speed, likely because of the increase in the number of sodium channels at the node (Arancibia-Cárcamo et al. 2017). In turn, the internode length hypothesis maybe even more complicated. Logically, a longer distance between nodes entails a faster signal transmission speed through saltatory conduction; however, no experimental data have been reported that prove this hypothesis (Castelfranco and Hartline 2016).

Metabolic support by myelin

As the neuronal axon is a structure that is tightly wrapped by myelin without energy storage, it receives energy from the outside poorly. To compensate for this difficulty in fulfilling energy demands, myelin plays a role in supporting the metabolic demands of axons. It has been demonstrated in recent experiments that oligodendrocytes deliver lactate to axons via the monocarboxylate transporter 1 (MCT1), which is accepted by the MCT2 expressed in axons (Philips and Rothstein 2017). Brown et al. (2003) found that the evoked compound action potentials (CAPs) in isolated optic nerves persisted for several hours in a glucose-rich environment, but were rapidly abolished in a glucose-deprived (aglycemia) environment, although this failure could be effectively prevented by supplying L-lactate to the system. However, recent research conducted by Meyer et al. (2018) suggests that glucose is the main energy source transferred from oligodendrocytes to axons in the corpus callosum. Therefore, axonal action potentials were examined by measuring CAPs in an aglycemic environment. Although the addition of lactate or pyruvate could not rescue axonal activation in this situation, it could be revived only when glucose was infused into oligodendrocytes using a patch pipette. More interestingly, the injection of glucose into astrocytes, which is better known as metabolic support for axons, could not induce the activation of axons in an aglycemic environment. These results suggest that oligodendrocytes are the only metabolic supporters in the corpus callosum and act by transferring glucose, but not lactate or other carbohydrate products. Although oligodendrocytes in different regions (optic nerve and corpus callosum) may use different metabolic sources, it is clear that these cells play a critical role as metabolic support to axons.

Myelin plasticity

During the life span, the human body encounters numerous damageable events that take place internally or externally, and that sometimes results in the collapse of body parts. However, the body can react quickly to repair damage and regenerate itself, for optimization via the replacement of old or damaged cells with newly proliferated cells. The nervous system has a mechanism that responds quickly to the environment and immediately enters the repairing step when damage occurs. Neurogenesis, which is the process by which neurons are produced from neural stem cells, occurs in the hippocampal subgranular zone (SGZ) and subventricular

zone (SVG), and other glial cells (astrocytes and the oligodendrocyte lineage) are also newly generated in the SGZ, SVG, and locally (Arai and Lo 2017).

OPCs have been suggested to be a type of multipotent stem cells in the brain (Richardson et al. 2011). In fact, OPCs can become both astrocytes and oligodendrocytes during the prenatal period (El Waly et al. 2014), although they can only differentiate into oligodendrocytes after birth. To investigate the proliferation and differentiation of OPCs in the adult stage, Rivers et al. (2008) generated tamoxifen-dependent PDGFRα-Cre transgenic mice (Pdgfra-CreER::Rosa26-YFP) to label and track the fate of PDGFRα-positive cells in the adult brain. Tamoxifen was administered at P45 or P180 in this mouse line to trace the PDGFRα-positive OPCs in the adult brain. The prevalence of cells expressing both YFP and PDGFRα decreased over time, which suggests that OPCs can proliferate and differentiate into other cell types. Those differentiated cells were identified as pre-myelinating and myelinating cells via the investigation of the co-expression of oligodendrocyte markers, such as 2',3'-Cyclic-nucleotide 3'-phosphodiesterase (CNPase) and myelin basic protein (MBP). Over 20% of the oligodendrocytes in the corpus callosum were newly generated and differentiated in the adult stage in that study, suggesting the presence of myelin plasticity during adulthood. In support of this hypothesis, several subsequent studies showed that OPCs can be differentiated into new oligodendrocytes in the brain, spinal cord, and optic nerve of adult mice (Dimou et al. 2008; Kang et al. 2010; Young et al. 2013). However, the role of oligodendrogenesis and myelination plasticity in adulthood are not well understood.

Many researchers believe that oligodendrogenesis is simply the process of replacing old or damaged oligodendrocytes with new ones. However, recent studies have shown that adult-born oligodendrocytes could add new myelin to partially myelinated axons throughout the life span, without loss of pre-existing internodes (Tripathi et al. 2017). Tripathi et al. (2017) conducted an experiment to trace adult-born oligodendrocytes by generating a mouse line carrying tamoxifen-dependent Cre recombinase and a Cre-inducible reporting gene (*Opalin–iCreERT2:Tau–mGFP or Opalin–iCreERT2:Rosa–YFP*). Tamoxifen was administrated at P60 and labeled cells were traced thereafter. The labeled oligodendrocytes generated at P60 survived more than 1 year without decaying or turning over, although the survival rates of cells varied depending on the brain region. These results indicated that adult oligodendrogenesis was not required for the replacement of cells or myelin turnover; rather, it represented a novel form of neural plasticity that modified the myelination of the existing neuronal circuit. In addition, several other studies showed that myelin plasticity is possible in different situations, such as the learning process (Steadman et al. 2020), social interaction deficit (Liu et al. 2012; Bonnefil et al. 2019), and the suppression or activation of sensory perception (Hughes et al. 2018; Lazari et al. 2018), indicating that the disruption of oligodendrogenesis can impair memory consolidation (Steadman et al. 2020). Accumulating evidence suggests that myelin plasticity not only plays a complementary role but also provides powerful insights regarding the interpretation of neural plasticity.

Several factors, such as neuronal activity, axonal size, and molecular signals may modulate myelin plasticity. Among them, activity-dependent modulation is a well-documented mechanism. An optogenetic study using zebrafish showed the increased occurrence of myelination on the photoactivated axon compared with the non-activated axon, suggesting that neuronal activation is an important factor for axonal myelination. Although myelination may be initiated in oligodendrocytes with large-sized axons without neuronal activation, the myelination is maintained only on the axons with neuronal activity (Hines et al. 2015). Interestingly, these mechanisms persist even in adulthood and induce myelin plasticity. A study conducted by Gibson et al. (2014) reported that optogenetic neuronal stimulation in the motor cortex could induce OPC proliferation within 3 h, which subsequently resulted in increased myelin thickness and behavioral changes (fine motor function) 4 weeks later. A more recent study conducted on the somatosensory cortex identified a similar pattern (Hughes et al. 2018). In this research, the authors designed a special housing with hanging beads on top of the cage, to enhance the sensory function of whiskers, and observed an increased number of new oligodendrocytes in the somatosensory cortex without alteration in the length of the existing myelin sheaths. Myelin plasticity occurs not only in enhancement but also in depression (reviewed in Lazari et al. 2018). Sinclair et al. (2017) conducted an experiment to investigate myelin plasticity in the auditory system by impairing the hearing of young (P10) and adult (P65) mice for 10 days using earplugs and later allowed to recover for 15–25 days. They found that the myelination pattern was significantly altered in young mice, with a decreased proportion of large axons (> 3.5 μm), decreased overall axonal caliber size, and decreased myelin thickness compared with the negative controls. Although the level of alteration was not as high as that observed in young mice, a similar pattern was observed in adult mice. Furthermore, a recent study using zebrafish demonstrated that phagocytosis of microglia is the main process leading to myelin pruning (Hughes and Appel 2020).

Myelin plasticity is a conserved phenomenon that is commonly observed across numerous vertebrate species, including humans. Scholz et al. (2009) investigated whether a new movement training can alter the structure of the white matter in the human brain. In that study, the authors recruited volunteers to practice juggling for a total of 5 weeks, at a frequency of 5 days per week. The brains of volunteers were

subjected to scanning using diffusion tensor imaging (DTI) before and after juggling training. Interestingly, a significant alteration was detected in the structure of the white matter after juggling training, indicating that new motor learning can alter not only neuronal plasticity but also the structural pattern of the white matter in humans. Similarly, it has been reported that musical practice can induce changes in the white matter structure of the brain (Bengtsson et al. 2005; Steele et al. 2013). Strikingly, myelin plasticity was observed in quite old (mean age, 61 years) human subjects, although myelin plasticity gradually weakened with age (Scholz et al. 2009; Steele et al. 2013). Engvig et al. (2012) examined whether 8 weeks of memory training in an old-aged group caused changes in the structure of the white matter in the brain using DTI technology. They found that the memory-trained group exhibited a significantly increased level of fractional anisotropy (FA), a parameter that indicates increased diffusivity along the axon, which can also represent evidence of greater myelination. Taken together, these results show clearly that various types of neural activities, regardless of age, can cause neuronal plasticity, often associated with myelin plasticity.

Multiple sclerosis

Myelination plays highly important roles in various brain functions, such as neuronal signal transmission and neuronal plasticity. Given this neurophysiological importance of myelination, abnormal myelin can lead to serious neurological diseases. Multiple sclerosis is one of the well-known myelin-associated diseases. Multiple sclerosis is a chronic autoimmune disease that exhibits demyelination in the CNS, including the spinal cord and brain, and results in permanent damage to nerve cells. About 80% of patients with multiple sclerosis initially suffer periodic relapses that are normally followed by remissions (Ohtomo et al. 2018). It is known that the recovery of myelin during remissions is incomplete in these patients because the remyelination can not achieve the original length and thickness of the myelin (Ohtomo et al. 2018). Repeated relapses and remissions eventually lead to chronic pathological loss of myelin, which results in serious axonal lesions (Ohtomo et al. 2018). The symptoms of multiple sclerosis can vary depending on the number of nerves that are damaged. Patients with severe multiple sclerosis may lose their ability to move, although many suffer from long-term remissions that appear periodically without adding new pain. The most typical symptoms of multiple sclerosis are numbness and weakness of the limbs and uncoordinated limb movement, such as limping. Vision problems, such as partial or complete loss of vision, pain with eye movement, prolonged double vision, and blurry vision, are also commonly observed among patients with multiple sclerosis. Moreover, the symptoms may include slurred speech, fatigue, dizziness, tingling, or pain in parts of the body, and problems with sexual, bowel, and bladder function. However, appropriate treatments for multiple sclerosis have not been developed because its exact etiology is not completely understood. Nevertheless, it is estimated that several genetic and environmental factors cause multiple sclerosis. The *ERMN* gene (encoding Ermin) is one of the potential causative genes of multiple sclerosis, as its downregulation is generally observed in these patients (Salek Esfahani et al. 2019). Ermin is a cytoskeletal protein that is expressed in oligodendrocytes, and a mutation in its actin-binding site leads to abnormal actin distribution and morphology in oligodendrocytes, suggesting a pivotal role for Ermin in myelination (Brockschnieder et al. 2006). Although the onset of multiple sclerosis can be associated with defects of oligodendrocytes themselves, it may also be attributed to reduced migration and maturation of OPCs in lesioned areas (Ohtomo et al. 2018). While several inhibitory factors and mechanisms for the failure of cell migration and differentiation are present in the lesion microenvironment, researchers have suggested that critical factors and mechanisms likely exist in interactions between oligodendrocyte lineages and other types of cells, including astrocytes, neurons, and microglia (Lampron et al. 2015). For example, i.c.v injection of microglia activated by IL-4 increased oligodendrogenesis and attenuated the abnormal phenotypes in multiple sclerosis rodent models (Butovsky et al. 2006; Bar and Barak 2019). As discussed above, neurons interact strongly with oligodendrocyte lineages and control myelin plasticity. A recent study revealed that astrocyte-derived lipids are required for the myelination of oligodendrocytes (Camargo et al. 2017). The removal of myelin debris from myelin sheaths damaged by microglia is also a critical step of remyelination (Lampron et al. 2015), and M2 microglia have been reported to maintain myelin homeostasis by promoting OPC differentiation (Miron et al. 2013). However, those kinds of cell–cell interactions may yield the opposite results. Astrocyte-derived endothelin-1 (ET-1) was shown to provide a negative regulatory effect on OPC differentiation and remyelination by promoting Jagged1 expression (Hammond et al. 2014). In addition, microglia can also recognize oligodendrocytes as antigens and cause myelin loss in some conditions (Goldmann and Prinz 2013). Although the mechanisms underlying the cell–cell interactions remain unclear, increasing evidence shows that these interactions will likely provide a pivotal clue for the enhancement in the understanding of multiple sclerosis pathology and the identification of an adequate treatment for multiple sclerosis.

Alzheimer's disease

Alzheimer's disease is a neurodegenerative disease that has generally been considered as a gray matter dysfunction that is caused by the accumulation of amyloid-β (Aβ) plaques, neurofibrillary tangles resulting from the hyperphosphorylation of the tau protein, the structural change of dendrites, synaptic autophagy (Bahn and Jo 2019; Bahn et al. 2019; Lee and Kim 2019). However, increasing evidence has demonstrated that white matter alterations can be a reliable marker of Alzheimer's disease incidence (Kao et al. 2019). In recent studies, white matter alterations were observed in the preclinical period of Alzheimer's disease, even before the appearance of clinical symptoms, such as cognitive impairment (Puzo et al. 2019). The white matter alterations in Alzheimer's disease were also demonstrated in a postmortem study in the form of a decreased number of olig-2-positive cells (Behrendt et al. 2013) and a decreased oligodendrocyte nuclear diameter, without alteration of neuronal nuclei (Gagyi et al. 2012). White matter alterations were also observed in non-human animal models of Alzheimer's disease. A previous study showed that the 3·Tg-AD mouse model (carrying the human amyloid precursor protein Swedish mutant (*APPS*) transgene, a presenilin-1 (*Psen1*) knock-in mutation, and the tau P301L mutant transgene) of Alzheimer's disease exhibited a lower expression level of myelin-associated proteins and a relatively low number of myelinating oligodendrocytes, whereas the proportion of non-myelinating oligodendrocytes was increased (Desai et al. 2010). Although Aβ plaques are barely found in the white matter, cells in the white matter can be exposed to Aβ, given that soluble Aβ can penetrate these tissues (Collins-Praino et al. 2014). Previous studies showed that Aβ can also be toxic to oligodendrocytes. The exposure of a primary oligodendrocyte culture to Aβ induced oxidative stress and mitochondrial DNA damage, consequently leading to oligodendrocyte death and dysfunction (Xu et al. 2001). A more recent article reported that treatment with oligomeric Aβ can trigger OPC senescence (Zhang et al. 2019); in contrast, an Aβ oligomer enhanced the level of oligodendrocyte differentiation in another study (Quintela-López et al. 2019). Furthermore, a more recent study that used *in situ* sequencing in the mouse brain, which is a method that overlaps spatial information in expression data, showed that the level of expression of the oligodendrocyte gene module (OLIG) was related to amyloid plaque location to a greater extent compared with the genotypes of transgenic mice (Chen et al. 2020), suggesting the presence of myelin disturbances in Alzheimer's disease.

Huntington's disease

Huntington's disease is a genetic neurodegenerative disease caused by the expansion of a CAG repeats within the huntingtin (*HTT*) gene. The symptoms of Huntington's disease include cognitive, psychiatric, and motor impairments. The neurodegeneration initiates in the striatum, followed by the white matter tracts and cortex. Given the disease progression, it has been suggested that the white matter dysfunction is a secondary effect of the loss of gray matter volume. However, increasing evidence suggests that the white matter impairment in Huntington's disease is independent of neuronal degeneration (Dumas et al. 2012; Di Paola et al. 2014; Casella et al. 2020). In support of the independence of the white matter impairment in Huntington's disease, the 24-month-long longitudinal study conducted by Tabrizi et al. (2012) showed a greater volumetric decrease in the white matter compared to in the gray matter. Furthermore, alterations in the corpus callosum and the white matter of the sensory-motor cortex have been reported in patients with Huntington's disease years before the onset of clinical symptoms (Dumas et al. 2012; Di Paola et al. 2014). The white matter abnormality has been demonstrated in rodent models, by showing the presence of thinner myelin accompanying the decreased level of myelin-associated proteins in PLP-150Q and BACHD mice (Huang et al. 2015; Bardile et al. 2019). Furthermore, a recent study conducted by Bardile et al. (2019) showed that the *HTT* deletion mutation specifically in oligodendrocytes (NG2-cre) ameliorated the thinning of myelin and behavior abnormalities in BACHD mice, suggesting that the white matter abnormality is independent of the neuronal degeneration. However, most studies of white matter abnormalities in Huntington's disease were based on neuroimaging approaches. Although neuroimaging techniques are noninvasive and very useful methods for the diagnosis and study of neurological disorders, they present limitations regarding the improvement of our understanding of the mechanisms and pathological processes that are required for the development of drugs or treatments. Therefore, multidisciplinary approaches aiming at elucidating the white matter abnormalities in Huntington's disease are required in future studies.

Metabolic syndrome and white matter

Obesity, as one of the most serious metabolic-related diseases, has a significant adverse effect on the health of modern humans worldwide. Although obesity is simply diagnosed based on excessive weight and body mass index values, systematic studies are needed to address the side effects of obesity that occur through various complex processes. Obesity can cause diabetes, hypertension, hypoxia,

hormone disturbance, metabolism disturbance, a reactive immune system, etc., which are complications that are associated with neuronal dysfunction (Seong et al. 2019).

A neuroimaging study of patients with obesity revealed an alteration of brain volume in both the white and gray matter (Dekkers et al. 2019). In particular, research using the DTI technique, which can be regarded as a non-invasive method for the investigation of the microstructure of the white matter, showed altered diffusivity in the white matter of these patients (Dekkers et al. 2019), suggesting the existence of a defect in myelination. The presence of confounders and various candidate factors prevents the clear elucidation of the cause of the white matter defect observed in obesity. Diabetes is one of the well-studied complications of obesity. Diabetes itself has several symptoms, such as hyperglycemia, insulin resistance, hyperinsulinemia, diabetic ketoacidosis, and hypoglycemic events, which can cause brain injury (Hamed 2017). The pathogenesis of diabetes on brain injury is quite complex and is caused by combinations of several factors, such as vascular disease, oxidative stress, neuroinflammation, mitochondrial dysfunction, apoptosis, reduction of neurotrophic factors, acetylcholinesterase activation, neurotransmitter changes, impairment of brain-repair processes, impairment of the brain glymphatic system, accumulation of Aβ and tau phosphorylation, and neurodegeneration (reviewed in Hammed 2017). Obesity-induced inflammation, which has also been studied well in peripheral organs, such as adipose tissues, release inflammatory mediators, and causes inflammation that spreads throughout the body (Ellulu et al. 2017). Obesity-induced inflammation can also be observed in the CNS (Kim et al. 2019), and can break down the BBB, thus promoting macrophage infiltration (Stranahan et al. 2016). Obesity hypoventilation syndrome (OHS) is a clinical entity characterized by the coexistence of obesity and hypercapnia during wakefulness (Castro-Añón et al. 2015). More severe symptoms of this disease can lead to hypoxia or brain dysfunction. Among them, vascular-associated factors are pathologically validated in terms of brain function, such as cognition. In general, vascular cognitive impairment syndrome is caused by impairment of the blood supply to the brain. Low blood supply may have adverse effects on the brain in complex manners, with BBB disruption, activation of glia, and oxidative stress (Ohtomo et al. 2018). Although the nature of the association between the factors described above and white matter abnormalities is unclear, recent research suggests the association between obesity-induced diseases and white matter defects (Dekkers et al. 2019). Volumetric and structural alterations of the white matter were observed in human patients with obesity (Dekkers et al. 2019), as well as in non-human animal models (Hashimoto et al. 2013; Venkat et al. 2015). Moreover, the association among the complications of obesity has been suggested to be related to white matter abnormalities based on the presence of white matter rarefaction in a vessel occlusion model, as well as white matter damage and gliosis in a model of hypertension (Hashimoto et al. 2013; Venkat et al. 2015). In addition, impaired myelination was identified in a leptin-deficient obese model (Hashimoto et al. 2013; Venkat et al. 2015). However, additional questions remain to be answered and the underlying mechanisms warrant elucidation. Because obesity is a complex disease that is accompanied by numerous complications, such as diabetes, hormone resistance, and cardiovascular disorders, a more careful investigation and deep consideration are necessary for future studies.

Other neurological diseases associated with abnormal myelination

The development of white matter including myelination begins 29th gestational week (~post natal day 1–3 in rodent) and it is known to continue to adult in humans (Semple et al. 2013). The highest proportion of myelination occurs during childhood (~5 years old), and which suggests that factors disturbing myelination during childhood can cause neurodevelopmental disorders. Williams syndrome is one of the neurodevelopmental genetic disorders (deletion of about 25 genes on the long arm of chromosome 7) encompassing abnormal myelination. The patients with Williams syndrome show hyper-sociability and anxiety (Nir and Barak 2020). Although the underlying mechanisms have not been elucidated, a study by Barak et al. (2019) sheds a light on the possible molecular mechanism of this disorder. In this study, the neuron-specific deletion of Gtf2i which is one of the deleted genes in Williams syndrome showed a similar pattern of abnormality with the disorder. Further, the abnormality was rescued by restoring myelination properties with clemastine or increasing axonal conductivity by AP-4. Other leukodystrophies (genetic white-matter brain disorders), vanishing white matter (VWM)/childhood ataxia with central hypomyelination (CACH), have been reported. These disorders are known to be caused by defects in eIF2B (Schiffmann and van der Knaap 2004; van der Knaap et al. 2006). The Guillain–Barré Syndrome is another myelin-associated disorder. The symptoms of this disorder are numbness, paresthesia, weakness, pain in the limbs, or some combination of these. Although pathological processes of Guillain–Barré Syndrome is far to be elucidated, substantial evidence supports the autoimmune response as causes of it (Yuki and Hartung 2012).

Conclusion and further studies

Although the white matter has been underestimated in past years, its important roles in brain functions have begun to be recognized by many neuroscientists recently. The white matter is a complicated brain structure, rather than a simple tract

of fibers. The processes of white matter formation encompass complicated communications between neurons and glial cells, such as astrocytes, microglia, and oligodendrocytes. Moreover, because myelination is considered as one of the mechanisms underlying neuronal plasticity, as demonstrated by recent research, proper white matter formation is essentially required for normal brain function. Although abnormal white matter structure increasingly has been reported in various neurological diseases, such as Huntington's disease, multiple sclerosis, and Alzheimer's disease, and even in metabolic diseases by neuroimaging approaches, the studies for underlying mechanisms of these abnormalities have still lacked. As we discussed above, the white matter abnormality in the various neurological diseases is not simply a secondary effect of neuronal degeneration anymore. Therefore, to achieve a better understanding of the relationship between the white matter and neurological diseases, the elucidation of the physiological and molecular mechanisms underlying the association between abnormal white matter and neurological diseases is necessary, which might represent a breakthrough in the development of novel curative or therapeutic approaches to manage neurological diseases. As we discussed above, the mechanisms of myelination is not simply wrapping the neuronal axon. The precursor cells have to migrate, differentiate, and finally properly form the myelin. During the process, neurons, astrocytes, microglia, and oligodendrocytes closely communicate and interact. Therefore, future studies for underlying mechanisms of abnormal myelination in neurological disease might need to focus on the ability of myelin formation and cell-cell interaction.

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Compliance with ethical standards

Conflict of interest The authors declared that they have no competing interests.

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