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Stroke in CNS White Matter: Models and Mechanisms

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Introduction/abstract

Subcortical white matter stroke (WMS) is demarcated by the continuous formation of small ischemic lesions within white matter tracts of the central nervous system. WMS is prevalent in older adults and stands as the second leading cause of dementia. In a startling statistic, most human beings will present with WMS by the age of 80 (de Leeuw et al., 2001). Early infarctions in human beings are asymptomatic, hence they are part of a category of “silent stroke”. However, WMS is progressive with both an increase in infarction size and amount throughout subcortical white matter of the central nervous system, resulting in cognitive and motor dysfunction. Pathological analyses of post mortem brain tissue samples from WMS patients reveal the disruption of white matter architecture as a chief hallmark of infarction. Furthermore, the recent development of reliable mouse models of WMS has provided corroborating evidence of the centrality of the central nervous system’s limited capacity to remyelinate following WMS. Taken together, these data provide an impetus to investigate the pathophysiological mechanisms that underpin demyelination and remyelination in the central nervous system following ischemic injury. This review addresses the current understanding of myelin biology and oligodendrocyte biology, human WMS etiology, the mechanisms of remyelination failure in mouse models of WMS, and the development of potential therapeutic strategies founded upon recent advances in our understanding of myelin plasticity.

Structure, source, and function of white matter

White matter tracts in the brain

White matter tracts are composed of a dense array of myelinated and unmyelinated axons, which allow for rapid communication between various regions of the central and peripheral nervous system. In the brain, white matter tracts can be categorized into three groups, based upon their projection pattern: projection pathways, association pathways, and commissural pathways (Andronikou, 2012). Projection tracts connect cortical regions with subcortical structures such as the basal ganglia and spinal cord. Association pathways are cortico-cortical intrahemispheric projections which connect cortical regions within the same brain hemisphere. Commissural pathways are cortico-cortical interhemispheric pathways that connect cortical regions across both brain hemispheres. Of three defined telencephalic

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commissure pathways - anterior commissure, hippocampal commissure, and the corpus callosum – the corpus callosum is the most prominent in the human brain (Raybaud, 2010). The corpus callosum, which is located just ventral to the cortex, is composed of roughly 20 million axons, of which a majority form homotopic connection with the contralateral cortex – though a minority do form heterotopic connections (Patel et al., 2013).

CNS white matter is composed of myelin and is derived from oligodendrocytes

White matter is found throughout the central and peripheral nervous system and is produced by two glial subtypes – oligodendrocytes in the central nervous system and Schwann cells in the peripheral nervous system. White matter is composed of myelin, a lipid rich extension of membrane from oligodendrocytes (Baumann and Pham-Dinh, 2001). Each oligodendrocyte extends multiple myelinated sheaths, termed internodes, and forms multilayered, compacted, concentric wraps around neighboring large caliber axons (Baumann and Pham-Dinh, 2001; Hughes et al., 2018; Klingseisen and Lyons, 2018).

Myelin function: insulation, salutatory conduction, metabolic support

Myelin allows for the rapid and efficient propagation of action potentials along axons. Thick, multilamellar sheaths of myelin formed around individual axon fibers by neighboring oligodendrocytes results in both an increase in resistance and decrease in capacitance of the underlying axolemma, allowing for faster conduction velocity and efficiency of an action potential (Chang et al., 2016). Furthermore, developmental studies in nodes of Ranvier, 1 μ m gaps situated in between individual internodes, have demonstrated that molecular cascades initiated by the interaction between the axon and oligodendrocyte, in part signals the recruitment and enrichment of voltage-gated sodium channels at nodes of Ranvier (Rasband and Peles, 2016). Nodal formation allows for the regeneration of the action potential as it traverse down the myelinated axon (salutatory conduction). Finally, there is evidence that oligodendrocytes also provide metabolic support via lactate transport, to the underlying axon, which is critical in axonal survival (Hinman, 2014). Genetic disruption of the monocarboxylate transporter 1 (MCT1), a lactate transporter enriched in oligodendrocytes, results in axon degeneration in the central nervous system (Lee et al., 2012b). Finally, in vivo monitoring of ATP demonstrate that MCT1/2 disruption reduces ATP levels in axons of the central nervous system (Trevisiol et al., 2017).

Oligodendrocytes are derived from OPCs during development and into adulthood

Oligodendrocytes are derived from a population of mitotic small stellate shaped resident stem cell/precursor cells known as oligodendrocyte precursor cells (OPC). Fate mapping of OPCs in the mouse central nervous system demonstrate that differentiation into mature oligodendrocytes begins during early post-natal life and continues into adulthood (Rivers et al., 2008; Kang et al., 2010). Using a tamoxifen inducible Cre recombinase cytosolic GFP reporter line, Kang et al. 2010 demonstrated that OPCs generated rapidly in both white and gray matter at post-natal day 5 (P5). Within 5 days of recombination (P5+5), 35% of GFP positive OPCs downregulated markers for the OPC lineage (PDGFR α and NG2) while retaining markers of the oligodendrocyte lineage (Olig2 and Sox10). At 11 days (P5+11), the majority of recombined OPCs produced oligodendrocyte-like processes and at 28 days (P5+28), these cells expressed markers for mature oligodendrocytes (CC1). Induction of

recombination at postnatal day 30 (P30) and 70 (P70) also demonstrated the production of oligodendrocytes, though the rate of differentiation of OPCs into mature oligodendrocytes was significantly decreased relative to P5 brains. Furthermore, visualization of de novo myelin, using an inducible Cre recombinase membrane bound GFP line, demonstrated that adult-born oligodendrocytes also form myelin. Electron microscopic analysis coupled with silver enhanced immunogold labeling against GFP at P30+150 demonstrated that adult born oligodendrocytes form compacted myelin in both white and gray matter (Kang et al., 2010). These data indicate that while OPC generation and myelination is robust in early post-natal life, the adult rodent brain maintains the capacity to continuously myelinate.

OPC mitosis and myelination

OPCs are mitotic cells that are organized into a dynamic, non-overlapping, web across the grey and white matter of the central nervous system (Hughes et al., 2013). OPC morphology is complex, with highly arborized processes and motile filopodia that survey their environment. The homotypic repulsive properties of OPCs ensure that they arrange themselves in a tiled pattern in the brain (Hughes et al., 2013). Proliferation and migration of OPCs into newly vacated parenchymal spaces following OPC loss via death or differentiation ensures a constant density of OPCs throughout the brain (Hughes et al., 2013). The primary known function of OPCs are to differentiate into mature oligodendrocytes both during early post-natal development and into adulthood. Oligodendrogenesis necessitates their exit from their cell cycle, which varies in length throughout early post-natal development and adulthood. The length of the OPC cell cycle is directly correlated with the change in rate of de novo myelin formation in the postnatal brain. As the brain ages, cell cycle time for OPCs increases. OPCs in the corpus callosum during early development – post natal day 6 – require 2 days to complete their cell cycle before exit and maturation. At postnatal day 240–540, that time increases to 70 days (Psachoulia et al., 2009). Even at an advanced age such as 8 months, the rodent brain continues to generate oligodendrocytes from OPCs (Psachoulia et al., 2009). However, it should be noted that the genesis of oligodendrocytes does not necessitate OPC division as an immediate precursor step – though it does not preclude it. In vivo analysis of GFP labeled OPCs in the cortex over the course of several weeks demonstrate that only a fraction of recorded differentiation events (7 of 107) were directly preceded by cell division (Hughes et al., 2013).

Myelin and non-synaptic forms of plasticity

Recent evidence in both mice and humans demonstrate that myelin is plastic, is actively modulated by neuronal input, and that this phenomenon may be instrumental to the acquisition of certain types of motor memory (McKenzie et al., 2014; Fields, 2015; Kaller et al., 2017). The canonical understanding of plasticity in the central and peripheral nervous system places neuronal synapses at its center. However, recent studies in non-synaptic forms of plasticity reveal other, non-synapse, neural structures and glial cells to be inherently plastic as well and involved in the active modulation of neuronal input. For example, the axon initial segment (AIS), which functions in part as the site of synaptic integration and action potential induction, is involved in neural plasticity via altering either its length or position along the axons thereby tuning neural firing (Grubb and Burrone, 2010; Rasband,

2010; Grubb et al., 2011). Both chronic depolarization and optogenetic stimulation of dissociated hippocampal cultures results in a shift in AIS position relative to the soma, producing a change in the neuron's current threshold for action potential spiking (Grubb and Burrone, 2010). Together, this data indicates that the idea of non-synaptic forms for plasticity are not unprecedented. Indeed, evidence from the emerging myelin plasticity field now demonstrate that the production of de novo myelin and potentially the restructuring of pre-established myelin sheaths are also part and parcel of the homeostatic mechanisms that govern brain plasticity. The underlying mechanism of action for myelin plasticity is the CNS actively modulating the conduction speed of the action potential by directly altering the level of myelin on an individual axon (Bergles and Richardson, 2016). This means that axons can stimulate myelination through a local signaling action: the more active an axon the more it might enhance or alter its pattern of myelination. The available evidence suggests that axons actively signal, through a variety of signaling mechanisms, onto neighboring oligodendrocyte precursor cells (OPCs), driving them to differentiate into myelinating oligodendrocytes (Purger et al., 2016; Almeida and Lyons, 2017). Furthermore, there is also evidence in zebrafish and in vitro models that neurons signal directly onto myelin sheaths, altering their geometry (remodeling) and ultimately affecting neural processing (Purger et al., 2016; Almeida and Lyons, 2017).

Human WMS: predictors, pathology, behavioral consequences

White matter stroke (WMS) constitute a subtype of lacunar stroke – ischemic lesions, which form within subcortical regions of the brain including, white matter, basal ganglia, and brain stem – and account for 20% of all stroke subtypes and 25% of all ischemic strokes (Gouw et al., 2008; Bailey et al., 2012). Lacunar lesions are the result of abnormalities and occlusion of deep penetration small perforating vessels and are the pathological outcome of cerebral small vessel disease (cSVD) (Gouw et al., 2008; Wardlaw et al., 2015; Loos et al., 2018). Human neuroimaging in patients suggest that WMS begins as acute infarcts, of which 10% are transient (Wardlaw et al., 2015). These lesions present at hyperintensities in both white matter (white matter hyperintensity) and gray matter on T2 weighted, proton density weighted, and fluid attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) sequences (Wardlaw et al., 2015). White matter hyperintensities that remain continue in the same form or cavitate into 3–5mm cerebral spinal fluid filled lacunes (Wardlaw et al., 2015). The etiology of the WMS is unknown. However, WMS is highly correlated with age and a population based MRI analysis of human patients suggests that most people will have WMS by 80 years of age (Leeuw et al., 2001) Furthermore, an MRI analysis of human patients demonstrates metabolic syndrome, an increasing common condition of obesity, hypertension and hypercholesterolemia, to be correlated with the formation of subcortical white matter lesions, silent lacunar infarcts, and periventricular hyperintensities (Bokura et al., 2008; Park et al., 2008).

WMS post mortem analyses

Pathological analyses of WMS in post mortem human brains demonstrate white matter damage, microglia activation, astrogliosis, inflammatory cell infiltration, and axon degeneration (Wardlaw, 2008; Bailey et al., 2012; Wardlaw et al., 2015).

Immunofluorescence analysis of node of Ranvier and paranodal architecture in human WMS samples demonstrate a specific disruption of these subcellular structures in areas up to 150% of the infarct diameter. Curiously, in this study, neurofilament and myelin basic protein immunostaining demonstrate that axon and myelin structure are relatively intact in these areas (Hinman et al., 2015). Disorganization and loss of nodes of Ranvier and associated paranodal structures are a common pathological consequence of neural injury and disease in mouse models and suggest a disruption in the interaction between the axon and the oligodendrocyte (Susuki, 2013). These studies demonstrate that the peri-infarct region in white matter is susceptible to the disassembly of axo-oligodendrocyte interactions and suggests that this event precedes myelin and axon degeneration.

Behavioral consequences of WMS

Early formation of WMS is often asymptomatic or produces subtle neurological deficits such as visual field impairment, motor disturbances, and frailty, which often go unnoticed by the patient (Vermeer et al., 2007). Hence, they are considered a form of “silent stroke”.. Progression of WMS results in profound motor and cognitive deficits. WMS is associated with hemiparesis, gait abnormalities, verbal processing deficits, and disruption of executive function (Sozmen et al., 2012). WMS is also associated with an increase in depression and is amongst the leading causes of human dementia, “vascular dementia” (Iadecola, 2013; Wardlaw et al., 2015). One thing that is under-appreciated in the field is the degree that WMS produces motor impairments. The location and number of white matter hyperintensities in humans affect gait: stride length is shorter and balance is poorer with a higher density of white matter hyperintensities, resulting in increased falls and greater physical decline (Whitman et al., 2001; Baezner et al., 2008; Soumaré et al., 2009). In older adults without cognitive impairment or dementia, gait deterioration is associated with declining cognitive abilities (Hausdorff et al., 2005; Yogev-Seligmann et al., 2008; Rosano et al., 2012). Gait abnormalities also predict the development of non-Alzheimer (or white matter stroke) dementia (Rosano et al., 2012). This association between altered gait and cognition with aging in white matter disease has been attributed to disruption of longitudinal tracts within the brain, especially those located in periventricular and subcortical regions that link motor function and executive control of gait (kanth et al., 2010; Moscufo et al., 2011; Koo et al., 2012; Nadkarni et al., 2015)

Modeling White matter stroke

A key question in modeling WMS or vascular dementia in rodents, is what kind of stroke or ischemic process is being modeled? Is white matter stroke or vascular dementia in humans associated with global brain hypoperfusion, or is white matter stroke and vascular dementia instead associated with focal ischemia and accumulation of these ischemic lesions? If global hypoperfusion is responsible for white matter stroke and vascular dementia, then rodent models of global brain reduced blood flow might be useful to study the human condition. If focal ischemia is the source of white matter stroke, and this accumulates to produce more confluent lesions and vascular dementia, then a focal ischemic model would better mimic the human condition. The evidence from humans is not totally clear in differentiating from these two conditions. There is an age-related decline in cerebral blood flow, but this is

matched with the age-related decline in brain metabolism (Leenders et al., 1990; Marchal et al., 1992; Petit-Taboué et al., 1998). However, in aging and in white matter ischemia, and vascular or mixed dementia there is not a general or progressive state of brain hypoperfusion (Henriksen et al., 2017; Yew et al., 2017). Further, detection of low blood flow in human dementia is confounded by the fact that sick neurons will likely have reduced blood flow due to reduced metabolism, and neurons are dysfunctional very early in dementing illnesses, before clear structural or other imaging evidence for disease (Altmann et al., 2015.; Kempainen et al., 2017). This means that older blood flow imaging studies that detected brain global hypoperfusion in dementia, including vascular dementia, likely reflect “effect” and not “cause”. A second reason for concern for animal models of white matter stroke and vascular dementia that use global hypoperfusion is that these models produce neuronal cell death in many areas, including throughout the brain and even in the retina (Khan et al., 2018). Further, global brain ischemia models in rodents produce white matter damage throughout the brain, including the optic nerve—patterns of white matter damage that are not consistent with white matter stroke and vascular dementia in humans (Wakita et al., 1994; Farkas et al., 2004; Shibata et al., 2004; Sozmen et al., 2012).

Thus, rodent models that utilize progressive arterial constriction or other global brain or forebrain hypoperfusion are not actually human white matter stroke models but rather, diffuse brain cell death models, and do not model a human condition of generalized brain hypoperfusion that is present in white matter stroke or vascular dementia. There may be widespread vascular dysfunction in human white matter stroke in blood brain barrier dysfunction or in cerebral autoregulation, and these are valid points for animal modeling, but these are not deficits of global hypoperfusion (Toth et al., 2016; Lin et al., 2017; Sweeney et al., 2018).

N5-(1-iminoethyl)-L-ornithine (LNIO)

A recently developed mouse model of WMS, which involves the focal microinjection of the vasoconstrictor N(5)-(1-iminoethyl)-L-ornithine HCL (LNIO) into the corpus callosum, has provided substantial information on the pathological consequences of focal ischemic injury in white matter tracts (Rosenzweig and Carmichael, 2013, 2015; Sozmen et al., 2016). LNIO is an nitric oxide synthase inhibitor with greater effect on the endothelial isoform, which has no known off target paracrine effects in the white matter and has been used in multiple models of ischemic brain injury across several species (Slooten et al., 2015; Nunez et al., 2016).

WMS across ages: pathology and motor deficits

The first characterization of the LNIO focal microinjection as a model of WMS was conducted by Rosenzweig et al. 2013. In this study, WMS was induced in the corpus callosum ventral to the motor cortex in three aged cohorts of mice - “young” (3 month), “middle-aged” (15 month), “aged” (24month) – and tissue and motor outcomes were assessed. Mice subjected to ischemic white matter injury presented typical pathological damage regardless of age. All groups showed pronounced white matter atrophy, axon degeneration, and oligodendrocyte apoptosis. However, degeneration was more severe in aged mice. Neutrophil and microglial/macrophage infiltration was localized to the infarct in

young animals, while they were found to be distributed across the motor cortex in middle-aged and aged mice. Furthermore, motor deficits were detected in all three groups, however recovery was seen only in the young brain. These data suggest that the young rodent brain retains innate mechanisms for white matter recovery, which are lost later in life. One potential mechanism is a failure of OPC differentiation into mature oligodendrocytes. Indeed, prior analyses of OPC dynamics in other white matter injury models, such as inflammatory or toxin-induced white matter injury, demonstrate decreased rates of differentiation (Sim et al., 2002).

OPCs fail to differentiate following WMS

Sozmen et al. 2016 conducted an analysis of OPC dynamics following WMS. In this study, they determined that OPCs fail to differentiate into myelinating oligodendrocytes, a phenomenon which is underpinned by NgR1 signaling. Following WMS, OPCs become hyper proliferative in the peri-infarct. However, a majority of these cells remain in an immature progenitor state, while a minority (4–13%) are differentiated into GFAP positive astrocytes. Shunting of OPCs into astrocytes was not detected in the uninjured corpus callosum and has been reported before in rodent injury models of traumatic brain injury and in cultured OPCs derived from the optic nerve and the cortex (Kondo and Raff, 2000; Alonso, 2005; Zhu et al., 2008). Indeed, OPCs have been reported to express surface markers for immature astrocytes such as nestin and vimentin following stab wound in the rat brain and subsequently become integrated into the glial scar (Alonso, 2005). Transcriptional analysis of the corpus callosum following WMS demonstrated NgR1 and its co-receptor Lingo-1 as the candidate signaling molecules involved in OPC differentiation failure. Indeed, both NgR1 and Lingo-1 signaling have been implicated in oligodendrocyte maturation and myelination in the mouse central nervous system. Knockout of both NogoA and MAG, myelin associated ligands of NgR1, results in disrupted myelination, internode formation, and oligodendrocyte differentiation in the mouse CNS (Pernet et al., 2008; Chong et al., 2012). NgR1 knockout disrupts paranodal loop structure and myelin decompaction in descending myelinated axons of the spinal cord (Lee et al., 2017). Finally, deletion of myocilin, an astrocyte derived secreted glycoprotein, which interacts with Lingo-1, in the optic nerve resulted in myelin deficits, decreased, oligodendrocyte differentiation, and abnormal visual function as assessed by flash visual evoked potentials (Kwon et al., 2014).

Analysis of NgR1 signaling systems in young (3 month) and aged (24 month) mice following white matter was conducted at 2 time points: 5 days post WMS upon which OPC proliferation is enhanced and 10 days post WMS upon which OPC proliferation is limited (Sozmen et al., 2016). WMS reduced expression of three negative regulators of NgR1: leucine-rich glioma inactivated 1 (Lgi1), cartilage acidic protein-1B (LOTUS), and disintegrin and metalloproteinase domain-containing protein 22 (ADAM22). Reduction of all three NgR1 negative regulators is worsened in the aged brain. Finally, a variety of chondroitin sulfate proteoglycans CSPGs, which are known interactors of NgR1, are upregulated following WMS. Indeed, it well established that NgR1 interacts with extra cellular matrix proteins such as CSPGs and heparin sulfate dermatan sulfate proteoglycans, glypicans, and syndecans (Mironova and Giger, 2013; Shen, 2014). Following WMS, there

is an increase in expression of aggrecan, versican, and brevican, and the heparan sulfate proteoglycan core proteins glypican 2 and syndecans 1 and 3.

Activity induced myelination in the healthy adult brain

The observation that WMS induces an environment that is inhibitory to oligodendrocyte differentiation myelination points to a necessity for a mechanistic understanding of innate CNS signaling systems that drive remyelination in the healthy brain. Indeed, the white matter field has produced data that demonstrates that neurons retain the capacity to actively signal onto OPCs in the adult brain and drive their differentiation into adult, myelinating oligodendrocytes. Indeed, simultaneous calcium imaging of OPCs and stimulation of co-cultured neurons demonstrate that OPCs display calcium transients in response to neural activation (Stevens et al., 2002; Wake et al., 2011, 2015). Furthermore, there is also evidence that motor activity in both humans and rodents drive myelination dynamics and that direct activation of cortical motor circuits drives OPC proliferation and differentiation (Kaller et al., 2017). These data demonstrate that novel mechanisms may be utilized to rebuild myelin in the infarcted and injured brain

Neurons drive myelination

In vitro evidence has pointed to the existence of a several neuronal signaling molecules that drive OPC proliferation and maturation. One such signaling molecule is glutamate. OPCs express a variety of NMDAR and AMPAR specific glutamate receptor subtypes including NR1 and GluR1, GluR2, GluR3, GluR3 and GluR4 (Gudz et al., 2006; Biase et al., 2011). Electrical stimulation of dorsal root ganglion neurons results in OPCs trafficking and upregulating transferrin receptor (TfR), activated Fyn kinase, and cell adhesion molecule L1 - proteins necessary for the cell to cell interaction between oligodendrocytes and neurons – as well as local synthesis and compartmentalization of myelin basic protein in cultured OPC processes (Wake et al., 2011). Furthermore, OPCs co-cultured with a mixture of dorsal root ganglion neurons that were either treated with botulinum A – an inhibitor vesicular release - or left untreated showed preferential interaction with and formation of compact myelin sheaths (presumably from those OPCs that differentiated into mature oligodendrocytes) around electrically active control axons (Wake et al., 2015). Though, not all glutamate receptors are necessarily involved in myelination, some play instrumental roles in other OPC processes. $\alpha\beta3$ mediated OPC migration is modulated by AMPAR signaling. (Gudz et al., 2006). Incubation of cultured OPCs with an agonist for AMPA and kainate-specific glutamate receptors drove OPC migration, while addition of NMDA had no effect (Gudz et al., 2006). Furthermore, *in vivo* ablation of Nr1, an NMDAR subunit, from OPCs failed to disrupt myelination or their differentiation in either the grey or white matter in adult mice (Biase et al., 2011). These data suggest that while glutamate activates signaling cascades in the OPCs, the receptor subtype may prove instrumental in the specification of OPC differentiation and maturation programs. Another consideration is the role other neuronal signaling cascades play in OPC differentiation and myelination in the central nervous system.

In a study conducted by Stevens et al. 2002, it was shown that adenosine drives myelination in *in vitro* OPC cultures. OPCs express at least four purinergic receptor subtypes including A1, A2a, A2b, and A3 (Stevens et al., 2002). Evoked action potentials in dorsal root ganglion neurons co cultured with OPCs resulted in an increase in intracellular calcium in OPCs, which was inhibited upon incubation with purinergic receptor blockers (Stevens et al., 2002). An analysis of isolated dorsal root ganglion axons following neural stimulation demonstrates that ATP is released from volume-activated anion channels (Fields and Ni, 2010). Furthermore, application of adenosine to OPCs co cultured with dorsal root ganglion neurons resulted in a decrease in OPC proliferation and a significant increase in myelinating oligodendrocytes. Previous work suggests that ATP is immediately hydrolyzed by ecto-enzymes into adenosine (Zimmermann et al., 1998). Indeed, addition of a nonhydrolyzable form of ATP to OPCs in *in vitro* preparations fail to drive myelination while stimulation of dorsal root ganglion neurons produces spikes of ATP that return to base line concentrations within 7 minutes of stimulation (Stevens et al., 2002; Fields and Ni, 2010). This data suggests that adenosine released from activated neurons inhibits cell cycle progression and promotes differentiation of OPCs into adult oligodendrocytes.

These data suggest the neural activity directly coordinates myelination in the nervous system. This points to the possibility that activating neural circuits via behavior or optogenetic stimulation can drive myelination via the modulation of lineage progression in OPCs and oligodendrocytes.

Stimulating myelination: motor activity and optogenetics

There are several studies that demonstrate that motor learning drives myelination in the healthy human and rodent brain (Kaller et al., 2017). Longitudinal human neuroimaging studies demonstrate that acquisition of a complex visuo-motor skill such as juggling, results in alterations in myelin structure in the intraparietal sulcus, a region of brain involved in motor coordination and correction of movement errors (Grefkes and Fink, 2005; Scholz et al., 2009). Furthermore, a related cross sectional human neuro imaging study demonstrates that adults who learned to play the piano in their childhood have increased myelin signal in the bilateral posterior limbs of the internal capsule, a myelinate fiber tract composed of cortico-spinal axons (Paus et al., 1999; Bengtsson et al., 2005).

Similar in the rodent, training on learned motor tasks drives myelination in the subcortical white matter tracts. Rats trained on skilled reach, a learned repetitive motor task, demonstrates increased myelin signal in subcortical white matter in the hemisphere contralateral to the trained limb (Sampaio-Baptista et al., 2013). Measurement of both myelin basic protein immunohistochemical signal intensity and MRI fractional anisotropy (FA) - a measurement of directional dependence of water diffusion across cellular structures - indicates that increased myelin signal correlated with the learning rate in rats (Sampaio-Baptista et al., 2013). In a similar study in mice, animals trained on a complex wheel – a running wheel with irregular spaced rungs of which the mouse has to develop motor strategies to master – results in increased OPC proliferation and oligodendrogenesis (McKenzie et al., 2014). Average speed attained at the complex wheel was hindered in animals in which genetic knockout of myelin regulatory factor (*myrf*), a transcription factor

involved in OPC differentiation, was induced prior to the training (Bujalka et al., 2013; McKenzie et al., 2014). Curiously, induction of myrf knockout after the acquisition of the motor program failed to disrupt running speed (McKenzie et al., 2014). This suggests that acquisition of the complex wheel motor program required active myelination while recall does not.

Finally, direct stimulation of neurons has been shown to drive myelination dynamics in the central nervous system. The first study to demonstrate this *in vivo* came from an analysis of myelination after high frequency stimulation of the medullary pyramid in the adult rat (Li et al., 2010). Histological analysis of the dorsal cortical spinal tract after stimulation demonstrated an increase in OPC proliferation (Li et al., 2010). In a later study conducted by Gibson et al. 2014, optogenetic stimulation of neurons in the motor cortex of juvenile and adult mice resulted in an increase in OPC proliferation, oligodendrogenesis, and myelin basic protein signal in both the motor cortex and underlying corpus callosum. Transmission electron microscopic analysis of the corpus callosum following stimulation indicated thicker myelin sheaths (Gibson et al., 2014)

The data suggest that neuronal activity directly cues oligodendrocyte lineage progression in the healthy adult brain. OPCs maintain a molecular profile of receptors that allows for their response to neurotransmitter release from neurons in *in vitro* preparations. Finally, modulation of neural circuits by either acquisition of complex motor programs or direct stimulation drives myelination in the healthy adult rodent brain. Interestingly, recent evidence also suggests that absent neuronal cues, oligodendrocytes maintain an innate capacity to myelinate axons of a specific diameter.

Axon diameter and myelination

Myelination is reserved for axons of a specific diameter range. In the central nervous system, minimal myelination threshold for axon diameter ranges from 0.2–0.8 μ m (Hildebrand et al., 1993). A recent analysis of axon diameter myelination thresholds was conducted where OPCs were cultured, in the presence of the OPC mitogen platelet derived growth factor (PDGF), with electron spun poly (L-lactin) acid (PLA) nanofibers of diameters ranging from 0.2–4.0 μ m for two weeks (Lee et al., 2012a). Analysis of OPCs after this period demonstrated a preference for wrapping of large diameter fibers alongside upregulation of myelin proteins such as myelin associated glycoprotein (MAG) and myelin basic protein (MBP). While OPCs did successfully differentiate into oligodendrocytes and form membranous sheaths around small diameter fibers, no concentric wraps or compact myelin sheaths were apparent (Lee et al., 2012a). A further comparison of myelination dynamics in cortex derived oligodendrocytes versus spinal cord derived oligodendrocytes cultured with PLA nanofibers for 2 weeks demonstrated that both populations indeed maintain the capacity to form myelin wraps around fibers of diameters ranging from 0.5–4 μ m (Bechler et al., 2015). However, there was a significant increase in sheath length in larger diameter fibers for both oligodendrocyte populations while spinal cord derived populations showed longer sheaths in all fiber diameters relative to cortex derived populations (Bechler et al., 2015). These data suggest that absent active neuronal cues, oligodendrocytes maintain the capacity to myelinate fibers within defined geometric

parameters. Though, the sheaths formed are poorly organized relative to those found *in vivo*. This suggests that despite these innate processes, neurons do indeed provide pro and anti-myelination cues, mechanisms that may play a role in the regulation and fine tuning of myelination in the central nervous system (Chang et al., 2016).

Conclusion

White matter stroke (WMS) is a debilitating disorder of which most people will succumb. It is demarcated by axon degeneration, oligodendrocyte death, demyelination, inflammation, and cognitive and motor dysfunction. The development of a mouse model of WMS has provided a means to study the pathological and behavioral consequences of ischemic injury in white matter. Recent analysis of this model has revealed that following WMS, OPCs fail to differentiate into myelinating oligodendrocytes, a consequence of NgR1 signaling and the deposition of the growth inhibitory NgR1 ligands and extracellular matrix proteins in the infarcted corpus callosum. Indeed, circumventing the growth inhibitory environment of the infarcted white matter may prove instrumental in the development of viable therapeutic approaches for post WMS recovery. One potential approach comes from studies of the interaction between neurons and OPCs, which demonstrate that stimulation of neurons drives OPC lineage progression into mature myelinating oligodendrocytes. Indeed, direct neural stimulation via optogenetics or activation of motor circuits via learned motor tasks drives OPC differentiation in the healthy adult brain. Though it is unclear as to whether similar methods can be employed in human patients, these data point to the necessity of implementing these approaches in rodent mouse models of WMS as a means to explore the molecular mechanisms that underpin this form of recovery.

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References

- Almeida RG, Lyons DA (2017) On Myelinated Axon Plasticity and Neuronal Circuit Formation and Function. *J Neurosci* 37:10023–10034. [PubMed: 29046438]
- Alonso G (2005) NG2 proteoglycan-expressing cells of the adult rat brain: Possible involvement in the formation of glial scar astrocytes following stab wound. *Glia* 49:318–338. [PubMed: 15494983]
- Altmann A, Ng B, Landau SM, Jagust WJ, Greicius MD, Initiative A (n.d.) Regional brain hypometabolism is unrelated to regional amyloid plaque burden. *Brain* 138:3734–3746. [PubMed: 26419799]
- Andronikou S (2012) See Right Through Me. :71–100.
- Baezner H, Blahak C, Poggesi A, Pantoni L, Inzitari D, Chabriat H, Erkinjuntti T, Fazekas F, Ferro J, Langhorne P, O'Brien J, Scheltens P, Visser M, Wahlund L, Waldemar G, Wallin A, Hennerici M, behalf of the Group O (2008) Association of gait and balance disorders with age-related white matter changes: The LADIS Study. *Neurology* 70:935–942. [PubMed: 18347315]
- Bailey EL, Smith C, Sudlow CL, Wardlaw JM (2012) Pathology of Lacunar Ischemic Stroke in Humans—A Systematic Review. *Brain Pathol* 22:583–591. [PubMed: 22329603]
- Baumann N, Pham-Dinh D (2001) Biology of Oligodendrocyte and Myelin in the Mammalian Central Nervous System. *Physiol Rev* 81:871–927. [PubMed: 11274346]
- Bechler ME, Byrne L, French-Constant C (2015) CNS Myelin Sheath Lengths Are an Intrinsic Property of Oligodendrocytes. *Curr Biol* 25:2411–2416. [PubMed: 26320951]

- Bengtsson SL, Nagy Z, Skare S, Forsman L, Forssberg H, Ullén F (2005) Extensive piano practicing has regionally specific effects on white matter development. *Nat Neurosci* 8:nn1516.
- Biase LM, Kang SH, Baxi EG, Fukaya M, Pucak ML, Mishina M, Calabresi PA, Bergles DE (2011) NMDA Receptor Signaling in Oligodendrocyte Progenitors Is Not Required for Oligodendrogenesis and Myelination. *J Neurosci* 31:12650–12662. [PubMed: 21880926]
- Bujalka H, Koenning M, Jackson S, Perreau VM, Pope B, Hay CM, Mitew S, Hill AF, Lu RQ, Wegner M, Nivason R, Svaren J, Willingham M, Barres BA, Emery B (2013) MYRF Is a Membrane-Associated Transcription Factor That Autoproteolytically Cleaves to Directly Activate Myelin Genes. *Plos Biol* 11:e1001625. [PubMed: 23966833]
- Chang K-J, Redmond SA, Chan JR (2016) Remodeling myelination: implications for mechanisms of neural plasticity. *Nat Neurosci* 19:190–197. [PubMed: 26814588]
- Chong CS, Rosenberg SS, Fancy SP, Zhao C, Shen Y-AA, Hahn AT, McGee AW, Xu X, Zheng B, Zhang LI, Rowitch DH, Franklin RJ, Lu RQ, Chan JR (2012) Neurite outgrowth inhibitor Nogo-A establishes spatial segregation and extent of oligodendrocyte myelination. *Proc National Acad Sci* 109:1299–1304.
- de Leeuw F-E, de Groot J, Achten E, Oudkerk M, Ramos L, Heijboer R, Hofman A, Jolles J, van Gijn J, Breteler M (2001) Prevalence of cerebral white matter lesions in elderly people: a population based magnetic resonance imaging study. The Rotterdam Scan Study. *J Neurology Neurosurg Psychiatry* 70:9–14.
- Farkas E, Inostóris Á, Domoki F, Mihály A, Luiten P, Bari F (2004) Diazoxide and dimethyl sulfoxide prevent cerebral hypoperfusion-related learning dysfunction and brain damage after carotid artery occlusion. *Brain Res* 1008:252–260. [PubMed: 15145763]
- Fields DR (2015) A new mechanism of nervous system plasticity: activity-dependent myelination. *Nat Rev Neurosci* 16:756–767. [PubMed: 26585800]
- Fields DR, Ni Y (2010) Nonsynaptic Communication Through ATP Release from Volume-Activated Anion Channels in Axons. *Sci Signal* 3:ra73–ra73. [PubMed: 20923934]
- Gibson EM, Purger D, Mount CW, Goldstein AK, Lin GL, Wood LS, Inema I, Miller SE, Bieri G, Zuchero BJ, Barres BA, Woo PJ, Vogel H, Monje M (2014) Neuronal Activity Promotes Oligodendrogenesis and Adaptive Myelination in the Mammalian Brain. *Science* 344:1252304. [PubMed: 24727982]
- Gouw AA, van der Flier WM, Pantoni L, Inzitari D, Erkinjuntti T, Wahlund LO, Waldemar G, Schmidt R, Fazekas F, Scheltens P, Barkhof F (2008) On the Etiology of Incident Brain Lacunes. *Stroke* 39:3083–3085. [PubMed: 18703801]
- Grefkes C, Fink GR (2005) REVIEW: The functional organization of the intraparietal sulcus in humans and monkeys. *J Anat* 207:3–17. [PubMed: 16011542]
- Grubb MS, Burrone J (2010) Activity-dependent relocation of the axon initial segment fine-tunes neuronal excitability. *Nature* 465:1070. [PubMed: 20543823]
- Grubb MS, Shu Y, Kuba H, Rasband MN, Wimmer VC, Bender KJ (2011) Short- and Long-Term Plasticity at the Axon Initial Segment. *J Neurosci* 31:16049–16055. [PubMed: 22072655]
- Gudz TI, Komuro H, Macklin WB (2006) Glutamate Stimulates Oligodendrocyte Progenitor Migration Mediated via an α v Integrin/Myelin Proteolipid Protein Complex. *J Neurosci* 26:2458–2466. [PubMed: 16510724]
- Hausdorff JM, Yogev G, Springer S, Simon ES, Giladi N (2005) Walking is more like catching than tapping: gait in the elderly as a complex cognitive task. *Exp Brain Res* 164:541–548. [PubMed: 15864565]
- Henriksen O, Hansen N, Osler M, Mortensen E, Hallam D, Pedersen E, Chappell M, Lauritzen M, Rostrup E (2017) Sub-Clinical Cognitive Decline and Resting Cerebral Blood Flow in Middle Aged Men. *Plos One* 12:e0169912. [PubMed: 28095458]
- Hildebrand C, Remahl S, Persson H, Bjartmar C (1993) Myelinated nerve fibres in the CNS. *Prog Neurobiol* 40:319–384. [PubMed: 8441812]
- Hinman JD (2014) The back and forth of axonal injury and repair after stroke. *Curr Opin Neurol* 27:615. [PubMed: 25364952]
- Hinman JD, Lee MD, Tung S, Vinters HV, Carmichael TS (2015) Molecular disorganization of axons adjacent to human lacunar infarcts. *Brain* 138:736–745. [PubMed: 25614025]

- Hughes EG, Kang SH, Fukaya M, Bergles DE (2013) Oligodendrocyte progenitors balance growth with self-repulsion to achieve homeostasis in the adult brain. *Nat Neurosci* 16:668–676. [PubMed: 23624515]
- Hughes EG, Orthmann-Murphy JL, Langseth AJ, Bergles DE (2018) Myelin remodeling through experience-dependent oligodendrogenesis in the adult somatosensory cortex. *Nat Neurosci*:1–11.
- Kaller M, Lazari A, Blanco-Duque C, Sampaio-Baptista C, Johansen-Berg H (2017) Myelin plasticity and behaviour—connecting the dots. *Curr Opin Neurobiol* 47:86–92. [PubMed: 29054040]
- Kang SH, Fukaya M, Yang JK, Rothstein JD, Bergles DE (2010) NG2+ CNS Glial Progenitors Remain Committed to the Oligodendrocyte Lineage in Postnatal Life and following Neurodegeneration. *Neuron* 68:668–681. [PubMed: 21092857]
- kanth V, Phan TG, Chen J, Beare R, Stapleton JM, Reutens DC (2010) The location of white matter lesions and gait—A voxel-based study. *Ann Neurol* 67:265–269. [PubMed: 20225293]
- Kemppainen N et al. (2017) Brain amyloid load and its associations with cognition and vascular risk factors in FINGER Study. *Neurology* 90:e206–e213. [PubMed: 29263220]
- Khan S, Yuldasheva NY, Batten T, Pickles AR, Kellett K, Saha S (2018) Tau pathology and neurochemical changes associated with memory dysfunction in an optimised murine model of global cerebral ischaemia - A potential model for vascular dementia? *Neurochem Int*.
- Klingseisen A, Lyons DA (2018) Axonal Regulation of Central Nervous System Myelination: Structure and Function. *Neurosci* 24:7–21.
- Kondo T, Raff M (2000) Oligodendrocyte Precursor Cells Reprogrammed to Become Multipotential CNS Stem Cells. *Science* 289:1754–1757. [PubMed: 10976069]
- Koo B-B, Bergethon P, Qiu W, Scott T, Hussain M, Rosenberg I, Caplan LR, Bhadelia RA (2012) Clinical Prediction of Fall Risk and White Matter Abnormalities: A Diffusion Tensor Imaging Study. *Arch Neurol-chicago* 69:733–738. [PubMed: 22332181]
- Kwon H, Nakaya N, Abu-Asab M, Kim H, Tomarev SI (2014) Myocilin Is Involved in NgR1/Lingo-1-Mediated Oligodendrocyte Differentiation and Myelination of the Optic Nerve. *J Neurosci* 34:5539–5551. [PubMed: 24741044]
- Lee J, Kim M, Li L, Velumian AA, Aui P, Fehlings MG, Petratos S (2017) Nogo receptor 1 regulates Caspr distribution at axo-glial units in the central nervous system. *Sci Reports* 7:8958.
- Lee S, Leach MK, Redmond SA, Chong CS, Mellon SH, Tuck SJ, Feng Z-Q, Corey JM, Chan JR (2012a) A culture system to study oligodendrocyte myelination processes using engineered nanofibers. *Nat Methods* 9:nmeth.2105.
- Lee Y, Morrison BM, Li Y, Lengacher S, Farah MH, Hoffman PN, Liu Y, Tsingalia A, Jin L, Zhang P-W, Pellerin L, Magistretti PJ, Rothstein JD (2012b) Oligodendroglia metabolically support axons and contribute to neurodegeneration. *Nature* 487:nature11314.
- Leenders K, Perani D, Lammertsma A, Heather J, Buckingham P, Healy M, Gibbs J, Wise R, Hatazawa J, Herold S (1990) Cerebral blood flow, blood volume and oxygen utilization. Normal values and effect of age. *Brain J Neurology* 113 (Pt 1):27–47.
- Li Q, Brus-Ramer M, Martin JH, nald JW (2010) Electrical stimulation of the medullary pyramid promotes proliferation and differentiation of oligodendrocyte progenitor cells in the corticospinal tract of the adult rat. *Neurosci Lett* 479:128–133. [PubMed: 20493923]
- Lin J, Wang D, Lan L, Fan Y (2017) Multiple Factors Involved in the Pathogenesis of White Matter Lesions. *Biomed Res Int* 2017:1–9.
- Loos C, Makin S, Staals J, Dennis MS, van Oostenbrugge RJ, Wardlaw JM (2018) Long-Term Morphological Changes of Symptomatic Lacunar Infarcts and Surrounding White Matter on Structural Magnetic Resonance Imaging. *Stroke* 49:STROKEAHA.117.020495.
- Marchal G, Rioux P, Petit-Taboué M-C, Sette G, Travère J-M, Poec C, Courtheoux P, Derlon J-M, Baron J-C (1992) Regional Cerebral Oxygen Consumption, Blood Flow, and Blood Volume in Healthy Human Aging. *Arch Neurol-chicago* 49:1013–1020. [PubMed: 1417508]
- Marin MA, de Lima S, Gilbert H-Y, Giger RJ, Benowitz L, Rasband MN (2016) Reassembly of Excitable Domains after CNS Axon Regeneration. *J Neurosci* 36:9148–9160. [PubMed: 27581456]
- McKenzie IA, Ohayon D, Li H, de Faria J, Emery B, Tohyama K, Richardson WD (2014) Motor skill learning requires active central myelination. *Science* 346:318–322. [PubMed: 25324381]

- Mironova YA, Giger RJ (2013) Where no synapses go: gatekeepers of circuit remodeling and synaptic strength. *Trends Neurosci* 36:363–373. [PubMed: 23642707]
- Moscufo N, Guttmann C, Meier D, Csapo I, Hildenbrand PG, Healy BC, Schmidt JA, Wolfson L (2011) Brain regional lesion burden and impaired mobility in the elderly. *Neurobiol Aging* 32:646–654. [PubMed: 19428145]
- Nadkarni NK, Perera S, Studenski SA, Rosano C, Aizenstein HJ, VanSwearingen JM (2015) Callosal Hyperintensities and Gait Speed Gain From Two Types of Mobility Interventions in Older Adults. *Arch Phys Med Rehab* 96:1154–1157.
- Nunez S, Doroudchi MM, Gleichman AJ, Ng KL, Llorente IL, Sozmen EG, Carmichael TS, Hinman JD (2016) A Versatile Murine Model of Subcortical White Matter Stroke for the Study of Axonal Degeneration and White Matter Neurobiology. *J Vis Exp Jove*.
- Patel R, Moore S, Crawford DK, Hannsun G, Sasidhar MV, Tan K, Molaie D, Tiwari-Woodruff SK (2013) Attenuation of Corpus Callosum Axon Myelination and Remyelination in the Absence of Circulating Sex Hormones. *Brain Pathol* 23:462–475. [PubMed: 23311751]
- Paus T, Zijdenbos A, Worsley K, Collins LD, Blumenthal J, Giedd JN, Rapoport JL, Evans AC (1999) Structural Maturation of Neural Pathways in Children and Adolescents: In Vivo Study. *Science* 283:1908–1911. [PubMed: 10082463]
- Pernet V, Joly S, Christ F, Dimou L, Schwab ME (2008) Nogo-A and Myelin-Associated Glycoprotein Differently Regulate Oligodendrocyte Maturation and Myelin Formation. *J Neurosci* 28:7435–7444. [PubMed: 18632947]
- Petit-Taboué MC, Landeau B, Desson JF, Desgranges B, Baron JC (1998) Effects of Healthy Aging on the Regional Cerebral Metabolic Rate of Glucose Assessed with Statistical Parametric Mapping. *Neuroimage* 7:176–184. [PubMed: 9597659]
- Psachoulia K, Jamen F, Young KM, Richardson WD (2009) Cell cycle dynamics of NG2 cells in the postnatal and ageing brain. *Neuron Glia Biol* 5:57–67. [PubMed: 20346197]
- Purger D, Gibson EM, Monje M (2016) Myelin plasticity in the central nervous system. *Neuropharmacology* 110:563–573. [PubMed: 26282119]
- Rasband MN (2010) The axon initial segment and the maintenance of neuronal polarity. *Nat Rev Neurosci* 11:552–562. [PubMed: 20631711]
- Rasband MN, Peles E (2016) The Nodes of Ranvier: Molecular Assembly and Maintenance. *Csh Perspect Biol* 8:a020495.
- Raybaud C (2010) The corpus callosum, the other great forebrain commissures, and the septum pellucidum: anatomy, development, and malformation. *Neuroradiology* 52:447–477. [PubMed: 20422408]
- Rivers LE, Young KM, Rizzi M, Jamen F, Psachoulia K, Wade A, Kessaris N, Richardson WD (2008) PDGFRA/NG2 glia generate myelinating oligodendrocytes and piriform projection neurons in adult mice. *Nat Neurosci* 11:1392–1401. [PubMed: 18849983]
- Rosano C, Studenski SA, Aizenstein HJ, Boudreau RM, Longstreth WT, Newman AB (2012) Slower gait, slower information processing and smaller prefrontal area in older adults. *Age Ageing* 41:58–64. [PubMed: 21965414]
- Rosenzweig S, Carmichael TS (2013) Age-Dependent Exacerbation of White Matter Stroke Outcomes. *Stroke* 44:2579–2586. [PubMed: 23868277]
- Rosenzweig S, Carmichael TS (2015) The axon–glia unit in white matter stroke: Mechanisms of damage and recovery. *Brain Res* 1623:123–134. [PubMed: 25704204]
- Sampaio-Baptista C, Khrapitchev AA, Foxley S, Schlagheck T, Scholz J, Jbabdi S, DeLuca GC, Miller KL, Taylor A, Thomas N, Kleim J, Sibson NR, Bannerman D, Johansen-Berg H (2013) Motor Skill Learning Induces Changes in White Matter Microstructure and Myelination. *J Neurosci* 33:19499–19503. [PubMed: 24336716]
- Scholz J, Klein MC, Behrens TE, Johansen-Berg H (2009) Training induces changes in white-matter architecture. *Nat Neurosci* 12:nn.2412.
- Shen Y (2014) Traffic lights for axon growth: proteoglycans and their neuronal receptors. *Neural Regen Res* 9:356–361. [PubMed: 25206823]

- Shibata M, Ohtani R, Ihara M, Tomimoto H (2004) White Matter Lesions and Glial Activation in a Novel Mouse Model of Chronic Cerebral Hypoperfusion. *Stroke* 35:2598–2603. [PubMed: 15472111]
- Sim FJ, Zhao C, Penderis J, Franklin RJ (2002) The Age-Related Decrease in CNS Remyelination Efficiency Is Attributable to an Impairment of Both Oligodendrocyte Progenitor Recruitment and Differentiation. *J Neurosci* 22:2451–2459. [PubMed: 11923409]
- Slooten AR, Sun Y, Clarkson AN, Connor BJ (2015) I-NIO as a novel mechanism for inducing focal cerebral ischemia in the adult rat brain. *J Neurosci Meth* 245:44–57.
- Soumaré A, Elbaz A, Zhu Y, Maillard P, Crivello F, Tavernier B, Dufouil C, Mazoyer B, Tzourio C (2009) White matter lesions volume and motor performances in the elderly. *Ann Neurol* 65:706–715. [PubMed: 19557865]
- Sozmen EG, Hinman JD, Carmichael TS (2012) Models That Matter: White Matter Stroke Models. *Neurotherapeutics* 9:349–358. [PubMed: 22362423]
- Sozmen EG, Rosenzweig S, Llorente IL, DiTullio DJ, Machnicki M, Vinters HV, Havton LA, Giger RJ, Hinman JD, Carmichael TS (2016) Nogo receptor blockade overcomes remyelination failure after white matter stroke and stimulates functional recovery in aged mice. *Proc National Acad Sci* 113:E8453–E8462.
- Stevens B, Porta S, Haak LL, Gallo V, Fields RD (2002) Adenosine A Neuron–Glial Transmitter Promoting Myelination in the CNS in Response to Action Potentials. *Neuron* 36:855–868. [PubMed: 12467589]
- Suzuki K (2013) Node of Ranvier Disruption as a Cause of Neurological Diseases. *Asn Neuro* 5:AN20130025.
- Sweeney MD, Sagare AP, Zlokovic BV (2018) Blood–brain barrier breakdown in Alzheimer disease and other neurodegenerative disorders. *Nat Rev Neurol* 14:133. [PubMed: 29377008]
- Toth P, Tarantini S, Csiszar A, Ungvari ZI (2016) Functional Vascular Contributions to Cognitive Impairment and Dementia (VCID): Mechanisms and Consequences of Cerebral Microvascular Dysfunction in Aging. *Am J Physiology Hear Circulatory Physiology* 312:ajpheart.00581.2016.
- Travisol A, Saab AS, Winkler U, Marx G, Imamura H, Möbius W, Kusch K, Nave K-A, Hirrlinger J (2017) Monitoring ATP dynamics in electrically active white matter tracts. *Elife* 6:e24241. [PubMed: 28414271]
- Vermeer SE, Longstreth WT, Koudstaal PJ (2007) Silent brain infarcts: a systematic review. *Lancet Neurology* 6:611–619. [PubMed: 17582361]
- Wake H, Lee PR, Fields DR (2011) Control of Local Protein Synthesis and Initial Events in Myelination by Action Potentials. *Science* 333:1647–1651. [PubMed: 21817014]
- Wake H, Ortiz FC, Woo D, Lee PR, Angulo M, Fields DR (2015) Nonsynaptic junctions on myelinating glia promote preferential myelination of electrically active axons. *Nat Commun* 6:7844. [PubMed: 26238238]
- Wakita H, Tomimoto H, Akiguchi I, Kimura J (1994) Glial activation and white matter changes in the rat brain induced by chronic cerebral hypoperfusion: an immunohistochemical study. *Acta Neuropathol* 87:484–492. [PubMed: 8059601]
- Wardlaw JM, Hernández MC, Muñoz-Maniega S (2015) What are White Matter Hyperintensities Made of? Relevance to Vascular Cognitive Impairment. *J Am Hear Assoc* 4:001140.
- Whitman G, Tang T, Lin A, Baloh R (2001) A prospective study of cerebral white matter abnormalities in older people with gait dysfunction. *Neurology* 57:990–994. [PubMed: 11571322]
- Yew B, Nation DA, Initiative A (2017) OUP accepted manuscript. *Brain* 140:1987–2001. [PubMed: 28575149]
- Yogev-Seligmann G, Hausdorff JM, Giladi N (2008) The role of executive function and attention in gait. *Movement Disord* 23:329–342. [PubMed: 18058946]
- Zhu X, Bergles DE, Nishiyama A (2008) NG2 cells generate both oligodendrocytes and gray matter astrocytes. *Development* 135:145–157. [PubMed: 18045844]
- Zimmermann H, Braun N, Kegel B, Heine P (1998) New insights into molecular structure and function of ecto-nucleotidases in the nervous system. *Neurochem Int* 32:421–425. [PubMed: 9676740]

Highlights

- White matter stroke is a prominent stroke subtype, the second leading cause of dementia (vascular dementia) and commonly co-occurs with Alzheimer's disease ('mixed dementia')
- Unlike similar sized white matter lesions in multiple sclerosis and animal models of multiple sclerosis, there is no cellular repair process in white matter stroke
- Several animal models of white matter exist, each with strengths and limitations
- Recent studies have defined the effects of age and of specific molecular systems on outcomes in white matter stroke