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White Matter Injury in Ischemic Stroke

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Abstract

Stroke is one of the major causes of disability and mortality worldwide. It is well known that ischemic stroke can cause gray matter injury. However, stroke also elicits profound white matter injury, a risk factor for higher stroke incidence and poor neurological outcomes. The majority of damage caused by stroke is located in subcortical regions and, remarkably, white matter occupies nearly half of the average infarct volume. Indeed, white matter is exquisitely vulnerable to ischemia and is often injured more severely than gray matter. Clinical symptoms related to white matter injury include cognitive dysfunction, emotional disorders, sensorimotor impairments, as well as urinary incontinence and pain, all of which are closely associated with destruction and remodeling of white matter connectivity. White matter injury can be noninvasively detected by MRI, which provides a three-dimensional assessment of its morphology, metabolism, and function. There is an urgent need for novel white matter therapies, as currently available strategies are limited to preclinical animal studies. Optimal protection against ischemic stroke will need to encompass the fortification of both gray and white matter. In this review, we discuss white matter injury after ischemic stroke, focusing on clinical features and tools, such as imaging, manifestation, and potential treatments. We also briefly discuss the pathophysiology of WMI and future research directions.

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Conflict of interest

1. Introduction

The mammalian neocortex is a sizeable structure with lamellar architecture and enlarges rapidly during early development. During primate evolution, the neocortex expanded greatly in size and this was paralleled by improvements in cognitive function. For example, the sum of neocortical gray matter (GM) and nearby white matter (WM) occupies only 10% to 20% of whole brain volume in insectivores, but accounts for 80% of whole brain volume in humans (Zhang and Sejnowski, 2000). According to neuroimaging studies, the volume of WM is 456 ± 48 cm^3 in men and 392 ± 42 cm^3 in women, which accounts for ~40% of total human brain volume (Pausova et al., 2007). The majority of WM tracts communicate across cortical areas and the rest join the cortex with subcortical structures. As the size of the brain enlarges during development, the WM immediately below the cortex expands disproportionally faster than cortical GM in order to unite distant cortical regions. Similar to GM, WM is critically dependent on a continuous supply of oxygen and glucose. However, WM receives less collateral circulation than GM and has a smaller blood supply, leading to extreme susceptibility to ischemia. Therefore, ischemic stroke rapidly and profoundly damages WM.

In the ischemic environment, glutamate and adenosine triphosphate (ATP), two major excitatory neurotransmitters, play pivotal roles in the pathophysiologic cascades of WMI after stroke. Glutamate and ATP lead to inflammation and oxidative stress (Matute and Ransom, 2012) and eventually induce oligodendrocyte death, axonal demyelination, WM structural damage, and neurobehavioral disorders (Lo et al., 2003). Hence, both GMI and WMI contribute significantly to neurological dysfunction in stroke. Preclinical and clinical studies of stroke have emphasized GMI over WMI, perhaps contributing to the failures of neuroprotectants designed to target neuronal death pathways (Ho et al., 2005; Wang and Shuaib, 2007). Thus, there is an urgent need for additional basic and clinical research on WMI, in the context of the entire brain as a sensitive organ system with highly heterogeneous cellular constituents.

2. Anatomy of WM

The principal components of GM include neuronal cell bodies, dendrites, and axons for local information processing, whereas WM mainly contains long extensions of myelinated and unmyelinated axons that are organized into tracts and surrounding glial cells and blood vessels. WM is classified into *periventricular WM* and *deep WM* based on anatomical location. Periventricular WM is found immediately adjacent to the ventricles (within ~1 cm) whereas deep WM is distinctly isolated from the ventricles and found beneath the cortex (Scheltens et al., 1992). WM tracts can be divided into three major categories according to their connectivity and functionality: (1) projection fibers—ascending and descending tracts connecting parts of the cerebral cortex and subcortical structures such as deep gray nuclei,

the brainstem, cerebellum, and spinal cord—include pyramidal tracts, thalamic radiations and optic radiations, (2) association fibers—connections between various cortical subregions within the ipsilateral hemisphere—can be long or short and include subcortical U fibers, the cingulum, superior and inferior longitudinal fasciculi, the occipitofrontal fasciculus, and the uncinate fasciculus, (3) commissural fibers—the link connecting homologous areas of the bilateral hemispheres—include the corpus callosum and the anterior commissure (Wycoco et al., 2013).

Microscopically, WM consists of axons, oligodendrocytes, and astrocytes. Axons are the largest element of WM by volume and occupy about 87% of its space (Wang et al., 2008). Axons are tightly wrapped by vast myelin sheets whose integrity is critical for the accuracy and speed of nerve signal conduction (Susuki and Rasband, 2008). As a vital storage space for the neurotransmitter glutamate (Alix et al., 2008), axons act not only as cables that conduct action potentials, but also passageways for transporting biological mediators/nutrients between the cell soma and the synapse. Anterograde axonal transport provides nutrients such as glucose, proteins, and lipids to the distal synapse and to mitochondria for local energy production, whereas retrograde transport delivers a) misfolded and aggregated proteins from the axon terminal to the soma for clearance and b) trophic signals to the soma. Efficient conduction of electrical signals via WM demands a persistent supply of energy along the entire length of the axon. Thus, reduction of the local blood supply may destroy the electrophysiological properties of an entire axon.

Oligodendrocytes are myelin-producing cells responsible for axonal myelination under normal conditions and remyelination after axonal damage. Astrocytes—the most heterogeneous and abundant type of glial cell in the CNS—play important roles in maintaining homeostatic equilibrium and influence myelination (Lundgaard et al., 2014). Glutamate overload may cause excitotoxicity in oligodendrocytes by activation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainate or N-methyl-D-aspartate (NMDA) receptors. Astrocytes within WM express higher levels of glutamate transporters and exhibit greater capacity for glutamate metabolism compared to astrocytes within GM (Goursaud et al., 2009), supporting the view that glutamate clearance by astrocytes in WM is critical for the maintenance of healthy oligodendrocytes and robust myelination/remyelination. The architectural integrity and connectivity of interneuronal networks in the brain profoundly influences neural activity and function and is associated with behavioral performance and cognitive abilities (Paus et al., 2014). In a review of combined diffusion tensor imaging (DTI) and functional magnetic resonance imaging (fMRI) studies, Bennett described that the relationship between WM integrity and neural activity varies with aging and is influenced by the spatial proximity of the neural measures (Bennett and Rypma, 2013). The correlation between WM intactness and neural viability is positive in younger adults and in regions with direct, first-order connections, whereas there is an inverse correlation between these measures in older adults and in regions connected indirectly.

3. Pathophysiologic mechanisms underlying WMI in ischemia

3.1. Vulnerability of WM to cerebral ischemia

As mentioned earlier, WM is affected in most cases of human stroke, accounting for half of the lesion volume. However, WMI has largely been neglected in animal studies and in clinical trials, partially because 1) the oft-used rodent has much less WM relative to humans and 2) neurons are traditionally held to be more vulnerable to ischemia than oligodendrocytes. However, WM has lower blood flow than GM and there is little collateral circulation, especially in deep WM (Iadecola et al., 2009). Furthermore, oligodendrocytes, especially oligodendrocyte precursor cells (OPCs), are highly sensitive to ischemia-induced oxidative stress (Husain and Juurlink, 1995), excitotoxicity (McDonald et al., 1998; Karadottir et al., 2005; Salter and Fern, 2005; Micu et al., 2006; Domercq et al., 2007), and inflammation, which contribute to OPC death and WMI after ischemia. Importantly, WM becomes more susceptible to ischemia with age (Correa et al., 2011). In sum, WM is highly vulnerable to ischemia and is often injured more severely than GM.

3.2. Mechanisms

Ischemic stroke is a complex pathophysiological process influencing both GM and WM. The pathophysiologic mechanisms underlying ischemia have been mainly focused on animal studies and the potential mechanisms underlying human ischemic stroke remain poorly investigated and largely unknown. Nevertheless, animal studies indicate that excessive release of glutamate, activation of ATP receptors, oxidative stress, inflammation, and apoptosis all contribute to oligodendrocytic death and axonal damage after ischemic brain injury (Mifsud et al., 2014). Recent studies also report these mechanisms in human ischemic stroke. Below we summarize recent advances in mechanistic studies focusing on human ischemic stroke.

3.2.1 Excitotoxicity—The ubiquitous excitatory neurotransmitter glutamate is mostly located in intracellular vesicular stores in the brain. Abnormally high levels of glutamate in the extracellular fluid exert neurotoxic effects upon surrounding tissues under pathological conditions. Excessive glutamate in plasma and cerebrospinal fluid (CSF) contribute to the progressive neurological deterioration and infarct growth in stroke victims (Boyko et al., 2014). NMDA receptors are known to participate in glutamate-mediated brain injury, and are pivotal players in the neurotoxicity of brain ischemia. Dambinova and colleagues have reported that acute ischemic stroke patients exhibit higher levels of NMDA receptors in the bloodstream than healthy individuals, and that this characteristic has 97% sensitivity and 91% predictive value for diagnosing ischemic stroke within 72 hours after symptom onset (Dambinova et al., 2003). Furthermore, Campos *et al* demonstrated that high glutamate oxaloacetate transaminase concentrations in blood are associated with superior neurological outcomes in stroke patients (Campos et al., 2011).

3.2.2. Inflammation—Inflammatory reactions are common in stroke, even in the absence of infections, and induce activation of resident microglia and astrocyte, infiltration of peripheral immunocytes, and production of proinflammatory mediators, thereby leading to tissue necrosis and eventual brain damage (Jin et al., 2010). There is a positive association

between elevated concentrations of inflammatory indicators in the peripheral circulation—including C-reactive protein (CRP), MMP-9 and interleukin-6 (IL-6)— and the initial severity as well as poor prognosis of ischemic stroke. In addition, these biomarkers are independent predictors of the first cerebral infarction and recurrent ischemic events (Nardi et al., 2012). Oh *et al* reported that multiple plasma inflammatory factors—such as MMP-9 and interleukin-18 (IL-18) receptor accessory protein—are modified in the acute stages of ischemic stroke, suggesting that immunity and inflammation participate in the development and progression of stroke (Oh et al., 2012). Zhang *et al* found that natural killer cell infiltrations peak between 2 and 5 days after ischemia in the ischemic hemispheres in humans, and induced necrosis and BBB damage through cytotoxic cytokines (Zhang et al., 2014d).

3.2.3. Oxidative stress—Oxidative stress is a major contributor to the pathogenesis of ischemic stroke. Increased production of free radicals elicts ischemia/reperfusion injury in the plasma membrane and intracellular components through the oxidative modification of lipids, protein and carbohydrates, resulting in necrosis or apoptosis (Nakka et al., 2008). Enhanced formation of advanced glycation end product, a marker of oxidative stress, was discovered in the skin of patients with chronic ischemic stroke or silent brain infarction (Ohnuki et al., 2009). Uric acid, which can alleviate glucose-driven oxidative stress, has been associated with a reduction in infarct volume and better prognosis in ischemic stroke patients (Amaro et al., 2015).

Cell apoptosis, endothelial dysfunction, and destruction of the integrity of the BBB, all play a role in the pathophysiologic processes underlying ischemia/reperfusion injury. These pathways do not work in isolation, but overlap and interact synergistically.

4. The relationship between WMI and ischemic stroke

Cerebral WMI is detected in more than half of normal elderly individuals (de Leeuw et al., 2001) and in 64-86% of stroke patients (Fu et al., 2005; Li et al., 2013). Furthermore, WMI progression is present in 8-28% of non-demented elderly patients (Enzinger et al., 2007) and 32% of ischemic stroke patients (Cho et al., 2015), implying that WMI has a dynamic course through late life and after injury.

4.1. WMI: a predictor of stroke

Cerebral WMI is probably caused by chronic hypoperfusion (Kurumatani et al., 1998; Debette et al., 2010) and is more frequent and severe in stroke patients than in healthy controls. It also is an important risk factor for stroke. The Framingham heart study demonstrated that the presence of severe WMI at baseline increases the risk of stroke death by two-fold and the risk of subsequent dementia four-fold (Debette et al., 2010). In the second ARTerial disease-Magnetic Resonance (SMART-MR) study, Conijn and colleagues reported that the presence of lacunar infarcts increases the risk of vascular and nonvascular mortality (Conijn et al., 2011). The severity of WMI is associated with an increased risk of vascular death and ischemic stroke, regardless of the co-existence of cerebrovascular disease. Lacunar infarcts and WMI are predictors of poor prognosis in patients with atherosclerotic diseases.

As argued above, WMI is a robust indicator of stroke (Leonards et al., 2012). There is a linear correlation between the National Institutes of Health Stroke Scale (NIHSS) and infarct volume (r=0.591; P<0.001), while this association falls with aggravated WMI burden from r=0.786 (P<0.001; absent WMI) to r=0.498 (P<0.001; severe WMI). Both WMI and infarct size are related to the NIHSS deficit. With increasing WMI load, similar infarct volumes cause more severe functional impairments. Helenius and Henninger demonstrated that pre-existing WMI is related to infarct volume and NIHSS (Helenius and Henninger, 2015). One study on a large single-center cohort (2485 intravenous thrombolysis-treated patients with ischemic stroke) showed that WMI on non-contrast CT scans upon admission is linked with a two-fold increase in symptomatic intracerebral hemorrhage (sICH) (Curtze et al., 2015a). It is also related to poor recovery 3 months after stroke. Not surprisingly, WMI load is an independent risk factor for adverse outcomes in IVT–treated patients with stroke (Curtze et al., 2015b). Furthermore, the severity of pre-existing WMI is an independent predictor of unfavorable long term functional outcomes in acute ischemic stroke patients undergoing endovascular therapy (Zhang et al., 2014b). Podigorska and colleagues report that the mortality at 1 year after stroke was 45.8% in patients with WMI, but 28% in those without WMI (Podgorska et al., 2002). WMI leads to a loss of WM bundle architecture and functional integrity (Lawrence et al., 2014), which may damage cerebral plasticity and impair compensatory mechanisms during post-stroke recovery (Ruber et al., 2012).

4.2. Stroke: a cause of WMI

As argued above, WMI can influence stroke risk. Conversely, ischemic stroke is an established cause of WMI. WM is profoundly injured by infarction in the supplying territory of small perforating vessels that link into the centrum semiovale and deeper fiber pathways. Occlusion of the large intracranial arteries, which supply both superficial GM and WM, offers an additional opportunity for WMI (Goldberg and Ransom, 2003). Several studies have demonstrated that the predominant lesions caused by stroke are located in subcortical regions, which comprise more than 85% of the total number of strokes (Wessels et al., 2006). Ho *et al* demonstrated that WM occupies a median of 49% of the infarct volume. About 95% of infarcts present with some involvement of WM bundles. As the connection between WMI and ischemic stroke is critically related to clinical outcomes, neuroprotection of WM should be more widely considered in designing therapeutic strategies (Ho et al., 2005).

In a prospective and longitudinal study, the cortical thickness and microstructural integrity of connecting fiber tracts were measured in 32 patients at both stroke onset and 6 months after the event (Duering et al., 2015). Duering and colleagues reported that focal cortical degenerative changes induced by acute infarcts were more significant in the areas with dense connections with the core region of injury, indicating that acute infarcts cause secondary neurodegeneration in remote brain regions via connecting fiber tracts. Cheng *et al* also reported a direct impact of focal subcortical ischemic lesions on remote cortical atrophy, secondary to retrograde or anterograde degeneration. These authors also discovered adaptive reconstruction in areas sharing connections with the ischemic infarct zone during stroke recovery (Cheng et al., 2015). Liu *et al* used diffusion tensor imaging (DTI) in 18 patients with acute subcortical infarcts at 1, 4 and 12 weeks after ischemia onset and found that the

severities of motor deficits of patients at 4 and 12 weeks were greater than those at 1 week (Liu et al., 2015). Progressive degeneration of motor-related fiber pathways above and below the ischemic lesion occurred early after stroke and lasted for up to 3 months. Furthermore, progressive structural remodeling of contralateral WM tracts related to motor, cognitive, and sensory processing was positively associated with motor function recovery in the acute and sub-acute stages of stroke. The compensatory changes in fiber tracts in non-motor regions of the unaffected hemisphere after acute infarction reflect the significance of WM architectural integrity and plasticity, which enables the brain to mitigate the impact of the primary motor impairment.

5. Imaging analysis of WMI

5.1. Magnetic resonance imaging (MRI)

MRI is a noninvasive technique that can provide three-dimensional assessment of tissue morphology, metabolism, and function and has been widely applied to display the architecture and function of WM.

5.1.1. Routine MRI—Due to the differences in water content and myelination, T1, T2, and fluid-attenuated inversion recovery (FLAIR) sequences used in conventional MRI can accurately distinguish GM and WM (Forkel et al., 2014) and measure the volume of WM (Perrin et al., 2009). In theory, the volume of WM represents the quantity of axons, their diameter, the thickness of the medullary sheath, as well as their compactness (Paus et al., 2014). WMI presents as WM hyperintensities on T2-weighted or FLAIR sequences, and hypointensities on T1-weighted images relative to normal white and grey matter (Fig.1).

5.1.2. Diffusion-weighted imaging (DWI)—DWI is sensitive to thermal movement of water molecules and can detect hyperacute infarction in the deep WM or in the brainstem (Oliveira-Filho et al., 2000). Swift attenuation of the apparent diffusion coefficient (ADC) in ischemic tissue produces hyperintensity on DWI that enables early diagnosis of ischemic stroke (Fig. 2). There is often a time-dependent change of ADC in WM fibers following ischemia. After a prompt decrease within one hour after stroke onset, the mean ADC in WM remains persistently low for 1 to 4 days, and then increases slowly. From one hour to a few days after stroke onset, there is a decline in ADC parallel with the WM fibers, while there is an increase in ADC perpendicular to the fiber bundles. This phenomenon might be attributed to the progression of the focal intracellular edema in glial cells and axons (Tamura et al., 2009).

5.1.3. Diffusion tensor imaging (DTI)—DTI can detect the magnitude and directionality of water molecules in live tissue and is more sensitive than conventional MRI in detecting WMI (Fig. 3). As the movement of the water molecules in the GM is equivalent in every direction, the fractional anisotropy (FA) value of GM is very low. In contrast to GM, water in WM moves swiftly along the direction of the axon due to the axonal tract, while myelination inhibits water movement vertical to the fasciculation, presenting a high FA value (Beaulieu, 2002). By calculating the mean diffusivity (MD) and FA of water diffusion, DTI can assess the integrity and connectivity of WM tissue from a network

perspective, and reconstruct the distribution of WM pathways in the brain three-dimensionally (Yap et al., 2013). Besides MD and FA, other diffusion metrics such as axial (AD) and radial (RD) diffusivity, which measure diffusivities parallel and perpendicular to the principal direction of the tensor respectively, can help determine the WM microstructural pathophysiology underlying the FA change (Burzynska et al., 2010). Attenuation in RD usually means ameliorative myelination, whereas an increase in AD reflects axon morphological damage (Tang et al., 2012). Using DTI in stroke patients, the RD enhancement is more general than the AD enhancement, which is interpreted as more severe and widespread demyelination than axonal degeneration (Song et al., 2003).

5.1.4. Diffusion kurtosis imaging (DKI)—DKI is an improvement over DTI that captures the non-Gaussian quality of water diffusion *in vivo* (Umesh Rudrapatna et al., 2014) and exhibits enhanced sensitivity to the microstructural heterogeneity and complexity of brain tissue (Cheung et al., 2012). By supplying primary information, DKI compliments DTI well in demonstrating the structural tissue changes that reflect post-stroke tissue remodeling.

5.2. Magnetization transfer imaging (MTI)

MTI reveals the degree of myelination indirectly. Magnetization transfer ratio (MTR), or the exchange of magnetization between free water and combined water bound to macromolecules (McGowan, 1999), is positively associated with myelin amounts (Schmierer et al., 2008). Because macromolecules such as proteins and myelin lipids are the main source of this signal in WM (Kucharczyk et al., 1994), this parameter is also influenced by axonal cytoskeleton components that contain the same macromolecules (Nossin-Manor et al., 2013). A low MTR value means that the ability of macromolecules in the brain tissue to exchange magnetization with ambient water molecules decreases, indicating damage to myelin and axonal membrane (Patel and Markus, 2011).

5.3. Magnetic resonance spectroscopy (MRS)

MRS reveals the brain metabolism of critical metabolites such as N-acetylaspartate, total creatines, total cholines, and myoinositol, and exhibits higher sensitivity to underlying neuroaxonal injury or dysfunction than conventional imaging. N-acetylaspartate is an indicator of neuronal and axonal function and is often reduced in ischemia (Fig. 4). Creatines are found primarily in neurons, oligodendrocytes, and astrocytes and reflect the synthesis and degradation of phospholipid membranes. Myoinositol is a glial metabolite and often observed to be increased after stroke, which is interpreted as chronic gliosis. In addition, lactate, a by-product of anaerobic glycolysis, usually appears in ischemic regions (Fig. 4).

5.4. Blood oxygen-level dependent functional MRI (BOLD-fMRI)

BOLD-fMRI assesses cerebral blood flow by testing the magnetic susceptibility of deoxygenated versus oxygenated hemoglobin. BOLD-fMRI reflects the capacity of the networks in the brain and calculates the cerebral vascular reactivity reliably and reproducibly. Activated neurons increase regional blood flow and oxygenated hemoglobin, leading to a variation in BOLD signal. By mapping the fluctuations of BOLD signal related

to an executive task, structural and functional information can be acquired simultaneously (Baird et al., 2005). Several studies have demonstrated that high WMI load is correlated with a dampening of BOLD signal (Patel et al., 2012), suggesting altered WM integrity in the neural network and neurological dysfunction. captures the non-Gaussian quality of water diffusion *in vivo* (Umesh Rudrapatna et al., 2014) and exhibits enhanced sensitivity to the microstructural heterogeneity and complexity of brain tissue (Cheung et al., 2012). By supplying primary information, DKI compliments DTI well in demonstrating the structural properties of the central nervous system.

Various imaging modalities for assessment of WMI are summarized in Table 1.

5.5. CSF and blood biomarkers

Ischemic insults in the brain affect both GM and WM, as reflected in the biochemical composition of nearby CSF and blood. Hjalmarsson *et al* examined the content of glia-related inflammatory factors, such as YKL-40, glial fibrillary acidic protein (GFAP), monocyte chemotactic protein 1(MCP-1), and glycoprotein CD14, and neurodegeneration-related markers of myelin and cytoskeleton such as neurofilament light polypeptide (NFL), myelin basic protein (MBP), and T-Tau in CSF (Hjalmarsson et al., 2014). The authors reported that the CSF concentrations of NFL, T-tau, MBP, YKL-40 and GFAP were higher in patients with acute ischemic stroke than healthy subjects, and these markers were positively correlated with clinical stroke severity. Furthermore, the myelinated axon marker NFLcorrelated with the degree of WMI. Elevated CSF/serum albumin ratios indicate BBB dysfunction and are correlated with WMI in subcortical ischemic vascular disease patients with dementia (Wallin et al., 2012). Other biomarkers such as plasma CRP, IL-6, homocysteine, urine albumin/creatinine ratio, and CSF MMP-9—all which are involved in inflammation and endothelial dysfunction—have been associated with WMI in patients with subcortical ischemic vascular disease (Vilar-Bergua et al., 2015).

In sum, the available information about candidate biomarkers in blood and CSF highlights multiple interconnected pathways in the pathogenesis of WMI caused by ischemia. However, data on human CSF biochemical parameters related to stroke are very limited, and the sensitivity and specificity of these biomarkers in blood and CSF are still unknown. Future studies on specific biomarkers in blood and CSF after WMI may shed more light on underlying mechanisms, thereby advancing diagnostic strategies and improve our ability to monitor the efficacy of treatments.

5.6. Electrophysiological examination

Transcranial magnetic stimulation (TMS), a non-invasive tool to map electrophysiological changes in cortical excitability, has revealed new insights into the physiological mechanisms behind motor disturbances and neuroplasticity after ischemic stroke (Dimyan and Cohen, 2010). Lyseniuk *et al* have demonstrated that the absence of motor evoked potentials (MEP) in the affected hemispheres is associated with poor functional recovery, while recordable MEP (even if reduced in amplitude and prolonged in latency) is associated with better prognosis in patients with ischemic stroke (Lyseniuk et al., 2014). Furthermore, increases in central motor conduction time (CMCT), which indicates axonal or demyelinating damage of

the corticospinal tract, has been reported in the affected hemisphere (Prashantha et al., 2013). MEP, when combined with CMCT, evaluates the functional integrity of corticospinal pathways, and reveals neurophysiological changes in these tracts in ischemic stroke (Dimyan and Cohen, 2010). Using TMS, Prashantha *et al* showed that the resting motor threshold (rMT), which is linked with neuronal membrane excitability and white matter microstructure, was reduced over time in the unaffected side in stroke patients, suggesting a progressive increase in cortical excitability of the contralateral hemisphere that can be attributed to damaged transcallosal inhibition and intracortical inhibition in the contralateral hemisphere (Prashantha et al., 2013). Jiang *et al* concluded that BMSC transplantation can reduce cerebral infarct volume and improve functional outcomes in rat, perhaps through electrophysiological effects on the motor cortex and associated pathways (Jang et al., 2011).

Brainstem auditory evoked potentials (BAEP), which are generated from auditory nerves and the brainstem, and somatosensory evoked potentials (SEP), which are generated from the spinal cord and the dorsal column-lemniscal system, can be used to assess the integrity of two different afferent pathways in patients (Burghaus et al., 2013). In several clinical studies, BAEP and SEP have been used as predictors of stroke prognosis. Zhang *et al* demonstrated that the bilateral absence of short-latency SEP N20 and BAEP wave V had 100% specificity and positive predictive value for poor outcomes in patients with massive hemispheric infarction (Zhang et al., 2011b). Joo *et al* discovered that constraint-induced movement treatment improved motor recovery in rats with ischemic stroke and coincided with beneficial changes in SEP suggesting that the reestablishment of somatosensory pathways likely contribute to functional recovery (Joo et al., 2012).

Electroencephalography (EEG) records the electrical activity created by the brain with a high temporal resolution and provides a dynamic view of rapid variations in functional activity (Duru et al., 2015). EEG functional connectivity is determined to a great extent by WM axons, especially cortico-cortical axons (Wan et al., 2011). The velocity of impulse transmission is highly plastic and mainly dependent on myelination. The synchrony of electrical activities between different cortical areas is essential for optimal neuropsychological performance. By relying on multiple spatiotemporal dynamic scalp patterns, such as frequency, phase spectra, covariance, and coherence, EEG can provide explicit multi-scale assessments of functional continuity in the brain, and WMI breaks this normal EEG coherence (Nunez et al., 2015). It has been demonstrated that resting state theta rhythm power detected by EEG is linked with default mode network activity in a set of brain regions that are active when an individual is at wakeful rest (Scheeringa et al., 2008).

In sum, electrophysiological examinations reflect the network connectivity and functional continuity in the brain, and can reveal robust neurophysiological changes after stroke and during rehabilitation. Establishment of electrophysiological criteria for the diagnosis of WMI in ischemic stroke may help us quantitatively evaluate the severity of WMI and the effectiveness of treatment interventions.

6. Clinical manifestations

WMI may cause cognitive dysfunction, emotional or affective disorders, sensorimotor impairments, gait disturbances, disequilibrium, as well as urinary incontinence and pain. These clinical manifestations are mainly related to the subcortical/WM topography of stroke and damage to WM tracts, in particular junctional or nodal areas with massive fiber convergence. The destruction of WM integrity is therefore thought to play an important role in neurological impairments (Corbetta et al., 2015).

6.1. Cognitive dysfunction

Cognitive dysfunction exists in about 64% of patients with stroke, of which, up to one third develop dementia (Nichols and Holmes, 2002). Decreased WM integrity induced either locally or remotely by ischemia has been reported to contribute to cognitive deficits in stroke (Molko et al., 2002). Cognitive dysfunction depends on volume and strategic location of brain infarction, site and range of cerebral WM, bilaterality and number of stroke lesions, and other co-existent pathologies (Grysiewicz and Gorelick, 2012). Some studies have shown that cognitive dysfunction is correlated with WMI in the frontal lobes, basal ganglia, and thalamus of stroke patients—in whom fronto-striato-thalamic pathways are impaired— and subsequent involvement of the dorsolateral prefrontal cortex and anterior cingulate, regions known to support attention and executive function (Cumming et al., 2013).

In a community-based sample of older adults free of clinical stroke, Dong *et al* found a negative relationship between WMI burden and cognitive performance, irrespective of brain atrophy (Dong et al., 2015). Chaudhari *et al* demonstrated that, in addition to poor educational background, location of infarct, and baseline stroke severity, WMI load is also an independent predictor for post-stroke cognitive dysfunction (Chaudhari et al., 2014). In the Tel Aviv Brain Acute Stroke Cohort (TABASCO) study, MRI scans were performed on 142 mild to moderate stroke or transient ischemic attack patients within seven days of stroke onset (Kliper et al., 2014). Patients were cognitively assessed again one year after the event. Patients with preexisting WMI were more susceptible to cognitive dysfunction, independent of the volume and location of ischemic lesions. The integrity of the normal appearance of WM may be a marker for "brain reserve properties" and an indicator of higher cognitive abilities. In a single-center study, 426 subjects with cerebral small vessel disease without dementia (between 50 and 85 years old) were recruited and underwent MRI scanning (Tuladhar et al., 2015). There was an inverse relationship between WMI burden and cortical thickness in frontotemporal regions, representing a region-specific association. WMI load was positively correlated with cortical thickness in paracentral areas, which may be a compensatory reaction to increased WMI. Furthermore, heavy WMI burden was linked with decreased global efficiency and increased distance of pathways, indicating that network breakdown contributes to the development of cognitive disturbances.

Lacunar infarcts account for more than 20% of stroke and commonly involve WM (Fern et al., 2014). Compared with healthy individuals, the general mental status, memory, attention, executive function, and language abilities are lower in patients with silent lacunar infarcts in the basal ganglia. Fern *et al* demonstrated that tract-specific damage of WM and region-specific lesions and network disruption accompanied cognitive declines and eventually led to

dementia. DTI of patients with lacunar infarcts reveal decreased FA and increased MD across several WM regions either close to or relatively far from lesions, implying that WM damage not only influences nearby areas, but also extends across considerable distances (Chen et al., 2015b). Lunven *et al* directed a prospective, longitudinal study that measured microstructural markers of neglect restoration after ischemia in the MCA territory (Lunven et al., 2015). They found that disruption of WM fronto-parietal circuits (intrahemispheric disconnection) is a critical element of spatial neglect. In addition, dynamic changes in WM of the splenium of the corpus callosum (interhemispheric disconnection) contributes to the persistence of long-term neglect. These two findings underscore the clinical significance of network integrity and continuity, both within and across the hemispheres. Dacosta-Aguayo *et al* examined the relationship between changes in cerebral WM integrity and cognitive recovery in patients 3 months after ischemic stroke (Dacosta-Aguayo et al., 2014). In comparison to healthy individuals, WM integrity was affected in both hemispheres in stroke patients. Patients with poor cognitive recovery who performed worse in attention, motor, executive and processing speed functions experienced greater WMI in the non-injured hemisphere.

In addition to affecting lesion volume and localization, WM changes are also instrumental in the manifestation and severity of neurological impairments and predict recovery or secondary cognitive dysfunction after stroke.

6.2. Depression

Depression is a frequent and severe emotional disorder that emerges in approximately 33% of stroke survivors (Esparrago Llorca et al., 2015) and is closely linked with additional disability, cognitive deficits, and even death (Whyte and Mulsant, 2002). Several studies have shown that WMI in the frontal and temporal lobes are related to depressive symptoms. In addition, WMI involvement in specific WM fiber tracts, such as the cingulum bundle, uncinate fasciculus, and superior longitudinal fasciculus may be an underlying cause of depression (Taylor et al., 2013). In comparison to healthy controls, a reduction in FA was found in the bilateral anterior limb of the internal capsule in stroke patients, although no patient exhibited frank lesions at this site (Yasuno et al., 2014). There was a negative correlation between the increase in FA values and a reduction in depression scores 6 months after stroke. Yasuno *et at* also argued that the decrease in FA is linked with an attenuation of dementia risk, indicating that microstructural breakdown in WM is the result of axonal damage, which may be induced by Wallerian degeneration secondary to neuronal death (Thomalla et al., 2004). Consistent with these views, the anterior limb of the internal capsule —an intercept point in the frontal-subcortical loops (Axer and Keyserlingk, 2000)—plays an essential role in behavior and emotional control (Duran et al., 2009). As a result, the destruction of WM within frontal-subcortical circuits may help trigger the onset of depressive symptoms (Budde et al., 2007).

6.3. Motor deficits

Motor circuits execute motor movements in a synergistic fashion and their integrity is a predictor of motor function following stroke (Gauthier et al., 2014). Wu *et al* reported that acute stroke lesions in WM are linked with more severe neurological deficits at admission

and long-term disabilities (Wu et al., 2015). Zhang *et al* showed that WM structural complexity, which is negatively correlated with motor disability changes in the stroke-affected hemisphere, is lower than in the unaffected hemisphere (Zhang et al., 2008). Riley *et al* also found that damaged motor tracts, specifically those descending from the primary motor and dorsal premotor cortices, can benefit from behavioral therapy in individuals with chronic stroke (Riley et al., 2011). Furthermore, tract-specific lesions are more significant than infarct size or baseline behavioral status at predicting prognosis, which can be used to identify those subjects who might benefit the most from treatment. By reinforcing 'fungible' trajectories, neuroplasticity can help restore brain function after stroke (Zaaimi et al., 2012). This success of neuroplasticity after stroke depends on the viability and integrity of the remaining tissue and the extent of functional reconstruction that they are able to reach (Lindenberg et al., 2012).

7. Management and treatment

WM is intimately involved in the relay of motor and sensory information to and from the cerebral cortex, and determines the degree of cognitive function. If only neuronal somas but not axons were protected after stroke, the axonal demyelination and damage would still interfere with neuronal signal transduction and function. Thus, interventions targeted at both GM and WM are expected to improve post-stroke quality of life. Thus far, however, all treatments targeting WMI are still limited to preclinical animal studies and there is no specific treatment for human WMI in ischemic stroke. Potential treatments targeting WMI include risk factor management, thrombolytic therapy, prevention of WMI, stimulation of oligodendrogenesis and axonal plasticity, and cell therapy.

7.1. Risk factor control

Studies have confirmed that hypertension plays a role in the loss of BBB integrity (Choi et al., 2015) and is a strong predictor of WMI. Adequate control of hypertension might alleviate the progression of WMI. Godin *et al* (Godin et al., 2011) prospectively compared subjects exhibiting high systolic blood pressure (SBP) (160 mmHg) at baseline with or without antihypertensive medication. They found that subjects with antihypertensive treatment had smaller increases in WMI volume at a 4-year follow-up than those without hypertensive treatment (0.24 cm^3 vs. 1.60 cm^3, P=0.008). Individuals with diabetes mellitus are more likely to suffer severe and early WMI (J et al., 2009). Consistent with these findings, Chen *et al* found that hyperglycemia aggravates WMI in the ischemic area and worsens functional prognosis in diabetic mice (Chen et al., 2011). The underlying mechanism may be that hyperglycemia inhibits the proliferation and survival of OPCs by promoting oxidative stress and stimulating MMP-9 activity (Yatomi et al., 2015).

Homocysteine is a risk factor for WMI in stroke subjects (Tseng et al., 2009). Cloonan *et al* demonstrated a positive correlation between WMI load and homocysteine (β=0.11, p=0.003) as well as hemoglobin A1c levels (β=0.1, p=0.008), both of which are associated with endothelial dysfunction *via* oxidative stress (Cloonan et al., 2015). Obviously, controls of other traditional cardiovascular risk factors such as diabetes mellitus, hyperlipidemia, and chronic renal failure may also ameliorate the destruction of WM.

7.2. Thrombolytic therapy

To date, recombinant tissue-type plasminogen activator (r-tPA) is the only effective approach for the treatment of acute ischemic stroke, both for GMI and WMI. Pantoni *et al* demonstrated that patients with acute lacunar infarcts have a good clinical response to thrombolysis (Pantoni et al., 2014). In addition to thrombolytic function, tPA can inhibit oligodendrocyte apoptosis and maintain WM integrity after ischemic stroke through an epidermal growth factor-like effect (Correa et al., 2011). However, less than 5% of ischemic stroke patients qualify for tPA treatment. Thus, other approaches that can either prevent WMI or stimulate oligodendrogenesis and axonal plasticity are urgently needed for stroke recovery.

7.3. Pharmacological neuroprotectants

Neuroprotection from ischemic injury includes the goal of quelling harmful molecular and cellular pathways that lead to ischemic cell death and is defined as a correction of pathophysiological manifestations of ischemic brain damage. As a supplementary or adjunct approach to thrombolysis, a number of pharmacological neuroprotectants, such as free radical scavengers, anti-inflammatory drugs, and excitatory amino acid antagonists, have shown efficacy and safety in animal stroke models (Table 2).

7.3.1. Prevention of WMI—Antioxidants and anti-inflammatory agents have been shown to attenuate WMI (Shereen et al., 2011). The antioxidant ebselen can reduce oligodendrocyte and axonal damage and enhance neurological outcomes when administered 2 hours after the onset of stroke (Imai et al., 2001). Arundic acid downregulates inducible nitric oxide synthase in astrocytes. With decreased nitric oxide production, there is less toxicity in neighboring cells such as oligodendrocytes. Furthermore, arundic acid may reduce the expression of S100 calcium-binding protein, which is primarily expressed in astrocytes and is correlated with the lesions (Aurell et al., 1991). Citicoline is an essential component of membrane phospholipids, which are degraded into fatty acids and free radicals in cerebral ischemia. Citicoline has been extensively tested in clinical trials (Clark et al., 1997; Clark et al., 1999; Davalos et al., 2002; Alix et al., 2008; Davalos et al., 2012). Although largely negative results were reported, thus far citicoline is the only neuroprotective drug with consistent neuroprotective benefits against stroke, especially in less severely injured elderly patients. In addition to its neuroprotective effects, citicoline can also prevent WMI (Lee et al., 2009).

Minocycline is a potent anti-inflammatory agent and has been shown to be beneficial in patients with acute ischemic stroke in several clinical trials (Lampl et al., 2007; Amiri-Nikpour et al., 2015). It is highly likely that minocycline exerts its neuroprotective effects by targeting both gray matter injury (GMI) and WMI. In line with this view, minocycline was reported to be protective against WMI in ischemic stroke by targeting multiple mechanisms underlying WMI. For example, minocycline inhibits the activation of MMP-9, thereby alleviating WMI induced by hypoxia in spontaneously hypertensive/stroke prone rats (Jalal et al., 2015). As mentioned above, minocycline also has potent anti-inflammatory effects and may prevent WMI by inhibiting microglial activation in neonatal models of hypoxia-ischemia (Carty et al., 2008).

Treatments targeting excitotoxicity have been quite promising in preclinical studies. Blockers of axonal Na^+ ion channels reverse Na^+-Ca^{2+} exchange and decrease Na^+-dependent glutamate transport, thereby inhibiting excitotoxic damage to oligodendrocytes. Glutamate transport inhibitors are thought to block the glutamate efflux triggered by the collapse of ionic gradients, especially the transmembrane Na^+ gradient (Li et al., 1999; Baltan et al., 2008; Alix and Fern, 2009).

Finally, inhibition of histone deacetylase may also reduce stroke injury, rescue neurons from apoptosis, and sustain WM function (Baltan et al., 2013).

7.3.2. Stimulation of oligodendrogenesis and axonal plasticity—

Oligodendrogenesis and axonal plasticity play important roles in maintaining the structure and function of axons. Therefore, interventions targeting oligodendrogenesis and axonal plasticity might improve behavioral outcomes. Ischemic stroke induces endogenous oligodendrogenesis and there are large numbers of newly generated OPCs in the subventricular zone after ischemia. However, only a small amount of OPCs are able to survive, migrate to, and differentiate into mature myelin producing oligodendrocyte in the ischemic region. Therefore pharmacological drug/growth factors that can stimulate and protect endogenous oligodendrogenesis are critical for WM reorganization. Aspirin, a standard therapy for the prevention and treatment of ischemic stroke, possesses a variety of pharmacological activities and neuroprotective effects. Chen *et al* reported that aspirin can accelerate the proliferation and differentiation of OPCs as well as oligodendrocyte myelination after WMI (Chen et al., 2014c).

Brain-derived neurotrophic factor (BDNF) stimulates oligodendrogenesis, resulting in enhanced remyelination and fiber connectivity and superior functional outcomes in rats subjected to subcortical damage in ischemic stroke (Ramos-Cejudo et al., 2015). Nicotinamide phosphoribosyltransferase (NAMPT) has also been implicated in neuroprotection against ischemic brain injury. NAMPT is secreted into extracellular space after ischemia, where it binds to and protects WM against ischemic injury, suggesting a novel role for secreted NAMPT in WM protection after ischemic injury (Jing et al., 2014). Erythropoietin inhibits OPC apoptosis, stimulates oligodendrogenesis, and improves neurological outcomes after neonatal hypoxic ischemic injury (Iwai et al., 2010). Erythropoietin has also been reported to enhance WM reorganization, restore local cerebral blood flow, and expedite functional recovery (Li et al., 2009).

Despite the successes in animal models, almost all the pharmacological agents that show potential in pre-clinical studies of ischemic injury have failed to translate into positive outcomes in clinical trials (Hoyte et al., 2004).

7.4. Cell therapy

Cell-based therapies can increase neuroplasticity and improve the architecture and physiology of cerebral tissue, which promote neurological recovery after ischemic stroke (Chen et al., 2014b). The underlying mechanisms contributing to these therapeutic effects include cell replacement, nutritional support, immunoregulation, and activation of

endogenous pro-survival processes such as neurogenesis, vasculogenesis, and oligodendrogenesis (Liu et al., 2014).

Adipose-derived mesenchymal stem cell (ADMSC) administration can facilitate the reconstruction of WM fiber tracts and alleviate functional deficits in an experimental model of subcortical stroke with WMI. Through paracrine effects, immunomodulatory actions, and trophic factor production, ADMSC therapy can reduce lesion volume, inhibit cell death, stimulate axonal growth, and increase oligodendrocyte proliferation and myelin formation (Otero-Ortega et al., 2015). Human umbilical cord blood cells (HUSBC) transplantation attenuates inflammation, enhances vascular remodeling and promotes white matter axonal recovery (Yan et al., 2015). Bone marrow stromal cells (BMSC) are the most popular cell type for stroke cell therapy because of an abundant supply, simple isolation procedure, and convenient intravenous route of administration. Intravenously delivered BMSCs can cross the BBB and migrate to peri-infarct regions, where they accelerate axonal remodeling by upregulating the secretion of axonal regeneration markers and down-regulating the release of axonal extension inhibitory molecules in reactive astrocytes (Shen et al., 2008). In combination with Niaspan, BMSCs can increase the numbers of OPCs and oligodendrocytes, the density of myelin and axons, and the expression of synaptic proteins, which is related to WM reconstruction (Ye et al., 2013). Grafted neural progenitor cells selectively migrate towards the ischemic boundary regions and enhance WM reorganization after stroke (Jiang et al., 2006). Transplanted OPCs have shown potent WM protective effects and enhance spatial learning and memory after hypoxic ischemic brain injury. OPCs prevent WMI by multiple mechanisms; OPCs generate a myelin sheath, stimulate BDNF expression, enhance the proliferation of neural stem cells, and inhibit hypoxia-induced neuronal apoptosis (Chen et al., 2015a). As a large amount of OPCs can be produced *in vitro*, OPC therapy is a very promising avenue for WMI therapy.

At present, the field of cell-based therapy in stroke is still in its infancy. Several small clinical trials of cell transplantation have been completed but have not yielded satisfactory evidence favoring substantial clinical improvements. In addition, multiple issues, such as target populations, type and source of cells, cell dosage, optimal timing and administration routes must be given more attention (Leak et al., 2014). In the meantime, safety considerations, such as the potential for malignant transformation and side effects such as epilepsy, injection site injury, and immune allergic reactions remain important concerns (Ding et al., 2013).

7.5. Non-pharmaceutical therapies for WHI

7.5.1. Physical exercise—Through adjustment of blood pressure, weight control, improvement of metabolic disorders, and clearance of abnormal rheological properties of blood, regular physical exercise can protect endothelial function and prevent degenerative changes (Zhang et al., 2011a). In addition to well-established musculoskeletal and cardiorespiratory effects, physical activity contributes to a reduced risk and initial severity of stroke and amelioratives neurobehavioral outcome. Furthermore, early and more frequent exercise within the first 6 months after stroke is associated with improved mobility, greater independence, and reduced disability (Egan et al., 2014). Physical exercise improves stroke

outcomes via multiple mechanisms, including mitigation of inflammatory responses, attenuation of apoptosis, enhancement of angiogenesis, neurogenesis and even synaptogenesis, improvements in cerebral blood circulation, inhibition of glutamate over-activation, and strengthening of brain microvascular integrity (Zhang et al., 2014c).

In a rat ischemic model subjected to transient MCA occlusion, Ding *et al* demonstrated that exercise pre-conditioning significantly decreased infarct size and cerebral edema in the frontoparietal cortex and the dorsolateral striatum, with significant improvements in neurological outcomes. In contrast to pre-exercised rats, ischemic rats without exercise exhibited ultrastructural alterations with reduced luminal area, swollen astrocyte end-feet, parenchymal edema, and abnormally thin basal lamina were (Ding et al., 2006). Epidemiologic studies have shown that physical exercise is related to a reduced risk and severity of stroke in humans (Ding et al., 2004). Using T1 WI and DTI, an increase in GM volume in the prefrontal cortex and microstructural changes of FA in corresponding WM regions were observed in healthy humans after intensive exercise (Taubert et al., 2010).

Zheng *et al* found that post-stroke exercise effectively facilitates axonal regeneration of newborn projection neurons and promotes the rehabilitation of new neuronal networks within the basal ganglia after the ischemia insult, all of which is pivotal for the recovery of motor behavioral function (Zhang et al., 2013). Zhang *et al* demonstrated that exercise training facilitates the recovery of motor performance and contralesional pyramidal tract regeneration after cerebral infarction (Zhang et al., 2014a). In addition, Seo *et al* found that early motor balance and coordination training with treadmill training after stroke enhanced the production of synaptophysin, which is thought to reflect axonal sprouting and synaptogenesis in subcortical regions of the ischemic hemisphere, along with improvements in sensorimotor abilities and brain plasticity (Seo et al., 2010). Clinical evidence suggests that physical activity after stroke is associated with behavioral improvement and structural alterations in the brain (Kim et al., 2005). Wan *et al.* reported that intensive rehabilitation programs for patients with nonfluent aphasia led to structural changes in the right hemisphere, and this was correlated with improvements in speech, indicating that intensive therapy might induce contralateral WM changes in chronic stroke patients with Broca's aphasia (Wan et al., 2014).

Physical exercise triggers endogenous neuroprotection and is an effective strategy to alleviate ischemia/reperfusion brain damage from stroke. However, the potential mechanisms underlying this therapy are complex and manifold, and the protection of WMI is still undefined. On the other hand, some studies suggest that excessively intense exercise exacerbates brain damage, perhaps due to stress-induced increase of corticosterone levels (Ploughman et al., 2005). As a result, the most effective timing, intensity and duration of physical activity needs to be clearly defined.

7.5.2. Acupuncture—Acupuncture is an important modality of traditional Chinese medicine and has been applied to the treatment of various neurological disorders. A number of clinical studies and evidence-based literature analyses have demonstrated that acupuncture has a positive effect on post-stroke rehabilitation (Huang et al., 2012). However, the underlying mechanisms are still unclear. Clinical trials suggest that acupuncture can

modulate the balance between neurochemicals, regulate cerebral microcirculation, and influence the metabolism and activity of neurons. Preclinical studies have shown that acupuncture exerts its protective effect on stroke through mitigation of inflammatory reactions and promotion of neurogenesis and angiogenesis (Li and Wang, 2013).

Using DTI, Shen *et al* found that the FA values in the infarct areas and cerebral peduncles were higher in stroke patients with acupuncture than control subjects (Shen et al., 2012). These results suggest that acupuncture may postpone Wallerian degeneration and facilitate structural reorganization in and beyond ischemic lesion areas, which is associated with functional recovery after stroke. A positron emission tomography study showed that electroacupuncture in stroke patients can bilaterally excite cerebral structures related to motor function, demonstrating that acupuncture influences the neural network related to brain plasticity, thereby contributing to the recovery of motor performance (Fang et al., 2012). Furthermore, Li *et al* speculated that acupuncture has a preconditioning effect that can induce cerebral ischemic resistance via antioxidant and anti-apoptotic pathways (Li and Wang, 2013).

Before clinical application of acupuncture treatment, acupuncturists require intensive training and practice, and the evidence of the efficacy of acupuncture for stroke is not sufficiently strong due to a dearth of strict standards and randomized controlled trials. These weaknesses obstruct the clinical promotion of acupuncture in the treatment for stroke.

7.5.3. Brain stimulation—Rehabilitation is crucial for stroke patients. Repetitive transcranial magnetic stimulation (rTMS) is a new non-invasive brain stimulation technique. Applying rTMS over the primary sensory cortex might alleviate WMI. Brodie *et al.* showed that WM volume in the cortex underlying the TMS coil may be a novel predictor for the behavioral response to the application of 5-Hz rTMS over the ipsilateral primary somatosensory, followed by motor practice (Brodie et al., 2014). Zheng *et al* found that a combination of transcranial direct current stimulation and physical therapy can facilitate the microstructural restoration of WM fibers in descending motor tracts, which are related to positive clinical outcomes after stroke (Zheng and Schlaug, 2015).

7.6. Hypothermia

Therapeutic hypothermia may be a potent neuroprotective treatment for patients with acute brain injury, as hyperthermia contributes to poor prognosis (Baldwin et al., 2010). Hypothermia mitigates ischemic brain injury by retarding metabolism and energy depletion, suppressing the release of excitatory amino acids, diminishing oxygen free radical production, attenuating inflammatory response, regulating gene expression, preventing BBB destruction, and balancing cell survival and death pathways (Han et al., 2015). A meta-analysis of 101 publications reporting the efficacy of hypothermia in animal models with ischemic stroke showed that induced hypothermia resulted in 44% average reduction in infarct volume and 46% average improvement in functional scores (van der Worp et al., 2007). An *in vitro* OPC culture study demonstrated that mild hypothermia regulates the balance between apoptosis/differentiation and proliferation, leading to an increase in cell number (Imada et al., 2010). Several experimental studies indicate that hypothermia has

beneficial effects on neurogenesis, angiogenesis, and synapse organization after stroke, all of which are associated with neural network reconstruction and functional recovery (Han et al., 2015). In humans, therapeutic hypothermia has been shown to be effective and safe in patients with global cerebral ischemia induced by cardiac arrest or neonatal hypoxic-ischemic encephalopathy (Hemmen and Lyden, 2009). For example, the "cooling for acute ischemic brain damage" study reported that therapeutic hypothermia is feasible and safe in patients with acute ischemic stroke (Krieger et al., 2001). The growth of the lesion size on DWI is less in hypothermic patients than in control subjects (De Georgia et al., 2004). Five observational case series including 112 patients with severe MCA infarction demonstrated that hypothermia reduces mortality, improves prognosis in survivors, and exerts an anti-edema effect after malignant MCA infarction (Bardutzky and Schwab, 2007). However, the "intravenous thrombolysis plus hypothermia for acute treatment of ischemic stroke" study showed that there were no differences in sICH rates, clinical recovery level, and long term death rates between the hypothermia and normothermia groups, and that more patients developed pneumonia after hypothermia (Hemmen et al., 2010). Furthermore, a meta-analysis including seven parallel-controlled clinical trials demonstrated that hypothermia did not affect stroke severity and mortality. The researchers suggested that this result might be subject to the high heterogeneity and limited sample size of included studies and that large randomized controlled clinical trials are still needed (Lakhan and Pamplona, 2012).

To date, induced hypothermia is considered an ideal modality for stroke therapy in animal studies, but clinical trials have yet to yield conclusive evidence to confirm efficacy, safety, and feasibility. Furthermore, issues such as the depth and duration of cooling, therapeutic window, methods for hypothermia delivery, rewarming rates, and adverse effects still need to be resolved before clinical application of therapeutic hypothermia (Faridar et al., 2011).

Berger *et al* found that a combination of hypothermia and BDNF therapy reduce infarct volumes through a synergistic reduction in striatal glutamate (Berger et al., 2004). Goossens *et al* reviewed all neuroprotective strategies that have been combined with therapeutic hypothermia in experimental models of ischemic stroke, and found that hypothermia is a promising therapy to combine with other neuroprotective compounds (Goossens and Hachimi-Idrissi, 2014). However, only rt-PA, caffeinol, and decompressive hemicraniectomy have been combined with hypothermia in the clinic.

7.7. Ischemic conditioning

Ischemic conditioning or ischemic tolerance of the brain is a naturally protective but transient mechanism induced by exposure to subtoxic insults. In this phenomenon, subtoxic insults promote the recovery of cells or tissues from a subsequent, more severe ischemic and hypoxic episode (N et al., 2015). The mechanisms underlying the induction and maintenance of ischemic/hypoxic resistance in the brain are complex and intertwined, and include the reinforcement of the neurovascular network, improvements in cerebral circulation, regulation of the expression of neurotrophin, reductions in inflammation, and modulation of survival/ apoptotic signaling pathways (Wang et al., 2015). A large number of preclinical studies have shown ischemic preconditioning as well as postconditioning reduce infarct volume and facilitate brain recovery after stroke in animal models (Prasad et al., 2012).

Transient ischemic attacks without apparent structural damage as identified by imaging may protect the brain against a subsequent "stroke," as manifested by superior clinical presentation and outcome, and reductions in infarct size (Stetler et al., 2009). According to Selim *et al*, ischemic conditioning should be applied in the primary and secondary prevention of stroke, as an additive intervention for acute ischemic stroke, and as a prophylactic therapy against delayed ischemic injury in subarachnoid hemorrhage (Selim and Wang, 2015).

Large adequately powered clinical trials are still needed to standardize optimal protocols for the ischemic conditioning procedure and to further assess the potential benefits of ischemic conditioning in human brain ischemia (Wang et al., 2015).

8. The future of WMI research and therapies

The majority of mechanisms and hypotheses of ischemic WMI have been studied and verified in animal stroke models, but remain poorly investigated in human ischemic stroke. There are major differences between human and animal models and the human condition is far more complex than rodent injury models. Furthermore, we only have limited access to central nervous system in humans. The establishment of animal models with a more complex brain that is not so different from the human brain would be a welcome trend for future WMI research. Furthermore, more mechanistic studies need to be performed in human ischemic stroke.

Although ischemic GMI and WMI share some common characteristics, WMI exhibits unique properties. Furthermore, axons, oligodendrocytes, and astrocytes, along with surrounding microglia, progenitor cells, and vasculature constitute a highly complex framework for WM-targeting strategies. Multiple cell types and intercellular signaling cascades contribute to the maintenance of WM integrity and connectivity (Hayakawa and Lo, 2015). Thus, further investigations of WMI should emphasize cellular networks rather than solely focusing on oligodendrocytes and axons.

WM is involved in the relay of sensorimotor information and is intimately linked with cognitive function. Although there is a natural increase in oligodendrogenesis under ischemic conditions, the scale of this response is not sufficient for full neurorecovery. Therefore, therapeutic approaches that promote oligodendrogenesis are urgently needed for WM repair. Given that stem cells can differentiate into multiple neural cell types and that the brain has only limited and transient capacity for endogenous neurogenesis and oligodendrogenesis after ischemia, stem cells may be the most promising approach for WM and GM recovery.

Accumulating evidence suggests that non-pharmacological approaches, such as therapeutic hypothermia and ischemic/hypoxic conditioning might salvage brain tissue in both GM and WM and provide new opportunities for stroke (Chen et al., 2014a).

Ischemic WMI is a complex process involving multiple intertwined mechanisms. One of the many lessons we have learned from the failure of clinical neuroprotectant trials is that treatments of ischemic stroke need to target multiple underlying mechanisms over time,

perhaps with a "cocktail" approach. Therefore, a combination of pharmacological and non-pharmacological strategies, such as hypothermia combined with neuroprotective reagents, stem cell therapy with brain stimulation, ischemic conditioning with revascularization may yield more positive results in the future.

9. Conclusion

WM is involved in the relay of motor and sensory information to and from the cerebral cortex and subcortical structures. As a consequence, WMI results in profound cognitive dysfunction, emotional disorders, and impairments in motor function. WM is exquisitely vulnerable to ischemic brain injury; thus, stroke generally involves both GM and WM. Most studies have emphasized GM and overlooked the critical role of WM in neurorecovery after ischemic stroke. However, true and long-lasting neuroprotection cannot be attained without parallel protection of WM. Protecting the integrity and connectivity of WM is expected to facilitate the rehabilitation of axonal networks and improve stroke prognosis. Therefore future stroke therapies need to be designed to be inclusive of both GM and WM.

Acknowledgments

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Abbreviations

AD	axial diffusivity
ADC	apparent diffusion coefficient
ADMSC	adipose-derived mesenchymal stem cell
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
ATP	adenosine triphosphate
BAEP	Brainstem auditory evoked potential
BBB	blood brain barrier
BMSC	bone marrow stromal cells
BOLD-fMRI	blood oxygen-level dependent functional MRI
Ca^{2+}	calcium ion
CMCT	central motor conduction time
CNS	central nervous system
CRP	C-reactive protein
CSF	cerebrospinal fluid
CT	computer tomography
DKI	diffusion kurtosis imaging
DTI	diffusion tensor imaging
DW-MRI	diffusion-weighted magnetic resonance imaging

DWI	diffusion-weighted imaging
EEG	electroencephalography
FA	fractional anisotropy
FLAIR	fluid-attenuated inversion recovery
fMRI	functional magnetic resonance imaging
GFAP	glial fibrillary acidic protein
GluRs	glutamate receptors
GM	gray matter
GMI	gray matter injury
HUSBC	human umbilical cord blood cells
IL-6	interleukin-6
IL-18	interleukin-18
MBP	myelin basic protein
MCA	middle cerebral artery
MCP-1	monocyte chemotactic protein 1
MD	mean diffusivity
MEP	motor evoked potential
MMP-9	matrix metalloproteinase 9
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
MT	magnetization transfer
MTR	magnetization transfer ratio
NFL	neuroinflament light polypeptide
NIHSS	National Institutes of Health Stroke Scale
NMDA	*N*-methyl-D-aspartate
OPCs	oligodendrocyte progenitor cells
RD	radial diffusivity
rMT	resting motor threshold
ROS	reactive oxygen species

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rTMS	repetitive transcranial magnetic stimulation
r-tPA	recombinant tissue-type plasminogen activator
SEP	somatosensory evoked potential
SBP	systolic blood pressure
sICH	symptomatic intracerebral hemorrhage
SMART-MR	Second Manifestations of ARTerial disease-Magnetic Resonance
TABASCO	Tel Aviv Brain Acute Stroke Cohort
TMS	transcranial magnetic stimulation
WM	white matter
WMI	white matter injury
Zn^{2+}	zinc ion
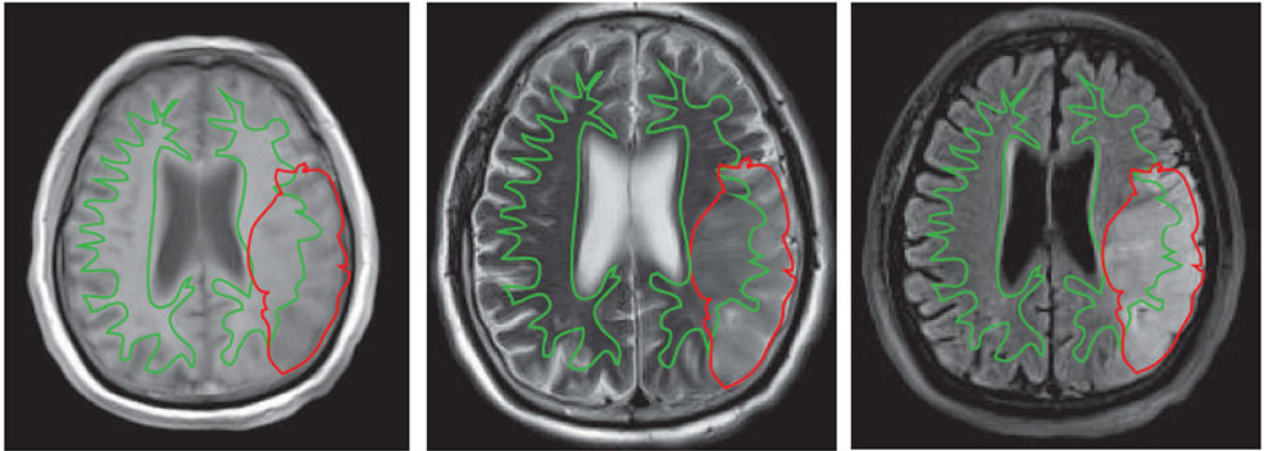
Figure 1.
Transverse images in a 73-year-old man 48 hours after left middle cerebral artery (MCA) occlusion. T1 WI (a) shows mixed areas of abnormal signal intensity in the GM and WM of the temporal lobe. T2 WI (b) and FLAIR (c) images demonstrate high intensity signal in the infarct zone with subtle prominence of WM. WM is traced with a green line and the infarct region is traced with a red line. WM infarct regions are enclosed by both the red and green outlines, whereas GM infarct regions are defined as red regions outside the green outline.

a. ADC   b. DWI
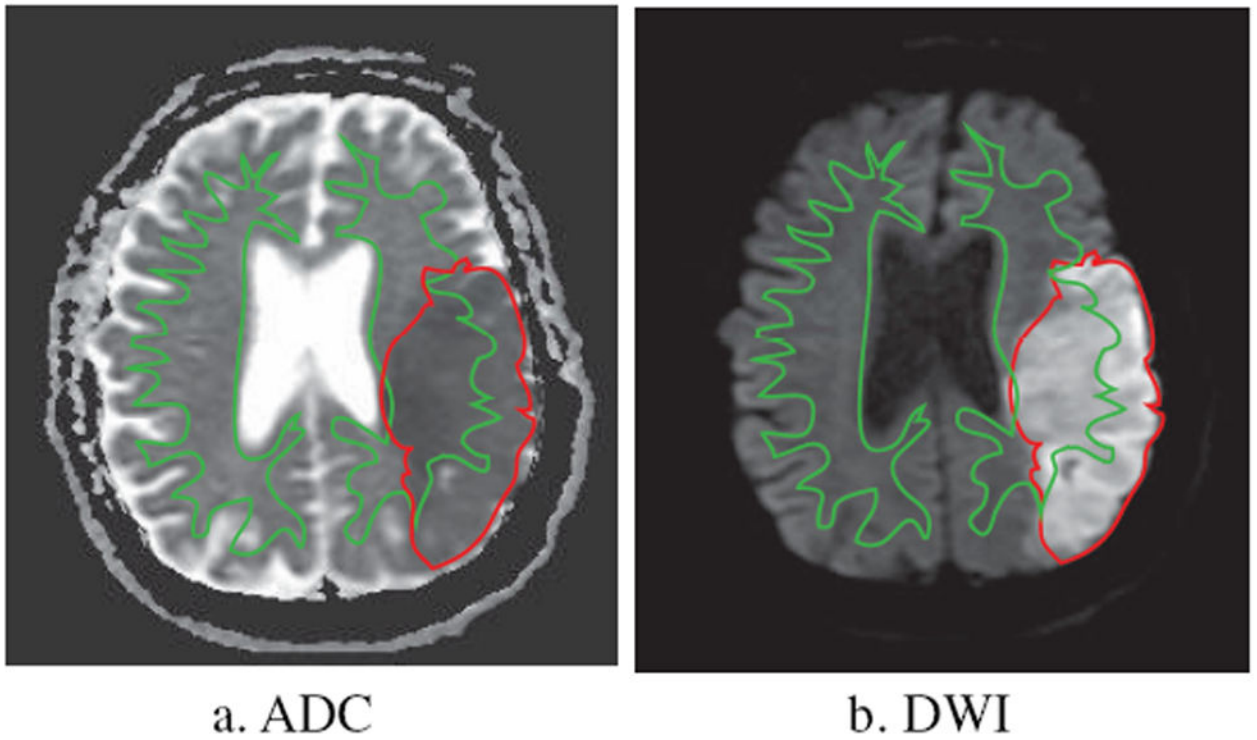
Figure 2.
DWI image in the same patient as in Figure 1. *a*. ADC shows mixed areas of decreased signal intensity in the GM and WM of the temporal lobe. *b*. DWI demonstrates increased signal intensity in the infarct zone. WM infarct regions are enclosed by both the red and green outlines, whereas GM infarct regions are defined as red regions outside the green outline.
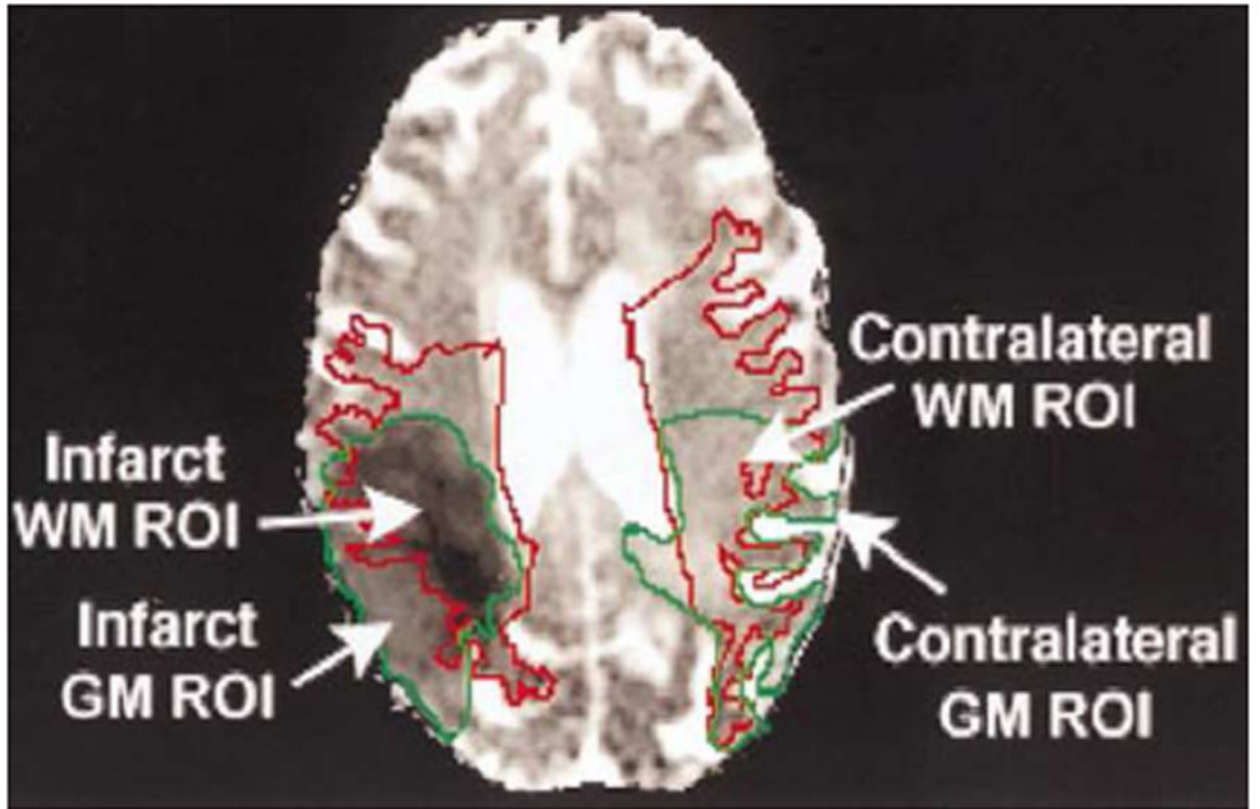
Figure 3.
DTI image in an 87-year-old woman 3–4 days after middle cerebral artery occlusion. The region of interest (ROI) in WM was traced as a red line in both ipsilateral and contralateral hemispheres. The infarct regions were outlined with green lines. Infarct WM is enclosed by both the red and green outlines. The regions enclosed by the green outline but outside the red outline are infarct GM (adapted from Radiology 2000, 215:211-220 with permission).
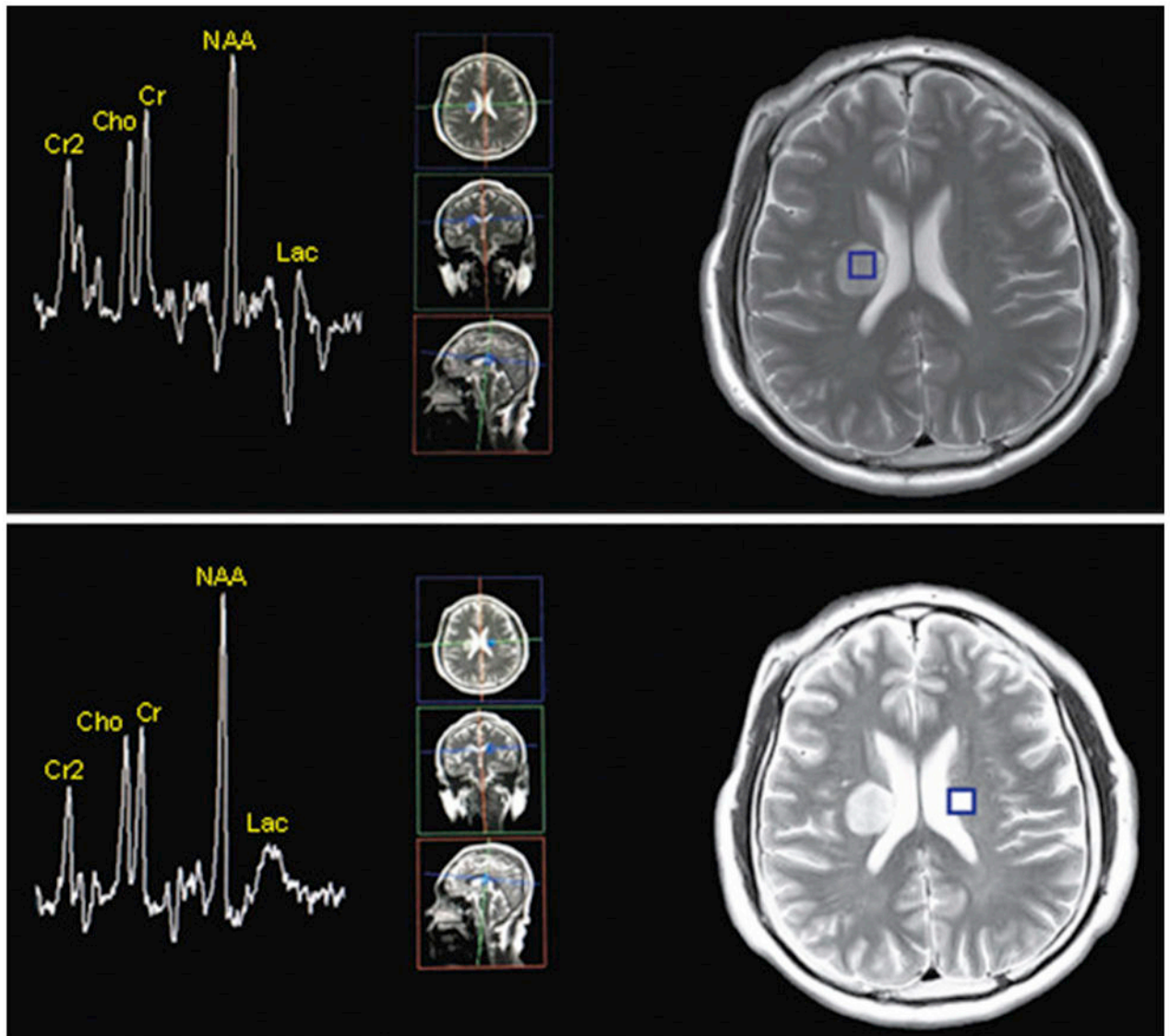
Figure 4.
MRS images in a 43-year-old man 5 days after right MCA infarction. Compared with the MRS image in homologous parts of the contralateral hemisphere (b), the MRS image in the infarction area (figure a) shows decreases in N-acetylaspartate (NAA), total creatines (Cr) and total cholines (Cho), and an inversed peak of lactate (lac) appears in the infarction area. I: integral, A: amplitude

Table 1

Imaging modalities for detection and quantitation of WMI

	Primary attribute	**Imaging manifestations of WMI**
Routine MRI	Distinguishes GM and WM, measures the volume of WM	Hyperintensity on T2-weighted or FLAIR, hypointensity on T1-weighted images
DWI	Detects hyperacute infarction in deep WM or in the brainstem	Hyperintensity on DWI; time-dependent change of ADC in WM following ischemia
DTI	Assesses the integrity and connectivity of WM, reconstructs the distribution of WM pathways three-dimensionally.	Decreased FA values and increased MD values indicate structural breakdown of axons and disconnection/distortion of tracts.
DKI	Reflects post-stroke tissue remodeling, provides independent and complementary information relative to DTI	Increased MK, decreased FA, and MD value
MTI	Reveals the degree of myelination	Decreased MTR value
MRS	Measures the brain metabolism	Decreases in NAA, total Cr and total Cho

Table 2

Pharmacological neuroprotectants for WMI under investigation

Class	Representative drugs	Potential mechanisms
Antioxidant	Ebselen, Arundic acid, Citicoline	Scavenger of free radicals and ROS; decrease of NO production and S100 calcium-binding protein expression
Anti-inflammatory	Minocycline	Inhibition of MMP-9 and microglia activation, attenuation of apoptosis
Anti-excitotoxicity	Magnesium	Blocker of glutamate transport and efflux, reverser of Na^+-Ca^{2+} exchange
Growth factors	BDNF, NAMPT, Erythropoietin	Stimulation of oligodendrogenesis, inhibition of OPC apoptosis

Table 3

Neurorepair based on cell therapy for WMI under investigation

Source of stem cells	Potential mechanisms
ADMSC	Immunomodulation, anti-apoptotic, promotion of trophic factor production, stimulation of axonal growth and oligodendrogenesis,
HUSBC	Anti-inflammatory, enhancement of vascular remodeling
BMSC	Stimulation of axonal growth and oligodendrogenesis
OPCs	Stimulation of BDNF expression, enhancement of neurogenesis, anti-apoptotic and remyelinated the damaged axon