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Neurofluid Dynamics and the Glymphatic System: A Neuroimaging Perspective

Toshiaki Taoka, MD, PhD[1, 2], Shinji Naganawa, MD, PhD[2]

[1]Departments of Innovative Biomedical Visualization (iBMV) and [2]Radiology, Nagoya University Graduate School of Medicine, Nagoya, Japan

The glymphatic system hypothesis is a concept describing the clearance of waste products from the brain. The term "glymphatic system" combines the glial and lymphatic systems and is typically described as follows. The perivascular space functions as a conduit that drains cerebrospinal fluid (CSF) into the brain parenchyma. CSF guided to the perivascular space around the arteries enters the interstitium of brain tissue via aquaporin-4 water channels to clear waste proteins into the perivascular space around the veins before being drained from the brain. In this review, we introduce the glymphatic system hypothesis and its association with fluid dynamics, sleep, and disease. We also discuss imaging methods to evaluate the glymphatic system.

Keywords: *Glymphatic system; Cerebrospinal fluid; Interstitial fluid; Magnetic resonance imaging, Diffusion imaging; Contrast media*

INTRODUCTION

The glymphatic system hypothesis is a concept associated with cerebrospinal fluid (CSF) and interstitial fluid (ISF) dynamics in the central nervous system. This hypothesis does not represent the discovery of a previously unknown anatomical structure but rather a brain-wide paravascular pathway for CSF and ISF exchange that facilitates the efficient clearance of solutes and waste from the brain. CSF enters the brain along para-arterial channels to exchange with the ISF, which is in turn cleared from the brain along para-venous pathways (1). After first being proposed by Iliff et al. in 2012 (2), this concept has attracted attention from a wide range of fields and many associated reports were published shortly thereafter. This review introduces the glymphatic system hypothesis in association with neurofluid dynamics, as well as its association with sleep and disease.

The term "neurofluids" was first used by Professor Toro, an applied mathematician at the University of Trento, Italy (3). "Neurofluids" is defined as a collective term for the fluids in which the central nervous system is immersed, such as the blood, CSF, and ISF (3, 4). This term is helpful for understanding the dynamics of these fluids.

The Old and New Concepts of CSF Dynamics

The concept established by Cushing, Weed, and others in the early 20th century regarding the production, circulation, and absorption of CSF, a neurofluid, has long been supported (5, 6). According to this concept, CSF is produced in the choroid plexus of the lateral ventricle, flows into the subarachnoid space through the ventricular system, is absorbed from the arachnoid villi on the brain surface, and eventually returns to the systemic circulation through the veins. CSF secretion in adults varies between 400 mL per day to 600 mL per day and 60–75% of CSF is produced by the choroid plexuses of the lateral ventricles and the tela choroidea of the third and fourth ventricles (7). However, this concept has been questioned since the end of the 20th century and a wide range of contradictory evidence has been presented.

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Corresponding author: Toshiaki Taoka, MD, PhD, Department of Radiology, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan.
• E-mail: ttaoka@med.nagoya-u.ac.jp
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A recently supported concept is that CSF is mainly produced because of hydrostatic pressure in the capillaries of the brain. In addition to the above-mentioned subarachnoid space, the involvement of the ependymal tissue, pia mater on the brain surface, and intercellular substances in the brain parenchyma has been demonstrated (8-10). The absorption of CSF by the arachnoid villi has also been questioned (11). In addition to the arachnoid villi in the skull, the known pathways for CSF absorption include the arachnoid villi in the spinal cord and lymphatic systems in the dura and nasal cavity, among other locations. Tracer experiments with resin injected into the CSF space have demonstrated tracer flow into the lymphatic system in the nasal cavity via the cribriform plate in various mammals, including humans (12). Another reason against the hypothesis that the arachnoid villi are a major site of CSF absorption is that arachnoid villi are not present in humans or sheep before birth, but develop postpartum and increase in number with age (10). For the past 30 years, although the precise percentages remain unknown, several studies have confirmed the transport of substances from the brain to the cervical lymph nodes via the lymphatic system in the nasal cavity and other areas (11, 13). In other words, under physiological conditions, the nasal lymphatic system is the main pathway for CSF clearance, whereas the arachnoid villi are a pathway activated only when intracranial pressure is increased (13, 14).

Glymphatic System Hypothesis

Nedergaard and Goldman (15) hypothesized that the perivascular spaces constitute a system equivalent to the lymphatic system in the brain and named this system the glymphatic system (2) by combining the glial and lymphatic systems. Their hypothesis can be summarized as follows. The perivascular space functions as a conduit that drains CSF into the brain parenchyma. The driving force of this conduit includes arterial pulsation and convective bulk flow of ISF. CSF, guided to the perivascular space around the arteries, enters the interstitium of the brain tissue via aquaporin-4 (AQP4) water channels distributed in the foot processes of astrocytes that constitute the outer wall of the perivascular space. CSF entering the interstitium collects waste proteins from tissues. After clearing intercellular spaces in this way, the CSF/ISF then flows into the perivascular space around the veins and is drained from the brain (Fig. 1).

Under the above-mentioned hypothesis, Iliff et al. (2) observed a subcortical area of the mouse brain *in vivo* (at a depth of 100 μm) using two-photon microscopy that enables observation of the live brain using a highly transmissive

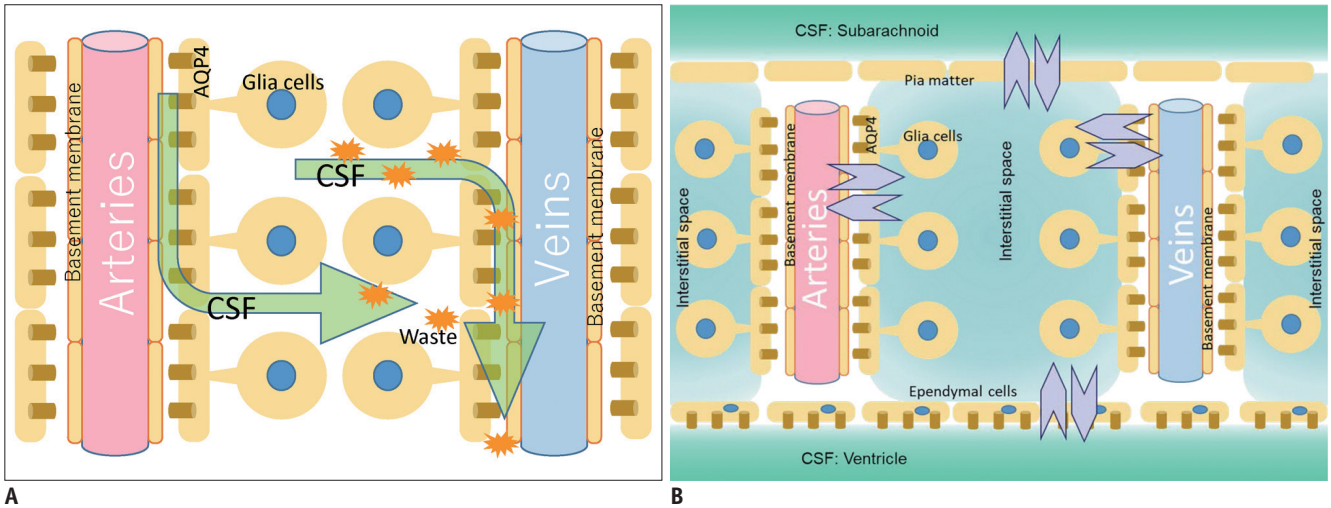

Fig. 1. Overview of glymphatic system and neurofluid concept.
A. Illustrates original concept of glymphatic system. CSF flows into brain parenchyma through periarterial space and enters interstitial space of brain tissue through AQP4-controlled water channels distributed at endfeet of astrocytes that comprise outer wall of perivascular space. CSF entering interstitial space removes waste proteins from tissue. CSF then flows into space around veins and is excreted outside brain. **B.** Illustrates concept of neurofluids in brain tissue. Interstitial space or CSF space of brain tissue is considered common space that functions not only as support structure but also as space for mass transport, immune function, and/or intercellular signaling. Common space is filled with neurofluids. Neurofluid is term that refers to any type of fluid that fills central nervous system, such as CSF, ISF, and blood. There is exchange between neurofluid compartments. Adapted from Taoka et al. *J Magn Reson Imaging* 2020;51:11-24 (4). AQP4 = aquaporin-4, CSF = cerebrospinal fluid, ISF = interstitial fluid

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infrared laser light. They marked the subcortical vessels with transarterially administered fluorescent substances and then labeled the CSF with two types of fluorescent substances. The behaviors of these substances were observed over time. The tracers were observed around the arteries immediately after injection and around the veins one hour after injection. Tracers directly injected into the brain parenchyma accumulated around veins. These findings are the basis of the hypothesis that the CSF flows from the periarterial space into the interstitium, from which it is drained via the perivenous space. Another study confirmed that arterial pulsation drives CSF/ISF in the perivascular space around the arteries (16).

Controversies Surrounding the Glymphatic System Hypothesis

The glymphatic system hypothesis proposes a unidirectional flow through the perivascular space of the arteries or arterioles to the perivascular space of the veins, as observed by two-photon microscopy. Although some reports support this glymphatic system hypothesis as above, several others have refuted it, particularly the idea that arterial pulsation provides the driving force for interstitial flow (bulk flow), which is associated with the transfer from the CSF to ISF in tissue. In a study using mathematical modeling, Asgari et al. (17) demonstrated that the driving force generated by arterial pulsation was too small to transport substances by flowing fluid and that they might instead be transported through the perivascular space by diffusion instead of "bulk flow," such as interstitial flow. Another study using mathematical modeling also refuted the involvement of AQP4, one of the key elements of the glymphatic system. Models based on the Navier–Stokes and convection-diffusion equations, which are associated with fluid motion, showed that the resistance against permeation of water molecules through astrocyte endfeet is much higher than that through the surrounding spaces between the endfeet. Thus, the transport of substances by the bulk flow of extracellular fluid is unlikely to be modulated by changes in the water permeability of AQP4 (18). In these models, diffusion rather than bulk flow is a factor in the transport of substances in the extracellular fluid. In addition, Spector et al. (19) questioned many aspects of the hypothesis developed by Nedergaard et al. For example, their hypothesis ignores the transport of substances to the brain parenchyma via the pia mater on the brain surface and ependyma. CSF in the perivascular space is reportedly nearly stagnant or in a to-and-fro state. Moreover, conditions during two-photon microscopic observations differ from those of the physiological environment (19). Despite these controversies, the concept of the glymphatic system helps radiologists or radiology researchers to understand neurofluid dynamics better.

Imaging Evaluation of the Glymphatic System/ Neurofluid Dynamics in Humans

A variety of methods is used to evaluate the glymphatic system/neurofluid dynamics. In humans, non-invasive methods are necessary; thus, the selection of potential methods is limited. The MRI methods reported so far to evaluate the dynamics of neurofluids; namely, the blood, CSF, and ISF, are described below (Fig. 2).

Tracer Studies to Evaluate Glymphatic/Neurofluid Dynamics

Gadolinium-based contrast agents (GBCAs) have been in use for more than 30 years (20-22). Evaluation using intrathecally injected GBCAs as tracers has also been reported in humans. For example, there was one report of an accident in a clinical setting in which relatively high doses of GBCAs were intrathecally injected (23) and other reports in which small doses of GBCAs were systematically injected into the intrathecal space for diagnostic purposes (24-

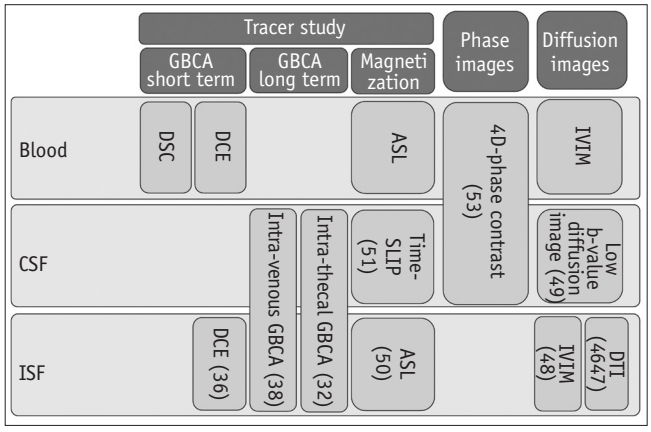

Fig. 2. MRI methods for evaluating glymphatic system/ neurofluid dynamics. Several MRI methods have been reported for evaluation of neurofluid (blood, CSF, and ISF) dynamics. Although methods for evaluating blood or CSF dynamics are established, those for evaluating ISF dynamics are under development. Numbers indicate representative references. ASL = arterial spin labeling, DCE = dynamic contrast-enhance, DSC = dynamic susceptibility contrast, GBCA = gadolinium-based contrast agent, IVIM = intravoxel incoherent motion, SLIP = spatial labeling inversion pulse, 4D = four-dimensional

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26). All reports have shown that GBCAs penetrate and flow from the brain surface to the cortex and further deep brain tissues in humans. One study examined the distribution of a CSF tracer in the human brain using MRI over a prolonged time, reporting that GBCAs distributed centripetally from the surface toward structures in the deep parts of the brain and that vascular pulsations mediated by the CSF seemed to play an important role in tracer entry into the brain (26). These findings confirm that CSF also flows from the brain surface into the parenchyma in humans, as stated by the glymphatic system hypothesis, and suggest that GBCAs can be used to evaluate system activity. There are also reports of intrathecal injection of GBCAs for the evaluation of decreased glymphatic system activity in normal pressure hydrocephalus (26, 27). In a recent study, human subjects underwent MRI before and at multiple time points after the intrathecal administration of a contrast agent. Measurements of signals at locations including the ventricles and brain parenchyma, predefined as the "glymphatic pathway" showed that the delayed clearance of the "glymphatic pathway" was related to aging. The study also examined heavily T2-weighted fluid-attenuated inversion recovery images to visualize putative meningeal lymphatic vessels; the delayed visualization of meningeal lymphatics compared to that of the "glymphatic pathway" indicated that meningeal lymphatics are downstream of the "glymphatic pathway" (28). Practically, the intrathecal injection of GBCAs has not been approved by U.S. Food and Drug Administration (FDA), making its clinical application impossible. Regarding this issue, one report discussed the safety profile and feasibility of intrathecal contrast-enhanced glymphatic MR performed in 100 consecutive patients. The study clinically registered short- and long-term adverse events using patient interviews after the intrathecal administration of 0.5 mL of gadobutrol (1.0 mmol/mL) along with 3 mL of iodixanol (270 mg I/mL). In the series, serious anaphylaxis occurred in one patient with a known allergy to iodine-containing contrast agents (1%); other adverse events during the first 1–3 days after contrast injection included severe headache (28%) and severe nausea (34%) (29).

Intravenous injection of gadolinium to evaluate the glymphatic system has also been reported. Regarding the evaluation of the brain parenchyma, one study that assessed the permeation of intravenously injected gadolinium into normal brain tissue by permeability imaging reported an elevated blood-brain barrier transfer coefficient in patients with Alzheimer's disease (30). Several reports have also used permeability imaging to evaluate the correlation between glymphatic function and blood-brain barrier function (31, 32). One study using dynamic GBCA-enhanced MRI to quantify blood-brain barrier permeability demonstrated that enlarged perivascular spaces were associated with compromised blood-brain barrier integrity supporting the hypothesis that blood-brain barrier dysfunction may be involved in the pathogenesis of enlarged perivascular spaces (31). Another report used ^{17}O, a stable isotope of oxygen, as an MRI tracer to evaluate blood-brain barrier function. The study observed the effect of an AQP4 facilitator, TGN-073, and showed increased ISF turnover through the system, suggesting that the AQP4 system produces a water gradient within the interstitial space that promoted ISF circulation within the blood-brain barrier in addition to providing the necessary water for proper glymphatic flow (32).

The transfer of intravenously injected gadolinium into the CSF has also been confirmed in humans. Intravenously administered GBCAs are reported to leak into the CSF even in healthy subjects (33). At approximately 4 hours after intravenous injection of gadolinium, transfer of gadolinium into the CSF and Virchow-Robin space at the base of the brain can be observed on heavily T2-weighted fluid-attenuated inversion recovery images (34-38). It is also interesting that intravenously administered GBCAs show leakage from the cortical veins with delayed imaging after injection, with the leakiness of the cortical veins significantly correlated with age (39). Using this imaging method, the space between the pial sheath surrounding the cortical veins and the cortical venous wall was reported to be enhanced; this enhancement appeared to be connected to the meningeal lymphatics running along the superior sagittal sinus (40).

Diffusion Images to Evaluate the Glymphatic System/ Neurofluid Dynamics

Attempts have also been made to evaluate glymphatic system activity using diffusion images. In tracer studies, the behaviors of tracers after injection are assessed using integral evaluation. Meanwhile, the assessment of diffusion images uses differential evaluation as the behavior of water molecules in the tissue at the time of imaging is evaluated (4). The latter may enable the evaluation of glymphatic system activity at any given time point. While hypothesizing that diffusion capacity limited to the running direction

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of the perivascular space correlates with the activity of the glymphatic system, we have proposed an evaluation technique, termed diffusion tensor image analysis along the perivascular space (DTI-ALPS), in which the behavior of water molecules in the deep white matter is evaluated using DTI (41). When the diffusion capacity of water molecules in the brain is evaluated, the effects of diffusion along large white matter fibers are so substantial that the evaluation of diffusion along perivascular spaces is difficult. However, if the large white matter fibers and perivascular space intersect at a right angle, the effects of the former should be separable. In the human brain, the medullary arteries and veins intersect with the ventricular wall, at a right angle to the white matter on the outer side of the body of the lateral ventricle. In other words, the medullary arteries and veins run horizontally on the-cross section. In a region proximal to the lateral ventricle, projection fibers, including the pyramidal tract, run in the vertical direction. On the outer side of the projection fibers, the commissural fibers, including the superior longitudinal fascicles, run in the anteroposterior direction. Thus, in this region, diffusion along the perivascular spaces of the medullary arteries and veins can be measured separately from the diffusion along large white matter fibers. In the DTI-ALPS technique, the diffusion capacity along the perivascular space in the white matter on the outer side of the body of the lateral ventricle is evaluated as a ratio of the diffusion capacity along the perivascular space to that in a direction perpendicular to the running direction of the main white matter fibers (ALPS index). Evaluations performed in healthy volunteers, patients with mild cognitive decline, and patients with Alzheimer's disease showed that the ALPS index significantly inversely correlated with the Mini-Mental State Examination score and significantly correlated with age (Fig. 3). Thus, the ALPS index might be an indicator of glymphatic system function.

Other studies have also evaluated the glymphatic system using diffusion images. One study utilized multishell diffusion tensor imaging (b-values = 0, 50, 300, and 1000 s/mm^2) to measure the slow and fast components of the apparent diffusion coefficient (ADC) of water in the brain. The study uncovered both increases in slow ADC and decreases in fast ADC in relation to sleep, which could reflect the distinct biological significance of fast- and slow-ADC values and sleep-induced changes in CSF volume (42). Another study utilized the intravoxel incoherent motion (IVIM) method to investigate the intermediate diffusion component using a nonnegative least-squares method to evaluate glymphatic system function. Using this method, values for both parenchymal diffusivity and microvascular perfusion were detected and perivascular fluid motion was evaluated in relation to the glymphatic system (43). Diffusion study can also be applied not only to the brain parenchyma but also to the CSF space. A study evaluating CSF signal intensity on b=500 s/mm^2 diffusion-weighted imaging in the ventricles and other cerebrospinal spaces reported significantly lower CSF signal intensities in the lateral and 3rd ventricles of subjects with hydrocephalus. In addition, the signal void in the Sylvian fissure significantly positively correlated with age (44).

Other Imaging Methods to Evaluate Glymphatic System/ Neurofluid Dynamics

MRI tracer studies using an inversion pulse supplied to arterial blood; i.e., the arterial spin labeling method, have also been used to evaluate glymphatic function. An animal study applied multiple echo time arterial spin labeling to the mouse brain to assess blood-brain interface water permeability by calculating the exchange time of magnetically labeled intravascular water across the blood-brain interface. A significant increase in exchange time in AQP4-deficient mice was observed compared to their wild-type counterparts, demonstrating the sensitivity of the technique to a lack of AQP4 water channels (45).

Time-spatial labeling inversion pulse MRI is another approach for the visualization of CSF motion by applying a slab of inversion pulse at the region of interest in the CSF space, utilizing the CSF as a tracer following magnetization. CSF was found to flow from the third to the lateral ventricles in healthy individuals, suggesting active CSF exchange between these ventricles through the foramen of Monro in the healthy brain; in contrast, no such CSF reflux was observed in patients with hydrocephalus (46).

The phase-contrast method has also been utilized to visualize fluid flow. Recently, the visualization of CSF dynamics using four-dimensional phase-contrast (4D-PC) has been developed, which determines the quantitative spatiotemporal velocity distribution of CSF motion as vector cine images (47). One study using 4D-PC reported significantly lower CSF velocity in the posterior part of the lateral ventricle around the choroid plexus than that in other regions, a finding that challenged the traditional theory that choroid plexus pulsation is the driving force of CSF flow (48).

Even computed tomography (CT) can provide some

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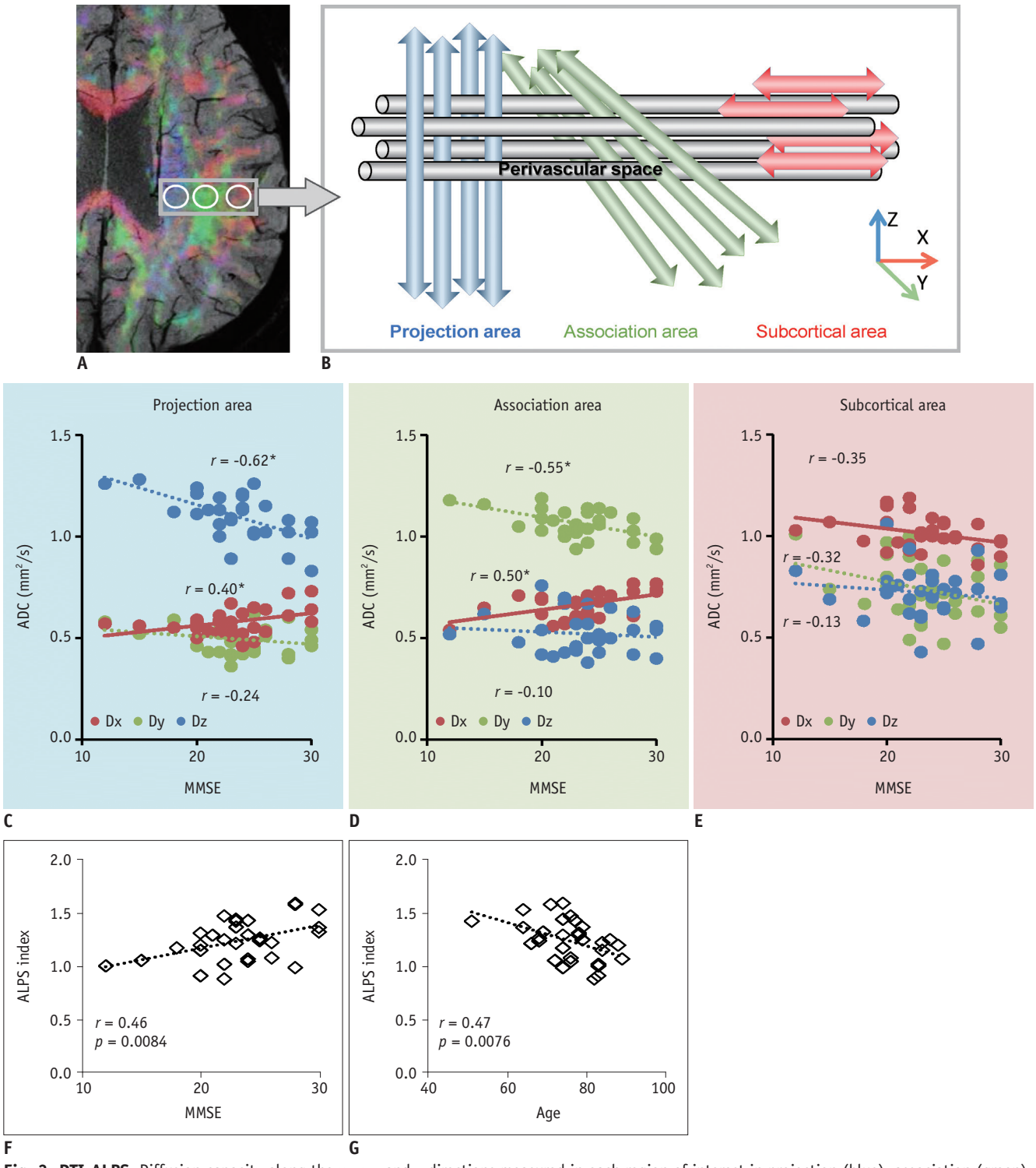

Fig. 3. DTI-ALPS. Diffusion capacity along the x-, y-, and z-directions measured in each region of interest in projection (blue), association (green), and subcortical (red) areas in radiate crown **(A, B)**. In projection **(C)** and association **(D)** areas, diffusion capacity along projection (z-direction: blue) and association (y-direction: green) fibers is inversely correlated with MMSE score. Diffusion capacity in running direction of perivascular space (x-direction: red) is correlated with MMSE score. In other words, with more severe Alzheimer's disease, diffusion capacity tends to decrease. In subcortical area **(E)**, diffusion capacity is inversely correlated with MMSE score in all directions of perivascular space and white matter fibers. We evaluated diffusion capacity along perivascular space using ratio of diffusion capacity along perivascular space, to that in direction perpendicular to running direction of main white matter fibers (ALPS index). ALPS index = mean (Dxproj, Dxassoc) / mean (Dyproj, Dzassoc). ALPS index is significantly inversely correlated with MMSE score **(F)** and significantly correlated with age **(G)**, suggesting that ALPS index might be indicator reflecting glymphatic system function. Adapted from Taoka et al. *Jpn J Radiol* 2017;35:172-178, with permission of Japan Radiological Society (41). ADC = apparent diffusion coefficient, DTI-ALPS = diffusion tensor image analysis along the perivascular space, MMSE = Mini-Mental State Examination

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information on the glymphatic system. The images in a study aiming to demonstrate glymphatic clearance of extravasated iodine empirically following perforation incurred during endovascular therapy on serial CT showed progressive absorption and eventual disappearance of the contrast medium by the brain parenchyma (49).

Glymphatic System and Sleep

The glymphatic system hypothesis has attracted attention for its association with sleep. Drainage by the glymphatic system is inhibited during wakefulness and markedly enhanced during sleep. Xie et al. (50) used two-photon microscopy to observe fluorescent tracers injected into the CSF space of rats, finding that glymphatic system activity was associated with sleep under physiological conditions. The system was markedly more efficient during sleep than during wakefulness. This difference was attributed to a reduction in glial cell volume during sleep, resulting in increased interstitial space expansion compared to during wakefulness, thus promoting substance transport in tissue (50). Similar effects have been observed during anesthesia. The volume fraction of the interstitial space in tissue ranges from 13% to 15% during wakefulness and from 22% to 24% during sleep (50). One study showed that the glymphatic system was more efficient when rats were placed in the lateral position during sleep than in the prone position (51). Based on these findings, the glymphatic system has been associated with various physiological changes associated with sleep.

Neurological Diseases Suspected to be Associated with Glymphatic System Impairment

The following neurological diseases have been associated with glymphatic system impairment. Because the concept of the glymphatic system is only a hypothesis, as described above, its association with these neurological diseases has not been confirmed. However, consideration in the context of this hypothesis facilitates understanding of the pathology and physiology of some neurological diseases.

Alzheimer's Disease

Amyloid β, a protein associated with Alzheimer's disease, aggregates to form amyloid plaques between cells and contributes to disease progression (52). The above-mentioned report on the glymphatic system also presented results regarding amyloid clearance in healthy and AQP4-knockout mice (2). Evaluation of amyloid β clearance over time after direct injection into the brain tissue showed delayed clearance in AQP4-knockout mice. This indicates that the glymphatic system including the AQP4 water channel is involved in amyloid β clearance. This accumulation of amyloid β causes glymphatic system dysfunction, which leads to further amyloid β accumulation. This vicious cycle may occur in affected tissues.

There are few reports of attempts to evaluate the glymphatic system in patients with Alzheimer's disease. Intrathecal injection of GBCAs has not been approved by FDA because of the possibility of serious adverse reactions. Consequently, evaluation in tracer studies via intrathecal injection of media is difficult to perform. As described above, the DTI-ALPS technique has been introduced based on the assumption that the diffusion capacity limited to the running direction of the perivascular space in the radiate crown correlates with glymphatic system activity (41).

Traumatic Brain Injury

Chronic brain injury, a progressive encephalopathy caused by repeated injuries to the brain such as cerebral concussion, presents with abnormal accumulations of amyloid β and transactive response DNA-binding protein 43. In recent years, tauopathy has been reported in chronic brain injury (53). In a mouse model of moderate to severe trauma, Iliff et al. (54) demonstrated a significantly decreased transfer of tracers injected into the cortex in the perivascular space on the ipsilateral side of the injured brain that was detectable 28 days after trauma. Although no studies have yet directly associated chronic brain injury with glymphatic system dysfunction, these conditions may be associated. A larger number of dilated perivascular spaces have been observed on T2-weighted and fluid-attenuated inversion recovery images in patients with mild chronic brain injury than that in healthy volunteers. However, whether this report provides collateral evidence for the association between conditions is uncertain (55).

Normal Pressure Hydrocephalus

Idiopathic normal pressure hydrocephalus is a type of communicating hydrocephalus in which the intracranial pressure is often maintained within the normal range despite the presence of enlarged ventricles. The characteristic imaging findings include an enlarged Sylvian fissure, narrowing of the CSF space in the parietal region,

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and narrowing of the callosal angle. However, many aspects of the pathophysiology of this disease remain unclear, particularly the CSF dynamics. In the past, cisternal contrast-enhanced CT and cisternal scintigraphy have been used for diagnosis; however, this disease is often difficult to diagnose. A Norwegian institution published a study in which GBCAs were intrathecally injected in both patients with normal pressure hydrocephalus and in control subjects. The normal pressure hydrocephalus group showed reflux of the contrast agent into the ventricles, which is a well-known finding of cisternal contrast-enhanced CT. Furthermore, in both the normal pressure hydrocephalus and control groups, the CSF space was first densely stained, followed by dense staining of the brain parenchyma. However, observations over 24 hours revealed that dense staining of the parenchyma tended to be delayed in the normal pressure hydrocephalus group. Based on these findings, the Norwegian report indicated that glymphatic system dysfunction may be associated with the pathology of this disease (27).

A study using the DTI-ALPS technique to evaluate the diffusion capacity limited to the running direction of the perivascular space reported a lower diffusion capacity along the perivascular space in patients with normal pressure hydrocephalus than that in control subjects, suggesting that the DTI-ALPS technique could be used to evaluate glymphatic system dysfunction in patients with normal pressure hydrocephalus (56).

Small Vessel Disease

In small vessel diseases/microangiopathies, including cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, the perivascular space is often dilated. These diseases present with the deposition of amyloid β and other abnormal proteins in tissues. The association between the two events is difficult to explain in terms of vascular wall damage. However, consideration in the context of glymphatic system impairment reveals that the accumulation of abnormal proteins in tissues and the consequent dilation of the perivascular space may be mutually associated events (57). Moreover, in amyloid angiopathy, glymphatic system dysfunction is also reportedly involved in amyloid deposition (58). As discussed in section 'Diffusion Images to Evaluate the Glymphatic System/Neurofluid Dynamics,' the combination of IVIM and nonnegative least-squares methods can be used to evaluate glymphatic function in small vessel disease. One study showed the relationship between the volume fraction of the intermediate diffusion component with white matter hyperintensities and enlarged perivascular spaces. This correlation could indicate aberrant amounts of ISF in degenerated tissue or perivascular edema preceding tissue degeneration in cases with small vessel disease (43).

Other Neurological Disorders

There are several neurological diseases for which the relationship to the glymphatic system has been discussed, including subarachnoid hemorrhage (SAH) and ischemic stroke. One of the very early animal studies visualizing glymphatic system function using a GBCA revealed system impairment hours after SAH induction in mouse models (59). The report also mentioned glymphatic insufficiency in ischemic stroke and that intracerebroventricular injection of tissue-type plasminogen activator improved glymphatic perfusion after SAH or ischemic stroke (59). However, another study reported persistent malfunction of glymphatic and meningeal lymphatic drainage and related neuropathological damage after SAH (60). Diabetes is also a disorder for which with a proposed relationship to the glymphatic system. One MRI-based study of a rat model of type 2 diabetes mellitus demonstrated that the clearance of CSF GBCA from the interstitial space was slowed by a factor of three in the hippocampus of type 2 diabetes mellitus rats compared to that in the non-diabetic rats, a finding confirmed by fluorescence imaging analysis (61).

CONCLUSION

Data on how waste products are excreted from the brain and how CSF/ISF is involved have accumulated not only from the studies on the glymphatic system described above but also in other studies such as those on intra-arterial wall pathways (5, 11, 62, 63). However, the glymphatic system hypothesis may have attracted attention as it shows an association between lifestyle and brain health based on the enhanced clearance of waste products in the brain during sleep, in addition to being labeled with the impactful term, "glymphatic." Although no imaging techniques have yet been established that clearly depict the dynamics of the glymphatic system and neurofluids, various techniques have been attempted. Future studies should enhance understanding of the association between the glymphatic system and various diseases.

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Conflicts of Interest
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ORCID iD
Toshiaki Taoka
https://orcid.org/0000-0001-9227-0240
Shinji Naganawa
https://orcid.org/0000-0002-0214-613X

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