Advances in Magnetic Resonance Imaging Techniques for the Human Brain Glymphatic System: A Postprint

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Abstract

The glymphatic system is a recently discovered anatomical structure in neuroscience that regulates interstitial fluid movement, facilitates waste clearance, and potentially participates in brain immunity, thereby playing a crucial role in central nervous system physiology and pathology. With advances in imaging technology, an increasing number of magnetic resonance imaging (MRI) techniques have been applied to investigate the human brain glymphatic system. Currently, commonly employed MRI techniques include dynamic contrast-enhanced MRI, diffusion tensor imaging analysis along the perivascular space, and novel multimodal ultrafast MRI techniques, among others. This article provides a comprehensive review of the current application status of these techniques in glymphatic system research, aiming to serve as a reference for future imaging studies of the glymphatic system.

Full Text

Advances in Magnetic Resonance Imaging Technology Applied to Human Brain Glymphatic System

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Abstract

The glymphatic system is a recently discovered anatomical structure in the field of neuroscience with functions such as regulation of interstitial fluid movement, waste removal, and potential brain immunity, playing an important role in central nervous system physiology and pathology. With the development of imaging technology, an increasing number of magnetic resonance imaging (MRI) techniques have been applied to study the human brain glymphatic system. Currently, commonly used MRI techniques include dynamic contrast-enhanced MRI, diffusion tensor image analysis along the perivascular space, and novel multimodal ultra-fast magnetic resonance techniques. This article summarizes and reviews the current application status of these techniques in the brain glymphatic system to provide a reference for imaging research on the glymphatic system.

Keywords: Glymphatic system; Central nervous system; Lymphatic system; Magnetic resonance imaging; Dynamic contrast-enhanced magnetic resonance imaging; Diffusion tensor imaging-analysis technique along the perivascular space; Ultra-fast magnetic resonance imaging

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Introduction

In 2012, Iliff et al. [1] reported the existence of a glial lymphatic system in mouse brains mediated by astrocytes that facilitates waste clearance, which has become a frontier research topic and hotspot in neuroscience. Subsequently, in 2015, Louveau et al. [2] and Aspelund et al. [3] reported lymphatic-like vessels within the dural sinuses of mice, and in 2017, Absinta et al. [4] non-invasively observed meningeal lymphatic vessels (mLV) in humans and non-human primates using magnetic resonance imaging (MRI). In 2019, Ahn et al. [5] discovered that basal mLVs in rat models are the primary region for clearing macromolecules from cerebrospinal fluid, with both mLV integrity and cerebrospinal fluid drainage impaired with aging. In 2023, Møllgård et al. [6] reported in *Science* a novel

meningeal structure between the arachnoid and pia mater in mouse and human brains—the subarachnoid lymphatic-like membrane, where immune cells can prevent peripheral immune cells from directly entering deep cerebrospinal fluid. The glymphatic system plays important roles in cerebrospinal fluid (CSF) transport, clearance of toxic proteins and metabolites, and immune surveillance in the central nervous system. Most knowledge about the glymphatic system has been obtained from animal experiments [5,7-8], and due to differences between animals and humans, verification in human studies remains necessary. Multiple imaging techniques have been applied to glymphatic system research [8-10], though commonly used two-photon imaging and immunofluorescence imaging are primarily limited to animal experiments due to their invasive nature. MRI offers advantages such as real-time imaging, non-ionizing radiation, and non-invasiveness, making it the most widely used imaging technique in clinical research. This article summarizes several MRI techniques used in human glymphatic system research, as the combination of multiple MRI techniques will provide more comprehensive tools and deeper understanding for studying the human brain glymphatic system.

1 Dynamic Contrast-Enhanced Magnetic Resonance Imaging

Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) involves rapid injection of contrast agents during MRI to obtain time-signal intensity changes in tissues for studying perfusion and permeability characteristics. Gadolinium-based contrast agents (GBCAs) are commonly used. Human glymphatic system DCE-MRI research employs two methods: intrathecal and intravenous GBCA administration.

In 2013, Iliff et al. [11] first applied MRI to study the glymphatic system in rats, using DCE-MRI after intrathecal injection of two GBCAs with different molecular weights to observe CSF-interstitial fluid (ISF) exchange in rat brains. This imaging technique visualized para-arterial CSF inflow and discovered molecular size-dependent CSF-ISF exchange, using fluid dynamic parameters to characterize CSF-ISF exchange efficiency. Similar to animal experiments, initial human glymphatic system imaging also used intrathecal GBCA injection for DCE-MRI [12]. In 2015, Eide et al. [13] from Oslo University Hospital in Norway first dynamically demonstrated gadobutrol transport in the brain using three-dimensional T1-weighted imaging (3D-T1WI) sequences in a patient with low-pressure headache. The study found symmetric signal increases in all brain regions after intrathecal injection, with higher signal intensity in the supratentorial periventricular and white matter regions compared to subcortical areas, and higher signals in the infratentorial spinal cord and brainstem compared to cerebellum and around the fourth ventricle, demonstrating CSF and CSF-ISF exchange transport throughout the brain.

In 2017, the same team conducted a 24-hour MRI study on a patient with idiopathic normal pressure hydrocephalus (iNPH) [14]. The study found that tracer signal (gadobutrol) enhanced centripetally along the pial arteries, peaking

after one night, while iNPH patients showed delayed peak tracer signal and slower distribution, with more residual tracer around the middle cerebral artery (inferior frontal gyrus), suggesting the role of intracranial pulsation and sleep in glymphatic system function. Watts et al. [15] obtained images at multiple time points (baseline and 3.5, 4.5, 6, 8.5, 10, 26, 50, and 79 hours post-administration) in a 55-year-old male, finding that gadobutrol peaked in cortical signals at 10-26 hours and was almost completely cleared by 79 hours, with delayed enhancement and clearance in the upper subarachnoid space [Figure 1: see original paper]. CSF flow after intrathecal GBCA injection in human brains is much slower than in rodents, where maximum cortical concentration can be observed within 30 minutes to 1 hour [11].

Intravenous GBCA DCE-MRI studies have confirmed the challenging scientific question of "lymphatic vessels existing in the dura mater." In 2017, Absinta et al. [4] localized human mLVs using MRI-T2 fluid-attenuated inversion recovery (FLAIR) and T1-weighted black-blood imaging techniques by exploiting different chemical properties of gadobutrol and gadofosveset. Subsequently, Ding et al. [16] studied mLVs in Parkinson's disease (PD) patients and found significantly reduced flow through mLVs along the superior sagittal and sigmoid sinuses, with markedly delayed perfusion of deep cervical lymph nodes. Wang et al. [17] reconstructed concentration-time curves of perivascular spaces (PVSs) using 3D T1-vibe sequences to quantify gadobutrol perfusion and excretion in PVSs, finding that obstructive sleep apnea-hypopnea syndrome (OSAHS) patients had glymphatic drainage obstruction due to hyperperfusion with insufficient drainage, which improved after one month of continuous positive airway pressure ventilation. Lee et al. [18] conducted a circadian cycle comparative imaging study in 25 healthy subjects, finding higher GBCA clearance after nighttime sleep, suggesting that sleep is associated with better glymphatic clearance, consistent with Eide et al.' s findings [14]. These studies suggest that impaired glymphatic system function is a new mechanism for multiple neurological diseases, and the glymphatic system may represent a new therapeutic direction.

GBCAs are the most widely used MRI contrast agents in clinical practice, with over 300 million patients worldwide having undergone MRI enhancement examinations over the past 30 years. The probability of acute severe systemic adverse reactions after GBCA injection is extremely low, and they have long been considered relatively safe. However, in 2000, Cowper et al. [19] first reported that GBCAs could cause nephrogenic systemic fibrosis, and in 2014, Kanda et al. [20] discovered that repeated GBCA use could cause abnormal T1WI hyperintensity in the dentate nucleus and globus pallidus of adult brains, with similar findings confirmed in pediatric studies [21]. Both macrocyclic and linear contrast agents can deposit in the brain even with single-dose administration [22], and autopsy studies have observed gadolinium deposition in cerebral vascular endothelium and neural interstitium years after gadolinium exposure [23]. When the blood-brain barrier is disrupted or vessels are abnormal, gadobenate ions may more readily infiltrate damaged brain tissue [24]. Intrathecal injection below 1.0 mmol/kg is relatively safe without significant brain deposition, but the sever-

ity of adverse events increases proportionally when doses exceed 1.0 mmol/kg [25-26]. GBCA-related gadolinium deposition has attracted researchers' attention, though the mechanisms, adverse reactions, relative deposition rates, and clearance rates of gadolinium in the brain remain unclear. GBCAs are not clinically approved for intrathecal use and have only been used in exploratory studies among a small number of hydrocephalus patients with lumbar puncture indications who provided informed consent [27-28], with some linear GBCAs restricted for MRI enhancement examinations [29].

The introduction of DCE-MRI has enabled the transition of glymphatic system research from animal to clinical studies, visualizing the temporal and spatial flow characteristics of the glymphatic system and mLVs, quantifying fluid inflow and outflow efficiency in the glymphatic system, and demonstrating functional changes under normal physiological and various pathological conditions. However, considering gadolinium contrast agent deposition in the brain and the invasive nature of intrathecal injection, there is an urgent need for a non-invasive, safer MRI imaging method that does not require contrast agents.

2 Diffusion Tensor Image Analysis Along the Perivascular Space (DTI-ALPS)

In 2017, Taoka et al. [30] proposed a non-invasive method—DTI-ALPS—to evaluate human brain glymphatic system activity, enabling non-invasive clinical research on the glymphatic system.

DTI is a quantitative MRI technique that measures water movement within microstructures by applying diffusion gradients in multiple directions. At the level of the lateral ventricle body in DTI, deep medullary veins run perpendicular to the lateral ventricle, with projection fibers, association fibers, and subcortical fibers arranged sequentially adjacent to the lateral ventricle. Consequently, the perivascular space around medullary veins (left-right direction) is also perpendicular to the lateral ventricle, with the perivascular space oriented perpendicular to projection fibers (superior-inferior direction) and association fibers (anterior-posterior direction). In projection and association fiber regions, the primary difference in water molecule diffusivity between the left-right direction and the direction perpendicular to it lies in the presence of perivascular spaces. The glymphatic system is based on CSF and ISF movement within perivascular spaces, which constitute the main space for CSF-ISF exchange in the glymphatic system, with medullary veins serving as drainage veins of the glymphatic system. Therefore, water molecule movement in perivascular spaces can be calculated based on DTI to reflect glymphatic system function [Figure 2: see original paper]A-C. The DTI-ALPS index can reflect glymphatic system function strength, with higher values indicating better glymphatic system function.

Hsu et al. [31] compared the ALPS index with positron emission tomography (PET) and found that cognitively normal individuals showed low amyloid and

tau protein deposition on PET with high ALPS indices, while Alzheimer' s disease (AD) patients showed high amyloid and tau protein deposition with low ALPS indices [Figure 2D: see original paper]. Zhang et al. [32] validated the consistency between DTI-ALPS indices and glymphatic system function results shown by DCE-MRI in cerebral small vessel disease patients, finding that those with delayed intracranial distribution peak and slow clearance after intrathecal GBCA injection had low ALPS indices, and vice versa [Figure 2E: see original paper].

The DTI-ALPS method is non-invasive, does not require GBCA injection, and needs only a single scan without special timing requirements, attracting numerous researchers' attention. In recent years, DTI-ALPS has been increasingly applied to study glymphatic system function changes in patients with various diseases, soon revealing decreased ALPS and impaired glymphatic system function in multiple conditions including type 2 diabetes [33], cerebral infarction [34], dementia [35], idiopathic normal pressure hydrocephalus [36], hypertension [37], Parkinson' s disease [38], traumatic brain injury [39], and epilepsy [40].

3 Three-Dimensional Ultra-Fast Magnetic Resonance Brain Imaging

Three-dimensional ultra-fast magnetic resonance brain imaging can image the entire brain within 100 ms, eliminating mixing of cardiopulmonary pulsation signals, with 3D measurement minimizing motion-induced spin effects [41]. Synchronizing 3D ultra-fast magnetic resonance brain imaging with electroencephalography and cardiopulmonary function monitoring enables imaging of whole-brain physiological pulsation spatiotemporal evolution. Iliff et al. [42] have demonstrated that arterial pulsation partially drives glymphatic system CSF-ISF exchange, though cardiac pulsation may provide no more than 15%-25% of the driving force, suggesting that other fluid dynamics driving CSF exchange should be explored [43]. Kiviniemi et al. [44] first demonstrated the propagation of cardiac, respiratory, and vasomotor pulsation patterns in the human brain, showing that resting-state glymphatic system CSF dynamics have three distinct physiological pulsation mechanisms: the fastest is cardiovascular pulsation, propagating from basal arteries around the Circle of Willis to the cerebral cortex at approximately 1 Hz; the second is respiration, primarily propagating centripetally from cortical venous perivascular spaces at approximately 0.3 Hz; the third is vasomotor waves in low-frequency (0.027-0.073 Hz) and very low-frequency (0.01-0.027 Hz) ranges, with low-frequency waves propagating more extensively into white matter than cardiac and respiratory effects, almost uniformly covering the entire brain, while very low-frequency waves show the most complex spatiotemporal dynamics, initially propagating posteriorly from the frontal region then returning anteriorly from the occipital region. MRI techniques are typically static, but 3D ultra-fast magnetic resonance brain imaging finely captures brain physiological pulsations with better image quality and fewer artifacts, opening a new perspective for measuring brain fluid dynamics.

Additionally, chemical exchange saturation transfer (CEST) methods have been applied to study changes in small molecule metabolites. CEST technology indirectly obtains information about solutes with exchangeable protons (i.e., signal changes) by detecting free water signal changes, enabling detection of compounds at lower concentrations than magnetic resonance spectroscopy imaging [45-46]. This emerging potential spectroscopic MRI technique can be used for various human imaging applications and is expected to reveal changes in multiple solutes such as lipids and amyloid-β protein under pathological conditions, holding promise for glymphatic system research.

Conclusion

In summary, researchers have explored the structure and function of the human brain glymphatic system from multiple perspectives. DCE-MRI has enabled visualization of CSF inflow, brain parenchymal metabolism, and mLV outflow processes, though its limitations of multiple imaging sessions and gadolinium deposition in the brain restrict clinical research applications. DTI-ALPS technology overcomes DCE-MRI limitations and has therefore been widely applied in research, with ALPS indices decreased in various neurological disease states compared to healthy populations. The ALPS index reflects diffusivity changes of fluid in perivascular spaces around deep medullary veins, necessitating research on analytical methods for whole-brain glymphatic system function. Three-dimensional ultra-fast magnetic resonance brain imaging provides three driving mechanisms for intracranial pulsation propagation in the glymphatic system, offering new possibilities for understanding the pathophysiological mechanisms of glymphatic system function decline and protein deposition. CEST research uses endogenous markers to generate contrast effects without exogenous contrast agent injection for studying intracranial compound changes, with finer detection advantages than magnetic resonance spectroscopy imaging. These techniques continuously update our understanding of glymphatic system structure, function, influencing factors, and related diseases. Nevertheless, research on the human brain glymphatic system remains incomplete, requiring more in-depth studies to explore structural characteristics of the glymphatic system and mechanisms driving central nervous system glymphatic pathways and their roles throughout the lifespan. Development of MRI imaging technology combined with other examination techniques (such as PET, CT, ultrasound, EEG, etc.) is expected to provide safer and more effective imaging methods for glymphatic system research.

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