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REVIEW

Magnetic Resonance Imaging Studies of Neurodegenerative Disease: From Methods to Translational Research

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Abstract Neurodegenerative diseases (NDs) have become a significant threat to an aging human society. Numerous studies have been conducted in the past decades to clarify their pathologic mechanisms and search for reliable biomarkers. Magnetic resonance imaging (MRI) is a powerful tool for investigating structural and functional brain alterations in NDs. With the advantages of being non-invasive and non-radioactive, it has been frequently used in both animal research and large-scale clinical investigations. MRI may serve as a bridge connecting micro- and macro-level analysis and promoting bench-to-bed translational research. Nevertheless, due to the abundance and complexity of MRI techniques, exploiting their potential is not always straightforward. This review aims to briefly introduce research progress in clinical imaging studies and discuss possible strategies for applying MRI in translational ND research.

Keywords Magnetic resonance imaging · Neurodegenerative disease · Translational research · Alzheimer's disease · Parkinson's disease

Background

The aging of the world population is continuously progressing [1]. Among many diseases of the elderly, neurodegenerative diseases (NDs), represented by Alzheimer's disease (AD) and Parkinson's disease (PD), involve > 50 million older adults [2]. They can cause severe dementia, paralysis, and other consequences, imposing heavy burdens on families and society [3, 4]. At present, the clinical treatment of NDs is still mainly based on symptom management. There is a lack of reliable early diagnostic measures and disease-modifying therapies [5].

The understanding of pathophysiological mechanisms is fundamental to lowering the harmfulness of NDs, and the continuous invention of research tools has brought much progress. Taking AD as an example, since its pathology was first discovered in 1906, AD research has experienced many upsurges such as histopathology, biochemistry, and genetics [6]. With modern neuroscience methods, we have gained a richer and more detailed understanding of AD pathology. The medical imaging revolution that began in the 1990s also brought a new dawn to the research on NDs. Among them, positron emission tomography (PET) and magnetic resonance imaging (MRI) have become the core research methods of many longitudinal multicenter projects due to their non-invasive and multimodal advantages, such as the Alzheimer's Disease Neuroimaging Initiative (http://adni.loni.usc.edu), the Parkinson's Progression Markers Initiative (https://www.ppmi-info.org). Imaging plays a crucial role in revealing the dynamic development of a disease and implicating pathological mechanisms. With progress in various fields, a new question is how to integrate micro-and macro-level research to improve diagnosis and treatment.

Specifically, laboratory studies can reveal structural and functional changes at the level of cells, tissues, and neural circuits, but the translation into clinical applications is often uncertain. On the other hand, medical imaging can reveal the trajectory of macroscopic brain degeneration in aging [7] and NDs [8] that is tightly associated with clinical

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impairments. Nevertheless, the pathologies behind imaging abnormalities are often complex and need careful explanation. By combining macro- and micro-scale research tools, translation from basic disease mechanism studies to clinical scenarios might be more direct. As nuclear imaging is relatively straightforward and some related reviews have already been published [9], we focus on MRI. For this purpose, we first briefly describe current theories on the pathogenesis of ND and the progress of clinical MRI research, using AD and PD as examples. We have no intention of including all the disease mechanisms and imaging methods but only provide information necessary for related discussions. Further, we will mention several possible strategies and directions for conducting translational research using MRI.

Basic Pathologies and Neural Circuit Changes in NDs

AD pathology is characterized by the presence of amyloid plaques, neuritic plaques, and neurofibrillary tangles. The "amyloid cascade hypothesis" is the mainstream theory [10] regarding the development of pathology in AD; it has been suggested that the increase of amyloid-β (Aβ) is key to triggering tau pathology followed by neuronal death. Under the action of genes, environmental toxins, aging, and other factors, Aβ is gradually deposited in the brain and causes tau protein deposition through mechanisms that are not yet fully understood. Tau protein spreads in the brain through synaptic connections [11, 12], starting from the hippocampus and entorhinal cortex and gradually to the posterior cortex. Cognitive impairment is more strongly associated with tau-related brain damage than the Aβ burden [13]. On the circuitry level, the hippocampal network is most important and has been extensively studied [14, 15]. The default mode network (DMN) [16], which was first discovered in human imaging studies and verified in rodents [17], has been consistently reported to be damaged in AD [18].

Apoptotic cell death of dopamine neurons in the substantia nigra (SN) induced by Lewy body deposition is the core pathological mechanism of PD. According to the traditional Braak pathological staging [19], Lewy body pathology starts from the olfactory bulb, medulla oblongata, and pons. It gradually spreads to the midbrain and limbic system, and eventually to the cortical gray matter. While abundant evidence suggests that the pathological α-synuclein aggregates originates in the peripheral nervous system and spreads retrogradely into the brain, a brain-first pattern is also possible [20]. When the loss of SN dopamine neurons reaches as high as 30% or more, it leads to an imbalance of nigrostriatal circuit function, breaking the balance between direct/indirect motor pathways in the basal ganglia–thalamocortical circuit [21], leading to movement disorders. Dysfunction of the cerebellar circuit is associated with the tremor [22] and freezing of gait [23] in PD.

Cerebrovascular degeneration [24], neuroinflammation [25], and glymphatic dysfunction [26, 27] may contribute to the development of NDs, before or after disease onset. During aging, intracranial blood vessels often develop sclerosis, collagen deposition, stenosis, and other pathologies, which lead to the gradual decline of cerebral blood flow (CBF) [28]. On the other hand, the blood-brain barrier (BBB) becomes weak and its permeability gradually increases, causing leakage of blood cells and harmful substances into the brain parenchyma [29]. Homeostatic imbalance and the invasion of exogenous substances may cause immune responses. Misfolded and aggregated proteins in various NDs can also trigger neuroinflammation, characterized by a reactive morphology of both astrocytes and microglial cells [25]. Chronic neuroinflammation can lead to various forms of brain damage (such as demyelination and axon damage) and accelerates neurodegeneration [30]. Research on the glymphatic system [31] has received extensive interest in recent years. Glymphatic dysfunction not only reduces the rate of brain metabolic waste removal and accelerates the accumulation of pathological proteins but also worsens inflammatory responses and further accelerates ND progression [26, 31].

Pathologies often do not exist in isolation [32]. AD is frequently accompanied by vascular pathologies [33]. A neuropathological study [34] showed that 79.9% of patients diagnosed with AD have cerebrovascular pathologies. In patients with dominantly-inherited AD, the burden of white matter hyperintensity (WMH), an imaging sign considered to be associated with small vessel degeneration, increases 6 years before the expected symptom onset [35]. In patients with PD, one-third of those with cognitive impairment and one-half of those with dementia have elevated AD biomarkers in the cerebrospinal fluid (CSF) [36]. The presence of tau can be as high as 100% in LRRK2 PD [37]. Therefore, increasing studies have begun to make simultaneous measurements on common ND pathologies [38], such as Aβ, tau, TDP-43, α-synuclein, and vascular damage. In this way, we can investigate the interaction of different neuropathologies to understand their contribution to disease progression [39].

Brain MRI Methods

As summarized in Fig. 1, many imaging methods have been used for investigating brain degeneration and aiding the diagnosis of ND. Generally, MRI markers are not disease-specific, but their spatial patterns are closely associated with core pathologies. For example, AD-related brain atrophy is prominent in the hippocampus and medial temporal lobe due to early tau pathology in these regions, while PD patients

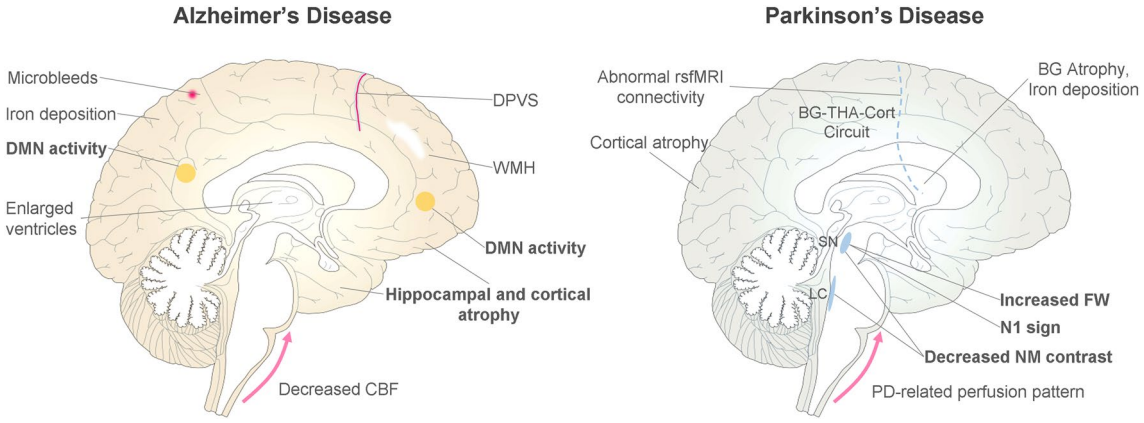

Fig. 1 Common imaging abnormalities on MR images of AD and PD patients. In AD, brain damage is consistently found in the hippocampus and DMN, with frequent vascular degeneration. In PD patients, imaging abnormalities are more related to the dysfunction of the substantia nigra and BG-THA-Cort circuit. Markers in bold have been extensively tested and have successfully demonstrated clinical value. dPVS: dilated perivascular space; WMH, white matter hyperintensity; DMN, default mode network; CBF, cerebral blood flow; BG, basal ganglia; THA, thalamus; Cort, cortex; N1, nigrosome-1; FW, free water; NM, neuromelanin.

only demonstrate significant brain atrophy in late stages of the disease. In AD, brain iron deposition is associated with amyloid plaques that extensively involve cortical areas. On the other hand, iron deposition in PD is due to dopamine neuronal death and is most marked in the SN. Choosing methods based on the understanding of disease pathologies can maximize the efficiency of experimental designs.

Structural Imaging

Structural MRI has long been used for assessing brain atrophy in NDs. For example, atrophy in the midbrain and pons can differentiate PD from progressive supranuclear palsy [40]. Hippocampal atrophy is the core brain imaging marker of AD. However, it is not a marker with good specificity because many other diseases, such as vascular degeneration, can also lead to hippocampal atrophy [41]. If atrophy in the whole brain is simultaneously considered, the diagnostic accuracy can be much higher. SPARE-AD, a brain atrophy score derived from whole-brain analysis using automated segmentation methods, separates AD from controls with high accuracy [42]. Deep-learning-based methods are excellent for recognizing complex image patterns and may outperform traditional methods [41]. The increase in field strength and imaging resolution has allowed more precise quantification of structural abnormalities. On 7T MRI, the analysis of hippocampal atrophy can be pushed to the subregional level [43], allowing the detection of more subtle and early changes (a background hypothesis is that certain hippocampal subregions are more vulnerable to AD pathology and the hippocampus does not degenerate at a uniform rate).

Different weighting methods can enhance the visualization of various brain structures and lesions. For general purposes such as atrophy assessment, segmentation, and registration, T1-weighted imaging with gray\white matter contrast enhancement is recommended. T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences can demonstrate vascular-related changes, such as WMH and dilation of perivascular spaces (PVSs) commonly seen in older adults. Susceptibility weighted imaging (SWI) can display venopathy [44] and microbleeds, and quantify iron deposition. In AD, iron loading is a prominent feature of activated microglia [45], although how macrophages accumulate, store, and utilize intracellular iron is still not completely understood. In PD, the loss of nigrosome-1 can be visualized on SWI. Appearing as swallowtails or loops, they are valuable markers for PD diagnosis [46, 47].

As brain damage progresses very slowly in NDs, it can take an exceptionally long time for macroscopic changes to occur, and imaging at finer resolution is desired. Restrained by physical rules, the current limit of *in vivo* human brain imaging is only at the sub-millimeter level. To further understand microscopic changes at the tissue level, the apparent properties of brain tissues within each voxel can be used to infer its composition, which is the basic idea of "Microstructural Imaging" [48]. The typical approach assumes the properties (the most common is water molecule diffusion) of several types of cells and components, sets a mathematical model, and collects data to solve it. Then, disease-related changes at microscopic levels can be inferred. Usually, these models need to be first evaluated on animal brains or *ex vivo* brains to confirm that the derived parameters well reflect the tissue properties. Despite the fact that that model fitting is never perfect, some parameters have demonstrated very robust associations with clinical manifestations and can be used as valuable biomarkers for ND studies, such as

diffusion tensor imaging (DTI) [49], neurite orientation dispersion density imaging [50]), and free water imaging [51].

Functional Imaging

Intuitively, neuronal functions might have already altered before the death of neurons. Therefore, functional imaging is believed to be more sensitive to early brain changes than structural imaging. Blood-oxygen-level dependent (BOLD) imaging is the most widely used functional imaging method. Traditional task-related functional magnetic resonance imaging (fMRI) has good specificity. It can reveal changes in brain activation patterns when patients engage in different tasks, providing information for understanding the degeneration and remodeling of the neural circuits underlying clinical impairments. For example, episodic memory tasks have been used in early AD patients to assess their hippocampal functions [52]. Sensorimotor [53] and executive tasks [54] have been extensively used in PD to demonstrate changes related to dopamine deficiency. Interestingly, functional imaging can be combined with electromyography to reveal brain oscillations associated with resting tremors [55].

Because task-related fMRI requires a high degree of patient cooperation, it is usually difficult to carry out in severe disease conditions and routine clinical practice. The resting-state fMRI does not require patients to perform specific tasks; it detects brain abnormality by measuring fluctuations in the local BOLD signal [56] or associations between different brain regions [57]. The premise that resting-state fMRI can detect disease-related abnormalities is that resting-state activity is associated with the inherent "trait" of disease damage. Alteration of resting-state brain activity in the DMN has been consistently reported in AD patients as well as persons with mild cognitive impairment (MCI) carrying AD pathology [58, 59]. Although the phenomenon is reliable, clinical diagnosis based on resting-state fMRI is difficult due to individual differences in brain recruitment and changes in psychophysical conditions. Since the completion of brain function usually requires the collaborative work of multiple regions, the efficiency of large-scale brain networks is crucial. Functional network analysis based on graph theory is suitable for analyzing complex brain networks by revealing higher-order network properties [60, 61].

Due to the rapidly-changing human brain activity and the inherently low signal-to-noise ratio (SNR) of the BOLD signal, fMRI is often criticized for its low reproducibility. BOLD imaging on 7T MR scanners can achieve a higher SNR and sub-millimeter resolution with customized coils. In recent years, various new noise-reduction methods and multiple comparison correction methods have improved the reliability of fMRI research. In ND research, there is another crucial interference factor in fMRI—neurovascular coupling. Lower blood perfusion and hemodynamic alterations may also change global or regional BOLD signals and mix with signals elicited by neural activity. How to distinguish neuronal from vascular-related alterations has been discussed in some recent reviews and is worthy of further research [62]. Brain atrophy, prominent in the elderly, can exaggerate signal overlap in adjacent cortical gyri. Imaging at higher resolution and the application of surface-based processing methods may alleviate this problem [59].

Vascular and Perfusion Imaging

Aging-related changes in cardiac output, vessel wall pulsatility, and parenchymal resistance can lead to chronic hypoperfusion and accelerate neurodegeneration [63]. General vascular morphometry and plaques can be well displayed with time-of-flight angiography and black-blood vessel wall images. Although narrowing and occlusion of large vessels are not major pathologies of NDs, they can lead to vascular dementia or vascular parkinsonism and need to be considered in clinical practice. Small vessel disease (SVD) is more common in the elderly and dramatically increases with age. Because arterioles and capillaries are too small to be seen on MR images, some indirect imaging signs have been widely used to reflect SVD severity [64], including WMH of presumed vascular origin, lacunae, microbleeds, recent small subcortical infarct, dilated perivascular space (PVS), and superficial siderosis. WMH and cortical microbleeds are quite common in AD patients [65, 66] due to the deposition of Aβ in vessel walls.

The measurement of BBB integrity mainly includes methods based on contrast agents [67] or water diffusion [68]. They assume different water compartments (vascular and brain tissue) in the brain and calculate the exchange rate across the barriers. Increased BBB leakage at the hippocampus has been consistently found in AD [69] and vascular cognitive impairment [70] using dynamic contrast-enhanced (DCE) imaging methods. Because BBB damage in aging and NDs is only mild-to-moderate, it is vital to select the appropriate scanning parameters and mathematical models for accurate measurement [71]. Due to its invasiveness and concerns of Gadolinium deposition in the brain, DCE-MRI is rarely used in large-scale studies. New BBB imaging methods [68, 72] that use labelled water as the tracking agent may be more applicable in community and preclinical cohorts. Nevertheless, BBB alterations measured by water exchange are different from traditional methods. Because water molecules are small, the loss of tight junctions is not necessary for increased permeability. Assessing BBB permeability to substances with different molecular sizes may better reveal disease pathologies [73].

The arterial spin-labelling method can measure blood perfusion in different brain regions without injecting a contrast agent and thus has been widely used in clinical

investigations [74, 75]. Notably, aging-related alterations in the vessel wall and brain stiffness can lead to slow blood flow, which may potentially bias blood perfusion measurement. By setting different post-labelling delays and fitting a mathematical model, the arterial arrival time can be calculated, reflecting hemodynamic alterations [76]. Interestingly, hemodynamic changes also influence CSF hydrokinetics associated with brain waste clearance (see below) and further neurodegeneration. Previous studies have shown that AD patients may have significantly reduced CBF in the hippocampus and precuneus [77], while PD patients have increased blood flow in the basal ganglia and decreased blood flow in some cortical regions [78].

Glymphatic Imaging

Although animal studies have consistently found an association between glymphatic dysfunction and ND, validation in humans is rare. Glymphatic clearance can be directly assessed by intrathecal or intravenous injection of Gadolinium contrast agent [79]. After the injection, image acquisition is repeated several times at delays of hours or seconds depending on the purpose. Signal enhancement at different brain sites and cervical lymph nodes are then recorded to reflect the arrival of the contrast agent and the rate of glymphatic clearance [80]. This method is easy to use in animals [81] or human subjects [80], making it a useful tool for translational research. A recent study investigated glymphatic dysfunction in 375 PD patients using this method and found reduced flow through the meningeal lymphatic vessels along the superior sagittal sinus and sigmoid sinus [31]. The foundation of glymphatic clearance is CSF\interstitial fluid motion and exchange, to which MRI is sensitive [82]. Phase-contrast MRI can detect bulk flow at the midbrain aqueduct and foramen magnum [83], where fluid motion is relatively rapid. Diffusion imaging can reflect slow water molecule motion in the perivascular space [84] and brain parenchymal [85]. Under disease conditions, pathological proteins and cell debris may deposit in PVS and cause compensatory PVS dilation. The dilated PVS can be seen on T2-weighted images and has been widely used as a marker of glymphatic dysfunction. High-resolution imaging and artificial intelligence (AI)-based segmentation methods can better quantify dilated PVS volume and reveal its association with clinical factors [86]. Many new glymphatic imaging techniques are still being developed and have been introduced in some recent reviews [87, 88].

Other Imaging Methods

MRI can also detect brain alterations at the molecular level. Based on the principle that different molecules have different resonant frequencies, MR spectroscopy (MRS) can detect various products of brain metabolism, such as lactate, N-acetylaspartate, glutamine/glutamate. With new imaging sequences, whole-brain MRS could be applied in clinical imaging research, demonstrating distinct spatial patterns of brain metabolites in NDs [89, 90]. Chemical exchange saturation transfer (CEST) imaging can enable the indirect detection of metabolites with exchangeable protons located on proteins. A few attempts have been made to detect proteins associated with different pathological processes in NDs. For example, a significantly lower amide-weighted signal (3.5 ppm) is associated with Aβ deposition in AD mice [91], and lower CEST signals at 1 and 2 ppm are associated with markers of neuroinflammation [92]. Furthermore, ultra-small superparamagnetic iron oxide nanoparticles can be designed to detect specific substances, such as Aβ1–42 peptides in animal models [93], but translation into human subjects may be a long road.

Multimodal, Longitudinal Imaging

As discussed above, the development of human NDs is usually driven by various pathologies with complex interactions. In this regard, multimodal imaging and longitudinal observations are necessary [94]. By analyzing brain alterations from multiple aspects, a whole picture can be put together for inferring underlying pathologies and making clinical decisions. For example, by using quantitative susceptibility imaging to investigate SN degeneration and resting-state fMRI to investigate brain network changes, a link between the primary pathology and downstream mechanisms can be built up [95]. Aging-related WMH lesions, fiber tract damage, and cortical activity can be simultaneously displayed, allowing the understanding of coherent brain structural-functional impairment [96] (Fig. 2). By combining PET with structural MRI, information about pathological molecules and macrostructural changes can be incorporated to understand how AD pathology causes brain atrophy, microbleeds, and clinical impairments [97, 98]. Based on longitudinal data, causality between different pathologies and brain damage can be inferred. However, in clinical research, patients usually cannot hold their heads still during a long scan time. The scan parameters must be optimized to best match the study purpose and patient compliance.

MRI in Translational Research

Benefiting from its *in vivo* feature, MRI can be a powerful tool in translational research. With proper validation and interpretation, imaging features can bridge the gap between micro-and macro-level research, or between animal research and clinical application (Fig. 3). On 3T clinical scanners, 0.5–1 mm imaging resolution can be

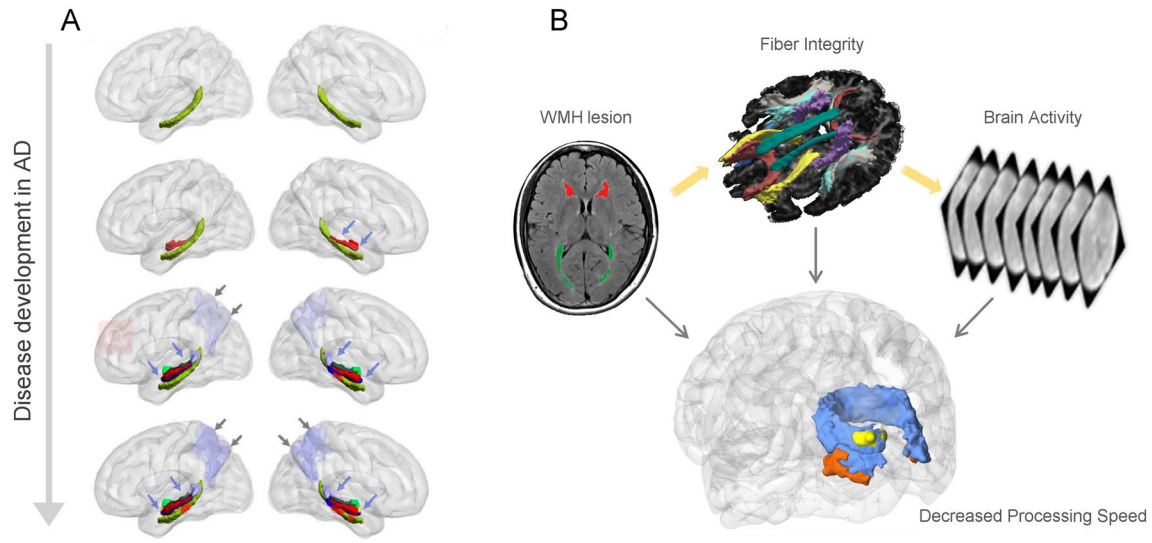

Fig. 2 Using multimodal imaging to study disease evolution and structural-functional coherent changes. **A** The severity of AD increases from top to bottom, stratified by AD biomarkers. The green structure represents the cingulum-angular bundle (CAB) tracts. The red segments of the CAB indicate a significant group difference from normal controls. The colorful structures above the green structure represent the hippocampal (HP) subfields. The lavender area in the posterior region represents the precuneus volume. In summary, the degeneration of HP subfields, CAB, and precuneus are aggravated with higher disease stages [94]. **B** WMH can lead to a slower processing speed in the elderly. By combining information from different modalities, a coherent damaging pattern is seen in the occipital lobe, supporting the WMH–Tract–Function–Behavior link [96].

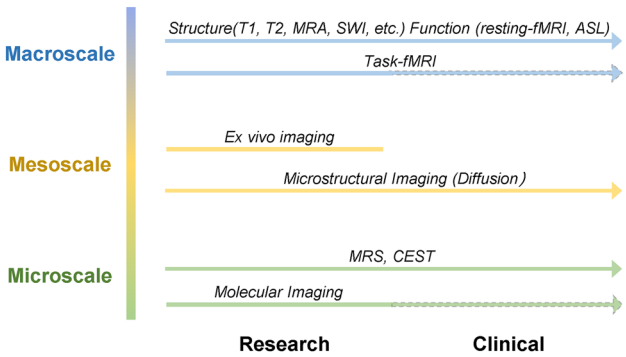

Fig. 3 The information that MR imaging techniques provide on different scales and their potential for clinical applications. Task-fMRI may be difficult to implement on patients due to impaired motor or cognitive functions. Molecular imaging may have safety issues and needs extensive pre-clinical studies. MRA, MR angiography; SWI, susceptibility-weighted imaging; ASL, arterial spin labelling; MRS, MR spectroscopy; CEST, chemical exchange saturation transfer.

achieved for structural imaging and 2–4 mm for functional imaging. Most MRI methods can be easily implemented in clinical settings, but some are difficult. The success rate of task-fMRI may be low in patients, and molecular imaging methods need extensive preclinical tests before human imaging. Here, we discuss several translational imaging research paradigms for NDs (Fig. 4).

Imaging-Histology Comparison

While structural imaging is very robust for measuring volumetric and morphometric changes, the restriction of imaging resolution limits the detection of small lesions. For example, microbleeds detected by MRI are ~ten times larger at postmortem examination [99]. When one microinfarct is seen on MRI, the actual number of such lesions can be substantially higher [100]. Using ultra-high field MRI and optimized scanning parameters could improve detection efficiency. The number of microbleeds [101], microinfarcts [102], dilated PVS [103], and other structures are significantly higher on 7T images than at 3T. Imaging-histology comparison can reveal quantitative differences that can be used when inferring the severity of underlying pathologies in clinical practice. The interpretation of signal changes, common in clinical investigations, may be complex depending on different clinical scenarios. WMH can be induced by increased water content, demyelination, inflammation, or protein deposition [104]. Imaging-histology comparisons in different diseases may show distinct driving factors. By comparing MRI with histological images, the effect of fiber tracts and iron deposition on MR susceptibility can be quantified to guide clinical applications [105].

In some imaging methods that need extensive mathematical modelling (such as diffusion imaging and BBB imaging), the derived imaging parameters are more difficult to interpret. Although DTI has been successfully

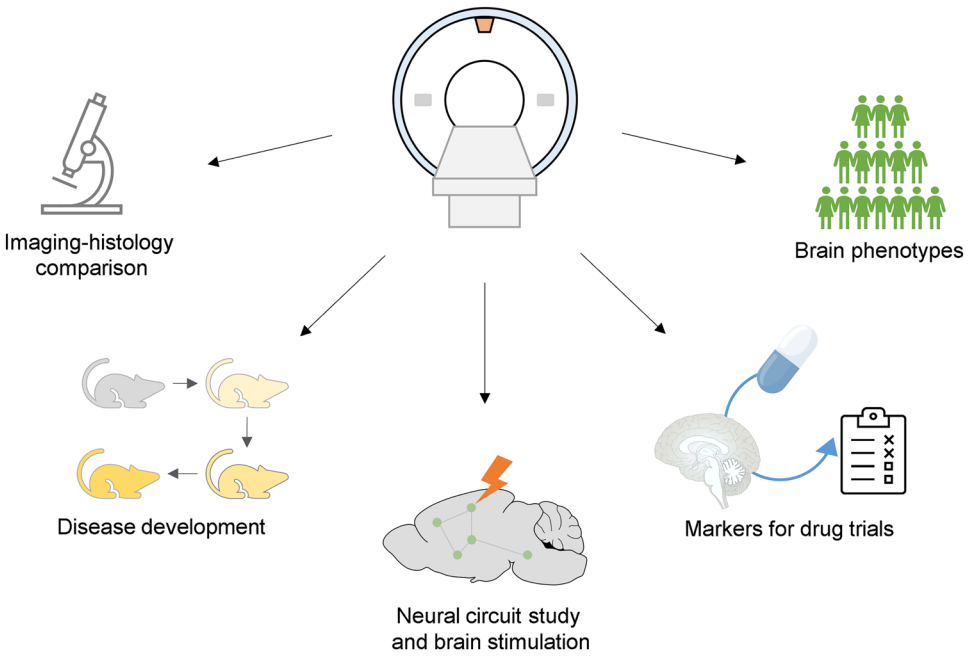

Fig. 4 Possible applications of MRI in translational ND research.

applied in demonstrating fiber tract changes in various brain diseases, the association between diffusion parameters and specific disease pathologies (such as demyelination and axon damage) is not specific [106]. Furthermore, problems such as fiber crossing [107] and water contamination [108] can lead to substantiate biases. In novel methods aimed at solving these problems, the complexity of the diffusion models increases, and thus simulation and validation of these advanced models are vital. Imaging-histology comparison can provide effective validation [109].

Although the correspondence between MR imaging features and true pathologies is not always simple and straightforward, clarifying their associations can be of tremendous help for understanding disease mechanisms and improving clinical practice. Due to the complexity of diseases, many unique imaging abnormalities are consistently discovered without knowing the specific pathologies [110, 111]. For example, inferior frontal sulcal hyperintensity observed on FLAIR images is supposed to be associated with glymphatic dysfunction [110], because the inferior frontal sulci are just superior to the cribriform plate where some CSF drains to the nasal lymphatics, but the actual pathology remains unknown. Furthermore, lesion patterns and spatial features can provide key information for inferring pathology [112]. The topological connection between microbleeds and venules observed on 7T suggest a contribution of disrupted BBB in venules to microbleeds [112]. The fact that incident lacunae are preferentially localized to the edge of WMH indicates hypoperfusion around WMH lesions [113].

Dynamic Imaging in Animal Models

Through dynamic imaging, association and causalities among different disease pathologies and macroscopic brain changes can be better demonstrated. For example, the association between β-amyloid deposition and decreased CBF can be shown by longitudinal PET\MR imaging in amyloid precursor protein transgenic mouse models [114]. This is of value for revealing early brain degeneration, which is difficult to understand in patients due to late diagnosis. Studies using MRI to visualize the pathophysiology in animal models of amyloidosis have been well summarized in a recent review [115]. *In vivo* imaging is vital for studying certain pathophysiological processes that are best studied in living animals, such as brain activation or glymphatic function. Because waste clearance is a dynamic process and depends on fluid flow and exchange driven by physiological processes such as respiration and cardiac pulsatility, it needs *in vivo* observations. Even the structure of the PVS (the major route for waste clearance) may shrink and cannot be accurately measured in post-mortem studies due to fixation methods [116]. By injecting a contrast agent into the ventricles and carrying out continuous MRI scans, researchers can analyze the enhancement in various brain regions at different time points, so the path and speed of waste clearance can be inferred [80]. Using this method, researchers have demonstrated the influences of hypertension [117] and diabetes [81] on glymphatic clearance, and the association between waste clearance and AD pathology [118]. Importantly, this method can also be implemented in human subjects. After intrathecal or intravenous injection of contrast agent,

the effects of aging [79], sleep deprivation [119] and NDs [31] on waste clearance have been investigated with great interest.

Neural Circuit Study and Brain Stimulation

MRI is useful for studying neural circuitry. Large fiber bundles can be tracked and visualized with good reliability, especially using advanced models [120]. Thin fiber tracts connecting smaller brain structures can also be analyzed with higher imaging resolution and probabilistic tractography methods [121]. Coordination among different cortical regions and subcortical nuclei can be investigated using functional connectivity analysis based on fMRI. Although not as precise as electrophysiological recordings, since these methods can be used in both animals and humans, they can facilitate comparison and translation across species [122]. With an ultra-high magnetic field and fast imaging acquisition methods, the temporal resolution can be pushed down to 100 ms [123] with full brain coverage, and the spatial resolution can achieve a sub-millimeter level [124]. Unfortunately, these limits cannot be reached at the same time. Choices for spatial and temporal resolution must be made to best match research goals.

These advantages can aid translational research on developing new strategies for deep brain stimulation (DBS). As a useful treatment method for late-stage PD, the optimization of DBS targets and stimulating frequencies have first been performed on rodents [125] and large animals [126]. The modulating effect is well demonstrated by using fMRI to monitor the brain activation elicited. With this knowledge, structural and functional imaging are performed before DBS surgery to predict the treatment effect [127, 128] and guide electrode placement [129]. In recent years, non-invasive brain stimulation has shown good efficacy in treating NDs. Repetitive transcranial magnetic stimulation (rTMS) of the dorsolateral prefrontal cortex can improve cognition both in MCI and AD [130]. Stimulation of the motor cortex can improve motor functions in PD. Circuit mapping using structural and functional MR can provide a precise target for rTMS and enhance its therapeutic efficacy [131, 132]. New brain stimulation techniques such as transcranial focused ultrasound can target much deeper brain regions [133], and the activation-stimulation research paradigms have tremendous potential for ND treatment.

MRI in Drug Trials

In drug development, medical imaging can be helpful during participant selection and the evaluation of effectiveness. Due to the long disease course and irreversible neuronal damage, clinical trials on NDs usually need to be performed in early-stage patients to best demonstrate their protective effect. Confirming disease risks by evaluating amyloid deposition and neurodegeneration during patient enrollment can reduce the required sample sizes of AD clinical trials by 45% to 60% [134]. At the same time, the effect of drug treatment and neurodegeneration during a short research period might be too mild to be demonstrated by clinical assessments, and confounded by subjective evaluation biases and the patients' psychophysical conditions. Therefore, many clinical trials have adopted objective imaging parameters as secondary outcomes [135]. In studies on small vessel degeneration, WMH and diffusion imaging parameters [135] have already become essential assessment tools in clinical trials [136, 137]. By applying these markers, the sample size required for a 3-year clinical trial on SVD was dramatically reduced [138] compared to measuring cognitive functions (124 *versus* 6135 subjects). In PD, SN free water measurements have achieved an effect size similar to nuclear imaging methods in reflecting longitudinal SN degeneration [139], and has been used to assess whether specific drugs have a protective effect [140]. Using neuroimaging markers, the cost of large-scale clinical trials may be significantly reduced. MRI can help monitor and control adverse effects in clinical trials. Amyloid-related imaging abnormalities (ARIA), including ARIA-E (with effusion or edema) and ARIA-H (hemosiderin deposits), have been found in patients taking drugs aimed at removing amyloid plaques from the brain [141]. Evaluating the severity of SVD at baseline could also help to control ARIA.

Brain Phenotype Studies

Brain degeneration and NDs are associated with countless demographic, genetic, environmental, and lifestyle factors that are impossible to simulate in experimental conditions. Large-scale population studies using the non-invasive, non-radiative MRI methods provide opportunities for revealing weak associations and promoting the discovery of new theories. For example, the UK Biobank project plans to collect multimodal brain images, as well as phenotypic and genetic information of 100,000 people. This provides a foundation for understanding how some basic features of the human brain are affected by various risk factors. Genetic-Brain imaging association studies in over 8000 subjects revealed 21 genes [142] important for iron metabolism, axon growth, and brain plasticity. A study focused on aging found heterogeneous brain degeneration patterns showing distinct functional and structural brain changes, which were associated with different genetics, lifestyle, cognition, physical measures, and diseases [143]. Similarly, the association between brain degeneration and genetic variations has been explored in specific disease cohorts [144, 145]. Further research into the genetic and biochemical mechanisms behind these superficial associations may provide new knowledge regarding

brain degeneration and disease treatment. In another way, the effect of modulating the related pathways can be easily assessed on animals as they are originally derived from imaging studies.

Investigating brain phenotypes based on large imaging datasets is vital for understanding disease heterogeneity [146, 147] and choosing therapeutic strategies [148]. For example, PD patients may exhibit tremor-dominant or rigidity-dominant motor symptoms, with or without cognitive impairment. Such heterogeneity cannot be fully explained by overall pathology burdens but is ascribed to individual variations in brain organization, regional vulnerability to disease pathology, and diversity of pathology. Brain imaging is powerful for revealing different phenotypes of brain degeneration. Based on brain atrophy patterns, two PD biotypes have been discovered that have distinct clinical symptoms and disease progression rates [149]. Regional radiomics similarity networks derived from structural images have been used to screen MCI subjects with a higher probability of dementia progression [150]. Furthermore, the structural connections of white matter reflect differences in individual brain organization or functional network properties [151, 152]. Compared to subtyping based on clinical features, imaging phenotypes are more objective and stable, but they still need extensive external validation [153]. It is better to consider both disease-specific and subtype-specific features to avoid non-related trivial clustering results when dealing with heterogeneity. For example, a depression-related or cognition-related brain pattern may not be specific to PD patients and could not add additional clinical value.

Future Directions

MRI techniques are still undergoing rapid development. 7T MR scanners with clinical modes have been installed in many universities and hospitals, and several 11.7T scanners are being tested at some research centers. Recently, a 5T imaging system has been announced, which could be more versatile in clinical imaging research. In high-resolution imaging, the impact of head movement is more serious, and the use of prospective head movement correction methods can help achieve more accurate *in vivo* structural imaging [154]. With increased spatial and temporal resolution, MRI can be used to visualize smaller brain structures, helping detect more covert disease-related brain changes and connect with fundamental research at the tissue and circuit levels. Due to limited accessibility, clinical research using ultra-high-field MR scanners has been mainly performed in small samples. Large cohort studies and clinical applications would be much easier with more facilities installed at clinical sites.

AI may play a crucial role in this new era. With the help of deep-learning-based reconstruction algorithms, the scanning time of multimodal imaging can be significantly reduced [155]. Imaging at higher spatial and temporal resolution, the amount of information to be processed has also increased exponentially. AI-based detection and segmentation algorithms can be very good at identifying brain lesions and providing quantitative measures [156–158], and they also have great potential in diagnosis and prognosis. However, due to limited imaging modalities, most previous studies were focused on using T1 structural images to build classification models. Future studies should consider incorporating other imaging features, such as brain susceptibility in PD and SVD features in AD. Notably, with more complex models, cross-validation in large and multicenter datasets is necessary to validate their generalizability [153]. Data harmonization based on specifically-designed phantoms or post-processing methods is expected to remove inter-vendor variability and improve data consistency [159].

Due to the difficulty in early diagnosis, disease evolution and brain degeneration in the early stages of NDs remain largely unknown. Constructing prodromal cohorts at high risk for specific NDs and performing longitudinal imaging observations are necessary for revealing the trajectories of brain degeneration and discovering diagnostic markers [160]. Multi-scale translational research on animal models could help clarify the association between macro- and micro-level changes and describe the causal interactions among ND pathologies, brain phenotypes, and functional impairments in different stages of disease. With new imaging techniques and clinical imaging discoveries continuously validated, MRI will be more powerful for translational ND research in the future.

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