Use of Multimodal Magnetic Resonance Imaging Techniques to Explore Cognitive Impairment in Leukoaraiosis

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Leukoaraiosis, also referred to as white-matter hyperintensities (WMHs) or age-related white matter changes, is the most frequently seen lesion on brain magnetic resonance images (MRI) in the elderly. LA is a subject of intense research interest, and is correlated with stroke, cognitive impairment or dementia, disturbances, affective disorders, and poor prognoses. Rapid advances in neuroimaging have enabled greater understanding of LA associated with aging-related cognitive decline or dementia. Recently, the techniques of multimodal MRI, such as structural MRI (sMRI), resting-state functional MRI (rs-MRI), cerebrovascular reactivity (CVR), diffusion tensor imaging (DTI), magnetic resonance spectroscopy (MRS), and dynamic contrast-enhanced MRI (DCE-MRI), have been used to explore the underlying mechanism of cognitive impairment in patients with LA. These multimodal MRI techniques may provide further insights into the structural and functional changes of LA with cognitive dysfunction.

MeSH Keywords:  
Cognition • Diffusion Tensor Imaging • Leukoaraiosis • Magnetic Resonance Imaging • Magnetic Resonance Spectroscopy

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Background

Leukoaraiosis (LA), also referred to as white matter lesions (WMLs) or age-related white matter changes, describes diffuse white-matter hyperintensities (WMHs) on MRI scans, and is often seen in the elderly. The 3 severity degrees were assessed according to the modified scale of Fazekas et al. (Figure 1). As a radiographic marker of cerebral small vessel disease (CSVD), the pathogenesis of LA includes demyelination, neuronal loss, loss of glial cells, axon destruction, reactive gliosis, and arteriolosclerosis [1]. It has been increasingly recognized to be correlated with cognitive dysfunction or dementia, stroke, and some neurodegenerative disorders. The effects of LA on cognitive function are insidious and can be difficult to detect at an early stage but are nevertheless crucial. There is a growing body of evidence that the burdens of LA influence cognitive function in multiple domains, mainly attention/executive function, processing speed, and memory [2]. However, the underlying pathogenesis remains unclear, which may be due to the dysfunction of fronto-subcortical pathways [3].

The purpose of this study was to summarize the pathogenesis of LA and its impact on cognition, and also to evaluate different imaging techniques to explore the pathophysiology of cognitive decline. Table 1 summarizes these advanced MRI techniques and also shows the pathophysiology of cognitive decline in LA. Our review highlights the potential of these recent developments to achieve faster adoption of these technologies in LA studies. Furthermore, the techniques of multimodal MRI are critical to assessing the relationship between brain structural and functional changes in LA with cognitive decline.

Structural Magnetic Resonance Imaging (sMRI)

WMHs and brain atrophy often coexist in the elderly. Voxel-based morphometry (VBM) is an automated technique widely used for quantitative measurements of white matter in separate regions. It utilizes T1-weighted images to perform voxel-wise statistical tests to discover subtle brain volume changes [4]. Understanding the specific relationship between LA and whole-brain structure may shed light on the pathophysiology of cognitive disorders in LA. There was a link between regionally specific brain atrophy and cognitive dysfunction in LA [5]. It was reported that LA patients had significantly reduced gray matter volume in the right supramarginal gyrus, right angular gyrus, right middle temporal gyrus, and right anterior cingulum [6]. This was in line with another study that found the LA group had a significantly decreased gray-matter density in left middle frontal gyrus and in the anterior and middle cingulate cortex [7]. LA may independently predict brain structural changes relevant to cognitive function, especially atrophy of the hippocampus and frontal lobes. The Cardiovascular Health Study also found that LA was inversely correlated with gray matter volume, with the greatest volume loss in the frontal cortex [8]. Recently, positive associations were also found between WMHs load and the voxel-based model of gray matter, specifically in the right anterior prefrontal cortex and the medial prefrontal cortex.

Figure 1. The 3 severity grades of ischemic leukoaraiosis according to Fazekas scale (A, mild; B, moderate; C, severe).
The main findings

Cerebrovascular reactivity (CVR) measurements

Dysfunctional CVR may contribute to the progression of white matter disease

Diffusion tensor imaging (DTI)

Evaluate permeability and integrity of blood-brain barrier (BBB); quantitative tissue perfusion such as blood volume, mean transit time, mean transit time

Higher BBB permeability was associated with higher LA burden and cognitive decline

Magnetic resonance spectroscopy (MRS)

Metabolic changes suggested that MRS can be explored as a marker for cognitive dysfunction in patients with LA

and cingulate gyrus [9]. However, more longitudinal data are needed to confirm the exact relationship between the load of LA and the decline in cognitive function.

Previous VBM studies have suggested that cortical atrophy is regionally distributed in LA, but few studies have assessed cortical thickness in LA. It was reported that cortical thickness was significantly lower in multimodal integration regions in LA, which suggested that LA patients were more likely to exhibit cortical thinning, especially in multimodal integration and recognition-related regions. The current morphometry data provided further evidence for LA-associated structural plasticity [10]. Another study of cortical thickness also found that higher WMHs load was related to lower cortical thickness in frontotemporal regions. Network analyses also revealed that measures of network disruption were associated with WMHs and cognitive performance. Cognitive performance was related to cortical thickness in frontotemporal regions and network measures [11]. The evidence that cortical thickness has an independent influence on the cognitive impairments suggests that the association between WMHs and cognitive impairments may be mediated by cortical thinning [12]. The above findings have some important implications in understanding the relationship between WMHs, cortical morphology, and the possible accompanying cognitive decline and dementia.

Resting-State fMRI (rs-fMRI)

The technique of rs-fMRI can identify the intrinsic spontaneous brain neural activity during resting state without task performance, which is increasingly used to investigate brain function. The amplitude of low-frequency fluctuations (ALFF) from rs-fMRI signals can be used to detect such intrinsic spontaneous brain activity and provide valuable insights into the pathophysiology of central nervous system disease. Patients with LA exhibited significant cognitive impairment, which was related with different amplitude fluctuations of rs-fMRI signals [13–15]. Recently, a study from China also showed that LA caused a significant decrease in the ALFF in the left parahippocampal gyrus (PHG) and an increased ALFF in right superior orbital frontal gyrus (SOFG); increased functional connectivity (FC) between the right insular region and the right SOFG and between the right calcarine cortex and the left PHG; significant differences in functional alterations of the default-mode network (DMN).
of white matter disease [25]. Cerebral autoregulation and CO
suggesting that impaired CVR contributes to the progression
sociated with subtle changes in the tissue integrity of NAWM,
meta-analysis [24]. Recently, impaired CVR has been as
on CVR in patients with CSVD have been summarized in a re
control analysis in clinical fMRI [23]. Currently available studies
hold CVR mapping is an essential component of quality con
diologic techniques, which also include MRI [22]. The breath-
variety of ultrasonographic, nuclear medicine, and neuro-ra
of brain conditions and disorders. CVR can be assessed by a
vides important information about vascular health in a range
(AN). The findings of wide alterations of inter-network connectivity
mainly involving the SMN, DMN, FPCN and DAN highlight the
importance of FC in understanding the effects of LA on cog-
nitive dysfunction [20]. Furthermore, the dysfunction of RSNs
might be a consequence of decreased white matter structural
connectivity, which further affects cognitive performance [21].
Thus, the technique of rs-fMRI could be quite useful in exploring
specific cognitive dysfunction by detecting spontaneous brain
neural activity and FC.

Cerebrovascular Reactivity (CVR)

The impaired cerebral autoregulation and vasodilatory capacity
may play in role in the pathogenesis of LA. Cerebrovascular re-
activity (CVR) is an indicator of cerebrovascular reserve and pro-
vides important information about vascular health in a range of
brain conditions and disorders. CVR can be assessed by a
variety of ultrasonographic, nuclear medicine, and neuro-ra-
diologic techniques, which also include MRI [22]. The breath-
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on CVR in patients with CSVD have been summarized in a re-
cent meta-analysis [24]. Recently, impaired CVR has been as-
associated with subtle changes in the tissue integrity of NAWM,
suggesting that impaired CVR contributes to the progression
of white matter disease [25]. Cerebral autoregulation and CO₂
reactivity are 2 distinct processes related to blood pressure
levels and duration of hypertension. Greater nocturnal dipping
was associated with higher cerebral autoregulatory index (ARI)
values, suggesting preservation of autoregulation in patients
with ischemic subcortical white matter disease, with increased
vulnerability to reduced cerebral perfusion [26]. Evaluation
of CVR is important in determining vascular chronic damage
to the brain and neurocognitive dysfunction by a variety of
mechanisms, including white matter lesion, brain atrophy, and
impairment of cerebral connectivity [27]. CVR mapping is an
evolving standard for clinical functional imaging and needs to
be further clarified.

Diffusion Tensor Imaging (DTI)

DTI is ideally suited to investigate the cortical disconnection
as it provides indices of structural integrity within interconnected
neural networks [28]. DTI is widely used to assess the
microstructural integrity of white matter and to provide infor-
mation about the structural characteristics of white matter.
A growing body of evidence indicates that cognitive function is
strongly associated with white matter integrity detected by
DTI [29]. Furthermore, the parameters of fractional anisotropy
(FA) could serve as a potent biomarker to detect the invisible
alteration of white matter integrity and to explore its poten-
tial cognitive relevance in LA [30]. A recent tract-based spatial
statistics (TBSS) study also showed that the atrophy and re-
duced diffusion anisotropy of the corpus callosum may indi-
cate diffuse deep white matter damage in LA, which may ex-
plain global cognitive impairment and progression of vascular
daemia [31]. Another voxel-based analysis study revealed
that FA and whole-brain mean diffusivity (MD) are sensitive
tools for use in evaluating its relationship with cognition in pa-
ients with LA [32]. Our study also demonstrated that DTI may
provide some important information about the cognitive dys-
function in patients with LA, which may be largely attributed
to the “disconnection” of cortico-subcortical pathways [33].

Dynamic Contrast-Enhanced MRI (DCE-MRI)

Blood-brain barrier (BBB) disturbance has been proposed to
play a pivotal role in the pathophysiology of LA. However,
the relationship of LA and quantification of regional BBB perme-
ability has not been well clarified. BBB leakage increased with
hypertension and the burden of both WMHs and normal-ap-
ppearing white matter (NAWM) [34]. It was also reported that
white matter permeability was significantly higher in LA, and
the increased BBB permeability in NAWM also supported a
close relationship between BBB disruption and the progression
of LA [35]. Absolute blood pressure levels and their variations
over time (i.e., blood pressure variability) were significantly
associated with white matter disease burden and cognitive impairment [36–39]. Recently, we also found that higher BBB permeability was associated with higher WMHs burden and cognitive decline. Our study further indicates that the compromised BBB integrity may be a critical contributor to the pathogenesis of LA and cognitive impairment [40]. As a result, DCE-MRI may be helpful to evaluate the permeability of BBB and its relationship with cognitive impairment. Future studies are needed to determine the relationship between BBB damage and development of WMHs [41].

Magnetic Resonance Spectroscopy (MRS)

The technique of MRS facilitates non-invasive imaging to identify metabolic changes in brain tissue. It was reported that the estimates of neuro-metabolite levels provide additional and useful information on cognitive function in LA [42]. Our study found that this relationship between cognitive function and metabolic changes suggests that MRS can be explored as a marker for cognitive dysfunction in patients with LA [43]. The combined DTI and MRS study also found the techniques of MRS can be used to investigate pathological changes in the anterior and posterior periventricular white matter, which may be correlated with executive function changes in patients with LA [29]. The MRS studies were consistent with neuronal loss in patients with LA, and cognitive dysfunction was also correlated with MRS-indexed biochemical changes.

Conclusions

To date, the pathophysiology of LA has not been clearly determined. LA is associated with increased risk of cognitive impairment; however, the underlying pathological changes and their relationship to cognitive impairments are obscure. In the present review, we suggest that the techniques of multimodal MRI are critical to examining the relationship between brain structural and functional changes in LA with cognitive decline. However, confirmation of our hypothesis and the exact relationship between LA and cognitive deficit requires further investigation.

Conflicts of interest

None.
26. Birns J, Jarosz J, Markus HS et al: Cerebrovascular reactivity and dynamic autoregulation in ischaemic subcortical white matter disease. J Neurol Neurosurg Psychiatry, 2009; 80: 1093–98
27. Lattanzi S, Carbonari L, Pagliariccio G et al: Neurocognitive functioning and cerebrovascular reactivity after carotid endarterectomy. Neurology, 2018; 90: e307–15
28. Bennett IJ, Madden DJ: Disconnected aging: Cerebral white matter integrity and age-related differences in cognition. Neuroscience, 2014; 276: 187–205
29. Li C, Ling X, Liu S et al: Abnormalities of magnetic resonance spectroscopy and diffusion tensor imaging are correlated with executive dysfuction in patients with ischemic leukoaraiosis. J Clin Neurosci, 2012; 19: 718–22
30. Zhong G, Zhang R, Jiaerken Y et al: Better correlation of cognitive function to white matter integrity than to blood supply in subjects with leukoaraiosis. Front Aging Neurosci, 2017; 9: 185
31. Otsuka Y, Yamauchi H, Sawamoto N et al: Diffuse tract damage in the hemispheric deep white matter may correlate with global cognitive impairment and callosal atrophy in patients with extensive leukoaraiosis. Am J Neuroradiol, 2012; 33: 726–32
32. Della Nave R, Foresti S, Pratesi A et al: Whole-brain histogram and voxel-based analyses of diffusion tensor imaging in patients with leukoaraiosis: Correlation with motor and cognitive impairment. Am J Neuroradiol, 2007; 28: 1313–19
33. Yuan JL, Wang SK, Guo X et al: Disconnections of cortico-subcortical pathways related to cognitive impairment in patients with leukoaraiosis: A preliminary diffusion tensor imaging study. Eur Neurol, 2017; 78: 41–47
34. Munoz Maniega S, Chappell FM, Valdes Hernandez MC et al: Integrity of normal-appearing white matter: Influence of age, visible lesion burden and hypertension in patients with small-vessel disease. J Cereb Blood Flow Metab, 2017; 37: 644–56
35. Huisa BN, Caprihan A, Thompson J et al: Long-term blood-brain barrier permeability changes inBinswanger disease. Stroke, 2015; 46: 2413–18
36. Liu Z, Zhao Y, Zhang H et al: Excessive variability in systolic blood pressure that is self-measured at home exacerbates the progression of brain white matter lesions and cognitive impairment in the oldest old. Hypertens Res, 2016; 39: 245–53
37. Lattanzi S, Brigo F, Vernieri F et al: Visit-to-visit variability in blood pressure and Alzheimer’s disease. J Clin Hypertens (Greenwich), 2018; 20: 918–24
38. Lattanzi S, Luzzi S, Provinciali L et al: Blood pressure variability in Alzheimer’s disease and frontotemporal dementia: The effect on the rate of cognitive decline. J Alzheimers Dis, 2015; 45: 387–94
39. Yamaguchi Y, Wada M, Sato H et al: Impact of ambulatory blood pressure variability on cerebral small vessel disease progression and cognitive decline in community-based elderly Japanese. Am J Hypertens, 2014; 27: 1257–67
40. Li Y, Li M, Zhang X et al: Higher blood-brain barrier permeability is associated with higher white matter hyperintensities burden. J Neurol, 2017; 264: 1474–81
41. Taheri S, Gasparovic C, Huisa BN et al: Blood-brain barrier permeability abnormalities in vascular cognitive impairment. Stroke, 2011; 42: 2158–63
42. Gasparovic C, Prestopnik J, Thompson J et al: 1H-MR spectroscopy metabolite levels correlate with executive function in vascular cognitive impairment. J Neurol Neurosurg Psychiatry, 2013; 84: 715–21
43. Wang S, Yuan J, Guo X et al: Neurochemical correlates of cognitive dysfunction in patients with leukoaraiosis: A proton magnetic resonance spectroscopy study. Neurol Res, 2012; 34: 989–97