Imaging Small Vessel Disease
Lesion Topography, Networks, and Cognitive Deficits Investigated With MRI

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Abstract—Small vessel disease is a major contributor to the growing burden of cognitive impairment and dementia. In addition to diagnosis, MRI techniques provide a means to investigate mechanisms of cognitive decline. Studies that incorporate diffusion tensor MRI show that variance in cognitive performance is largely accounted for by alterations in brain structure. Unresolved questions about the link between structure and function include: (1) the relative importance of a small number of strategic lesions versus the cumulative effect of multiple lesions; (2) the underlying basis for the characteristic profile of cognitive impairment, with selective deficits of executive function, processing speed and working memory. This update focuses on MRI approaches to these problems and techniques to analyze spatial distribution of damage in relation to the networks that subserve major cognitive functions. Lesion mapping and voxel-based analysis, and the application of diffusion tensor MRI tractography to reconstruct critical white matter projections, are highly promising approaches for improving understanding of the relationship between structure and function and the mechanisms of cognitive decline. (Stroke. 2010;41[Suppl 1]:S154-S158.)

Key Words: CADASIL syndrome ■ diffusion-weighted imaging ■ lacunes ■ leukoaraiosis ■ vascular cognitive impairment ■ white matter disease

Cerebral small vessel disease (SVD) refers to a spectrum of clinical, cognitive, and behavioral abnormalities linked to pathology of small penetrating arteries and arterioles in the brain. In its common sporadic form, SVD occurs in the context of vascular risk factors, notably hypertension and diabetes mellitus. Growth in interest in SVD has been interwoven with advances in noninvasive brain imaging. The advent of computed tomography in the early 1970s led to renewed interest in Binswanger disease, which until this period had been considered rare. As part of this renaissance, the term leukoaraiosis was coined to describe the diffuse changes seen on computed tomography. The spectrum of classical lesions now recognized on MRI includes leukoaraiosis, lacunae, and more recently cerebral microbleeds.

Cognitive impairment is a leading cause of morbidity in SVD. Characteristic lesions on MRI may support a diagnosis of vascular cognitive impairment. However, MRI techniques can also help elucidate the mechanisms of cognitive decline. This update focuses on this issue, reviewing briefly the contribution of MRI to date, outlining remaining puzzles, and providing 2 examples of state-of-the-art approaches to solve them.

SVD and Cognition
Cognitive impairment was recognized as a prominent feature in early clinical series. Markers of SVD are also associated with cognition in healthy older adults. The question of whether structural damage plays a causal role in these deficits has been controversial, partly because the correlation between leukoaraiosis on T2-weighted MRI and cognitive performance is weak. However, the fact that the presence of leukoaraiosis was known to be only a weak indicator of the extent of underlying neuronal damage left the door open to new structural techniques that might show stronger relationships with function.

More of the variance in cognitive function can be explained if multiple lesion types, rather than just leukoaraiosis, are taken into account. However, in terms of quantifying important structural changes, diffusion tensor MRI (DTI) has produced the most important step forward. As axons and myelin are lost from coherent white matter tracts, anisotropy, a measure of directionality of diffusion, diminishes, whereas diffusivity averaged in all spatial directions increases. When DTI and conventional MRI are combined, 50% to 74% of variance in cognitive scores can be accounted for by brain structure. Although proving a causal role is challenging, these studies go some way to assuaging old objections and support the notion that cognitive deficits arise from a form of cerebral disconnection.
The relative contribution of strategic lesions is unknown. Most studies have measured only the total cumulative burden of lesions. However, strategic lesion locations are well-described.\textsuperscript{16}

The basis of selective deficits in executive function and working memory is unknown.\textsuperscript{13}

Simple, landmark-based approaches to lesion location have provided some insights: in the Rotterdam Study, the effects of thalamic and nonthalamic incident lacunae on cognitive decline have been contrasted and found to differ.\textsuperscript{17} However, approaches to location have so far been crude with respect to the anatomy of cognitive networks. Networks for functions such as attention, memory, and executive function are simultaneously both widely distributed\textsuperscript{18,19} and display a precise, fine-grained segregation at a small scale. To understand the relationship between lesion location and cognitive function requires imaging approaches that localize lesions precisely, at a scale which matches the underlying functional neuroanatomy, and can map them on to the relevant distributed cognitive networks.

Mapping the Spatial Distribution of Lacunar Lesions

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a genetic SVD that provides an attractive model to investigate mechanisms of cognitive impairment. Lacunar lesions are frequent, have the strongest collective effect on cognition,\textsuperscript{11} and proven strategic effects\textsuperscript{16,20} so are a natural starting point for analysis of topography.

T1-weighted scans were collated from participants in the Paris-Munich CADASIL study,\textsuperscript{11} registered to the corresponding FLAIR images, and then automatically segmented into 4 tissue classes. The lowest intensity tissue class was automatically labeled as cerebrospinal fluid/lacunar lesions. Expert raters validated all segmented lesions by confirming that they were: (1) consistent in appearance, size, and location with lacunar infarcts, and (2) displayed cerebrospinal fluid intensity on corresponding FLAIR images. Enlarged perivascular spaces were excluded from lacune maps.

Each individual lacune map was then normalized to a standard atlas space with Statistical Parametric Mapping (SPM5, www.fil.ion.ucl.ac.uk/spm) and summed to produce a prevalence map for the whole patient group (Figure 1).

The distribution of lesions was compared across different grades of total lesion burden. In the less affected group lesions were restricted to the mediodorsal thalamus (Figure 2A). Anterior thalamic lesions occurred more frequently in those with high lesion loads. This effect was highly significant, even when total lesion load was entered as a covariate (Figure 2C). These findings suggest a true shift of location toward the anterior thalamus as the disease progresses, rather than simply a spatially random spread of lesions. Such an effect was found in the thalamus but not in any other region. The thalamic region more affected in those with advanced disease is in close proximity to the mamillothalamic tract and corresponds to sites of single strategic infarcts that cause amnesia (Figure 3).\textsuperscript{21} Spread of lesions into this region is therefore one potential mechanism of accelerated cognitive decline.
Voxel-based approaches can be used to map quantitative measures of white matter integrity from DTI as well as lesions. In the CADASIL model, this approach suggests that there are critical regions within areas of leukoaraiosis where integrity correlates most strongly with executive function.22

Figure 2. Lesion load and pattern of thalamic lesions in CADASIL. A, Sum of lacune maps for the 56 subjects in the lower half for total lacunar lesion volume. B, Total lacune map for all 112 patients. C, Results of an independent t test between upper and lower halves for total lacunar lesion volume. Lesions of anterior and medial thalamic regions are found only in patients with higher total lesion loads, a tendency which is statistically significant (familywise error $P<0.05$). Lacune maps are unsmoothed and thresholded at a lacune frequency of 0.5. Lesions outside the thalamus not shown.

Tractography in the Brain Damaged by SVD
Comparison of results from voxel-based analyses with atlases of brain structure can generate hypotheses about which white matter fasciculi are involved, which might lead to hypotheses about the basis of selective deficits. For example, in the voxel-based analysis described above,22 one critical site for executive function seemed to overlie the cingulum bundle. Diffusion tensor tractography23 might allow these hypotheses to be tested directly.24 One tractography-based study has already provided partial corroboration of the association between the cingulum bundle and cognition in SVD.25 The principal concern about the application of tractography to SVD is the impact that white matter injury might have on the veracity of tractography algorithms. Regions of low anisotropy lead to increased uncertainty about fiber direction, which can lead to both premature termination and tracking of aberrant, artifactual connections.26

There have been no systematic studies to date of the reliability of tractography approaches in SVD. However, our initial experience suggests that reliability is tract-
specific and that reliable, plausible reconstructions are possible for some tracts. Figure 4 shows a series of reconstructions of the uncinate fasciculus—a hook-shaped tract connecting the anterior temporal to inferior frontal lobe, implicated in memory processes in both monkeys and humans—in patients with increasing leukoaraiosis. Using a relatively simple scheme of anatomic landmarks we were able to generate reconstructions, and tract-specific measurements in all 4 individuals. However, these are merely examples. Systematic studies are needed to assess the reliability of tractographic reconstructions of this and other fasciculi in the context of SVD. Indeed, other tracts may prove more challenging than the uncinate fasciculus, which is largely peripheral to the regions most commonly affected by leukoaraiosis. Ultimately, measures derived from tractography will also need to be validated against histological measures of tract integrity.

**Conclusion**

MRI techniques have made a significant contribution to our understanding of how structural alterations in SVD contribute to cognitive deficits. The neuroanatomy of cognitive networks is complex and the spatial distribution of lesions is an important factor to consider to develop a richer understanding of the links between structure and cognitive function. Voxel-based mapping and diffusion tensor tractography are evolving areas that show promise in application to SVD. Generating hypotheses from voxel-based analyses to be tested by tractography is one example of how emerging techniques can work in synergy to provide powerful approaches to elucidate disease mechanisms.

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References

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