

Diffusion MRI studies in vascular cognitive impairment and dementia

Estudos de ressonância magnética funcional (imagens tensores de difusão) nos quadros de prejuízo cognitivo vasculares e demências

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Abstract Since its introduction more than two decades ago, Magnetic Resonance Imaging (MRI) has not only allowed for visualization of the macrostructure of the CNS, but also has been able to study dynamic processes which constitute the substrate of currently available MRI variants. While conventional Diffusion Weighted Imaging (DWI) permits a robust visualization of lesions just a few minutes after the onset of cerebral ischemia, Diffusion Tensor Imaging (DTI) measures the magnitude and direction of diffusion, leading to the characterization of cerebral white matter (WM) microstructural integrity. In this paper, the potential role of MRI techniques, particularly DTI, for the study of the relationship between changes in the microstructural integrity of WM and cognitive impairment in the context of cerebrovascular disease are discussed. Significant correlations between scores of behavioral measures of cognitive function and regional anisotropy values are an example of the potential efficacy of DTI for in vivo studies of brain connectivity in vascular neurodegenerative conditions.

Keywords Magnetic resonance. Functional neuroimaging. Diffusion. Tensor. DWI. DTI. White matter. Vascular dementia. Vascular cognitive impairment. Brain connectivity.

Resumo Desde a sua introdução há mais de duas décadas, as Imagens de Ressonância Magnética (MRI) não somente permitiram a visualização da macroestrutura do sistema nervoso central, mas também foram capazes de estudar múltiplos processos dinâmicos, os quais são o substrato para as variantes atuais da técnica. Enquanto que as Imagens de Difusão Ponderada permitem uma robusta visualização de lesões, apenas há minutos de iniciar-se a isquemia cerebral, as Imagens de Tensores de Difusão medem a magnitude e direção da difusão, caracterizando a integridade estrutural da substância branca (WM) cerebral. Neste artigo, discute-se a utilidade potencial das técnicas de MRI, particularmente DTI, para o estudo da relação entre mudanças da integridade microestrutural da WM e a deterioração cognitiva, no contexto da doença cerebrovascular. As correlações significativas entre as magnitudes obtidas de provas conductuais das funções cognitivas e os valores de anisotropia, constituem um exemplo da utilidade potencial de DTI para estudos in vivo da conectividade cerebral em doenças vasculares neurodegenerativas.

Descritores Ressonância magnética. Neuroimagem funcional. Difusão. Tensor. DWI. DTI. Substância branca. Demência vascular. Disfunção cognitiva vascular. Conectividade cerebral.

Introduction

The vast majority of the neuroimaging techniques currently available for clinical purpose imply the use of either X-rays or the Magnetic Resonance (MR) principle. Hence, based on the differences in the attenuation of the x-rays emitted by the CT scanner or in the differences of tissue response to the MR radiofrequency pulses, it is possible to distinguish normal com-

pounds of the Central Nervous System (CNS) as well as macrostructural abnormalities that may be present.

On the other hand, *functional* neuroimaging techniques have made possible the visualization of different physiologic, biochemical, cellular or molecular processes, even in the presence of seemingly normal neural tissue. A remarkable example of this development is the appearance of several MR modali-

ties – fMRI, perfusion, diffusion, spectroscopy – that have been used for the study and characterization of brain functioning and CNS microstructure.

Perhaps the most successful of the currently available functional MR techniques is the so called Diffusion Weighted Imaging (DWI), which exploits differences in water diffusion properties among tissues and provides important clues of their structure and geometric organization. The contribution of DWI has been remarkable given the robust visualization of lesions that it permits just few minutes after the onset of cerebral ischemia,¹⁻⁵ as well as White Matter (WM) microstructural changes in the context of different neuropathological insults.⁶

In a sophisticated variant of DWI, the newer Diffusion Tensor Imaging (DTI), diffusion gradients are oriented on at least six non-collinear simultaneous directions – not only in x, y, z directions. This allows for the measuring of diffusion independently of patient position or fiber orientation. Consequently, both the direction and average magnitude of water diffusion can be determined in a better way than in the DWI.⁷

In this paper, we wanted to review the contribution that MR imaging (MRI) techniques – particularly those based on molecular diffusion – have made to the current knowledge about the role of WM compromise in the pathophysiology of the cognitive impairment associated with cerebrovascular disease and the later development of dementia. Also, we emphasized the importance of these techniques in the early diagnosis and preventive strategies for these highly prevalent diseases.

Vascular dementia and white matter dysfunction

Vascular dementia (VAD) constitutes the second most common type of dementia after Alzheimer's disease, occurring in 5.2% of people aged over 90 years.⁸ Cognitive decline in VAD is associated with widespread small ischemic or vascular lesions throughout the brain, predominantly in the basal ganglia, hippocampus and white matter.⁹

Additionally, in Alzheimer's disease (AD), the importance of vascular lesions has promoted research into AD plus cerebrovascular disease (CVD).¹⁰ At least a third of AD subjects bear a significant amount of cerebrovascular pathology.⁸ There is still debate as to how these mixed cases are best conceptualized. Although it has been common practice to classify AD and VAD as distinct entities, both clinico-pathological and epidemiological evidence suggest that dementing disorders in the elderly constitute a spectrum with 'pure AD' at one end and 'pure VAD' at the other, with increasing degrees of vascular and white matter disease along the spectrum.⁸

Several morphologic varieties of VAD have been described, including: multiinfarct dementia, small vessel infarct dementia, strategic infarct dementia, subcortical vascular dementia (SVD), multilacunar state, mixed cortico-subcortical type, granular cortical atrophy, and post-ischemic encephalopathies.¹¹ Among them, subcortical vascular dementia may be the most common form; it is phenomenologically characterized by frontal lobe signs (especially impairment of executive function), global cognitive decline, and affective symptoms. A salient structural feature of subcortical vascular dementia is widespread

white-matter changes in the brain.¹² The cognitive dysfunction of subcortical vascular dementia is related with cerebral blood flow abnormalities in frontal areas.¹³

Depressive disorder is a prodrome of VAD and commonly persists among the patients. Once the cognitive dysfunction is clinically established, the demented patients appear to be susceptible to depression.¹⁴ Demyelination of subcortical circuits resulting in disconnection may be the underlying factor in these cases.¹⁵⁻¹⁷

Imaging tools for the study of vascular cognitive impairment

Subcortical vascular disease is also a significant cause of vascular cognitive impairment (VCI), a deterioration not reaching criteria for dementia, in the general population, often preceding the later development of dementia.¹⁸

Single acute ischemic lesions, although small, in patients with chronic subcortical microangiopathic lesions, can trigger unexpectedly severe clinical syndromes. This suggests the existence of a precariously balanced system, compensating for subclinical structural damage in these patients.¹⁹

Several studies suggest that subcortical small vessel disease with white matter abnormalities and multiple lacunar infarcts, obeying to global vascular risk factors, constitute the underlying pathology related to VCI. This pathology is now amenable to radiological methods which, combined with clinical criteria, can potentially allow for early diagnosis.²⁰

Conventional MRI

In subcortical vascular disease, MRI often reveals diffuse white matter hyperintensity (WMH), also called leukoaraiosis.²¹ MR imaging is more sensitive than CT for the detection of white matter changes.²²

On the other hand, WMH in the brain of otherwise normal elderly subjects are thought to represent an early form of subcortical arteriosclerotic encephalopathy; the association between WMH progression and cognitive changes needs to be further explored.²³ The majority of the evidence shows an association between WMH and cognitive impairment.²⁴

Vascular depression in the elderly studied with standardized MRI has later age of onset and a less effective response to antidepressant treatment when WMH is more severe.²⁵

DTI

Notwithstanding the advent of quantitative methods that permit a reliable segmentation of WMH volume,²⁶ the information obtained from white matter through conventional MRI has only one dimension, based on intensity values.

Diffusion tensor imaging (DTI) is a newer MRI method to study myelin *in vivo*.²⁷ It is based on the physiological fact that myelin is a barrier for water molecules. DTI uses a special MRI protocol (echo planar imaging) that detects water diffusion in space. Once detected, this molecular motion is expressed for each voxel by means of a tensor, a mathematical concept that allows for complete tridimensional description and in depth pathophysiological inference. Due to the directionally insulated structure of white matter tracts, selective diffusion in a par-

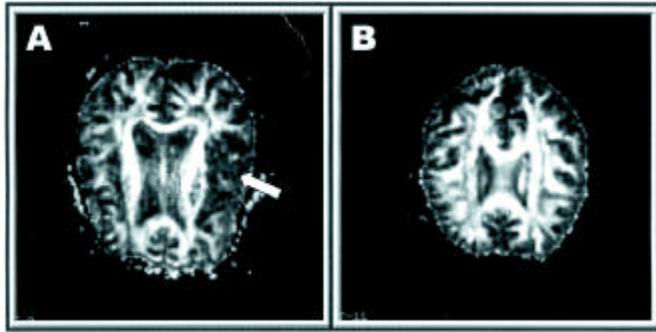


Figure – Fractional Anisotropy maps created in: **A)** A patient that has recently suffered a stroke. The primary lesion is visible as an extensive area where anisotropy is severely reduced (arrow). **B)** Same-age normal control.

ticular direction (anisotropy) is a direct indicator of structural integrity of fibers. Anisotropy is reliably measured through DTI, which constitutes a window to look at white matter at a microscopic scale.

In all patients with ischemic WM changes (WMC) studied with DTI, a characteristic abnormal pattern was found, with

loss of anisotropy and increased mean diffusion in the white matter²⁸ (Figure).

While T2-weighted changes, defined as WMH, provide little information about the pathophysiological nature of the underlying pathology, and correlate poorly with cognitive dysfunction, DTI is able to detect subtle changes in normal appearing white matter and their relationship with cognitive function.²⁶

Diffusion imaging at high b value was shown to be highly sensitive to white matter pathology. It showed areas of abnormal white matter that were not detected by other MRI methods.²⁹

Conclusion

Since progression of cognitive impairment after stroke is common, preventive strategies are essential.³⁰ It may be possible to prevent VAD by control of hypertension, use of statins and folic acid. Treatment, on the other hand involves the use of cholinergic agents (among others).³¹ MRI, especially DTI methods, to study myelin *in vivo*, allow for early detection of white matter disruption, detailed follow up for treatment control, and fine anatomical abstraction of involved connections.

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