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Advanced diffusion MRI and biomarkers in the central nervous system: A new approach☆

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Abstract The introduction of diffusion-weighted sequences has revolutionized the detection and characterization of central nervous system (CNS) disease. Nevertheless, the assessment of diffusion studies of the CNS is often limited to qualitative estimation. Moreover, the pathophysiological complexity of the different entities that affect the CNS cannot always be correctly explained through classical models. The development of new models for the analysis of diffusion sequences provides numerous parameters that enable a quantitative approach to both diagnosis and prognosis as well as to monitoring the response to treatment; these parameters can be considered potential biomarkers of health and disease. In this update, we review the physical bases underlying diffusion studies and diffusion tensor imaging, advanced models for their analysis (intravoxel coherent motion and kurtosis), and the biological significance of the parameters derived.

PALABRAS CLAVE
Resonancia magnética;
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Tensor de difusión;
Biomarcadores

RM-Difusión avanzada y biomarcadores en el sistema nervioso central: un nuevo enfoque

Resumen La introducción de las secuencias potenciadas en difusión ha supuesto una revolución para la detección y caracterización de la patología del sistema nervioso central. Sin embargo, en numerosas ocasiones, la valoración de dichos estudios se limita a una estimación cualitativa. Además, la complejidad fisiopatológica de las distintas entidades que afectan al

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sistema nervioso central no siempre puede ser correctamente explicada por los modelos clásicos. El desarrollo de nuevo modelos para el análisis de las secuencias de difusión aporta numerosos parámetros que podrían permitir un abordaje cuantitativo tanto desde el punto de vista del diagnóstico como pronóstico, así como para llevar a cabo la monitorización terapéutica, y podrían ser considerados como potenciales biomarcadores de salud y enfermedad. Realizamos por este motivo una actualización que incluye las bases físicas de los estudios de difusión y tensor de difusión, sus modelos de análisis avanzado (IVIM y Kurtosis) y la significación biológica de los parámetros derivados.

Introduction

Diffusion weighted magnetic resonance imaging (DWI-MRI) are capable of providing us with non-invasive estimates of the movement of water molecules in a biological environment.[1] DWI-MRI studies allow us to perform quantitative and qualitative assessments of such movement and provide us with anatomical and functional information on the tissues.

The design of DWIs has been perfected thanks to multiple technical innovations. This is how we have been able to reduce the times of acquisition and the artifacts and improve the signal-noise correlation. Other technical optimizations of DWIs have allowed us to develop diffusion tensor imaging (DTI) – a tool that has revolutionized the assessment of white matter in the central nervous system (CNS).

DWIs have proven to be of great utility for the study of CNS diseases. However, the physical bases of DWIs have remained unchanged during the last 20 years. This is why, today, innovations focused on the phase of analysis and interpretation of the data obtained in the acquisition phase.

Small modifications in the acquisition process but, above all, it is the use of different mathematical and biological models for the analysis of signal intensity drops that is allowing us to understand more accurately the physiopathological processes that occur in the CNS.

Such analytical models will allow us to obtain multiple parameters that will be potentially used as biomarkers. In this update we will discuss in a more pedagogical way the physical bases of the conventional models of DWI and DTI, and delve into new analytical models based on the intravoxel incoherent motion (IVIM) and Kurtosis models. The origin and biological significance of the different parameters derived from these analytical models and the prospective clinical applications of such parameters will be fully explained in detail.

Physical and acquisition bases of classic DWIs and DTIs

The classic DWI sequences are based on the implementation of two (2) diffusion gradients (identical in magnitude and duration) into one spin echo (SE) sequence. Technical innovations have made it possible to develop sequences based on turbo spin echo (TSE) sequences and, above all, the most widely used today – the echo-planar imaging (EPI) sequences.[2]

The first gradient implemented will dephase water molecules and after a while, the second gradient will rephase such molecules in the same proportion that they were dephased in the first place. The molecules that remain stationary after the second gradient will fully recover their initial energetic state, which will translate into high signal intensities in high *b* values of the diffusion sequence, the so-called ''diffusion restriction''. On the other hand, the molecules experimenting movement during the time elapsed between both gradients will lose their position and will not be able to recover it completely, meaning that their energetic state will be lower and that signal attenuation proportional to the degree of movement will occur, the so-called ''free or facilitated diffusion''.[3] This is how DWIs make distinctions between different kinds of tissues based on the freedom of water movement inside them (Fig. 1).

Diffusion may be considered isotropic or anisotropic based on the direction of water movement.[4] In isotropic diffusion, water movement occurs with equal probability in all directions of space, whether such space is limited or not. In anisotropic diffusion, there is a dominant direction of water movement in a given tissue that is usually conditioned by the existence of anatomical and physiological barriers. This is the case of water movement inside axons and between myelin sheaths where the dominant direction of movement occurs across the long axis of the axon (Fig. 2). For the study of anisotropic diffusion, and as a technical optimization of the DWI sequences, the diffusor tensor imaging (DTI) has been developed.[5]

DTIs are based on the implementation of diffusion gradients into multiple orthogonal directions in space (at least 6). This is the what to assess the mobility of water molecules in every direction and detect if there is one dominant diffusion direction. From the mathematical standpoint one 3×3 matrix is generated that will diagonalize the dominant direction in each plane of space represented by one vector (eigenvector) of a determined magnitude (eigenvalue).[3]

One of the added values that DTIs provide us with is the performance of tractography studies.[6] Tractographies are based on 3D representation of white matter bundles through