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Translating state-of-the-art spinal cord MRI techniques to clinical use: A systematic review of clinical studies utilizing DTI, MT, MWF, MRS, and fMRI

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ABSTRACT

Background: A recent meeting of international imaging experts sponsored by the International Spinal Research Trust (ISRT) and the Wings for Life Foundation identified 5 state-of-the-art MRI techniques with potential to transform the field of spinal cord imaging by elucidating elements of the microstructure and function: diffusion tensor imaging (DTI), magnetization transfer (MT), myelin water fraction (MWF), MR spectroscopy (MRS), and functional MRI (fMRI). However, the progress toward clinical translation of these techniques has not been established.

Methods: A systematic review of the English literature was conducted using MEDLINE, MEDLINE-in-Progress, Embase, and Cochrane databases to identify all human studies that investigated utility, in terms of diagnosis, correlation with disability, and prediction of outcomes, of these promising techniques in pathologies affecting the spinal cord. Data regarding study design, subject characteristics, MRI methods, clinical measures of impairment, and analysis techniques were extracted and tabulated to identify trends and commonalities. The studies were assessed for risk of bias, and the overall quality of evidence was assessed for each specific finding using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework.

Results: A total of 6597 unique citations were identified in the database search, and after full-text review of 274 articles, a total of 104 relevant studies were identified for final inclusion (97% from the initial database search). Among these, 69 studies utilized DTI and 25 used MT, with both techniques showing an increased number of publications in recent years. The review also identified 1 MWF study, 11 MRS studies, and 8 fMRI studies. Most of the studies were exploratory in nature, lacking a priori hypotheses and showing a high (72%) or moderately high (20%) risk of bias, due to issues with study design, acquisition techniques, and analysis methods. The acquisitions for each technique varied widely across studies, rendering direct comparisons of metrics invalid. The DTI metric fractional anisotropy (FA) had the strongest evidence of utility, with moderate quality evidence for its use as a biomarker showing correlation with disability in several clinical pathologies, and a low level of evidence that it identifies tissue injury (in terms of group differences) compared with healthy controls. However, insufficient evidence exists to determine its utility as a sensitive and specific diagnostic test or as a tool to predict clinical outcomes. Very low quality evidence suggests that other metrics also show group differences compared with controls, including DTI metrics mean diffusivity (MD) and radial diffusivity (RD), the diffusional kurtosis imaging (DKI) metric mean kurtosis (MK), MT metrics MT ratio (MTR) and MT cerebrospinal fluid ratio (MTCSF), and the MRS metric of *N*-acetylaspartate (NAA) concentration, although these results were somewhat inconsistent.

Conclusions: State-of-the-art spinal cord MRI techniques are emerging with great potential to improve the diagnosis and management of various spinal pathologies, but the current body of evidence has only showed limited clinical utility to date. Among these imaging tools DTI is the most mature, but further work is necessary to standardize and validate its use before it will be adopted in the clinical realm. Large, well-designed studies with a priori hypotheses, standardized acquisition methods, detailed clinical data collection, and

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robust automated analysis techniques are needed to fully demonstrate the potential of these rapidly evolving techniques.

Contents

1. Background

The advent of magnetic resonance imaging (MRI) in the mid-1980s transformed the field of spinal cord imaging and provided clinicians with high-resolution anatomical images, directly leading to improved clinical decision-making. Conventional MRI techniques (spin echo, gradient echo, and inversion recovery sequences, with T1-, T2-, or proton density-weighting) have continued to mature over 3 decades of use, establishing MRI as the imaging modality of choice for most spinal disorders. However, conventional MRI provides little information regarding the health and integrity of the spinal cord tissue itself, due to the fact that signal intensity changes are non-specific and do not correspond directly with aberrant physiological processes (Wada et al., 1995). This is reflected in the poor correlation of conventional MRI data with neurological and functional impairment in various spinal cord pathologies (Tetreault et al., 2013; Wilson et al., 2012), and failure to provide reliable prognostic information. In the degenerative condition cervical spondylotic myelopathy (CSM), weak correlates with clinical status have been identified using T2-weighted hyper-intensity (T2w-HI), T1-weighted (T1w) hypo-intensity, and measures of cord compression (Matsuda et al., 1999; Tetreault et al., 2013; Wada et al., 1995). In multiple sclerosis (MS), numerous studies have found that spinal cord lesion load is less important than atrophy, measured as the cross-sectional area (CSA) of the cord (Stevenson et al., 1998). As a result, conventional MRI techniques are of limited value in developing imaging biomarkers or predicting clinical outcomes because they are not sensitive and specific measures of the degenerative and regenerative changes that occur within the spinal cord at the microstructural and functional levels.

A 2013 international meeting of spinal cord imaging experts, sponsored by the International Spinal Research Trust (ISRT) and the Wings for Life (WfL) Spinal Cord Research Foundation, outlined 5 emerging MRI techniques that have the potential to revolutionize the field, by elucidating details of the microstructure and functional organization within the spinal cord (Stroman et al., 2014; Wheeler-Kingshott et al., 2014). This group highlighted the following techniques due to their ability to characterize microstructural features of the spinal cord: diffusion tensor imaging (DTI), magnetization transfer (MT), myelin water-fraction (MWF), and magnetic resonance spectroscopy (MRS). DTI measures the directional diffusivity of water, and several of the metrics that it produces correlate with axonal integrity, and to a lesser degree, myelination (Wheeler-Kingshot et al., 2002). MT involves an off-resonance saturating pre-pulse that takes advantage of the chemical and magnetization exchange between protons bound to lipid macromolecules and nearby water protons, and provides a surrogate measure of myelin quantity (Graham and Henkelman, 1997). This is most often expressed in a ratio between scans with and without the pre-pulse (MTR) or between the spinal cord and cerebrospinal fluid (MTCSF). MWF estimates the fraction of tissue water bound to the myelin sheath,