Evaluation of Intravoxel Incoherent Motion in the Spinal Cord of Multiple Sclerosis Patients

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Introduction:

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) which leads to demyelination and neurodegeneration[1]. MS affects mobility, balance, vision, and cognition making it the leading cause of non-traumatic disability in young adults worldwide[2]. Despite its global prevalence little is known of the etiology of MS and its progression is highly variable. Early and accurate diagnosis of MS is critical and is done through a combination of reported clinical symptoms and positive radiological findings on magnetic resonance imaging (MRI)[3]. MS is categorized as either relapsing-remitting or primary progressive, with most patients being diagnosed with relapsing-remitting MS. Relapsing-remitting MS most commonly affects young people with the average presentation of symptoms occurring at 30 years old with a predominance of cases being diagnosed in females[3]. Relapsing-remitting MS consists of time periods of neurological dysfunction or relapse, followed by periods of remission with no symptoms[4]. Primary progressive MS patients on the other hand show a slow and progressive decline in neurological function over time[5]. However, patients with relapsing-remitting MS can progress into secondary primary progressive MS when the disease course switches and there are no relapses, just a steady increase in disability [5].

The pathogenesis of MS is not completely understood, however, there is growing evidence that a vascular component may contribute to the progression of the disease [6-8]. This idea of vascular involvement is strengthened by the location of MS lesions that predominantly develop around central veins, metabolic dysfunction due to hypoperfusion, and microvascular occlusions indicating ischemic conditions [7-9]. Advanced magnetic resonance imaging techniques, including perfusion weighted imaging (PWI), have been used to better characterize and understand MS[10]. PWI techniques can be categorized into contrast and non-contrast based techniques. Contrast based PWI techniques require the administration of gadolinium based contrast agents (GBCA) to assess perfusion. However, the use of GBCA has come under scrutiny recently with reports confirming deposition of gadolinium in the brain[11]. This is of special concern in the MS population as they undergo serial MRIs with GBCA [12].

Previous PWI studies in MS have revealed alterations of cerebral perfusion compared with healthy controls. Acute MS lesions have shown increased perfusion when compared to normal-appearing-white-matter (NAWM)[13-15]. This hyper-perfusion is thought to reflect the inflammatory process[16,17]. In contrast, PWI studies of the parenchymal tissue have reported reduced cerebral blood flow (CBF) and cerebral blood volume (CBV) in NAWM [8,17-22]. This hypoperfusion in NAWM suggests that perfusion deficits extend beyond MS lesions, and changes in perfusion may serve as a clinically relevant biomarker[20,23]. However, all of the PWI work in MS has been done in the brain leaving a gap of information in regards to perfusion changes in the spinal cord caused by the progression of MS [24].

Intravoxel incoherent motion (IVIM) offers an elegant non-contrast way to study the microcirculatory blood and provide in-vivo perfusion information[25]. IVIM also does not require complex tagging strategies or additional hardware like its non-contrast PWI counterpart, arterial spin labeling (ASL)[26]. IVIM is based on the principle of diffusion-weighted imaging (DWI), which measures the random Brownian motion of water molecules in tissue[27]. Furthermore, IVIM also considers the presence of microvascular perfusion, which results in a more complex signal decay that can be modeled using two or more diffusion-relaxation components[27]. IVIM can be used to quantify the perfusion fraction (f), which reflects the proportion of blood vessels that are perfused and contribute to the signal decay, and the pseudo-diffusion coefficient (D*), which reflects the combined effects of diffusion and perfusion on the signal decay[27]. IVIM has been shown to be a useful tool for estimating microvascular perfusion in a variety of tissues, including the brain[28], heart[29], liver[30], kidney[31], and pancreas[32]. Moreover, IVIM studies

have shown a good degree of correlation between IVIM perfusion metrics and physiologically and pharmaceutically induced changes in perfusion[33,34]. IVIM has shown promise in providing more information about the underlying disease process than conventional MRI techniques and may help to improve the accuracy of diagnosis and disease monitoring[35]. Therefore, advanced MRI techniques like IVIM that allow for the evaluation and measurement of changes in perfusion offer a great tool to gain a better understanding of MS and allow for earlier detection[10].

In multiple sclerosis (MS) patients, the spinal cord is often affected by inflammation and demyelination, leading to axonal damage and neuronal loss[24]. Spinal cord abnormalities are visible on MRI in up to 90% of MS patients[36]. One of the potential advantages of IVIM over conventional MRI techniques is its ability to provide quantitative information on the microvascular perfusion and diffusion in the spinal cord[26]. This may be useful for differentiating between normal and abnormal tissue, as well as for monitoring the response to treatment. Here we evaluate the ability of IVIM to differentiate microcirculation changes in the spinal cord of MS patients. Given the previous sensitivity of advanced diffusion MRI techniques and the implication of altered perfusion kinematics in MS neuroimaging studies we hypothesize that IVIM will show hypoperfusion deficits in the spinal cord affected by MS.

Methods:

Fifteen healthy controls with a mean age of 29.0 ± 5.0 years (10 males, and 5 females), and fifteen MS patients with a mean age of 39.3 ± 6.1 years, (15 females) were enrolled and underwent MRI scanning. Subjects were recruited via ResearchMatch[37]. All MRI experiments were performed on a 3T scanner (Philips Achieva, Best, Netherlands) using a 16-channel phased array neurovascular coil. Imaging consisted of two-dimensional axial T_{2*} gradient echo (GRE) and two-dimensional axial diffusion weighted imaging (DWI) echo planar imaging (EPI) sequences. Multi-echo T_{2*} GRE ($0.65 \times 0.65 \times 5$ mm^3, TE = 7.1ms, TR = 753ms, flip angle = 28°) scans were acquired to obtain high-resolution anatomical images for visualization of the spinal cord white and gray matter. This sequence nicely shows the classic hyperintense "butterfly" of the gray matter surrounded by white matter in a healthy spinal cord[24] which allows for segmentation and co-registration. This sequence is also sensitive to locating hyperintense focal MS spinal cord lesions[24] (Figure 1). Fat suppressed multi-shell DWI ($1.25 \times 1.25 \times 10$ mm^3, TE = 65ms, TR = 3000ms, 96 directions, b-values = 0 – 2855 s/mm^2) were used to perform IVIM calculations. The IVIM technique is extremely sensitive to high fluid velocities, such as those found in the nearby pulsatile cerebrospinal fluid[26]. To reduce this as well as other physiological factors DWI scans were cardiac triggered. T_{2*} and DWI were acquired axially with slice prescriptions centered at the C3/C4 intervertebral disc level. Local institutional review board approval and written informed consent were obtained prior to scanning.

Image analysis and processing:

Overview of image analysis and post-processing steps are shown in Figure 2. Segmentation, co-registration, and metric extraction were performed using the open-source spinal cord toolbox[38] (https://github.com/spinalcordtoolbox). Spinal cord segmentation was performed on the T_{2*} GRE and DWI using a convolutional neural network[39] to delineate the spinal cord. Using the spinal cord segmentation, a mask was then applied around the spinal cord so T_{2*} and DWI images could be cropped to remove unnecessary pixels outside of the vertebral column. Motion correction (MOCO) was performed on the DWI volumes[40]. T_{2*} GRE images underwent additional deep learning segmentation[41] to produce white matter (WM) and gray matter (GM) tissue specific regions of interests (ROI). The T_{2*}

GRE and DWI images were then co-registered together using a non-rigid registration to allow for the transformations of the anatomical ROIs from the T_{2*} GRE to the DWI and then ultimately to the IVIM parametric maps[42] (Figure 3). IVIM calculations were performed using the open source IVIM-tool box[26] (https://github.com/slevyrosetti/ivim-toolbox) one-step fitting model[43]. The one-step fitting model was chosen as it has shown better parameter estimation performance compared to the two-step model for both noisy and high signal-to-noise ratio (SNR) data[26]. IVIM metrics for perfusion fraction (f_{IVIM}), pseudo-diffusion coefficient (*D**), water diffusion coefficient in tissue (*D*), and signal without diffusion encoding (S_0, diffusion b-value = 0 s/mm^2) were computed on the motion corrected DWI data. Individual f_{IVIM}, D*, *D*, and S_0 maps were generated for each subject. To enable the extraction of the spinal cord (SC), white matter (WM), and gray matter (GM) aggregate ROI values, the warping field used in the co-registration of the T2* GRE and DWI MOCO was applied to the IVIM parametric maps. To increase the signal to noise ratio (SNR) IVIM parametric maps were averaged across vertebral levels C2-C4.

IVIM in the spinal cord has shown poor reliability when analyzed at the single subject and single slice level[26]. Similarly, it has been shown that calculation of IVIM metrics is highly dependent on SNR. Therefore, an atlas averaged cross-sectional analysis was conducted to determine SC, WM, and GM differences in IVIM-derived indices between the healthy and MS cohorts. Two-sample T-test was performed using MiniTab (Minitab 18 Statistical Software, State College, PA) on the mean f_{IVIM}, *D**, *D* values in the SC, WM, and GM between healthy controls and MS patients. Significance threshold was set at $p<0.05$.

Results:

No significant differences were found (Figure 4) between the healthy controls and MS patient groups in the SC, WM, or GM ROIs for any of the IVIM indices (f_{IVIM}, *D**, *D*). However, the WM ROI perfusion fraction (f_{IVIM}) and pseudo-diffusion (*D**) measurements came close to statistical significance with *p*-values of 0.082 and 0.055 respectively (Table 1). The WM ROI reached the highest significance for all three IVIM metrics analyzed whereas the GM ROI showed the lowest. Looking at all the ROIs the GM showed the highest perfusion fraction (f_{IVIM}) with the WM ROI being the lowest. This relationship was also seen for the pseudo-diffusion coefficient (*D**) with WM showing the lowest followed by the SC and the GM exhibiting the highest value.

Discussion:

In this study, we investigated the use of the PWI technique IVIM to assess microvascular perfusion and diffusion in the spinal cord of MS patients. Although not reaching the level of significance there are several findings of interest in this study. The SC, WM, and GM in the MS cohort showed reduced perfusion fraction and pseudo-diffusion coefficient compared to the healthy controls. IVIM has been used to assess the microcirculation of various organs[29-32], including the brain[28]. However, to our knowledge, there has been only one study that has looked at IVIM of the spinal cord and this is the first study utilizing IVIM in the spinal cord in a patient population[26]. Despite the paucity of IVIM spinal cord research, our findings suggest that IVIM has potential as a tool for assessing the microcirculation of the human spinal cord in MS.

Overall, our findings are consistent with the current PWI literature focused on MS in the brain. MS PWI findings have shown decreased cerebral blood flow (CBF) and cerebral blood volume (CBV) in chronic MS lesions when compared to NAWM and controls[15-17,44,45]. Gray matter in MS patients also showed

reduced perfusion when compared to healthy controls[8,10,46]. Although this hypoperfusion has not reported for active MS lesions[9,10]. GM perfusion fraction was higher than that of WM which is consistent with the current literature[26]. However, using IVIM Yin et al[47] observed a significantly elevated perfusion fraction for non-enhancing lesions compared to NAWM in regions proximal and distal to the chronic lesions.

Acquiring and processing the IVIM data in the spinal cord is one of the major obstacles[26] and reasons there are limited studies using PWI techniques for the assessment of MS lesions in the spinal cord compared to the brain[24]. One of the main challenges is the technical difficulty in obtaining and processing the IVIM data, which requires the use of high-resolution imaging, multiple b-values, and complex mathematical modeling. The IVIM biexponential model is a signal representation very sensitive to biases from patient and physiological motion[48]. Additionally, the interpretation of the IVIM parameters in the spinal cord can be difficult due to the limited understanding of the underlying microstructural changes and the potential confounding factors, such as the partial volume effect, B_0 and B_1 inhomogeneities[26]. Several factors restrict the conclusions that we can draw from this study due to its limitations. First, the number of subjects under study was small and all the MS patients were female. The large slice thickness employed in this study may have further convoluted the various effects within each voxel, increasing the errors. The IVIM literature also reports a large variation in perfusion fraction and pseudo-diffusion coefficient for white and gray matter in healthy controls[49].

In conclusion, IVIM is a promising imaging technique for the evaluation of the spinal cord in MS patients. It has the potential to provide valuable information on the microvascular perfusion and diffusion in the spinal cord, which may be related to the disease progression and response to treatment. However, further research is needed to improve the technical and methodological aspects of IVIM and to better understand the underlying microstructural changes and the potential confounding factors. Additionally, more studies comparing IVIM with other imaging techniques, such as conventional MRI and histopathology, are needed to establish the clinical utility of IVIM in the spinal cord of MS patients.

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