DTI and Tractography of the Normal Human Thigh: In-depth Analysis

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Introduction: Diffusion Tensor Imaging (DTI) is a novel advanced imaging modality currently used in clinical settings to evaluate structures in the central nervous system. Skeletal muscle, which consists of highly ordered elongated muscle fibers, has proven to be an ideal candidate for DTI studies. However, major primary skeletal muscle disorders (such as inflammatory myopathies or muscular dystrophies) have not been well studied with this novel imaging technique. The aim of this study is to explore the ability of DTI to investigate the functional architecture of normal thigh muscles and changes in various DTI parameters from the within the muscle compartments by optimizing a skeletal muscle DTI acquisition protocol.

Methods: Non-contrast bilateral thigh muscle MRIs were collected from 4 healthy normal volunteers using a 1.5 T *(Siemens, Erlangen, Germany)* MRI scanner with legs in a relaxed state. The routine MRI acquisition protocols included standard clinical sequences such as PDw, T1w and T2w images with MR parameters suitable to reflect water changes. An optimized DTI acquisition protocol was used to acquire thigh muscle images. DTI was collected using an echo-planar-SE sequence with diffusion weightings b = 0, 800 s/mm^2 along 6 non co-linear directions with TR/TE = 6200/104 ms, number of slices = 32 (enough to cover the thigh), imaging time = 2.0 - 4.0 min.

Figure 1: ADC maps before and after DTI sequence optimization showing higher signal-to-noise ratio on the right.

DTI data was analyzed with DTI-studio *(S. Mori, John Hopkins)* to generate tensors and ADC maps, perform fiber-tractography, and draw regions of interest (ROI). ROIs were drawn around: 1) anterior compartment (AC), 2) posterior compartment (PC), and 3) each muscle in AC and PC on 3 different non-contiguous slices of each thigh of the volunteer. Mean ± S.D. for each DTI parameter for each ROI, that included fiber count, density, length, fractional anisotropy (FA) on an FA map and along fibers, and apparent diffusion coefficient (ADC) on ADC map and along fibers were determined. Comparisons and statistical analyses were performed to explore the differences between the left (L) and right (R) thigh muscles and compartments over different subjects. The analysis included evaluating DTI parameter differences between: 1) a single slice and average of all slices; 2) left and right thigh; 3a) AC and PC using compartment ROIs; 3b) AC and PC comparing all ROIs within compartments; 4) average values from the sub-compartment muscle ROI (an average of all muscle ROIs within the compartment) and the entire compartment ROI for AC and PC. Statistical significance was based on p ≤ 0.05.

Figure 2: Representative slice of a normal thigh muscle showing axial cuts of PDw, ADC map and 3D fiber tractography. ADC maps illustrate that PC compartment has increased water diffusivity patterns compared to the AC. 3D fiber tracking enabled visualization of fiber tracts that run as a thick bundle in Head-Foot direction in the PC.

Results and Discussion: The optimized DTI sequence yielded high-quality MR images with reduced distortion and susceptibility artifacts *(Figure1)*. A clear delineation of white matter tractography was observed in the computed DTI images *(Figure 2)*. Comparisons and statistical analyses were performed to explore the changes between the thigh muscles and its compartments over different subjects. It was found that ratio of the differences in DTI parameter values between a single slice evaluation over multiple slices was very small ($1.4 \times 10^{-3} \pm 2.6 \times 10^{-3}$). It was also observed that there was insignificant difference between the DTI parameters obtained from the R and L thigh for an individual volunteer and all volunteers combined (p = 0.39 ± 0.1). Interestingly, there was a significant difference between AC and PC in terms of FA (map), ADC (map), and ADC along the fibers (p = $3.32 \times 10^{-4} \pm 5.64 \times 10^{-4}$). For the normal subjects, average ADC along fibers was observed to be higher in PC (0.98×10^{-3} mm^2/s) than AC (0.73×10^{-3} mm^2/s). However, there was no significant difference between the AC and PC in terms of FA along the fibers, fiber count, fiber length, and density values 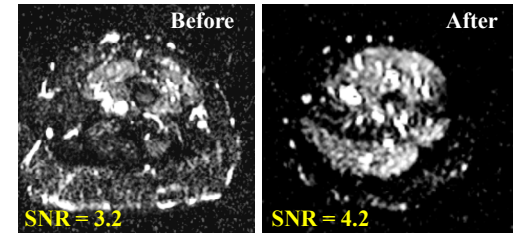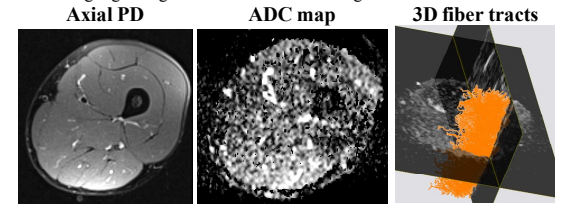of the AC and PC (p = 0.69 ± 0.24). There was a significant difference between AC and PC for FA (map) when comparing compartment ROIs (p= 1.63×10^{-3}), but no significant difference in any other parameter (p= 0.59 ± 0.27). Mean values for some of the relevant DTI parameters computed from a specific ROI on the AC and PC from R and L thighs are shown in **Table 1**. Possible explanations for

Table 1: Mean DTI parameters computed from AC and PC for both R and L thigh

Right Thigh	Mean ADC (x10⁻³ mm²/s)		Mean FA		Fiber Count	Fiber Length (mm)	Fiber density (fibers/pixel)
	ADC map-ROI	Along fibers	FA map-ROI	Along fibers			
Anterior Compartment	0.34 ± 0.14	0.71 ± 0.08	0.33 ± 0.08	0.73 ± 0.05	1092.78 ± 580.69	21.4 ± 5.57	4.12 ± 1.16
Posterior Compartment	0.59 ± 0.17	0.90 ± 0.21	0.46 ± 0.06	0.71 ± 0.05	1090.56 ± 443.52	20.75 ± 7.21	3.98 ± 1.04
Left Thigh	Mean ADC (x10⁻³ mm²/s)		Mean FA		Fiber Count	Fiber Length (mm)	Fiber density (fibers/pixel)
	ADC map-ROI	Along fibers	FA map-ROI	Along fibers			
Anterior Compartment	0.36 ± 0.12	0.76 ± 0.11	0.35 ± 0.09	0.71 ± 0.04	1333.11 ± 773.22	21.4 ± 5.57	4.12 ± 1.16
Posterior Compartment	0.61 ± 0.22	0.91 ± 0.22	0.49 ± 0.07	0.72 ± 0.07	1186.56 ± 873.21	20.75 ± 7.21	3.98 ± 1.04

these findings could be functional differences between the compartments, different levels of hydration, and different structural arrangements. We also did not observe any significant differences between the average DTI values from the sub-compartment muscle ROIs and a single ROI of the entire AC or PC compartment. (p = 0.41 ± 0.25 [AC], p = 0.57 ± 0.24 [PC]). Therefore we infer that the nervous, vascular, and connective tissues in the thigh muscle compartments do not appear to affect the values for the entire compartment to a significant extent. This result also shows us that a single compartment ROI can be used rather than multiple smaller ROIs over each compartment to evaluate pathological conditions that affect the thigh muscle. The similarity in L and R thigh DTI parameters will enable using DTI as a potentially biomarker to identify skeletal muscle disorders that occur as early focal abnormalities in a specific thigh.

Conclusion: We have been able to optimize and quantify DTI parameters in normal skeletal muscles and found significant measurable differences between skeletal muscles in different parts of the thigh. We were also able to demonstrate several quality control measures in analyzing DTI data of the thigh, such as the similarity between parameters in different thighs of a single patient and in different levels of the thigh. In the future, we hope to correlate these results with measureable differences between normal and diseased skeletal muscle. Application of these novel imaging markers may shed light on early detection, differential diagnosis and disease monitoring of various muscular pathological conditions such as inflammatory myopathies or muscular dystrophies.