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Dynamic diffusion tensor measurements in muscle tissue using Single Line Multiple Echo Diffusion Tensor Acquisition Technique at 3T

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Abstract

When diffusion biomarkers display transient changes, i.e. in muscle following exercise, traditional diffusion tensor imaging (DTI) methods lack temporal resolution to resolve the dynamics. This paper presents an MRI method for dynamic diffusion tensor acquisitions on a clinical 3T scanner. This method, SL-MEDITATE (Single Line Multiple Echo Diffusion Tensor Acquisition Technique) achieves a high temporal resolution (4s) (1) by rapid diffusion encoding through the acquisition of multiple echoes with unique diffusion sensitization and (2) by limiting the readout to a single line volume. The method is demonstrated in a rotating anisotropic phantom, in a flow phantom with adjustable flow speed, and in in vivo skeletal calf muscle of healthy volunteers following a plantar flexion exercise. The rotating and flow-varying phantom experiments show that SL-MEDITATE correctly identifies the rotation of the first diffusion eigenvector and the changes in diffusion tensor parameter magnitudes, respectively. Immediately following exercise, the in vivo mean diffusivity (MD) time-courses show, before the well-known increase, an initial decrease which is not typically observed in traditional DTI. In conclusion, SL-MEDITATE can be used to capture transient changes in tissue anisotropy in a single line. Future progress might allow for dynamic DTI when combined with appropriate k-space trajectories and compressed sensing reconstruction.

Keywords

Dynamic diffusion; DTI; Multiple Modulation Multiple Echo; Fast Acquisition; MEDITATE; skeletal muscle; exercise

Introduction

Diffusion tensor parameters (principal diffusivities (λ_1 , λ_2 and λ_3), mean diffusivity (MD) and fractional anisotropy (FA)) provide biomarkers of tissue anisotropy [1, 2], which have many applications in oriented anisotropic biological tissue (e.g. neural fibers [3], renal

tubules [4] and muscle tissue [5–8]). When these diffusion biomarkers display transient changes, as in muscle tissue following exercise (e.g. [9–13]), traditional diffusion tensor imaging (DTI) methods lack sufficient temporal resolution to resolve the dynamics of the DTI parameters. However, knowledge of diffusion biomarkers' dynamics can be useful as a differentiating diagnostic tool in pathologies which alter the dynamic response to stimuli, e.g. the post-exercise recovery of muscular dystrophies [14], myositis [15], or chronic exertional compartment syndrome [16, 17]. In this work, we aim to capture transient changes in tissue anisotropy with high temporal resolution and low spatial resolution using a linescan sequence with rapid diffusion encoding, Single Line Multiple Echo Diffusion Tensor Acquisition Technique (SL-MEDITATE) [18].

Dynamic diffusion tensor measurements find an interesting application in the dynamic changes and kinematic evolution of skeletal muscle tissue. Muscle dynamic behavior has been studied using a range of MR methods such as displacement encoding and spin tagging [7, 19], T_2 -relaxation [20, 21], BOLD-contrast [22–25], phosphorous spectroscopy [26–28] and Chemical Exchange Saturation Transfer (CEST) [29]. Several studies used diffusion MRI to sense subtle differences in muscle microstructure between different states of exertion [6,30–35] and pre- and post- exercise [9–11,13,16]. However, as they are limited to a single time point or coarsely timed measurements, the dynamics of the underlying microstructural changes are not yet clear, in particular immediately after cessation of the exercise [11]. Dynamic diffusion measurements of reactions to exertion may provide a unique microstructural view of muscle kinematics, potentially differentiating muscle disease activity (inflammatory processes whose effects may be reversible) and damage (a term encompassing structural alterations of the myofiber architecture that are generally irreversible) in complex muscle pathologies (dystrophy, compartment syndrome, dermatomyositis).

The SL-MEDITATE sequence acquires diffusion tensor information with a high temporal resolution, albeit with a lower spatial resolution. The high temporal resolution is driven by limiting the readout to a single line volume (Figure 1, [10, 36–39]). In addition, the high temporal resolution is facilitated by the rapid MEDITATE diffusion encoding which has been shown to be capable of acquiring apparent diffusion tensor maps in two scans in *in vivo* muscle tissue on a clinical 3T scanner [18]. This is achieved by modulating multiple echoes, generated by a train of RF-pulses, with different diffusion weighting in both magnitude and direction using a pattern of diffusion gradients. The MEDITATE sequence itself extends earlier non-clinical work [40–44] to clinical scanner platforms. This extension includes introducing extra RF-pulses in order to generate more high SNR echoes and exploiting longitudinal magnetization storage to reduce T_2 -weighting [18].

In this work, we demonstrate the feasibility of *in vivo* dynamic diffusion tensor measurements in human skeletal muscle. To this end, we first extend the previous MEDITATE-method [18] to a single line volume acquisition (Figure 1) and verify the volume selection. The capability of SL-MEDITATE to detect changes in diffusion parameters are then illustrated with a computer simulation in comparison to a more conventional temporal scheme of sequential directional sampling. Next, the validity of the method is demonstrated in a rotating anisotropic phantom (Supplementary material) and in a

flow phantom which displays diffusion magnitude changes. Finally, we apply the dynamic diffusion tensor measurement to study the post-exercise transient changes in *in vivo* human skeletal calf muscle of healthy volunteers.

Methods

SL-MEDITATE

(SL)-MEDITATE employs five RF-pulses and a pattern of diffusion gradients on three axes to generate 13 echoes (Figure 1), each encoded with a different diffusion weighting and direction [18, 40, 43]. As a result, two scans acquired with different diffusion weighting strengths suffice to isolate the diffusion weighting from T_1 , T_2 and proton density effects and to accurately estimate DTI-parameters. As described in previous work [18], the full b-matrix is calculated from the difference of b-matrices in the two scans, including both the diffusion gradients and the imaging gradients used for spatial localization. The diffusion gradients were optimized to minimize the condition number [45], a scalar metric quantifying the diffusion sampling quality; an optimal condition number of 4.42 was found. In addition, the RF-pulse flip angles were optimized to evenly distribute the available magnetization over the echoes taking into account the T_1 and T_2 relaxation times of *in vivo* human muscle tissue (muscle $T_1 = 1420 \pm 38.1$ ms, $T_2 = 32 \pm 2$ ms at 3T [46]). A single excitation line volume is selected by applying slice selection gradients along two directions [10, 37–39]. The final dimension of localization is achieved by limiting analysis to a subset of pixels along the linescan axis (Figure 2).

Experimental parameters

All images in this work were acquired using a 3T wide-bore Siemens MAGNETOM Skyra scanner (Siemens AG, Healthcare Sector, Erlangen, Germany) with a 15-channel unilateral knee coil (QED, Mayfield Village, OH, USA). SL-MEDITATE acquisitions had a repetition time TR of 2000 ms (phantoms)/1000 ms (*in vivo*) (hence, one diffusion tensor measurement per 4s/2s), a selected line dimension of $30 \times 30 \times 190$ mm (effective line dimension of $50 \times 62 \times 190$ mm (Figure 2)), a matrix size of 64 along the frequency encoding or linescan direction, flip angles $\alpha_1/\alpha_2/\alpha_3/\alpha_4/\alpha_5$ of $61^\circ/73^\circ/85^\circ/45^\circ/85^\circ$ and echo times of 90 – 245 ms. Only the latter 11 echoes were used due to minimal diffusion weighting of the first 2 echoes. The median isotropic b-value encoded in the echoes was 388 s/mm^2 (range 167–790 s/mm^2 , for the high diffusion-weighting scan, range 6–91 s/mm^2 for the reference scan), in accordance with the literature of *in vivo* skeletal muscle DTI [5, 6, 31, 47–50]. For all MEDITATE scans in this work, the excitation line was oriented anterior-posteriorly and placed using a gradient echo localizer image (Figure 2). Comparisons of accuracy were performed with single time point data acquired with standard twice-refocused spin echo TRSE-DTI (TR/TE = 7400/59 ms, $3 \times 3 \times 10$ mm resolution, 6 directions, b = 0, 500 s/mm^2 , 3 averages, 2:59 min) [51]. The SL-MEDITATE sequence was validated in three systems: an anisotropic rotating phantom (rotating asparagus stalks, Supplementary material), a dynamic flow phantom and *in vivo* calf muscles of healthy volunteers.

Linescan volume validation

In a set of validation scans, the selection of the line volume was verified by introducing phase encoding to the SL-MEDITATE sequence. Images were acquired by reading along the line volume and adding phase encoding, in two separate scans, to the two directions orthogonal to the line. In a third acquisition, the readout direction was also placed orthogonal to the line volume (Figure 2). While the spatial extent of images differed amongst the echoes in the MEDITATE train, the average was computed and illustrated as an approximate characterization of the SL-MEDITATE sensitization volume.

Simulations

The impulse response of the dynamic SL-MEDITATE acquisitions was simulated to estimate the impact of the different diffusion times of each echo and of measurement SNR. Input diffusion parameters $D(t)$ were calculated according to a short-time $\sqrt{t}$ -expansion [52,53] using male human calf muscle parameters (fiber size 61 μm , membrane permeability 20 $\mu\text{m/s}$, D_0 1.52 $\mu\text{m}^2/\text{ms}$; these parameter choices induce a fractional anisotropy (FA) of 0.4 at the diffusion time of $t = 1$ s.) [54,55]). For the simulation, echo amplitudes were generated and fitted for each timepoint using the sequence parameters and signal equations [18]. These simulations were repeated for different SNR-levels with Rician noise added to the echo amplitudes, using 400 samples for each timepoint at each SNR-level. The resulting dynamic diffusion parameters are compared with the dynamic input diffusion parameters at one diffusion time appropriate for each experimental scheme under consideration, here chosen to be $\Delta t = 200\text{ms}$ (SL-MEDITATE)/ $\Delta t = 59\text{ms}$ (TRSE). Several impulse changes of 10% were prescribed in the simulations: stepwise (1) axial, (2) radial and (3) both axial and radial diffusion increase; transient (4) simultaneous axial increase and radial decrease, and transient (5) axial increase followed by radial increase. Finally, simulations included the effect of pulse sequence structure on the processing of dynamic DTI information. The two pulse sequence structures compared were the MEDITATE pulse sequence and a conventional TRSE sequence. For the same input dynamic tensor evolution, data was gathered to estimate DTI metrics according to each sequence's structure. Namely, for TRSE, the 6 directions + 1 b_0 volume were derived from the nearest 7 timepoints to the timepoint of interest, sharing data over 7 timeframes. For MEDITATE, the tensor was estimated from two timepoints (weighted and unweighted) since all of its directions are contained in one scan. In this way, both the conditioning of each sequence's inversion and their required temporal sharing were included in the simulations.

Anisotropic rotating phantom

The anisotropic phantom consisted of asparagus stalks (dayfresh from a local grocery store; Organic produce from Peru) with the voids in between filled with agar gel (3.5%(w/w) agar (UltraPure Agarose, Invitrogen, Carlsbad, CA, USA)). The asparagus stalks were submerged in tap water (1h), after which they were cut to length and stacked parallel in a plastic container. This container was then mounted in an in-house constructed Perspex holder which fits tightly in the knee coil and allows precise rotation of the asparagus stalks by manual handling of a pulley system (Supplementary figure 1a). By virtue of its rotation capability,

this phantom was used to verify the angular precision and accuracy of the SL-MEDITATE sequence. (More details in Supplementary material.)

Dynamic flow phantom

A dynamic flow phantom [56] was used to verify the ability of the SL-MEDITATE sequence to detect changes in the magnitude of diffusion tensor parameters. This phantom was constructed by encapsulating a cellulose sponge (3M professional extralarge commercial size sponge O-cel-O (Tonawanda, NY)) trimmed down to dimensions $2.5 \times 2.5 \times 10 \text{ cm}^3$ with a mass density of $28.8 \text{ } \mu\text{g}/\text{cm}^3$ in a polyvinyl chloride (PVC) pipe (Figure 4a). The latter was attached to a peristaltic pump using Tygon[®] tubing and submerged in a reservoir of copper sulfate (CuSO_4)-doped water. Pressure transducer probes were placed in the tubing proximally and distally of the phantom, measuring the pressure difference by interfacing to a digital acquisition system (Powerlab 8/30, AD instruments, Inc, Colorado Springs, CO) (Figure 4a). Assuming a linear impedance behavior of the sponge, these pressure differences were designated as markers of the flow speed. The phantom setup used in this work is similar to a flow phantom used recently to simulate intravoxel incoherent motion (IVIM) MRI in tumor microvasculature [56]. It was shown that the phantom showed a nearly linear increase of apparent diffusivity with the pressure difference, as the flow through the sponge increased [56]. For this work, the diffusion tensor parameters in the sponge were measured during stepwise increases in the flow rate: one continuous SL-MEDITATE measurement during 2 minute stepwise flow increments and one protocol alternating TRSE-EPI and SL-MEDITATE measurements during 4 minute stepwise increments. In post-processing, a central region of 8.9 mm of the parametric line was sampled for SL-MEDITATE, and a circle with diameter 8.3 mm from the TRSE-DTI parametric maps was sampled for TRSE-DTI.

In vivo experiments

Dynamic SL-MEDITATE measurements of the right calf muscles were collected in healthy volunteers (3 male/4 female, age $27.5 \pm 4.3 \text{ y/o}$, BMI 23.2 ± 5.0) under a HIPAA-compliant research protocol with written informed consent approved by the local institutional review board. The calf muscles were scanned before and after a two minute plantar-flexion exercise against an exercise rubber band with cardiac-gating (ECG-triggered, trigger delay of 600–700ms from the R-wave). The trigger delay, i.e. the time between the ECG-trigger and the diastole in the muscle, was chosen for each volunteer based on a phase-contrast MRI of the same slice with the following parameters: TR/TE = 33/3.56ms, $1.44 \times 1.44 \times 10 \text{ mm}$ resolution, 23 phases, velocity encoding of 80 cm/s through plane, 0:24 min). Using vendor-supplied software, an ROI was placed on a large vessel and a time-course of the fluid velocity was inspected to determine the diastolic period in which MEDITATE data is collected. The excitation line was localized medially of the tibia in the anterior-posterior direction, thus sampling mainly the Gastrocnemius Medialis and Soleus muscles. An example placement of the linescan is shown in Figure 2. The nominal region of selection as determined by the prescribed slice widths is indicated, as is the enlarged selection volume identified in the spatial selection validation scans. For the longer *in vivo* dynamic measurements, the drift in the static applied 3T magnetic field [57] was mitigated by

subdividing the measurement in shorter sequences, forcing a frequency adjustment at every scan ($\pm 2:45 - 3:00$ min).

Data processing

The datasets were processed offline (Matlab, Mathworks) to extract diffusion tensor parameters as described previously [18] in a time-resolved manner. All diffusion gradients and imaging gradients are taken into account in determining the diffusion-encoding matrices (b-matrices) in this analysis. To improve signal to noise ratio, outliers were rejected ($> 30\%$ deviation from a smoothed time curve, $\pm 5\%$ of the points) and the time-curves were smoothed temporally (Gaussian filter, width 5 time-points = ± 10 s). In addition, when the ECG-trigger skipped a cardiac cycle, leading to increased TR and signal amplitude, the average amplitude of the echoes in the readout train was normalized to that of its temporal neighbors with equivalent weighting. Diffusion tensors were fitted to the diffusion weighted signals using a cylindrical tensor model [58] ($(\lambda_1, \lambda_2, \lambda_3) \rightarrow (\lambda_{axial}, \lambda_{radial}, \lambda_{radial})$). Regions of interest (ROI) were selected, averaging the diffusion tensor parameters over the ROI. ROIs were sampled including both Gastrocnemius Medialis and Soleus tissue (11.4 ± 2.1 voxels = 33.8 ± 6.2 mm along the line).

The *in vivo* post-exercise SL-MEDITATE diffusion parameter time-courses were fitted (non-linear least-squares fit, Matlab, Mathworks) using an empirical model function

$$f(t) = g(t) + l(t) = \left[PV \left(\frac{t}{TTP} \right)^\alpha e^{\alpha(1 - \frac{t}{TTP})} \right] + [l_0 + l_1 t] \quad (1)$$

which is the sum of a gamma variate function $g(t)$ and a linear function $l(t)$ [25,28,59,60]. The latter models signal drift over the long measurement time and was found to be necessary to obtain precise fits of the temporal response curves. In the gamma variate function $g(t)$, PV scales the function to the peak value, TTP is the peak time and α determines the rate of increase and recovery of the diffusion parameter. This empirical model function stems from observations of bolus transit patterns when tracer flows downstream of an injection point [59]. It has been successfully used to describe dynamic contrast enhanced MRI data in the brain [59], dynamic BOLD MRI of reactive hyperemia [60] and post-exercise recovery in skeletal muscle [25]. In this work, the transient changes in diffusion tensor parameters post-exercise are seen as a kind of bolus, described by the gamma variate function $g(t)$, in an interpretation similar to the use in BOLD MRI. Once fitted, the model function is used to derive parameters of post-exercise recovery [23,24,60] such as time to peak (TTP), Peak Value relative to the post-exercise value (PV) and peak value relative to the pre-exercise Baseline (PVTB). The pre-exercise diffusion parameter time-courses were averaged to generate a single value for use as the fitted pre-exercise values.

Results

Linescan volume validation

In the SL-MEDITATE sequence, a rectangular cuboid excitation volume is prescribed. Figure 2 illustrates the extent of the volume selected in a homogeneous agar gel phantom alongside localizer images of the same object, as well as overlaid onto a typical anatomical

calf image for reference. These measurements show that the excitation volume is a rectangular cuboid, though wider than the prescribed volumes (50×62 mm vs 30×30 mm).

Simulations

The simulated impact of the different echo times of SL-MEDITATE, SNR, and sequence structure on diffusion parameter changes measured with SL-MEDITATE is summarized in Figure 3a. In this figure, the responses to five different impulses, at two SNR-levels ($\text{SNR} = \pm 110$ and $\text{SNR} = \pm 22$), are plotted alongside the input diffusion parameters (dotted line) as calculated at a diffusion time of $\Delta = 200$ ms. As the SNR decreases, the absolute eigenvalues split further apart and the FA increases, though relative changes in the eigenvalues are still detectable. For the first three, stepwise, changes in eigenvalues (λ_{axial} , λ_{radial}) and MD, the changes are clearly identifiable at both SNR-levels, however, the resulting jumps in FA are not as conspicuous at the lower SNR level. It can also be seen that the amplitude of the detected jump (in % change) depends to a certain extent on the SNR level due to the eigenvalue splitting. For the stepwise increase in MD: MD / λ_{axial} / λ_{radial} , 9.99% / 9.76% / 10.18% at SNR 109 and 9.46% / 8.69% / 10.39% at SNR 22 vs the 10.00% / 10.00% / 10.00% simulated changes. In the fourth and fifth impulse response, which include opposite changes in λ_{axial} and λ_{radial} , the transient nature of the impulse is also perceptible. The latter impulse response, with delayed changes in λ_{axial} and λ_{radial} boasts a signature shape in the MD time trace. In general, these simulations show that the SL-MEDITATE sequence is able to identify transient changes in the diffusion tensor parameters, even at lower SNR.

In contrast to SL-MEDITATE, the simulated impulse responses (Figure 3b) of the simple approach to dynamic DTI, temporal sharing of TRSE-EPI images (1 b_0 and 6 diffusion directions, Figure 1), illustrate that this approach does not correctly identify the simulated transient changes. The stepwise changes in the eigenvalues are registered with a delay, and the last two, transient, impulse responses display stepwise jumps in the tensor parameters. As will be elaborated upon in the Discussion, the latter effect stems from the sliding window temporal sharing of data over a longer time period than the MEDITATE scheme.

Anisotropic rotating phantom

Measurements of an anisotropic rotating phantom illustrate the correct identification of the directionality of the first diffusion eigenvector (expressed in terms of the azimuthal angle) of rotating asparagus stalks (Supplementary figure 1a) in a dynamic diffusion tensor measurement. The SL-MEDITATE dynamic eigenvector direction agrees with the manually set orientations of the asparagus stalks and the static TRSE-EPI results recorded during a separate run (TRSE scan time 2:59 min, SL-MEDITATE time point 4 s). At an orientation of 150° there was a discrepancy between set and measured orientation. Scalar metrics compared favorably at each angular position between the MEDITATE and TRSE results. Specifically, for SL-MEDITATE, total variation and normalized standard deviation, respectively, were 11.6% / 2.9% for axial diffusion and 19.7% / 6.7% for radial diffusion, while for TRSE these values were 11.4% / 5.0% and 12.5% / 4.7%.

Dynamic flow phantom

Magnitude changes in diffusion tensor parameters were generated with the stepwise increase of flow in a sponge phantom (Figure 4a) and measured with SL-MEDITATE (Figures 4b and 5) and TRSE-EPI (Figure 5). The dynamic timecourses (Figure 4b) of the diffusion tensor parameters measured with SL-MEDITATE illustrate the stepwise increases in MD, λ_{axial} , λ_{radial} and FA upon increments of the flow through the sponge. Moreover, the SL-MEDITATE sequence also identifies the oscillations due to increasingly non-linear flow in the sponge at higher pressure differences. The linear relationships between the pressure difference and the diffusion tensor measures are plotted in Figure 5. When increasing the pressure difference, the flow through the sponge and consequently the apparent diffusion indices increase. As a result of the directionality of the flow, λ_{axial} rises faster than λ_{radial} which correspondingly increases FA. These increasing trends with pressure differences can be seen in the results of both TRSE-EPI (Figure 5a and 5c) and SL-MEDITATE (Figure 5b and 5d) measurements; however the magnitudes of the TRSE-EPI results are consistently higher than those of SL-MEDITATE due to the differences in echo times (59 ms vs. 90–245 ms) and b-value range (500 vs. 179–790 s/mm²) which make SL-MEDITATE differently sensitive to the IVIM-component of the diffusion signal. Specifically, the MEDITATE sequence omits some lower b-value signals that are the most flow sensitive, but also may include artifacts from the assumption of Gaussian diffusion in all echoes despite the non-Gaussian IVIM flow effects.

In vivo experiments

The *in vivo* measurements exhibit an average SNR over the last 5 unweighted echoes of 35.5 ± 10.4 . Figure 6a shows the dynamic percentage change in MD, measured with SL-MEDITATE, before and immediately after a 2 min plantar flexion exercise relative to baseline levels of *in vivo* calf muscles of a healthy volunteer. The post-exercise dynamic MD time-courses of each individual volunteer (Figure 6a) can be fitted to the empirical model function Eq. (1). The mean and standard deviation of the parameters of this model function (1) fitted to the λ_{axial} and λ_{radial} time-courses are listed in Table 1. The results of several volunteers (Figure 6c–e), indicate a large inter-volunteer variability. However, the average time-course and its confidence intervals (Figure 6c–e) point to a common behavior in agreement with the low temporal resolution results in literature (e.g. [9–11]) and static TRSE-DTI (Figure 6, before and after the dynamic measurements).

Discussion

The SL-MEDITATE method is capable of dynamic diffusion tensor measurements with high temporal resolution. This increased temporal resolution is facilitated by rapid diffusion encoding (MEDITATE [18,40,43]) and reduced spatial resolution, i.e. selecting a single line volume (Figure 1). SL-MEDITATE is shown to be sensitive to changes in diffusion direction (Supplementary Figure 1) and in diffusion magnitude (Figures 3, 4 and 5) in computer simulations and in phantoms with a temporal resolution of 4 s. Moreover, SL-MEDITATE also detects the transients in diffusion tensor parameters in *in vivo* skeletal muscle after exercise with a temporal resolution of 4 cardiac cycles (ECG-gating) (Figures 6).

The validity of dynamic diffusion tensor measurements with SL-MEDITATE is illustrated by computer simulations and phantom measurements. The computer simulations show that, although low SNR might split the eigenvalues and obscure changes in FA, transient relative changes in MD, λ_{axial} and λ_{radial} are correctly identified. In the rotating anisotropic phantom (Supplementary figure 1), the orientation of the first diffusion eigenvector rotates with the phantom, as correctly identified by TRSE-DTI and by SL-MEDITATE; the latter with a higher temporal resolution. One exception is the 150° position. This discrepancy stems from the underlying MEDITATE diffusion encoding scheme [18] which has a higher directional variance than e.g. the 6 direction dual-gradient sampling scheme of the TRSE sequence [61]. Similarly, in the flow phantom the magnitude changes in MD, λ_{axial} , λ_{radial} and FA, associated with changes in flow through the phantom, are detected both by TRSE-DTI and SL-MEDITATE; the latter again with a higher temporal resolution (Figure 4). Absolute values differ between the sequences, likely because of their different sampling of the non-Gaussian IVIM response of the flow phantom. However, since dynamic measurements of muscle kinematic behavior are often considered as relative changes, these systematic biases do not limit the applicability of SL-MEDITATE.

The *in vivo* dynamic diffusion tensor time-courses (Figure 6) show the capability of the SL-MEDITATE sequence to sample transient diffusion changes in human skeletal muscle. These time-courses were recorded before and immediately after a 2 min plantar flexion exercise of healthy volunteers. Notwithstanding the large inter-volunteer variability, the average post-exercise recovery pattern is clear with an initial decrease in MD and λ_{axial} followed by a return to baseline level for MD and slightly increased level for λ_{axial} . In contrast, λ_{radial} exhibits an immediate post-exercise increase before returning to baseline. The initial drop in MD and the slow return to baseline after the MD peak are in agreement with low temporal resolution DTI results in literature (initial drop, [11]; slow equilibration: [9, 10]).

The time-courses also reveal the different dynamics of the eigenvalues, with λ_{radial} peaking earlier and returning more quickly to equilibrium than λ_{axial} . λ_{axial} represents the diffusion along the main direction of the muscle fiber while λ_{radial} senses the diffusion restrictions perpendicular to the fibers [6,9,34,62]. Given the alignment of the myofibers and microvasculature in skeletal muscle, λ_{axial} is highly sensitive to changes in microvascular flow [63]. Similarly, λ_{radial} is highly sensitive to the size and integrity of the myofiber membranes (sarcolemma). With this interpretation, the results presented here suggest that there is a short-lived transient increase in the water content and size of the fibers, resulting in an increased λ_{radial} . Simultaneously, after an initial drop, the vascular supply to the muscle fibers, which contributes to λ_{axial} , increases and remains at an elevated level compared to pre-exercise for the duration of our experiment. It should also be noted that these results were obtained with brief and moderate exercise which can be achieved in supine position on the scanner bed. Longer and/or vigorous exercise is known to induce long-lived diffusion changes, particularly involving elevations of the radial diffusivity [16, 18]. Long term exercise also has been studied in detail in the literature, highlighting slow hypertrophy of muscle fibers with training [64]. The dynamic data in this study suggests there are also short term hypertrophic changes with any exercise session.

The dynamic MD time-courses of the different volunteers show a large variability due to the insufficiently standardized plantar flexion exercise and the different levels of fitness of the volunteers. Given the setup, plantar flexion against a rubber band, the intensity of the exercise depends on volunteer capability, motivation and individual strenuousness judgment. This variability can be minimized by the use of an ergometer setup with a load relative to the capabilities of the volunteers (e.g. [10, 11]).

The MEDITATE diffusion encoding and analysis scheme has a number of limitations. As mentioned before, the directional variance of the diffusion encoding [61] is higher than e.g. the 6 direction dual-gradient sampling scheme of the TRSE sequence [18]. However, for *in vivo* skeletal muscle measurements this issue can be managed since it is mainly problematic in specific tensor directions. When considering time-dependent diffusion, computer simulations show that, although the MEDITATE diffusion encoding scheme is sensitive to diffusion time-dependence when it is pronounced over the echotime range used, the effect is limited for *in vivo* skeletal muscle [18]. In addition, the specific multiple echo structure of the (SL)-MEDITATE diffusion encoding scheme prohibits the definition of a single effective diffusion time, although an effective diffusion time can be derived for each individual echo [18, 65]. The absence of a single effective diffusion time might hamper comparison with other methods. Furthermore, the SPAIR fat suppression method, though empirically determined to provide the best performance compared to frequency selective fat suppression, may be suboptimal for some echoes in the MEDITATE train. Other fat suppression methods may provide improved performance. On the analysis side, the cylindrical model is an approximation to DTI metrics in skeletal muscle, where differences in secondary and tertiary eigenvalues have been observed [47, 66]. Given the primary focus on dynamics with MEDITATE, we adopt this approximation to increase precision and retain differentiation of axial/radial diffusion. Finally, as previously mentioned, IVIM effects are not currently captured in the MEDITATE analysis scheme.

The rectangular cuboid volume selection excites a volume wider than the prescribed volume due to the imperfection of the slice selection and the different magnetization history of the echoes' coherence pathways. This extension of the prescribed volume in the directions orthogonal to the selected line is not problematic in the experiments presented here since both phantoms and the *in vivo* tissue expand beyond the prescribed volume. Notwithstanding this, care should be taken in selecting the prescribed volume. An additional limitation of the single line volume selection is the uncertain localization upon subject movement. In our experiments, additional localizer images confirmed that this effect was limited to a few millimeters. Furthermore, given the size of the selection volume, the possibility of contributions from flow in large vessels cannot be completely excluded.

Skeletal muscle has long been known to show an increased T_2 after exercise [9,10,67–69]. This is attributed to changes in water content [9,10] and to a lesser extent on temperature increase in exercising muscle [9] which can be as high as 6 °C in strenuous exercises [9]. Recently, it has been shown that a higher muscle T_2 results in higher SNR since diffusion-weighted images are intrinsically T_2 weighted [70]. If the baseline behavior is SNR limited and thus the diffusion eigenvalues are artificially separated by eigenvalue repulsion, increased SNR can lead to reduced λ_{axial} and FA and increased λ_3 . Hence, when interpreting

dynamic diffusion tensor time-courses of *in vivo* muscle following exercise, care has to be taken to not overlook this confounding effect. However, the diffusion changes both in this article and in substantial previous literature are supported by sufficient SNR to identify changes in diffusivity parameters separate from SNR levels and relaxation weighting. Also, while the 2-scan MEDITATE normalization scheme separates the variable relaxation weighting from diffusion weighting, coupled compartmental diffusion / relaxation effects may be a source of error to the MEDITATE analysis. However, for the range of echo times considered here, we expect that only the majority T_2 relaxation component of skeletal muscle of 30–50 ms is relevant [71] so this effect should be minimal.

Dynamic diffusion tensor measurement can potentially be used as a diagnostic tool in pathologies which alter the basic dynamic response to stimuli or in transient phenomena such as muscle fatigue, exertion, or reperfusion. Potential applications are muscular dystrophies [14], myositis [15] and chronic exertional compartment syndrome [16,17]. In successive developments, the accelerated diffusion encoding of MEDITATE might allow for dynamic DTI when combined with an appropriate k-space trajectory employing self-navigation [72, 73] and/or compressed sensing reconstruction [74, 75].

In conclusion, we present an MRI method, SL-MEDITATE, for the dynamic acquisition of diffusion tensor parameters with high temporal resolution. This high temporal resolution is facilitated by reduced spatial resolution using a linescan approach and by rapid diffusion encoding. MEDITATE encodes several echoes each with a different diffusion weighting in both magnitude and direction allowing acquisition of the diffusion tensor in two readouts. In a rotating anisotropic phantom SL-MEDITATE followed the rotation of the first diffusion eigenvector, while in a flow phantom SL-MEDITATE correctly identified stepwise increases in the directional diffusion magnitudes. In addition, in *in vivo* skeletal muscle of healthy volunteers, time-courses were recorded of diffusion tensor parameters before and after exercise. These time-courses show an increase in radial diffusion and a decrease in axial diffusion which is not typically observed since traditional DTI methods lack temporal resolution and fast DWI methods lack sensitivity to anisotropy. Hence, the dynamic diffusion tensor measurement method, SL-MEDITATE, can be used to measure transient changes in radial and axial diffusivities independently in phenomena such as muscle fatigue, exertion, or reperfusion with more temporal detail than previously possible.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BOLD

Blood Oxygen Level Dependent

CEST	Chemical Exchange Saturation Transfer
DTI	Diffusion Tensor Imaging
ECG	ElectroCardioGram
EPI	Echo-planar Imaging
FA	Fractional Anisotropy
GM	Gastrocnemius Medialis
IVIM	Intravoxel Incoherent Motion
MD	Mean diffusivity
MEDITATE	Multiple Echo Diffusion Tensor Acquisition Technique
PV	Peak Value
PVTB	Peak Value To Baseline
SL-MEDITATE	Single Line Multiple Echo Diffusion Tensor Acquisition Technique
SNR	Signal to Noise Ratio
SOL	Soleus
TRSE	Twice Refocused Spin Echo
TTP	Time To Peak

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Figure 1.

(a) Single Line MEDITATE sequence (SL-MEDITATE). Five RF pulses generate 13 echoes, each of which encodes a diffusion weighting and direction in three dimensions as determined by diffusion gradients (not shown). A linescan volume is selected by applying slice selection in two orthogonal directions, eventually allowing selection of a region of interest. Dynamic diffusion tensor measurements are obtained by repeated SL-MEDITATE acquisitions. (b) Two SL-MEDITATE repetitions acquired with different diffusion gradients suffice to calculate the diffusion tensor (using the 11 echoes with strongest diffusion weighting), a dynamic advantage over traditional spin echo diffusion tensor measurements which need 7 repetitions.

Figure 2.

Verification of SL-MEDITATE line selection in a homogeneous agar gel phantom. The selection of the excitation volume, i.e. the mean normalized selected volume of all echoes, along the read direction is illustrated in three planes (read-phase, slice-read, and slice-phase) relative to the prescribed excitation volume (red dotted lines). The selection profiles in phase (green) and slice (blue) directions are compared with the prescribed linescan volume (red dotted lines). Adjacent, localizer images are plotted of the same planes in the homogeneous agar gel phantom and in *in vivo* calf muscle. In the latter localizer images, the placement of the mean normalized selected excitation volume is superposed on the anatomy to illustrate the line selection *in vivo*.

a) SL-MEDITATE

b) TRSE-EPI

Figure 3.

Simulation of the impulse responses as would be measured with the SL-MEDITATE (a) and a TRSE-EPI (b) sequence: mean diffusivity (MD), eigenvalues (λ_{axial} , λ_{radial}) and fractional anisotropy (FA) in reaction to stepwise increases (10%) in λ_{axial} , λ_{radial} and MD ($\lambda_{axial} \uparrow$, $\lambda_{radial} \uparrow$) and simultaneous and delayed relaxation responses to an impulse ($\lambda_{axial} \downarrow$, $\lambda_{radial} \uparrow$). The diffusion parameters (mean calculated from 400 samples) at two SNR levels (squares: SNR = ± 110 , diamonds: SNR = ± 22) are compared to the input diffusion parameters (dotted lines).

Figure 4.

(a) Schematic of an MRI-compatible flow phantom. Water is pumped through a sponge with an adjustable pressure difference (distal pressure - proximal pressure), diffusion tensor parameters are measured using the SL-MEDITATE sequence. (b) Time-courses of MD, λ_{axial} , λ_{radial} and FA (dotted lines, left Y-axis) in the sponge of the flow phantom as measured by the SV-MEDITATE sequence. In each plot the pressure difference time-course (gray lines, right Y-axis) illustrates the stepwise evolution of the water flow through the phantom (2 min steps).

Figure 5.

MD, λ_{axial} , λ_{radial} and FA, measured in the flow phantom (Figure 4a) by TRSE-EPI ((a) and (c)) and SL-MEDITATE ((b) and (d)), plotted as a function of the water pressure difference over the sponge of the flow phantom (Figure 4). Mean and standard deviation are calculated over time (SL-MEDITATE and pressure) or ROI (TRSE-EPI), linear fits are added to aid visual interpretation.

Figure 6.

In vivo dynamic diffusion tensor measurements of the the Gastrocnemius Medialis (GM) and Soleus (Sol) muscles of healthy volunteers before and after a 2 minute plantar flexion exercise as measured by SL-MEDITATE. SL-MEDITATE measurements are compared to TRSE-EPI results before and after the dynamic time-course. Percentage MD (a), λ_{axial} and λ_{radial} (b) changes relative to the pre-exercise baseline in a representative single volunteer and average time-course of 7 volunteers of MD (c), λ_{axial} (d) and λ_{radial} (e). A gamma-variate model function (1), functional form and parameters indicated in (a) is fitted to the

post-exercise time-course of single volunteer data (a,b) and to the average time-course of 7 volunteers (c,d,e).

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Table 1

Mean and standard deviation of the model function parameters (Eq. 1) of the recovery of dynamic diffusion tensor parameters λ_{axial} and λ_{radial} after a 2 min plantar flexion exercise over 7 healthy volunteers (percentage difference to the pre-exercise baseline). Post-exercise Time To Peak (TTP), the Peak Value relative to the post-exercise value (PV) and relative to the pre-exercise Baseline (PVTB), and the linear term of the signal drift of the Gastrocnemius Medialis and Soleus averaged together are shown.

	λ_{axial}	λ_{radial}
TTP [s]	405 ± 355	265 ± 329
PV [%]	4.37 ± 18.94	6.95 ± 10.93
PVTB [%]	2.04 ± 22.18	5.75 ± 13.21
α [-]	1.51 ± 0.57	2.04 ± 2.09
l_{-1} [-]	0.003 ± 0.027	0.004 ± 0.018