Muscle Functional MRI as an imaging tool to evaluate muscle activity

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Synopsis

Muscle functional MRI (mfMRI) is an innovative technique that offers a non-invasive method to quantify changes in muscle physiology following the performance of exercise. The mfMRI-technique is based on signal intensity changes due to increases in the relaxation time (T2) of tissue water. In contemporary practice, mfMRI has proven to be an excellent tool for assessing the extent of muscle activation following the performance of a task and for the evaluation of neuromuscular adaptations as a result of therapeutic interventions. This article focuses on the underlying mechanisms and methods of mfMRI, discusses the validity and advantages of the method, and provides an overview of studies in which mfMRI is used to evaluate the effect of exercise and exercise training on muscle activity in both experimental and clinical studies.

Key words: exercise, magnetic resonance imaging, muscle

Dysfunction of the muscular system seems to play an important role in the occurrence, persistence or recurrence of associated pain and disability in individuals with musculoskeletal disorders. Changes in the physical structure (atrophy[19], fat infiltration[23, 25], muscle fiber type transformation[57]) and behavior of muscles (timing and activation level[7, 58]) are commonly observed and measured. Pertinent to clinical practice, programs to retrain muscle function have shown favorable responses in terms of improvements in pain, disability, and function. [17, 36, 59] Physical therapists must be able to use knowledge of the structure and function of the muscular system in order to accurately plan and evaluate the efficacy of therapeutic measures. Therefore, contemporary methods to understand the anatomy and physiology of the musculoskeletal system are needed.

The advent of modern imaging technology offers a variety of approaches for quantifying muscle structure and function.[54] In particular, magnetic resonance imaging (MRI) is frequently used to investigate anatomical information. In addition to its excellent spatial resolution, which permits good quality imaging of muscle structure, MRI offers a non-invasive method to quantify changes in muscle physiology following the performance of exercise. In particular, signal intensity changes due to increases in the relaxation time (T2) of tissue water can be measured to indicate exercise-induced activity of muscles.[40] This phenomenon was originally described in 1965, when Bratton et al[8] reported an increase in the T2 of isolated frog skeletal muscle following stimulated isometric contractions. Subsequently, Fleckenstein et al[31] reported the first similar phenomenon in living human subjects and as a consequence Fisher et al[29] suggested that this prolongation in T2 relaxation time could be used as a quantitative measurement for muscle activity. In contemporary practice this technique is referred to as muscle functional MRI (mfMRI) and has proven to be an excellent tool for assessing the extent of muscle activation following the performance of a task and for the evaluation of the neuromuscular adaptations as a result of therapeutic interventions.

The purpose of this article is to review the underlying mechanisms and methods of mfMRI, discuss the validity, reliability, advantages and limitations of the method, and provide an overview of studies in which mfMRI is used to evaluate the effect of exercise and exercise training on muscle activity in both experimental and clinical studies.

Mechanisms and methods of mfMRI

Basic principles of MRI.

An understanding of the basic mechanisms of mfMRI requires some discussion of nuclear magnetic resonance physics. A nuclear magnetic resonance signal arises from magnetic activity of hydrogen nuclei (protons) in tissue water and fat molecules.[43, 48] When a tissue is positioned in a strong magnetic field (B_0), the magnet bore of the scanner; most protons will align with that field and are then considered to be in a low-energy state. The result is a net magnetization vector along the longitudinal Z-axis. In this phase, the protons are in a state of equilibrium while spinning (precessing) at the frequency of the static magnetic field; B_0.

The protons become excited by the application of a radio frequency (RF) pulse (B_1) of a certain amplitude and time. Due to the RF pulse, the nuclei rotate so that the net magnetization flips from the longitudinal Z-axis into the transverse XY-plane. In addition, the pulse causes the nuclei to precess in phase in the XY-plane (phase-coherent oscillation). When the nuclei dephase, a detectable magnetic signal is generated and recorded. As protons prefer to be in a low energy state, they will emit their absorbed energy and return to the equilibrium state by re-aligning with the longitudinal Z-axis (the magnetic field; B_0). This process is called relaxation and can be divided in two independent parameters: T1 and T2 relaxation (FIGURE 1).

T1, or the longitudinal relaxation time, characterizes the rate at which the longitudinal component of the magnetization vector recovers and is defined as the time (in milliseconds) it takes for the longitudinal magnetization to reach 63% of its final value.[51] This component of the MR signal reflects structural aspects and is relatively insensitive to changes in the state of the muscle.

T2, or transverse relaxation time, characterizes the rate at which the magnetization vector decays in the transverse or XY plane. T2 is defined as the time (in milliseconds) it takes for the transverse signal to reach 37% (1/e) of its initial value.[51] In contrast to T1, T2 is sensitive to changes in relaxation time of muscle water.

Mechanism underlying mfMRI

The mfMRI-technique is based on an increase in T2 relaxation time of muscle water following exercise. Specifically, exercise results in a slower decay of the muscle water signal, which causes an enhancement in signal intensity of the activated muscles, and as a consequence, activated muscles look brighter on T2 weighted images when compared to muscles imaged in a resting state (FIGURE 2).[43]

Different studies have been performed to elucidate the underlying physiological mechanism of this shift in T2 relaxation time. [18, 22, 32] The simplest explanation is that the influx of fluid during activity is accompanied by an accumulation of osmolites (phosphate, lactate, sodium) in the cytoplasm and their presence prolongs the relaxation time of muscle water.[43] The T2 relaxation time of total muscle water is composed of multiple components, such as 1) protein bound intracellular water (34%), 2) free intracellular water (49%), and 3) extracellular water (14%), each experiencing a change in their respective T2 relaxation time.[53] The summed effect of changes in these components results in the net activity-induced increase in T2. Although all of the components act synergistically to increase overall T2, it should be clear that activity-dependent increases in T2 are believed to primarily result from intracellular events.[48]

Measurement protocols

The general mfMRI measurement protocol is that images are acquired at rest (pre-exercise image) and immediately following (post-exercise image) a specific exercise. Regions of interest (ROI) may then be developed for each muscle of interest. Care should be taken to avoid the inclusion of non-muscular tissue (e.g. fat, fascia or blood vessels) in all ROIs. For each ROI, the T2 value may then be calculated and the change in T2 value recorded from the pre- and post-exercise image is referred to as the T2 shift. From these calculations of T2 shifts, inferences regarding the activity level of specific muscles can be made and compared for different exercise protocols.

The half-life of exercise-induced changes in muscle T2 has been shown to be approximately 7 minutes[29], which requires the subjects to be accurately placed in the scanner immediately following the performance of the exercise. The time between the end of the exercise and the start of the scan will depend upon what body part is imaged and the imaging coils that are used. Future applications might enable patient to perform exercise in the scanner, thereby enabling scanning as soon as exercise is finished. Although there is a fast decay of T2, full recovery of muscle T2 is much slower, as T2 generally remains elevated for approximately 30 minutes following exercise. [29, 61] If the effect of different exercises on muscle activity is to be evaluated, it is recommended to permit at least 45 minutes of rest between exercise sets, as this would allow full-recovery of any established T2 shifts.[15]

Different sequences can be used of which multi-spin echo sequences are mostly applied. During a spin-echo pulse sequence, the RF field is applied in two pulses: a 90° RF pulse with a 180° RF pulse to rephrase spins to form an echo.[51] The time between the peak of the 90° RF pulse and the peak of the echo is called the echo time (TE). The time it takes to go through the pulse sequence once is called the repetition time (TR). Multi-echo spin-echo pulse sequences use multiple 180° RF pulses to generate multiple echoes in which each echo can be used to create a separate image. Turbo or fast spin echo sequences use the same sequence but instead of each echo forming a different image data set, all the echoes are used to create a single image data set at a faster rate, saving imaging time.

Key Points:

- T2 relaxation time characterizes the rate at which the magnetization vector decays in the transverse plane and is sensitive to changes in the state of the muscle.
- mfMRI is based on an activity-induced increase in the T2 relaxation time of muscle water which is directly responsible for the increased intensity of the MR signal on the T2 weighted imaging following exercise

- While the exact underlying mechanism behind T2-shifts is not yet fully understood, it is generally accepted that the T2 shift is associated with biochemical processes related to muscle activity
- T2 shifts can be recorded from the pre- and post-exercise images allowing quantification of the the activity level of specific muscles and such methodologies provides for comparison between different exercise protocols and their effects on muscular tissue.

Validity and reliability of mfMRI measurements

In an effort to validate mfMRI as an evaluation tool for muscle activity, the relationship between T2 shift and various other parameters of exercise has been investigated.[1, 29, 33, 35, 38, 61] Studies have shown that T2 shifts are quantitatively dependent on the intensity of skeletal muscle activation when exercises are performed over a wide range of intensities,[1, 29, 35, 38] supporting a linear relationship between T2 times and exercise intensity. Fisher et al[29] demonstrated that increases in T2 values of the human tibialis anterior were linearly related to the forces generated during exercise (r=0.87), whereas Jenner et al[35] demonstrated a similar correlation when exercise intensity was altered by increasing the rate of contractions at a constant target force (r=0.64; $p<0.01$). Similar results were found by Dickx et al[21] who investigated multifidus and erector spinae muscle activity during a trunk extension exercise at 5 increasing loads (from 40% to 80% of 1 repetition maximum) with both MRI and EMG. They demonstrated a linear association for the lumbar paraspinals ($R^2 = 0.92$; $p \leq 0.001$) and revealed that for both muscles an increase of 10% exercise intensity corresponds with an increase of the T2 value of 1.18 (95% CI: 0.89-1.47) ms. Studies by Fleckenstein et al[33], Mayer et al[42] and Cheng et al[14], however, do not support a linear relationship between T2 times and all levels of intensity of muscular activity, but rather support a sigmoid-shape relationship. Differences between studies can be attributed to differences in statistical approach (linear regression analysis compared to mixed model analysis) and methodology. For example, Mayer et al[42] performed the exercises at 3 different intensities on the same day, with 60 minutes of rest in between, whereas Dickx et al[21] tested subjects on 5 consecutive days, to allow the trunk musculature to recover. Residual fatigue in the lumbar muscles may have confounded muscle recruitment. However, it is still unknown whether the association also applies for lower and higher exercise intensities. It can be expected that changes in T2 reaches a ceiling, as the value depends on physiologic processes related to muscle output. Therefore, it is considered that T2 shifts are useful for inferences regarding moderate levels of muscle activity, but less valid for the lower and higher levels of activity.

Several studies have compared T2 contrast shifts and electromyography (EMG) signal amplitude of muscles in both the lower extremities and lumbar spine. [1, 21, 38, 52] Results vary among studies and muscles, and although MRI and surface EMG measurements are not in complete agreement, they demonstrate a consistent relationship. [1, 21, 38, 52] Lack of complete agreement between EMG and T2 shift recordings may be indicative of the different physiological basis of both measures. EMG signal amplitude reflects the electrical activation of muscle tissue, where T2 shifts record metabolic activity within the muscle tissue itself.

With regards to measurement reliability, measurements of T2 shifts have shown high inter-tester reliability with intra-class correlation coefficients and standard error of measurements ranging from 0.87 to 0.94 and 1.64 to 2.75 ms respectively (depending on the muscles evaluated).[10, 12, 24] This high reproducibility of results is an important advantage of the MRI method over surface and fine-wire EMG methods.[56]

Key Points:

- T2 shifts are useful for inferences regarding moderate levels of muscle activity, but less valid for the lower and higher levels of activity.
- No absolute agreement has been observed between EMG and mfMRI measures of muscle activity which is indicative of their different measurement properties.
- mfMRI is a highly reliable measurement tool of resting and exercised skeletal muscle, with a small amount of measurement error.

Advantages and limitations of mfMRI

MfMRI is a valuable complementary evaluation technique to EMG in measuring muscle behavior. While both techniques have unique measurement qualities, there are some advantages of mfMRI, making it a valuable evaluation method particularly with regard to the non-invasive access to deeper muscle structures and elimination of a common limitation with EMG measures; cross-talk.

<u>Non-invasive access to deep muscles</u>

MfMRI has some advantages over methods such as EMG in that it permits non-invasive measurements at multiple locations within multiple muscles from a single MRI scan. This is particularly advantageous for deeper muscle structures within the musculoskeletal system that, due to their depth and intimate proximity to structures such as visceral organs, may not be directly amenable to other methods of assessment such as surface or intramuscular EMG. Accordingly, mfMRI has gained popularity in studies evaluating muscle function including deep paraspinal muscles[9, 10, 15, 20, 24, 42] that were previously difficult to achieve and not without some risk with invasive EMG.[26, 27, 34, 46, 60]

<u>Elimination of measurement issues such as cross-talk</u>

While EMG measures have the advantage of evaluating the activity levels of muscles in real time, there are signal issues associated with surface EMG techniques. There is difficulty in obtaining an EMG signal representing isolated activity of the target muscle with surface EMG on the basis of the inaccessibility of deeper muscles with surface electrodes[55] and the generation of EMG signal by neighboring muscles resulting in signal cross-talk.[48] While it may be argued that the use of intramuscular EMG techniques eliminates cross-talk, a single intramuscular electrode will record signals from a population of motor units limited to its insertion site and therefore may not be representative of activity levels of the entire muscle. In contrast mfMRI permits measures to be taken with no issues of signal cross-talk. Additionally, mfMRI avoids other signal issues associated with EMG attributed to impedance from subcutaneous tissue and electrode type and placement.

Limitations of mfMRI measures

Besides the absolute contraindications for MRI, including pacemakers, brain aneurysm clips, metallic foreign bodies and claustrophobia, there are several limitations inherent to mfMRI.

At present, investigation using mfMRI is limited to evaluate spatial aspects (amount of activation) of muscle behavior that is in contrast to EMG techniques which have the advantage of evaluating both temporal (timing of activation) and spatial elements of muscle behavior in real time. Additionally mfMRI is a post-exercise evaluation of muscle activity and as yet the latency effects on the T2 shift measurement due to the delay between completion of the exercise and the commencement of the MRI scan is still not fully understood.

Secondly, mfMRI appears to be limited to evaluating exercise of at least moderate exertion such as resistance exercises, whereas evaluation of exercises at lower and higher intensities are expected to be less valid. Although several studies have demonstrated a relationship among exercise intensity, EMG signal amplitude, and T2 times, the lowest activity threshold to induce a significant shift in signal is still not known.[1, 33, 35] It would appear that EMG has a lower muscle activity detection threshold than MR imaging.[54] A sensitivity study revealed that changes in T2 times for the elbow-flexor muscles can be detected with as few as 2 repetitions (1 repetition being 1 second concentric and 1 second eccentric contraction) when performed at a high intensity (80% maximum voluntary contraction (MVC)).[15, 54, 61] Lower intensity exercises (25% MVC) may require up to 5 contractions before changes in T2 times can be appreciated.[61] In conclusion, while both mfMRI and EMG can be used independently to assess muscle activity relevant to research and clinical practice, their utility may depend on the nature of the muscular activity of interest. It is possible that combining both techniques will provide additional information when evaluating overall muscle function.

Lastly, while mfMRI is an emerging and exciting tool for evaluation of muscle activity, it is not without some inherent costs. Although mfMRI can be performed with the MR technology that is currently present in most hospitals for routine patient evaluation, it is primarily only available to research laboratories. Thus, the cost-effectiveness of utilizing such a potentially expensive modality for assessment and plan of care is currently unknown. Limiting practice variability at reduced costs is a major focus in delivering medical and rehabilitative services, worldwide. Thus, a cost-effectiveness study would be required before final recommendation that mfMRI become standard physical therapy and rehabilitation practice.

Key Points:

- MfMRI has the advantage, especially for the spinal muscles, to non-invasively evaluate muscle activity, adjacent muscles and even overlying muscles, without cross-talk.
- MfMRI is of questionable value in measuring muscles function during activities that are of a low intensity nature.
- While both mfMRI and EMG provide information regarding muscle function, they are complementary measures.
- The cost-effectiveness of using mfMRI for patient assessment and plan of care is currently unknown.

mfMRI and exercise

Early studies utilizing mfMRI measures investigated activity levels of specific muscles during exercise at specific intensity levels relative to maximal exertion, while others compared muscle activity over increasing intensity levels to maximal exertion. [2, 30, 31, 33, 35, 61] More recent studies have utilized mfMRI measures to specifically compare muscle activity during various clinically based exercises in healthy individuals and individuals with painful musculoskeletal disorders. [10, 12, 15, 24, 38, 40, 42, 44, 56] Therefore, T2 shift measures provide a powerful technique to assess 1) muscle function during specific exercise/rehabilitation protocols, 2) changes in activity patterns in patients with musculoskeletal disorders, and 3) the efficacy of interventions delivered over time.

Muscle function during specific exercise/rehabilitation protocols

Most studies utilizing mfMRI have investigated muscle activity patterns during commonly prescribed clinically based exercises. The superior spatial resolution of MRI provides a unique opportunity to study multiple muscles and demonstrate whether the target muscle has been activated, how effectively it has been activated, or whether substitution has occurred. Studies have evaluated muscle activity during exercise of the lower (knee extension, ankle extension and flexion, running, and cycling),[29, 35, 38, 39, 47, 50] and upper extremities as well as the spine.[10, 15, 24, 42, 43, 53, 56, 61]. Other studies have evaluated the impact on muscle activity of altering the parameters (type of contraction, velocity, intensity) of the exercise being performed.[20, 41, 42] For example the rectus femoris muscle has been shown to be more activated than the other portions of the quadriceps muscle during isokinetic knee extension exercise but not during isotonic knee extension exercise.[5, 49] Kulig et al[41] investigated the effect of contraction velocity on activity within the primary elbow flexors during 2 isotonic exercise protocols that differed in the velocity of their eccentric phase. Their findings demonstrated a variable response to the different velocity conditions that had not previously been detected with similar studies using EMG, indicating that mfMRI may be a more sensitive measure to explore this phenomenon. The findings suggest that signal intensity changes are associated with task-dependent differences and likely influenced by metabolic demand and/or neural activation.[3]

MfMRI also offers the clinician insight into the effectiveness of whether an exercise targets a specific muscle or muscle group. Takeda et al[56] demonstrated significantly greater increases in T2 relaxation time for the supraspinatus muscle in response to empty can and full can exercises (shoulder abduction performed in the scapular plane with thumb down and up, respectively) in comparison to a horizontal abduction exercise in healthy individuals. These findings suggest that these exercises (empty can/full can) may provide a better approach to specifically evaluate or train the performance (eg. strength, endurance) of the supraspinatus muscle.[37] Cagnie et al[10] used mfMRI to evaluate cervical flexor muscles activity during different cervical flexion exercises. It was determined that the deep longus capitis muscle was more active than the more superficial cervical flexor muscles during a craniocervical flexion exercise. This confirmed the appropriateness of craniocervical flexion as an exercise for patients with neck pain who are known to exhibit reduced activity of their deep cervical flexor muscles in the presence of heightened superficial flexor muscle activity. [28] These findings of cervical flexor function of Cagnie and colleagues were also consistent with those of a previous study utilizing EMG measures.[45] A comparable study has recently been undertaken by Elliott et al[25] utilising mfMRI to evaluate the impact of craniocervical orientation on cervical extensor muscle activity during extensor exercises in healthy individuals. While both the deep and superficial extensor muscles were active in both exercises evaluated, significantly greater T2 shifts were observed for the more superficial semispinalis capitis muscles when the exercise was performed with the craniocervical region in an extended orientation The findings of this study are of benefit to clinicians when prescribing exercise to train the cervical extensors.

<u>Changes in activation patterns in patients with musculoskeletal disorders</u>

There are only a few clinical studies which investigated changes in muscle activation pattern in patients with musculoskeletal disorders using mfMRI. Cagnie et al[12] investigated the cervical flexor muscles activity in patients with whiplash-associated disorders (WAD). Although not significant, there was a strong trend for lesser activity of the deep muscles in the group with WAD compared to the control group, which is in agreement with the results of a previously published EMG study.[28] O'Leary et al[44] performed a similar study for the cervical extensor muscles and found some alteration in the differential activation of the cervical extensors in patients with mechanical neck pain. Based on this study, they concluded that further investigation of this muscle group in neck pain disorders is warranted.

One potential challenge with mfMRI is that across individuals there is considerable variability in the activity-dependent T2 response. Accordingly, the use of T2 mapping to compare activation strategies and recruitment intensity among individuals remains controversial. The correlation between T2 and exercise intensity is stronger within a single individual than across individuals. Thus, analytical techniques that compare relative changes in signal intensity within individuals across time or exercise, or comparing the injured to the uninjured side appear most appropriate.[4]

Another approach to circumvent limitations of T2-shift measures, is to use an experimental pain paradigm. This offers the possibility to evaluate the influence of acute muscle pain on muscle activity within the same individual. Dickx et al[20] demonstrated that experimental pain, induced into the right longissimus muscle, resulted in a significant decrease in muscle activity of the lumbar multifidus, lumbar erector spinae, and psoas muscles. Cagnie et al[11, 13] recently undertook two experimental pain studies for the evaluation of both cervical flexor and extensor muscles with mfMRI. In both studies, the results suggest that local excitation of nociceptive afferents causes an immediate reorganisation of the cervical muscle activity similar to that identified in clinical populations, which support recommendations for evaluation of cervical muscle function early in the management of painful cervical spine injuries.

<u>The efficacy of interventions delivered over time</u>

MfMRI has also been used to evaluate neuromuscular adaptations as a result of resistance training. However, there is a paucity of available information in the literature to definitely ascribe and generalize its use to this aspect of clinical assessment.[6, 16, 49] Ploutz et al[49] and Conley et al[16] demonstrated that derecruitment of previously active muscles occurred when performing exercise with the same absolute loads after resistance training but that there was no change in the oxidative metabolic demand of muscle fibers, suggesting that fewer motor units were being activated when performing the exercise. Akima et al[6] concluded that resistance training prevents deconditioning of neuromuscular systems and or metabolic capacity and that this type of exercise could be useful for the prevention of muscle deconditioning.

<u>Key points</u>

- T2 shift measures provide a powerful technique to assess muscle function during specific exercise/rehabilitation protocols
- Clinical studies which investigate changes in activity pattern in patients are emerging

Future research

Studies with mfMRI are still sparse and there is a need for further research investigating the underlying mechanisms of mfMRI and the technical optimization of this technique. For example, efforts will need to be made to improve image quality, to reduce artifacts, and to expand the volume of muscles that can be investigated simultaneously. The potential of mfMRI to map spatial variation in activity within a muscle has been indicated in literature, however, to date, studies applying this method are lacking. Further, there is also a need for more clinical studies investigating changes in muscular function in individuals with musculoskeletal disorders.

Conclusion

MfMRI is a relatively new and innovative technique that is well-suited for examining normal and abnormal patterns of muscle activation within individuals during exercise. It has the advantage to non-invasively evaluate muscle activity of deep or closely adjacent and overlying muscles. Although the cost-effectiveness of using mfMRI for patient assessment and plan of care is currently unknown, this technique, alone or in conjunction with other non-invasive methods, may provide a powerful means for improving the assessment and management of patients with a range of musculoskeletal conditions.

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Figures

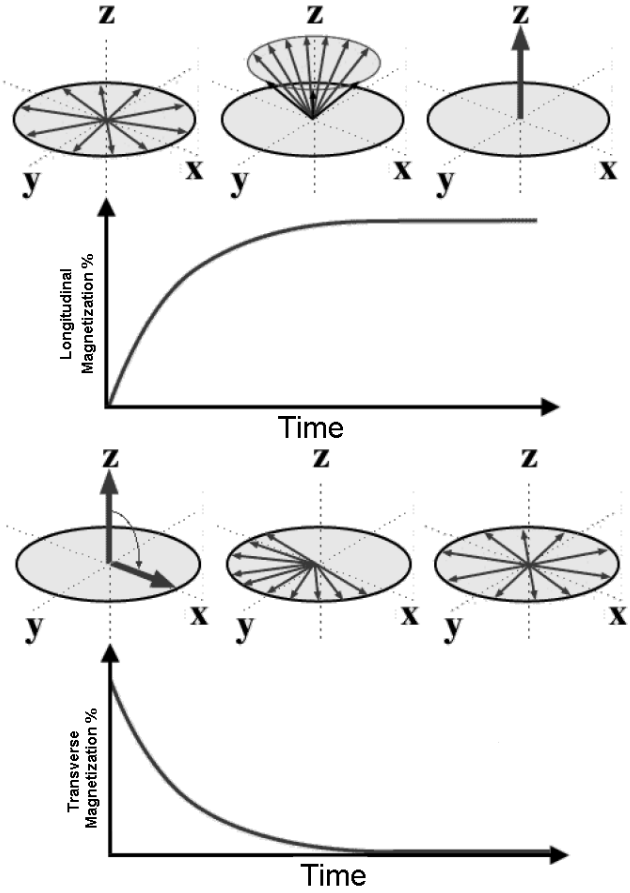

Figure 1 Definitions of T1- and T2 relaxation. T1, or the longitudinal relaxation time, characterizes the rate at which the longitudinal component (Z-axis) of the magnetization vector recovers and is defined as the time (in milliseconds) it takes for the longitudinal magnetization to reach 63% of its final value. T2, or transverse relaxation time, characterizes the rate at which the magnetization vector decays in the transverse or XY plane. T2 is defined as the time (in milliseconds) it takes for the transverse signal to reach 37% (1/e) of its initial value.

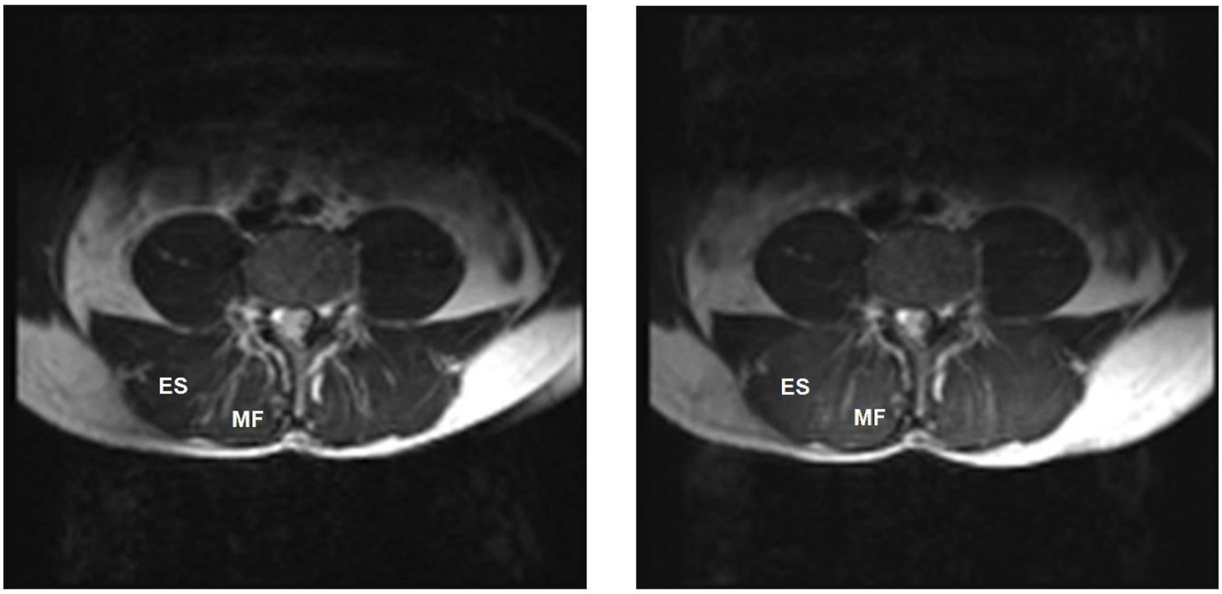

Figure 2: Illustration of a T2 weighted image at rest (A) and following exercise (B) (TR: 2500 ms; TE: 16 equidistant echoes ranging from 10.1 to 161.6 ms; 128 x 128 matrix and 256 mm FOV). There is an increased signal intensity (=brighter) for the m. multifidus (MF) and the m. erector spinae (ES). Although the changes in signal intensity are subtly visible, they are quantifiable using the calculation of T2 values.