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Use of Muscle Functional Magnetic Resonance Imaging With Older Individuals

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Muscle functional magnetic resonance imaging (mfMRI) has been widely used to study muscle recruitment in exercise in young healthy subjects, but has not been validated or used with older subjects. This study validates and demonstrates the use of mfMRI in older subjects. Subjects consisted of apparently healthy sedentary younger (n = 7) and older (n = 6) women. Proton transverse relaxation (T2)-weighted MRI scans were obtained of the quadriceps femoris at rest and immediately following three bouts of knee extension exercise (50%, 75%, and 100% of untrained 5 × 10 repetition maximum [RM]). Older subjects performed knee extension training for 12 weeks and repeated the MRI scan protocol using the same absolute loads. Training induced a 13% increase in 1 RM and a 25% increase in 5 × 10 RM. Older subjects had higher resting T2 values compared with younger subjects; however, the T2 response to exercise (slope) was similar among groups (young = 0.063 ± 0.003, older untrained = 0.055 ± 0.011, older trained = 0.053 ± 0.008; $p > .05$). In all cases, T2 increased linearly with load. Trained older subjects showed a lower T2 response when lifting the same absolute load compared with before training, which is consistent with results previously obtained from young subjects. In the older population, mfMRI is appropriate for use and offers benefits over other technologies.

RESISTANCE exercise training programs for elderly persons have gained significant attention in recent literature. Most studies have assessed muscle strength or hypertrophy in response to various training programs in a variety of elderly populations. Recently, more basic measurements to study the underlying physiology have been made in association with resistance training in elderly persons, such as inclusion of muscle biopsies (1,2) and 31^P spectroscopy to study metabolic characteristics of muscle (3−5), or inclusion of electromyography (EMG) to study the neuromuscular responses to training and aging (6,7).

Muscle functional magnetic resonance imaging (mfMRI) has been widely used to assess muscle recruitment in exercise (8−23). Standard proton transverse relaxation (T2)-weighted spin echo images of skeletal muscle show large (~30%) increases in signal intensity (SI) following exercise (11). This increase in SI and T2 has been shown to be a quantitative indicator of muscle use in exercise, and thus, mfMRI provides an ideal noninvasive tool to study muscle involvement in exercise (12,14,15,18,19). Because the exact biochemical mechanism of the exercise-induced increase in SI and T2 is unknown, it is important that the technique be validated for the individual populations and muscles studied. The original validation studies, and most subsequent studies, have used young healthy subjects and observed that T2 increases linearly with increasing load of resistance exercise for a wide variety of muscle groups (12,14,15,18,19). These studies suggest that mfMRI would be an ideal tool to study muscle recruitment in the elderly population because it is noninvasive, does not involve ionizing radiation, does not require awkward posture and subject instrumentation, and allows for outstanding spatial resolution of deep and superficial muscles. However, mfMRI has not been used previously with the aging population. Theoretically, it should be a valid tool to use with any healthy population; however, it is not known whether resting T2 or the magnitude of the exercise response is similar in skeletal muscle of young and older subjects. Young, trained subjects typically show a resting T2 of 26−30 ms, but it seems likely that sedentary and/or older subjects may show a higher resting T2 because of the likely presence of fat (which has high signal intensity) in and around the muscle. Therefore, the purpose of this study was to compare the T2 response to exercise in young and older subjects.

Methods

Subjects

Seven young women (mean age 23 ± 4 years) and six older women (mean age 66 ± 5 years) volunteered to participate in the study. All were sedentary healthy adults. Subjects were matched for body weight (mean ± *SD*; young = 61.8 ± 8.2 kg; older = 61.4 ± 4.5 kg). Written informed consent was obtained from each subject. The Institutional Review Boards of Syracuse University and State University of New York Upstate Medical University approved the study.

Design

After orientation, subjects participated in 1 RM (repetition maximum) and 5 × 10 RM strength tests of knee extension exercise using a knee extension dynamometer (MedX, Ocala, FL). MRI scans were taken of the quadriceps femoris (QF) muscle group before exercise and following three bouts of knee extension exercise at 50%, 75%, and 100% of the 5 × 10 RM. The scans were evaluated for the T2 response to exercise. The older subjects then performed knee extension training twice per week for 12 weeks. After the training program, the MRI scans were repeated on the older subjects.

Strength Tests

Subjects participated in several orientation sessions designed to familiarize them with isotonic exercise on a MedX knee extension dynamometer. Subjects were tested for the concentric bilateral 1 RM, the heaviest weight that could be lifted for one repetition. Lifting the weight 90% or more of a subject's unloaded range of motion was required for a successful lift. The 1 RM was reached when the subject lifted the same maximum weight on consecutive days. The 5 × 10 RM, the heaviest weight that could be lifted for five sets of 10 repetitions with a 2-minute rest between sets, was measured over several sessions. The two types of strength tests (1 RM and 5 × 10 RM) were always performed on different days.

MRI Scans

All subjects reported to the MRI facility in the morning and rested in the supine position for 30 minutes prior to the first MRI scan (rest). After the resting scan, subjects performed five sets of 10 repetitions of bilateral knee extension exercise at each of three intensities—50%, 75%, and 100% of the 5 × 10 RM. Shortly (~1–2 min) after each set of exercise, the MRI scans were obtained. Subjects rested for 60 minutes between exercise bouts, which is adequate time for the T2 to recover to resting levels (12). Transaxial spin-echo images of the quadriceps femoris were obtained using a Siemens Vision 1.5T system (Siemens, Munich, Germany) (repetition time = 2000; echo times = 30, 60; matrix size = 256 × 256; field of view = 40; slice thickness = 1 cm, no spacing; scan time 4:40, 10 slices). QF cross-sectional area (CSA) was determined using eight slices, representing the eight most superior slices that did not contain gluteal muscle. CSA was calculated by manually tracing the perimeter of the QF muscle group using a Power Macintosh 9500 computer (Apple Computer, Cupertino, CA) running the public domain NIH Image and Image J programs (developed at the U.S. National Institutes of Health, Washington, DC, and available on the Internet at http://rsb.info.nih.gov/nih-image/). The CSA values shown in the results represent the mean CSA over eight slices, which represent the largest area of QF. Muscle T2 was calculated on a pixel by pixel basis using two echo times and assuming a single exponential decay with no offset. Percentage of elevated pixels was determined as described previously (18). Briefly, pixels whose postexercise value exceeded the resting value + resting standard deviation were considered elevated. Histograms of the T2 distribution were determined for a 250-pixel region of interest in the most superior slice for each subject and condition. This region of interest was always chosen in the vastus lateralis muscle in an area that did not include visible fat or vascular structure. Individual subject histograms were summed to create a group average histogram for each group and exercise condition.

Training

The older subjects participated in knee extension resistance training twice per week for 12 weeks. Each training session consisted of a warm-up set and then three sets of 8–10 repetitions to failure. When a subject could complete more than 10 repetitions, the load was increased about 5%, or to a weight with which the subject could complete 8 repetitions.

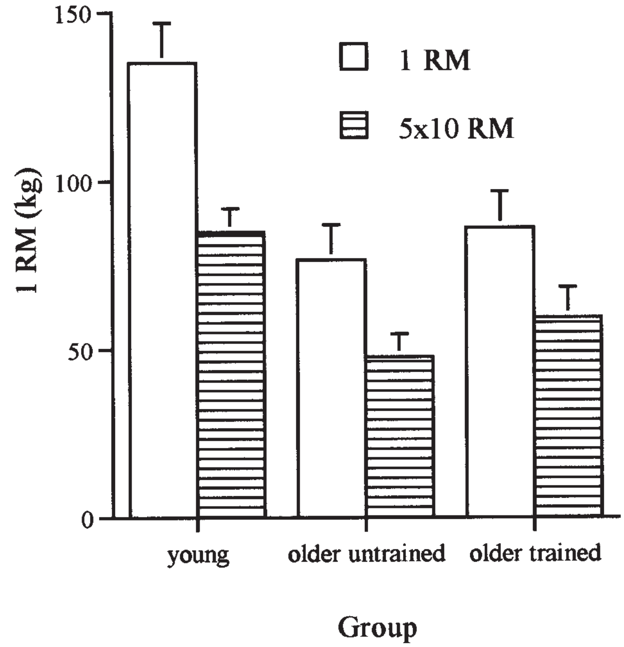

Figure 1. Bilateral 1 repetition maximum (RM) knee extension strength for 1 RM (open) and 5 × 10 RM (striped) for young (n = 7), older untrained (n = 6), and older trained (n = 6) subjects. Values are mean ± standard error. For each RM frequency, all three groups were significantly different from each other.

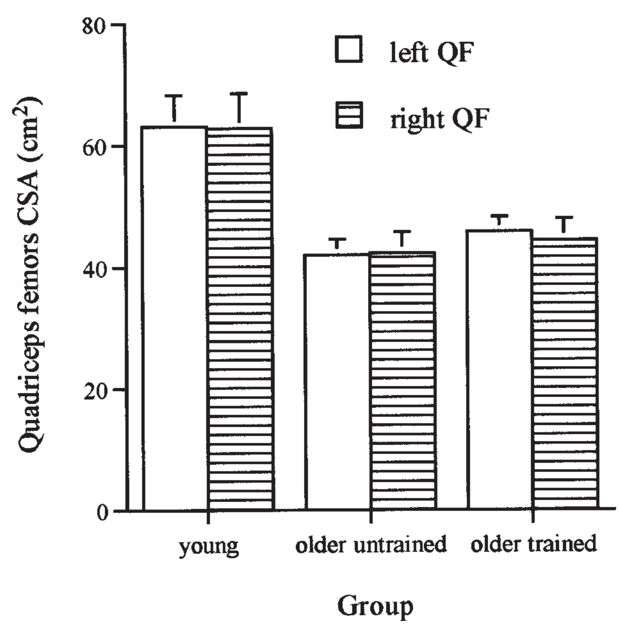

Figure 2. Quadriceps femoris cross-sectional area (CSA) for the right and left sides in young (n = 7), older untrained (n = 6), and older trained (n = 6) subjects. Values are mean ± standard error. There were no differences between sides. Each group was significantly different from each other.

Specific Tension

Specific tension of the QF was calculated as the 1 RM strength in kg divided by the QF CSA averaged over the eight slices described previously. Values are reported as kg/cm^2.

Statistical Analysis

Data were analyzed using analysis of variance (ANOVA), repeated measures ANOVA, and homogeneity of variance tests. Several analyses were performed. Muscle strength and cross-sectional area were compared using one-way ANOVA (SuperANOVA version 1.1, Abacus, Inc, San Francisco, CA). The T2 values and percent-elevated pixels in response to exercise were analyzed using three 3-way ANOVAs (group × side × intensity), where the group comparisons included young versus older untrained, young versus older trained, and older trained versus older untrained groups (repeated measure). In the case of significant interactions, a series of either two-way and/or one-way ANOVAs were used to determine where significant differences existed. The heterogeneity in T2 distribution was evaluated using the Bartlett-Box *F* homogeneity of variance test procedure (SPSS version 6, Statistical Product Service Solutions, Chicago, IL). Values are expressed as mean ± standard error (*SE*). A p value of $\leq .05$ was used to reject null hypotheses.

Results

Strength Comparisons

1 RM and 5 × 10 RM strength results are shown in Figure 1. The young subjects were significantly stronger than the older subjects, regardless of training status or type of strength test ($p \leq .05$). The older subjects did exhibit 13% higher 1 RM ($p \leq .05$) and a 25% higher 5 × 10 RM ($p \leq .05$) after the 12 weeks of training.

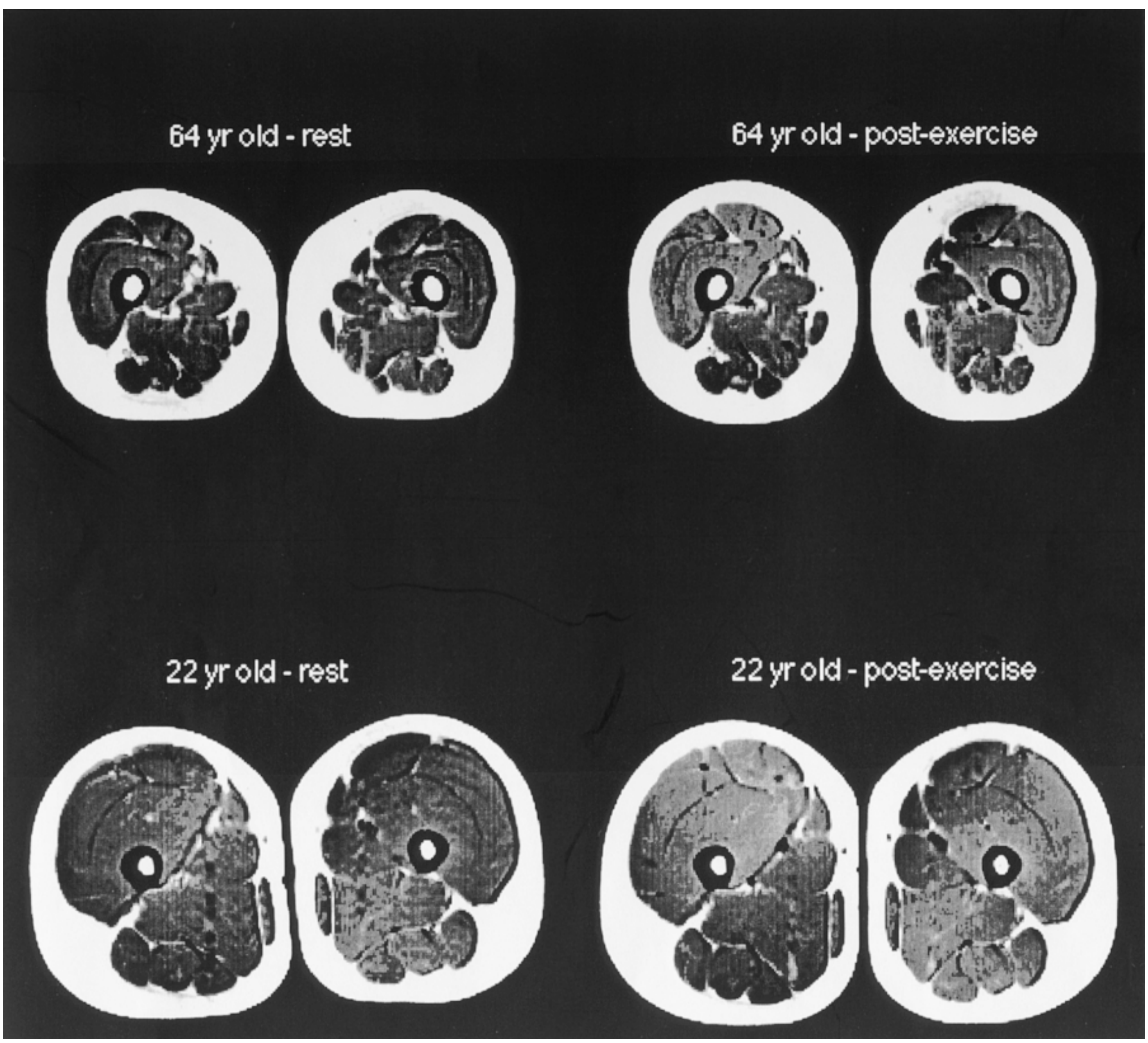

Figure 3. Representative examples of magnetic resonance images from one young and one older subject at rest and following the 100% of pretraining 5 × 10 repetition maximum load. Notice the visible differences in cross-sectional area and fat. The bright areas of the quadriceps femoris in the postexercise images represent areas with increased proton transverse relaxation (T2).

Muscle CSA

The QF CSA data are shown in Figure 2. The young subjects had a significantly greater CSA than older subjects, regardless of training status for both legs ($p \leq .05$). The training was associated with a 5% increase in CSA for the right ($p \leq .05$) and a 9% increase in CSA ($p \leq .05$) for the left QF in the older subjects. There were no significant bilateral differences in CSA ($p > .05$). Figure 3 shows representative example images from one young and one older subject. The rest images show an obvious difference in CSA.

Specific Tension

There were no differences among groups for specific tension ($p > .05$); training had no influence on specific tension ($p > .05$). The young subjects had a mean value ($\pm SE$) of 1.07 ± 0.06 kg/cm^2, older untrained $= 0.90 \pm .11$ kg/cm^2, and older trained $= 0.94 \pm .09$ kg/cm^2.

Resting T2

The older subjects, regardless of training status, had significantly higher T2 values at rest compared with young subjects (Figure 4; $p \leq .05$). The 24 training sessions did not affect the resting T2 in older subjects ($p > .05$).

T2 Response to Exercise—Absolute Loads

When the groups were compared at the same absolute loading intensity (which was prescribed as 50%, 75%, and 100% of pretraining 5×10 RM), the older subjects, regardless of training status, had significantly higher T2 values compared with young subjects at rest and at each exercise intensity ($p \leq .05$ for each load comparison; Figure 4). The older trained subjects were significantly different from both the young and the older untrained subjects when the analysis collapsed across load ($p \leq .05$ for each analysis). Generally, left-side values were higher than right ($p \leq .05$). Training-induced strength increases are not seen in Figure 4

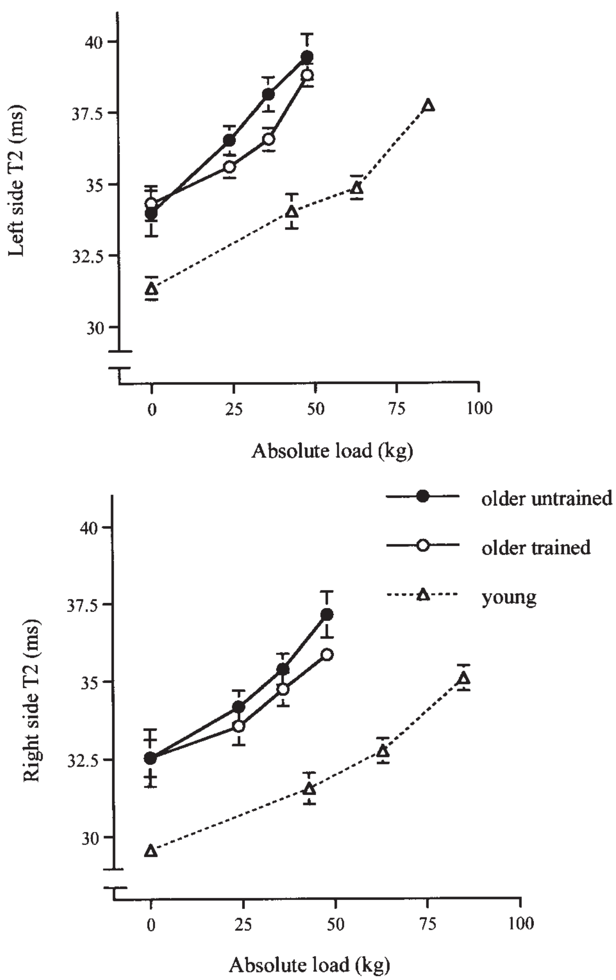

Figure 4. Proton transverse relaxation (T2) response to exercise at the same absolute load for young ($n = 7$), older untrained ($n = 6$), and older trained ($n = 6$) subjects for the left (top) and right (bottom) sides. There was a significant difference between each group when collapsed across load ($p < .05$). Left-side values were significantly higher than right-side values ($p < .05$). Training-induced strength increases are not seen here because the maximum load prescribed was 100% of pretraining 5×10 repetition maximum (RM). Values are mean ± standard error.

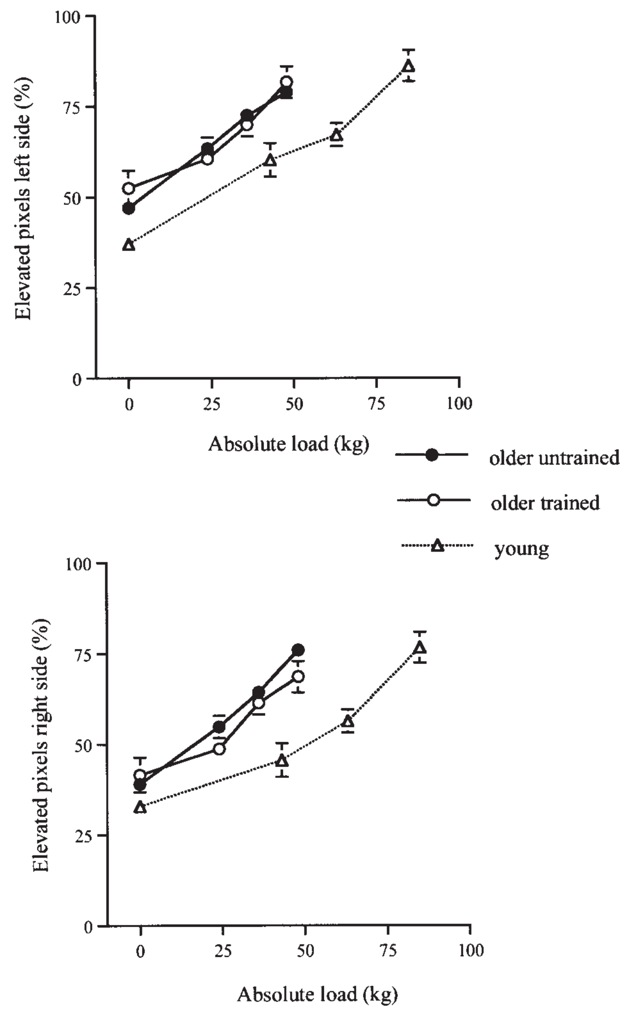

Figure 5. Percentage of elevated pixels at the same absolute load for young ($n = 7$), older untrained ($n = 6$), and older trained ($n = 6$) subjects for the left (top) and right (bottom) sides. There was a significant difference between young and older subjects ($p < .05$), and no significant difference between older pre- and posttraining ($p > .05$) when collapsed across load. Values are mean ± standard error.

because the maximum load prescribed was 100% of pretraining 5 × 10 RM.

When the data were expressed as a percentage of total muscle pixels whose T2 values were elevated, a similar pattern was observed, as is shown in Figure 5. Left-side values were higher than right ($p \leq .05$). There was a significant difference between young and older subjects ($p \leq .05$); however, no significant difference between older pretraining and older posttraining subjects ($p > .05$) when collapsed across load.

T2 Response to Exercise—Relative Loads

When the groups were compared at the same relative loading intensity, the slope of the lines was similar, indicating a similar magnitude of response (young = 0.063 ± 0.003, older untrained = 0.055 ± 0.011, older trained = 0.053 ± 0.008; $p > .05$) as observed in Figure 6. Because the exercise was prescribed as a percentage of untrained 5 × 10 RM, the data points for the older trained subjects along the x-axis are shifted to the left (lower values), reflecting the increase in strength with training. T2 values were significantly lower for young subjects when collapsed across load ($p \leq .05$). There were no differences between older, and trained and untrained, subjects ($p > .05$).

When the data were expressed as a percentage of total muscle pixels whose T2 value was elevated compared with the load relative to pretraining 5 × 10 RM, no statistical differences were observed ($p > .05$) among groups (Figure 7). There were significant differences among all loads ($p \leq .05$).

Distribution of T2

Histograms of the T2 values for the three groups are shown in Figure 8. Generally, there were differences in the

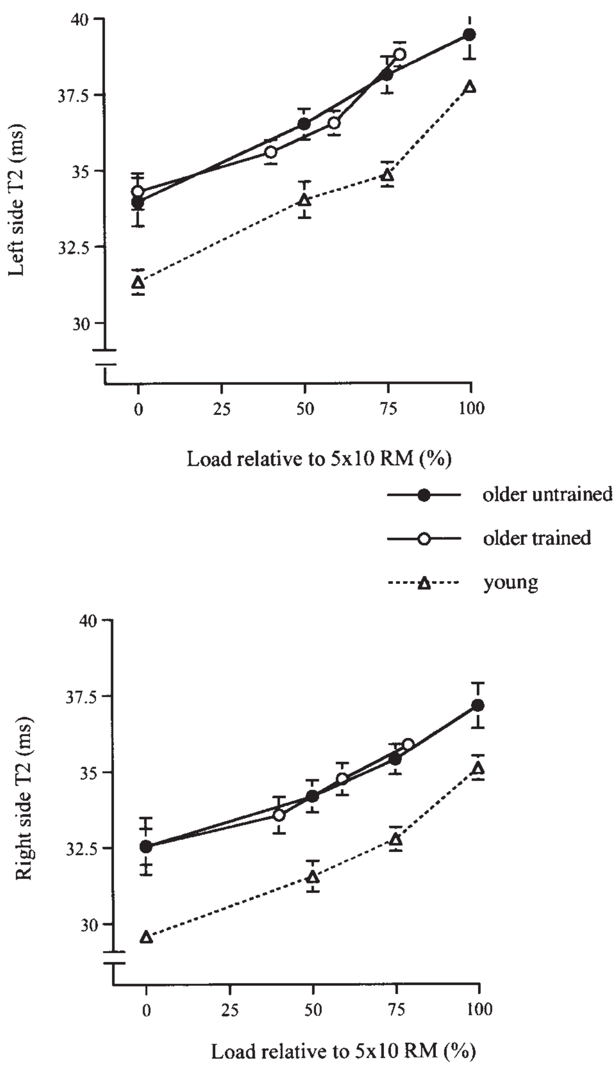

Figure 6. Proton transverse relaxation (T2) response to exercise at relative loads for young ($n = 7$), older untrained ($n = 6$), and older trained ($n = 6$) subjects for the left (top) and right (bottom) sides. There were no differences in slopes among groups ($p > .05$). Because the exercise was prescribed as a percentage of untrained 5 × 10 repetition maximum (RM), the data points for the older trained subjects along the x-axis are shifted to the left (lower values), reflecting the increase in strength with training. Values are mean ± standard error.

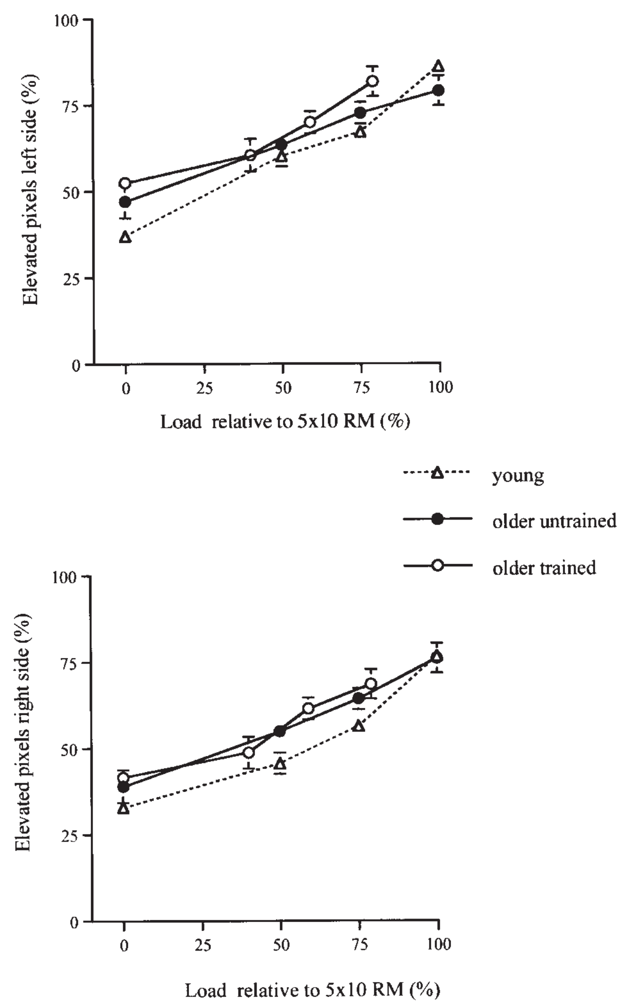

Figure 7. Percentage of elevated pixels at the same relative load for young ($n = 7$), older untrained ($n = 6$), and older trained ($n = 6$) subjects for the left (top) and right (bottom) sides. There were no significant differences in slope or percent elevated pixels ($p > .05$) among groups when collapsed across load. Values are mean ± standard error.

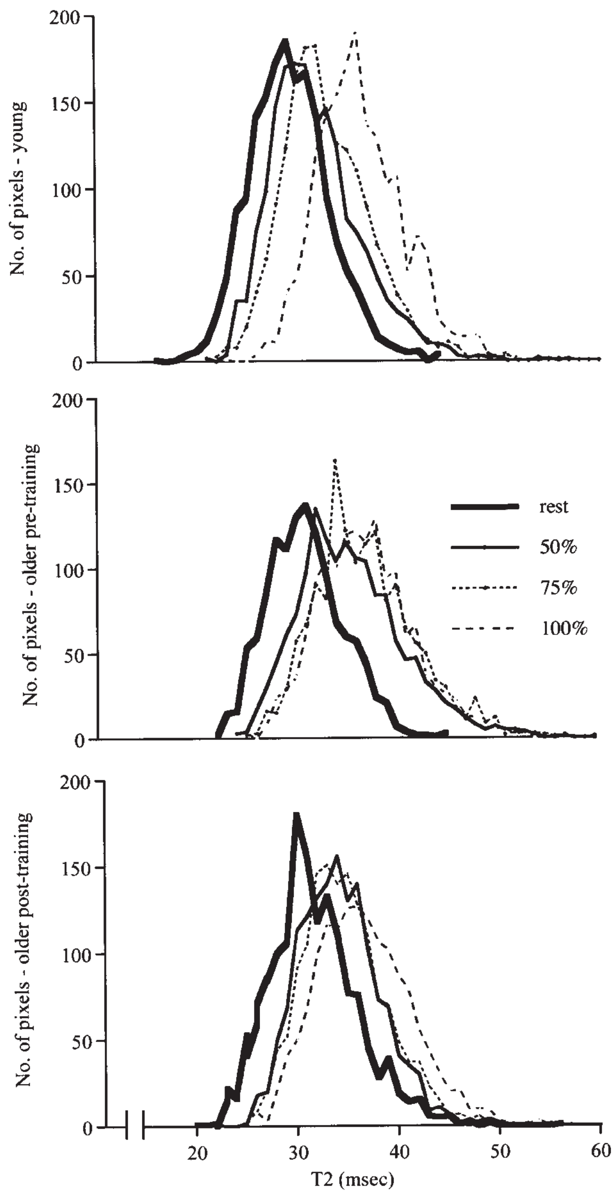

Figure 8. Histograms of proton transverse relaxation (T2) distribution for a visibly fat-free area of the vastus lateralis. Individual subject histograms were summed to create one for each group; young (n = 7), older pretraining (n = 6), and older posttraining (n = 6).

Table 1. Standard Deviation Values for T2 Distributions

	Young	Older Pretraining	Older Posttraining
Rest	3.96†	3.83†	4.37
50% maximum	4.54*†	5.47†	4.16
75% maximum	4.62*†	5.26†	4.38
100% maximum	4.53*	4.98	4.73

Note: Homogeneity of variance was tested using Bartlett-Box F test.

*indicates $p < .05$ versus older pre- and posttraining within an exercise condition (row); †indicates $p < .05$ versus older posttraining within an exercise condition (row).

variance associated with the T2 distribution when compared by age group (Table 1). The differences in variance tended to be greater at rest and less with more intense exercise. For example, in Table 1, only one pairwise comparison was significant at the 100% of maximum exercise (young vs older pretraining), whereas almost all other comparisons were significant for rest and the lower intensities of exercise.

Discussion

The major finding of this study was that the T2 response to exercise was linearly related to both absolute and relative load and similar in young and older subjects, thus validating the use of mfMRI with older individuals (Figures 4–7). This is the first report of mfMRI with older individuals; however, others have shown the T2 response to be linear with absolute and relative load in young subjects (12,18,19,24). Histograms of T2 images show normal distributions for young and older subjects (Figure 8). Training-induced increases in QF strength and CSA were associated with a slight decrease (downward shift in the line [Figure 4]) in the T2 response when expressed as an absolute load. This downward shift indicates that T2 is lower at the same absolute load after training compared with before training (Figure 4). This is considered a positive adaptation and has been observed following resistance training in young healthy subjects (19). Furthermore, an upward shift in the T2 response to absolute load is associated with muscle disuse (18). The fact that training causes similar changes in the T2 response in young and older subjects is further justification for the use of mfMRI with the older population. There are several possible explanations for the training-induced change in T2. Because similar responses are seen with integrated EMG (25,26), it is possible that neural changes associated with resistance training result in more efficient motor unit activation protocols (i.e., changes in synchronization), such that following training, fewer motor units are recruited for the same absolute load; thus, the lower overall T2. A second possibility is that metabolic changes, such as alterations in enzyme content or activity, may have occurred, which render the muscle more efficient in its energy usage. It seems likely that the mechanism of T2 change is related to intracellular osmotic changes (27). Therefore, any training adaptation that results in a more efficient handling of osmotic loads, likely results in a lower T2 response.

Another important finding was that the resting T2 was significantly greater in older subjects compared with younger subjects ($p \leq .05$), presumably because of increased amount of intramuscular fat. Even when obvious areas of fat and blood vessels are excluded from the analysis, this finding remains. The histogram analyses were performed using a 250-pixel area in the vastus lateralis, which was visibly free of nonmuscle tissue (fat, connective, vascular). Even when this apparently uniform area was analyzed, differences in resting T2 were observed among groups (young = 29.3 ms, older pretraining = 30.9 ms, older posttraining = 31.7 ms; $p \leq .05$). The age-related differences in resting T2 observed in the current study may be due to a higher fat content in the muscle of older subjects. Because fat has a high T2 value relative to muscle, larger intracellular fat stores would increase the overall mean T2 and the T2 of individual pixels. In fact, a recent study has assumed this and created algorithms that attempt to identify "fat-free CSA"; however, the specific threshold criteria were not defined (28). We cannot exclude the possibility that the higher resting mean T2 is due to factors other than fat, especially because 24 training sessions did not alter resting T2 of the whole muscle and, in fact, increased the resting T2 of the uniform 250-pixel area. Because we do not know the exact biochemical mechanisms that regulate T2, it is possible that resting muscle of older subjects inherently has a higher T2. Regardless of the resting values, the exercise response is similar in young and older subjects (Figures 4–7).

Figure 8 and Table 1 show the distribution of the T2 histograms for the young, older untrained, and older trained subjects. Even though a visibly uniform 250-pixel area was chosen for analysis, there were significant differences in the variance of the T2 distributions. Most interesting is that the least amount of variance among groups occurred at the highest exercise intensity (see Table 1). When considering the post-exercise T2 distributions, training generally resulted in less variance in the T2 distribution (significantly less for the 50% and 75% loads). There are some possible theoretical explanations for this observation. If training induced an increase in motor unit synchronization, then the T2 distribution might be less variable. The rationale for this explanation is that if more motor units are firing at the same time, then more muscle fibers will be contributing to the elevated pixel value and there would be fewer "resting" fibers. This could contribute to a less variable T2 distribution. A second possibility is that perhaps the training made the whole muscle more homogenous in terms of fiber type and/or metabolic profile. It has been shown that drastic differences in fiber type, such as those that occur in different rat hind-limb muscles, can influence the magnitude of T2 response (29). Theoretically then, training-induced fiber type changes, such as the rapid reduction of IIb fibers often observed following resistance training (30), could result in a less variable T2 distribution. Clearly, the MRI spatial resolution typically used in exercise studies is not able to differentiate individual muscle fibers or motor units. However, if the physiological changes (neural and/or metabolic) were of significant magnitude and spread over a large area of the muscle, changes in the T2 distribution might be observed. This is certainly an area that requires additional research.

There have been no gender effects previously observed related to T2 response to exercise in younger subjects, so it is unlikely that gender effects would be observed in older subjects. Future studies should document this.

In conclusion, mfMRI is appropriate for use with older healthy subjects. The T2 response is linearly related to load. The resting T2 values of older subjects are higher than their younger counterparts, but the T2 increase is comparable. It is critical that investigators consider the initial resting T2 before conducting exercise studies, especially with subjects of varying age. Clearly, mfMRI has enormous potential for use in the older population. The technique offers several advantages over other current methods of assessing muscle involvement in exercise. It is noninvasive, does not involve ionizing radiation, offers unparalleled anatomical resolution that allows for investigation of deep and superficial muscles, including very small muscles, and is highly repeatable and reliable.

Acknowledgments

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