

# Alterations in cervical muscles' transverse relaxation times after a computer typing task: a quasi-experimental, magnetic resonance imaging study

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## ABSTRACT

**Aims:** With the advancement of modernization, the prevalence of occupations requiring extensive computer use has markedly increased. The heightened incidence of neck pain observed among individuals engaged in such occupations is thought to be associated with altered activation mechanisms of the cervical musculature. The aim of the present study is to investigate the changes in transverse ( $T_2$ ) relaxation times of cervical muscles after a computer typing task.

**Methods:** Twenty-seven asymptomatic male students (mean age:  $20.41 \pm 0.74$  years) participated in the study. All participants were instructed to perform a computer-based task, in which they were asked to type the text displayed on the left laptop onto the right laptop as quickly as possible for 20 minutes. MRI scans were performed before and after the task.  $T_2$  relaxation times of individual muscles, as well as the ratios between deep and superficial flexor ( $FT_2$  ratio) and extensor ( $ET_2$  ratio) muscles, were measured ( $FT_2$  ratio =  $T_{2\text{-deep flexor muscles}} / T_{2\text{-superficial flexor muscles}}$  and  $ET_2$  ratio =  $T_{2\text{-deep extensor muscles}} / T_{2\text{-superficial extensor muscles}}$ ).

**Results:** After the task,  $T_2$  relaxation times of the superficial flexor and extensor muscles increased bilaterally ( $p < 0.05$ ). No significant changes were observed in the  $T_2$  relaxation times of the deep flexor and extensor muscles on either side ( $p > 0.05$ ). Both the  $FT_2$  ratio and  $ET_2$  ratio decreased bilaterally ( $p < 0.05$ ).

**Conclusion:**  $T_2$  relaxation times of the superficial cervical muscles tended to increase after the typing task. In individuals working in computer-based jobs, such imbalances in cervical muscles following task performance may contribute to the development of musculoskeletal disorders over time. Understanding these early muscle responses in asymptomatic individuals may help inform preventive strategies, including ergonomic adjustments and exercise-based approaches aimed at reducing the risk of future musculoskeletal problems.

**Keywords:**  $T_2$  relaxation time, cervical muscles, computer use, magnetic resonance imaging

## INTRODUCTION

In recent years, particularly in developing countries, sedentary work conditions, prolonged static loading, and inadequate workplace design have posed significant risks for the development of cervical musculoskeletal disorders.<sup>1</sup> The prevalence of neck pain is reported to have increased and neck pain is particularly common among those who work in seated positions, with most affected individuals employed in computer-based jobs.<sup>1,2</sup> Today, the use of visual display terminals (VDTs), such as laptops, notebooks, tablets, and mobile phones, is rapidly increasing, and their use has been linked to the development of neck disorders.<sup>1,3</sup> Even 10 to 20 minutes of VDT use may be sufficient to induce muscular fatigue and changes in muscle activities.<sup>4,5</sup> Increased muscle fatigue results in greater and more complex afferent input

from peripheral tissues to the central nervous system, thereby altering the signals sent from the central nervous system to the peripheral nervous system and the motor neurons of the muscles.<sup>6</sup>

In healthy individuals, maintaining a balance between the activation of superficial and deep cervical extensor and flexor muscles is essential for stability during both dynamic and static postures throughout normal neck movements.<sup>7,8</sup> Superficial muscles such as the sternocleidomastoid and upper trapezius become more active with large cross-sectional areas during movements producing torque and deep muscles such as the longus colli, multifidus, and semispinalis cervicis become more active during stabilizing activities requiring support.<sup>8,9</sup>

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In the event of fatigue and pain, the balance between the motor control of muscles is disrupted and increased compensatory activities are observed in superficial muscles following decreases in the activity of deep muscles.<sup>4,8,10-12</sup> Studies have shown that in people with neck pain increased activity of the superficial cervical muscles is evident even during the task of writing for 5 minutes and the complaints of the person start to increase as the time increases.<sup>12,13</sup> This suggests that muscular imbalances may be the underlying cause of the increased incidence of neck pain in office workers who spend a lot of time using computers.

In studies evaluating the architectural characteristics and activities of deep and superficial cervical muscles, ultrasound, electromyography (EMG), and magnetic resonance imaging (MRI) are used for evaluation.<sup>11,12</sup> Although EMG is capable of measuring muscle activity directly, muscle placement in the cervical region such as the deep longus colli, makes the use of EMG difficult. As a solution to this challenge, Falla<sup>14</sup> developed a nasopharyngeal EMG method. However, since this method is invasive and difficult, researchers may use MRI instead in muscular assessments.<sup>14-16</sup> The transverse (T<sub>2</sub>) relaxation times measurement method involves the excitation of the hydrogen nuclei in muscle tissue fluids and adipose molecules in a high magnetic field and showing simultaneous oscillations, disrupting synchronized oscillations after a while, and measuring the termination of the signals by damping the energies of the nuclei under different magnetic fields. This damping time is called the T<sub>2</sub> or transverse relaxation time and is measured in milliseconds. Signal intensity is related to the number of hydrogen nuclei in the tissue. Along with the metabolic increase after the exercise, especially the accumulation of protein, phosphate, lactate, and sodium lead to an increase in the T<sub>2</sub> relaxation time and a significant relationship between exercise intensity and increase in T<sub>2</sub> relaxation time is seen.<sup>16</sup> Another study showed that T<sub>2</sub> relaxation time measurements of muscles correlated with EMG measurements.<sup>17</sup>

Since it is more convenient to select exercises for cervical pathologies with respect to changes in the muscles, understanding cervical muscle activity changes in jobs involving intensive use of computers may play an important role in preventing neck problems. Therefore, this study aimed to investigate changes in deep and superficial cervical muscle activity using T<sub>2</sub> relaxation time measurements obtained by MRI after prolonged computer use, in order to better understand the mechanisms underlying neck pain in individuals working in computer-based jobs. Moreover, to the best of our knowledge, this study is the first in the literature to evaluate changes in T<sub>2</sub> relaxation times of the deep and superficial cervical flexor muscles following such a prolonged functional activity. In previous studies evaluating cervical muscle activation, short-duration tasks rather than prolonged activities were typically used, which represents one of the major distinctions of our study from the existing literature. Although our participants were asymptomatic, our study was based on the hypothesis that functional activity would lead to alterations in the activation ratios of the deep and superficial cervical flexor muscles.

## METHODS

A written consent form was obtained from all volunteers who participated in the study and approval was obtained from Hacettepe University Clinical Researches Ethics Committee (Date: 10.01.2019, Decision No: 2019/01-48). The study conforms with The Code of Ethics of the World Medical Association (Declaration of Helsinki), printed in the British Medical Journal (18 July 1964).

Twenty-seven male, asymptomatic, voluntary, university students were included in the study (with 90% power after power analysis). This study was conducted at Hacettepe University, Faculty of Physical Therapy and Rehabilitation, in collaboration with the Department of Radiology, Faculty of Medicine, between September 2019 and February 2020. Only male participants were recruited to minimize variability related to sex-specific differences in skeletal muscle structure and physiology. Previous research has shown that men and women differ in skeletal muscle mass distribution and fiber-type composition, with men generally exhibiting greater muscle mass and a higher proportion of type II fibers.<sup>18,19</sup> Moreover, studies have reported that males and females demonstrate different physiological responses to fatigue.<sup>20</sup> Therefore, restricting the sample to males was considered appropriate to ensure a more homogeneous study population and to reduce potential confounding effects of sex-related differences in muscle function and fatigue response. The dominant side of all individuals was the right. The exclusion criteria were being younger than 18 or older than 30, having a history of any surgical procedure of the vertebral column, inflammatory disease, rheumatologic disease, malignancy history, congenital spinal cord anomalies, congenital and/or subsequent spinal deformities, radiculopathy, myelopathy, other neurological disorders, vestibular disorder and/or trauma history, and conditions contraindicated for MRI. After the announcement, 34 volunteers applied to participate in the study and 27 of them were enrolled. Of the other 7 subjects, reasons for exclusion were scoliosis (n=2), cervical disc herniations (n=2), claustrophobia (n=3) (Figure 1).

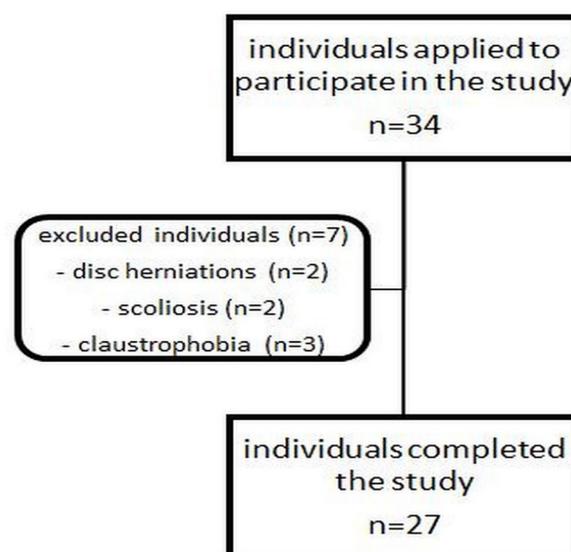


Figure 1. Flowchart

### Procedure

Because EMG assessment of deep cervical muscle activation is challenging and invasive, this study used MRI-based T<sub>2</sub> relaxation time measurements to evaluate cervical muscle activation. The initial MRI scans were obtained after collecting demographic data from all participants. Next, each individual was asked to type on a computer for 20 minutes. A standardized posture and task were designed to ensure all subjects to perform the activity under the same conditions. They were instructed to perform the task in their naturally adopted, commonly used non-ergonomic posture typical of their everyday computer use, rather than correcting or paying attention to their sitting ergonomics. No specific verbal instructions were given to impose a particular non-ergonomic posture; instead, participants were asked to maintain the posture they usually assume during routine computer work. The computer display was positioned at a 15-degree downward angle from eye level, and the keyboard was placed at a distance corresponding to the participant's natural arm position in slight flexion.<sup>4,21,22</sup> Similar to the task used in the study by Fang et al.,<sup>4</sup> the individual was seated with his body opposite an imaginary line assumed to pass through the middle of both computers. The laptops were placed at a 45-degree angle to horizontal line. The angle at which the computers met was adjusted to be in the middle of the body of the individual (V-shaped layout). Then, since all participants were right-handed, they were asked to type the text displayed on the left laptop to the right laptop as quickly as possible (Figure 2). The same text was used for all subjects. Twenty

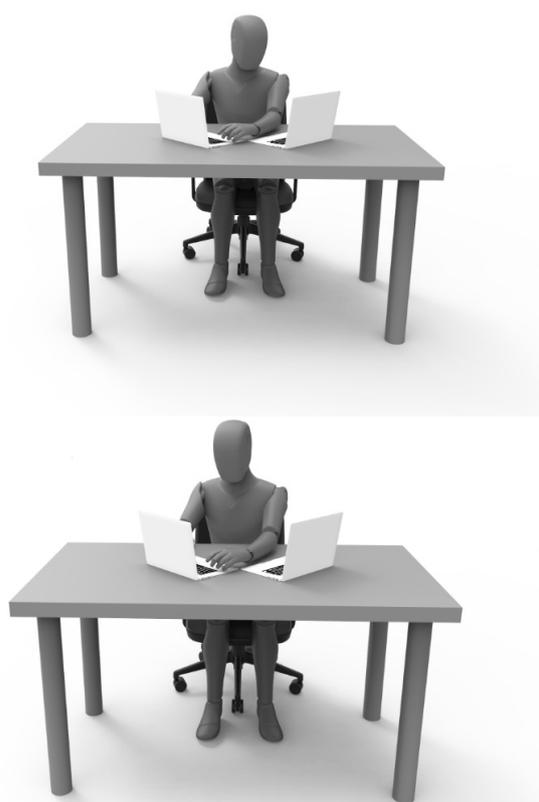


Figure 2. a-b. Visualisation of computer work. a: task copying from the left side computer. b: writing to the right side computer.

minutes later, the typing was stopped, and the individuals were immediately re-evaluated by MRI. The interval between the end of the task and the completion of the the T<sub>2</sub> weighted images was in a maximum of 10 minutes. Subsequently, T<sub>2</sub> relaxation times of the superficial muscles (upper trapezius and sternocleidomastoid) and deeper muscles (longus coli and multifidus/semispinalis cervicis) were calculated from the MRI images.

### Magnetic Resonance Imaging (MRI)

MRI measurements of the individuals were recorded on a 3-Tesla device (MAGNETOM Trio-Tim System; Siemens AG, Erlangen, Germany) available at the National Magnetic Resonance Research Center, Hacettepe University. A 12-channel head and 8-channel neck coil were used together. The individual lay comfortably in the supine position. The head was positioned in a neutral position without rotation, lateral flexion, or excessive lordosis. The T2W sagittal (TR: 4100 ms, TE: 119 ms, ST: 3mm, NEX:2.,0 FA:160.0), T2W axial (TR: 4500 ms, TE:100.0 ms, ST:2mm, NEX:3.0, FA:1500.0) and axial T2 mapping (TR:1000 ms, TE: 13.8 ms, ST:10mm, NEX:2.0 FA:1800.0) images were obtained with the same values from the same plane each time. The T2 axial images were evaluated in OsiriX Lite software (Pixmeo Sarl, Switzerland) by two specialist blind radiologist. The region of interests (ROIs) on axial T<sub>2</sub> mapping sections were drawn freely considering areas of examined muscles at the C4-5 level in all measurements (Figure 3). Because of the areas of examined muscles can be differentiated easily at the level of C4-5, images from this level are used in the analysis. As a result of the measurements, the mean T<sub>2</sub> relaxation time values of the deep and superficial flexor and extensor muscles before and after computer use were measured. From the data obtained, both the T<sub>2</sub> relaxation time of each muscle and the T<sub>2</sub> relaxation time ratios of flexor (FT<sub>2</sub> ratio) and extensor (ET<sub>2</sub> ratio) muscle groups ( $FT_2 \text{ ratio} = \frac{T_{2\text{-deep flexor muscles}}}{T_{2\text{-superficial flexor muscles}}}$  and  $ET_2 \text{ ratio} = \frac{T_{2\text{-deep extensor muscles}}}{T_{2\text{-superficial extensor muscles}}}$ ) were compared by statistical methods.

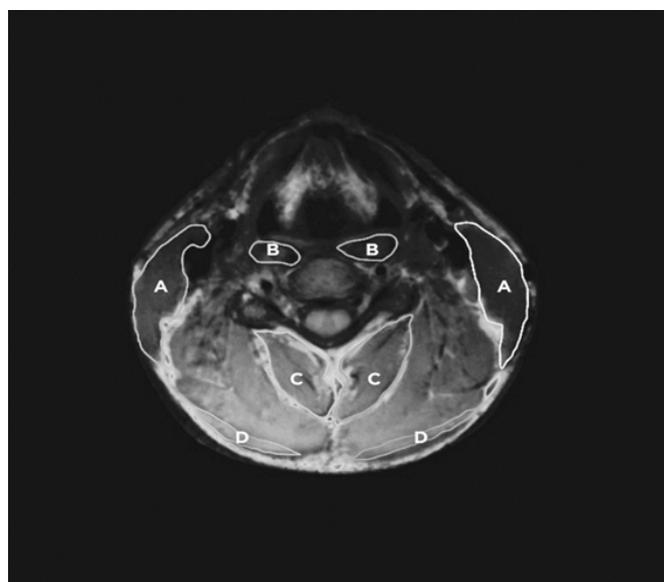


Figure 3. ROIs on axial sections; 'm' for muscle A: sternocleidomastoid m (superficial flexor); B: longus coli m (deep flexor); C: multifidus/semispinalis cervicis m (deep extensors); D: upper trapezius m (superficial extensor).

### Statistical Analysis

The data were analyzed by SPSS for Windows 26.0 (SPSS Inc, Chicago, IL, USA). Descriptive statistics were given as mean±standard deviation. The normal distribution of the variables was examined using visual (histogram graph) and analytical methods (Shapiro-Wilk test). A paired t-test was used for statistical significance between two dependent groups. The significance level was set at p<0.05.

### RESULTS

Twenty-seven male volunteers participated, with a mean age of 20.41±0.74 years (range: 19-22 years) (Table 1). All participants were right-hand dominant. When the T<sub>2</sub> relaxation times before and after computer use were compared, the T<sub>2</sub> relaxation times of the bilateral superficial flexor and extensor muscles increased significantly after the task (p<0.05). However, the changes in T<sub>2</sub> relaxation time of the bilateral deep flexor and extensor muscles were not statistically significant (p>0.05) (Table 2, Figure 4).

FT<sub>2</sub> and ET<sub>2</sub> ratios decreased bilaterally after computer use, indicating that the increase in superficial muscles activity

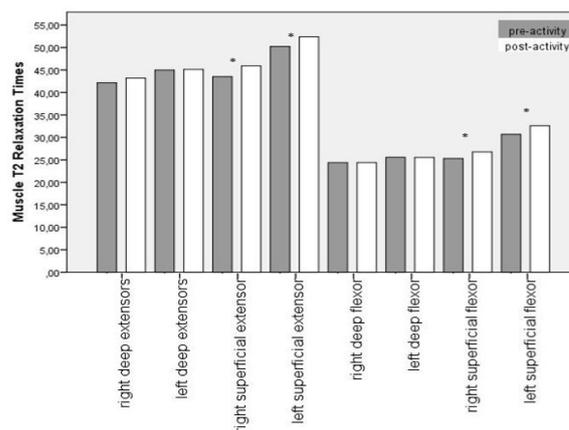


Figure 4. T<sub>2</sub> relaxation times of each muscle. \*: p<0.05

was greater than that of deep muscles. These decreases were statistically significant in all ratios on both sides (p<0.05) (Table 2, Figure 5).

### DISCUSSION

This study evaluated the alterations in the muscular activities of deep and superficial, flexor and extensor cervical muscles indirectly with T<sub>2</sub> relaxation time measurements in healthy individuals after computer use. At the end of this study, post-activity changes in the muscles revealed that T<sub>2</sub> relaxation times of the superficial flexor and extensor muscles were increased on both sides. Moreover, T<sub>2</sub> relaxation times of deep flexor muscles and deep extensor muscles on both sides were not changed. In addition, it was found that changes in T<sub>2</sub> relaxation time of the deep cervical muscles were less than those of the superficial cervical muscles.

Characteristics	Mean±SD	Range
Age (years)	20.41±0.74	19-22
Height (m)	1.77±0.61	1.67-1.90
Weight (kg)	69.93±9.53	53-90
BMI (kg m <sup>-2</sup> )	22.19±2.94	17.11-30.07

SD: Standard deviation, m: Meter, kg: Kilograms, BMI: Body-mass index

Muscles	Pre-activity		Post-activity		p*	Effect size (Cohen's d)**	
	Mean±SD	Min-max	Mean±SD	Min-max		Standardizer	Point estimate
<b>T<sub>2</sub> relaxation times (ms) of extensors</b>							
Deep extensors (right)	42.16±4.60	35.22-53.07	43.20±4.00	36.59-53.30	0.259	2.32464	0.151
Deep extensors (left)	44.98±4.46	37.57-55.37	45.12±3.52	39.84-52.15	0.933	3.03121	0.049
Superficial extensor (right)	43.51±9.79	26.37-64.91	45.90±10.53	26.98-70.83	<0.001	5.04983	0.474
Superficial extensor (left)	50.21±7.48	35.79-69.76	52.39±8.00	41.19-70.65	<0.001	5.08810	0.428
ET <sub>2</sub> ratio (right)	1.00±0.20	0.66-1.51	0.97±0.19	0.61-1.46	<0.001	0.10075	0.286
ET <sub>2</sub> ratio (left)	0.90±0.10	0.72-1.16	0.87±0.10	0.66-1.10	<0.001	0.06442	0.512
<b>T<sub>2</sub> relaxation times (ms) of flexors</b>							
Deep flexor (right)	24.38±2.90	15.55-29.32	24.39±2.52	19.37-28.90	0.155	2.92094	0.001
Deep flexor (left)	25.56±2.88	17.24-30.43	25.54±2.84	20.88-30.66	0.104	2.89703	0.008
Superficial flexor (right)	25.30±3.32	11.55-29.54	26.76±2.16	22.06-30.72	0.018	3.59630	0.406
Superficial flexor (left)	30.70±2.50	26.42-35.33	32.59±3.58	27.60-41.65	<0.001	3.43342	0.553
FT <sub>2</sub> ratio (right)	0.97±0.11	0.80-1.35	0.91±0.10	0.69-1.10	0.022	0.10923	0.535
FT <sub>2</sub> ratio (left)	0.83±0.07	0.65-0.99	0.79±0.11	0.54-1.04	<0.001	0.09458	0.452

\*paired samples t-test, deep extensors: multifidus/semispinalis cervicis; superficial extensors: upper trapezius; deep flexors: longus colli; superficial flexors: sternocleidomastoid; FT<sub>2</sub>ratio= T<sub>2</sub>-deep flexor muscles / T<sub>2</sub>-superficial flexor muscles; ET<sub>2</sub>ratio= T<sub>2</sub>-deep extensor muscles / T<sub>2</sub>-superficial extensor muscles; ms: milliseconds; SD: Standard deviation, Min: Minimum, Max: Maximum

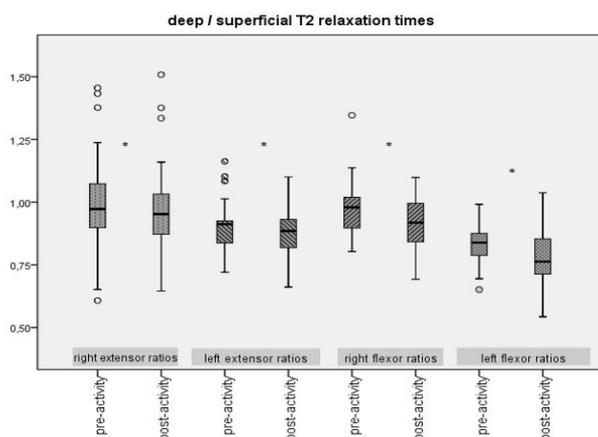


Figure 5. T<sub>2</sub> relaxation ratios of extensor and flexor muscles. \*: p<0.05

In developing societies, neck and back pain are increasing as a result of reasons such as long-term, stressful jobs, that mostly involve the use of VDTs, and the use of VDTs is starting at young ages with mobile phones and becoming an indispensable part of life as age progresses. In a study performed by Park et al.<sup>3</sup> in 2017, young individuals spent 16 minutes gaming on a smart phone, and a photo was taken and EMG measurements were made at 1, 6, 11, and 16 minutes. Significant increases in neck flexion angle and erector spinae and lower trapezius muscle activities were found in each measurement. At the end of the study, it was shown that neck pain occurred in the participants and this pain might be associated with the changes in muscle activities and deterioration in cervical alignment. In a study by Johnston et al.,<sup>13</sup> in which 85 active office workers (33, no pain; 52, pain) and 22 nonworking (control group) women participated, cervical muscle activities during a task were examined, and it was found that the workers with and without pain had higher levels of muscle activation during the tasks in the sternocleidomastoid, anterior scalene, and cervical erector spinae muscles than the controls, and the upper trapezius activity of all workers (with pain and without pain) was higher than that of the control group. In the conclusion of that study, it was stated that working people both with neck pain and without neck pain are at risk for cervical musculoskeletal problems.<sup>13</sup>

The current finding of an increase in T<sub>2</sub> relaxation times of the superficial flexor and extensor muscles was similar to the findings of studies by Park<sup>3</sup> and Johnston.<sup>13</sup> However, there was no such finding in the deep muscles of the individuals in current study. This may have been compensated by the increase in the ipsilateral superficial muscles. Similar to results of this study, Jull et al.<sup>10</sup> showed that the increase in the EMG activity of superficial muscles during the craniocervical test was greater than the increase in the activity of deep muscles, too. Also, a study conducted by Fang et al.<sup>4</sup> demonstrated that the use of dual monitors led to increased activation of superficial cervical muscles in healthy individuals. Similarly, a study conducted by Christensen and colleagues<sup>12</sup> showed a relationship between prolonged computer use, increased pain, and heightened activity of the trapezius muscle.

Although previous literature has established a relationship between muscle activation and pain, the absence of pain level measurements during computer use in current study represents a limitation in demonstrating how activation levels affect healthy individuals.

When the FT<sub>2</sub> ratio and ET<sub>2</sub> ratio were compared before and after the task, there were decreases on both sides. This result indicates that the increase in superficial muscles' activity was greater than in deep muscles. It was thought that the most important reason for the greater increase in the T<sub>2</sub> relaxation times of the superficial muscles was the rapid and repetitive head movements during the text copying activity, which was performed as fast as possible between the two computers. The knowledge that superficial muscles such as the sternocleidomastoid and upper trapezius become more active with large cross-sectional areas in more torque-releasing movements, and deep muscles such as the longus colli, multifidus, and semispinalis cervicis are more active in stabilizing activities<sup>8,9</sup> supported the opinion of the authors. Also findings from a study by Roijeson et al.<sup>8</sup> support the results of this study, showing that the central nervous system develops distinct mechanisms for the use of deep and superficial cervical muscles depending on task stability. In addition, the decreases in FT<sub>2</sub> ratio and ET<sub>2</sub> ratio may suggest that an imbalance between the motor controls of the muscles can be one of the important reasons underlying neck problems in office workers. Therefore, the training of deep muscles, which provide stabilization during neck movements, may play an important role in the prevention of musculoskeletal problems.

Baghi et al.<sup>23</sup> investigated activation of the cervical extensor muscles by examining muscle thickness changes using ultrasound in chronic nonspecific neck pain patients and healthy controls during a short arm-lifting task. They showed that the most significant thickness increase was in the multifidus muscle in both groups, but the multifidus thickness in the painful group was not as high as the thickness in the healthy group. Their study indicates that multifidus activation acts as a stabilizer during the increased compensatory activity of superficial muscles, especially in upper extremity tasks.<sup>23</sup> In cases where painful conditions become permanent, architectural changes in the multifidus prevent the muscle from assuming this task. Studies have shown that there could be fat infiltrations and a decrease in the cross-sectional area of the multifidus with pain.<sup>9,24</sup> Although muscle thickness was not measured in current study, multifidus T<sub>2</sub> relaxation times in healthy individuals were not increased, unlike the results reported by Baghi et al.<sup>23</sup> However, when the proportional changes were examined, it was seen that the increase in the relaxation time of the superficial muscles was more pronounced. The reason for this situation may suggest that a task such as typing with computer creates larger activity changes on the neck muscles and the deep muscles cannot offset these activity changes.

Cagnie et al.<sup>25</sup> found that the activity of the deep cervical flexor muscles decreased together with pain in their study in which they examined the T<sub>2</sub> relaxation times of the deep cervical flexor muscles during a craniocervical test. Schomacher et

al.,<sup>26</sup> in their study in which they examined the differences in semispinalis cervicis activity between healthy individuals and individuals with neck pain, showed that chronic neck pain reduced semispinalis cervicis activity and impaired neural control of deep cervical extensor muscles. The increase in upper trapezius muscle activity during upper extremity weight-bearing tasks is an important finding for explaining the pain caused by repeated activities. The absence of a similar increase in multifidus/semispinalis cervicis activity, despite increased upper trapezius activation, may act as a trigger for neck pain.

Previous study have shown that following activities involving muscle activation, such as exercise, the increase in T<sub>2</sub> relaxation time within the muscle can last up to 30 minutes, with a reported half-life of approximately 7 minutes.<sup>15</sup> Therefore, to accurately measure changes in T<sub>2</sub> relaxation time in the muscles after task completion, it is crucial to perform MRI scanning immediately after the task ends. In this study, the second imaging session was conducted as quickly as possible after task completion. Due to the inherent requirements of MRI procedures, including patient positioning, scanner preparation, and sequence completion, all scans were finalized within a maximum of 10 minutes. Thus, the imaging timeline in our study aligns with the previously reported duration and half-life of T<sub>2</sub> relaxation time changes in the literature.

### Limitations

This study has several limitations. Although the methodology involved MRI measurements at only a single anatomical segment, it would be beneficial for future research to evaluate muscle activation across additional segments. Furthermore, the absence of pain level assessments in current study represents a limitation, and correlating these data with changes in T<sub>2</sub> relaxation times in future studies would provide valuable insights. The study population consisted only of young male participants, which limits the generalizability of the findings. Therefore, future studies would benefit from including a broader population and conducting comparisons across groups such as males vs. females and younger vs. older individuals.

### CONCLUSION

In parallel with findings from other studies in the literature, it can be concluded that increased work intensity may lead to muscular imbalances during tasks such as computer use. Fatigue and pain may cause a greater increase in superficial muscle activity compared to deep muscles. This disruption in neural and motor control can contribute to the development of musculoskeletal disorders. Therefore, assessing changes in motor control and implementing treatment or preventive programs, including individualized exercises targeting underactive muscles or ergonomic interventions, may be beneficial. Enhancing control of both deep and superficial flexor and extensor muscles could improve the muscular response to increasing loads and stresses, thereby helping to prevent musculoskeletal disorders.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

This study has been approved by the Hacettepe University Clinical Researches Ethics Committee (Date: 10.01.2019, Decision No: 2019/01-48).

### Informed Consent

Written informed consent was obtained from all individual participants prior to their inclusion in the study. Participants were fully informed about the study's aims, procedures, potential risks and benefits, and their rights-including the right to withdraw at any time without consequence. All participants voluntarily signed a written informed consent form.

### Peer Review Process

This manuscript was subject to external peer review.

### Conflict of Interest

The authors declare no conflicts of interest related to this study.

### Financial Disclosure

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### Author Contributions

Conceptualization: E.K., N.K., H.K.K.O.; Methodology: E.K., N.K., C.T., H.K.K.O.; Data collections: E.K.; Data analysis: Ş.P.S., E.G.; Analysis: E.K., C.T.; Resources: N.K., H.K.K.O.; Writing: E.K., C.T., Ş.P.S., E.G.; Review and editing: All authors; Supervision: N.K., H.K.K.O.

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