

Investigation of the impacts of traumatic medullar injury on the neuroanatomic structure of sensorimotor cortical areas

Investigação dos impactos da lesão medular traumática na estrutura neuroanatômica de áreas corticais sensoriomotoras

Gabriela Dyonísio¹, Dhainner Rocha Macedo¹, Eduardo Batista de Carvalho¹, Túlio Augusto Alves Macedo², Andrea de Martino Luppi², Alcimar Barbosa Soares¹

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ABSTRACT: The loss of motor control is one of the most debilitating consequences of spinal cord injury. Partial or complete disruption of the sensory ascending and descending motor pathways renders the person unable to walk and perform various functional activities. The occurrence of spontaneous sensorimotor cortical reorganization immediately after injury and continuously over time may occur in specific areas, as well as in the entire cerebral cortex, as evidenced in previous studies. Understanding the complex interaction between anatomical changes, functionality, and cortical reorganization induced by spinal cord injury and defining its effects is crucial for evaluating current rehabilitation therapies and improving the subject's quality of life. In this study, magnetic resonance images were obtained from individuals with thoracic spinal cord injury to explore morphological changes in the cortical Gray Matter (GM) and White Matter (WM) of the cerebral cortex after the injury. Two groups of volunteers were recruited for this research (spinal cord injury - Experimental Group; and non-injured - Control Group). Intergroup comparison was performed considering time after injury. The global evaluation of the brain did not detect changes in the total GM volume. Volumetric differences in cortical GM were found in the precentral gyrus and lower precentral sulcus. The change observed in the precentral gyrus occurred in the left hemisphere, responsible for motor control of the right lower limb, compatible with the dominance of the volunteers of both groups (right-handed). The findings provide evidence that post-injury time does not have a significant influence on the overall volumetric loss. However, changes in specific regions associated with motor control of regions below the lesion were found in this study.

Keywords: Spinal cord injury, Paraplegia, Cortical changes, Neuroplasticity.

RESUMO: A perda do controle motor é uma das mais debilitantes consequências da lesão medular espinhal. A interrupção parcial ou completa das vias ascendentes sensoriais e vias descendentes motoras tornam o indivíduo incapaz de caminhar e realizar atividades de maneira funcional. A ocorrência da reorganização cortical sensorio-motora espontânea imediatamente após a lesão e continuamente ao longo do tempo pode ocorrer em áreas específicas, bem como em todo córtex cerebral, evidenciado em estudos prévios com uso de exames de imagem. Entender a complexa interação entre alterações anatômicas, funcionalidade e reorganização cortical induzidas pela lesão medular, bem como definir seus efeitos, é crucial para avaliação das terapias de reabilitação e consequente melhora na qualidade de vida do sujeito. Neste estudo, imagens de Ressonância Magnética foram obtidas para explorar alterações morfológicas na Substância Cinzenta (SC) e Substância Branca (SB) no córtex cerebral de indivíduos com lesão medular torácica. Dois grupos de voluntários foram recrutados para esta pesquisa (portadores de lesão medular - Grupo Experimental; e não-lesionados - Grupo Controle). A comparação intergrupos foi realizada considerando ainda o tempo pós-lesão. A avaliação global do encéfalo não detectou alteração no volume da SC total. Diferenças volumétricas na SC cortical foram verificadas no giro pré-central e no sulco pré-central inferior. A alteração observada no giro pré-central ocorreu no hemisfério esquerdo, responsável pelo controle motor do membro inferior direito, compatível com a dominância dos voluntários de ambos os grupos (destros). Os achados fornecem evidências de que o tempo pós-lesão não influenciou em maior perda volumétrica global significativa. No entanto, alterações em regiões específicas, associadas ao controle motor de regiões abaixo da lesão, foram evidenciadas neste estudo.

Palavras chave: Lesão medular; Paraplegia; Alterações corticais; Neuroplasticidade.

1. Federal University of Uberlândia, MG, Brazil. ORCID: Dyonísio G: <https://orcid.org/0000-0001-8342-1510>; Carvalho EB: <https://orcid.org/0000-0002-5734-7668>; Soares AB: <https://orcid.org/0000-0003-1100-3533>. Email: gabi_dyonisio@yahoo.com.br, dhainner@gmail.com, eduardobcarvalho@yahoo.com.br, alcimar.soares@gmail.com.
2. General Hospital of Uberlândia, MG, Brazil. Hospital de Clínicas da Universidade Federal de Uberlândia, Uberlândia, Minas Gerais, Brasil. ORCID: Macedo DB: <https://orcid.org/0000-0002-9547-5054>; Luppi AM - <https://orcid.org/0000-0002-2785-6605>. Email: andrealuppimed@gmail.com, amacedo@hotmail.com

Correspondence: Alcimar Barbosa Soares. Universidade Federal de Uberlândia, Faculdade de Engenharia Elétrica. Lab. de Engenharia Biomédica, Bloco 1E – Campus Sta Mônica Uberlândia, MG, Brasil. CEP: 38400-000. Email: alcimar.soares@gmail.com

INTRODUCTION

Spinal Cord Injury (SCI) interrupts the flow of information between the brain and regions below the injury. As a result, degeneration of the ascending and descending pathways, with consequent loss of motor control, reduction, or total absence of sensitivity in body segments below the level of the injury, and neuropathic pain affect injured people with a consequent deterioration in the quality of life^{1,2,3}.

In addition to the motor and sensory changes resulting from the injury, instantaneous and progressive molecular changes occur in the spinal cord and the Central Nervous System (CNS)^{4,5,6}. Cortical and spinal atrophy has been reported in several studies^{2,4,7,8,9} and occurs as a result of a combination of pathophysiological processes that include axonal demyelination, degeneration, and death of neurons¹⁰. In the CNS, a consequence of spinal trauma is the formation of new connections and the reorganization of cortical structures¹¹. These post-injury changes, however, are not always beneficial. For example, neuroplasticity can lead to phantom sensations and pain. In addition, regenerated axons can project to areas of the brain that are remapped, leading to rearrangements in cortical activation patterns and spatial changes in activation maps¹.

Cortical reorganization is not the only alteration detected in the cortex of individuals who have suffered trauma to the spine. For instance, a reduction in the white and gray matter has been detected in volunteers after SCI in the somatosensory cortex^{4,7,8,10,12}. However, other similar structural studies do not report the occurrence of cortical morphological changes^{3,13}. The differences between the studies can be attributed to methodological aspects, such as the level of spinal injury, time after trauma, rehabilitation therapies, secondary deficits, and age^{12,13}. Therefore, the effect of SCI on cortical reorganization is still not very clear, and further studies are needed to help elucidate the differences observed¹⁴.

Understanding the changes in the sensorimotor cortex of individuals who have suffered spinal cord trauma can allow for more information to be added to ongoing research, directly benefiting the effectiveness of rehabilitation therapies and technology development, with consequent improvement in the quality of life of affected individuals¹⁴. Furthermore, progressive cortical atrophy could represent a severe problem for current strategies used to develop assistive devices, such as brain-computer interfaces or neuroprostheses that directly interface with the central nervous system¹².

Given the above, this work aims to verify the occurrence of macrostructural changes in the cerebral cortex of individuals who suffered traumatic spinal cord injury and presented paraplegia as a sequela and analyze how such changes, if observed, are affected by the time following the lesion.

MATERIALS AND METHODS

Twelve volunteers participated in this research, six with thoracic SCI (Experimental Group – EG) and six volunteers non-injured (Control Group – CG). The level, extension, and severity of the injury were measured using the American Spinal Injury Association Impairment Scale (ASIA)¹⁵. EG inclusion criteria: spinal cord injury of traumatic etiology, absence of brain or cognitive impairment resulting from spinal cord trauma confirmed by Magnetic Resonance Images (MRI), and clinical neurological evaluation performed by a neurologist. All participants were informed about the purpose of the study and signed an informed consent form.

This research was approved by the National Research Ethics Committee (Protocol Number: 64580116000005152).

Image acquisition and processing

All volunteers underwent MRI to collect brain images. The acquisition of images was performed with MRI equipment Brand GE, model Signa HDxt 1.5 Tesla. The acquisition parameters used were: T1 volumetric sequence (3D) of the skull, resolution of 256 × 256, and voxels of 3×3×3 mm³.

During the image acquisition process, positioners were used to minimize head movement (Figure 1). In addition, earplugs were made available to the subjects. Contrasts were not administered to obtain the images.



Figure 1. Subject positioned on the MRI scanner.

The 3D images were processed and segmented to calculate Gray Matter (GM) and White Matter (WM) volumes. The total volumes (WM and GM) of each region of interest (ROI) were calculated using segmented images and expressed as fractions of their total (total intracranial) volume in voxels. Structural data were processed using FreeSurfer Software Suite V6.0.0. In this research, the ROIs were those primarily associated with sensorimotor control: precentral gyrus (PrCG), postcentral gyrus (PoCG), superior precentral sulcus (SPrCS), inferior precentral sulcus (IPrCS), and postcentral sulcus (PoCS) of the right and left hemispheres.

Statistics

The global brain volume and the volumes of the ROIs for GM and WM were calculated and compared

between the control and experimental groups. The student's t-test was used to compare the results between groups (independent samples), with a 95% confidence level. For intra-group and inter-group inferential analysis, the Hedges' g test was used¹⁶.

RESULTS

Table 1 summarizes the main characteristics of the volunteers recruited for the EG and CG from whom MRI data were collected (Figure 1).

Table 1. Characteristics of volunteers who participated in the study.

Group	Identif.	Sex	Age (years)	Time of Injury (years)	Etiology	AIS	Injury Level	Dominance
EG	EV1	M	30	06	MA	A	T4-T5	Right- handed
	EV2	F	20	01	MA	B	T5-T7	Right-handed
	EV3	M	53	03	MA	A	T3-T4	Right-handed
	EV4	M	45	14	FI	A	T12	Right-handed
	EV5	F	18	05	AA	A	T7-T8	Right-handed
	EV6	M	18	02	AM	A	T6	Right-handed
CG	CV1	F	43					Right-handed
	CV2	M	50					Right-handed
	CV3	M	27					Right-handed
	CV4	M	24					Right-handed
	CV5	F	21					Right-handed
	CV6	F	27					Right-handed

EG: Experimental Group; CG: Control Group; EV: Experimental group volunteer; VC: Control group Volunteer; MA: Motorcycle Accident; AA: Automobile Accident; FI: Firearm Injury; T: Thoracic.

Total volumes

After collecting the MR images, the volumetric proportions of the global brain structures for the GM of the volunteers in the CG and EG groups were calculated.

Figure 2 shows the comparison between groups for total and cortical GM volumes. Statistical analysis showed no statistically significant difference between groups for both cases (Table 2).

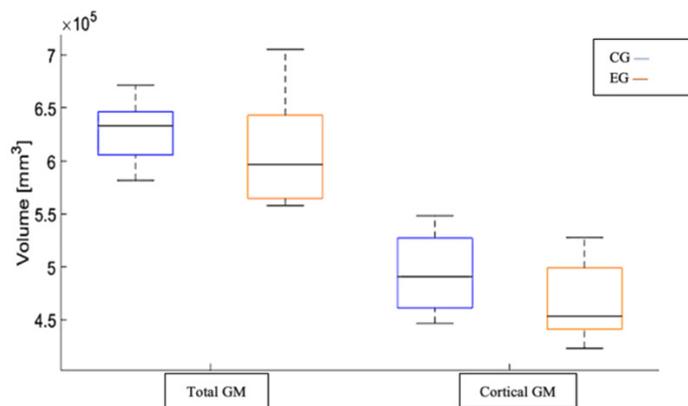


Figure 2. Comparison of total and cortical GM volume between EG and CG.

Table 2. Comparison of total and cortical GM volume between EG and CG.

	t Test		g Test	
	t	p-Value	g	Magnitude
Total GM	-0,69	0,51	-0,37	Small
Cortical GM	-1,19	0,26	-0,63	Medium

When comparing the total GM volume of each EG volunteer with the mean of the total GM of the CG volunteers in relation to the post-injury time (Figure 3a), we did not observe a possible pattern correlating changes

in the total GM volume with post-injury time. In addition, no significant correlation was observed between cortical GM volume and post-injury time (Figure 3b).

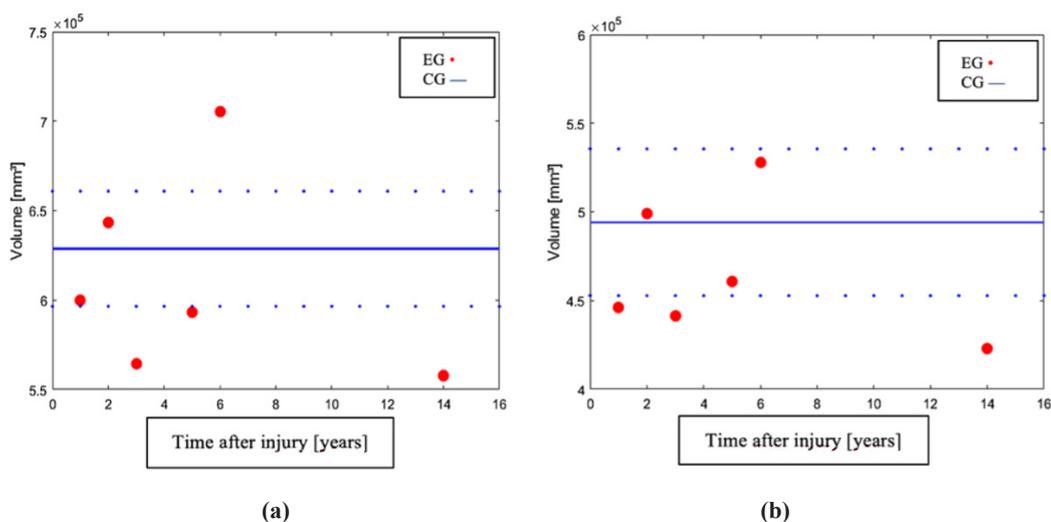
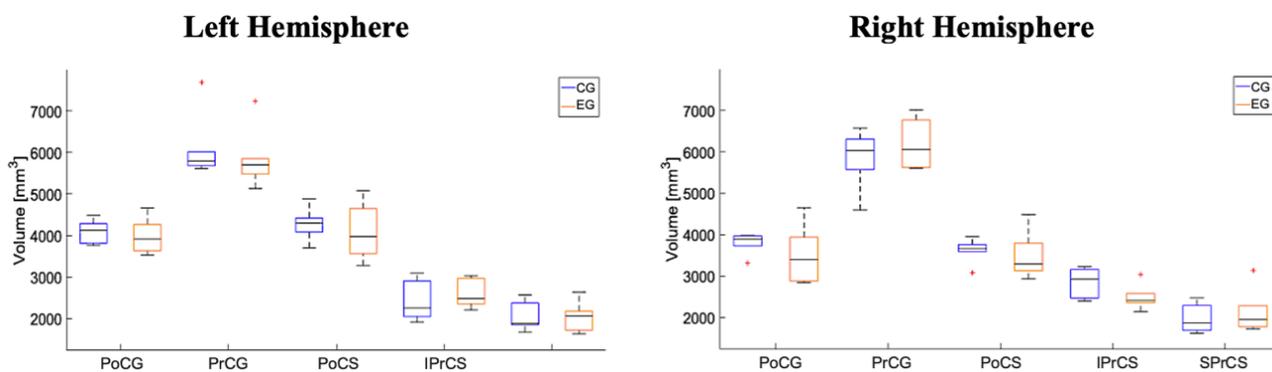


Figure 3. a) Total GM volume of EG volunteers compared to the mean total GM volume of CG volunteers (blue line), distributed according to post-injury time; b) Cortical GM volume of EG volunteers compared to the mean cortical GM volume of CG volunteers (blue line), distributed according to post-injury time.

Volume of ROIs

Figure 4 shows the comparisons of GM volumes of the ROIs in the sensorimotor regions for the control and experimental groups. The t-test did not show a statistically significant difference between the groups for any of

the ROIs. However, the g test (Table 3) showed a large magnitude of the effect (significant differences) when the GM volumes of the precentral gyrus of the left hemisphere and the inferior precentral sulcus of the right hemisphere were compared.



*: Large magnitude of effect for the Hedges' g test.

Figure 4. Distribution of GM volumes of the ROIs in the left and right hemispheres for both groups of volunteers.

Table 3. Comparison of the cortical GM volumes of the various ROIs between the EG and GC for the left and right hemispheres.

Hemispheres	ROIs	t Test		g Test	
		t	Valor-p	Hedges g	Magnitude
Left	PoCG	-0,53	0,61	-0,28	Small
	PrCG	-1,84	0,10	-0,98	Great
	PoCS	-0,62	0,55	-0,33	Small
	IPrCS	0,72	0,49	0,39	Small
	SPrCS	0,06	0,95	0,03	Insignificant
Right	PoCG	-0,93	0,38	-0,50	Small
	PCG	0,89	0,40	0,47	Small
	PoCS	-0,50	0,63	-0,27	Small
	IPrCS	-1,89	0,09	-1,01	Great
	SPrCS	0,65	0,53	0,35	Small

Figure 5 shows the GM volumes of the ROIs that showed the most significant differences in the statistical analysis (left PrCG (a) and right IPrCS (b)) for the EG

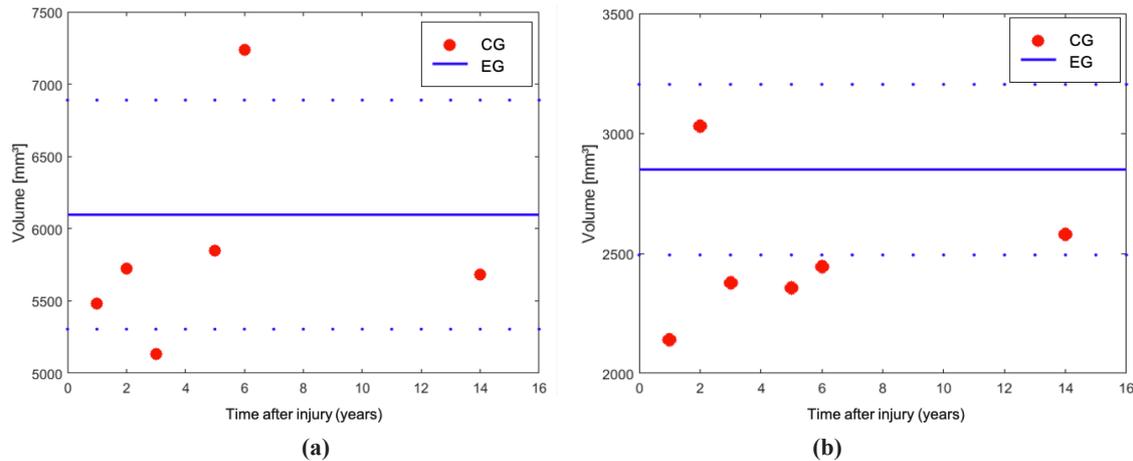


Figure 5. (a) Distribution of cortical GM volumes of the left PrCG of the EG volunteers in relation to the time after injury of each volunteer; (b) Distribution of cortical GM volumes of the right IPrCS of the EG volunteers in relation to the time after injury of each volunteer. The horizontal blue line represents the mean value of the GM volume of the regions for the CG volunteers. The dotted lines represent the maximum and minimum values for the CG volunteers.

The evaluation of the GM volumetric proportion in the left PrCG of the EG volunteers taking into account the time after injury, showed relevant differences in VE1 and EV3 compared to the CG mean GM volume. In the right IPrCS, differences were observed in the cortical GM volumes for four EG volunteers (EV1, EV2, EV3, EV5) compared to the CG mean GM volume.

DISCUSSION

Our results show that spinal cord injury causes noticeable changes in GM volume in the precentral gyrus and inferior precentral sulcus. In addition, cerebral atrophy was evident in the motor system that directly innervates the paralyzed lower limbs (precentral sulcus). Cortical alterations after SCI have been previously reported in the literature^{4,8,13,14,17}.

The total research sample included volunteers of both sexes, aged 18 to 54 years. All individuals were right-handed. The control group was chosen at random. Among volunteers with spinal cord injury, there was a prevalence of males, which corroborates world statistics, with a prevalence of spinal cord injury four times higher than in women^{18,19}. Post-injury time ranged from 1 to 14 years. The entire EG sample showed SC lesion at the thoracic level - therefore, homogeneous in terms of the level of the affected spine, allowing for intragroup comparisons. This characteristic of the experimental group is an essential aspect of the present study since inhomogeneity has been reported as difficult to achieve in previous studies¹⁴. Only traumatic injuries were included in this study. Worldwide

data indicate collisions between motor vehicles as the leading cause of traumatic spinal cord injury¹⁹. In this study, 83% of the injured volunteers suffered car accidents, with a prevalence of motorcycle accidents.

In addition to volumetric proportion measurements in the present study, the cortical GM surface area and mean thickness were obtained for several ROIs associated with sensorimotor control (precentral gyrus, postcentral gyrus, superior precentral sulcus, inferior precentral sulcus, and postcentral sulcus of the right and left hemispheres). Our results show important alterations in the left precentral gyrus, responsible for controlling the motor of the lower right limb, and compatible with the dominance of the volunteers in both groups (right-handed). Furthermore, a comparison of the GM volume in the precentral gyrus of the EG volunteers compared to the mean GM of the CG, considering the time after spinal cord trauma, showed various differences, but with a higher incidence of atrophy for the EG volunteers compared to the mean GM of CG volunteers. In the inferior precentral sulcus, smaller volumes of cortical GM were observed in the CG volunteers compared to the CG average for five of the six EG subjects (Time after injury equal to 1, 3, 5, and 6 years). The reduction in GM volume in the primary motor cortex is indicative of atrophy due to retrograde degeneration¹⁰. However, it can also result from decreased cortical connectivity due to a reduction in dendritic column density²⁰ or angiogenesis²¹.

The EG volunteer with 14 years of injury (VE4) had an equal mean GM volume compared to the mean for the CG. This result may be due to a long time after injury, the

unmasking of dormant synapses and axonal budding that can compensate for the loss of GM, rehabilitation therapies that can induce compensatory mechanisms in individuals with chronic SCI²².

As it can be seen, our results differ from the study of Chen et al.¹⁴, which did not show changes in the cortical volume of sensorimotor cortical areas of SCI individuals. Instead, the aforementioned authors found changes only in the dorsal anterior cingulate cortex, bilateral anterior insular cortex, orbital frontal cortex bilateral, and right superior temporal gyrus.

Comparisons of the total brain volumetric proportions between our groups of volunteers did not show statistical differences (Figure 2). Similar findings were observed in a previous study¹³, which did not show significant volumetric changes when comparing the volume of the entire brain between groups of injured and uninjured individuals. When comparing EG and CG, the total and the cortical gray matter volume did not show volumetric alterations (Figure 3). The detection of cortical atrophy seems to depend on the individualized assessment of the sensorimotor regions. Thus, such alterations in highly individualized regions are probably not enough to be observed in a global brain assessment^{8,12}. However, comparisons between the volumes of total GM and cortical GM between groups, EG and CG, considering the post-injury time, detected macrostructural changes. The findings corroborate the literature, where previous studies detected alterations in the cortex of animals and humans after spinal cord injury^{14,22,23}. The total GM of the EG compared to the mean of the total GM of the CG evidenced significant volumetric changes in one volunteer (EV1 - post-injury time of 6 years), with a greater volume of total GM (Figure 3a). Two volunteers from the EG (EV3 and EV4 - post-injury time of 3 and 14 years, respectively) presented a significant reduction in the total GM volume compared to the CG.

When comparing the volumetric proportion of the cortical GM of the EG with that of the CG, three volunteers showed a significant decrease (Figure 3b). Those individuals had various post-injury times (01, 03, and 14 years respectively). The volunteer with longer time after injury (14 years) showed more significant atrophy of the cortical GM. When the characteristics of the volunteers were analyzed to correlate with the changes observed, it was observed that two of the three individuals who showed a decreased volume of total and cortical GM were those with the highest age range (53 and 45 years old, respectively). Hence, age seems to influence changes in cortical volume after SCI. These findings do not corroborate the study carried out by Höller et al.¹², who analyzed atrophic changes in the somatosensory cortex of injured volunteers aged between 26 and 50 years and showed no evidence of age-related changes at the time of the injury.

Several researchers suggest that the changes that occur in the cerebral cortex after spinal cord trauma can

be caused by direct or secondary Wallerian degeneration. Freund et al.² observed atrophy of the corticospinal tract and a reduction of GM in the sensorimotor cortex only 40 days after spinal cord injury. The volumetric changes can be attributed to the demyelination of axons and the atrophy of neuronal cell bodies. Gray matter volume reduction has also been reported in the literature by other authors. For example, Chen et al.¹⁴ explored changes in brain gray matter volume after spinal cord injury considering post-injury time. The study showed a significant decrease in GM in the anterior cingulate cortex, bilateral anterior insular cortex, bilateral orbital frontal cortex, and right superior temporal gyrus. However, the association between time resulting from the injury and atrophy was not verified. Karunakaran et al.²³ attributed the structural changes to different levels of spinal injury. Volunteers with tetraplegia had a lower volume of GM when compared to the group of volunteers with paraplegia (both compared to a control group). The reduction in GM was positively correlated with post-injury time in both subgroups (paraplegia and quadriplegia). According to the authors, GM atrophy after SCI was affected by the lesion level, with greater volume loss associated with lesions occurring at the cervical level. Wang et al.²² detected GM atrophy in regions of the sensorimotor cortex, including bilateral sensorimotor cortex, supplementary motor area, as well as white matter reduction in the corticospinal tract. Changes in GM were positively correlated with time after injury. Atrophy in the corticothalamic-spinal pathways suggested that LM may result in degenerative changes in specific regions of the sensorimotor system, as evidenced in this study.

CONCLUSION

One of the most debilitating consequences of a spinal cord injury is the loss of motor control. The absence of lower limb movement causes rearrangements in cortical maps and macrostructural changes. Therefore, understanding the changes that may occur in the sensorimotor cortex has a prognostic value, as progressive cortical atrophy could represent an obstacle to rehabilitation therapies. In addition, the knowledge of how brain alterations occur and the factors that can influence them allows a better result in rehabilitation therapies, the development of technologies, and, consequently, an improvement in the quality of life of individuals. In general, the comparison between global brain volume among volunteers using magnetic resonance images did not show significant changes. In addition, no pattern or trend was observed related to a significant effect of time after injury on the total and cortical grey matter volumes. However, volumetric changes in gray matter were observed when specific regions responsible for motor control were analyzed (precentral gyrus and inferior precentral sulcus). The alteration observed in the precentral gyrus occurred in the left hemisphere, responsible for the

motor control of the right lower limb, compatible with the dominance of volunteers of both groups (right-handed).

In the inferior precentral sulcus, the alteration occurred in the left hemisphere.

Author contributions: *Dyonísio G:* Recruitment of volunteers, data and statistical analysis, main writer of the manuscript; *Carvalho EB* and *Macedo DR:* Magnetic Resonance Image collection, pre-processing/image processing and manuscript writing; *Macedo TAA* and *Luppi AM:* Patient and healthy assessment, definition of image collection protocols, analysis of clinical findings and manuscript writing; *Soares AB:* Head of the research project, clinical finding and image analyses and manuscript writing.

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