

Effects of virtual reality therapy on upper limb function after stroke and the role of neuroimaging as a predictor of a better response

Efeitos da terapia de realidade virtual na função do membro superior após AVC e o papel da neuroimagem como preditor de melhor resposta

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ABSTRACT

Background: Virtual reality therapy (VRT) is an interactive intervention that induces neuroplasticity. The aim was to evaluate the effects of VRT associated with conventional rehabilitation for an upper limb after stroke, and the neuroimaging predictors of a better response to VRT. **Methods:** Patients with stroke were selected, and clinical neurological, upper limb function, and quality of life were evaluated. Statistical analysis was performed using a linear model comparing pre- and post-VRT. Lesions were segmented in the post-stroke computed tomography. A voxel-based lesion-symptom mapping approach was used to investigate the relationship between the lesion and upper limb function. **Results:** Eighteen patients were studied (55.5 ± 13.9 years of age). Quality of life, functional independence, and dexterity of the upper limb showed improvement after VRT ($p < 0.001$). Neuroimaging analysis showed negative correlations between the internal capsule lesion and functional recovery. **Conclusion:** VRT showed benefits for patients with stroke, but when there was an internal capsule lesion, a worse response was observed.

Keywords: Stroke; neuroimaging; virtual reality exposure therapy.

RESUMO

Introdução: A realidade virtual (RV) é uma intervenção interativa que induz a neuroplasticidade. O objetivo deste estudo foi avaliar os efeitos da RV associado à reabilitação convencional na função do membro superior após o AVC e as características preditores de neuroimagem de melhor resposta a esta terapia. **Métodos:** os pacientes com AVC foram selecionados, e as características neurológicas, a função do membro superior e a qualidade de vida foram avaliadas. A análise estatística foi realizada por meio de modelo linear geral comparando resultados pré e pós-intervenção. As lesões foram segmentadas na tomografia computadorizada após o AVC. A abordagem de mapeamento da lesão-sintoma baseada em voxel foi utilizada para avaliar a relação entre a lesão e a função do membro superior. **Resultados:** Foram estudados 18 pacientes (8 mulheres, $55,5 \pm 13,9$ anos). A qualidade de vida, independência funcional, características funcionais e destreza do membro superior apresentaram melhora após RV ($p < 0,001$). A análise de imagem mostrou correlações negativas principalmente entre a cápsula interna e a recuperação funcional do membro superior. **Conclusão:** A RV mostrou benefícios para pacientes com AVC, mas quando houve lesão da cápsula interna apresentaram pior resposta à terapia.

Palavras-chave: Acidente vascular cerebral; neuroimagem; terapia de exposição à realidade virtual.

Stroke can be defined as a neurological deficit resulting from focal and acute central nervous system injury. It is considered a major cause of mortality and disability worldwide¹. Stroke is the second leading cause of death in Brazil and the leading cause of chronic disability in adults, resulting in socio-economic consequences and reduced quality of life. Therefore,

it is an important public health problem, particularly because of long-term dependence on public health services^{2,3}.

Cerebrovascular injury may damage the cells of the cortex and emerging axons, generating dysfunction of the upper motor neurons. Motor function can be impaired, reducing functional capacity, particularly that of the upper limbs⁴.

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Conflict of interest: There is no conflict of interest to declare.

Received 07 February 2018; Received in final form 28 June 2018; Accepted 29 June 2018.

Support: Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP). Processo 2016/17914-3.

Approximately 85% of individuals experience hemiparesis immediately after the stroke, particularly in an upper limb, and 55%–75% of these individuals have persistence of motor deficits, making it difficult to return to work and leisure, consequently worsening their quality of life⁵.

Epidemiological clinical studies have suggested that 33%–66% of stroke patients had no motor recovery after six months. Several techniques aiming to improve upper limb function are still being developed. However, the implementation of these techniques requires great team work, a high degree of specialization, and requires more time^{5,6}. Currently, there are new approaches to rehabilitation, and virtual reality is still developing, with the objective of restoring the functional capacity of individuals after stroke as an easy, interactive, and low-cost intervention^{7,8}.

The objective of stroke rehabilitation is to provide maximal physical, functional, and psychosocial recovery for the patients⁹. Comprehensive rehabilitation initiated early after stroke (within the first 24 hours) is generally accepted as being associated with better motor outcomes for these patients⁹. Strength training is an important part of the therapeutic process for upper-limb motor impairment after stroke¹⁰.

Virtual reality is defined as any hardware or software system that provides a simulated environment with real or imagined conditions that allow participating individuals to interact with the environment. The interaction is made by body movements using motion capture technology or by manipulating a device¹¹. This interaction generates information necessary for proper understanding of the movement with particular emphasis on the upper limbs¹². The technique consists of an avatar (graphic representation of the person) generated by the video game, where the individual manages a wireless control, directing the movement during the practice of different activities⁵. This is a good option for rehabilitation for individuals with stroke due to the variety of nonimmersive video game systems developed by the entertainment industry for home use.

This wide availability makes virtual reality an accessible and inexpensive rehabilitation method for rehabilitation centers¹³. Despite the ease of application, virtual reality therapy (VRT), added to conventional physical therapy has not been associated with a better outcome than recreational activity¹³. Adverse events usually are mild and the main effects described are transient dizziness and headache, pain and numbness^{13,14}. Time since the onset of stroke, severity of impairment, and the type of device (commercial or customized) usually do not influence the outcome¹⁴. However, the variable methodology is an important bias for these investigations¹⁴. Therefore, virtual reality is still a promising tool. Some authors have reported that VRT can be combined with conventional rehabilitation to improve upper limb function after stroke^{15,16}. The clinical situations wherein VRT may best be used have not yet been established in the literature. Also, the exact mechanism of action of this treatment modality is not yet fully understood.

The objectives of this study were to evaluate the effects of VRT combined with conventional rehabilitation for upper limb function in the recovery of individuals after stroke. Neuroimaging characteristics that could be used as predictors of a better response to VRT were also investigated.

METHODS

Participants, setting, and design

This was a prospective clinical study that evaluated the effect of a VRT program at the Hospital das Clínicas, Medical School of São Paulo State University, Botucatu Campus between March, 2015 and July, 2016. The study was a convenience sample with consecutive patients.

Inclusion criteria

Patients older than 18 years, who had a first ischemic stroke and who were within the window of three to six months after the stroke were included in the study. The diagnosis of all participants was defined and confirmed by neuroimaging [computed tomography (CT) or magnetic resonance imaging], and the level of motor function of the upper limb was equal or superior to that in the Chedoke-McMaster Stroke Assessment.

Exclusion criteria

Patients unable to cooperate, with a history of stroke, modified Rankin scale (mRS) > 2, uncontrolled hypertension, unstable angina or recent myocardial infarction (< 3 months), those participating in another clinical study involving drugs or physical therapy, shoulder subluxation, or fractures of the upper limb were excluded.

Clinical data and variables

Neurological characteristics were collected through the National Institutes of Health Stroke Scale (NIHSS), mRS, Barthel Index, and Scandinavian Stroke Scale. The functional characteristics of the upper limb were evaluated using the Chedoke-McMaster scale, Box and Block Test, and upper limb subset of the Motor Assessment Scale. Quality of life was assessed using the Stroke Impact Scale version 3.0.

Neurological characteristics

1) NIHSS: aims to quantify neurological deficits through items that address the level of consciousness, speech, language, visual field, somatognosia, eye movement, strength, coordination, and sensitivity. The maximum score is 42, indicating a high neurological score¹⁵;

2) mRS: aims to assess the degree of independence and determines whether the patient can provide self-care during activities of daily living¹⁷;

2) Barthel Index: aims to measure the functional independence of the individual in 10 activities: food,

bathing, personal care, ability to dress, bowel rhythm, urinary rhythm, toilet use, transfers, mobility, and climbing stairs. The maximum score is 100, indicating a high degree of functional independence¹⁷;

4) Scandinavian Stroke Scale: aims to quantify the severity of paresis and level of disability, with minimum and maximum scores of 2 and 58, indicating that the higher the score, the lower the neurological deficit¹⁸.

Functional characteristics of upper limbs

1) Chedoke-McMaster Stroke Assessment: ranges from 0 (worst degree of function) to 7 (best degree of function) and aims to classify the condition of the upper limb after stroke¹⁹;

2) Box and Block Test: evaluates upper limb dexterity using a box divided into two compartments. The patient is instructed to transfer cubes of 1 cm³ in diameter from one compartment to another in 60 seconds. Scored by the number of blocks transferred in three attempts; the greater the number of blocks transferred, the better the dexterity and function of the upper limb²⁰;

3) Motor Assessment Scale: Upper limb function, hand movements, and advanced activities (dexterity) are evaluated by a qualitative scale staggered from 3 to 18, indicating that the higher the score the better the dexterity and function of the upper limb²¹.

Quality of life scale

Stroke Impact Scale: specifically evaluates the quality of life after stroke. It includes nine domains and the individuals' perception of their recovery²².

Intervention

Patients in the convenience sample were evaluated against the inclusion criteria by the principal investigator of the study.

After the selection, an evaluator, blinded to the study, defined the neurological, functional, and quality of life characteristics of the participants, and these results were considered the beginning of the rehabilitation. All patients received standard rehabilitation (30 minutes of physiotherapy and 30 minutes of occupational therapy). Subsequently, the patients underwent VRT. They were placed in a room with natural light, six meters away from the screen. They were instructed to remain in the orthostatic position, with the hand-held control on the affected side.

The games used were Wii Sports Tennis and Wii Sports Bowling, which work on the automatic motor mechanics of the affected limb, and the Cooking Mama package, a cooking game consisting of activities, such as preparing food and making meals, each for 20 minutes, with a total of 60 minutes of therapy for 20 sessions, held twice a week.

After the treatment, the same blinded evaluator performed the final evaluations of the neurological, functional, and quality of life characteristics of the individuals.

Neuroimaging

High-resolution CT scans performed during hospitalization in the post-stroke phase were used. For this analysis, only patients with volumetric images were included. The images were obtained on a 16 channels Toshiba Activion system with a maximum voxel size of 0.46 × 0.46 × 1.25 mm, 1.0 second gantry rotation time, 120 kVp and 190 mA and field of view of 240 mm.

The lesions were semi-automatically segmented using the ITK-SNAP program²³. Images and lesions were registered in the standard space using the Clinical Toolbox tools²⁴ and SPM8 (Statistical Parametric Mapping)²⁵ running on the MATLAB platform²⁶. At this stage, the images were transformed into 1 mm isotropic voxels. After normalization, the images of individuals with right hemisphere lesions were flipped to the left. Finally, maps of image overlap, and location of damaged areas were performed using the MRICron program²⁷.

Gray matter lesions were mapped based on the Automated Anatomical Labeling atlas²⁸. White matter changes were mapped using the Johns Hopkins University white matter tractography atlas²⁹.

Statistical analysis

Statistical analysis was performed using the IBM SPSS Statistics Version 21. A multivariate analysis was performed using the general linear model for repeated measures. The difference between pre- and post-intervention performances was compared. Age, sex, and treatment received in the acute phase (thrombolysis) were used as confounding factors. A *p* value of < 0.05 was considered statistically significant.

For statistical analysis of the images, the regions of interest derived from the atlas mentioned above and the NiiStat program were used. A voxel-based lesion-symptom mapping approach was employed for the neuroimaging analysis. This technique is able to analyze the relationship between tissue damage and behavior on a voxel-by-voxel basis³⁰. Overlaid areas of structural abnormality (infarction) were correlated with the task performance. Therefore, NiiStat analyzes the segmented images (weighting all the regions of interest involved) and functional markers of the upper limb. To investigate the correlation between improvement or worsening in performance and changes in the image, the two clinical evaluations and the difference between them were used. This analysis was performed using the general linear model by applying a linear regression with a significance level of *p* < 0.05. Damaged voxels were considered dependent variables and performance scores were the independent variables. The results are standardized based on the group evaluated (*Z* score).

Ethics approval and consent to participate

This trial was approved by the Committee for Ethics in Research involving human subjects from the Botucatu Medical School. Upon inclusion, all patients or legal surrogates provided written informed consent in accordance with

the Declaration of Helsinki II. All invited patients agreed to participate in the study.

RESULTS

Eighteen patients were included (eight women; mean age, 55.5 ± 13.9 years; mean \pm standard deviation). Nine patients underwent treatment with cerebral reperfusion. Fourteen patients presented with right neurological deficits. The mean mRS was 2.4 ± 1.2 and 1.4 ± 1 before and after the intervention, respectively, with a mean difference of -1 ± 0.8 . The Barthel Index score was 80.6 ± 15.4 and 92.5 ± 9.4 before and after the intervention, respectively, with a mean difference of 11.9 ± 9.3 . The NIHSS scores were 3.6 ± 2.6 and 2 ± 1.8 before and after the intervention, respectively, with a mean difference of -1.6 ± 1.5 . Furthermore, the Scandinavian Stroke Scale evaluation showed a mean of 49.2 ± 4.7 and 54.1 ± 3.9 before and after the intervention, respectively, with a mean difference of 4.9 ± 4.1 . No adverse events were reported. All scales showed a significant difference between the pre- and

post-intervention stages ($p < 0.0001$), and no interactions with sex, age, and treatment with cerebral reperfusion were observed. Table 1 summarizes the clinical findings.

All functional scales also showed a significant difference between the pre- and post-intervention stages, with the following results: Chedoke-McMaster scale with $p = 0.004$ and no interactions with sex, age, and thrombolytic treatment; Motor Assessment Scale item 6 (arm movement; $p = 0.004$) and no interactions; Motor Assessment Scale item 7 (hand movement; $p = 0.011$) and no interactions; Motor Assessment Scale item 8 (advanced hand movement; $p = 0.004$) and interaction with sex variable ($p = 0.004$); Box and Block Test with $p < 0.0001$ and no interactions.

With regard to the Stroke Impact Scale, the following results were obtained in the nine domains studied: strength (pre- vs. post-intervention; 28.8 ± 10.1 vs. 72.2 ± 16.4 ; $p = 0.0004$), hand function (94.4 ± 10.5 vs. 99.3 ± 1.7 ; $p = 0.0041$), daily life activities (62.8 ± 11.0 vs. 91.8 ± 14.2 ; $p = 0.0001$), instrumental activities of daily living (95.0 ± 13.3 vs. 98.4 ± 6.7 ; $p = 0.248$), mobility (61.6 ± 16.2 vs. 79.5 ± 9.4 ; $p = 0.0004$), communication (59.7 ± 17.9 vs. 91.6 ± 23.2 ; $p = 0.0004$), emotion (27.1 ± 21.0 vs. 69.4 ± 28.9 ;

Table 1. Clinical features of 18 patients with stroke and upper limb impairment submitted to virtual reality therapy and conventional rehabilitation.

Variable	n	Before VRT	After VRT*
Age (years)	55.5 \pm 13.9		
Women	8		
Reperfusion treatment	9		
Modified Rankin Scale		2.4 \pm 1.2	1.4 \pm 1
Barthel index		80.6 \pm 15.4	92.5 \pm 9.4
NIHSS		3.6 \pm 2.6	2 \pm 1.8
Scandinavian Stroke Scale		49.2 \pm 4.7	54.1 \pm 3.9

VRT: Virtual reality therapy; NIHSS: National Institutes of Health Stroke Scale; *p-values < 0.0001 .

Table 2. Functional and quality of life results obtained before and after virtual reality therapy in 18 patients with stroke and upper limb deficit.

Variable	Before VRT	After VRT	p-value
Functional results			
Chedoke-McMaster Stroke Assessment Arm	4.1 \pm 1.9	5 \pm 1.6	0.004
Chedoke-McMaster Stroke Assessment – Hand	3.6 \pm 1.9	4.7 \pm 1.8	< 0.0001
Motor Assessment Scale - item 6	3.6 \pm 2.3	4.6 \pm 1.8	0.004
Motor Assessment Scale - item 7	3.3 \pm 2.3	4.1 \pm 2.2	0.011
Motor Assessment Scale - item 8	3 \pm 2.6	3.7 \pm 2.3	0.004
Box and Block Test	18.9 \pm 14.8	26.3 \pm 16	< 0.0001
Quality of life			
Strength	28.8 \pm 10.1	72.2 \pm 16.4	0.0004
Hand function	94.4 \pm 10.5	99.3 \pm 1.7	0.041
Daily living activities	62.8 \pm 11.0	91.8 \pm 14.2	0.0001
Instrumental daily living activities	95.0 \pm 13.3	98.4 \pm 6.7	0.248
Mobility	61.6 \pm 16.2	79.5 \pm 9.4	0.0004
Communications	59.7 \pm 17.9	91.6 \pm 23.2	0.0004
Emotions	27.1 \pm 21.0	69.4 \pm 28.9	0.0001
Memory	93.6 \pm 24.9	97.4 \pm 23.7	0.0736
Social interaction	60.6 \pm 23.0	77.1 \pm 23.0	0.0019

VRT: Virtual reality therapy.

p = 0.0001), memory (93.6 ± 24.9 vs. 97.4 ± 23.7; p = 0.0736), and social participation (60.6 ± 23.0 vs. 77.1 ± 23.0; p = 0.0019). Table 2 summarizes the stroke impact in the functional and quality of life before and after intervention with VRT.

The mean volume of lesions observed among patients was 24,172 ± 17,302 mm³. The mean volume of white and gray matter damage was 3,420 ± 2,645 mm³ and 21,012 ± 15,500 mm³, respectively. The main structures affected are shown in Tables 3 and 4.

Table 3. Main white matter cerebral structures injured in nine patients with stroke submitted to virtual reality rehabilitation. The anatomical structure was obtained using the Johns Hopkins University white matter tractography atlas.²⁹ The volumes indicates the amount of damage in the structure (sum of affected volume for all patients) followed by the mean and variance.

Anatomical structure	Volume (mm ³)	N
Upper longitudinal fasciculus	6,715; 1,343 ± 1326 (8–2,874)	5
External capsule	5,820; 970 ± 1454 (55–3,506)	6
Superior corona radiata	5,406; 901 ± (26–2,108)	6
Posterior thalamic radiation	2,240; 746 ± 773 (111–1,608)	3
Splenium of corpus callosum	2,134; 711 ± 878 (26–1,702)	3
Posterior limb of internal capsule	1,949; 390 ± 356 (64–983)	5
Longitudinal and fronto-occipital inferior	1,709; 569 ± 522 (80–1,120)	3
Anterior corona radiata	1,635; 545 ± 908 (8–1,594)	3
Posterior corona radiata	1,499; 250 ± 267 (19–749)	6
Cingulum	896; *	1
Retro-lenticular internal capsule	587; 146 ± 265 (6–545)	4
Fornix	585; 146 ± 172 (7–391)	4
Anterior limb of internal capsule	547; 136 ± 142 (15–317)	4
Superior fronto-occipital fasciculus	315; 105 ± 117 (17–238)	3
Body of corpus callosum	75; 37 ± 2 (36–39)	2
Tapetum of corpus callosum	66; 33 ± 31 (11–55)	2

Volume in mm³: sum of total affected volume in all patients followed by mean, standard deviation, minimal and maximal values (when available); n: number of patients with a lesion in the structure; *: mean not available (only one patient).

Table 4. Main gray matter cerebral structures injured in nine patients with stroke submitted to virtual reality rehabilitation. The anatomical structure was obtained using the Automated Anatomical Labeling atlas.²⁸ The volumes indicates the amount of damage in the structure (sum of affected volume for all patients) followed by the mean and variance.

Anatomical structure	Volume (mm ³)	N
Insula	23,765; 3,960 ± 5,228 (13–11,678)	6
Inferior temporal gyrus	20,292; 1,844 ± 2,038 (48–5,285)	4
Inferior frontal gyrus	17,025; 2,837 ± 2,038 (462–6,094)	2
Postcentral gyrus	17,011; 5,670 ± 5,263 (761–11,228)	3
Precentral gyrus	13,999; 3,499 ± 3,892 (63–8,926)	4
Fusiform gyrus	12,288; 4,096 ± 6,994 (53–12,172)	3
Rolandic operculum	12,191; 2,438 ± 3,760 (9–8,958)	5
Inferior parietal lobe	10,098; 3,366 ± 2,552 (557–5,542)	3
Giro lingual	8,827; *	1
Supramarginal gyrus	8,618; 2,872 ± 2,508 (126–5043)	3
Putamen	6,555; 1,638 ± 2,417 (137–5,248)	4
Middle occipital gyrus	6,214; 2,071 ± 1,325 (1,181–3,595)	3
Calcarine	4,216; 2,108 ± 2,865 (82–4,134)	2
Hippocampus	4,005; 1,335 ± 1,090 (205–2,381)	3
Inferior occipital gyrus	3,627; 1,813 ± 2,556 (6–3,621)	2
Thalamus	3,106; 776 ± 758 (7–1819)	2
Giro parahippocampal	3,073; 1,536 ± 1,191 (694–2,379)	2
Superior cerebellum	3,035; *	1
Superior parietal lobe	2,161; 720 (23–2007)	3
Heschl's gyrus	1,828; 609 ± 746 (1–1,442)	3
Pallidum	1,581; *	1
Cuneus	1,114; 557 ± 738 (35–1079)	2
Middle frontal gyrus	1,095; 365 ± 607 (7–1066)	3
Caudate	954; 318 ± 33 (279–339)	3
Pre cuneus	877; 292 ± 499 (4–869)	3
Angular gyrus	817; 408 ± 289 (133–684)	2
Paracentral lobule	356; *	1
Cingulum	165; 82 ± 103 (9–156)	2
Superior occipital gyrus	154; 77 ± 49 (42–112)	2
Amygdala	36; *	1
Superior frontal gyrus	25; *	1

Volume in mm³: sum of total affected volume in all patients followed by mean, standard deviation, minimal and maximal values (when available); n: number of patients with lesion in the structure; *: mean not available (only one patient).

Statistical analyses of white matter structures analyzed 18 affected regions of the 48 available in the template atlas (Figure A). The following correlations were observed: Chedoke-McMaster (arm) in the two evaluations with the posterior portion of the internal capsule ($Z = -2.2$ and $Z = -3$) and the difference between the evaluations with the inferior temporal gyrus ($Z = 2.3$); Chedoke-McMaster (hand) in the evaluation after intervention with the posterior portion of the internal capsule ($Z = -2.5$); Motor Assessment Scale item 6 in the difference of the evaluations with the inferior frontal gyrus triangular portion ($Z = 2.6$), medial and lateral orbito-frontal gyri ($Z = 2.4$ and 2.4) and caudate nucleus ($Z = 2.2$); Motor Assessment Scale item 8 in the two evaluations with the posterior portion of the internal capsule ($Z = -3.3$ and -2.5); Box and Block Test in the two evaluations with the posterior portion of the internal capsule ($Z = -2.4$ and -2.7).

For the gray matter, 52 affected regions of the 116 regions available in the template atlas were evaluated (Figure B). The correlations observed were the following: Chedoke-McMaster scale (arm) in the first evaluation with the middle occipital gyrus ($Z = 2.2$) and the difference

between the assessments with the amygdala ($Z = 2.3$); Chedoke-McMaster (hand) in the first evaluation with the middle occipital gyrus ($Z = 2.3$); Motor Assessment Scale item 6 in the difference between the evaluations and the superior frontal gyrus orbital portion ($Z = 2.6$), inferior frontal gyrus triangular and orbital portions ($Z = 2.6$ and 2.5), olfactory gyrus ($Z = 2.3$), middle frontal gyrus ($Z = 2.3$), gyrus rectus ($Z = 2.3$), and anterior cingulate gyrus ($Z = 2.3$).

DISCUSSION

The present study evaluated the effect of VRT combined with conventional rehabilitation on a series of stroke patients, showing positive results in improving the functionality of the upper limb.

Improvement was observed in all aspects of the neurological characteristics evaluated through the NIHSS, mRS, Barthel Index, and Scandinavian Stroke Scale. Therefore, VRT may be considered an important adjunctive therapy for the treatment of clinical changes that affect functional

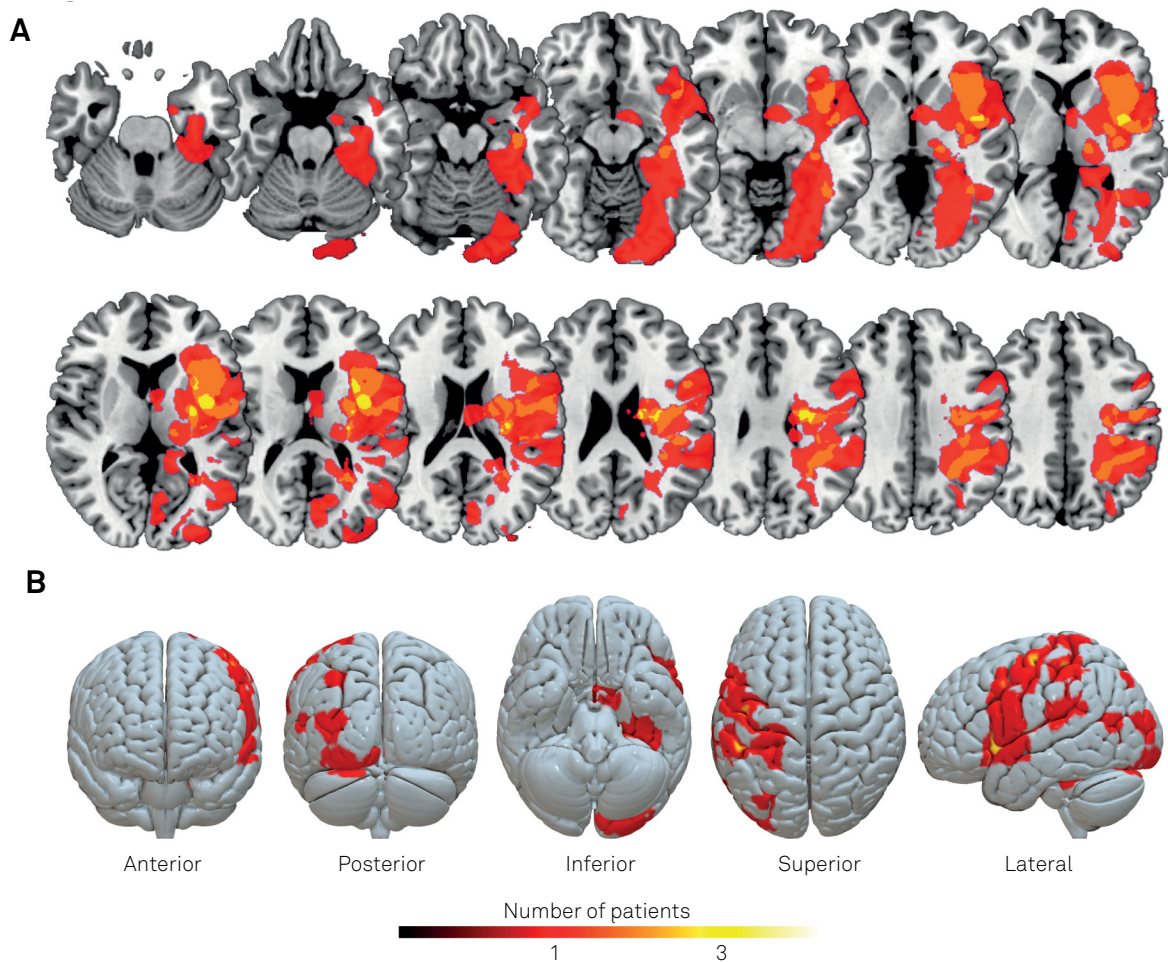


Figure. Brain areas affected in nine patients with stroke and upper limb impairment underwent virtual reality therapy (A). Findings are overlaid in a template of axial magnetic resonance image slices and in a three-dimensional model of the brain (B). The color code bar in the inferior portion of the figure indicates the number of patients with the area injured.

independence and compromise the quality of life of patients with stroke. Virtual reality appears to have a positive impact on brain plasticity, leading to the reduction of motor deficits. Previous studies have shown that repetition and movement intensity act directly as promoters of neural plasticity³¹. In this study, the activities proposed for rehabilitation were repetitive movements and exposure to tasks requiring specific functions.

Virtual reality therapy combined with conventional rehabilitation also showed a positive impact on the functionality and dexterity of the upper limb. Improvement was observed in all upper limb functional scales. Virtual reality is considered a computer technology that simulates motor learning³². The mechanism is related to a large number of repetitions of the task, generating increased feedback. The use of virtual reality requires substantial control of the upper limb and hand grip. This control is through neural mechanisms of feedback. When using a visual reference, achievement of a precise and functional goal while performing complex movements with the upper limb (reaching or targeting) requires great dexterity. During this process, areas related to function are activated in the central nervous system with progressive improvement of motor learning³³.

Adult brain neurons often increase the rate of firing in the sensorimotor cortex regions when participants observe or perform mirrored movements³⁴. The activation of this system, called mirror neurons, includes areas of the frontal, parietal, and temporal lobes, and may induce cortical reorganization after injury to the central nervous system. Virtual reality involves the use of technology in three dimensions with a computerized scenario, allowing the individual to interact with the environment. This procedure increases the rate of firing by the mirror neurons, capturing the interactive movement performed by the avatar^{35,36}.

In studies with normal participants, the use of VRT was associated with increased activation of the primary sensorimotor cortex on the contralateral side, which may have led to expanded motor references for daily activities and improvement in upper limb dexterity^{37,38}.

With regard to the quality of life, almost all items of the Stroke Impact Scale showed statistical significance. Therefore, VRT combined with conventional rehabilitation improved the quality of life of patients with stroke. This improvement, in part, is a reflex of the return to daily routine activities with minimal interference from the neurological deficit³⁹. In addition, VRT is a fun method, generating better interaction between therapists and patients. This collaboration makes therapy less exhausting than conventional methods and generates motivational feedback⁴⁰. Consequently, a positive effect was noted on cognition and physical function.

A positive relationship was observed between the differences in the assessments of the function of the upper limb in

the shoulder and elbow movements with lesions in the inferior frontal gyrus triangular portion, medial and lateral orbitofrontal gyri, and caudate nucleus. These structures are involved in the memorization of movements and in performing more complex movements automatically. These findings may indicate that these structures have greater neuroplasticity and, therefore, they have a better response to VRT when compromised⁴¹.

Similarly, the Motor Assessment Scale item 6 was also positively associated with lesions in the superior frontal gyrus orbital portion, frontal inferior gyrus triangular and orbital portion, olfactory gyrus, middle frontal gyrus, gyrus rectus, and anterior cingulate, showing that VRT combined with conventional rehabilitation improved the planning and execution of movement in these patients⁴¹.

Statistical analysis between white matter lesions and functionality and dexterity showed a negative correlation with the posterior portion of the internal capsule. The internal capsule comprises transmission axons to the cortex, and a lesion in this structure is responsible for most motor changes following stroke. The internal capsule is supplied by the middle cerebral artery. Damage in this region can result in motor impairment, particularly in the upper limbs^{42,43}. The negative correlation observed in the two evaluations using the Motor Assessment Scale, Box and Block Test, and Chedoke-McMaster (arm) suggest that this structure can be used as a marker for the indication of VRT combined with conventional rehabilitation. The negative correlation of these evaluations is related to less evidence of improvement and an intensification of the rehabilitation process may be required.

One of the limitations of this study was the small number of participants. Recruitment of patients was time consuming because of the strict inclusion criteria. The vast majority of patients treated at stroke units have a wide variety of comorbidities and extensive diseases preventing their inclusion. These factors limited the inclusion of participants. Another drawback was the lack of a control group. From the data obtained in this preliminary investigation, we hypothesize that VRT is safe and may be useful as adjunctive therapy. Additional studies comparing conventional rehabilitation and VRT are needed.

With regard to neuroimaging, the number of patients was smaller because not all patients underwent 3D CT. In addition, the quality of the examination had to be sufficient for accurate delimitation of the injured area. These issues were important limitations of this investigation and, consequently, results should be interpreted cautiously.

In patients with stroke treated with conventional rehabilitation and VRT, significant improvement in clinical characteristics and upper limb function was observed, as well as an improvement in the patient's perception of quality of life. Subcortical strokes with involvement of the posterior portion of the internal capsule presented the worst response to therapy.

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