Can robotic gait rehabilitation plus Virtual Reality affect cognitive and behavioural outcomes in patients with chronic stroke? A randomized controlled trial involving three different protocols

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Background: The rehabilitation of cognitive and behavioral abnormalities in individuals with stroke is essential for promoting patient's recovery and autonomy. The aim of our study is to evaluate the effects of robotic neurorehabilitation using Lokomat with and without VR on cognitive functioning and psychological well-being in stroke patients, as compared to traditional therapy. *Methods:* Ninety stroke patients were included in this randomized controlled clinical trial. The patients were assigned to one of the three treatment groups, i.e. the Robotic Rehabilitation group undergoing robotic rehab with VR (RRG+VR), the Robotic Rehabilitation Group (RRG-VR) using robotics without VR, and the Conventional Rehabilitation group (CRG) submitted to conventional physiotherapy and cognitive treatment. *Results:* The analysis showed that either the robotic training (with and without VR) or the conventional rehabilitation led to significant improvements in the global cognitive functioning, mood, and executive functions, as well as in activities of daily living. However, only in the RRG +VR we observed a significant improvement in cognitive flexibility and shifting skills, selective attention/visual research, and quality of life, with regard to the perception of the mental and physical state. *Conclusion:* Our study shows that robotic treatment, especially if associated with VR, may positively affect cognitive recovery and psychological well-being in patients with chronic stroke, thanks to the complex interation between movement and cognition.

Keywords: Augmenting reality—Robotic training—Cognitive rehabilitation—Ischemic stroke

Introduction

Stroke is one of the main causes of death and disability worldwide, and the costs of stroke-related treatment tends to rise rapidly.[1,2] The annual incidence of stroke is very high, involving about 180−240 patients per 100,000 inhabitants.[1] In addition, stroke can cause severe brain damages, leading to multiple disabilities, including motor and cognitive ones. Among the others, deficits in mobility and stability of the joints, muscle strength and endurance, and movement control can lead to problems with transferring, maintaining body position, mobility, balance and walking. Cognitive dysfunctions instead include executive, working memory, visuospatial and emotional deficits, with regard to depression/anxiety problems. These disorders may cause a negative impact on the quality of life (QoL) for both the patients and their family.[3−5] In the first 6 months after stroke, almost all patients have at least some degree of predictable recovery functionality, although some symptoms persist through the chronic

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phase, negatively affecting the autonomy in daily life.[6] The typical clinical recovery strategy in stroke patients is to minimize the initial injury and then improve the amount of functional recovery. In particular, the rehabilitation of cognitive and behavioral abnormalities in individuals with stroke is essential for promoting patient recovery and autonomy.[7]

Growing evidence is highlighting the potential effect of robotic rehabilitation on the functional recovery of neurological patients.[8–11] In fact, the use of robotic devices allows various advantages, including a smaller workforce, a longer and more intense exercise compared to traditional treatment, an objective and quantitative assessment of disability, which can be monitored over time while giving the possibility of multisensory stimulation of the patient. Among these machines, the Lokomat is an electronically controlled robotic device, which can be also connected to a virtual reality (VR) system, with visual feedback of the body movements.[12–14] Although robotic rehabilitation has proven useful in improving motor function, there is no clear evidence concerning its role in potentiating cognitive skills, which are often compromised in stroke patients. Previous studies have shown that robotic rehabilitation may be effective in improving some cognitive domains and in reducing anxiety and depressive states in patients with neurological pathologies.[9,13] In particular, patients with traumatic brain injury undergoing robotic treatment plus VR have achieved a greater increase in cognitive flexibility and attention shifting, as well as in executive and visuospatial skills, necessary to plan and manage daily life.[9]

To this end, we designed a randomized controlled experimental study aimed at evaluating the effects of robotic neurorehabilitation using Lokomat with and without VR on cognitive functioning and psychological well-being in stroke patients, as compared to traditional therapy.

Materials and methods

Participants and recruitment

Ninety stroke patients (mean ± SD age: 43.7 ± 11.3 years; 55.6% males) who attended our Behavioral and Robotic Neurorehabilitation Service from April 2019 to December 2019 were included in this randomized clinical controlled trial (Table 1). Enrolled patients were randomly assigned to one of the three groups using an automated computerized randomization program: 1) the Robotic Rehabilitation plus VR group (RRG+VR) underwent a rehabilitation training with the Lokomat-Pro, having a VR-screen; 2) the Robotic Rehabilitation Group without VR (RRG-VR) was trained with the Lokomat Nanos; and 3) the Conventional Rehabilitation Group (CRG) was submitted to conventional physical and cognitive therapy. Clinical assessors (who performed the tests and provided care) and statisticians (who differ from the clinical evaluators) were blind to the aim of the research and the treatment of the patients.

Inclusion criteria were: i) neurological diagnosis of stroke (either ischemic or hemorrhagic) in the chronic phase (at least 6 months from the acute event); ii) ability to sit for at least 30 minutes (including at least one minute without support); iii) presence of mild to moderate cognitive impairment (Montreal Cognitive Assessment [MoCA] from 16 to 24).

Exclusion criteria were: i) age >85 years; ii) presence of disabling sensory alterations, including hallucinations; iii) concomitant medical and psychiatric illness possibly interfering with the robotic/VR training.

This study was conducted in accordance with the Helsinki Declaration of 1964 and approved by the Ethics Committee of our Research Institute, and written informed consent was obtained from all participants. The study was registered on ClinicalTrials.gov: ID NCT03914313.

Data collection

Each participant was assessed by means of a neuropsychological evaluation before (T0) and immediately after the end of the training (T1). The tests included: Montreal Cognitive Assessment (MoCA) to assess the general cognitive state; Weigl Test and Frontal Assessment Battery (FAB) to examine frontal abilities; Visual Search (VS) and Trail Making Test (TMT) to measure the attention process, attentive shifting and visual research's abilities; Beck Depression Inventory-II (BDI-II) to evaluate mood; SF-12 Health Survey to evaluate quality of life (QoL) and physical state; Functional Independence Measure (FIM) to assess the patient's level of disability, autonomy in the daily-activities functioning (ADL), and change the patient's status in response to rehabilitation.

Study design

All patients underwent the same amount of rehabilitation, but using different approaches. CTG were submitted to 40 sessions of cognitive rehabilitation (CR) and 40 sessions of physiotherapy (PT); CR and PT were provided on the same day at a distance of at least 3 hour, five times a week for 8 weeks. RRG+VR and RRG-VR underwent 40 training sessions (i.e. five times a week for 8 weeks, as per our standard research and clinical protocol), each session lasting about one hour, besides 40 sessions of PT (also robotics and PT were provided in the same day).

Conventional rehabilitation

CR was based on a face-to-face approach between the therapist and the patient using pencil and paper tools. CR mainly focused on attention and executive and visuospatial skills. To improve attention, we used Attention Process Training (ATP), which includes targeting for sustained, selective, divided and alternating attention activities. The

Table 1. *Demographics characteristics at baseline.*

	RRG+VR	RRG-VR	CRG	All	p-value
Participants	30	30	30	90	
Age	48.0±12.1	40.1±10.7	43.1±9.7	43.7±11.3	0.90
Education	13.2±2.9	12.1±3.1	11.8±3.2	12.4±3.1	0.94
Gender					0.98
Male	19 (63.3%)	6 (20.0%)	16 (53.3%)	41 (55.6%)	
Female	11 (36.7%)	24 (80.0%)	14 (46.7%)	49 (54.4%)	
Interval-from stroke *Mean in months*	4.5 ± 1.5	4.2±1.0	4 ± 2	4.7 ± 1.3	0.78
Brain lesion					0.76
Cortical right	14	15	15	44	
Subcortical right	11	10	10	31	
Cortical left	2	3	3	8	
Subcortical left	3	2	2	7	

Quantitative variables were expressed as means ± standard deviations, categorical variables as frequencies and percentages.

* ***LEGEND****: Robotic Rehabilitation group with VR (RRG+VR); Robotic Rehabilitation group without VR (RRG-VR); Conventional Rehabilitation group (TG).*

training of executive functions was performed by working on categorization, planning, association, and analogical reasoning. PT was provided according to the Bobath approach, aimed at improving balance, reducing spasticity and increasing muscle strength.

Lokomat training

RRG+VR and RRG-VR were submitted to rehabilitation with the Lokomat device, respectively the Pro and Nanos type. The Lokomat is a robotic exoskeleton that consists of a motorized gait insole with computer-controlled linear actuators integrated on each hip and knee joint, a BWS and a treadmill.[12,15] The device allows adjusting the pace and the driving force according to the patient's needs, improving training on the sagittal, frontal and transverse planes.[16,17] The system can also evaluate the physiological stiffness of the patient's hip and knee and the isometric strength for the hip and knee extension of the L-STIFF and L-FORCE software module.[16] For treatment with the robotic system, the rehabilitation team defined the amount of body weight supported by the device initially at 70% of each patient's weight; then this was reduced based on load tolerance, although not less than 20%. The selected speed was adapted to the patient's need under the supervision of an experienced physiotherapist. The Lokomat-Pro type, as compared to the Nanos, has a feedback module based on VR. Feedback is instructive, interactive and connected to the patient's walk, projecting the results of the exercises on a flat screen to improve patient motivation. The exercises are mainly based on activities in which patients must collect and/or avoid objects randomly distributed in the virtual environment. By adjusting the intensity and level of difficulty, the exercises can be adapted to the motor and cognitive skills and to the specific needs of the patients, obtaining personalized feedback.[12−14]

Statistical Analysis

Data were analyzed using the SPSS version 16.0 considering $p < 0.05$ as statistically significant. The $\chi 2$ test was used to compare proportions in categorical variables. Instead, the Mann-Whitney U test to compare quantitative variables. Parametric analysis was performed because the Kolmogorov-Smirnov results indicated that the target variables were normally distributed. Thus, the Student T-tests were used to compare the two groups at baseline, when appropriate. We performed the repeated measures ANOVA to compare the scores of the three samples over time (T0-T1). The dependent variable consisted in the performances obtained in the different cognitive functions, measured with the scales/tests to evaluate the clinical assessment. The independent variables were the "Group" (1 = RRG-VR; 2 = RTG; 3=TTG); and "Time" (factor within the subject with two levels: T0, T1) (Table 2). As a post hoc test, pairwise comparisons of all levels were realized by Student's T-test.

Results

All patients completed the training, and no patients had any important side effects. No significant differences were found in age ($p = 0.90$), instruction ($p = 0.94$), brain lesions ($p = 0.78$) and proportion of gender ($p = 0.98$) between RRG+VR, RRG-VR, and CTG. Moreover, at baseline, no significant differences emerged between the scores of the three groups (Table 2). The ANOVA analysis showed the triple interaction between Group*Time*Tests/ Scales ($F_{(10,890)} = 32.17$, $p<0.001$). In particular, the ANOVA decomposition underlined that the scores of all the tests were influenced by the type of treatment, demonstrating how the effect of the three treatments was significantly different (Table 2). Post-hoc analysis results showed that both the rehabilitation, robotic and traditional, led to a significant improvement in global cognitive functioning,

Table 2. *ANOVA decomposition in Group*Time for all tests/scales.*

	Degree of freedom	Mean Square	F	P-value	η^2
MoCA	2, 87	52.51	73.7	**0.000**	**0.62**
BDI	2, 87	189.2	76.2	**0.000**	**0.63**
TMT-A	2, 87	29799.2	38.1	**0.000**	0.46
TMT-B	2, 87	56076.7	67.8	**0.000**	**0.60**
TMT B-A	2, 87	44211.4	44.5	**0.000**	**0.50**
VS	2, 87	309.8	44.1	**0.000**	**0.50**
WEIGL	2, 87	110.8	103.6	**0.000**	**0.70**
FAB	2, 87	101.8	80.1	**0.000**	**0.64**
SF TOT	2, 87	729.5	57.5	**0.000**	**0.57**
SF MENT	2, 87	583.5	69.4	**0.000**	**0.61**
SF PHY	2, 87	1068.7	121.4	**0.000**	**0.73**
FIM COGN	2, 87	122.33	22.9	**0.000**	0.34
FIM MOT	2, 87	316.8	15.5	**0.000**	0.26
FIM TOTAL	2, 87	806.6	33.6	**0.000**	**0.44**

Significant p-value are in bold.

Legend: Frontal Assessment Battery (FAB); Beck Depression Inventory - II (BDI II); Functional Independence Measure (FIM): Cognitive sub-scale (COGN); Motor sub-scale (MOT); Total (TOT); Montreal Cognitive Assessment(MoCA); Short Form-12 Health Survey Total (SF-12 TOT); Short Form-12 Health Survey Mental Health (SF-12 MH); Short Form-12 Health Survey Physical (SF-12 Ph); Trail Making Test – Form A (TMT-A); Trail Making Test – Form B (TMT-B); Trail Making Test – Form B-A (TMT B-A); Visual Search (VS); Weigl Test (WEIGL).

mood, and executive functions (i.e. perseveration, planning and classification), as well as in the patient's level of disability and activities of daily living (ADL) (Table 3). However, only in the RRG+VR we observed a significant improvement in cognitive flexibility and shifting skills, selective attention/visual research, and QoL, with regard to the perception of the mental and physical state. Finally, RRG + VR showed higher total FIM scores than the other two groups, whereas both the RRG + VR and RRG-VR had higher scores than the CRG concerning the motor FIM subitem.

Discussion

Our data show that the robotic training (with or without VR) improved cognitive functioning and behavioral outcomes in a similar way of traditional training, even if, unlike the latter, there was no specific CR for patients undergoing robotics. However, the training with Lokomat plus VR allows a greater improvement of the patient's cognitive abilities, supporting the idea of the potential role of VR in the rehabilitation of stroke patients, in line with our previous studies in individuals with multiple sclerosis and TBI.[9–18] In particular, the RRG+VR had a greater improvement in cognitive flexibility and shifting skills, as well as in selective attention/visual research, besides a significant increase in QoL e in ADL (as per the specific FIM subitems). These cognitive functions significantly affect patient’s autonomy and rehabilitation outcomes, allowing the patient to feel safer and more effective in daily activities.[19]

To the best of our knowledge, this is the first study evaluating the effects of Lokomat training plus VR on cognitive functions, as compared to either Lokomat without VR or conventional training, given that previous studies have assessed motor and/or cognitive outcomes comparing different robotic treatments or robotic and traditional treatments.[9, 12–15]

We believe that there are numerous aspects that could make the Lokomat-Pro more effective in functional recovery of neurological patients.[9]

In fact, patient’s improvement is enhanced by the intensity of training and the repetition of specific tasks. Training on a treadmill with robotic body weight support optimizes the sensory inputs relevant for step training, with a repeated practice of specific tasks, which boosts neuroplasticity.[9,12–14] Lokomat training is based on motor learning principles, as it involves patients in motivating activities, especially in the presence of VR, which consists of an increased feedback during robot-assisted gait training.[20] Indeed, VR can maximize the effect of the treatment by means of an avatar that performs the exercises, as action observation allows the activation of the mirror system, potentiating motor learning, and inducing profound cortical and subcortical changes at the cellular and synaptic level.[20] Therefore, we believe that the multisensory feedback and repeated implementation of the dual-tasks through the combination of the two tools (i.e. robotics and VR), could improve the patient's outcomes, potentiating not only motor function but also cognitive domains.[9] Indeed, the motor and cognitive aspects cannot be considered separately since they influence each other.[21–23] The sensory-motor-cognitive process is based on the overlapping of neuronal circuits involving the thalamus and basal ganglia, which, in turn, are connected to the brainstem and cerebellum, the latter playing a pivotal role in cognition, beyond motor control and balance.[24, 25] Since

Table 3. *Post hoc analysis results of the clinical scale used as assessment tool.*

Clinical scale			Mean±DS	*p-value*
MoCA	RRG+VR	T0-T1	21.8±2.7-26.0 ±2.5	**0,00**
	RRG-VR	T0-T1	22.6±2.5-23.5±2.3	**0,00**
	CRG	T0-T1	23.4±2.4-24.3±2.3	**0,00**
	RRG+VR - RRG-VR	T0-T0	21.8±2.7-22.6±2.5	0,31
	RRG+VR - CRG	T0-T0	21.8±2.7-23.4±2.4	0,03
	RRG-VR - CRG	T0-T0	22.6±2.5-23.4±2.4	0,22
	RRG+VR - RRG-VR	T1-T1	26.0 ±2.5-23.5±2.3	**0,00**
	RRG+VR - CRG	T1-T1	26.0 ±2.5-24.3±2.3	0,01
	RRG-VR - CRG	T1-T1	23.5±2.3-24.3±2.3	0,21
BDI	RRG+VR	T0-T1	13.0±4.8-5.6±3.2	**0,00**
	RRG-VR	T0-T1	11.7±4.0-10.4±3.7	**0,00**
	CRG	T0-T1	10.9±5.2-9.8±4.9	**0,00**
	RRG+VR - RRG-VR	T0-T0	13.0±4.8-11.7±4.0	0,26
	RRG+VR - CRG	T0-T0	13.0±4.8-10.9±5.2	0,12
	RRG-VR - CRG	T0-T0	11.7±4.0-10.9±5.2	0,54
	RRG+VR - RRG-VR	T1-T1	5.6±3.2-10.4±3.7	**0,00**
	RRG+VR - CRG	T1-T1	5.6±3.2-9.8±4.9	**0,00**
	RRG-VR - CRG	T1-T1	10.4±3.7-9.8±4.9	0,60
TMT-A	RRG+VR	T0-T1	155.4±84.2-76.1±41.4	**0,00**
	RRG-VR	T0-T1	132.3±111.1-133.2±111.7	0,66
	CRG	T0-T1	139.3±123.9-133.8±122.2	**0,00**
	RRG+VR - RRG-VR	T0-T0	155.4±84.2-132.3±111.1	0,37
	RRG+VR - CRG	T0-T0	155.4±84.2-139.3±123.9	0,56
	RRG-VR - CRG	T0-T0	132.3±111.1-139.3±123.9	0,82
	RRG+VR - RRG-VR	T1-T1	76.1±41.4-133.2±111.7	0,01
	RRG+VR - CRG	T1-T1	76.1±41.4-133.8±122.2	0,02
	RRG-VR - CRG	T1-T1	133.2±111.7-133.8±122.2	0,98
TMT B	RRG+VR	T0-T1	255.3±96.0-142.9±75.9	**0,00**
	RRG-VR	T0-T1	226.2±118.0-222.7±118.7	**0,00**
	CRG	T0-T1	226.3±128.0-216.5±133.2	**0,00**
	RRG+VR - RRG-VR	T0-T0	255.3±96.0-226.2±118.0	0,30
	RRG+VR - CRG	T0-T0	255.3±96.0-226.3±128.0	0,33
	RRG-VR - CRG	T0-T0	226.2±118.0-226.3±128.0	1,00
	RRG+VR - RRG-VR	T1-T1	142.9±75.9-222.7±118.7	**0,00**
	RRG+VR - CRG	T1-T1	142.9±75.9-216.5±133.2	0,01
	RRG-VR - CRG	T1-T1	222.7±118.7-216.5±133.2	0,85
TMT B-A	RRG+VR	T0-T1	211.3±121.5-113.3±84.3	**0,00**
	RRG-VR	T0-T1	160,1±149.5-158.9±149.8	0,01
	CRG	T0-T1	169.9±156.3-163.0±158.8	0,06
	RRG+VR - RRG-VR	T0-T0	211.3±121.5-160,1±149.5	0,15
	RRG+VR - CRG	T0-T0	211.3±121.5-169.9±156.3	0,26
	RRG-VR - CRG	T0-T0	160,1±149.5-169.9±156.3	0,80
	RRG+VR - RRG-VR	T1-T1	113.3±84.3-158.9±149.8	0,15
	RRG+VR - CRG	T1-T1	113.3±84.3-163.0±158.8	0,14
	RRG-VR - CRG	T1-T1	158.9±149.8-163.0±158.8	0,92
VS	RRG+VR	T0-T1	33.1±7.9-42.2±8.5	**0,00**
	RRG-VR	T0-T1	33.1±11.7-34.3±11.9	0,02
	CRG	T0-T1	37.1±10.3-38.4±11.1	0,01
	RRG+VR - RRG-VR	T0-T0	33.1±7.9-33.1±11.7	0,99
	RRG+VR - CRG	T0-T0	33.1±7.9-37.1±10.3	0,10
	RRG-VR - CRG	T0-T0	33.1±11.7-37.1±10.3	0,17
	RRG+VR - RRG-VR	T1-T1	42.2±8.5-34.3±11.9	**0,00**
	RRG+VR - CRG	T1-T1	42.2±8.5-38.4±11.1	0,14
	RRG-VR - CRG	T1-T1	34.3±11.9-38.4±11.1	0,18
WEIGL	RRG+VR	T0-T1	7.6±2.4-13.4±1.9	**0,00**
	RRG-VR	T0-T1	8.1±3.7-9.0±3.6	**0,00**

(*Continued*)

Table 3 (*Continued*)

Clinical scale			Mean±DS	*p-value*
	CRG	T0-T1	8.5±3.6-9.7±3.6	**0,00**
	RRG+VR - RRG-VR	T0-T0	7.6±2.4-8.1±3.7	0,59
	RRG+VR - CRG	T0-T0	7.6±2.4-8.5±3.6	0,27
	RRG-VR - CRG	T0-T0	8.1±3.7-8.5±3.6	0,64
	RRG+VR - RRG-VR	T1-T1	13.4±1.9-9.0±3.6	**0,00**
	RRG+VR - CRG	T1-T1	13.4±1.9-9.7±3.6	**0,00**
	RRG-VR - CRG	T1-T1	9.0±3.6-9.7±3.6	0,49
Clinical scale			***Mean±DS***	***p-value***
FAB	RRG+VR	T0-T1	11.1±2.7-16.5±1.2	**0,00**
	RRG-VR	T0-T1	14.5±2.2-15.3±2.1	**0,00**
	CRG	T0-T1	14.6±2.0-15.8±1.7	**0,00**
	RRG+VR - RRG-VR	T0-T0	11.1±2.7-14.5±2.2	**0,00**
	RRG+VR - CRG	T0-T0	0.8±1.0-14.6±2.0	**0,00**
	RRG-VR - CRG	T0-T0	14.5±2.2-14.6±2.0	0,74
	RRG+VR - RRG-VR	T1-T1	16.5±1.2-15.3±2.1	0,01
	RRG+VR - CRG	T1-T1	16.5±1.2-15.8±1.7	0,06
	RRG-VR - CRG	T1-T1	15.3±2.1-15.8±1.7	0,32
SF-TOT	RRG+VR	T0-T1	24.7±9.0-36.3±10.9	**0,00**
	RRG-VR	T0-T1	22.9±5.5-21.0±6.2	0,03
	CRG	T0-T1	28.7±8.0-30.1±8.2	0,04
	RRG+VR - RRG-VR	T0-T0	24.7±9.0-22.9±5.5	0,34
	RRG+VR - CRG	T0-T0	24.7±9.0-28.7±8.0	0,08
	RRG-VR - CRG	T0-T0	22.9±5.5-28.7±8.0	**0,00**
	RRG+VR - RRG-VR	T1-T1	36.3±10.9-21.0±6.2	**0,00**
	RRG+VR - CRG	T1-T1	36.3±10.9-30.1±8.2	0,02
	RRG-VR - CRG	T1-T1	21.0±6.2-30.1±8.2	**0,00**
SF MENT	RRG+VR	T0-T1	17.1±5.0-28.3±6.6	**0,00**
	RRG-VR	T0-T1	13.8±3.9-13.6±4.1	0,60
	CRG	T0-T1	16.9±6.4-18.0±6.9	0,15
	RRG+VR - RRG-VR	T0-T0	17.1±5.0-13.8±3.9	0,01
	RRG+VR - CRG	T0-T0	17.1±5.0-16.9±6.4	0,93
	RRG-VR - CRG	T0-T0	13.8±3.9-16.9±6.4	0,03
	RRG+VR - RRG-VR	T1-T1	28.3±6.6-13.6±4.1	**0,00**
	RRG+VR - CRG	T1-T1	28.3±6.6-18.0±6.9	**0,00**
	RRG-VR - CRG	T1-T1	13.6±4.1-18.0±6.9	**0,00**
SF PHY	RRG+VR	T0-T1	11.7±4.3-26.6±5.3	**0,00**
	RRG-VR	T0-T1	16±5.5-16.1±4.9	0,54
	CRG	T0-T1	14.3±4.6-14.8±4.4	0,44
	RRG+VR - RRG-VR	T0-T0	11.7±4.3-16±5.5	**0,00**
	RRG+VR - CRG	T0-T0	11.7±4.3-14.3±4.6	0,03
	RRG-VR - CRG	T0-T0	16±5.5-14.3±4.6	0,21
	RRG+VR - RRG-VR	T1-T1	26.6±5.3-16.1±4.9	**0,00**
	RRG+VR - CRG	T1-T1	26.6±5.3-14.8±4.4	**0,00**
	RRG-VR - CRG	T1-T1	16.1±4.9-14.8±4.4	0,29
FIM COGN	RRG+VR	T0-T1	25.8±2.2-34.5±1.3	**0,00**
	RRG-VR	T0-T1	26.2±3.5-30.7±3.9	**0,00**
	CRG	T0-T1	26.9±4.2-30.0±5.1	**0,00**
	RRG+VR - RRG-VR	T0-T0	25.8±2.2-26.2±3.5	0,60
	RRG+VR - CRG	T0-T0	25.8±2.2-26.9±4.2	0,24
	RRG-VR - CRG	T0-T0	26.2±3.5-26.9±4.2	0,53
	RRG+VR - RRG-VR	T1-T1	34.5±1.3-30.7±3.9	**0,00**
	RRG+VR - CRG	T1-T1	34.5±1.3-30.0±5.1	**0,00**
	RRG-VR - CRG	T1-T1	30.7±3.9-30.0±5.1	0,57
FIM MOT	RRG+VR	T0-T1	47.2±3.8-61.6±8.0	**0,00**
	RRG-VR	T0-T1	47.1±3.9-57.5±6.5	**0,00**

Table 3 (*Continued*)

Clinical scale			Mean±DS	*p-value*
	CRG	T0-T1	47.7±3.6-52.9±4.3	**0,00**
	RRG+VR - RRG-VR	T0-T0	47.2±3.8-47.1±3.9	0,94
	RRG+VR - CRG	T0-T0	47.2±3.8-47.7±3.6	0,63
	RRG-VR - CRG	T0-T0	47.1±3.9-47.7±3.6	0,59
	RRG+VR - RRG-VR	T1-T1	61.6±8.0-57.5±6.5	0,03
	RRG+VR - CRG	T1-T1	61.6±8.0-52.9±4.3	**0,00**
	RRG-VR - CRG	T1-T1	57.5±6.5-52.9±4.3	**0,00**
FIM TOT	RRG+VR	T0-T1	73.1±4.8-96.1±7.8	**0,00**
	RRG-VR	T0-T1	73.4±5.1-88.3±7.6	**0,00**
	CRG	T0-T1	74.6±6.4-83.0±7.5	**0,00**
	RRG+VR - RRG-VR	T0-T0	73.1±4.8-73.4±5.1	0,79
	RRG+VR - CRG	T0-T0	73.1±4.8-74.6±6.4	0,31
	RRG-VR - CRG	T0-T0	73.4±5.1-74.6±6.4	0,44
	RRG+VR - RRG-VR	T1-T1	96.1±7.8-88.3±7.6	**0,00**
	RRG+VR - CRG	T1-T1	96.1±7.8-83.0±7.5	**0,00**
	RRG-VR - CRG	T1-T1	88.3±7.6-83.0±7.5	**0,00**

Significant differences are in bold. Bonferroni p-level 0.005.

LEGEND: RRG+VR= Robotic Rehabilitation plus virtual reality Group; RRG-VR= Robotic Rehabilitation without virtual reality Group; CRG= Conventional Rehabilitation Group; T0 = evaluation at study enrollment; T1 = evaluation at the end of the study. Frontal Assessment Battery (FAB); Beck Depression Inventory - II (BDI II); Functional Independence Measure (FIM): Cognitive subscale (COGN); Motor subscale (MOT); Total (TOT); Montreal Cognitive Assessment(MoCA); Short Form-12 Health Survey Total (SF-12 TOT); Short Form-12 Health Survey Mental Health (SF-12 MH); Short Form-12 Health Survey Physical (SF-12 Ph); Trail Making Test – Form A (TMT-A); Trail Making Test – Form B (TMT-B); Trail Making Test – Form B-A (TMT B-A); Visual Search (VS); Weigl Test (WEIGL).

cognitive and motor processes are based on such shared circuits, every enhancement of these neural pathways could affect contemporaneously the cognitive, sensory, behavioural and motor processes, independently of the neurorehabilitative approach used.[26–28] The intensive and repetitive motor training coupled to the VR-increased feedback, thanks to the dual-task exercises, could have acted on the areas underlying the sensory-motor integration, ultimately leading to a better motor and cognitive recovery, as observed in the RRG+VR. This group performed complex exercises via the VR screen, which could affect gait during training in a different way than the training with the Lokomat Nanos (performed by the RGG-VR). In fact, the Lokomat-Pro training provides a VR-feedback requiring higher levels of patient's attention to perform the exercises than the simple visual feedback furnished by the Nanos. This VR-related dual-task training, also known as "concurrent performance", implies the execution of a primary task (i.e. walking) as the primary focus of attention and a secondary task (i.e. the deviation of objects), performed simultaneously. It has been shown that performing multiple tasks simultaneously (dual-task interference) changes the gait in healthy subjects, especially in the elderly.[29,30] Barbaruolo et al. have recently demonstrated that cognitive and motor rehabilitations carried out in combination, have a mutually enhancing effect on the motor outcome compared to their administration independently.[31] This could be due to the "positive" induction of a better adaptive neuroplasticity, thanks to the involvement of complex shared neural networks (brain stem, cerebellum, thalamus, fronto-parietal cortex, hippocampus, basal ganglia), most of which belonging to the mirror neuron system. Indeed, this network not only is involved in the motor control and function but allows also for planning and reasoning related to action plans, and this requires the involvement of attention and executive function further supporting the strict relation between movement and cognition. These issues better explain how cognitive process are involved in controlling gait and posture, also affecting the behavioral levels in the organization and execution of daily functioning.[21–25] In other words, VR may lead to better cognitive-motor-behavioral outcomes, increasing functioning in daily life activities, thanks to the dual-task training. This data is in line with current studies,[30,32] which claimed that dual-task motor-cognitive training through VR can encourage the generalization of the skills used in daily functioning with higher QoL outcomes, as observed in our promising study.

In fact, although the FIM increased significantly in all of the three groups, we observed significantly higher improvement in the RRG+VR, indicating higher levels of independence in ADL after the combined treatment. This further demonstrates how cognition and motor function may influence each other, potentially indicating that the higher the motor recovery, the higher the cognitive outcomes. Indeed, motor recovery may positively affect cognitive and behavioral outcomes in many ways. First of all, motor skills allow patients to adapt to the outside world and maintain a healthy lifestyle, amplifying active social participation and functional abilities of the person.[33,34] Motor skills not only influence the concept of the physical self, such as the self-esteem, but they may also affect mental health and the sense of life satisfaction. To this end, Schmidt et al. highlighted that the physical capacity reinforces the perception of self-efficacy, which in turn leads to an increase in the perceived physical competence, improving the level of self-esteem and the acceptance of one's own body. Consequently, poor performance in motor activities can cause a lowering of the sense of competence and general self-esteem that can be reflected in internalizing behaviors, such as social withdrawal, eventually leading to depressive symptoms.[35] Moreover, the motor activities allow to maintain high cardiovascular capacity over time, which has a positive effect on cognitive abilities over time, especially in memory.[36,37] Finally, aerobic training (as the one furnished by the Lokomat) can induce improvements related to the frontal and prefrontal brain areas, with positive effects on executive functions, memory, attention, working memory, concentration, planning, and processing speed.[38−41]

According to this complex interaction between movement and cognition, our findings support the idea that is possible to rehabilitate multiple functional deficits (i.e. cognitive and motor dysfunctions) through a single treatment, with regard to the robotic device plus VR. However, as use of these tools is currently limited by accessibility and costs,[11] further research is mandatory to confirm their potential in improving cognitive function.

Rehabilitation following stroke is a complex process based on a combination of spontaneous recovery and mediated processes. For this reason, it is essential to know the effects of the various treatments in order to define adequate and stimulating intervention plans for the functional recovery of the patients at different levels (motor, cognitive, psychological), through a specific enhancement of brain plasticity.

In conclusion, our study demonstrated that robotic treatment, especially when associated with VR, may positively affect the cognitive recovery, psychological well-being, as well as ADL functioning, in patients following stroke, also in the chronic phase. Further studies with larger samples and longer follow-up should be fostered to confirm these promising results.

Declaration of Competing Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References

1. Guzik A, Bushnell C. Stroke epidemiology and risk factor management. Continuum (Minneap Minn). J Cerebrovasc Dis 2017;23(1):15-39.
2. Dobkin BH. Clinical practice. Rehabilitation after stroke. N Engl J Med 2005;352:1677-1684.
3. Torrisi M, De Luca R, Pollicino P, et al. Post Stroke delusions: What about the neuroanatomical and neurofunctional basis? Appl Neuropsychol Adult 2018;19:1-5.
4. Maggio MG, Latella D, Maresca G, et al. Virtual reality and cognitive rehabilitation in people with stroke: an overview. J Neurosci Nurs 2019;51(2):101-105.
5. Maggio MG, De Luca R, Torrisi M, et al. Is there a correlation between family functioning and functional recovery in patients with acquired brain injury? An exploratory study. Appl Nurs Res 2018;41:11-14.
6. Eng JJ, Tang PF. Gait training strategies to optimize walking ability in people with stroke: a synthesis of the evidence. Expert Rev Neurother 2007;7(10):1417-1436.
7. De Luca R, Maggio MG, Maresca G, et al. Improving cognitive function after traumatic brain injury: a clinical trial on the potential use of the semi-immersive virtual reality. Behav Neurol 2019:9268179.
8. Maggio MG, Maresca G, De Luca R, et al. The growing use of virtual reality in cognitive rehabilitation: fact, fake or vision? A scoping review. J Natl Med Assoc 2019. pii: S0027-9684(18)30346-8.
9. Maggio MG, Torrisi M, Buda A, et al. Effects of robotic neurorehabilitation through lokomat plus virtual reality on cognitive function in patients with traumatic brain injury: A retrospective case-control study. Int J Neurosci2019:1-7.
10. Maggio MG, Russo M, Cuzzola MF, et al. Virtual reality in multiple sclerosis rehabilitation: A review on cognitive and motor outcomes. J Clin Neurosci 2019;65:106-111.
11. Maggio MG, De Luca R, Molonia F, et al. Cognitive rehabilitation in patients with traumatic brain injury: a narrative review on the emerging use of virtual reality. J Clin Neurosc 2019;61:1-4.
12. Calabrò RS, Cacciola A, Bertè F, et al. Robotic gait rehabilitation and substitution devices in neurological disorders: where are we now? Neurol Sci 2016;37(4): 503-514.
13. Calabrò RS, Reitano S, Leo A, De Luca R, Melegari C, Bramanti P. Can robot-assisted movement training (Lokomat) improve functional recovery and psychological well-being in chronic stroke? Promising finding from a case study. Funct Neurol 2014;29(2):139-141.
14. Calabrò RS, De Cola MC, Leo A, et al. Robotic neurorehabilitation in patients with chronic stroke: psychological well-being beyond motor improvement. Int J Rehabil Res 2015;38(3):219-225.
15. Morone G, Iosa M, Bragoni M, et al. Who may have durable benefit from robotic gait training?: a 2-year follow-up randomized controlled trial in patients with subacute stroke. Stroke 2012;43(4):1140-1142.
16. Hussain S, Xie SQ, Jamwal PK, Parsons J. An intrinsically compliant robotic orthosis for treadmill training. Med Eng Phys 2012;34:1448-1453.
17. Duschau-Wicke A, Caprez A, Riener R. Patient-cooperative control increases active participation of individuals with SCI during robot-aided gait training. J Neuroeng Rehabil210; 7(1).
18. Calabrò RS, Russo M, Naro A, et al. Robotic gait training in multiple sclerosis rehabilitation: can virtual reality make the difference? Findings from a randomized controlled trial. J Neurol Sci 2017;377:25-30.
19. Batbaatar E, Dorjdagva J, Luvsannyam A, Amenta P. Conceptualisation of patient satisfaction: a systematic

narrative literature review. Perspect Public Health 2015;135(5):243-250.
20. Calabrò RS, Naro A, Russo M, et al. The role of virtual reality in improving motor performance as revealed by EEG: a randomized clinical trial. J Neuroeng Rehabil 2017;14(1):53.
21. Maggio MG, De Luca R, Manuli A, et al. Do patients with multiple sclerosis benefit from semi-immersive virtual reality? A randomized clinical trial on cognitive and motor outcomes. Appl Neuropsychol Adult 2020;10:1-7.
22. Kalron A, Fonkatz I, Frid L, et al. The effect of balance training on postural control in people with multiple sclerosis using the CAREN virtual reality system: a pilot randomized controlled trial. J neuroengineering rehab 2016;13(1):13.
23. Lauenroth A, Ioannidis AE, Teichmann B. Influence of combined physical and cognitive training on cognition: a systematic review. BMC geriatrics 2016;16(1):141.
24. Sherman SM. Thalamic relays and cortical functioning. Progress in brain research 2005;149:107.
25. Holtzer R, Goldin Y, Zimmerman M, et al. Robust norms for selected neuropsychological tests in older adults. Arch Clinical Neurops 2008;23(5):531-541.
26. Lo OY, Halko MA, Zhou J. Gait speed and gait variability are associated with different functional brain networks. Front Aging Neurosci 2017;9:390.
27. Mahoney JR, Verghese J. Does cognitive impairment influence visual-somatosensory integration and mobility in older adults? J Gerontol A Biol Sci Med Sci 2019. pii:glz 117.
28. Bartolomé NA, Zorrilla AM, Zapirain BG. Can game-based therapies be trusted? Is game-based education effective? A systematic review of the Serious Games for health and education. In: 16th International Conference on 2011 CGAMES IEEE; 2011. p. 275-282.
29. Melzer I, Kurz I, Shahar D, Oddsson LI. Do voluntary step reactions in dual task conditions have an added value over single task for fall prediction? A prospective study. Aging Clin Exp Res 2010;22(5-6):360−366.
30. Rogers JM, Duckworth J, Middleton S, Steenbergen B, Wilson PH. Elements virtual rehabilitation improves motor, cognitive, and functional outcomes in adult stroke: evidence from a randomized controlled pilot study. J Neuroeng Rehabil 2019;16(1):56.
31. Barbarulo AM, Lus G, Signoriello E, et al. Integrated cognitive and neuromotor rehabilitation in multiple sclerosis: a Pragmatic Study. Front Behav Neurosci 2018;12:196.
32. Fritz NE, Cheek FM, Nichols-Larsen DS. Motor-cognitive dual-task training in neurologic disorders: a systematic review. J Neurol Phys Ther 2015;39:142.
33. Murray GK, Veijola J, Moilanen K, et al. Infant motor development is associated with adult cognitive categorisation in a longitudinal birth cohort study. J Child Psychol Psychiatry 2006;47(1):25−29.
34. Outermans J, Pool J, van de Port I, Bakers J, Wittink H. What's keeping people after stroke from walking outdoors to become physically active? A qualitative study, using an integrated biomedical and behavioral theory of functioning and disability. BMC Neurol 2016;16(1):137.
35. Schmidt M, Blum M, Valkanover S, Conzelmann A. Motor ability and self-esteem: The mediating role of physical self-concept and perceived social acceptance. Psychology of sport and exercise 2015;17:15-23.
36. Hötting K, Schauenburg G, Röder B. Long-term effects of physical exercise on verbal learning and memory in middle-aged adults: results of a one-year follow-up study. Brain Sci 2012;2(3):332−346.
37. Holzschneider K, Wolbers T, Röder B, Hötting K. Cardiovascular fitness modulates brain activation associated with spatial learning. Neuroimage 2012;59(3):3003−3014.
38. Hötting K, Röder B. Beneficial effects of physical exercise on neuroplasticity and cognition. Neurosci Biobehav Rev 2013;37(9 Pt B):2243−2257.
39. Hötting K, Holzschneider K, Stenzel A, Wolbers T, Röder B. Effects of cognitive training on spatial learning and associated functional brain activations. BMC Neurosci 2013;14:73.
40. Cassilhas RC, Tufik S, de Mello MT. Physical exercise, neuroplasticity, spatial learning and memory. Cell Mol Life Sci 2016;73(5):975−983.
41. Basso JC, Shang A, Elman M, Karmouta R, Suzuki WA. Acute exercise improves prefrontal cortex but not hippocampal function in healthy adults. J Int Neuropsychol Soc 2015;21(10):791−801.