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ORIGINAL ARTICLE

The impact of cognitive function deficits and their recovery on functional outcome in subjects affected by ischemic subacute stroke: results from the Italian multicenter longitudinal study CogniReMo

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ABSTRACT

BACKGROUND: The recovery of independence in activities of daily living is a fundamental goal of rehabilitation programs in subjects affected by subacute stroke. Rehabilitation is focused both on motor and cognitive aspects, and some evidence has reported cognitive deficits as prognostic factors of motor recovery. However, rehabilitation is a dynamic process during which executive functions and motor functions should be improved.

AIM: The aim of the study is to evaluate the relationships between impairments in cognitive functions and recovery of functional independence in stroke patients during the subacute phase.

DESIGN: Multicenter observational study.

SETTING: Intensive rehabilitation units.

POPULATION: A sample of 319 stroke patients in subacute phase (70.6±11.6 years, 40.4% females), consecutively admitted from November 2019 to July 2021 at sixteen rehabilitation centers were enrolled in this observational, prospective and multicentric study with longitudinal assessments.
METHODS: Cognitive and functional assessments were performed at hospital admission and discharge, including Oxford Cognitive Screen, modified Barthel Index, Functional Independent Measure, Fugl-Meyer assessment scale and National Institutes of Health Stroke Scale.
RESULTS: A regression analysis identified five predictors (out of about 200 tested variables) of functional recovery related to four aspects assessed at admission: functional status (P<0.001), lower limb functioning (P=0.002), attention (P=0.011), and executive functions (P=0.017). Furthermore, patients who recovered deficits in executive functions had the same recovery of those without deficits, whereas those who maintained deficits had a smaller recovery (P=0.019).
CONCLUSIONS: The relationship between cognitive and motor deficits is increasingly highlighted and the recovery of executive functions deficits seems to contribute to motor recovery.
CLINICAL REHABILITATION IMPACT: Our results suggest that the recovery of executive functions may promote the recovery of the functional outcome of the patient with subacute stroke. Future treatment protocols may benefit from paying more attention to the recovery of executive functions.

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KEY WORDS: Stroke rehabilitation; Executive function; Cognition; Activities of daily living.

Stroke is one of the main causes of mortality and disability worldwide, with a severe social and economic burden.[1, 2] It has been estimated that between 2017 and 2047 the percentage of subjects living with stroke disability will increase by 27%,[1] causing long-term sequelae, in terms of physical disability, cognitive damage, fatigue, and impairment of quality of life. This clinical occurrence causes severe burden for stroke patients and their families, as well as contributing to wider social and economic burdens.[3] Stroke patients report cognitive deficits in a very high proportion of cases, at least in one cognitive function in up to 83% of patients and in 50% in more domains, often followed by a good clinical recovery within 15 months after stroke.[4] However, cognitive impairments are still present in 41% of patients after 6 months, in 39% after two years of stroke onset,[5] and between 50% and 80% of patients after 10 and 15 years respectively.[6] The main impaired cognitive domains in stroke patients are represented by deficits in language, spatial attention, memory, praxis, speed of processing, and executive functions.[7] Cognitive impairment is an important target for rehabilitation, as it has been associated with reduced quality of life. It also interferes with motor recovery interventions and other aspects of rehabilitation.[8] It is well known that cognitive deficits, as well as the severity of neurological damage, decrease rehabilitation effectiveness and represent a negative prognostic factor of global functional recovery.[9, 10] Naturally, this has an impact on patients' activities such as daily living, global independence, and return to work.[11-14] In addition, the presence of specific neuropsychological deficits such as neglect and aphasia, especially with comprehension impairment, are predictive of lower functional outcome upon discharge from a rehabilitation facility. The presence of these cognitive impairments often interferes with rehabilitative programs resulting in reduced recovery of motor deficits.[15] Regarding motor recovery, there has recently been an increased interest in understanding the relationship between cognitive deficit and improvement in upper limb movement recovery, both in acute and in chronic phases of stroke.[16] Executive function abilities can constitute a predictor of motor recovery and participation in rehabilitation programs following stroke. It can also show a correlation between the quality of functional independence and the degree of preserved executive and cognitive functions.[17] Cognitive impairment present in the acute phase seems to predict long-term cognitive impairment, motor recovery and functional disability even after 3-6 months.[5] Visuospatial perception/construction, visual memory, visual neglect and attentive/executive disorders have a stronger relationship with the level of participation and social activities of patients, compared to a general cognitive index, even in the presence of good functional recovery.[18, 19] Furthermore, working memory, attention switching and inhibition represent fundamental elements in gait and balance control.[20, 21] In addition, attentive (especially inhibition and shifting) and executive deficits seem to limit the return to work in young patients at 7 years from stroke onset even in the presence of good physical recovery.[22] All this evidence suggests that motor and cognitive functions are strongly interconnected. Due to high prevalence and the important impact of cognitive deficits on functional outcome, the assessment of post-stroke cognitive deficits with appropriate tools becomes necessary in clinical practice. This allows physicians to tailor specific cognitive rehabilitation protocols in order to improve responsiveness and effectiveness of rehabilitation.[23] Worldwide, the most used tools for cognitive profile assessment are the Mini Mental State Examination (MMSE), the Montral Cognitive Assessment (MoCA) and the Addenbrooke's Cognitive Examination (ACE-R). However, these are primarily utilized for the evaluation of cognitive impairments in dementia, but are not specific tools for cognitive profile evaluation in stroke patients. Furthermore, these tools allow professionals to evaluate a general cognitive profile, not permitting the assessment of specific cognitive domains such as attention, memory, language, apraxia, whose evaluation is fundamental to estimate patient's cognitive performances.[18] The Oxford Cognitive Screen (OCS) is a short cognitive tool, designed to assess cognitive functions in stroke patients, investigating the domains of cognition deficits that frequently occur after stroke, including apraxia and unilateral neglect as well as memory, language, executive function, and number abilities. Domain-specific scores are useful for setting up targeted rehabilitative programs.[24, 25] Compared to a generalized cognitive screening such as MoCA, the OCS was more sensitive and reliable.[26] In a significant Italian sample of post-stroke patients, it was confirmed that the OCS is a more specific tool for cognitive evaluation in stroke, useful for detecting high incidence of stroke-specific cognitive impairments, not assessable by the MMSE. The OCS also demonstrates the importance of cognitive profiling to set up rehabilitative cognitive and motor programs.[27] The relationship between cognitive and motor deficits is increasingly highlighted and the recovery of cognitive deficits seems to contribute to motor recovery.[28] The aim of the study is to evaluate the relationship between cognitive function deficits and recovery of functional independence in subjects affected by ischemic subacute stroke.

Materials and methods

Participants

A total of 386 stroke patients in subacute phase (that is discharged from acute wards *i.e.* Stroke units or neurology wards), consecutively admitted from November 2019 to July 2021 at sixteen Italian rehabilitation centers, were enrolled in the study named Cognitive and Recovery of Motor functions (CogniReMo). Patients were of both genders (190 males, M, and 129 females, F), aged between 18 to 90 years, and of mixed levels of education. Sixty-seven patients dropped out and were transferred to other hospitals due to clinical worsening (F=26; M=41). The final study group was composed of 319 (F=103; M=149) patients.

Inclusion and exclusion criteria

The inclusion criteria were: 1) clinically confirmed diagnosis of ischemic stroke in subacute phase hospitalized for neurorehabilitation; 2) age between 18 and 90 years; 3) both male and female of any education level were admitted.

The exclusion criteria were: 1) hemorrhagic stroke; 2) presence of previous (*i.e.*, pre acute event) psychiatric or neurological diseases; 3) previous Barthel Index Score lower than 90; 4) history of drug and alcohol abuse. Patients admitted to rehabilitative wards before 72 hours or after 90 days from stroke onset were excluded. This last criterion was in line with the definition of the post-acute phase such as that in which the clinical conditions of the patients have been stabilized and the patient can be transferred to neurorehabilitation hospital to start cognitive and physical therapies.[29] Enrolled patients who refused to sign the informed consent were excluded from the study.

Study design

The study design was observational, prospective and multicentric with longitudinal assessments.

Ethical statement

The study was approved by the Ethical Committee of the South-East Tuscany with the number 15360. All patients received information about the aims of the study. All the participants signed the informed consent.

Procedure

All the patients enrolled in the CogniReMo study were admitted to the sixteen Italian rehabilitation centres between November 2019 and July 2021.

For each patient, information about age, gender, education level, previous Barthel Index and risk factors such as blood hypertension, diabetes, obesity (assessed by Body Mass Index, BMI) and atrial fibrillation were collected.

Stroke onset, admission, and discharge date were collected. Moreover, data regarding brain lesion localization (according to Bamford classification), acute phase treatment (fibrinolysis and/or thrombolysis) clinical complications (deep vein thrombosis, pulmonary embolism, bladder infection, pulmonary infection, septicemia), and discharge setting was collected.

All the evaluation scales were conducted and scored by members of the patient's rehabilitation care team.

The baseline examination (T_0) was conducted within 48 hours from admission. The follow-up was conducted within 48 hours before discharge.

During the hospital stay all subjects received conventional multidisciplinary stroke rehabilitation treatment. According to the Italian guidelines, conventional treatment for patients admitted at hospital rehabilitation wards received treatment for 3 hours per day, 6 days per week. Physiotherapy usually starts within 24 hours from admission and when necessary, trainings for cognitive rehabilitation, swallowing, bowel and bladder functions recovery had been added. Also, occupational therapy is administered for all patients. In particular, physiotherapy training for our sample, was based on exercises to improve trunk control, standing, balance, gait, coordination and resistance. Cognitive training was based on exercises to improve cognition, attention, memory, space cognition, language, praxis, and executive functions. Swallowing treatment for almost 30 min per day was administered when necessary.

Measures

All the patients enrolled in the study were assessed at admission and discharge by the following rating scales:

• National Institutes of Health Stroke Scale (NIHSS): The NIHSS[30] was designed to evaluate stroke severity. It consists of 11 items. The total score ranges from a minimum of 0 (normal neurological functioning) to a maximum of 42 (severe neurological damage);[30]

• Bamford Classification: the Bamford Classification[31] allows clinicians to categorize patients with cerebral infarction according to certain distinctive features. Clinicians can classify patients into four groups based on specific signs and symptoms: TACI (Total Anterior Circulation Infarcts), LACI (Lacunar Infarcts), PACI (Partial Anterior Circulation Infarcts), and POCI (Posterior Circulation Infarcts);[31]

• Oxford Cognitive Screen (OCS): The OCS[24] is a screening tool for a rapid and very early assessment of cognitive functions. It assesses five cognitive domains: attention and executive function, language, memory, number processing, and praxis. No scaling corrections are applied to raw data. The OCS can be administered in about 15 minutes and can be delivered at the bedside, whenever necessary. The Italian version of the scale, with normative data on a sample of 20- to 80-year-old individuals, was used;[24, 32]

• Fugl-Meyer Assessment (FMA): this scale is a quantitative measure of motor impairment in post stroke hemiplegic patients. It relies on direct observation of the motor performance at each item using a 3- point ordinal scale (0 cannot perform, 1 performs partially, and 2 performs fully). It is divided into two sections for upper and for lower limb assessment. The upper extremity score of FMA (FMA-UE) assesses flexion, extension and cooperative movement of the shoulder, elbow, and wrist, as well as wrist joint stability, coordination ability, and speed of small joint movement. The total maximum score indicating a good function is 66 points. The lower extremity (FMA-LE) maximum score is 34 points based on lower Extremity (0-28 points) and Coordination/Speed (0-6 points) scores. Motor function, sensory function, passive range of motion and pain during passive movement are evaluated by using the same ordinal 3-point scale. The non-motor domains of the FMA are Sensation, and Joint Passive. Joint Movement, and Pain are assessed both in the upper and lower limb. The Italian version of the scale was used;[33, 34]

• the modified version of Barthel Index (BI): The BI is an ordinal scale used to measure performance and independence in activities of daily living (ADL). Ten variables, describing ADL and mobility, are scored. A higher number correspond to greater abilities in functioning independently. The maximum total score is 100 points depending on the autonomy of the patients in performing the subtasks of the scale. Higher scores indicate higher autonomy in conducting daily activities;[35]

• Functional Independence Measure (FIM): the purpose of this scale is to assess disability for a variety of populations. It includes self-care, eating, grooming, bathing, dressing, toileting, swallowing, sphincter control, mobility, transfer, and locomotion. The scale is composed of 18 items. Based on the level of independence, each item is scored from 1 to 7. Lower scores indicate total dependence and higher scores represent complete independence. The total score ranges from 18 to 126.[36]

Statistical analysis

More than 200 variables were collected for each patient, including clinical data (Supplementary Digital Material 1: Supplementary Table I). Data are reported in terms of mean±standard deviation or relative percentage frequency if binary. Median and inter-quartile range (IQR) were also computed. Non-parametric tests were used because of the not normal distribution of data (Shapiro-Wilk Test). The Paired Wilcoxon Test was used to assess the change in clinical variables between admission and discharge. The Spearman coefficient (R) was used to assess correlations between variables.

A Binary logistic regression was applied with the forward stepwise method. Variables that were not originally binary were dichotomized with respect to their own medians. The modified Barthel Index score (widely used in Italy by the rehabilitative wards) at discharge was used as a dependent variable and 100 variables collected at admission (detailed in Supplementary Table I) as independent variables. We used a forward stepwise method, identifying which one of the 100 variables entered into the model explaining a positive functional outcome given by a BI-score higher than the median of the sample. For this binary logistic regression, we reported the coefficients (β), the odds ratios (OR) and the relevant 95% confidence intervals (95% CI).

Finally, the effectiveness was computed as the percentage change in the Barthel Index score divided by the maximum achievable improvement.[37] The effectiveness was compared between independent groups using the Mann-Whitney U-test. For all the analyses, the alpha level was set at 5%.

Based on data reported in previous studies[37-39] and fixing a power of analysis at 80% and alpha level at 5%, a minimum sample size of 285 patients was estimated as necessary.

Data availability

The data associated with the paper are not publicly available but are available from the corresponding author on reasonable request.

Results

Our sample was formed by 319 patients with stroke, with a mean age of 70.6±11.6 years. The mean schooling time was 9.0±4.3 years. Forty-four percent of the subjects were females.

Time from the acute event and admission to the neurorehabilitation ward was 18.6±15.8 days, with a length of stay in the hospital of 49.6±32.6 days. Stroke occurred in the right hemisphere in the 50.3% of cases, in the left in the 44.6%, and was bilateral in the 5.1% of patients. The Bamford classification revealed the following distribution: TACI: 20.3%, LACI: 22.1%, PACI: 40.2%, POCI: 17.4%. The median value of pre-stroke Barthel Index score was 100 (IQR=0). Hypertension was present in 84.0% of cases, diabetes in 21.9%, and atrial fibrillation in 21.0%. Thrombectomy was used in 19.9% of cases, whereas fibrinolysis in 25.5%.

Effectiveness of the treatment

Table I describes the clinical characteristics of the sample assessed at admission and discharge, with the p-values associated to testing the differences between the two assessments. The size effect was in general lower for cognitive functions, and it was not significant for many of the OCS-scores.

The median BI-Score at discharge was 70, and its choice as a threshold for a good rehabilitative outcome was in

Table I.—*Mean±standard deviation, median (and interquartile range) of clinical scores at admission and discharge, the P value of their comparison obtained by Wilcoxon Rank Test, and the effect size.*

Parameter	Admission	Discharge	P value	Effect size
Barthel Index	33.2±28.0, 25 (40)	64.6±29.7, 70 (45)	<0.001	1.121
Fugl-Meyer: Total Motor Functioning lower limb	20.5±10.0, 21 (14)	25.4±8.8, 28 (11)	<0.001	0.490
Fugl-Meyer: Total Motor Functioning upper limb	34.6±23.04, 39 (46)	44.1±22.2, 53 (37)	<0.001	0.412
FIM Score	58.4±27.1, 54 (38)	85.3±30.7, 91 (48)	<0.001	0.993
OCS – Picture naming	2.7±1.4, 3 (2)	3.1±1.2, 4 (1)	<0.001	0.286
OCS - Semantics	2.8±0.6, 3 (0)	2.9±0.5, 3 (0)	<0.001	0.167
OCS - Hearts time	161.3±36.0, 180 (30)	152.3±45.0, 180 (52)	0.001	0.250
OCS - Hearts Correct	33.1±16.4, 40 (27)	38.2±16.5, 45 (18)	<0.001	0.311
OCS - Executive functions	2.7±2.9, 1 (3)	2.6±2.9, 1 (3)	0.818	0.111
OCS - Orientation	3.5±1.0, 4 (1)	3.7±0.9, 4 (0)	<0.001	0.200
OCS - Visual field	3.6±1.1, 4 (0)	3.7±0.8, 4 (0)	<0.001	0.091
OCS - Sentence reading	11.2±5.3, 14 (7)	12.4±4.8, 15 (3)	<0.001	0.226
OCS - Number writing	2.2±1.2, 3 (2)	2.3±1.1, 3 (1)	<0.001	0.083
OCS - Number calculation	2.9±1.3, 3 (2)	3.1±1.2, 4 (1)	<0.001	0.154
OCS - Object asymmetry	1.4±3.0, 0 (1)	1.2±3.1, 0 (1)	0.275	0.067
OCS - Space asymmetry	3.0±4.4, 1 (4)	2.7±4.4, 1 (3)	0.111	0.068
OCS - Imitation	8.9±3.7, 10 (5)	9.9±3.2, 11 (3)	<0.001	0.270
OCS - Semantic memory	2.1±1.4, 2 (2)	2.4±1.4, 3 (3)	<0.001	0.214
OCS - Episodic memory	3.1±1.2, 3 (1)	3.4±1.1, 4 (1)	<0.001	0.250
NIHSS vigilance	0.0±0.3, 0 (0)	0.0±0.1, 0 (0)	0.008	0.001
NIHSS - Facial palsy	0.8±0.8, 1 (1)	0.5±0.8, 0 (1)	<0.001	0.375

line with previous literature reporting this value as an important cut-off between mild and moderate-severe dependency in activities of daily living[40-42] and also between low and high risk of difficult discharge.[43]

The prediction model

Among all the accounted variables (Supplementary Table I), only five entered into the model of logistic regression because associated to a statistically significant level of p to predict the Barthel Index at discharge, as shown in Table II. The model explained the 77.5% of data variance. The sensitivity of the model in identifying patients with a poor outcome (below the own median) was 82.6%, whereas the specificity in identifying patients with a good outcome (above the median) was 71.5%. The possibility of obtaining a good outcome was more than 5 times higher in subjects with a higher Barthel Index at admission, and almost 3 times higher in patients who showed a good performance in the OCS-subtask of cancelling hearts at admission, a task related to attention. The effect of Fugl-Meyer Lower Limb Assessment was statistically significant but with a small effect (OR=1.045). On the contrary, subjects who spent more time completing the heart OCS-subtask, as well as showing a deficit in executive functions, had double the risk of being discharged with a poor independence in the activities of daily living (Barthel Index).

Among the variables not entered into the model, five approached the statistically significant level: time from stroke at admission to the neurorehabilitation ward (P=0.058), visual field (P=0.058), facial palsy (P=0.062), Functional Independence Measure score (P=0.072), and space-time orientation (P=0.083). The Barthel Index score at admission was significantly correlated with all of these five variables not entered into the model (P<0.001) and also with all of them entered into the model (P<0.011), including the two parameters related to attention (number of correct responses and relevant time in the OCS subtask of cancelling hearts: R=0.418, P<0.001; R=-0.125, P=0.036, respectively), but not with executive functions (R=-0.007, P=0.911).

Another difference between attention and executive functions was the significant improvement of the two parameters related to attention, as shown in Table I, whereas executive functions did not significantly improve (P=0.111).

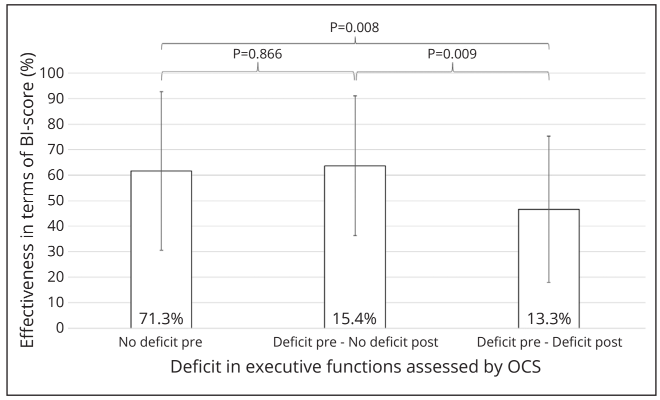

Figure 1.—*Post-hoc* analysis.

Post-hoc analysis

To clarify this aspect, a post-hoc analysis, taking into account the variations in the executive functions, along the neurorehabilitation period was performed. The 71.2% of patients did not show deficit in the executive functions at admission. Of the remaining 28.8% with deficits in executive functions, 15.3% recovered this cognitive domain and moved from pathological to normal scores before discharge. However, as shown in Figure 1, the effectiveness in terms of improvement in BI-Score was significantly different among these three groups (P=0.019). A recovery of executive functions was associated with a level of effectiveness not significantly different to those of patients without any deficit. Conversely, a significantly lower effectiveness of rehabilitation was observed in patients who had, and maintained, a deficit in the executive functions.

Discussion

The purpose of the present study was to verify the interplay between cognitive and motor impairments, to evalu-

Table II.—*The results of Binary Logistic Regression (β are the angular coefficients of the regression line, OR stands for odds ratio coinciding with the exponential of β and reported together with their 95% confidence interval CI).*

Prognostic factor	β coefficient	Standard error	P value	OR Exp (β)	95% CI of exp (β)
Barthel Index	1.698	0.312	<0.001	5.464	2.962-10.078
OCS - Number of correct cancelled hearts	1.072	0.307	<0.001	2.920	1.601-5.327
FMA-LE Fugl Meyer Assessment lower limb	0.044	0.014	0.002	1.045	1.016-1.074
OCS- heart cancellation -Total time	-0.743	0.294	0.011	0.476	0.267-0.846
Executive functions	-0.814	0.342	0.017	0.443	0.227-0.865

ate the role of cognitive impairments in motor recovery and functional independence after intensive neurorehabilitation in stroke patients.

Our results showed a significant increment in the Barthel Index and the FIM after rehabilitation. As expected, the higher the Barthel score is at admission, the higher it is at discharge.[37, 38] The latter score was also influenced by motor functionalities of lower limb and cognitive domains such as attention and executive functions that seems to be strong predictor of functional recovery mediated by rehabilitation processes in stroke patients. Therefore, a routine assessment of cognitive functions might be provided, in rehabilitative setting, to design a tailored treatment to recover the independence in activities of daily living.[44-48]

Some variables reported in previous studies to be a prognostic factor of Barthel Index at discharge, such as time from stroke,[49] functional independence,[37] and orientation,[50] were only close to being statistically significant in our analysis. This slight difference was probably due to the fact that other cognitive functions possibly affected these variables and explained the majority of variance when entered into the model, thus pushing time from stroke, functional independence, and orientation out of the model. The explained variance covered about 3/4 of the sample, and the model was solid in identifying patients with poor outcome. On the contrary, in some cases, it underestimated a good recovery.

Regarding motor functions, lower limb functionality at admission is significantly related to a better level of independence at discharge. This result is in line with the assumption that lower limb recovery affects the global score of Barthel Index more than the upper limb recovery.[51]

Among the many cognitive domains assessed, attention and executive functions emerged as the best predictors of a good level of independence at discharge. Attention showed an improvement during rehabilitation. This was not statistically significant for executive functions.

A post-hoc analysis showed that the proportion of subjects with an improvement in global independence, measured by effectiveness[36] in terms of the Barthel Index, was significantly correlated to the absence or the recovery of the executive functions during the rehabilitation period. On one hand, this finding can be explained because the presence of cognitive impairment is associated with less autonomy and greater disability. It is well known that cognitive impairment has a significant impact on post-stroke quality of life.[52] On the other hand, our results suggest a more specific relationship with an impairment in executive functions that may impact learning ability in planning and the starting of self-directed activities in the problem-solving capacity and in the understanding and retention of task rehabilitative instructions that are the basis of motor and functional recovery.[53]

According with literature, our results support the suggestion that functional outcome and independence are directly linked to executive functions that are involved in appropriately modifying behaviour and adapting movement to changing environmental conditions.[54] Further studies should investigate if cognitive deficits may reduce the patients' participation level to the proposed neuromotor protocol, being active participation a determinant of a good functional outcome.[55]

These findings are in line with the literature reporting that deficits in executive functions are strongly associated with post-stroke functional impairment and related to the risk of an earlier permanent institutionalization.[56] An original result of our study is that the recovery of executive function deficits during neurorehabilitation improved the functional outcome. This result goes beyond the already known relationship between executive functions and functional outcome,[47] pointing out the importance of cognitive treatment aiming at recovering executive function also for promoting a functional recovery. To do that there is the need of detailed and repeated neuropsychological examinations, also to differentiate between deficits in executive functions, depression and dementia.[57]

In fact, principles applied in stroke rehabilitation evolve year by year in more specific and functional task-oriented methodologies which boost neural plasticity that is at the base of motor recovery through learning principles.[58] Regarding the global ability recovery, our results suggest that a greater recovery of attention plays a key role in the recovery of independence in activities of daily living.

The influence of the executive function during the rehabilitation process was already known, both for walking recovery as well as for upper limb functions (reaching and grasping).[17, 20, 57] Moreover, in recent years, the growing interest of professionals in new technologies applied to rehabilitation, has highlighted the role played by cognitive functions in allowing patients to have access to such treatments.

Among the cognitive domains, executive function seems to be the most important in determining the applicability of these technologies to rehabilitation.[56, 59, 60]

In accordance with this, our main assumption is that it appears to be fundamental to appropriately introduce the cognitive profile in clinical practice, as cognitive status affects rehabilitative outcome.

To our knowledge, this is the first article that specifically investigates both the role of executive functions on rehabilitation outcome and the importance of patients' recovery during hospitalization.

The originality of this multicentre longitudinal study is that cognitive improvement changes were analysed over time. The recovery of executive functions recorded in some patients leaded to an improvement in global subjects' functional independence. This improvement was less significant (lower-not present) in patients who did not have a recovery of executive functions.

Limitations of the study

Due to the fact that this was a multicentric study, there could have been differences among the participating centres in administration of conventional cognitive and neuromotor therapy. In order to reduce the potential differences in treatment among the participating centres we planned a focused meeting before starting the study. During the meeting we focused on the meaning of "conventional cognitive and neuromotor therapy" in terms of length, total number of treatments, as well as intensity of training of each session.[61] All the centres participating to this study were in Italy and followed Italian laws and rules for admission and treatment, and it further mitigates the possible differences between centers. Then, we limited the ascertain of pre-stroke cognitive status to the anamnestic presence of psychiatric or neurological diseases pre-stroke, that was used as an exclusion criterion.

Moreover, the number of patients from the sample size calculation, should have mitigated the supposed biases related to specific neuromotor treatment depending on different centres. On the other hand, this study represents the real world of the rehabilitation and the results we highlighted are more likely related to cognitive impairment rather than to specific rehabilitative approaches. Despite our wide sample size, it was not enough ample to allow a validation of the results on other dataset or to perform a training/testing procedure based on data splitting. Future studies are needed test the model found in this study to other data.

In our study, 28.8% of patients showed an impairment in executive functions. On one hand it could limit the solidity of our results because related to a limited subgroup. On the other hand, this percentage is in line with the prevalence of this deficit as reported by Baker-Collo and colleagues (30.4%),[62] and within the range defined by literature (from 18.5% to 39%).[63]

Lastly, we did not take in account some dimensions such us depression, personality changing and behavioural impairment. This could be explored in a further researches.

Conclusions

In conclusion, the relationship between cognitive and motor deficits is increasingly highlighted and the recovery of executive functions deficits seems to contribute to motor recovery.

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The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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SUPPLEMENTARY DIGITAL MATERIAL 1

Supplementary Table I.—Table of variables collected for each patient.

Type and number (n) of analysed variables		**Variables**	**Time of assessments and total number (N) of collected variables**
Independent Variables (N=100)	Demographical variables (n=14)	Age, Gender, Education level, Civil Status, Type of work (classified in 5 variables: employee, freelancer, unemployed, retired, home-worker, other), Caregiver presence, Body mass Index (classified in 4 variables: malnutrition, normal weight, overweight, obesity)	Admission (N=14)
	Stroke variables (n=10)	Time from stroke and admission in hospital, affected hemisphere, side of lesion, type of lesion, Bamford classification (4 variables: LACI, PACI, POCI, TACI), fibrinolysis, thrombectomy	Admission (N=10)
	Comorbidities (n=3)	Diabetes, Hypertension, Atrial fibrillation	Admission (N=3)
	Clinical variables (n=10)	Complications during recovery (classified in 10 different types)	Discharge (N=10)
	Oxford Cognitive Screen (n=15)	Picture naming, Semantics, Attention (Hearts Time), Attention (Hearts Correct), Executive Functions, Orientation, Visual Field, Sentence Reading, Number Writing, Number calculation, Object Asymmetry, Space Asymmetry, Imitation, Semantic Memory, Episodic Memory	Admission and discharge (N=30)

	NIH-Stroke Severity Scale (n=15)	Vigilance, Eye Movements, Comprehension, Visual field, Facial palsy, Left motor arm, Right motor arm, Left motor leg, Right motor leg limb, Ataxia, Sensory, language, Speech, Extinction and Inattention, Dysarthria, Total score	Admission and discharge (N=30)
	Fugl-Meyer Upper limb (n=7)	Wrist, Hand, Coordination and velocity, Sensibility, Passive movements, Pain, Total score	Admission and discharge (N=14)
	Fugl-Meyer lower limb (n=5)	Coordination and velocity, Sensibility, Passive movements, Pain, Total score	Admission and discharge (N=10)
	Functional Independence Measures (n=19)	Eating, Grooming, Bathing, Dressing upper body, Dressing lower body, Toileting, Bladder management, Bowel management, Transfers - bed/chair/wheelchair, Transfers – toilet, Transfers - bath/shower, Walk/wheelchair, Stairs, Comprehension, Expression, Social interaction, Problem solving, Memory, Total Score	Admission and discharge (N=38)
	Barthel Index (n=11)	Feeding, Bathing, Grooming, Dressing, Bowels, Bladder, Toilet use, Transfers, Mobility, Stairs, Total score	Pre-stroke estimation, admission (N=22)
Dependent Variable (N=1)	Barthel Index (items: n=10, total score=1)*		Discharge (N=11) improvements (N=11)

*For the Barthel Index each one of the following items have been collected as for the other scales, but only the total BI-scores were analysed. The BI-score at admission and that pre-stroke were used as independent variables, that at discharge as dependent variable.