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Cognitive, Behavioral and brain lesional factors in the neurorehabilitation of stroke patients: prognostic and clinical outcomes

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ABSTRACT. Stroke is the second most common cause of death worldwide and the main cause of adult disability in Western Countries, with 40% of stroke survivors reporting problems in activities of daily living. functional and clinical outcomes of the rehabilitative process may vary as a function of a number of variables, and predicting the degree of recovery after stroke, although essential, can be challenging, such that patients with similar baseline impairments might show different recovery trajectories.
In the present study, we explored this issue in a sample of 48 stroke patients (right hemisphere damage) admitted to the IRCCS Santa Lucia Foundation, a neurorehabilitation hospital located in Rome, Italy. Specifically, we focused on cognitive, neuropsychiatric and brain lesion measures to predict clinical outcome.
Results revealed that age, baseline neuro-functional, neuro-cognitive and neuropsychiatric data, along with sparing of temporal pole and inferior frontal regions, mediate post-stroke recovery. Such results could provide further hints in considering the clinical variables involved in functional recovery and return to work in stroke patients.

Kew ywords: *Stroke, Stroke recovery, cognition, brain lesion.*

RIASSUNTO. Fattori cognitivi, comportamentali e lesionali nella neuroriabilitazione di pazienti con esiti di ictus: indicazioni prognostiche e outcome clinici.
L'ictus è una delle principali cause di morte e disabilità nei paesi occidentali, con circa il 40% dei pazienti che riportano deficit nelle attività quotidiane. Malgrado siano diversi gli studi che hanno indagato le variabili in grado di spiegare il recupero funzionale nei pazienti con stroke, i risultati sono molto eterogenei. Il presente studio ha lo scopo di analizzare il valore predittivo di variabili cliniche (età, grado di indipendenza, volume e localizzazione della lesione cerebrale), neurocognitive (memoria episodica, attenzione e prassie, funzioni esecutive) e neuropsichiatriche (depressione ed ansia) sul recupero funzionale di pazienti con stroke inseriti in un programma di neuroriabilitazione presso la Fondazione Santa Lucia di Roma.
Dai risultati è emerso che diversi fattori sono significativamente associati ad un buon recupero funzionale, quali l'età, il grado di indipendenza iniziale, la memoria a lungo termine e la depressione e il risparmio di aree cerebrali temporali e frontali.
I risultati possono offrire utili indicazioni cliniche nella predizione del recupero funzionale in pazienti con stroke.

Parole chiave: ictus, recupero, fattori cognitivi, lesione cerebrale.

1. Introduction

Stroke, which occurs when blood circulation to the brain fails, is the second most common cause of death worldwide, the first being heart disease. Despite the improvements in prevention and treatment of the acute phase, stroke remains the main cause of adult disability in Western Countries, with 40% of stroke survivors reporting problems in activities of daily living (1). Since stroke permanently damages brain function, survivors are often left with lasting brain damage and/or permanent disabilities (including cognitive, motor and functional impairment) requiring long-term neurorehabilitation and care. Its high prevalence produces a great impact on our society and it is estimated that in the coming years, due to the ageing of population, it will increase more, which will generate a greater number of people in need of care. The majority of studies suggest that neurological recovery occurs in the first three months with maximum recovery estimated in the first 4-6 weeks after the stroke (2). It is important to point out that the therapeutic and neurorehabilitation processes in stroke patients requires a multidisciplinary team in order to address and quantify the deficit caused, including physicians specializing in physical medicine and neurorehabilitation, neurologists, psychologists, speech pathologists, physiotherapists and many others.

The goal of the neurorehabilitation of stroke survivors is to achieve the maximum capacity (motor, cognitive, functional and social) enabling them to be reintegrated into their previous activities. In this view, the neurorehabilitation programs have indisputably confirmed their effectiveness in reducing both mortality and the degree of disability and dependency (3). In this setting, early initiation of treatment, the application of high intensity with specific goals and active therapies, and the coordinated work and multimodality of a specialized team play a major role.

It has been suggested that recovery of an initial deficit follows an almost linear progress with a fixed improvement range (4), a phenomenon often referred to as proportional recovery. However, functional and clinical outcomes of the rehabilitative process may vary as a function of a number of variables, and predicting the degree of recovery after stroke, although essential, can be challenging, such that patients with similar baseline impairments might show different recovery trajectories.

Several observational studies have demonstrated that initial severity of deficits, measured with either disability or impairment scales, is the best predictor of recovery (e.g. (5)). Other predictors used in regression models have included age, demographics, nonmotor clinical features, infarct side and location, and stroke subtype (e.g. (6)).

However, given the heterogeneity of the disorders of stroke patients, a more complex model for predicting recovery is a urgent need. This would be beneficial for: (a) patients, caregivers and clinicians; (b) planning subsequent clinical pathways and goal setting; and (c) identifying whom and when to target, and in some instances at which dose, with interventions for promoting stroke recovery.

In the present study, we explored this issue in a sample of 48 stroke patients (right hemisphere damage) admitted to the IRCCS Santa Lucia Foundation, a neurorehabilitation hospital located in Rome, Italy. Specifically, we focused on cognitive, neuropsychiatric and brain lesion measures to predict clinical outcome.

2. Methods

2.1 Patients

Patients were recruited from the Neurorehabilitation Centre of I.R.C.C.S. Fondazione Santa Lucia. Exclusion criteria were:) age < 18 or > 85 years, 2) previous strokes or diffuse structural brain alterations, 3) presence of peripheral vestibular deficits, 4) presence of global aphasia, 5) presence of severe or moderate cognitive deficit as assessed by the Mini Mental State Examination (7) (score < 17).

All recruited patients (average post-stroke time interval: 2.4 ± 1.6 months) suffered from a unilateral hemispheric brain lesion, as a consequence of ischemia in the region of the middle cerebral artery.

2.2 Neuropsychiatric Assessment

Depressive symptom severity was evaluated with the Hamilton Rating Scale for Depression (Ham-D), (8) a 17-item inventory composed of psychological (PSY) and somatic (SOM) subscores that together contribute to the total score. The PSY subscale consisted of 6 questions about depressed mood, guilt, suicide, work, loss of interest, anxiety, and insight; the SOM subscale consisted of 11 questions regarding insomnia (initial, middle, and delayed), retardation and agitation, somatic anxiety, somatic gastrointestinal symptoms, general somatic symptoms, genital somatic symptoms, loss of weight, and hypochondriasis.

Severity of anxiety symptoms was measured with the Hamilton Rating Scale for Anxiety (Ham-A) (9).

2.3 Neuropsychological Assessment

Global cognitive functioning was evaluated with the MMSE. To assess performance in specific cognitive domains, the patients were administered the Mental Deterioration Battery (MDB), (10) a standardized and validated neuropsychological battery including the Rey's 15-word test: Immediate Recall (RIR) and Delayed Recall (RDR), to evaluate short- and long-term verbal memory; the Copy Drawings (CD) and Copy Drawings with Landmarks (CDL), to evaluate simple and constructional praxis, and the Stroop Word-Color Test (SWCT) (11) for the evaluation of executive functions of attention-shifting and control.

2.4 Functional Assessment

We used the Barthel Index (BI) (12) to evaluate functional abilities. The BI is considered a reliable disability scale for stroke patients and is used to measure performance in 10 common activities of daily living (8 related to personal care and 2 related to mobility). Each performance item is rated on this scale with a given number of points assigned to each level. A total score of 100 is the highest degree of functional independence in activities of daily living.

2.5 MRI acquisition and lesion mapping

All participants underwent the same imaging protocol, which included 3D T1-weighted, T2-weighted and FLAIR sequences using a 3T Achieva MR scanner (Philips Medical Systems, Best, The Netherlands) with a 32-channel receiving-only head coil. Whole-brain T1-weighted images were obtained using a fast-field echo sequence (echo time/repetition: time = 5.3/11 ms, flip angle = 9°, voxel size = 1 × 1 × 1 mm3).

Lesions were traced directly onto patient's image using MRIcron software by expert neuro-radiologists unaware about the aims of the study. For MRI data, images were non-linearly transformed to match the MNI152 T1 template with lesion cost function masking (13) using FSL software (www.fmrib.ox.ac.uk/fsl/). Normalization parameters were applied to lesion maps in order to obtain a normalized binary lesion.

2.6 Potential Predictors and Outcome Measures

The main purpose of this study was to identify predictors of a favorable recovery after neurorehabilitation in stroke patients admitted to in-hospital care, more specifically concerning daily activity independence and participation. We considered the outcome at 6 months post-discharge (dependent variables) to be favorable if the BI score was 75 or higher (14).

The following independent variables (predictors) were baseline indicators, more specifically: age, baseline BI score, cognitive performance (RIR, RDR, CD, CDL, SWCT), neuropsychiatric variables (HAM-D, HAM-A) and lesion volume (in mm^3).

3. Statistical Analyses

In order to estimate the odds of predicting longitudinal outcome, three separate binomial logistic regressions were conducted on group membership as the dependent variable (good/poor recovery as for BI < or > 75) considering predictors as independent. Specifically, we computed a first model including age, baseline BI and lesion volume (Model 1), a second model including cognitive predictors (Model 2) and a third model including neuropsychiatric predictors (Model 3). In all models age was included as nuisance variable.

Further, in order to investigate the role of brain lesion location in predicting clinical outcome, we run a lesion subtraction analysis (15). This analysis is performed as follows: first, two groups of subjects are defined according to behavioural results (i.e. good vs poor longitudinal outcome). Then, the lesions of all subjects in the first group (i.e. subjects whit a BI score < 75) are added together to create an overlapping image that shows regions of mutual involvement. Third, the lesions of the second group of subjects are subtracted from the first group's overlapping image. Finally, the results of the subtraction is plotted graphically on the same template image, which shows regions commonly damaged in subjects of the first group but spared in those of the second group.

4. Results

According to inclusion and exclusion criteria, 48 stroke patients were recruited (22 females and 26 males, age: 69.43 ± 7.06 years, mean ± SD; education level: 8.6 ± 4.7 years, see Table I).

At admission (baseline) the mean BI was 61 (± 11.5) and the mean lesion volume was 95 cm^3 (± 40). Twenty five out of the 48 patients showed a positive recovery (BI > 75) at discharge.

Table I. ***Demographic and cognitive characteristics of the 48 patients***

Variables	Mean (SD, %)
Age	69.4 (7)
Education	8.6 (4.7)
Gender (females)	22 (46)
Mini Mental State Examination (MMSE)	26.23 (3.7)
Baseline BI	61 (11.5)
Follow-up BI	75.7 (10.2)
Lesion volume (mm^3)	95 (40)
MDB Rey's 15-word Immediate Recall (RIR)	34.8 (10.5)
MDB Rey's 15-word Delayed Recall (RDR)	7.1 (2.8)
Copying Drawings (CD)	6.4 (4)
Copying Drawings With Landmarks (CDL)	31.1 (16)
Stroop Word–Color Test (SWCT) reading (sec)	52.2 (25.1)
Stroop Word–Color Test (SWCT) naming (sec)	54.2 (25.4)
Stroop Word–Color Test (SWCT) interference (sec)	94.4 (41.8)
Trial Making Test (TMT A)	50.79 (15.95)
HAM-A	11.9 (6.5)
HAM-D	12.6 (4.5)

Logistic regression models revealed that outcome significant predictors were baseline BI and age (and partially lesion volume) for Model 1, RDR for Model 2 and HAMD for Model 3 (see Table II).

Table II. ***Results from logistic regressions***

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
Model 1									
		B	S.E.	Wald	df	Sig.	Exp(B)	Lower	Upper
Step 1ª	BI_baseline	,183	,057	10,357	1	,001	1,201	1,074	1,343
	age	-,149	,064	5,334	1	,021	,862	,759	,978
	lesion_volume	-,021	,011	3,408	1	,065	,979	,958	1,001
	Constant	1,465	4,264	,118	1	,731	4,329		
Model 2									
		B	S.E.	Wald	df	Sig.	Exp(B)	Lower	Upper
Step 1ª	RIR	,075	,086	,752	1	,386	1,078	,910	1,277
	RDR	,777	,351	4,901	1	,027	2,176	1,093	4,331
	CD	,163	,139	1,380	1	,240	1,178	,897	1,547
	CDL	-,028	,028	,987	1	,320	,973	,921	1,027
	SWCT_read	,001	,017	,005	1	,941	1,001	,968	1,036
	SWCT_name	-,026	,019	1,923	1	,165	,974	,939	1,011
	SWCT_inter	,009	,012	,620	1	,431	1,009	,986	1,033
	Constant	-7,505	3,741	4,024	1	,045	,001		
Model 3									
		B	S.E.	Wald	df	Sig.	Exp(B)	Lower	Upper
Step 1ª	HAMA	-,036	,049	,550	1	,459	,964	,876	1,062
	HAMD	-,165	,077	4,547	1	,033	,848	,729	,987
	Constant	2,590	1,103	5,513	1	,019	13,329		

Lesion subtraction analysis revealed that the brain areas associated with a good recovery (i.e. spared in patients with follow-up BI > 75 and damaged in patients with a follow-up BI < 75) were the temporal pole, the insula and the inferior frontal lobe (pars orbitalis, opercularis and triangularis (Figure 1).

5. Discussion

In the present study we investigated the impact of a number of clinical variables on stroke recovery in a neurorehabilitation setting. Results from multivariate analyses revealed that showing a lower baseline disability, being younger and, although partially, showing a smaller brain lesion volume, were significant clinical predictors of good recovery. Also, showing a better performance in long-term memory tasks and being less depressed were significantly associated with a better outcome on discharge. Finally, we showed that the temporal pole and the inferior frontal lobe were the brain areas that, if spared from stroke, were associated with a better recovery.

Currently, in Italy there are over one million people suffering from long-term disability after stroke. However, the care pathway for stroke neurorehabilitation is mainly focused mainly on the acute and sub-acute phases. Indeed, the difficulty in accessing neurorehabilitation services after the acute phase makes the needs of patients during the chronic phase partially neglected (16). Such organizational model could be due to a poor knowledge of the mechanisms and variables involved in stroke recovery (17). Within this scenario, the definition of a multidomain set of clinical factors that correlate prospectively with long-term recovery and disability after stroke is mandatory.

As a first result we found that lower baseline disability and younger age (and to a lesser extent a lower lesion volume) accounted for better recovery and less disability. The result is somewhat not surprising, since several lines of evidence highlighted that degree of independence and disability prior to admission after suffering a stroke is the leading factor that will determine the functionality of patients at hospital discharge (18). Along the same line of reasoning, there is evidence that age is another key factor in determining neurorehabilitation outcome after stroke, since the full recovery potential can be achieved engaging brain plasticity processes that are, in turn, modulated by age (19).

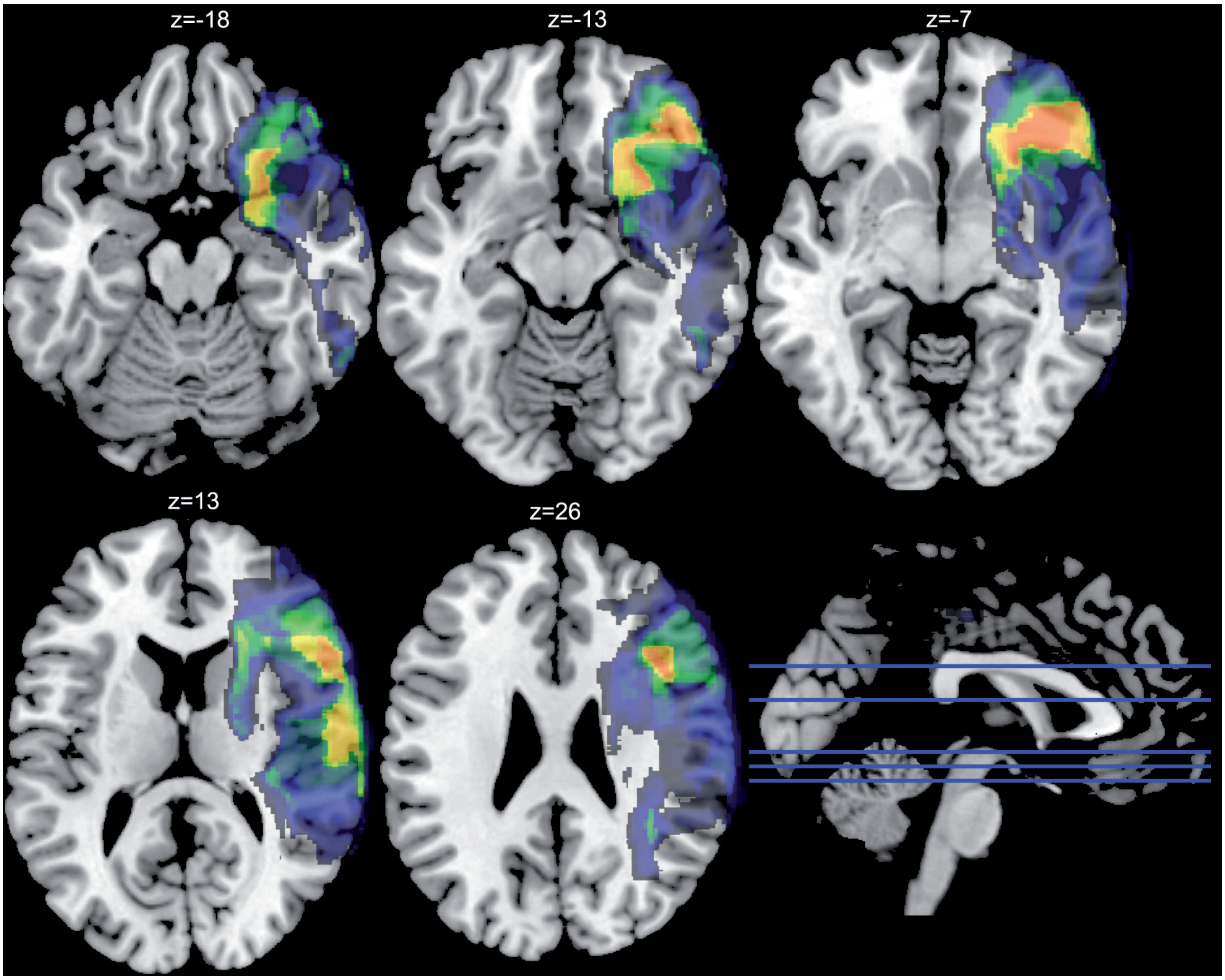

Figure 1. ***Results from the subtraction analysis. Orange-to-red areas are those spared in patients showing a good recovery and damaged in patients showing poor recovery***

We also found that baseline verbal long-term memory performance was associated to clinical outcome. Post-stroke cognitive deficits are common (20) and add to the challenges already faced by stroke-survivors. A previous survey by the Stroke Association found that 77% of stroke survivors show memory deficits and yet nearly 50% of stroke-survivors reported that the support they received for their memory problems was poor (21). It can be easily assumed that the cognitive impairment can lower participation in neurorehabilitation therapy, and memory deficits may impede learning protocols or procedures needed to be independent after stroke (22). Indeed, the function of memory in neurorehabilitation after stroke is of key clinical relevance since the ability to manipulate and maintain information might provide better performance in neurorehabilitation (23). Decline in memory impairs activities in daily lives, the ability to be independent and secure, and the capacity of learning skills to overcome neurological deficit. In neurorehabilitation training, memory can play an important role in learning how to act with devices, and following stepwise instructions (22).

Another important finding of the present study is the predictive role of depression on clinical outcome. The association between stroke and depression is not new and has been studied since late ‘50s (24). Patients with post-stroke depression show a greater risk of mortality (25), higher rates of suicide (26), increased cognitive impairment (27), and a poorer quality of life (28,29). Moreover, accordingly to the results of the present study, it has been shown that post-stroke depression has a negative impact on neurorehabilitation outcome. Such negative effect could be due to the fact that patients with post-stroke depression show a higher degree of disability (30), are usually less participative in the rehabilitative processes (31). On the other hand, reducing depressive symptoms through treatment would lead to better functional recovery and prognosis (32). In this view, it has been suggested that the mechanisms of depression (eg, neurotransmitter depletion leading through some pathophysiology to the clinical manifestations of decreased concentration and energy) may be the cause of poor recovery. On the other hand, it could also be speculated that the effect of depression on physical impairment may be mediated by psychological rather than physiological mechanisms. For example, depressed patients may be hopeless about the future and thus may be less psychologically motivated to put any effort into neurorehabilitation or recovery. This could lead to slowed recovery in the depressed patients.

Finally, we found that the brain areas associated to better recovery were the temporal pole and the inferior frontal lobe. Both areas have been previously associated to post-stroke memory deficits and depression (33,34), two variables that have been shown to predict functional recovery in the present study. However, a mere association between a brain area and a function could provide a partial overview of the complex dynamics playing fundamental roles in stroke recovery. Indeed, recovery after stroke is attributed to plastic reorganization in the central nervous system. Reorganization commonly refers to recruitment of areas previously not (or less) engaged in a given task, in order to substitute for directly lesioned or disconnected areas. However, stroke impacts extend beyond the lesion site. Focal lesions have important remote effects on the function of distant brain regions that contribute significantly to the observed deficits and to post-stroke recovery (35). Although damage from the initial lesion is focal, remote dysfunction can occur in regions connected to the lesion (36). For instance, changes in remote locations can be observed in the first hour after stroke in animal models (37) and a lesion may also disturb the complex balance of excitatory and inhibitory influences within a network (38). Therefore, it could be the case that the temporal pole and the inferior frontal regions are key contributors to such complex network balance, thus leading, when spared from stroke, to enhance recovery.

To conclude, in the present study we investigated a number of contributors to functional recovery in stroke patients. Results revealed that age, baseline neuro-functional, neuro-cognitive and neuropsychiatric data, along with sparing of temporal pole and inferior frontal regions, mediate post-stroke recovery. Such results could provide further hints in considering the clinical variables involved in functional recovery and return to work in stroke patients.

Future studies including a higher number of patients and clinical measures, as well as additional neuroimaging techniques (e.g. exploring the brain connectome) should deepen the complex issue of post-stroke recovery.

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