NeuroImage 308 (2025) 121059

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Clinical and neurophysiological predictors of the functional outcome in right-hemisphere stroke

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A R T I C L E I N F O

Keywords:
Stroke
Electroencephalography
Functional independence measure
Brain connectivity
Support vector machine

A B S T R A C T

Objective: The aim of the present study is to examine the relationship between EEG measures and functional recovery in right-hemisphere stroke patients.
Methods: Participants with stroke (PS) and neurologically unimpaired controls (UC) were enrolled. At enrolment, all participants were assessed for motor and cognitive functioning with specific scales (motricity index, trunk control test, Level of Cognitive Functioning, and Functional Independence Measure (FIM). Moreover, EEG data were recorded. At discharge, participants were re-tested with the FIM
Results: Powers in the delta, theta, alpha, and beta bands and connectivity within the fronto-parietal network were compared between groups. Then, the between-group discriminative EEG measures and the motor/cognitive scales were used to feed a machine learning algorithm to predict FIM scores at discharge and the length of hospitalization (LoH). Higher delta, theta, and beta and impaired connectivity were found in PS compared to UC. Moreover, motor/cognitive functioning, beta power, and fronto-parietal connectivity predicted the FIM score at discharge and the LoH (accuracy=73.2 % and 85.2 % respectively).
Conclusions: Results show that the integration of motor/cognitive scales and EEG measures can reveal the rehabilitative potentials of PS predicting their functional outcome and LoH.
Significance: Synergistic clinical and electrophysiological models can support rehabilitative decision-making.

1. Introduction

Left Hemi-Spatial Neglect (LHSN) is a common impairment associated with long-term disability in persons affected by right-hemisphere stroke (Buxbaum et al., 2004; Corbetta and Shulman, 2011). LHSN is a neuropsychological syndrome characterized by a reduced ability to attend to and perceive the left contralesional space. In particular, LHSN patients fail to attend to any stimulus coming from the left space and showed motor deficits over the contralesional limbs (i.e., hemiplegia). These cognitive and motor deficits can affect the ability to carry out many everyday tasks (i.e., activities of daily living, ADL, Katan and Luft, 2018; Wolfe, 2000), such as walking, eating, reading, and getting dressed. Moreover, these patients, as a direct consequence of the brain injury are also often affected by anosognosia for hemiplegia, which is the lack of awareness about motor and cognitive deficits. This condition hinders motor and cognitive recovery, predisposes to falls and reduces independence. In the LHSN population, the level of independence in the ADL is strongly related to the functional recovery of motor and cognitive functions (Di Gregorio et al., 2021b, 2023; Di Gregorio and Battaglia, 2024; Di Monaco et al., 2011). For this reason, functional recovery represents a key target for neurorehabilitation programs (Duncan et al., 2021). Consequently, accurate assessments and predictions of global functional recovery at an early stage are critical to selecting the best neurorehabilitation protocol that would maximize the outcome and set treatment objectives (Di Monaco et al., 2011; Katz et al., 1999). However, although motor and cognitive impairments after stroke and LHSN

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https://doi.org/10.1016/j.neuroimage.2025.121059
Received 2 July 2024; Received in revised form 17 January 2025; Accepted 27 January 2025
Available online 28 January 2025
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are very common, functional assessment and outcome prediction remain considerable challenges (Campbell et al., 2019; Ekker et al., 2018; Furie, 2020; Rost et al., 2022; Wolfe, 2000).

In recent years, there has been a growing interest in clinical measures assessing functional status, level of independence in the ADL, motor and cognitive functioning in patients with stroke (Fidali et al., 2020). For instance, the Functional Independence Measure (FIM) is a multidomain scale that assesses the motor and cognitive domains to provide a global measure of patients' functional and motor independence in the ADL (Kidd et al., 1995; Nilsson and Tennant, 2011). Although useful for the assessment of the current patient's motor/cognitive status, the FIM^{tm} does not provide accurate outcome prediction for stroke and traumatic patients at discharge from rehabilitation (Dijkland et al., 2020; Fidali et al., 2020). Therefore, recent studies proposed to predict the functional outcome based on demographic and clinical factors. Specifically, higher initial levels of motor and cognitive functioning (measured with the Motricity Index, the Trunk Control Test and the Level of Cognitive Functioning) after unilateral left or right stroke predict higher levels of motor independence in the ADL at discharge (Bland et al., 2012; Campagnini et al., 2022; Di Monaco et al., 2010; Franchignoni et al., 1997; Gialanella et al., 2013; Gialanella and Ferlucci, 2010; Masiero et al., 2007; Meyer et al., 2015; Shelton et al., 2001). These results were further corroborated by machine learning methods, forecasting functional outcomes in patients with stroke. Specifically, machine learning methods identified potential demographic and clinical predictors (such as age, gender, side of the lesion, time since stroke and baseline Fugl-Meyer assessment scale (FMA) and National Institutes of Health Stroke Scale (NIHSS) scores) of post-stroke motor recovery, thus advocating for its integration into clinical practice for personalized treatment (Campagnini et al., 2022; Thakkar et al., 2020; Zu et al., 2023).

However, the aforementioned clinical and demographic predictors do not explain the full variance as functional outcome prediction has been shown to depend also on additional cognitive and neural factors which influence recovery (Kim and Winstein, 2017; Özdemir et al., 2001). A promising approach to investigate interindividual functional recovery after stroke encompasses the temporal dynamics and the organization of the neural networks based on electroencephalographic (EEG) data. Notably, a loss of power in the higher frequency bands (alpha/mu: 8–13 Hz and beta: 14–30 Hz) with a concomitant increase in the lower bands (delta: 1–3 Hz and theta: 4–7 Hz) have been linked to a poor outcome (Bentes et al., 2018; Cassidy et al., 2020; Finnigan and van Putten, 2013; Finnigan et al., 2007; Gallina et al., 2021; Leon-Carrion et al., 2009; Pietrelli et al., 2019; Sheorajpanday et al., 2011). Moreover, larger connectivity within the fronto-parietal motor network in the first weeks after stroke seem to be positively related to better subsequent motor recovery, while later connectivity increases were associated with poorer clinical outcomes (Gale and Pearson, 2012; Hoshino et al., 2021; Kim and Winstein, 2017; Lim et al., 2021; Min et al., 2020; Nicolo et al., 2015). These results highlight that EEG signals may track underlying neural mechanisms of plasticity and connectivity able to index outcome prediction. Importantly, timing of testing is extremely relevant here to adequately predict clinical improvements (Dacosta-Aguayo et al., 2014; Lim et al., 2021; Min et al., 2020; Puig et al., 2017, 2011; Zhu et al., 2010).

In the studies investigating the EEG pathophysiological correlates (i.e., EEG biomarkers) of patients with stroke, the clinical outcome is often measured using the modified Rankin Scale, the motricity index, or specific cognitive and behavioral scales (e.g., Mini mental State Examination MMSE, NIHSS; Bentes et al., 2018; Boyd et al., 2017; Cuspineda et al., 2007; Finnigan et al., 2007, 2004; Forkert et al., 2015; Hoshino et al., 2021; Keser et al., 2022; Nicolo et al., 2015; Sheorajpanday et al., 2011; Stinear, 2017; Tscherpel et al., 2020; Vecchio et al., 2019). Therefore, the global level of functional independence (i.e. the result of the combined contribution of motor and cognitive functioning of the patient's independence in the ADL, as measured by the FIM), although extremely relevant for the patients, is scarcely considered for the investigation of the EEG biomarkers (Cassidy et al., 2020).

Indeed, to the best of our knowledge, there are no studies considering clinical and EEG measures for the prediction of functional outcomes based on FIM scores. However, considering current evidence, we hypothesized that EEG might support the prediction of functional outcomes in stroke population with LHSN (Cuspineda et al., 2007; Di Gregorio et al., 2022a; Erani et al., 2020; Fuggetta et al., 2014; Ibanez et al., 2024; Schleiger et al., 2014; Sutcliffe et al., 2022; Trajkovic et al., 2021). To test this hypothesis, we aimed to investigate the possible added value of EEG biomarkers recorded on admission to the prediction of the functional outcome at discharge in patients with right-hemisphere stroke with contralesional motor impairments.

2. Materials and methods

2.1. Study design

This is a secondary prospective study originating from an ongoing multicenter Randomized Controlled Trial (Di Gregorio et al., 2021a) aiming at assessing the efficacy of an inhibitory rTMS protocol on LHSN-related symptoms in a population of right-sided hemispheric stroke. For the purpose of this study, we selected only participants with stroke (PS) to the original study who were randomized in the control group and completed all study procedures. PS underwent EEG assessment on enrollment and received usual stroke rehabilitation care without any rTMS stimulation, unlike those randomized in the intervention group. To reach the main aim of the study we employed also EEG data from neurologically unimpaired controls (UC). At enrollment (i.e., T0), EEG data were collected in four consecutive days during different recording sessions (see also Di Gregorio et al., 2023). Data were collected following the International guidelines for clinical EEG recording (i.e., standard clinical EEGs; Babiloni et al., 2020). Thus, the EEG-based measures for each subject were derived from four different EEG sessions. This approach enabled analysis of four distinct EEG sessions at the time of enrollment (T0). Additionally, it allowed us to evaluate the variability of EEG-based measures at T0, thereby enhancing the reliability of these measures for predicting functional outcomes. All the procedures described in this study were conducted in accordance with the Declaration of Helsinki (World Medical Association, 2013) and approved by the local Ethical Committee (CE num. 17075) Bologna, Italy.

2.2. Participants with stroke: inclusion and exclusion criteria

Inclusion criteria were (Di Gregorio et al., 2021a): 1. Diagnosis of ischemic stroke of the right middle cerebral artery or right intracranial hemorrhagic stroke, confirmed by encephalic CT scan or MRI; 2. Diagnosis of hemiplegia confirmed by specific motor scales (Motricity Index and FIM). 3. Inpatient or outpatient rehabilitation setting; 4. Age between 18 and 80 years; 5. Time after stroke between 1 week and 4 weeks; 6. Adequate language comprehension to give informed consent. Exclusion criteria were: 1. Medical instability at the time of enrollment; 2. Presence of epileptogenic alterations of the EEG and/or previous epileptic seizures; 3. Presence of alteration in the consciousness-vigilance rhythm; 4. Previous diagnosis of cognitive impairment. A control group included age-matched, voluntary neurologically unimpaired participants (Unimpaired Controls, UC), as described in a previous study (Di Gregorio et al., 2023). UC participants did not report any relevant medical condition and were not hospitalized under inpatient or outpatient care at the moment of enrolment. All participants were recruited at UOC Medicina Riabilitativa e Neuroriabilitazione of the IRCCS Istituto delle Scienze Neurologiche di Bologna, Italy, among the italian population.

2.3. Participants with stroke: clinical data and measures

2.3.1. Demographic and clinical variables

Participants' demographic information was collected and reported in specific case report forms. We also recorded any intravascular therapy administered to patients with ischemic stroke at the beginning of the acute phase (i.e., intravenous thrombolysis and/or mechanical thrombectomy). This information was included as these acute therapeutic procedures for ischemic stroke can influence functional outcomes (Sallustio et al., 2018; Suzuki et al., 2021). We also recorded the length of hospitalization (LoH).

FIM^{tm} . The FIM total scores at enrolment (T0) and discharge (T1) were recorded. The FIM is a multidimensional outcome assessment scale that investigates cognitive and motor functions (Linacre et al., 1994; Nilsson and Tennant, 2011). The FIM comprises 18 items, divided into two subscales (i.e., the motor and cognitive subscales). All items are scored from 1 (total assistance) to 7 (complete independence) (Maritz et al., 2019; Nilsson and Tennant, 2011). The FIM is applied in clinical and research environments to determine the disease severity, define motor recovery, and plan rehabilitation programs (Maritz et al., 2019; Nilsson and Tennant, 2011). Finally, two additional motor scales (i.e., the Motricity Index, MI and the Trunk Control Test, TCT) and one cognitive scale (i.e., the Level of Cognitive Functioning, LCF) known to be correlated to the functional outcome were recorded at T0 (Di Monaco et al., 2010; Shelton et al., 2001).

Trunk Control Test. The Trunk Control Test (TCT) is an ordinal measurement scale assessing trunk control in patients with stroke. The TCT consists of 4 simple trunk movements with incremental difficulty (Di Monaco et al., 2010; Franchignoni et al., 1997). The total score can vary from a minimum of 0 points to a maximum of 100.

Motricity index. The motricity index gives an overall indication of a neurological patient's limb impairment. It is an ordinal measurement scale aimed at measuring muscle strength and motor abilities in the patient's limbs. The Motricity Index (MI) is divided into 4 parts, each of which analyzes in detail the specific motor abilities of a limb (Collin and Wade, 1990; Demeurisse et al., 1980; Sunderland et al., 1989; W Bohannon, 1999). The total score can vary from a minimum of 0 (complete paralysis) to a maximum of 100 (normal strength) for each limb.

LCF. The Levels of Cognitive Functioning Scale is a behavioral rating scale, developed for the assessment of cognitive functioning within the earliest phases after brain injury. The LCFS was intended to categorize the patient's current level of consciousness and cognitive and behavioral functioning into one of eight cognitive levels (Flannery, 1998; Galeoto et al., 2020; Gouvier et al., 1987).

2.4. EEG data

EEG data were used to extract quantitative and functional connectivity measures known to be associated with motor and cognitive functioning. Four EEG sessions per participant were recorded. Notably, stroke may induce focal brain lesions that affect oscillatory brain activity and produce remote effects via neural network activity. EEG measurements in patients with stroke assess residual brain activity and modifications in neural networks post-damage (Kawano et al., 2017). In the present study, quantitative and connectivity analyses reflect this residual activity. However, as the risk of measurement error is high in the region of interest post-stroke, an expert EEG technician checked the quality of each EEG registration before the analyses. Registrations with strong artifact were not considered for the analyses.

2.4.1. EEG data collection

Eye-open resting-state EEG data were collected for five minutes. Participants were comfortably seated in a silent room with dimmed light and were prompted to fix a central fixation cross in a computer screen. An expert technician monitored eye movements and whenever participants lost the central fixation provided feedbacks to recover it. This procedure allows us to study how much residual function remains when processing incoming information (Gorantla et al., 2020; Hussain et al., 2018; Kan et al., 2017; Wang et al., 2022). This last point is particularly relevant for the aim of our study, that is to investigate EEG correlates able to predict cognitive-motor outcome after stroke. Moreover, within this procedure, a more active and controllable condition among patients performing a fixation task is maintained with stable attentional levels. EEG data were recorded using the BrainVision recorder system. In particular, we employed 19 Ag/AgCl-cup electrodes positioned according to the 10/20 system and referenced to the linked ear lobes. The EEG signal was recorded from the following scalp electrodes: Fz, Cz, Pz, C4, C3, P4, P3, F4, F3, Oz, O1, and O2. The Common Mode Sense (CMS) and the Driven Right Leg (DRL) electrodes were used as reference and ground electrodes. Impedance for EEG and electrooculogram (EOG) electrodes were kept below 10 kΩ. The vertical and horizontal electrooculogram (EOG) was recorded from electrodes above and below the right eye and on the outer canthi of both eyes. EEG and EOG data were continuously recorded at a sampling rate of 1024 Hz. Offline, all electrodes were re-referenced to the average reference, re-sampled to 500 Hz, and filtered with a 0.5–30 Hz band-pass filter.

2.4.2. EEG data pre-processing

EEG data were analyzed using EEGLAB v14.0.085 and custom routines written in MatLab R2015b (The Mathworks, Natick, MA, USA). Data were segmented in epochs of 1000 ms. Epochs contaminated with artifacts were excluded using the pop_autorej function in EEGLAB v14.0.0, which first excludes epochs with voltage fluctuations higher than 1000 μV and then excludes epochs with data values outside five standard deviations using an iterative algorithm. After epochs rejection procedure, a mean of 14.96 % (Standard error of the mean, SE = 1.83 %) of epochs were excluded. An independent components analysis (ICA) was performed for each participant's EEG (Bell and Sejnowski, 1995; Delorme and Makeig, 2004) to correct the remaining artifacts. To this end, independent components (ICs) representing stereotyped artifact activity, such as horizontal (saccades) and vertical (blinks) eye movements, and muscle artifacts were identified through a multistep correlational template-matching process implemented in CORRMAP v1.0289. Topographies of ICs labeled as artifacts by the CORRMAP procedure were visually inspected and then calculated out of the data using inverse matrix multiplication.

2.4.3. Quantitative EEG (qEEG) measures

The Power Spectral Density was extracted in specific Regions of Interest (ROI) within the fronto-parietal network (left and right frontal and parietal ROIs). Power spectral data from the averaged epochs and separately for each EEG session and participant were calculated using the "pop_spectopo" function on EEGLAB. The power spectral data expressed in μv^2/Hz were divided into specific frequencies: delta (1–3 Hz), theta (4–7 Hz), alpha/mu (8–13 Hz), beta (14–30 Hz)(Di Gregorio et al., 2022b; Sitt et al., 2014; Trajkovic et al., 2023). The power was calculated as the mean value in each frequency band. Moreover, we computed two measures of power ratio: delta/alpha (DAR) and the power ratio index (PRI, generated by dividing the low delta and theta frequency powers by the high alpha and beta frequency powers) known to predict functional outcome and cognitive deficits in the population with stroke (Bentes et al., 2018; Finnigan et al., 2016; Schleiger et al., 2014; Shen et al., 2024).

2.4.4. EEG measures of functional connectivity

EEG-based functional connectivity estimates the association between electrode signals. There are several methods for quantifying functional connectivity based on EEG data (Di Gregorio and Battaglia, 2023; Imperatori et al., 2019). In particular, the Phase Lag Index (PLI) is a functional connectivity index based on associations between phases (Hardmeier et al., 2014; Stam et al., 2007). For the PLI computation, the artifact-corrected EEG data were filtered using a spatial filter (i.e., the

Laplacian filter). The Laplacian filter subtracts from each electrode the mean activity of four neighboring electrodes to correct for local volume conduction effects. Importantly, the EEG data were referenced to the common average (CAR), subtracting the mean activity across all scalp electrodes from each electrode to control for general scalp effects. In our study, while CAR was applied to account for global electrode activity, the Laplacian filter specifically addressed localized volume conduction effects. Together, both CAR and the Laplacian filter helped reduce the risk of false-positive connectivity due to the effects of general electrode activity and common neural sources on adjacent electrodes. Connectivity measures were then extracted in specific ROIs: right fronto-parietal, left fronto-parietal, parietal interhemispheric ROIs.

For the PLI estimation, the time-frequency data were first calculated via convolution with complex Morlet wavelets, separately for each EEG session and participant. Convolution was performed via frequency-domain multiplication (Cohen, 2015, 2014). In order to prevent the artifact of the "edges", the signal was re-epoched in epochs of 2 s. The PLI evaluates the consistency of the phase differences between two time-series (Stam et al., 2007; Trajkovic et al., 2021) (e.g. EEG signal over specific electrodes). The PLI was calculated on the individual EEG dominant frequency in the alpha/mu frequency range (Di Gregorio et al., 2023, 2022a; Trajkovic et al., 2021). PLI values can range from 0 to 1, where a higher value indicates a consistent phase difference between two signals.

2.5. Statistical analyses

Statistical analyses were divided into two steps: 1. EEG features selection procedure and 2. Identification of functional outcome and LoH predictors with Machine learning models.

2.5.1. EEG features selection

This step was based on statistical comparisons between the PS and UC. In particular, to select those EEG features able to reflect post-stroke impairments, we compared EEG measures between groups (PS vs. UC). Between-subjects planned comparisons were analyzed using mixed-model ANCOVAs with repeated measurements (for qEEG and connectivity measures) and two-tailed independent samples *t*-tests with 1000 bootstrap samples. The repeated measures statistical procedure was used to control for the effects of the factor "EEG session" that might influence the dependent measure of interest (i.e., qEEG and connectivity) (Schneider et al., 2015). Specifically, the ANCOVA allowed us to test if the different EEG sessions at the time of the enrolment were comparable across subjects (see also study design). To perform ANCOVA analyses, we first verified the analysis of variance assumptions and tested for: 1. normally distributed data, 2. repeated measures (i.e., violations of sphericity, Greenhouse and Geisser, 1959), and 3. Homogeneity of variance (i.e., equal variance across groups) (Sawyer, 2009). 1. Data were considered normally distributed for the non-significant Shapiro-Wilk test (i.e., > 0.05). 2. Greenhouse-Geisser correction (Greenhouse and Geisser, 1959) was applied whenever necessary (i.e., significant Mauchly's Test) to compensate for violations of sphericity in the analysis of variance. 3. Equal variance was assumed for non-significant Levene's test (i.e., > 0.05). Finally, the covariate values were mean-centered to validate between-subject comparisons in the ANCOVA (Schneider et al., 2015). For the ANCOVAs, the within-subject variable ROI was calculated over electrodes for qEEG measures (P3, P4, F3, and F4) and over electrode pairs for PLI connectivity (P3-P4, F3-P3 and F4-P4). To test the effect of the assessment timing, the factor EEG session was included as a covariate in the analyses with 4 levels ($T0_1$ $T0_2$ $T0_3$ $T0_4$). This resulted in three-factors mixed model ANCOVAs for all EEG measures. For all measures, the significance level was set at $p < .05$, and Bonferroni corrected for multiple comparisons (Bonferroni corrected p values for PSD = 0.003 and Connectivity = 0.008) was applied. Effect sizes were reported as Cohen's d (d) for the *t*-test and partial eta squared (ηp^2) for the ANCOVAs. As an additional features selection procedure, the pre-selected EEG features were correlated using Pearson correlation with the FIM score at T1, corrected for the initial FIM score at T0 (i.e., difference score). The significant instances were used to feed a machine learning algorithm, as explained in the next section.

2.5.2. Identification of EEG predictors

To identify the best clinical and EEG predictors of the functional outcome, we used a machine learning algorithm (i.e., the Support Vector Machine, SVM) to maximize the informative value provided by the EEG biomarkers and clinical data in predicting the functional outcome in patients with stroke at discharge (see also Di Gregorio et al., 2022). To this aim, only PS were considered in the analyses. The most discriminative EEG features selected based on the statistical results of step 1 were aggregated in matrices where the rows (i.e., instances) represented the participant EEG sessions (4 EEG sessions per participant) and the columns represented the values of the features. Additional clinical features (i.e., scores in the LCF, MI, and TCT at T0) were entered to investigate the combined contribution of EEG and clinical data in the prediction of functional outcome at discharge. The accuracy of the combined clinical and EEG model (i.e., combined model) in the prediction of the FIM was compared with the accuracy of predictive models solely based on clinical scales or EEG measures (i.e., uncombined models). This allowed us to investigate the additive value of synergistic clinical and electrophysiological model for the prediction of the functional outcome and LoH compared to uncombined models.

2.5.3. Classification method

A Support Vector Machine (SVM) algorithm was fed with the variable matrix described above. The SVM was used to discriminate two classes of data through a linear kernel (Noble, 2006). The linear SVM is one of the most used supervised machine learning algorithms used for two-group classifications. SVM has been already used in previous research studies on the prediction of functional outcomes after stroke (Forkert et al., 2015), and it was recommended by the International Federation of Clinical Neurophysiology for EEG research (Babiloni et al., 2020). All instances were first randomized. Then, a 10-fold cross-validation was applied. Within this procedure, instances were split into 10 groups with the same number of instances. Each group was used once as a validation dataset, with the remaining data as the training data for 10 iterations with randomized shuffling of instances. This approach provides a robust and widely accepted evaluation method for small datasets by minimizing biases related to data splitting and ensuring that all instances are used for both training and testing across different folds. While this method does not replace validation on an independent dataset, it offers a reasonable alternative within the constraints of this study. The percentage of correctly classified instances was calculated averaging the accuracy of each iteration. For the SVM model, we used the functional outcome at discharge as a categorical grouping variable. To this aim, the FIM raw ordinal total scores were first converted to the corresponding Rasch scaled values, according to a recent validation of the FIM (Maritz et al., 2019). Then, the participants were divided into two groups (high vs low FIM scores) for the binary estimation of the SVM, based on the median split of the FIM score at T1 corrected for the initial FIM score at T0 (estimated cut-off value = +15.7 points at T1 FIM; average FIM gain in the high group = +31.8, and low group = +7.27). Additionally, we investigated whether the same combined clinical and EEG SVM model can predict the LoH. For this analysis, LoH was calculated as the difference in days between stroke onset (i.e., enrolment) and patients' discharge from inpatients rehabilitation settings. As for the SVM analysis on the functional outcome, the participants were divided into two groups (short vs long LoH) for the binary estimation of the SVM, based on the median split of the LoH (estimated cut-off value = 63 days; average LoH in the short group = +41.7, and long group = +137.4). Distributions of predictor variables (i.e., features) were tested for normality with the Shapiro-Wilk test and transformed, if necessary, before to entry into the SVM.

Classification performance metrics were calculated in terms of accuracy, specificity, and sensitivity. In particular, Accuracy measures the proportion of correct predictions made by the model out of all predictions made. For the calculation of Sensitivity and Specificity we considered the following measures:

True Positives (TP). These are the cases where the model correctly predicted a positive outcome (e.g., a patient is classified as having a higher level of functional independence or shorter LoH, when they truly belong to that group).

False Negatives (FN). These are the cases where the model incorrectly predicted a negative outcome (e.g., a patient is classified as having a lower level of functional independence or longer LoH, when they actually belong to the higher group).

False Positives (FP). These are the cases where the model incorrectly predicted a positive outcome (e.g., a patient is classified as having a higher level of functional independence or shorter LoH, when they actually belong to the lower group).

True Negatives (TN). These are the cases where the model correctly predicted a negative outcome (e.g., a patient is classified as having a lower level of functional independence or longer LoH, when they truly belong to that group).

Thus, Specificity measures the proportion of true negative cases (i.e., patients with lower EEG and clinical measures and lower functional outcome/longer LoH) correctly identified by the model out of all actual negative cases (i.e., all patients with a lower functional outcome/longer LoH; Specificity=TN/(TN+FP)). Sensitivity measures the proportion of true positive cases correctly identified by the model (i.e., patients with higher EEG and clinical measures and higher functional outcome/shorter LoH) out of all actual positive cases (i.e., all patients with a higher functional outcome/shorter LoH; Sensitivity=TP/(TP+FN)). Finally, we calculated positive likelihood ratio as LR+ = sensitivity/1-specificity and negative LR- = specificity/1-sensitivity. These metrics provide insights into the overall performance and effectiveness of the classification model in accurately predicting outcomes. Moreover, the F-test was employed here to evaluate the null hypothesis that there is no significant difference between the classifiers' performance in the single and combined models (Nasejje et al., 2022). Using an F-test to compare two classification models in machine learning helps assess if the variance in performance between the classifiers is statistically significant. Thus, we compared classifiers' performance metrics (i.e., accuracy, sensitivity and specificity) across the 10 interactions between the single and combined models, using repeated-measures F-test.

2.6. Sample size estimation and statistical software employed

The sample size was calculated with the software: "sample-size calculators for designing clinical research" (available online at: https://sample-size.net/sample-size-means/). Parameters used in the analyses were derived from a preliminary study on the endpoint PSD. The following parameters were used: α (two-tailed) = 0.05 (Threshold probability for rejecting the null hypothesis. Type I error rate); $\beta = 0.2$ (Probability of failing to reject the null hypothesis under the alternative hypothesis. Type II error rate); q1 = 0.5 (Estimated proportion of subjects that are in Group 1); $E = 0.18$ (effect size calculated on preliminary data); $S = 0.17$ (standard deviation of the outcome on preliminary data). The resulting sample size, using these parameters, was 30 subjects.

All statistical analyses were performed with the SPSS software (Version 13) and the classification learner in MATLAB. The feature extraction was performed using custom-made routines in MATLAB 2015b (The MathWorks, Inc., Natick, Massachusetts, United States) and EEGLAB (v. 14.0.1).

3. Results

3.1. Clinical scale results

30 participants were enrolled and four EEG sessions per participant were recorded for a total of 120 EEG recordings. 15 patients, enrolled in inpatient rehabilitation settings, suffered from right hemispheric stroke (PS), while 15 unimpaired participants were additionally included as a control group (UC group). No patients were enrolled as outpatients. 1 EEG session was excluded due to strong artifacts. 1 Participant dropped out. Thus, a total of 115 EEGs were analyzed. Demographic data and lesion profiles are reported in Table 1. However, lesion size analyses were not reported. In fact, lesion data were collected from MRI or TC (see inclusion criteria), thus we cannot provide a coherent measure of the lesion size for all patients

Among PS, 12 PS were treated in the acute phase with mechanical thrombectomy (5 patients) or intravenous thrombolysis (7 patients). For clinical reasons, three patients did not receive such stroke therapies. Clinical data from the motor and cognitive scales are reported in Table 2 for all PS. The mean number of days post-stroke at the time of study enrollment was 9.92 days, SE = 1.98 days. The PS mean (M) LoH was 89.13 days (Standard Error, SE = 11.75 days).

3.2. EEG features selection

3.2.1. qEEG results

PSD was analyzed for the between-subject factor Group and for the covariate EEG session in all considered ROIs (i.e., scalp electrodes). A visual assessment of the figures (Fig. 1A-B) shows a general higher power in the Delta and Theta bands in the PS group compared to the UC and lower suppression in the beta band. Statistical analyses confirmed these impressions.

The analysis of variance assumptions for the PSD analysis were met (Shapiro-Wilk test > 0.298; Levene's test = 0.279). The ANCOVA on the PSD showed a significant triple interaction Frequency*ROI*Group ($F(9,1008) = 5.862$, $p < .001$, $\eta p^2 = 0.050$), with larger Delta and Theta power over the electrode P4 in the PS group compared to the UC group (Table 2). Moreover, results showed larger Beta suppression in all the considered ROIs in the UC compared to the PS group (Table 3). Finally, we analyzed two measures of power ratio, but neither DAR nor PRI were discriminative between groups (*all* $Fs(1112) < 1.197$, *all* ps > 0.276, *all* $\eta p^2 < 0.011$). No effects of the covariate EEG session emerged ($F(1112) = 0.436$, $p = .510$, $\eta p^2 = 0.004$). Correlational results showed a significant correlation between the FIM score at T1 and the frontal right ($r = 0.255$, p=.050) and left ($r = 0.324$, p=.012) beta powers.

3.2.2. Connectivity results

The functional connectivity was analyzed for the between-subject factor Group and for the covariate EEG session in all considered ROIs (i.e., scalp electrode pairs). The functional connectivity matrix (Fig. 2) showed generally larger connectivity for the UC compared to the PS. Statistical analyses confirmed this impression. The analysis of variance

Table 1
Demographic and lesional data.

	Sex (M, F)	*Age (years)*	*Stroke type (Hem, Isch)*	*Lesion Location (Areas)*
PS group	8 M, 7 F	53.3 (4.51)	5 Hem, 10 Isch	rPPC, rFPC, rTha, rTS, ACC
UC group	7 M, 7 F	49.3 (3.23)	—	—

M = male, F = female. PS = Participants with Stroke, UC = Unimpaired Controls, Hem = hemorrhagic stroke, Isch = Ischemic stroke Means are reported and standard errors of the mean are in brackets. *r* = right, PPC = Posterior Parietal Cortex, Tha = Thalamic nuclei, FPC = Fronto-Parietal Cortex, TS = Temporal Sulcus, ACC = Anterior Cingulate Cortex.

Table 2
Clinical scales.

	MI	TCT	LCF	FIM	
				T0	T1
PS group	26.87 (3.94)	30.66 (3.41)	5.73 (0.11)	51.26 (1.93)	71.66 (2.34)

Clinical data include the motor (MI, TCT) and cognitive (LCF) scales at enrolment (T0) and for the FIM at discharge (T1). Means and standard errors of the mean (in brackets) are reported for the included scales. MI = Motricity Index, TCT = Trunk Control Test, LCF = Level of Cognitive Functioning, PS = Participants with Stroke.

assumptions for the connectivity analysis were met (Shapiro-Wilk test > 0.298 and Levene's test = 0.438) and the ANCOVA showed a significant interaction ROI*Group (F(2224) = 17.138, p = .001, $\eta p^2 = 0.133$). In particular, the UC group showed larger inter-hemispheric and right fronto-parietal connectivity compared to the PS group (Table 3). As for the qEEG results, also for the connectivity results, no effects of the covariate EEG session emerged (F(1112) = 0.168, p = .683, $\eta p^2 = 0.001$). Finally, the right fronto-parietal connectivity significantly correlated with the FIM score at T1 (r = 0.556, p<.001).

3.3. Machine learning results

Sixty instances were considered for this analysis (i.e., all EEG sessions from the PS). EEG Features for the SVM model were pre-selected based on the results of the first step of analysis. In particular, the initial number of considered features was 19. After the features selection procedure, the selected features for the SVM analysis were three: two qEEG features (i.e., Beta F3 and Beta F4) and one functional connectivity feature (i.e., Right fronto-parietal P4-F4 PLI). For the initial uncombined SVM models, we used clinical scales or EEG measures separately as predicting variables, with the FIM score at T1 as the target variable. Then, the EEG features, along with the clinical scales, were used to feed the combined SVM model and to investigate the accuracy of the combined EEG and clinical data in the prediction of the functional outcome. Results from the combined clinical and EEG model (Fig. 3A) showed a statistically significant increase of accuracy (+7.81 %) sensitivity (+5.33 %) and specificity (+9.18 %) compared to the uncombined models (Table 4), *all Fs*(1,9) > 53.45, *all* ps < 0.001, *all* $\eta p^2 > 0.856$. Furthermore, we investigated whether the same combined clinical and EEG model can predict the length of patients' hospitalization (LoH; Fig. 3B). Results showed high model mean accuracy in the LoH prediction (Table 4) with strong increasing of average accuracy (+18.32 %) sensitivity (+12.35 %) and specificity (+23.85 %) compared to the uncombined models, *all Fs*(1,9) > 17.62, *all* ps < 0.002, *all* $\eta p^2 > 0.662$. In general, these results showed that higher initial levels of LCF, MI, and

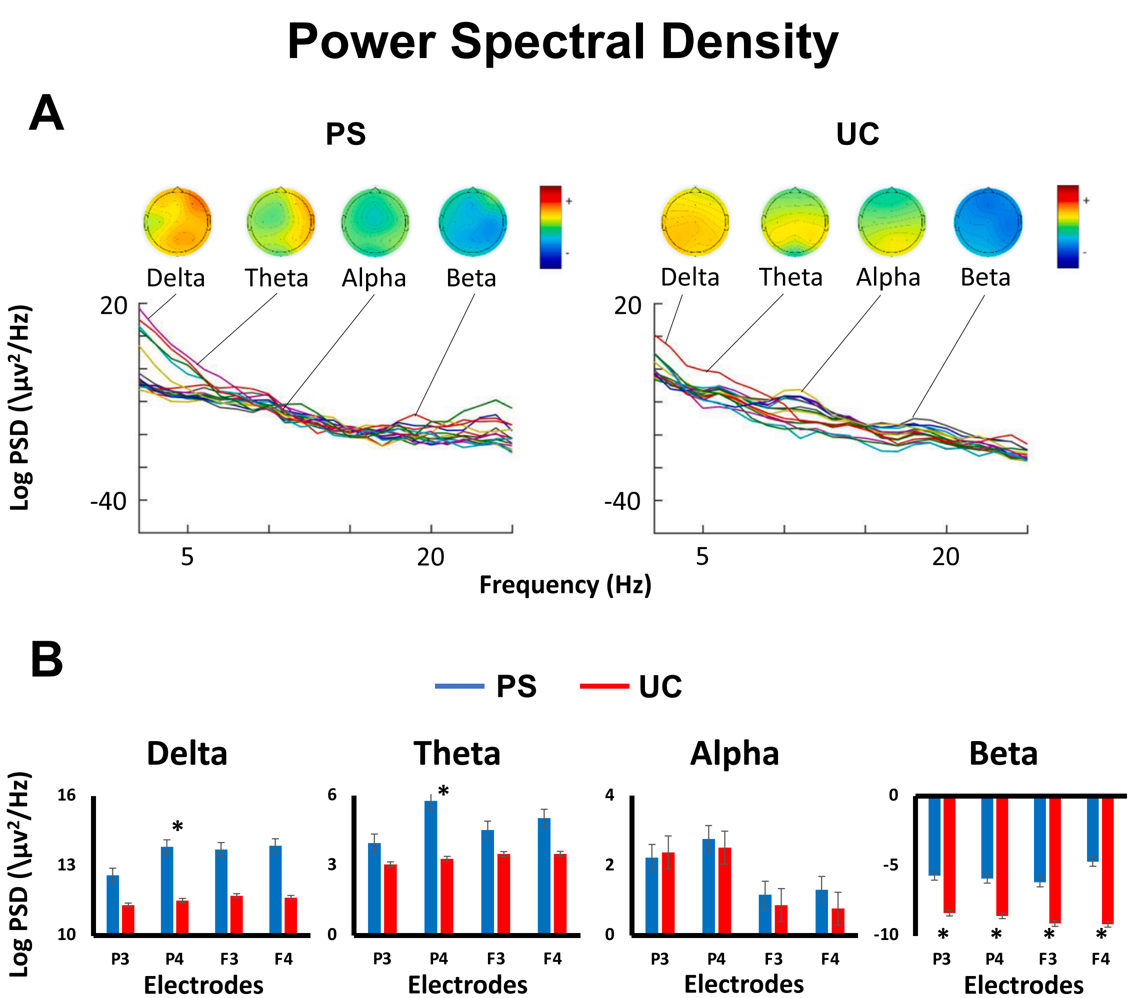

Fig. 1. A. Power spectral Density (PSD), averaged across sessions and participants, over all electrodes. Topographies show power scalp distribution of Delta, Theta, Alpha, and Beta bands for the Participants with stroke (PS) and the Unimpaired Controls (UC). B. Mean PSD in all considered frequency bands across ROIs (i.e., scalp electrodes) for all groups. Two-tailed t-test statistical significance Bonferroni corrected is reported (*p < .003). Error bars represent the standard error of the mean for the qEEG measures. Power was expressed in decibel units (dB = $\log_{10}$ (μv^2/Hz). µv = microvolt, Hz = Hertz.

Table 3
Planned comparisons.

	Variable	Statistics			Planned Comparisons
		t-stat	p-value	d	
PSD	*Delta P4*	3.826	.002	0.357	PS>UC
	Theta P4	4.098	.001	0.382	PS>UC
	Beta P3	4.272	.001	0.399	PS>UC
	Beta P4	3.899	.001	0.383	PS>UC
	Beta F3	4.374	.001	0.408	PS>UC
	Beta F4	4.671	.001	0.436	PS>UC
Connectivity	*P3-P4*	6.688	.001	0.624	PS<UC
	F4-P4	3.604	.001	0.336	PS<UC

t-test statistics (t-stat) with degree of freedom = 113, p values and Cohen's d are reported for the significant planned comparisons. PS = Participants with Stroke, UC = Unimpaired Controls.

TCT, larger right fronto-parietal connectivity and beta activity in the frontal electrodes predicted higher scores in the FIM at T1. The same clinical and EEG measures predict shorter patients' LoH (Table 4).

4. Discussion

Functional recovery after stroke represents a key target for neurorehabilitation programs. However, the prediction of functional outcomes remains challenging for clinicians. Thus, in the present study, we proposed the EEG as a safe and accessible tool in complex neurorehabilitative environments to support clinical decision-making. Specifically, we investigated clinical and EEG predictors of the functional outcome in patients with right-hemisphere stroke (PS), LHSN and left hemiplegia. We demonstrated that the EEG can support functional outcome prediction, thus informing clinical and rehabilitative decision-making.

The most important result of this study showed that the combination of clinical and EEG measures is highly accurate for the outcome prediction of patients with stroke. Indeed, as already reported in the literature, the initial level of motor/cognitive impairments after stroke (i.e., T0 phase) can predict the functional outcome at discharge (i.e., T1 phase; Gialanella and Ferlucci, 2010; Shelton et al., 2001). Here, we confirmed and expanded this result showing the contribution of EEG biomarkers not only in the prediction of the functional outcome but also of the patients' LoH. Specifically, oscillatory brain activity in the beta band plays an important role in functional outcome and LoH predictions. The EEG results indeed showed a relative increase of frontal beta power (i.e., less suppressed power) in patients with stroke and unilateral motor impairments compared to unimpaired participants. The evidence of less suppressed oscillatory activity in the higher frequency bands (alpha and beta) after right-hemisphere stroke is in accordance with several previous studies which investigated motor and cognitive deficits after stroke (Bartur et al., 2019; Bentes et al., 2018; Carino-Escobar et al., 2021; Cuspineda et al., 2007; Finnigan and van Putten, 2013; Finnigan et al., 2007, 2004; Schleiger et al., 2014; Szelies et al., 2002). In particular, beta oscillatory activity has been associated with the functioning of the sensorimotor system (Athanasiou et al., 2018; Pfurtscheller et al., 1996; Roopun et al., 2006) and while beta suppression is considered a robust measure of the production of voluntary movements, abnormal beta activity was observed after stroke, lesions of the motor cortex and in neurodegenerative diseases of the motor neuron system (Pfurtscheller and Lopes da Silva, 1999; Proudfoot et al., 2017; Schulz et al., 2021; Shreve et al., 2019; Wu et al., 2016). In line with this literature, our results show an increase in Beta power (i.e., less suppressed beta activity) in the PS group compared to UC and the beta power at frontal electrodes is a predictor of the functional outcome. Thus, we could hypothesize that increased power in the beta band within the fronto-parietal areas may reflect motor impairments in stroke patients.

Predominant delta and theta band oscillations usually emerge and have higher amplitudes in the core lesion of patients with stroke (Cassidy et al., 2020; Murri et al., 1998; Rabiller et al., 2015). Accordingly, in the present study, we found higher delta and theta power in the ipsilesional parietal areas in PS compared to UC. The inverse relationships between lower (i.e., delta and theta) and faster (alpha and beta) oscillatory activities and between delta activity and clinical outcome in PS are common during the acute stroke period (Cassidy et al., 2020; Shreve et al., 2019; Wu et al., 2016). However, delta and beta may have differential roles in motor and cognitive functioning (Leon-Carrion et al., 2009; Schleiger et al., 2014; Schulz et al., 2021; Wagner et al., 2016). Although delta and theta power did not directly predict functional outcomes in PS, a unilateral predominant delta activity is a sign of poor cognitive functioning in the acute and subacute phases of stroke (Assenza et al., 2013; Burghaus et al., 2007; Cassidy et al., 2020; Chiarelli et al., 2020; Cillessen et al., 1994; Rabiller et al., 2015; Tecchio et al., 2007). Indeed, the severity of cognitive symptoms in PS was

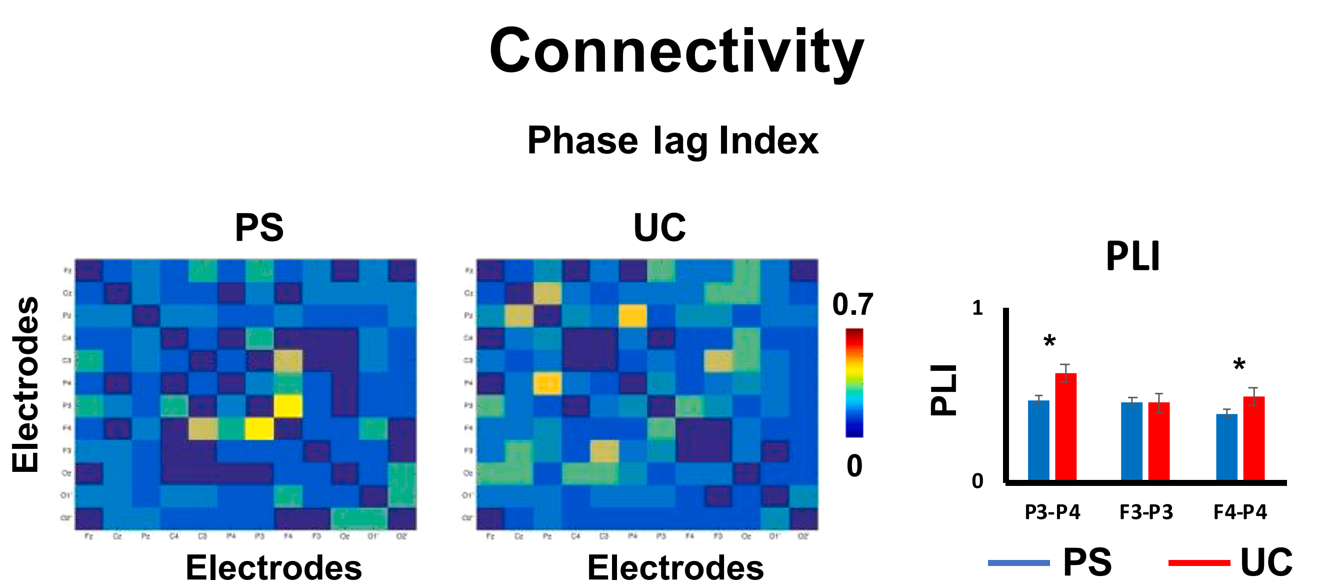

Fig. 2. Correlation matrices of the Phase Lag Index for the Participants with Stroke (PS) and the Unimpaired Controls (UC) over all electrodes and averaged across sessions and participants. Bar graphs reflect the mean PLI over ROIs (i.e., electrode pairs) for the two groups. Two-tailed *t*-test statistical significance Bonferroni corrected is reported (**p* < .008). Error bars represent the standard error of the mean, PLI = Phase Lag Index.

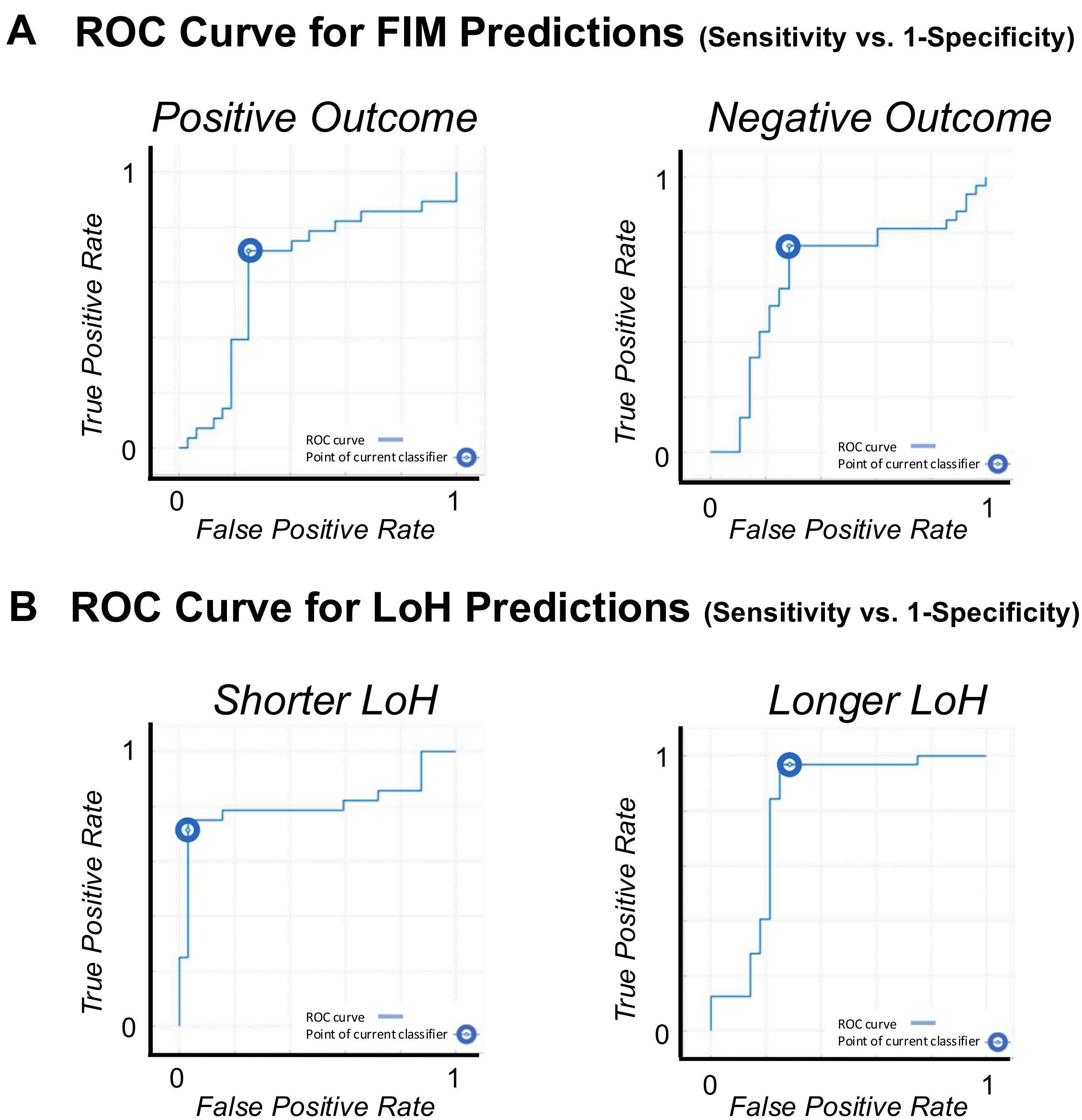

Fig. 3. ROC curve for FIM predictions and LoH predictions, where sensitivity (True Positive Rate) is plotted on the y-axis and 1-specificity (False Positive Rate) on the x-axis. True Positives (TP): Instances where the model correctly predicts a positive outcome/shorter LoH. False Negatives (FN): Instances where the model incorrectly predicts a negative outcome/longer LoH. False Positives (FP): Instances where the model incorrectly predicts a positive outcome/shorter LoH. True Negatives (TN): Instances where the model correctly predicts a negative outcome/longer LoH. Sensitivity is calculated as TP / (TP + FN), and specificity is calculated as TN / (TN + FP). The ROC curve plots sensitivity as a function of 1-specificity, illustrating the model's ability to discriminate between outcomes at different threshold levels. FIM = Functional Independence Measure.

Table 4
Machine learning results.

	Accuracy	Sensitivity	Specificity	Likelihood Ratio	
	(%)	(%)	(%)	Positive	Negative
Functional Outcome					
Uncombined Models	65.33 (0.89)	66.07 (0.72)	65.51 (1.41)	1.92	0.52
Combined Model	73.14 (0.16)	71.40 (0.01)	74.69 (0.31)	2.82	0.38
Length of Hospitalization					
Uncombined Models	66.85 (1.58)	65.56 (2.23)	68.45 (1.36)	2.08	0.51
Combined Model	85.17 (0.39)	77.92 (2.61)	92.30 (2.06)	10.12	0.24

Machine Learning results of the Support Vector Machine (SVM) analyses in percentage for the combined clinical/EEG and uncombined models are reported in terms of mean accuracy, sensitivity, specificity and standard errors of the means (in brackets). Positive likelihood ratio (LR) = sensitivity/1-specificifty and negative LR = specificity/1-sensitivity are also reported.

associated with a larger inter-hemispheric imbalance with a relative increase of the ipsilesional delta power (de Vos et al., 2008; van Putten and Tavy, 2004) while lower delta/theta activity in the lesioned hemisphere predicts a better outcome (Cillessen et al., 1994; Rabiller et al., 2015). Instead, in the neurologically unimpaired population, delta-band synchronizations were found during demanding cognitive tasks and during dual cognitive-motor tasks (Bohle et al., 2019; Ozdemir et al., 2016). More specifically, delta frequency increases when dual tasks include a challenging motor condition (Ozdemir et al., 2016) and during complex working memory and cognitive tasks (Harmony, 2013). This effect on delta neural synchronization after stroke and during complex motor-cognitive tasks in unimpaired participants can be interpreted as a general neurophysiological mechanism that responds to higher task demands. In general, delta power increases when the activity in a specific functional neural network has to be enhanced during information processing (Babiloni et al., 2017). In the case of PS, abnormal larger delta power can reflect the need for higher cognitive load due to motor-cognitive deficits (Boyd et al., 2017). Finally, it is important to notice that, the performance in dual motor-cognitive tasks is particularly impaired in PS and associated with an increased risk of falls and poor clinical outcomes (Benedetti et al., 2012; Beyaert et al., 2015; Ou et al., 2021).

Another important result of the present study highlighted the role of functional connectivity within the fronto-parietal network in the prediction of the functional outcome at discharge and LoH. In particular, the right ipsilesional fronto-parietal functional connectivity shows a high between- group discriminative power and predictive value. More specifically, larger connectivity at T0 was found in the UC compared to the PS and the residual connectivity in PS predicted higher scores in the FIM at T1. Our results support the importance of long-range brain connectivity as a predictor of the functional outcome after stroke (Athanasiou et al., 2018; Babiloni et al., 2017; De Vico Fallani et al., 2017; Eldeeb et al., 2019; Hoshino et al., 2021; Min et al., 2020; Philips et al., 2017; Vecchio et al., 2019). Indeed, previous EEG and fMRI studies already reported that stroke lesions lead to altered inter-hemispheric (De Vico Fallani et al., 2017, 2013; Di Gregorio et al., 2023; Hallett et al., 2020) and fronto-parietal connectivity (Di Gregorio et al., 2023; Inman et al., 2012; Naro et al., 2022; Oostra et al., 2016). Accordingly, our data showed impaired inter-hemispheric connectivity in PS and pointed to the role of residual connectivity in the fronto-parietal network for functional recovery after stroke. These findings suggest a large-scale topographical and functional reorganization of the brain activity after stroke with unbalanced hemispheric interactions. These changes in functional connectivity among brain areas which are crucial to motor programming and execution (Naro et al., 2022) directly predict functional outcomes and, after right unilateral stroke, ipsilesional connectivity dysfunctions can impair contralateral voluntary movements. However, it is important to notice that the spatial resolution of EEG methods is low, thus the identification of specific brain network dysfunctions should be interpreted with caution.

The results of the present study have important clinical implications. First of all, we used standard clinical EEG for the prediction of functional outcomes at discharge and demonstrated how the analyses of the EEG signals (i.e., the oscillatory activity and the functional connectivity) can be integrated with clinical data to support rehabilitative decision-making processes. Specifically, synergistic models based on combined clinical and EEG data, collected at an early stage after stroke onset, can increase the accuracy (+7.81 %) of the outcome predictive model solely based on uncombined predictors. Moreover, the same mixed clinical and EEG data can predict the LoH with high accuracy (85.17 %) and an additive increase of accuracy up to +18.83 % compared to the uncombined models. The LoH has important emotional and clinical implications (Ostir et al., 2008b, 2008a) for the patients and their caregivers, and longer LoH is linked to increased risk of burden and clinical complications (Hernandez et al., 2021). Machine learning models based on standard motor/cognitive and psychophysiological data can help to optimize predictions about rehabilitative potentials and may facilitate shorting LoH and early supported discharge (Anderson et al., 2002; Baniasadi et al., 2020; Teasell et al., 2003; Teng et al., 2003).

4.1. Study limitations

The results of the present study should be considered in light of some limitations. Considering the clinical nature of the study, we could not control for the time between admission/enrolment and discharge, thus the indications we provide regarding the timing of the functional outcome are rather variable. Additional plasticity changes can indeed act also after hospital discharge, thus modifying the functional outcome. Moreover, the study collected data only from patients with right-hemisphere stroke and controls. On the one hand, this allowed us to study a homogeneous subgroup of patients with similar clinical characteristics and specific stroke over the middle cerebral artery. However, the stroke and unimpaired control groups differ in terms of clinical characteristics and variance of EEG and motor/cognitive measures. To correct problems linked to variance differences (Schneider et al., 2015), we used statistical methods to control for generic between-groups differences in the context of the ANCOVA. However, replications of the analysis using a larger sample size (with different clinical populations) collected within prospective multicentric studies and using multiple follow-up time points in the same population (e.g., 3 months, 6 months, and 1-year follow-up) are desirable to support the stability and generalizability of the present results and of our machine learning model. In this sense, the EEG is easy to implement also in complex medical environments, thus our model can be applied and replicated in different clinical populations, and medical and rehabilitative contexts. Finally, it is important to notice that the methodological choice to use multiple observations per participant (four EEG recordings per individual) for the ROC analysis resulted in a total of 60 instances derived from 15 participants. While this approach enhances the statistical resolution and granularity of the ROC curves, as seen in the segmentation of sensitivity steps in Fig. 3A, it may also reduce sample variance due to intra-subjects reduced variance.

5. Conclusions

The functional outcome after stroke depends on the complex relationship between motor and cognitive functioning. In the present study, we show that clinical data, EEG-based oscillatory activities, and functional connectivity reflect and predict the motor-cognitive functional outcome of patients with stroke and it is highly predictive of their length of stay in rehabilitative settings. Many recent studies investigated neurophysiological correlates of specific cognitive and motor functions. However, in clinical settings is also crucial to collect information about the global and functional rehabilitative potentials of patients with stroke. The present study provides neurophysiological and clinical indicators of the possible rehabilitative trajectories of patients with stroke using standard motor/cognitive scales and clinical EEG.

CRediT authorship contribution statement

Francesco Di Gregorio: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Giada Lullini:** Writing – review & editing, Validation, Supervision, Conceptualization. **Silvia Orlandi:** Writing – review & editing, Methodology, Formal analysis. **Valeria Petrone:** Writing – review & editing, Investigation, Data curation. **Enrico Ferrucci:** Writing – review & editing, Data curation. **Emanuela Casanova:** Writing – review & editing, Data curation. **Vincenzo Romei:** Writing – review & editing, Validation, Supervision. **Fabio La Porta:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding

V.R. and F.D.G are supported by the Italian MUR – Ministry of University (P2022XAKXL). V.R. is supported by the Italian MUR – Ministry of University (2022H4ZRSN), by the Ministerio de Ciencia, Innovaciòn y Universidades, Spain (PID2019-111335GA-100) and Bial Foundation, Portugal (033/22). The publication of this article was supported by the 'Ricerca Corrente' funding from the Italian Ministry of Health.

Data availability

Data will be made available on request.

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