

Neurophysiological prognostic factors of motor function and spasticity after stroke

S. Cherkasov

State institution “Institute of Gerontology named after D.F. Chebotarev of National Academy of Medical Sciences of Ukraine”, Kyiv, Ukraine

Abstract

Purpose: Understanding the neural mechanisms of recovery of motor control and development of spasticity after stroke is paramount importance for neurorehabilitation.

Methods: For this purpose, we have analyzed several TMS and EEG variables and their association with motor recovery and development of spasticity. Forty-two subjects with stroke have taken part in the investigation. The neurophysiological examination included assessments by transcranial magnetic stimulation (TMS), intra- and inter-hemispheric EEG coherence in different frequency bands (e.g. Theta (4.0–7.99 Hz)) as determined by quantitative electroencephalography (qEEG). Motor function has been measured by Fugl-Meyer (FM), spasticity has been measured by modified Ashworth scale. Multiple univariate and multivariate linear regression analyses have been performed to identify the predictors for motor function and spasticity.

Results: Univariate analyses have shown a significant interaction of amplitude and motor threshold (MT) of injured and MT, central motor conduction time of uninjured hemisphere with motor function according to Fugle-Meyer (FM). Also significant interaction has been shown between MT of injured hemisphere and spasticity.

Multivariate analyses have shown a significant interaction of MT and beta coherence in injured, uninjured hemisphere and interhemispheric in prediction of motor function by FM.

Also significant interaction of MT of injured hemisphere, delta and theta coherence between C3-C4 and spasticity has been shown.

These interaction suggests that higher beta activity in the lesioned hemisphere strengthens the association between MT and FM scores. Higher beta activity in the uninjured hemisphere strengthens the association between MT and FM scores. Higher interhemispheric beta activity between C3-C4 strengthens the association between MT and FM scores. Higher delta and theta interhemispheric activity between C3-C4 strengthens the association between MT and Ashworth scores.

Conclusions: Our results suggest that MT of both hemispheres is the strongest predictors of motor recovery after stroke. Moreover, cortical activity in the injured and uninjured hemisphere measured by qEEG provides additional information, specifying the association between MT and FM scores. MT of injured hemisphere in the association with low-frequency cortical activity are the strongest predictors of spasticity after stroke.

Thus, the combination of EEG and TMS in predicting the recovery of motor control after stroke provides additional opportunities in the study of nonlinear relationships of influencing the interhemispheric networks, uninjured hemisphere and the release of subcortical activity

Key words: stroke; neural plasticity; transcranial magnetic stimulation (TMS); quantitative electroencephalography (qEEG); spasticity; motor recovery

Introduction. Stroke is the second leading cause of death and the leading cause of long-term disability around the world. After the acute stage up to 80% of patients have a polymorphic picture of motor disorders [1, 2].

The degree of motor recovery determines the quality of patients' life, it reduces their ability to perform daily activities and limits their independence. Despite the success of acute stroke therapy, patients need an intensive rehabilitation program that will partially determine the extent of their recovery. These rehabilitation programs aim to stimulate neuroplasticity to improve motor function and functional recovery. However, what determines the recovery of motor control is still unknown. Indeed, the search for neurophysiological markers that would help to predict and enhance post-stroke recovery stays a problem. Identification of these biomarkers is critical in the treatment of stroke patients. In the field of stroke research, much attention is paid for the study of cortical reorganizations of motor representations and their role in the whole neuroplasticity process. However, the studies of biomarkers of stroke recovery are still limited, especially with the use of neurophysiological tools [3, 4, 5]

Recovery of motor functions is caused by activation of primary motor representations around an infarct region whereas development of maladaptive plasticity is interconnected with complex process of reorganization, both the injured, and intact hemispheres [6, 7]. It has been shown that the regression of paresis correlated with the recovery of corticospinal innervation due to TMS data. At the same time, the development of spasticity is not directly related to the degree of impairment of corticospinal innervation. These disorders are associated with a complex maladaptive reorganization with the involvement of secondary, ipsilateral motor representatives, hyperactivation of the motor representatives of the contralateral hemisphere and the release of subcortical activity [7-10].

A combination of TMS and electroencephalography (EEG) methods are used to study the reorganization of the functions of remote from the injured regions of the brain [8, 10, 11]. The following changes in the bioelectrical activity of the brain have been demonstrated: decrease in alpha rhythm activity and slowdown of the EEG in the perinfarction region, which is associated with a negative prognosis of recovery and release of subcortical activity [12–15]. The increase in delta rhythm power in the intact hemisphere is associated with interhemispheric dissociation [16–19]. Restoration of alpha activity in the central regions is associated with physiological reorganization. Preservation of beta activity in the affected hemisphere indicates pathological reorganization and lack of recovery. The shift of coherence with the contralateral hemisphere and the preservation of power in the beta-frequency range indicates a maladaptive reorganization [10, 20–22].

According to the high prevalence, severity of stroke and insufficient study of the mechanisms of brain reorganization, we consider it a topical and promising issue to study neurophysiological markers of motor control recovery using complementarity of transcranial magnetic stimulation and quantitative electroencephalography, among patients that suffer from cortical ischemic stroke.

Material and methods of research. The study has been conducted at the department of "Neurorehabilitation" of the "Institute of Gerontology named after D.F. Chebotarev of National Academy of Medical Sciences of Ukraine». All patients have undergone clinical neurological examination, laboratory tests, ultrasound (ultrasound duplex scanning) of extra- and intracranial vessels of the head and neck, as well as EEG.

The study has involved 24 men and 18 women with hemispheric ischemic stroke, the average age has been 63.55 ± 9.82 years old. The control group has included the results of examination of 21 patients without neurological deficiency with a diagnosis of chronic

ischemia of I-II stages. All patients have received written informed consent to participate in the study [23].

The criteria for patients for being included in the study were: confirmed diagnosis of stage I-II of chronic ischemia, ischemic stroke of hemispherical localization in the recovery period of the disease.

The Criteria of exclusion patients from the study: the presence of implanted magnetizing devices (plates, screws, stents, shunts, etc.), the presence of a heart rate driver and any other devices that control body functions, severe somatic pathology, epilepsy or signs of convulsive readiness on the electroencephalogram.

The study of the bioelectrical activity of the brain has been performed on a 16-channel electroencephalograph "Nihon Kohden neurofax 1100" with standardized parameters (Sensitivity - 7 μ /mm, Time constant - 0.03 s, High Cut Filter - 15 Hz). The electrodes have been installed according to the international scheme "10-20". The recording time is 10 minutes. The spectral power of the EEG has been calculated by the method of rapid Fourier transformations for epochs lasting 15 s. The parameters of the frequency spectrum amplitude in delta (0.50–3.99 Hz), theta (4.0–7.99 Hz), low alpha (8.0–10.49 Hz), and high alpha were used for analysis. (10.5–12.99 Hz), low beta (13.0–23.99 Hz), high beta (24–35 Hz) EEG ranges.

We have determined interhemispheric (F3-F4, C3-C4, P3-P4), and intrahemispheric anteroposterior coherence of the inner hemisphere (fronto-central: F3-C3 or F4-C4, central parietal: C3-P3 or C4-P4 and fronto-occipital: F3 -O3 or F4-O4), separately in the affected and intact hemispheres. We have used the MATLAB mathworks package for the coherence function. "Mscohere" uses the averaged modified Welch periodogram to calculate the estimation of the coherence of a quantity squared, which is a function of the power spectral density and the cross-spectral density of two channels. Coherence values from 0 to 1 have been calculated for each frequency point and each pair of channels. Then we have averaged these values across specific bands, including delta, theta, low alpha, high alpha, and low beta, and high beta. The pairs of channels have selected based on the EEG 10-20 system.

First we have performed univariate linear regression analysis in which the result variable is a Fugle-Meyer, or Ashworth score and the independent variable is an EEG variable (eg, C3-C4 Theta coherence), a TMS variable (eg, amplitude, central motor conduction time), or demographic characteristics. Lesioned and non-lesioned hemispheres have been also tested separately. Also we are adding independent variables age, time after stroke, sex and the side of the lesion for determining effects on confounders.

After applying the univariate regression analysis, we have directly selected the data into the multivariate model, the data have been included if p is less than 0.20. The multivariate regression model uses EEG and TMS data together. For each model, the interaction term has been studied for the TMS and EEG variables and the confider. The normality of the residuals has been checked using the Shapiro-Wilk W test. We have calculated the mean variance of the inflation rate (VIF) of the final model to test for collinearity.. For statistical analysis, we have used statistical software SPSS 21 of IBM company.

Results

We have included 42 patients whose characteristics are detailed in Table1 (mean age 63.55 SD:± 9.82;18 females).

Table 1. Demographic and baseline characteristics

Demographic and baseline characteristics	
	(Mean±SD)
Age (year)	63.55±9.82
Gender, (%)	
Male	57.14
Female	42.86
Hemispheric side, (%)	
Right	28.58
Left	71.42
Time since stroke	
Months	11.26±7.55

Univariate analysis

We have initially performed a univariate analysis to identify variables associated with motor function and spasticity. Motor function is indexed according to the Fugl-Meyer scale, and spasticity - according to the modified Asworth scale. The following variables are significantly correlated with Fugl-Meyer and Ashworth's estimates, as discussed below.

TMS Variables - univariate analysis.

There is a significant main effect of MT in the affected and unaffected hemispheres on Fugl-Meyer score ($p = 0.029$, $-coeff = -0.17$, $adjR2 = 0.12$), of the amplitude of injured and CMCT of uninjured hemisphere. Indicating that a higher motor threshold of injured and lower motor threshold of uninjured hemisphere, lower amplitude of injured and shorter CMCT of uninjured hemisphere are associated with degree of impairment of motor function. No major

effect is found for latency and CMCT of injured and for amplitude and latency of uninjured hemispheres. The results are summarized in table 2.

Table 2. Results for univariate linear regression analyses in which the outcome variable was Fugl-Meyer or Ashworth and independent variable was parameters of TMS measure

Lesioned hemisphere					Unlesioned hemisphere			
Fugl Meyer	Amplitude; P	Latency; P	MT; P	CMCT; P	Amplitude; P	Latency; P	MT; P	CMCT; P
		0.021	0.446	0.046	0.095	0.464	0.376	0.050
Ashworth	0.412	0.878	0.013	0.274	0.586	0.193	0.247	0.234

Bold numbers indicate a p value smaller than 0.05

Interhemispheric coherence and intrahemispheric coherence are not associated with FM in univariate analysis. The results are summarized in table 3.

Table 3. Results for univariate linear regression analyses in which the outcome variable was Fugl-Meyer and independent variable was EEG coherence

Power band	Interhemispheric			Lesioned hemisphere			Unlesioned hemisphere		
	Electrode F3-F4	Electrode C3-C4	Electrode P3-P4	Fronto-central	Centro-parietal	Fronto-occipital	Fronto-central	Centro-parietal	Fronto-occipital
Delta	0.40	0.44	0.93	0.52	0.65	0.39	0.78	0.82	0.46
Theta	0.44	0.46	0.89	0.20	0.67	0.90	0.40	0.77	0.81
Low Alpha	0.94	0.71	0.87	0.89	0.86	0.60	0.79	0.99	0.98
High Alpha	0.96	1.00	0.54	0.89	0.71	0.48	0.37	0.94	0.89
Low Beta	0.21	0.22	0.55	0.18	0.61	0.33	0.11	0.26	0.72
High Beta	0.52	0.14	0.50	0.80	0.60	0.48	0.62	0.46	0.75

Bold numbers indicate a p value smaller than 0.20

During univariate analysis we have identified the association between degree of spasticity and increasing of interhemispheric coherence only in Theta rhythm between C3-C4 ($p = 0.029$, $-coeff = -0.17$, $adjR2 = 0.12$). The results are summarized in table 4.

Table 4. Results for univariate linear regression analyses in which the outcome variable was modified Ashworth scale and independent variable was EEG coherence

Power band	Interhemispheric			Lesioned hemisphere			Unlesioned hemisphere		
	Electrode F3-F4	Electrode C3-C4	Electrode P3-P4	Fronto-central	Centro-parietal	Fronto-occipital	Fronto-central	Centro-parietal	Fronto-occipital
Delta	0.713	0.077	0.574	0.550	0.984	0.921	0.351	0.187	0.673
Theta	0.303	0.039	0.208	0.784	0.322	0.437	0.509	0.362	0.570
Low Alpha	0.325	0.706	0.826	0.731	0.494	0.819	0.986	0.800	0.490
High Alpha	0.498	0.920	0.462	0.862	0.807	0.964	0.365	0.695	0.911
Low Beta	0.778	0.936	0.766	0.739	0.824	0.952	0.477	0.904	0.736
High Beta	0.953	0.729	0.902	0.859	0.956	0.816	0.667	0.708	0.974

Bold numbers indicate a p value smaller than 0.20

Demographic variables

We have also analyzed the main effect of age, time after stroke, sex and the side of the lesion, but the main effect for none of these variables has been observed.

Multivariate analysis

Based on the results of univariate analysis, we have considered MT as our main predictor and tested each EEG variable together with MT in the same model. EEG variables have been included in the model if their p value in the univariate analysis is less than 0.20 (Table 2). There are main significant effects of MT on the intrahemispheric coherence of the lesion, non-lesion hemisphere and interhemispheric coherence for three different models for the dependent variable FM (Table 3). (1) Frontocentral low-beta coherence in the lesion hemisphere ($p = 0.003$, coefficient = -25.09) and MT in the damaged hemisphere ($p = 0.019$, -coeff = -0.16); (2) Centroparietal low-beta coherence in the non-lesioned hemisphere ($p = 0.015$, -coeff = -25.32) and MT in the non-lesioned hemisphere ($p = 0.010$, -coeff = -0.18); (3) Interhemispheric high-beta coherence between C3-C4 ($p = 0.002$, -coeff = -24.11) and MT in the lesioned hemisphere ($p = 0.005$, -coeff = -0.20). The results are summarized in table 5.

Also there are main significant effects of MT on the interhemispheric coherence for the different models for the dependent variable of Ashworth (Table 3). (1) C3-C4 in Delta rhythm ($p = 0.05$, coefficient = -25.09) and MT in the lesioned hemisphere ($p = 0.019$, -coeff = -0.16); (2) C3-C4 in Theta rhythm and MT in the lesioned hemisphere ($p = 0.015$, -coeff = -25.32). The results are summarized in table 6.

Table 5. Results from three significant main models including the interaction term between independent variables

Variables	Model 1			Model 2			Model 3		
	LMT	B1F3C3	Interaction term	UMT	B1F4C4	Interaction term	LMT	B2C3C4	Interaction term
B coefficient	0.223	0.835	0.438	0.727	0.748	0.316	0.223	-0.638	0.239
P value	0.046	0.18	0.05	0.05	0.11	0.012	0.046	0.14	0.04
Adj R2			0.136	0.148		0.186			

Table 6. Results from two significant main models including the interaction term between independent variables

Variables	Model 1			Model 2		
	LMT	Delta C3-C4	Ineraction term	LMT	Theta C3-C4	Ineraction term
B coefficient	0.721	0.606	0.701	0.721	0.59	0.675
P value	0.044	0.077	0.05	0.05	0.039	0.02
Adj R2			0.479			0.442

Discussion

In the course of the study, our results confirm the opinion that the recovery results of motor control have a heterogeneous nature, depending from a lot of factors, for example: the damage of the primary motor representatives, integrity of corticospinal tract, which is accompanied by the reorganization of the affected and intact hemispheres and their dominance role (Stinear et al. 2010; Schulz et al. 2015; Boyd et al. 2017). An increase of the activity of the ipsilateral hemisphere, with an increase in M1 activation, is accompanied by the recovery of physiological control, the involvement of secondary motor representations and the contralateral hemisphere describe the development of maladaptive and pathological plasticity (Sheng et al. 2017; Boyd et al. 2017; Cassidy et al. 2020).

Our main results of multivariate analysis are:

1. Parameters of tms of ipsi- and contralateral hemispheres are associated with motor function;
2. The parameters of the TMS motor threshold of lesioned hemisphere have a certain relationship with spasticity;
3. The combination of TMS and EEG is a significant predictor motor function and the spasticity. At the same time, the separate use of EEG has not interaction with spasticity or motor function.

In a single sample analysis, we have found that the growth of the motor threshold is a good predictor of reduced recovery of motor function, also have a high level of reliability associations between the amplitude of the affected hemisphere and the central motor conduction time of the unaffected hemisphere. The decrease of motor threshold of MEP of injured hemisphere is a strongest predictor of spasticity.

McDonnell et al. (2017) has demonstrated that neurophysiological effects of stroke are primarily localised to the affected hemisphere, and there is no clear evidence for hyper-excitability of the unaffected hemisphere or imbalanced interhemispheric inhibition. This indicates that facilitating affected M1 excitability directly may be more beneficial than suppressing unaffected M1 excitability for promoting post-stroke recovery.

At the same time, taking into account only parameters of TMS predicting the overall level of recovery and the development of the syndrome of spasticity may be insufficient, since the recovery process is associated with functional reorganization of the brain.

Complementary use of several methods has been widely adopted. Simis et al. (2016) has shown that multivariate model of TMS and EEG could predict motor function in stroke better than model analyzing these data separately. They confirmed the notion that enhanced activity of the unlesioned hemisphere, concomitant with decreased activity in the lesioned hemisphere, is associated with poor motor function (Simis et al. 2016).

The using of beta band in the study of the general level of motor recovery in patients after stroke has a fairly broad scientific base (Pfurtscheller et al. 1996; Gerloff et al. 2006; Simis et al. 2016). Using separately the EEG method, no reliable data have been shown regarding prognostic markers of recovery or the development of spastic syndrome. In our study we have used the model previously described by Simis et al.(2016). We have shown that EEG variables (beta coherence in lesioned, unlesioned hemisphere and interhemispheres) became significant in predicting FM scores and when analyzed with MT in a multivariate model, and lead to higher adjusted R^2 value in the final model.

At the same time if functional recovery is conditioned by the motor threshold MEP and plastic changes in both hemispheres, the remaining symptoms of damage to the UMN, for example, spasticity and pathological synergies, are conditioned by maladaptive plasticity (Sheng al. 2017). Spasticity is the velocity-dependent increase in muscle tone due to the exaggeration of stretch reflex. The causing mechanism of spasticity disrupts the balance of supraspinal inhibitory and excitatory inputs directed to the spinal cord, leading to a state of disinhibition of the stretch reflex.

Cassidy et al. (2020) has shown that low-frequency oscillations reflect on both injury and recovery after stroke and may be useful biomarkers in stroke recovery and rehabilitation. In the study Kozelkin A.A. (2013) has shown that the nature of low-frequency rhythms is from subcortical structures. Larger infarct volume is related to higher delta band power in bilateral hemispheres and to higher delta band coherence between iM1 and bilateral regions. In subacute stroke, higher delta coherence between iM1 and bilateral areas correlate with poorer motor status, at the same time higher delta power bilaterally in chronic stroke correlate with better motor status (Cassidy et al. 2020). At the same time only the decreases in interhemispheric coherence between iM1 and contralesional M1 correlate with better motor recovery and not only in improvement of functional independency level. This finding shows that increasing of coherence in low-frequency oscillations between central motor regions indicates the recovery process and can be interpreted as a process of normal plasticity, at the same time functional improvement, with increasing level of independency but the persistent level of spasticity and pathological synergies indicates maladaptive or pathological plasticity. So the recovery of motor control depends on improvement of upper cortical control above subcortical structures.

In our study we have shown that spasticity is associated with the increase of the motor threshold of the ipsilateral hemisphere and the increase of the coherence of low-frequency Delta and Theta rhythms between the central regions. These findings can be interpreted as maladaptive plastic reorganization due to severity of injury of ipsilateral M1 according to motor threshold of MEP data and released spontaneous subcortical activity.

Clinical applications and limitations

The study of patterns of reorganization after a stroke is important because it gives an opportunity to answer the questions about the nature of the formation of a polymorphic picture of motor disorders, provides objective criteria for predicting the motor recovery, developing the intervention programs and predicting the level of functional independency in the course of rehabilitation.

In our study we have shown that process of recovery is affected both hemispheres. A lot of studies have shown neuroplasticity compensates for the loss of motor function after stroke. However, neuroplasticity activates both physiological and maladaptive mechanisms of recovery of motor control, the second are limited recovery and due to developing of maladaptive motor control patterns – pathologic synergy, spasticity, limited of range of

motion and learning of new movement strategy. Due to Sheng Li et al. (2017) motor recovery is reappearance of elemental motor patterns present before a stroke. In stroke patients with severe impairment the compensatory of substitutive movements including the movements of uninjured side are encouraged to maximize functional ability.

Our results confirmed this notion, we have shown that functional recovery according to Fugl-Meyer are depend on changes of motor threshold of MEP and active reorganization according to Beta rhythms in both hemispheres. At the same time the development of maladaptive pattern according to spasticity depends on the different mechanisms from functional recovery – severity of injury of ipsilateral motor areas and increasing of coherence of low-frequency rhythms between central regions.

These results support the view for heterogeneous nature of motor impairment after stroke and describe the needs to differentiate the approaches for groups of patients with kind of severities.

Comparative studies of TMS with EEG can be possible implemented in the process of prediction of motor recovery and functional ability after stroke, developing the treatment approaches according to prognostic value of group of patients according to their severity.

Conclusions

The parameters of MEP combining with EEG data in the separate model in prediction of post-stroke motor recovery are complementary tools. We confirm and provide the additional data confirming the notion that enhanced activity of the unlesioned hemisphere, concomitant with decreased activity in the lesioned hemisphere, is associated with poor motor function. The decreased activity in the lesioned hemisphere and increased interhemisphere coherence of low-frequency rhythms are associated with spasticity.

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