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ORIGINAL ARTICLE

The relationships of motor-evoked potentials to hand dexterity, motor function, and spasticity in chronic stroke patients: a transcranial magnetic stimulation study

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Abstract The standardization of patient evaluation and monitoring methods has a special importance in evaluating the effectiveness of therapeutic methods using drugs or rehabilitative techniques in stroke rehabilitation. The aim of this study was to investigate the relationships between clinical instruments and transcranial magnetic stimulation (TMS)-evoked neurophysiological parameters in stroke patients. This study included 22 chronic post-stroke patients who were clinically assessed using the Motricity Index (MI), finger-tapping test (FTT), Motor Activity Log (MAL) 28, Brunnstrom motor staging and Ashworth Scale (ASH). Motor-evoked potential (MEP) latency and amplitude, resting motor threshold (rMT) and central motor conduction time (CMCT) were measured with TMS. Shorter MEP-latency, shorter CMCT, higher motor-evoked potential amplitude, and diminished rMT exhibited significant correlations with clinical measures evaluating motor stage, dexterity, and daily life functionality. rMT exhibited a negative correlation with hand and lower extremity Brunnstrom stages ($r = -0.64$, $r = -0.51$, respectively), MI score ($r = -0.48$), FTT score ($r = -0.69$), and also with amount of use scale and quality of movement scale of MAL 28 scores ($r = -0.61$, $r = -0.62$, respectively). Higher MEP amplitude and diminished rMT showed positive correlations with reduced ASH score ($r = -0.65$, $r = 0.44$, respectively). The TMS-evoked neurophysiologic parameters including MEP latency, amplitude, rMT and CMCT generally have positive correlation with clinical measures which evaluate motor stage, dexterity and daily life functionality. Additionally, spasticity has also remarkable relationships with MEP amplitude and rMT. These results suggest that TMS-evoked neurophysiological parameters were useful measures for monitoring post-stroke patients.

Keywords Dexterity · Motor-evoked potential · Neurorehabilitation · Spasticity · Transcranial magnetic stimulation

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Introduction

Various clinical instruments and neurophysiological methods with which to evaluate and monitor post-stroke patients are available [1, 2]. Recently, transcranial magnetic stimulation (TMS)-evoked potentials have sparked growing interest as a possible tool for determining prognosis and objectively monitoring clinical progression during recovery from stroke [3–5]. The value of the early presence of the motor-evoked potential (MEP) for predicting a good prognosis is generally accepted [6], and motor recovery is associated with improved corticospinal conduction [7]. In a systematic review of the literature involving 15 papers, 14 of them indicated that early presence of MEPs after acute stoke was a reliable tool for predicting motor recovery and functional outcome [8]. However, the absence of early MEPs after acute stroke was not necessarily related to a bad prognosis [6, 9]. The associations between neurophysiological parameters and clinical functionality likely depend on the stage of recovery in the early phase [4]. So, the early presence of MEPs could be an additional reliable prognostic measure of eligibility to transfer to a rehabilitation unit after acute stroke [8].

The evaluation of functionality following a stroke mainly uses clinical scales to assess motor dexterity, ability in activities of daily living, and spasticity, but these show wide variability [1]. Additionally, the sensitivity of these scales to sensorimotor changes and their relationship with objective reorganization parameters remain questionable [4]. Studies have shown that TMS parameters have the potential to identify cortical reorganization after stroke and, to some extent, are meaningfully related to motor performance [5, 10]. However, there are no data supporting this finding for chronic post-stroke patients. It may be helpful to assess the relationships between clinical and electrophysiological measures so as to provide better insight regarding the neurophysiology of recovery and to better monitor clinical progression and cortical reorganization following stroke. Commonly, post-stroke patients are followed clinically during rehabilitation using clinical outcome measures. Nonetheless, clinical measures might not be sufficient for monitoring and identifying changes in the functional status of patients. TMS-evoked motor potentials might be objective parameters in neurorehabilitation practice [1, 11, 12]. Therefore, the identification of relationships between clinical measures and electrophysiological parameters might provide crucial data for patient monitoring in clinical practice and for further rehabilitation research.

The objective of this study was to investigate the possible correlations between TMS-evoked electrophysiological parameters and widely used clinical measures of motor performance, activities of daily living and spasticity in chronic post-stroke patients.

Methods

Study design and participants

This was a correlational, cross-sectional study of 22 adult (13 males, 9 females, age >18 years) chronic post-stroke patients who suffered from a unique stroke (post-stroke duration ≥6 months) (Table 1). Data were gathered during the selection of participants for a follow-up study carried out in two tertiary hospitals. This study was approved by the institutional Ethics Committee according to the Declaration of Helsinki, and informed consent was obtained from each patient according to local guidelines [13]. Exclusion criteria were patients who had a cardiac pacemaker, any cranial metallic implants, a history of neurosurgery or epilepsy, hemorrhagic stroke, cognitive deficiencies (Mini-Mental State Examination score <24), or other neuromuscular disorders such as Parkinson's disease, and patients whose resting motor threshold (rMT) could not be determined.

Clinical measures

The patients were examined in detail using the following clinical instruments: the Barthel Index (BI) of activities of daily living, the Motricity Index (MI) for the upper limbs, the finger-tapping test to measure motor ability in the upper limb and hand, the motor activity log 28 to assess daily functionality of the upper limb, Brunnstrom motor staging for motor function, and the ASH to evaluate spasticity.

The Barthel Index is a measure of activities of daily living skills, including feeding, transfers, personal hygiene, toileting, bathing, ambulation, stair climbing, dressing, and bowel and bladder control. Scores range from 0, denoting

Table 1 Patient characteristics

Demographic	Mean (range)
Age (years)	63.9 ± 9.3 (45–82)
BMI (kg/cm^2)	25.6 ± 5.5 (16–37)
Height (cm)	164 ± 8.6 (150–180)
Weight (kg)	68.9 ± 17.2 (36–102)
Male (N [%])	13 (59.1)
Dominant right hand	20 (90.9)
Mean post-stroke time (months)	17.2 ± 6.6 (range 6–24)
Nature of stroke (number of patients)	
Cortical	10
Subcortical	3
Corticosubcortical	9

full dependence, to 100, indicating full independence [1, 14]. The MI evaluates motor function according to three separate subscales for the arm, leg, and trunk. Each subsection is scored from 0 to 100, where 0 designates complete motor function loss and 100 indicate normal motor function. For the current study, only the arm subsection, which includes pinch grip, elbow flexion and shoulder abduction, was used. Each joint was scored from 0 (no motor activity) to 33 (normal muscle strength), and the final score was calculated by adding 1 to the total count of these three subscores [15, 16]. The finger-tapping test (FTT) consists of tapping on a computer mouse with the index finger as many times as possible within 10 s. This test was performed three consecutive times with 30-s rest intervals, and the best score was used [17]. The motor activity log (MAL) 28 is a structured interview developed to measure the actual use of the more impaired arm following stroke in individuals outside a treatment setting. During the interview, patients were asked to rate how well (quality of movement scale) and how much (amount of use scale) their more impaired arm was used to accomplish each of 28 activities of daily living movements. Both MAL 28 scales are anchored at six points (0: never used, 5: same as pre-stroke), and participants could select scores at any point between the anchors. The scale total was calculated as the mean of the item scores [18]. The Brunnstrom motor staging is a six-stage evaluation tool for motor recovery in stroke patients; it has three sections that measure the upper extremity, lower extremity, and hand [19]. The ASH for spasticity is a simple 5-point Likert scale in which the observer's subjective opinion of the subject's resting muscle tone ranges from a low score of 0 (normal) to a high score of 4 (rigid) [20, 21].

Neurophysiological parameters

The TMS evaluations were performed using a MagVenture MagPro X100 transcranial magnetic stimulator (Denmark, 2009) and parabolic coil (MMC 140 parabolic; MagVenture, Denmark, 2009) while the patients were positioned comfortably in a chair. The concave surface of the coil was used for cranial stimulation, and the convex surface for spinal stimulation. Electromyographic data were recorded from the contralateral abductor digiti minimi with surface electrodes using a Medtronic Keypoint Portable unit (Medtronic/Dantec, USA/Denmark, 2008).

The rMT, MEP latency and amplitude, and central motor conduction time (CMCT) were measured in both the unaffected and affected hemispheres using the contralateral abductor digiti minimi muscle according to published guidelines [2, 22]. The motor threshold was determined to be the lowest stimulus intensity required to elicit MEPs of more than 50 μV peak-to-peak amplitude in at least 50 % of consecutive trials during a resting period. The rMT was determined from 5 MEPs recorded from 10 consecutive stimuli from each hemisphere. The patients were in the resting position, lying on an examination table with the limb posture stable with no contractions. To ensure rest, surface electrodes were used and no needle electromyography was used. The stimulation intensity was 20 % above the threshold or increased gradually up to 100 % of the stimulator output if no response was obtained. The CMCT was defined as the difference in latency between MEPs induced by stimulation of the motor cortex and those evoked by spinal (motor root) stimulation.

Statistical analysis

All statistical analyses were performed with SAS software v9.3 and v9.4 (SAS; Cary, NC); and all statistical plots were created in R software v3.1.2 (R Core Team (2014)). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, (http://www.R-project.org/.) and the demographic variables of the patients were analyzed using descriptive statistics. The Kolmogorov–Smirnov test for normality of distribution revealed that all clinical and neurophysiological parameters were distributed normally except MEP amplitude evoked by stimulation of the lesioned hemisphere. Differences between the neurophysiological parameters of the lesioned and non-lesioned hemispheres were analyzed by independent-sample t tests, and correlations were assessed using Pearson's test. Inter-hemispheric comparisons of MEP amplitude were assessed using the Mann–Whitney U test, and correlations were evaluated using Spearman's correlation test. Sensitivity analyses were conducted to investigate the age effect on neurophysiological measures by separating patients into <65 and >65 years old groups and also using the age as a continuous factor. A p value <0.05 was deemed statistically significant for all analyses.

Results

Of the 22 patients, 14 (64 %) had a right and eight (36 %) had a left hemiplegic limb. There were no differences between the participants according to lesion side in any clinical or electrophysiological measure ($p > 0.05$). The clinical and neurophysiological parameters of the patients are summarized (Tables 2, 3). MEP latency and CMCT were significantly delayed, the MEP amplitude was significantly decreased, and rMT was significantly increased in the lesioned hemisphere relative to the non-lesioned hemisphere ($p < 0.001$; Table 3).

Table 2 Clinical outcome scores of the patients (mean ± standard deviation)

Clinical characteristics	Mean ± sd
Barthel Index	80 ± 12.05
Brunnstrom motor stage	
Upper extremity	3.41 ± 1.33
Hand	3.36 ± 1.53
Lower extremity	3.86 ± 1.25
Ashworth score	
Upper extremity	1.64 ± 0.95
Hand	1 ± 0.98
Lower extremity	1.59 ± 1.05
Motricity index	56.95 ± 21.57
Finger tapping test	8.23 ± 8.78
Motor activity log	
Amount of use scale	1.17 ± 0.98
Quality of movement scale	1.43 ± 1.16

sd standard deviation

Correlations between clinical measures of the affected limb and neurophysiological parameters of the affected hemisphere

No significant correlations were observed between Barthel Index scores and any of the TMS parameters (all p values >0.05). MEP latency exhibited a negative correlation with hand and lower-extremity BR scores, the FTT score, and the quality of movement scale score of MAL 28, indicating that shorter MEP latency was associated with improved functionality. Similarly, the CMCT showed a negative correlation with all BR scores, the FTT score, and all MAL 28 scores, indicating that faster CMCT was related to improved functioning. MEP amplitude exhibited a positive correlation with all BR scores, the MI, the FTT score, and all MAL 28 scores and a negative correlation with the ASH hand score. This could be interpreted to mean that higher MEP amplitude was associated with improved functioning and lower spasticity. The rMT exhibited a negative correlation with hand and lower extremity BR scores, the MI, the FTT score, and with all MAL 28 scores, and it showed a positive correlation with the ASH hand score. This suggests that reduced rMT is related to improved functioning and lower spasticity (Tables 4, 5, 6).

Correlations between clinical measures of the affected limb and neurophysiological parameters of the unaffected hemisphere

No significant correlations were observed between clinical scores of the affected limb and any of the TMS parameters (all $p > 0.05$) of the unaffected hemisphere. Likelihood ratio tests failed to show any statistically significant effect of age on neurophysiological measures on subjects older than 65 years old vs younger ($p > 0.05$ on all measures). Hence, age was not found as a factor in TMS measures.

Discussion

The shorter MEP latency and faster CMCT were positively correlated with improved functional outcomes on clinical measures, including the Brunnstrom motor stage, finger tapping test and MAL 28. Higher MEP amplitude and lower rMT were related to better outcomes on all clinical instruments assessing the motor performance and dexterity of the upper limb. In addition, spasticity was significantly associated with MEP amplitude and rMT.

Previous investigations had generally focused on the prognostic value of evoked potentials in the early post-stroke period [23, 24], whereas their potential value for monitoring stroke patients during the chronic stage has been relatively less studied. The typical method for the follow-up of patients during stroke rehabilitation depends on the use of clinical outcome instruments [1]. However, in some cases, clinical measures may be insufficient for monitoring clinical status and identifying changes in functionality [11, 12]. The standardization of the patient

Table 3 Neurophysiologic parameters of the lesioned and unlesioned hemispheres

Electrophysiological parameters	Lesioned hemisphere (mean ± sd)	Unlesioned hemisphere (mean ± sd)	Effect sizes	*t* Test statistic (*df*)	*p* value
MEP latency (ms)	28.83 ± 5.87	20.48 ± 1.67	1.57	7.38 (21)	<0.001
MEP amplitude (mV)	1.1 ± 1.89	3.19 ± 1.6	−1.03	−4.82 (21)	<0.001
rMT	49.86 ± 9.55	37.09 ± 5.01	1.29	6.04 (21)	<0.001
CMCT (ms)	15.33 ± 5.89	7.67 ± 1.47	1.41	6.60 (21)	<0.001

MEP motor-evoked potential, *rMT* resting motor threshold, *CMCT* central motor conduction time, *rMT* % of the stimulator output, *sd* standard deviation, *df* degree of freedom

Table 4 Correlation analyses between Barthel Index, Brunnstrom motor stage of affected limb and the neurophysiologic parameters of affected hemisphere

		Neurophysiologic parameters of the affected hemisphere			
		MEP latency (ms)	MEP amplitude (mV)	rMT	CMCT (ms)
Barthel Index	c.c. (*p* value)	−0.37 (0.09)	0.30 (0.18)	−0.29 (0.19)	−0.34 (0.13)
Brunnstrom motor stage					
Upper extremity	c.c. (*p* value)	−0.38 (0.09)	0.57 (0.01)	−0.38 (0.08)	−0.44 (0.04)
Hand	c.c. (*p* value)	−0.50 (0.02)	0.83 (<0.001)	−0.64 (0.001)	−0.54 (0.01)
Lower extremity	c.c. (*p* value)	−0.48 (0.02)	0.55 (0.008)	−0.51 (0.01)	−0.50 (0.02)

c.c. correlation coefficient, *MEP* motor-evoked potential, *rMT* resting motor threshold, *CMCT* central motor conduction time

Table 5 Correlation analyses between the spasticity score of affected limb and the neurophysiologic parameters of affected hemisphere

		Neurophysiologic parameters of the affected hemisphere			
		MEP latency (ms)	MEP amplitude (mV)	rMT	CMCT (ms)
Ashworth spasticity score					
Upper extremity	c.c. (*p* value)	0.04 (0.87)	−0.33 (0.14)	0.09 (0.68)	0.14 (0.52)
Hand	c.c. (*p* value)	0.22 (0.32)	−0.65 (0.001)	0.44 (0.04)	0.36 (0.10)
Lower extremity	c.c. (*p* value)	−0.06 (0.80)	0.11 (0.63)	−0.11 (0.61)	−0.01 (0.96)

c.c. correlation coefficient, *MEP* motor-evoked potential, *rMT* resting motor threshold, *CMCT* central motor conduction time

Table 6 Correlation analyses between the motor function measures of affected limb and the neurophysiologic parameters of affected hemisphere

		Neurophysiologic parameters of the affected hemisphere			
		MEP latency (ms)	MEP amplitude (mV)	rMT	CMCT (ms)
Motor function measures of affected limb					
Motricity index	c.c. (*p* value)	−0.26 (0.25)	0.64 (0.001)	−0.48 (0.02)	−0.38 (0.08)
Finger tapping test	c.c. (*p* value)	−0.62 (0.002)	0.73 (<0.001)	−0.69 (<0.001)	−0.66 (0.001)
Motor activity log					
Amount of use scale	c.c. (*p* value)	−0.41 (0.06)	0.60 (0.003)	−0.61 (0.002)	−0.47 (0.03)
Quality of movement scale	c.c. (*p* value)	−0.42 (0.049)	0.65 (0.001)	−0.62 (0.002)	−0.49 (0.02)

c.c. correlation coefficient, *MEP* motor-evoked potential, *rMT* resting motor threshold, *CMCT* central motor conduction time

evaluation and monitoring methods have special importance to evaluate the effectiveness of therapeutic methods either via drugs or rehabilitative techniques. There are various clinical and neurophysiologic methods to monitor post-stroke patients. In this context, novel and objective measures and parameters are needed, and TMS-evoked motor potentials represent a relatively new and promising technique in the field of neurorehabilitation. The use of TMS-evoked parameters is a non-invasive, painless, and relatively safe technique and has the potential to provide information about the integrity of central motor pathways and the excitability of the motor cortex [23, 25]. Initial studies in this field aimed to reveal any relationships between TMS parameters and clinical outcomes and to investigate the responsiveness of these parameters to rehabilitative interventions. The presence of more sensitive clinical or neurophysiological measures for monitoring post-stroke patients will enhance the statistical power of therapeutic rehabilitative research [12].

This study found that, of the variables studied, only the BI was not correlated with any of the neurophysiological parameters. This may be due to the relatively small sample size of this study, but it has also become evident in recent years that the sensitivity of the BI to stroke treatment is controversial. A recent systematic review investigating the psychometric properties of the BI and the Modified Rankin Scale following pharmacological treatment for stroke noted that the BI may not be an appropriate scale to measure treatment effects [26]. This should not lead to the conclusion that the BI is not suitable for further stroke follow-up studies but it is clear that the relevance of this index for stroke follow-up studies is questionable, and there is need for further comprehensive studies.

In general, shorter MEP latency and faster CMCT were positively correlated with improved functional outcomes on clinical measures including the Brunnstrom, FTT and MAL 28, but not the MI. The Brunnstrom lower extremity score was correlated in the same manner, which is interesting in terms of motor mapping because the MEP was recorded from the abductor digiti minimi muscle, which mainly reflects the excitability of the upper-extremity motor cortex. The correlations of MEP latency and CMCT with the lower extremity Brunnstrom score may reflect the improvement in motor functionality in both upper and lower limbs. Alternatively, it may be the result of interactions among the cortical motor networks of different motor areas due to reorganizational changes. It is difficult to explain this correlation with the existing data, but it also appears to be more than merely coincidental based on the positive correlation of the lower-extremity Brunnstrom score with MEP amplitude and its negative correlation with rMT.

Additionally, a higher MEP amplitude and lower rMT were related to better outcomes on all clinical instruments assessing the motor performance and dexterity of the upper limb. Thickbroom et al. [5] found that grip strength was correlated with both MEP amplitude and threshold, whereas the McCarron score for hand motor dexterity was not. In contrast, in the present study, hand dexterity (as evaluated by MI, FTT and MAL 28) showed positive relationships with MEP amplitude and motor threshold. This difference may be the result of the use of different clinical instruments or of differences in patient characteristics. The main difference between the population in the previous study and the current study was post-stroke duration, which was 6–24 months here and ranged from 1 month to 23 years in the Thickbroom et al.; in another study, the relationships between hand function (assessed by finger tapping, peg placing, and strength evaluation) and cortical excitability were investigated. They found associations between diminished hand function and lower MEP amplitude as well as between lower motor threshold and better hand function [4]. In conjunction with the current findings, these results reveal that TMS-evoked MEP parameters exhibit a strong correlation with several clinical instruments.

A neurophysiological study of post-stroke patients that did not use TMS evaluated the clinical correlations of neurophysiological measures and found that total stiffness indices, stretch reflex threshold speed, and stretch reflex area were highly correlated with the ASH score [27]. Relatively, few prior studies have investigated the relationship between spasticity and TMS parameters. According to initial findings, the silent period has been proposed as a prognostic factor for post-stroke spasticity in the early stages following a stroke [28]. In the present study, the associations between spasticity and TMS parameters including MEP latency and amplitude, rMT, and CMCT were investigated in chronic post-stroke patients. Higher MEP amplitude and lower rMT were found to have strong correlations with lower spasticity, which suggests that MEP amplitude and rMT may be objective follow-up measures during spasticity treatment trials and could play a role in the dose adjustment of drugs for spasticity in the future. In a previous study, Bernard and Seidler investigated the motor cortex organization of both brain hemispheres of cognitively healthy younger and older adults with using TMS. They found that older adults had larger contralateral MEP amplitudes and a longer contralateral MEP latency but there was no significant difference in motor threshold [29]. In the present study, the age was not found as a factor in TMS measures of the post-stroke patients. The current findings are preliminary but may be useful for the direction of future studies.

There are some limitations to this prospective study. First, the sample size was small. Having a large number of covariates in this small sample precluded us from fitting multivariate models and making definite conclusions in this patient population. Second, multiple physical examinations were performed. We performed multiple comparisons, especially for correlations, but our type I error rate was not adjusted for multiple comparisons. The type I error rate may be inflated. If we had performed adjustment for multiplicity, results might have been different. These findings are preliminary and might be useful for future studies.

In conclusion, TMS-evoked neurophysiological parameters are useful for monitoring post-stroke patients during rehabilitation and medical therapy. However, it is too early to conclusively determine this, and further follow-up studies with higher patient numbers are needed.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study was approved by the local Ethics Committee and performed according to the tenets of the declaration of Helsinki.

Informed Consent Informed consent was obtained from all individual participants.

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