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Research paper

Longitudinal study on modulated corticospinal excitability throughout recovery in supratentorial stroke

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HIGHLIGHTS

- Corticospinal excitability is modulated over 6 months recovery in stroke.
- Asymmetry in CSE reaches normal levels after ~1 month after stroke onset.
- Lesion size and severity correlate positively with reduced CSE.

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ABSTRACT

Corticospinal excitability (CSE) is modulated by stroke-induced lesions affecting the brain. This modulation is known to be dependent on the timing of the evaluation, and strongest abnormalities are often found in the acute stage. Our study aimed to characterize changes in CSE asymmetry between the affected and the unaffected hemisphere (AH and UH) during the first month after stroke onset and at 6 month follow-up. Neuronavigated transcranial magnetic stimulation (nTMS) was used to assess the CSE of the abductor pollicis brevis (APB) muscle of the hand and tibialis anterior (TA) muscle of the leg in 16 patients over 5 time-points. AH excitability recovered significantly during 6 months, whereas interhemispheric asymmetry remained significant up to 1 month post-stroke in the APB muscle. Greater initial CSE was associated with good motor function at 6 months. The motor cortical excitatory recovery initiated within week of the stroke and was most prominent within 1 month after stroke onset. Lesion size correlated with CSE of the UH at 10 days, while overall severity of the symptoms correlated inversely with CSE of the AH. This study demonstrates the quick improvement in the CSE via estimation of interhemispheric asymmetry; however, the recovery in the asymmetry continues to normalize even after reaching the threshold for normal values in CSE.

1. Introduction

Stroke lesions in the brain induced by hemorrhage or ischemia lead to structural and functional changes, which modulate corticospinal excitability (CSE) [23]. The changes in CSE tend to be observed on the affected hemisphere (AH), while the CSE on the contralesional unaffected hemisphere (UH) is often less altered [3,4,30]. This interhemispheric asymmetry has been reported to be greatest in the acute stage, after which it begins to recover [3,30]. Recovery from stroke is based at least partly on the reorganiza-

Abbreviations: AH, affected hemisphere; aMT, active motor threshold; APB, abductor pollicis brevis; BI, barthel index; CSE, corticospinal excitability; EMG, electromyography; FAC, functional ambulatory category; M1, primary motor cortex; MEP, motor evoked potential; MSO, maximum stimulator output; nTMS, neuronavigated transcranial magnetic stimulation; rMT, resting motor threshold; SSS, scandinavian stroke scale; TA, tibialis anterior; TMS, transcranial magnetic stimulation; UH, unaffected hemisphere.

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tion of the surviving parts of the brain and rebuilding of functional networks [23,26].

Transcranial magnetic stimulation (TMS) is used to activate neuronal circuits in the central and peripheral nervous system [1]. Due to commonly occurring motor dysfunction in stroke, TMS is an appropriate tool to assess cortical and peripheral motor tract integrity and motor function recovery after stroke [9,33]. In stroke patients, abnormal motor evoked potential (MEP) characteristics have been reported [2,9,33]. In the acute stage, MEPs are often seemingly absent when TMS is applied to the AH [9,17], but during recovery, they may begin to reappear [9,11,32]. This behavior demonstrates the recovery or regeneration of cortical connections in the motor network. Liepert et al. demonstrated that also in the chronic stage of stroke, reorganization of the motor cortical neurons still may continue as shown by increased MEPs and shift of cortical presentation [14].

Our aim was to longitudinally assess CSE with TMS in the acute stage and during a recovery period of 6 months focusing on the first few weeks during which the most fundamental changes in CSE should occur. We hypothesized that the known interhemispheric asymmetry observed in CSE would recover during the follow-up period, and that the time-line of the recovery could be observed. We also aimed to understand the CSE modulation through assessment of relations between the CSE, lesion size and clinical symptoms. Although several studies have investigated CSE and its asymmetry in stroke, only few longitudinal studies have focused on the acute stage.

2. Materials and methods

2.1. Subjects

16 patients (8 female, age 64 ± 9 years) with MRI-verified supratentorial stroke participated in this study. The patients had suffered ischemic ($n = 10$) or hemorrhagic ($n = 6$) stroke. Five patients had a multifocal (2 or 3) lesion. The mean lesion diameter (including oedema), as determined from structural MRI, was 39 ± 20 mm. 15 of the primary lesions were located in the vicinity of the motor cortex (cortical or striatocapsular type, 6 involving M1) and 1 in the thalamus. The AH was the left hemisphere in 8 and right hemisphere in 8 patients. The mean Barthel index (BI) [16] in the beginning of the study was 51 ± 27 and the Scandinavian Stroke Scale (SSS) [10] was 39 ± 10.

The patients were selected for this study based on the following criteria within 10 days after stroke:

1) supratentorial stroke, (Modified Rankin Scale 0–2)
2) functional ambulatory category (FAC) 0–3 [12,21]
3) remaining ability to move the leg of the affected side
4) BI 20–100 points
5) body mass index <32
6) otherwise in good health

Patients received a three-week period of intensive inpatient gait-oriented rehabilitation in the acute care hospital [21]. The local research ethics committee approved the study (2/2005). A written informed consent was given by each patient. Patient demographics are shown in Table 1.

2.2. Study protocol

The patients were studied in five sessions: (1) within 10 days of stroke onset (mean 8 days), and (2) 3 days, (3) 14 days, (4) 21 days after the first session, as well as (5) 6 months after stroke onset. For simplicity, we later refer to the previous time-points using 10 days, 13 days, 24 days, 31 days and 6 months, respectively. During the first session, the primary motor cortex (M1) was mapped bilaterally to localize the optimal representation sites of left and right abductor pollicis brevis (APB) and tibialis anterior (TA) musculatures using navigated TMS (eXimia version 2.0, Nexstim Plc, Helsinki, Finland). The stimulation was conducted using Magstim BiStim (Magstim Company Ltd, Whitland, UK) with a figure-of-eight-shaped 70-mm coil and monophasic pulse wave-form. Navigated TMS utilized T1-weighted 3D MRIs imaged with Siemens Magnetom Avanto (Siemens Healthcare, Erlangen, Germany). The FAC was evaluated prior to the first session (FAC_{10d}) as well as after the last session (FAC_{6mo}) to evaluate motor function recovery.

Initial mapping for the optimal stimulation site was performed using suprathreshold stimulation intensity producing motor evoked potentials (MEPs) of ~1 mV at maximum. The sites where stimulation consistently produced the largest MEP in the APB or TA muscles were assigned as optimal stimulation sites. Subsequently, and during each session, the resting motor threshold (rMT) for these sites was determined using the Rossini-Rothwell method [25] with MEP peak-to-peak amplitude threshold of 50 μV. Thereafter, 5 MEPs were recorded at 130% of rMT. MEPs were recorded with surface electromyography (EMG) using ME6000 amplifier (Mega Electronics Inc., Kuopio, Finland). Only resting MEPs were analyzed. The experiments comply with the early guidelines of the IFCN [24]. For patients in whom we could not achieve high enough TMS intensity to elicit any MEPs, value 100%-MSO

Table 1
Patient and lesion characteristics.

subject	gender	age (years)	affected hemisphere	lesion type	lesion diameter (mm)	SSS	BI	FAC_{10d}	FAC_{6mo}
1	F	64	left	ICH	34	48	100	3	5
2	F	79	left	ICH	80	44	40	0	4
3	F	43	right	CI	48	33	35	0	5
4	F	53	left	ICH	47	34	30	0	4
5	F	68	left	CI	22	42	75	2	5
6	M	57	right	CI	15	48	95	2	4
7	M	70	right	ICH	70	48	55	0	5
8	M	66	right	CI	29	18	35	0	1
9	F	58	right	CI	24	57	95	3	5
10	M	58	right	CI	18	32	25	0	4
11	M	65	left	CI	60	26	25	0	2
12	M	62	left	CI	19	44	40	0	3
13	F	74	right	CI	45	28	20	0	1
14	F	68	left	ICH	36	39	45	1	4
15	M	74	right	CI	25	46	60	0	3
16	M	59	left	ICH	56	35	35	0	3

Abbreviations: BI = Barthel Index, CI = cerebral infarction, FAC_{10d} = Functional ambulatory category at 10 days, FAC_{6mo} = Functional ambulatory category at 6 months, ICH = intracerebral hemorrhage, M = male, F = female, SSS = Scandinavian Stroke Scale.