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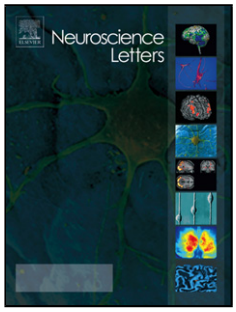

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Longitudinal study on modulated corticospinal excitability throughout recovery in supratentorial stroke

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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

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.

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

Keywords: Corticospinal excitability; motor evoked potential; transcranial magnetic stimulation; motor threshold; stroke

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 reorganization 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 studied CSE and its asymmetry in stroke, only few longitudinal studies have focused on the acute stage.

Materials and methods

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 Ranking 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 25–75 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.

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 ~1mV 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 50μV. 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 recorded. 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 was assigned for rMT and 0μV for MEP amplitude. The rMT and peak-to-peak MEP amplitude were evaluated as measures of CSE.

Motor threshold asymmetry index

Asymmetry index was only computed for rMT due to characteristically lower inter- and intra-individual variability in responses compared to MEPs [6, 13, 27]. Asymmetry index for the rMTs was computed as:

$$\text{Asymmetryindex} = \frac{rMT(AH) - rMT(UH)}{rMT(AH) + rMT(UH)}, \quad (1)$$

in order to study the differences between the AH and UH over the course of recovery. The asymmetry index was considered to represent interhemispheric differences between the AH and UH with their respective rMTs. Asymmetry index was computed in a similar manner as done with imaging data [5] or electroencephalography [22]. Positive asymmetry index indicates higher rMT on the AH than on the UH.

A baseline level for normal rMT asymmetry was computed based on data from our previous study with 65 healthy subjects [27] to gain the 95% confidence interval for the absolute value of the asymmetry index. This effort was made to detect when the asymmetry index of the patient population had begun to overlap with that of the healthy population. The methods used to measure the rMTs for the APB and TA muscle representations on both hemispheres were similar to this study though with a different TMS-stimulator with biphasic wave-form.

Statistical analysis

The statistical analysis was performed for the rMTs and MEPs separately for both muscles using repeated measures analysis-of-variance (ANOVA) with session number (recovery time) and stimulated hemisphere (AH or UH) as factors. Post-hoc comparisons were performed using paired-samples *t*-test to compare hemispheres and consecutive time-points. Asymmetry index was analyzed time-point-wise using difference contrast. Correlation analyses between rMT parameters, functional motor symptom severity (SSS), recovery and structural parameters were assessed using

non-parametric Spearman's rho. To limit the number of analyses, only data from first and the last session were used in the correlation analyses. Two-tailed tests with threshold level for statistical significance $p<0.05$ were used. The statistical analyses were performed with SPSS Statistics 22 (IBM Corporation, Somers, NY).

Results

Corticospinal excitability

The stimulated hemisphere had a significant effect on rMT (F=12.08, p=0.003 for APB and F=14.79, p=0.002 for TA) and MEP amplitude in APB (F=6.64, p=0.021 for APB). Time from stroke onset (session number) had a significant effect on rMT of APB (F=3.31, p=0.037) (Figure 1). A significant session x hemisphere interaction was observed in APB (F=5.33, p=0.012). Post-hoc tests showed that the rMT was significantly greater on the AH than the UH in all sessions, while the MEP amplitudes on the AH were significantly lower in all but the last session. For APB, the rMT asymmetry index was significantly affected by time (F=5.10, p=0.015) and was present up until 24 days, after which it decreased (Figure 2A). TA did not exhibit such behavior (Figure 2B). Sufficiently high TMS intensity to determine the rMT was not reached in several subjects on the AH, especially for TA (Figure 3).

Group-level comparison with healthy population

Based on the baseline level of asymmetry index in rMT computed for healthy population, we found that asymmetry index of the stroke patients approached the levels of healthy subjects in APB muscle at 24 days, while no significant asymmetry was observed in the TA compared to healthy population (Figure 2).

Correlations between TMS-parameters, recovery, stroke severity and lesion size

$\underline{FAC_{10d}}$: The rMTs of APB on the UH correlated with FAC_{10d} at 10 days (rho=-0.729, p=0.001). Such correlations were not found in TA. FAC_{10d} did not correlate with asymmetry index.

$\underline{FAC_{6mo}}$: The rMTs and MEP amplitudes of APB on the AH correlated with FAC_{6mo} at 10 days (rho=-0.500, p=0.048 and rho=0.527, p=0.036, respectively) and at 6 months (rho=-0.705, p=0.002 and rho=0.516, p=0.041, respectively). Only the rMTs of APB on the UH correlated with the FAC_{6mo} at 10 days (rho=-0.573, p=0.020) and at 6 months (rho=-0.574, p=0.020). The rMTs and MEP amplitudes of TA on the AH correlated also with the FAC_{6mo} at 6 months (rho=-0.621,

p=0.010 and *rho*=-0.630, *p*=0.009, respectively), and on the UH at 6 months (*rho*=-0.535, *p*=0.033). FAC_{6mo} did not correlate with asymmetry index.

SSS: The rMT and MEP amplitude in the APB muscle on the AH correlated with SSS at 10 days (*rho*=-0.805, *p*<0.001 and *rho*=0.773, *p*<0.001, respectively) and 6 months (*rho*=-0.571, *p*=0.021 and *rho*=0.520, *p*=0.039, respectively). On the UH, only rMT correlated with SSS at 10 days (*rho*=-0.517, *p*=0.040). In TA, rMT and MEP amplitude on the AH, correlated with SSS at 6 months (*rho*=-0.497, *p*=0.050 and *rho*=0.538, *p*=0.031, respectively). No correlations were observed with asymmetry index.

Lesion size: Lesion size correlated with asymmetry index in the TA at 10 days (*rho*=0.803, *p*<0.001). Lesion size correlated also with the rMTs of APB and TA on the UH at 10 days (*rho*=0.517, *p*=0.040 and *rho*=0.636, *p*=0.008, respectively), but not with other TMS-parameters.

Discussion

CSE is modulated significantly after stroke with supratentorial lesion during the first few weeks and up until 6 months. The modulation is strong especially on the AH, and was emphasized in APB. The strongest abnormalities in CSE are observed at very early stage, and improve for about one month due to the recovery (Figure 1). Our findings agree with earlier studies on the modulation of CSE after stroke [3, 31]. The rMTs of the UH corresponded well with those reported in the healthy population [28] and agree with earlier reports in stroke patients, which demonstrate that in general the CSE of the contralesional corticospinal tract is within normal limits in the acute and chronic stages [2, 30]. In the present study, we made observations on the CSE changes over time in a more precise time-window. We also found that lesion size, functional characteristics as well as recovery correlated with the CSE findings.

Long lasting decrement of CSE has been reported after stroke [20]. It is often considered that disinhibition present after stroke on the AH [4, 15] leads to rapid clinical improvement, while some structural contributors as well as the uncontrolled input from UH may also affect [23]. In the present study, the asymmetry in rMT began to diminish with time, approached values of normal population after about 31 days after stroke onset in the APB muscles and tended to reduce more towards 6 months (Figure 2). Comparison with healthy population [27] indicated that no significant asymmetry was observed in the TA of patients. The reason for the non-significant finding in TA muscle is likely the inefficiency of the monophasic pulse [6] to stimulate the motor cortex of

patients with reduced CSE. Use of biphasic waveform could have improved the count of successful measurements of rMT due to more powerful stimulation effect [6] potentially making the recovery of AH excitability steeper in figure 1. This means that when no rMT was achieved, it was marked as rMT of 100 %-MSO, and hence the asymmetry would have remained low, since the lower limb muscles often demonstrate much higher rMTs even in healthy individuals (Figure 3) [27]. Therefore, the analysis of TA asymmetry index likely underestimates the true asymmetry in CSE, and rMT in TA is not sensitive to detect such stroke-related asymmetries.

Despite the limitations found to involve TA measurements, we found that the lesion size correlated with the rMTs of APB and TA on the UH at 10 days. It is possible that in the acute stage, the level of CSE of the UH is increased depending on the size of the lesion, and the decrease in CSE reaches the UH before quick recovery to normal. This phenomenon was found to be separate from the relation between CSE and stroke severity, since severity did not correlate with lesion size (p=0.439). As a general finding, the stroke severity correlated with the CSE on the AH: the more severe the stroke, the less excitable the corticospinal tract. Earlier, the severity of stroke has been found to be closely related to the modulation of CSE, not only with the acute stage functional impairment but with the clinical outcome [18, 31]. In the present study the FAC_{6mo} correlated with acute stage CSE on the AH. This was not observed in TA on the AH, which could be explained by the insufficient power of TA to induce responses (Figure 3). It must be acknowledged that the location of the lesions was not controlled in the analyses, which could affect the correlations. The location of the lesion may have different consequences on MEP or rMT, independently of the severity of stroke.

Di Pino et al. introduced a bimodal balance–recovery model that links interhemispheric balance and functional recovery to the structural reserve contributing to recovery and is not affected by the stroke lesion [8]. Therefore, if the structural reserve is high, the normally balanced inhibition between the hemispheres is disrupted resulting in reduced inhibition on the UH and increased inhibition on the AH. The balance of activity between the hemispheres tends to recover toward the previous equilibrium. If the structural reserve is low, persistence of interhemispheric imbalance promotes compensatory plasticity. In agreement with the model, we found that AH suffered from increased inhibition observed as the CSE imbalance between the hemispheres, which tended to recover towards normal values (Figure 2). If we assume that lesion size correlates with the structural reserve, the only observed significant correlation between the lesion size and the CSE of the UH may be indicative of disturbed excitation-inhibition balance between AH and UH. We did

not study the disinhibition on the UH, and therefore cannot make related conclusions, although some non-significant tendency toward reduced MEP amplitude of UH was observed after 13 days (Figure 1C). The model predicts that persistence of interhemispheric imbalance serves a predictor of poor recovery [7], which was also observed in the present study through associations between acute stage CSE and 6-month functional recovery.

The observed decrease in the CSE of AH immediately after stroke may involve changes in axonal membrane properties stimulated by TMS as well as reductions in the number of conducting corticospinal axons. It is possible that the location of stroke may influence the principal mechanism behind the observed change in CSE. In cortical stroke, oedema and altered ion concentrations in the extracellular fluid could decrease membrane excitability thereby increasing the rMT, which may resolve quite quickly after stroke and subsequently account for the observed rapid changes in rMT and MEP. In contrast, subcortical strokes are less likely to induce changes in excitability of cortical neurons, but instead cause interruption to corticospinal fibres, seen as increase in the rMT and decrease in the MEP amplitude. Again, possible resolution in the early recovery stage may explain the rapid changes in CSE in the acute stage [29]. Although, the apparent CSE recovery seen in figure 1 appears strong, some previous studies have concluded that the rMT is influenced by multiple structural and functional characteristics of both cortical and spinal neurons negatively affecting its ability to act as a reliable biomarker regarding inter-hemispheric differences in excitability [7, 19].

In this longitudinal study, considering the variety of lesion sizes and types of stroke, generalization of the results certainly requires further studies with larger number of subjects. Due to insufficient amount of patients in the hemorrhagic group, we were unable to compare reliably the CSE and recovery of the ischemic and hemorrhagic patients. Even with the heterogeneous group of 16 patients we were able to detect longitudinal changes within the group and showed how severity of stroke relates closely to rMT. Furthermore, we did not include a patient-matched control-group but instead utilized our previously published large-population material [27]. The baseline level for asymmetry index in CSE was measured with different TMS-stimulator pulse waveform than what was used for the patients, which should not have a great effect on relative measure of the asymmetry index, instead of the absolute rMTs known to differ due to different stimulator and waveforms [6, 27].

Conclusions

We found that asymmetry in the CSE was especially detectable in the corticospinal tract of the APB, and that the severity of the stroke was closely related to CSE. Recovery of asymmetry to nearly normal levels took place during the first weeks after diagnosis. This demonstrates that the brain can make large functional repairs quite quickly, while the network changes still continue months after stroke.

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Conflicts of interest

PJ has received unrelated consulting fees and JK works as a part-time advisor for Nexstim Plc, manufacturer of nTMS systems.

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Figure Captions

Figure 1: rMTs (A and B) and MEP amplitudes (C and D) of the AH and UH (mean ± standard error of mean, SEM) within each session for APB (A and C) muscle and TA muscle (B and D). Repeated measures ANOVA statistics have been presented over the plot, while post-hoc analysis within each session has been indicated (***p<0.001, **p<0.01, *p<0.05). In the post-hoc comparisons, only consecutive time-points and hemispheres were compared. The grey area in the background of A) indicates 95% confidence interval (with dashed line representing the mean) for the rMT measured from 10 healthy subjects in for the APB muscle with the same TMS-stimulator and measurement protocol as used in the present study [28].

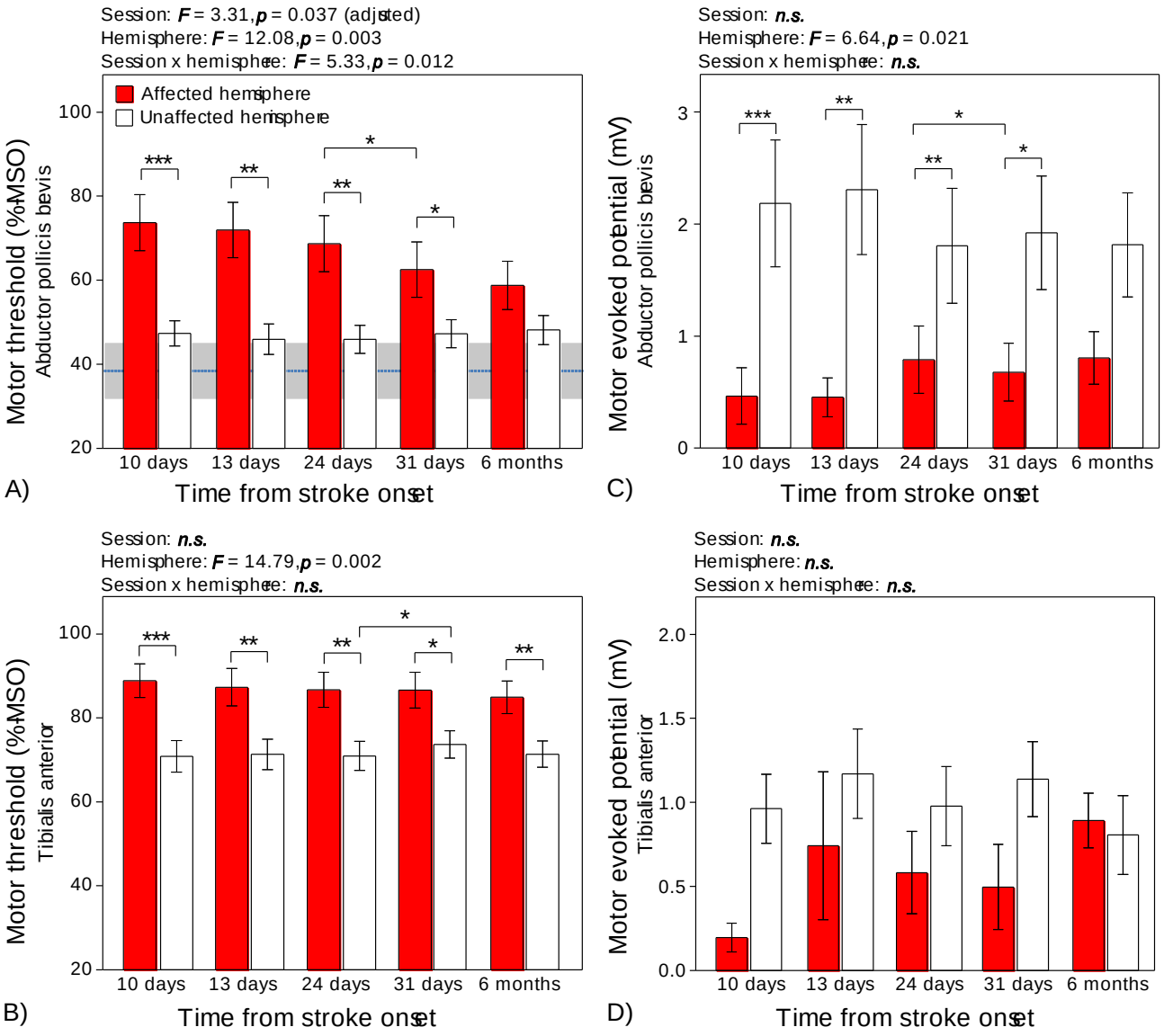
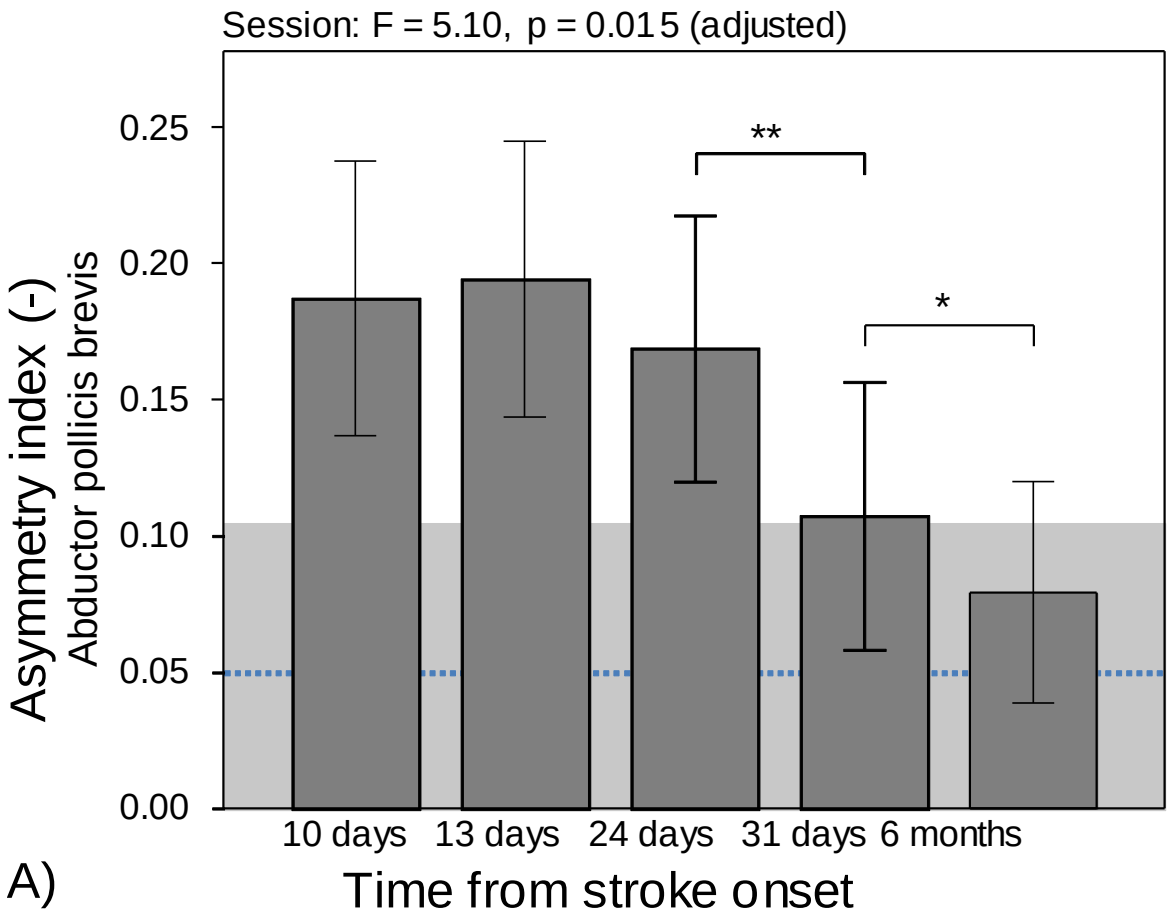
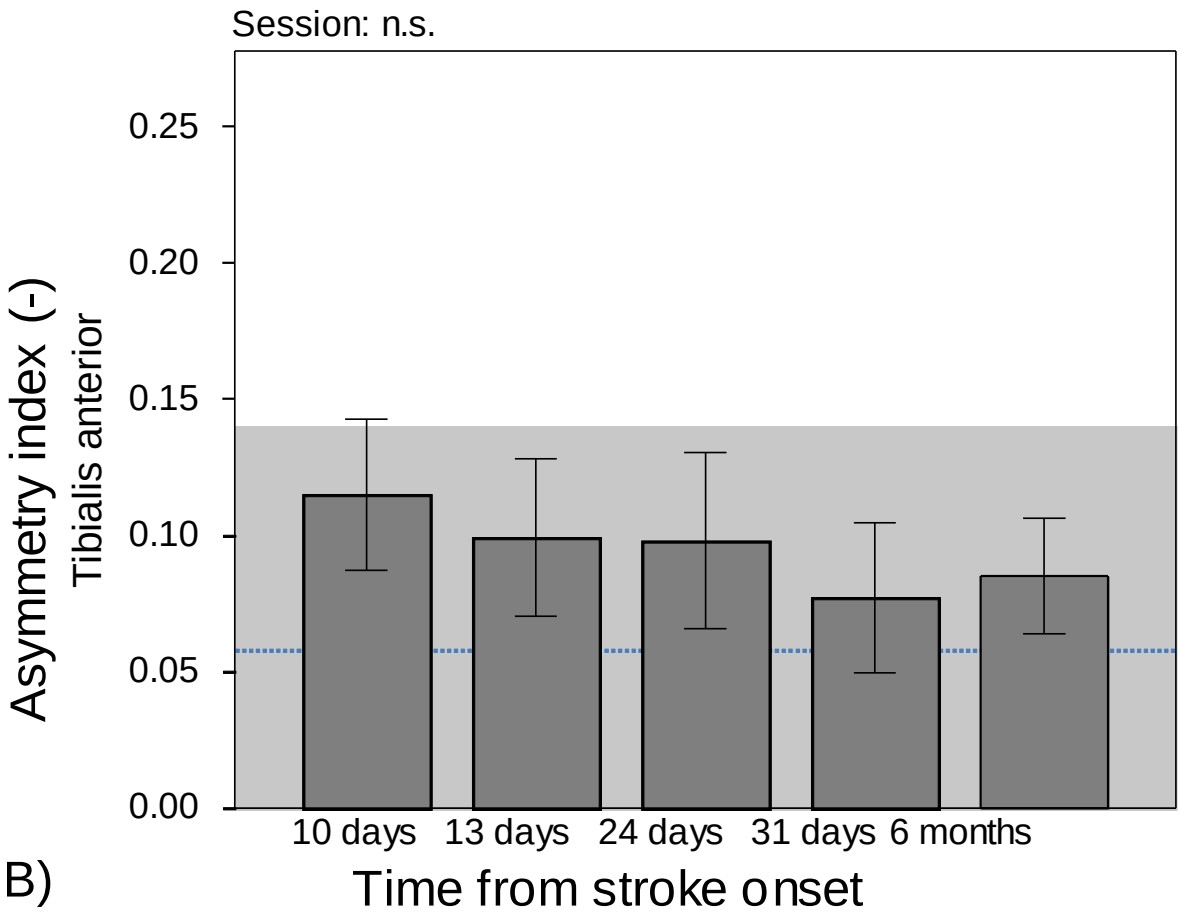


Figure 2: Asymmetry indices for the interhemispheric differences in rMT (mean ± standard error of mean, SEM) within each session for A) APB muscle and B) TA muscle. Repeated measures ANOVA statistics have been presented over the plot, while post-hoc analysis with difference contrast have been indicated (**p<0.01, *p<0.05). The grey area in the background indicates 95% confidence interval (with dashed line representing the mean) for absolute value of the asymmetry index measured from healthy population in [27].

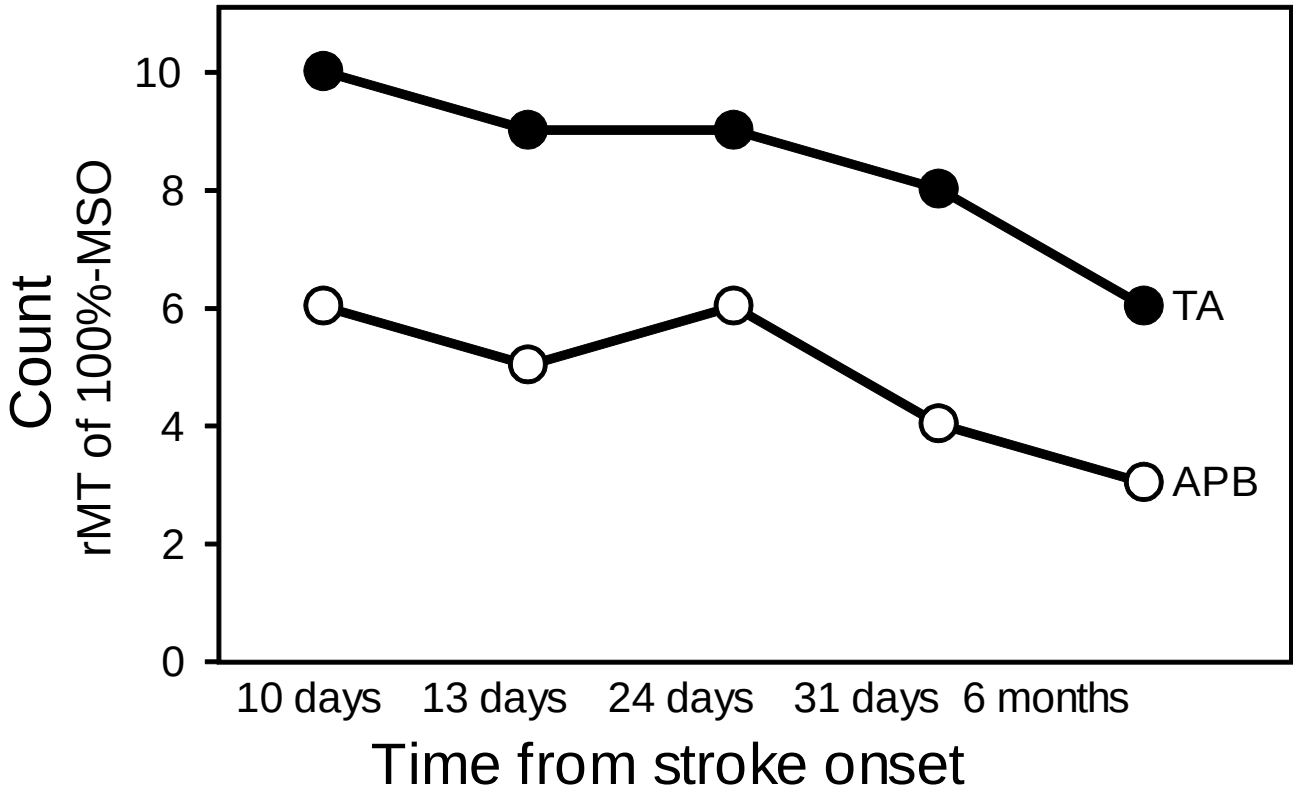


A)



B)

Figure 3: The number of patients (out of 16) in whom we were unable to reach a high enough TMS intensity to measure the rMT or MEP on the AH. The number of patients was higher in TA than in APB. Many of these patients recovered to a level when the rMT could be measured. In all patients, we were able to measure the rMT in all time-points on the UH for both muscles.



Tables

Table 1: Patient and lesion demographics.

subject	gender	age (yrs)	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