

*Original Research*

# Evaluation of Relationships between Corticospinal Excitability and Somatosensory Deficits in the Acute and Subacute Phases of Stroke

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## Abstract

**Background:** Somatosensory deficits are common symptoms post stroke. Repetitive transcranial magnetic stimulation (rTMS) over the motor cortex is able to promote motor rehabilitation, whereby its impact on somatosensory functioning remains unknown. This study was designed to evaluate the association between somatosensory deficits and corticospinal excitability following stroke, with the purpose to provide insights on rTMS interventions for the management of somatosensory deficits. **Methods:** Somatosensory functioning and corticospinal excitability (motor-evoked potential, MEP; cortical silence period, CSP) were evaluated from a group of sixteen patients with unilateral ischemic stroke in the acute or subacute phase. **Results:** Results indicated that the uncommon presentation of larger MEPs in ipsilesional vs. contralesional motor cortex was associated with worse somatosensory function compared to those with a smaller MEP in ipsilesional motor cortex. Moreover, increased MEP ratio (ipsilesional vs. contralesional motor cortex) was associated with better somatosensory function in patients with well-preserved somatosensory function. **Conclusions:** In well-recovered patients, an increased MEP ratio between the ipsilesional and contralesional motor cortex could be an indicator of improved somatosensory functioning following stroke.

**Keywords:** stroke; somatosensory deficits; TMS; MEP; CSP

## 1. Introduction

Somatosensory deficits are common post-stroke symptoms characterised by sensory losses, numbness. It is estimated that about 50–80% of post-stroke survivors demonstrate somatosensory deficits, which have clear adverse influence on motor functioning and overall recovery from stroke [1,2]. Repetitive transcranial magnetic stimulation (rTMS) is a safe and non-invasive form of brain stimulation which is able to induce neuroplastic changes [3,4]. It has been used in the management of depression [5,6], chronic pain [7,8], and post-stroke motor rehabilitation [9,10]. Studies have been focussed on motor rehabilitation with motor cortex rTMS (see reviews in [11,12]), however, the potential benefits of rTMS on somatosensory deficits remain unclear. Overall, there is a lack of effective treatment for somatosensory deficits in clinical settings [13–15].

Although most rTMS studies aimed at improving somatosensory function following stroke have focused on targeting the primary somatosensory cortex (S1) [16–18], the primary motor cortex (M1) may be an alternative target. Although the motor cortex is predominantly involved in mo-

tor control, it is also responsible for somatosensation via its anatomical and functional connections with somatosensory cortices and the thalamus [19]. In fact, motor cortex rTMS has a clear impact on the transmission of sensory information from the body parts [20–22]. This argument is also consistent with findings that motor recovery following stroke is positively associated with sensory functioning [2]. Moreover, motor cortex rTMS has demonstrated potential benefits on motor rehabilitation following stroke [12], although recent studies have called this argument into question [23,24].

In addition to the site of stimulation, it is important to determine the relationship between somatosensory deficits and corticospinal excitability, in order to facilitate the design of stimulation protocols for somatosensory improvement. Somatosensory deficits following stroke are associated with the impairment of somatosensory pathways (e.g., the medial lemniscal pathway for discriminative touch and proprioception, the spinothalamic pathway for pain and temperature) [25–27], which transmits sensory signals from body parts. Our group has previously demonstrated that bottom-up sensory transmission is able



to inhibit corticospinal excitability measured by motor-evoked potential (MEP) and cortical silent period (CSP) [21]. MEP amplitude provides a simple and direct measurement of the excitation of corticospinal pathways. Meanwhile, CSP is able to indicate intracortical inhibition supported by gamma-aminobutyric acid (GABA<sub>B</sub>) mediated neurotransmission [28]. As rTMS can efficiently modulate corticospinal excitability, building up the relationships between corticospinal excitability and somatosensory deficits would provide direct insights into the management of somatosensory deficits with rTMS.

This study was designed to evaluate the association between somatosensory deficits and corticospinal excitability following stroke. Somatosensory functioning and corticospinal excitability were evaluated from patients with unilateral ischemic stroke. We have specified this study to acute and subacute phases of stroke to reduce heterogeneity. It is hypothesised that decreased corticospinal excitability in the ipsilesional (*vs.* contralesional) motor cortex would be associated with poorer somatosensory functioning.

## 2. Materials and Methods

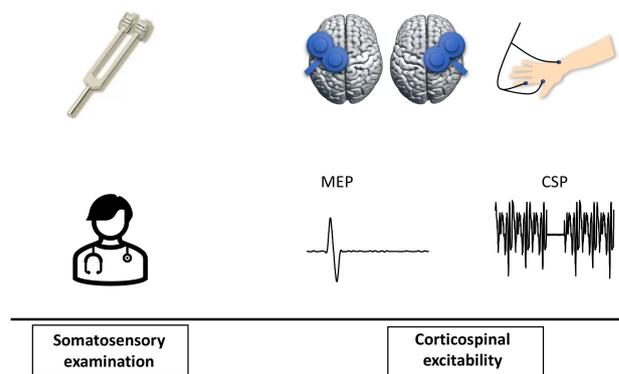
### 2.1 Participants

A total of thirty-nine patients were screened, among which sixteen participated in this study. All patients had unilateral ischemic stroke observed on a diffusion-weighted magnetic resonance imaging (MRI) scan. The inclusion criteria were: (1) unilateral ischemic stroke in the acute and subacute phase of stroke (<6 months) [11]; and (2) with somatosensory deficits caused by ischemic stroke; and (3) 18–80 years old; and (4) were on regular stroke medicines. The exclusion criteria were: (1) TMS contradictions such as current or a history of seizure or implanted devices (pacemaker, medical pumps) [29]; or (2) severe mental disorders assessed with hamilton depression (HAMD) or anxiety (HAMA) [30,31]; or (3) aphasia or cognitive disorders assessed with the Mini-Mental State Examination (MMSE) [32]; or (4) not able to communicate with a doctor; or (5) severe disorders caused by other conditions such as tumour or severe heart or lung malfunctioning; or (6) the modified Rankin Scale (mRS) >2; or (7) somatosensory deficits not caused by ischemic stroke, e.g., diabetes pain. mRS was used to include mostly mild impairment as somatosensory deficits are more prominent for these patients compared to motor deficits in patients with severe stroke. All participants provided a written informed consent before study commencement. This study was approved by the Ethics Committee in the Affiliated Hospital of Hangzhou Normal University (2021-E2-HS-029) and was conducted in accordance with the Declaration of Helsinki.

### 2.2 Study Design

This was an observational study (Fig. 1). All the patients visited our research centre once. Somatosensory function was evaluated during the testing, and corticospinal

excitability was recorded with single-pulse TMS-evoked MEPs.



**Fig. 1. Study design.** Somatosensory function was initially evaluated on both sides of body. Corticospinal excitability was then recorded from both hemispheres with single-pulse TMS-evoked MEPs.

### 2.3 Somatosensory Functioning

Somatosensory functioning was evaluated using the modified Fugl-Meyer and Lindmark Assessment [33,34], which included superficial sensation (pain, temperature, and touch), deep sensation (proprioception, motion perception, and vibration), cortical sensation (two-point discrimination, stereognosis), and subjective sensation. Subjective sensation was added due to the fact that some patients (3/16 in this sample) tended to report somatosensory deficits that could not be identified by any of the three sensory dimensions (superficial, deep, and cortical sensation). The assessment of somatosensory function systematically covered trunk, limbs, and head with 29 items (superficial = 10; deep = 13, cortical = 3, and subjective = 3), and had a total score of 58 (three levels: 0, 1, 2). The score of somatosensory functioning assessed both the ipsilesional and contralesional sides, whereby deficit scores (determined by deficit item and level) were deducted from the total score of 58 [27]. It is noted that motor functioning was not systematically evaluated with Fugl-Meyer Assessment (FMA) as this type of patients generally had no complains on motor functioning compared to somatosensory deficits during the visit to our hospital.

### 2.4 Resting Motor Threshold (RMT) and Corticospinal Excitability

Each session started with the assessment of resting motor threshold (RMT). RMT was defined as the minimum intensity to induce motor-evoked potentials (MEPs) >0.05 mV of the first dorsal interosseous (FDI) muscle in 5/10 trials. Single pulses to the hand region of the motor cortex (45° to the midline, handle pointing backward) at 5 s ± 10% jitter intervals were sent by a figure-eight coil connected to

**Table 1. Demographics and clinical information of patients. Higher numbers represent better somatosensory functioning in the last column.**

Gender	Age	Lesions	Duration (month)	Somatosensory function
F	69	Left thalamus	2	57
M	70	Right thalamus	1	51
M	68	Right temporal cortex	1	50
M	58	Left thalamus	0.1	49
F	68	Right pons	0.5	49
F	73	Left thalamus	1	48
F	52	Right pons	1	51
M	66	Right ventricle	5	55
M	67	Right basal ganglia	1	53
F	57	Left temporal cortex	0.1	50
M	56	Left pons	0.5	56
M	57	Left midbrain	1	54
F	59	Left ventricle	0.1	49
M	56	Left centrum semiovale	0.3	51
F	67	Right thalamus	0.1	56
M	67	Right thalamus	0.1	51

a Magstim Rapid<sup>2</sup> system (Magstim Company Ltd, Whitland, UK). RMT over the ipsilesional and contralesional motor cortex were assessed respectively.

Corticospinal excitability was measured with MEP amplitude and CSP at rest and during a sustained voluntary FDI muscle contraction respectively [21,35]. A total of 40 single pulses (20 of each) were consecutively delivered to the hand region of the motor cortex at 110% RMT (45° to the midline, handle pointing backward). It is worth noting that CSP was evaluated following MEP as the muscle contraction during CSP may have an impact on MEP amplitude [36]. Corticospinal excitability was evaluated from both sides of the brain respectively and the sequence was counterbalanced across hemispheres.

### 2.5 Data Analyses

MEP amplitude was calculated by peak-to-peak amplitude. The calculation of CSP duration was based on the Mean Consecutive Difference (MCD) [37], which was highly recommended by a recent expert review [35]. The MCD methodology is briefly described here: (1) All silent period trials were rectified using the absolute value and then were averaged; (2) The MCD of 100 ms EMG data before a TMS pulse was calculated, in which the MCD is the mean successive difference between individual data points; (3) Thresholds were set at:  $\pm\text{MCD} \times 2.66$  (i.e., 3 standard deviations), which covers 99.76% of possible pre-TMS EMG data points; (4) Silent period onset was determined as the time point at which the post-TMS EMG falls below the variation threshold for three consecutive data points, while the silent period offset was defined as the point at which the post-TMS EMG returns above the variation threshold for three consecutive data points.

### 2.6 Statistical Analyses

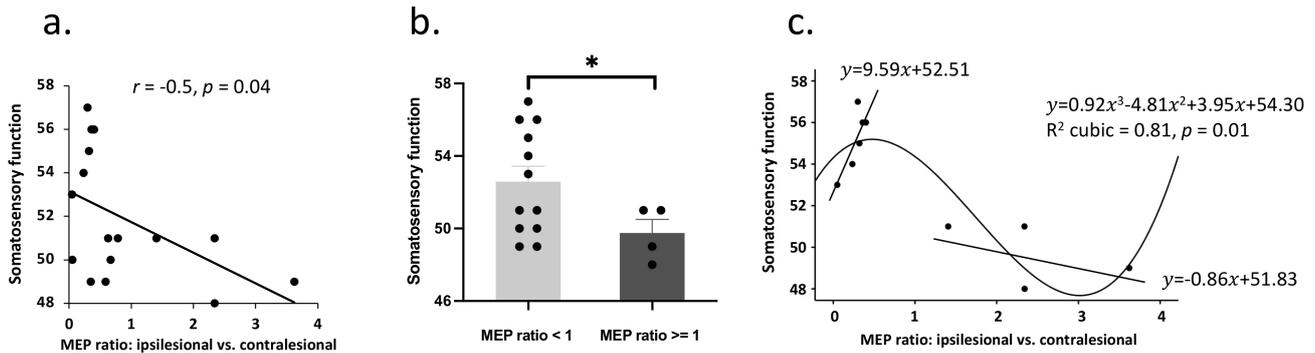
Paired *T*-tests were performed to compare the ipsilesional and contralesional motor cortex in terms of RMT, MEP amplitude, and CSP. We have also calculated the ratio between the ipsilesional and contralesional motor cortex in terms of corticospinal excitability and associated them with somatosensory function using bivariate correlations and partial correlations controlling for covariates. Independent *T*-tests were performed where possible when patients were categorised based on results from corticospinal excitability (i.e., MEP ratio, see Results section). All the significant statistics were reported at  $p < 0.05$ . Somatosensory function was further broken down into sensory dimensions to explore the sensory profiles.

### 2.7 Supplementary Analyses

In addition to MEP amplitude and CSP, we have also evaluated MEP latency and its association with somatosensory functioning. MEP latency was defined as the time point where rectified EMG signals exceeded two standard deviations of the mean background EMG of 100 ms before the stimulus artifact [38,39]. A paired *T*-test was performed to compare MEP latency from the ipsilesional and contralesional motor cortex.

## 3. Results

The demographics and clinical information of patients were presented in Table 1. Patients had a mean age of 63.13 (male vs. female, 9:7). Lesions of the brain were mainly distributed in the thalamus, followed by damages to the brainstem and cortical regions such as the temporal cortex. Somatosensory functioning was overall preserved in our patients with a mean score of 51.88 out of a total score of 58. Patients had normal (5,  $n = 9/16$ ) or slightly impaired (4,  $n$



**Fig. 2. Corticospinal excitability and the association with somatosensory function.** (a) group comparison indicated decreased somatosensory functioning in patients with higher MEP amplitude on the ipsilesional (vs. contralesional) motor cortex. (b) A linear model was fitted between MEP ratio and somatosensory function in patients with a larger MEP amplitude in the ipsilesional compared to the contralesional motor cortex. This model was not significant potentially due to a small sample size. (c) In patients with well preserved somatosensory function, increased MEP ratio was associated with better somatosensory function. \* denotes  $p < 0.05$ ; MEP denotes motor-evoked potential.

= 7/16) muscle strength as indexed by the muscle strength grading scale (0–5).

A paired  $T$ -test indicated comparable MEP amplitude ( $p > 0.05$ ), CSP ( $p > 0.05$ ), and RMT ( $p > 0.05$ ) in the ipsilesional vs. contralesional motor cortex. There was a negative correlation between the MEP ratio (ipsilesional vs. contralesional motor cortex) and somatosensory functioning ( $r = -0.50$ ,  $p = 0.04$ ) (Fig. 2a). Raw values were used here but this result remained the same when z-scores were used.

It is clear that this negative relationship between MEP ratio and somatosensory function was driven by the uncommon presentation of patients with even larger MEPs in ipsilesional vs. contralesional motor cortex. An independent  $T$ -test (decided by equal MEP amplitude) was further performed on somatosensory function, which revealed worse somatosensory function in patients with a larger MEP amplitude in the ipsilesional compared to the contralesional motor cortex ( $t_{10.77} = -2.50$ ,  $p = 0.03$ ) (Fig. 2b).

We further performed curve estimation between MEP ratio and somatosensory function. A cubic model could best fit the relationship between MEP ratio and somatosensory function ( $R^2$  cubic = 0.81,  $p = 0.01$ ), in a sample consisting of patients with well-preserved somatosensory function ( $>$ median,  $n = 6$ ) and patients with a larger ipsilesional MEP ( $n = 4$ ) (Fig. 2c). Piecewise linear functions further revealed a positive relationship in patients with well-preserved somatosensory function ( $R^2$  linear = 0.67), as well as a negative relationship in patients with a larger ipsilesional MEP ( $R^2$  linear = 0.27).

No significant relationship was found between CSP changes and somatosensory functioning ( $p > 0.05$ ). There was a significant covariance between changes in MEP ratio and CSP ratio ( $r = 0.50$ ,  $p = 0.02$ ). There was also no significant association between somatosensory functioning and RMT ratio or RMT in either side ( $p_s > 0.05$ ), but we

did observe a strong negative correlation between RMT ratio (ipsilesional vs. contralesional motor cortex) and MEP ratio ( $r = -0.78$ ,  $p = 0.001$ ).

A breakdown of somatosensory functioning indicated most damage to subjective sensations (percent change = 29.33%), followed by superficial sensations (16.65%), deep sensations (5.69%), and cortical sensations (1.67%).

Supplementary analyses indicated no significant difference in MEP latency between the ipsilesional and contralesional motor cortex ( $t_{20} = -1.03$ ,  $p = 0.32$ ). Further correlation analysis revealed no significant relationship between MEP latency and somatosensory functioning ( $p > 0.05$ ).

#### 4. Discussion

This study was designed to evaluate the relationship between corticospinal excitability and somatosensory deficits following stroke. Results indicated that the uncommon presentation of larger MEPs in ipsilesional vs. contralesional motor cortex was associated with worse somatosensory function compared to those with a smaller MEP in ipsilesional motor cortex. Moreover, increased MEP ratio (ipsilesional vs. contralesional motor cortex) was associated with better somatosensory function in patients with well preserved somatosensory function. MEP and CSP changes in the ipsilesional (vs. contralesional) motor cortex were parallel following stroke.

Our data indicated a negative relationship between MEP ratio (ipsilesional vs. contralesional motor cortex) and somatosensory functioning. However, this finding does not necessarily have clinical implications for somatosensory improvement as it was driven by patients with larger MEPs in ipsilesional vs. contralesional motor cortex. Our data indicated individual differences in MEP ratio whereby some patients (4/16, 25%) demonstrated an even larger MEP amplitude in the ipsilesional vs. contralesional motor cortex

(see Fig. 2). Further analysis demonstrated a significant lower somatosensory functioning in patients with a larger MEP amplitude in the ipsilesional motor cortex compared to those with a smaller one. This result highlights the clinical implications for MEP ratio in which a larger MEP amplitude in the ipsilesional versus contralesional motor cortex indicates more prominent somatosensory deficits following stroke. The ipsilesional motor pathway is believed to generate a smaller MEP compared to the contralesional hemisphere [40]. However, it remains to be determined why a certain proportion of patients respond with a reverse pattern of MEP amplitude between the two hemispheres [41]. We also tried to model the relationship and present a potential negative relationship between MEP ratio and somatosensory functioning in patients with a larger MEP amplitude in the ipsilesional motor cortex. If this model reaches statistical significance in future studies with a larger sample, our preliminary finding could indicate the significance for somatosensory improvement by rebalancing corticospinal excitability between two hemispheres.

In addition, an increased MEP ratio (ipsilesional vs. contralesional motor cortex) was associated with better somatosensory function in patients with well-preserved somatosensory function as determined by the median of the overall sample. As discussed earlier, the effects of motor cortex rTMS have not been evaluated on somatosensory deficits in spite of a relatively large body of evidence on motor rehabilitation [11,12]. Our data therefore provide novel findings that increasing MEP ratio (ipsilesional vs. contralesional motor cortex) may be able to indicate somatosensory improvement following stroke. In line with the motor recovery with rTMS, this could be achieved by exciting the ipsilesional motor cortex and/or inhibiting the contralesional motor cortex [9,10]. Overall, our preliminary findings demonstrate the potential of corticospinal excitability in guiding rTMS treatments for somatosensory deficits following stroke.

It is interesting to find somatosensory functioning to be associated with MEP ratio but not with CSP ratio. It is consistent with our previous study in which sensory transmission was able to inhibit corticospinal excitation (i.e., MEP) rather than inhibition (i.e., CSP) [21]. Although we observed a significant covariance between changes in MEP ratio and CSP ratio, CSP measurements were not able to predict changes in somatosensory functioning whatsoever. These results indicate that MEP is more directly associated with changes in somatosensory functioning following stroke which could serve to direct TMS interventions for somatosensory improvement.

It would be more straightforward to consider targeting the primary sensory cortex (S1) for the improvement of somatosensory function following stroke. There is extensive evidence indicating TMS to be able to modulate S1 response in healthy subjects (for a review see [16]). For instance, a line of evidence indicates that stimulation of the

sensory cortex is able to drive somatosensory cortex excitability and tactile sensations [42–44]. In stroke patients, one study further demonstrated daily S1-TMS for five days to facilitate motor learning [17], and one recent study combined S1-TMS with sensory stimulation (including sensory training, mirror therapy, and transcutaneous electrical nerve stimulation) to improve somatosensory function [18]. Overall, the efficacy of S1 stimulation is well supported for the improvement of somatosensory function following stroke. Moreover, stimulation of the dorsolateral prefrontal cortex is also able to modulate sensations like pain experience [45–47]. These findings are not mutually exclusive with our data. Future studies may wish to evaluate rTMS efficacy in post-stroke somatosensory functioning by targeting different brain regions.

This study was limited as it only evaluated MEP and CSP of the corticospinal pathway. Other protocols like short interval intracortical inhibition (SICI) and intracortical facilitation (ICF) are further able to evaluate GABA<sub>A</sub>-mediated and glutamatergic neurotransmissions of the corticospinal pathway [48–50]. In addition, somatosensory deficits could also be evaluated with neurophysiological techniques such as MRI, and TMS [51–53]. Although it is well established that motor impairments could change corticospinal excitability [54], a quick assessment of muscle strength revealed fairly normal to normal muscle strength of our patients and thus no relationship with corticospinal excitability was revealed in our data. However, motor functioning was not systematically examined with Fugl-Meyer Assessment (FMA) here [33,34]. Although muscle strength had no clear impact on the relationship between MEP ratio and somatosensory function, it remains to be determined how specific domains of motor impairments evaluated by FMA could modulate this pattern of relationship. It is noted that the cubic model could significantly fit the relationship between MEP ratio and somatosensory function in patients with well-preserved somatosensory function or patients with a larger ipsilesional MEP. The rest of the patients did not fit into the model. Nonetheless, the above two groups of patients had clear clinical implications.

Our findings provide insights for future studies. Our findings indicate the need for future investigations with a larger sample and more diversity in the phase of stroke. Building on these findings, future TMS protocols could be designed to improve somatosensory deficits by targeting corticospinal excitability following stroke.

## 5. Conclusions

To conclude, MEP ratio between the ipsilesional and contralesional motor cortex could indicate the improvement for somatosensory functioning following stroke. These findings indicate the importance to increase MEP ratio in patients with a lower ipsilesional MEP amplitude, as well as to rebalance corticospinal excitability in patients with an excessive ipsilesional MEP amplitude.

## Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author (XC) on reasonable request.

## Author Contributions

ZG, JW, and XC contributed to study design, data collection, data analysis, and writing-up. QC, HF, JH, ZH, YJ, BT, YW, and YC contributed to data collection and manuscript drafting. All authors listed here have contributed significantly to this study and have agreed for this study to be published. All authors read and approved the final manuscript.

## Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee in the Affiliated Hospital of Hangzhou Normal University (2021-E2-HS-029) and was conducted in accordance with the Declaration of Helsinki. All participants provided a written informed consent before study commencement.

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Not applicable.

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## Conflict of Interest

The authors declare no conflict of interest.

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