



## Increased facilitation of the primary motor cortex in de novo Parkinson's disease

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### ABSTRACT

**Introduction:** Paired-pulse transcranial magnetic stimulation (TMS) is useful to estimate the balance between inhibitory and facilitatory circuits of the primary motor cortex (M1) in Parkinson's disease (PD). Results of earlier studies are, however, incongruent: some reports describe normal short-interval intracortical inhibition (SICI), but others describe reduced SICI. We hypothesize that exaggerated intracortical facilitation masks normal inhibition, and that a triple-pulse method can reveal masked inhibition in PD.

**Methods:** Ten PD patients who had not been exposed to dopaminergic medications were enrolled. Results were compared with those obtained from 10 age-matched healthy volunteers. We measured TMS-elicited motor evoked potential (MEP) as an index of M1 excitability. We tested SICI, intracortical facilitation (ICF), and short-interval intracortical facilitation (SICF), which has three distinct facilitatory peaks, using the paired-pulse TMS paradigm. A triple-pulse protocol, SICI + SICF, was investigated as described in our earlier study. This protocol examined SICF in the presence of SICI, thereby allowing our test of true inhibitory influence on a specific component of MEP-generating mechanism known as I3 wave.

**Results:** In PD patients, SICI estimated using the conventional method was decreased, whereas SICF was enhanced around its second peak out of the three. Results for SICI + SICF were comparable between PD patients and healthy controls, suggesting normal inhibition of I3 waves in PD patients.

**Conclusion:** We confirmed the SICF enhancement in drug naïve PD patients. We propose that I3 wave inhibition by a subthreshold pulse shown by SICI paradigm is unaffected in PD. The triple-pulse method can reveal masked inhibition.

### 1. Introduction

Motor symptoms are the major feature of Parkinson's disease (PD). Pathological changes lie predominantly in the nigrostriatal dopaminergic system, but other structures in the basal ganglia-thalamocortical loop play cardinal roles [1,2]. The primary motor cortex (M1) is engaged in this loop, serving as the final output of the motor system to the body. Investigation of the balance between excitation and inhibition in M1 is therefore relevant for evaluating motor function in PD. In fact, networks involving M1 are affected at an early stage of dopaminergic loss [3].

Paired-pulse transcranial magnetic stimulation (TMS) has attracted interest as a probe to investigate the excitation and inhibition of M1.

Different paired-pulse protocols can assess different inhibitory [4] and facilitatory [5] networks in human M1, each of which is presumably based on a distinct pathway mediated by a distinct neurotransmitter [6]. Results of earlier studies of PD are, however, not congruent. Some reported normal [7,8] although others reduced [9,10] short-interval intracortical inhibition (SICI), which is a marker for gamma-aminobutyric acid A (GABA<sub>A</sub>)-mediated inhibition within the M1 [11,12].

We hypothesized that two factors be regarded as estimating M1 excitability in PD patients using paired-pulse TMS: interaction between inhibition and facilitation, and influence of medication. In human TMS studies, it is difficult to activate inhibitory or facilitatory networks purely, simply, and selectively. Consequently, what can be estimated should necessarily be a mixture of inhibition and facilitation.

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Medications for PD, which are associated with neurotransmitters, can be another confounding factor. Since chronic treatment of such medications can alter network balance and hence TMS results, investigation without influence of medication is important.

Can we estimate true inhibition from net inhibition studied with paired-pulse TMS? Inhibition revealed using conventional SICI has been proposed as contaminated by simultaneous facilitation [13]. This proposal seemingly implies that decreased inhibition can be attributed to exaggerated facilitation when SICI is tested conventionally. Indeed, this idea was confirmed experimentally in a later study by demonstrating enhanced short-interval intracortical facilitation (SICF) in PD patients [14]. This study demonstrated that decreased SICI can be, at least partly, a result of enhanced SICF. If some method was able to estimate the amount of inhibition without contamination, then it would be possible to show true inhibition in PD patients. Along this line, an earlier report by the authors described a triple-pulse paradigm combining SICI and SICF in a healthy population [15], which we designate as SICI + SICF protocol. In brief, using this protocol, SICF is canceled out under simultaneous SICI in a specific condition, which we propose as a measure of the pure inhibitory network in the M1.

Exposure to dopaminergic medication is another potentially confounding factor when estimating brain function. A review of earlier studies of paired-pulse TMS of PD patients revealed varied medication status. Because medications can affect paired-pulse TMS results [6], a group of drug naïve PD patients would be the best population to investigate pure and early change occurring in PD M1. Few studies have investigated SICI or SICF in PD patients without dopaminergic medication.

In this study, based on the background presented above, we aimed at elucidating true inhibition within M1 in de novo PD patients. In addition to conventional SICI, intracortical facilitation (ICF), and SICF, the results obtained using a more or less novel method, i.e. SICI + SICF, were compared between PD patients and age-matched healthy volunteers. Some findings were presented at the International Congress of Parkinson's disease and Movement Disorders 2018, Hong Kong.

## 2. Methods

### 2.1. Participants

We examined 10 patients with PD who were naïve to dopaminergic medication and 10 age-matched healthy volunteers as a control group (HC). Characteristics of the participants are presented in Tables 1 and 2. Diagnosis of PD was based on the UK Brain Bank Criteria [16]. Patients with severe tremor to interfere with the recordings were not recruited. None had contraindication to TMS [17]. Written informed consent was obtained from all participants according to the study protocol approved by the local ethics committee of the Graduate School of Medicine, The University of Tokyo.

**Table 1**  
Clinical features of patients with Parkinson's disease.

| No. | Age (y) | Sex | Disease duration (y) | More affected side | UPDRS part III |
|-----|---------|-----|----------------------|--------------------|----------------|
| 1   | 72      | M   | 1                    | R                  | 20             |
| 2   | 62      | M   | 3                    | R                  | 28             |
| 3   | 69      | M   | 9                    | R                  | 28             |
| 4   | 68      | M   | 2                    | R                  | 20             |
| 5   | 47      | M   | 5                    | R                  | 13             |
| 6   | 76      | M   | 2                    | L                  | 29             |
| 7   | 51      | F   | 4                    | L                  | 12             |
| 8   | 66      | F   | 2                    | R                  | 29             |
| 9   | 64      | M   | 1                    | R                  | 11             |
| 10  | 64      | M   | 1                    | L                  | 10             |

**Table 2**  
Data summarized by group.

|                                       | HC          | PD          | P-value           |
|---------------------------------------|-------------|-------------|-------------------|
| Age (y)                               | 62.7 ± 10.6 | 63.9 ± 8.9  | 0.79              |
| Sex (female:male)                     | 3:7         | 2:8         | 0.61 <sup>a</sup> |
| Disease duration                      | n.a.        | 3.0 ± 2.5   | n.a.              |
| RMT (%MSO)                            | 59.6 ± 10.3 | 56.2 ± 13.6 | 0.54              |
| AMT (%MSO)                            | 39.4 ± 5.9  | 40.6 ± 10.5 | 0.76              |
| Test intensity for SICI/ICF (%MSO)    | 77.4 ± 10.9 | 74.0 ± 16.5 | 0.59              |
| Baseline MEP for SICI/ICF (mV)        | 0.48 ± 0.16 | 0.49 ± 0.21 | 0.95              |
| Test intensity for SICF (%MSO)        | 79.2 ± 10.3 | 73.1 ± 17.0 | 0.34              |
| Baseline MEP for SICF (mV)            | 0.49 ± 0.25 | 0.50 ± 0.19 | 0.97              |
| Test intensity for SICI + SICF (%MSO) | 90.4 ± 8.4  | 78.8 ± 16.5 | 0.06              |
| Baseline MEP for SICI + SICF (mV)     | 0.51 ± 0.28 | 0.46 ± 0.16 | 0.65              |

n.a., not applicable; HC, healthy control; PD, Parkinson's disease; %MSO, percentage of maximum stimulator output.

<sup>a</sup> Chi-square test; otherwise the *p*-values are obtained using *t*-tests.

### 2.2. Electromyography

Surface electrodes were placed over the first dorsal interosseous (FDI) muscle on the more affected side in PD and on the right side in HC with the belly-tendon montage. Signals were filtered from 100 Hz to 3 kHz, digitized at 20 kHz, and stored in a computer for later off-line analyses.

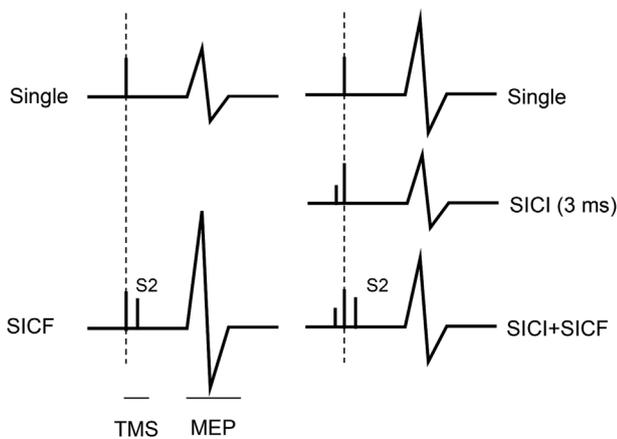
### 2.3. Transcranial magnetic stimulation

TMS was conducted using up to three stimulators (Magstim200<sup>2</sup>; The Magstim Co. Ltd., UK) and a hand-held figure-of-eight coil (70-mm; The Magstim Co. Ltd.). Three stimulators were connected using a custom-made connecting module so that outputs from the three stimulators were delivered to a single coil. The coil was held to induce a current in the latero-posterior to medio-anterior direction in the brain, approximately 45° from the sagittal plane. The hand motor area was determined as the point where the largest MEP was elicited constantly. This point was marked with a felt pen for coil re-positioning. Resting motor threshold (RMT) was defined as the lowest stimulus intensity that elicited at least 50 μV MEP in more than half of the trials in the resting FDI. Furthermore, the active motor threshold (AMT) was defined as the lowest stimulus intensity that elicited at least 100 μV MEP in more than half of the trials under slight voluntary contraction of FDI. Stimulus intensity necessary to obtain MEP with 0.5 mV peak-to-peak amplitude, on average, was estimated and was designated as SI<sub>0.5</sub>. The stimulus intensity was expressed as a percentage of the maximum stimulator output (%MSO).

### 2.4. Study procedure

SICI/ICF and SICF were tested separately. Participants were asked to relax the tested hand. Trials with contamination by voluntary contraction before the TMS pulse were rejected off-line later. The first or conditioning stimulus for SICI/ICF was set at 0.9 AMT, with the second, a test pulse, at SI<sub>0.5</sub>. Paired-pulse trials with eight inter-stimulus intervals (ISIs; 2, 3, 4, 5, 6, 8, 10, and 15 ms) were tested 10 times each, along with 10 trials with single-pulse TMS to obtain a baseline. The order of trials was randomized using software (Pulse Timer II; Medical Try System, Tokyo, Japan). For SICF, the first stimulus (S1) was set at SI<sub>0.5</sub>; the second (S2) was set at 1.4 AMT, which was close to or just below RMT (Table 2). ISIs from 1.5 to 5.0 ms in 0.5 ms steps were tested. Ten trials for each and ten single-pulse trials were given in randomized order.

The triple-pulse paradigm SICI + SICF was conducted based on our earlier study [15], with the key concept depicted in Fig. 1. The first pulse was delivered at 1.2 AMT. The intensity for the second one was adjusted so that the double pulse with an ISI of 3 ms caused MEPs with



**Fig. 1.** Schematic description of the SICI + SICF paradigm in comparison to SICF.

Vertical bars denote TMS pulses. The resulting MEPs are shown on the right side of the bars. *Left:* In SICF, adding the second pulse (S2) results in larger MEP amplitude at particular interstimulus intervals (ISI) through I-wave facilitation. *Right:* In SICI + SICF, facilitation is measured by comparing the triple-pulse condition (bottom) to the paired-pulse, SICI condition (middle), so that the MEP amplitude in the SICI condition is comparable to the single-pulse condition in SICF. At the baseline, i.e. SICI condition, I3 wave is suppressed, resulting in smaller MEP. Therefore, in the SICI + SICF condition, further I3 facilitation is presumed to be precluded.

0.5 mV amplitude on average. The third, last pulse was set at 1.4 AMT, i.e., corresponding to S2 of SICF. The ISI between the first and second pulses was fixed at 3 ms. Eight ISIs between the second and third pulses were included similarly to SICF (Fig. 1). Ten MEPs were collected for each ISI. Ten trials were conducted using single-pulse TMS and paired-pulse TMS using the first and second pulse alone as well.

### 2.5. Data analyses

MEP amplitudes were normalized for SICI/ICF, SICF, and SICI + SICF separately in each participant. As a baseline for normalization, the mean MEP amplitude for single-pulse TMS (SICI/ICF and SICF), or that for the double (i.e., the first and second) pulse (SICI + SICF) was calculated (Fig. 1). Values greater than one indicate facilitation, whereas those less than one indicate inhibition.

Results of the paired-pulse and triple-pulse measurements were inspected using analysis of variance (ANOVA) for SICI/ICF, SICF, and SICI + SICF separately. Results of SICI/ICF were analyzed with a

between-subjects factor GROUP with two levels (HC and PD) and a within-subject factor ISI with eight levels (2, 3, 4, 5, 6, 8, 10, and 15 ms). Similarly, analysis of SICF and SICI + SICF used GROUP and ISI (1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, and 5.0 ms) as factors of ANOVA. When necessary, Greenhouse–Geisser method was applied to correct for non-sphericity. If ANOVA revealed a significant result, then *post-hoc* group comparison between HC and PD was performed with *t*-test.

The analyses were conducted using software (SPSS Statistics ver. 25; IBM Corp.). Significance was inferred for  $p < 0.05$ . Values were reported as mean  $\pm$  standard deviation unless otherwise described.

### 3. Results

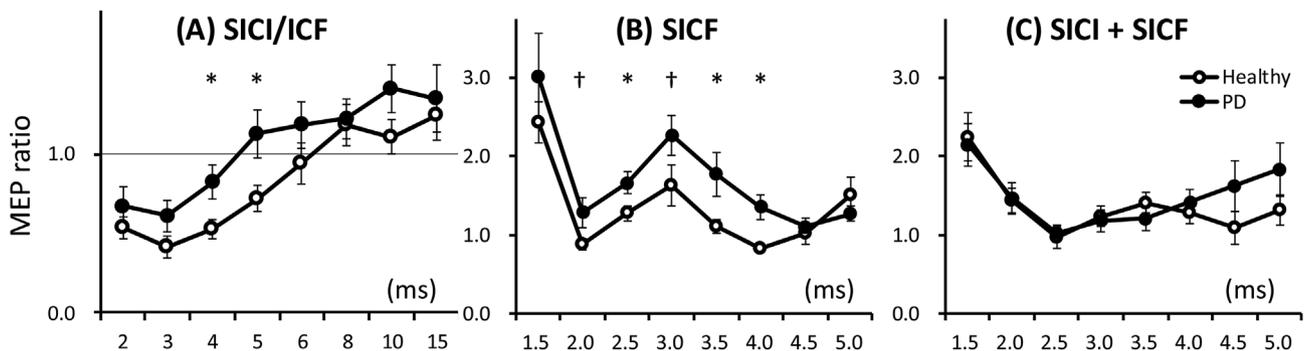
No participants reported side effects of TMS. Two groups were similar in terms of age, RMT, AMT, test intensity, and baseline MEP amplitude (Table 2). We found a trend for higher test intensity in HC in SICI + SICF, which probably reflected that more inhibition was produced by the first pulse in this protocol in HC. This idea is supported by a trend towards larger MEP amplitude with single-pulse TMS in HC ( $2.23 \pm 1.46$  mV) than PD patients ( $1.31 \pm 0.69$  mV,  $p = 0.09$ ) in the SICI + SICF. Representative waveforms are presented as Supplementary Fig. 1 with selected ISIs.

Results of SICI/ICF are presented in Fig. 2A, depicting less SICI in PD patients. ANOVA revealed a main effect of ISI ( $F_{7,126} = 21.14$ ,  $p < 0.001$ ), whereas the main effect of GROUP ( $F_{1,18} = 3.07$ ,  $p = 0.097$ ) and ISI\*GROUP interaction ( $F_{7,126} = 0.78$ ,  $p = 0.60$ ) were not. *Post-hoc* analysis indicated significance at 4 ms ( $p = 0.029$ ) and 5 ms ( $p = 0.027$ ), suggesting less inhibition in PD patients at these ISIs.

SICF was enhanced in PD patients around its second peak (Fig. 2B). Both main effects were significant (ISI:  $F_{2,6,46.0} = 16.34$ ,  $p < 0.001$ , GROUP:  $F_{1,18} = 5.07$ ,  $p = 0.037$ ), although their interaction was not ( $F_{7,126} = 1.24$ ,  $p = 0.29$ ). *Post-hoc* analysis revealed significant difference at 2.5 ms ( $p = 0.031$ ), 3.5 ms ( $p = 0.045$ ), and 4.0 ms ( $p = 0.007$ ). Additionally, a trend was apparent for 2.0 ms ( $p = 0.058$ ) and 3.0 ms ( $p = 0.096$ ).

Quite in contrast with SICF, HC, and PD were similar under the SICI + SICF paradigm (Fig. 2C). The main effect of ISI was significant ( $F_{3,7,66.3} = 8.04$ ,  $p < 0.001$ ), but *post-hoc* tests revealed no group difference (all  $p > 0.17$ ). Neither the main effect of GROUP ( $F_{1,18} = 0.44$ ,  $p = 0.52$ ) nor the interaction ( $F_{7,126} = 1.21$ ,  $p = 0.30$ ) was significant.

We found no significant correlation between the degree of SICF and clinical severity as indicated by the UPDRS part III. The UPDRS part III was not correlated with the other physiological parameters, i.e., SICI or SICI + SICI + SICF, either. Correlation between SICI (ISI = 4 and 5 ms) and SICF (ISI = 2.5, 3.5, and 4.0 ms) were not significant either



**Fig. 2.** Time course of the MEP ratio.

Time courses of SICI/ICF (A), SICF (B), and SICI + SICF (C) are shown. The X-axis shows the interstimulus interval (ISI) in ms; the Y-axis shows the MEP ratio. Circles denote healthy controls (HC), whereas dots denote patients with Parkinson's disease (PD).

(A) SICI is decreased in PD patients at 4 and 5 ms-ISI. (B) SICF is enhanced in PD patients at around the second peak, i.e. 2.5–3.0 ms. (C). Error bars represent the standard error of the mean.

\* denotes significance ( $p < 0.05$ ).

† denotes a trend ( $0.05 \leq p < 0.10$ ).

in HC or PD (all  $p > 0.25$ ).

#### 4. Discussion

We demonstrated in de novo PD patients that SICI estimated using the conventional method is reduced, but that this reduction can be attributed to contamination of SICF, given comparable suppression of the second peak of SICF in the SICI + SICF. Three key points are useful to discuss our results. (1) SICI is mediated mainly by the inhibition of late I-waves, especially I3 wave. (2) The second peak of SICF is likely to be attributable to additional recruitment of the I3 component. (3) We earlier argued cancellation of I3 facilitation in the SICI + SICF protocol.

Single-pulse TMS provokes multiple descending volleys originating from a network in M1. The multiple descending volleys have distinct components termed D-wave and a few I-waves, among which I1 wave is presumed to have the lowest threshold in the current study [18]. Although functional correlates of the D-wave and I-waves are not completely elucidated, later (i.e., I2 and I3) waves might be associated with fine hand movements [19]. Different paired-pulse protocols can modulate different I-waves selectively; SICI results from reduction of I3 (and partly I2) wave [20,21]. Few studies have investigated modulation of each I-wave in PD. Hanajima et al. demonstrated that SICI tested with an opposite coil orientation can result in normal inhibition, probably because the coil orientation mainly induces I3-wave rather than I1-wave [22].

SICF is regarded as resulting from I-wave facilitation: the first peak of SICF is produced by an additional I2 wave, the second by I3 wave, and so forth. This inference was based on an observation that intervals between the multiple descending volleys are approximately 1.5 ms [23], which is comparable to intervals found between the peaks of SICF [5,13,15,24,25]. Later studies confirmed this idea experimentally for the first peak of SICF at 1.5 ms [12,26]. The enhanced second peak of SICF in PD patients is most likely representative of I3-wave facilitation.

Earlier, we sought to elucidate interaction between inhibitory and facilitatory circuits within M1 using the SICI + SICF protocol [15]. Our present results resemble those presented in the original report, describing suppression of the second peak of SICF. Later I-waves including I3 wave were inhibited by the first pulse in the SICI + SICF, which was likely to preclude later I-wave facilitation that should have been invoked by the third pulse. Importantly, this suppression of the second peak of SICF was observed comparably in de novo PD patients (Fig. 2C).

Taken together, a plausible explanation for the results is that the primary change in PD M1 is an enhanced facilitatory process represented by SICF. SICI studied using the conventional method appeared to decrease, probably because of “contamination” by SICF [13], which is exaggerated in PD patients. In the paired-pulse paradigm testing SICI, facilitatory circuits would invariably be activated along with inhibitory ones. Consequently, we observe a net inhibition or facilitation. The situation can contrast greatly to the SICI + SICF (triple-pulse) protocol, thereby facilitating our evaluation of pure inhibition. The SICI + SICF paradigm uses 3-ms SICI condition as a baseline (Fig. 1). In this baseline condition, the first pulse suppressed the I3 component which would have been induced by the second pulse, even though the resulting MEP elicited by the double pulse might be contaminated by SICF. Then, the third pulse was unable to facilitate the I3 component any further, leading to suppression of the second peak of SICF in the SICI + SICF paradigm (Fig. 1). Interestingly, MacKinnon et al. reported reduced SICI in PD with higher conditioning intensity [7]. Given SICF is increased with higher intensity, our results are in line with the previous study.

For our study population, we found no significant correlation between the (enhanced) SICF and UPDRS part III. A report of an earlier study described that the medication-induced change in SICF was correlated with that in UPDRS [14]. Future studies should explore the clinical meaning of the enhanced SICF. The fact that we studied only de novo patients in their off state might partly explain the lack of

correlation.

We investigated inhibitory and facilitatory circuits in de novo PD patients to elucidate initial changes happening in the disorder. Few reports of the relevant literature describe studies that have explored this same topic. Our results agree with those of an earlier report [27] in terms of SICI, but they reported decreased ICF. Such a discrepancy should be resolved by a larger study. A good future direction would be testing acute and chronic influences of dopaminergic and non-dopaminergic medications for PD patients. Many measures of M1 inhibition/facilitation were reportedly affected by medications [9,10,14,28,29], but some were not [8]. By incorporating our new protocol of SICI + SICF, relations between intracortical inhibition/facilitation and (especially dopaminergic) medications can be illustrated better.

This study has several limitations. First of all, the sample size was small. Thus, statistical analysis could have been underpowered, leaving a possibility that some of the non-significant results may turn out to be significant with a larger sample size. Second, the study population was not completely homogeneous. Importance of homogeneity in terms of clinical features cannot be more emphasized. Since we recruited only PD patients naïve to dopaminergic medications to reduce heterogeneity, our results would add new insights in this particular population. Nevertheless, a more confirmatory, larger study is certainly needed to reveal precise cortical function and dysfunction of drug-naïve PD.

In conclusion, we argue that the apparent reduction of GABAergic function inferred from results of conventional SICI in PD is an epiphenomenon of exaggerated SICF. Addition of SICI + SICF protocol might delineate a true decrease of inhibition and contamination of facilitation.

#### Conflicts of interest

The authors have no conflict of interest to declare. Financial contributions are described in acknowledgements below.

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#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.parkreldis.2019.07.022>.

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