Increased motor cortical facilitation and decreased inhibition in Parkinson disease

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ABSTRACT

Objective: To identify the changes in motor cortical facilitatory and inhibitory circuits in Parkinson disease (PD) by detailed studies of their time courses and interactions.

Methods: Short-interval intracortical facilitation (SICF) and short-interval intracortical inhibition (SICI) were measured with a paired-pulse paradigm using transcranial magnetic stimulation. Twelve patients with PD in both ON and OFF medication states and 12 age-matched healthy controls were tested. The first experiment tested the time course of SICF in PD and controls. The second experiment tested SICI at different times corresponding to SICF peaks and troughs to investigate whether SICI was affected by SICF.

Results: SICF was increased in PD OFF state and was reduced by dopaminergic medications. The reduction in SICF from the OFF to ON state correlated with the improvement in PD motor signs. SICI was reduced in PD OFF state and was only partially normalized by dopaminergic medications. At SICF peaks, improvement in SICI with medication correlated with improvement in PD motor sign. Principal component analysis showed that variations of SICF and SICI were explained by the same principal component only in the PD OFF group, suggesting that decreased SICI in the OFF state is related to increased SICF.

Conclusions: Motor cortical facilitation is increased and inhibition is decreased in PD. Increased cortical facilitation partly accounts for the decreased inhibition, but there is also impairment in synaptic inhibition in PD. Increased cortical facilitation may be a compensatory mechanism in PD. *Neurology*® 2013;80:1746-1753

GLOSSARY

AMT = active motor threshold; **ANOVA** = analysis of variance; **GABA** = γ -aminobutyric acid; **ICF** = intracortical facilitation; **ISI** = interstimulus interval; **I-wave** = indirect wave; **M1** = primary motor cortex; **MEP** = motor-evoked potential; **PD** = Parkinson disease; **RMT** = rest motor threshold; **S1** = first stimulus; **S2** = second stimulus; **SICF** = short-interval intracortical facilitation; **SICI** = short-interval intracortical inhibition; **TMS** = transcranial magnetic stimulation; **UPDRS** = Unified Parkinson's Disease Rating Scale.

The cardinal symptoms of Parkinson disease (PD) arise from dysfunctions of the motor system.¹ Cortical motor commands originate from the primary motor cortex (M1), which is a primary target of basal ganglia output. The balance and interactions between cortical inhibitory and facilitatory circuits determine motor cortical excitability and output. Short-interval intracortical inhibition (SICI) represents a cortical inhibitory process that is measured by paired-pulse transcranial magnetic stimulation (TMS) with a subthreshold first stimulus (S1) suppressing the motor-evoked potential (MEP) generated by a subsequent suprathreshold second stimulus (S2) at interstimulus intervals (ISIs) of 1 to 5 milliseconds.² Short-interval intracortical facilitation (SICF) represents a cortical facilitatory process whereby a threshold-level S2 facilitates a supra-threshold S1 at 3 distinct peaks of ISIs (1.1–1.5, 2.3–2.9, and 4.1–4.4 milliseconds).³ The ISIs and stimulus intensities for eliciting SICI and SICF overlap considerably.^{4,5} SICI studies in patients with PD reported variable results: some studies reported that SICI was decreased,^{6–8} whereas others found unchanged SICI in PD.^{9–12} Particularly, SICI in PD was normal at lower S1 intensities and was reduced only at higher S1 intensities.¹⁰ This raised the possibility that

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decreased SICI in PD is due to increased cortical facilitation rather than reduced inhibition because higher S1 intensities potentially activate SICF in the M1. We hypothesized that SICF is increased, and this leads to decreased SICI in patients with PD.

METHODS Subjects. We studied 12 patients with mild to moderate PD (5 women, aged 63.3 ± 2.3 years; table e-1 on the *Neurology*[®] Web site at www.neurology.org) and 12 right-handed healthy subjects (5 women, aged 62.1 ± 2.4 years). The more affected side of the patients was studied both in the practically defined OFF and the ON states.

Standard protocol approvals, registrations, and patient consents. All subjects provided written informed consent, and the protocol was approved by the University Health Network (Toronto) Research Ethics Board.

Transcranial magnetic stimulation. Surface EMG was recorded from the first dorsal interosseous muscles at the rest condition. TMS was applied to the M1 contralateral to the recording side with a figure-of-eight coil connecting 4 Magstim 200² stimulators with a “four-to-one” connection box (Magstim, Whitland, Dyfed, UK). The coil was placed in the optimal position for activation of the target muscle with induced current in the brain in the posterior-anterior direction.^{13,14} Rest and active motor threshold (RMT and AMT) and the TMS intensity to elicit “1 mV” MEP were measured.

Experiment 1: SICF. We tested whether SICF at individual peaks and troughs (ISIs with peak facilitation and with no facilitation) were increased in PD in all subjects. S1 intensity was set at 1 mV and S2 intensity was set at RMT. ISIs were 1.0 to 5.0 milliseconds with increments of 0.2 millisecond. Because motor cortical output was influenced by the different thresholds for recruitment of facilitation and inhibition and by the interaction between facilitation and inhibition,^{4,5} we further tested whether changes in SICF in PD depended on the S2 intensity in 10 patients and 10 healthy controls. S1 intensity was set at 1 mV. S2 intensities varied from 0.6 to 1.1 RMT with increments of 0.1 RMT. The ISIs selected were the 3 SICF peaks and 2 SICF troughs.

Experiment 2: SICI at SICF peaks and troughs. We tested different ISIs for SICI,² and whether it was affected by SICF in all subjects. S1 intensity was set at 95% AMT and S2 intensity was set at 1 mV. The ISIs for SICF peaks and troughs were selected. ISI of 1 millisecond was also tested because the underlying mechanisms for SICI at 1 millisecond may be different from those at other ISIs.^{15,16} Intracortical facilitation (ICF) represents a facilitatory process that a subthreshold S1 facilitates the response to a subsequent superthreshold S2 at ISIs of 6 to 30 milliseconds.² We tested ICF with ISIs of 10 and 15 milliseconds. We further tested whether changes in SICI in PD depended on the S1 intensities in 7 patients and 7 controls. S1 intensities varied from 0.4 to 1.4 AMT at increments of 0.2 AMT and S2 intensity was set at 1 mV. The ISI for SICF peak 1, which showed maximum facilitation, and the ISIs for SICF trough 1 and 1 millisecond were tested.

Data and statistical analysis. Values are reported as mean $\pm$ standard error. MEP amplitudes were measured peak-to-peak. The MEP amplitudes evoked by paired-pulse stimulation were expressed as a percentage of the mean MEP amplitude of test stimulus alone. Separate repeated-measures analysis of variance (ANOVA) were used to examine the effects of PD OFF vs PD ON, PD OFF vs control, and PD ON vs control for SICF and

SICI. PD OFF vs ON was entered as within-subject factor (repeated measure) whereas PD OFF or ON vs control was entered as between-subject factor. ISI and S1/S2 intensity were within-subject factors. Post hoc *t* tests with Bonferroni corrections for multiple comparisons were used to examine at which ISI or stimulus intensity PD OFF was different from PD ON (paired) and control (unpaired) groups. Principal component analysis is a method to examine the relationship between correlated variables and it generates a set of linearly uncorrelated variables known as principal components. We used it to examine how SICI, SICF, and ISI affect MEP amplitude and the relationships with each other in each subject group (PD OFF, PD ON, and control). MEP values for SICI and SICF at 6 ISIs (1 millisecond, 3 SICF peaks, and 2 troughs) from experiments 1 and 2 were entered into the analysis with SICI, SICF, and ISI as variables. Further analysis with Pearson correlation tested the relationship between SICF and SICI at the ISIs for SICF peaks and troughs in the PD OFF group. The relationships between changes in SICF/SICI and changes in Unified Parkinson's Disease Rating Scale (UPDRS) scores with medication (difference between OFF and ON states) were also tested. The threshold for significance was set at $p < 0.05$. Further details of the methods are provided in appendix e-1.

RESULTS UPDRS scores were higher in PD OFF compared with ON state ($t_{11} = 6.85$, $p < 0.001$). There was no difference in RMT, AMT, “1-mV” intensity, and the timing of the SICF peaks and troughs among the different subject groups (appendix e-1).

Experiment 1: Increased SICF in PD. ANOVA revealed increased SICF in the PD OFF group compared with PD ON ($F_{1,220} = 9.04$, $p = 0.012$) and controls ($F_{1,440} = 8.88$, $p = 0.007$) with significant effects of ISI (PD OFF vs ON, $F_{20,220} = 11.21$, $p < 0.001$; PD OFF vs controls, $F_{20,440} = 11.46$, $p < 0.001$) and group $\times$ ISI interactions (PD OFF vs ON, $F_{20,220} = 1.65$, $p = 0.044$; PD OFF vs controls, $F_{20,440} = 1.72$, $p = 0.027$). Post hoc *t* tests confirmed that SICF was increased in the PD OFF group at peaks but not troughs (figure 1). No difference was found between PD ON and controls.

For the effects of different S2 intensities at SICF peaks and troughs (figure 2), 3-way ANOVA for PD OFF vs ON showed main effects of group ($F_{1,180} = 10.89$, $p = 0.009$), ISI ($F_{4,180} = 34.32$, $p < 0.001$), S2 intensity ($F_{5,180} = 20.39$, $p < 0.001$) and 2-way interactions of group $\times$ intensity ($F_{5,180} = 2.42$, $p = 0.050$), ISI $\times$ intensity ($F_{20,180} = 10.00$, $p < 0.001$) but no group $\times$ ISI or 3-way interaction. For PD OFF vs controls, there were effects of group ($F_{1,360} = 8.60$, $p = 0.009$), ISI ($F_{4,360} = 26.29$, $p < 0.001$), and S2 intensity ($F_{5,360} = 31.59$, $p < 0.001$) with 2-way interactions (group $\times$ ISI, $F_{4,360} = 2.81$, $p = 0.032$; group $\times$ intensity, $F_{5,360} = 4.13$, $p = 0.002$; ISI $\times$ intensity, $F_{20,360} = 12.86$, $p < 0.001$) but no 3-way interaction. PD ON was not different from control. Post hoc *t* test confirmed that SICF in PD OFF was increased compared with PD ON and control groups at the peaks but not at the troughs.

Figure 1 Time course of short-interval intracortical facilitation

(A) Recordings (average of 20 trials for S1 alone and 10 trials for paired-pulse) of SICF at different ISIs from representative subjects. SICF was exaggerated at its peaks in the PD OFF medication state and this was normalized in the PD ON medication state. (B) Data obtained from 12 patients with PD and 12 healthy controls. The abscissa indicates the ISI between S1 and S2. The ordinate indicates the degree of SICF. It represents the amplitude of paired-pulse (S1-S2) induced MEP expressed as a percentage of the MEP amplitude induced by S1 alone. Values more than 100% indicate facilitation. Filled circles indicate SICF in patients with PD OFF medication. Triangles indicate SICF in patients with PD ON medication. Open circles indicate SICF in controls. The 3 SICF peaks and 2 troughs are labeled. * $p < 0.05$, ** $p < 0.01$, comparing PD OFF with control. # $p < 0.05$, ## $p < 0.01$, comparing PD OFF with PD ON, results of post hoc t tests. Error bars represent standard error. Note that at ISIs of 1.4, 1.6, 1.8, 2.6, 2.8, 3.0, and 4.4 milliseconds, the PD OFF group showed significant increase in SICF compared with PD ON (paired t test) and control (unpaired t test) groups. These ISIs corresponded to the 3 SICF peaks. ISI = interstimulus interval; MEP = motor-evoked potential; PD = Parkinson disease; S1 = first stimulus; S2 = second stimulus; SICF = short-interval intracortical facilitation.

Experiment 2: Decreased SICF in PD. ANOVA showed reduced SICF in PD OFF compared with ON state (group, $F_{1,55} = 15.45$, $p = 0.002$; ISI, $F_{5,55} = 9.32$, $p < 0.001$; interaction, $F_{5,55} = 5.21$, $p = 0.003$) (figure 3, A and B). Post hoc t test found decreased SICF for OFF compared with ON at 3 SICF

peaks. ANOVA also showed reduced SICF in PD OFF compared with controls (group, $F_{1,110} = 24.55$, $p < 0.001$; ISI, $F_{5,110} = 13.68$, $p < 0.001$; interaction, $F_{5,110} = 4.84$, $p < 0.001$). Post hoc t tests confirmed reduced SICF at SICF peaks, trough 1, and 1-millisecond ISIs in PD OFF compared with controls. ANOVA showed reduced SICF in PD ON compared with controls (group, $F_{1,110} = 5.02$, $p = 0.035$; ISI, $F_{5,110} = 12.71$, $p < 0.001$) with no interaction. Post hoc t test found that the SICF was decreased for PD ON compared with controls at SICF trough 1 and 1-millisecond ISI. ICF was similar for different groups and ISIs (figure 3C).

Three-way ANOVA testing SICF at different S1 intensities and ISIs (figure 4) revealed decreased SICF in PD OFF compared with ON ($F_{1,60} = 16.20$, $p = 0.007$) with effects of ISI ($F_{2,60} = 12.76$, $p = 0.001$), intensity ($F_{5,60} = 7.20$, $p < 0.001$), and 2-way interactions of ISI $\times$ intensity ($F_{10,60} = 5.07$, $p < 0.001$) and trend for the interaction of group $\times$ ISI ($F_{2,60} = 2.84$, $p = 0.098$) but no group $\times$ intensity or 3-way interaction. For the PD OFF vs controls comparison, there was similar effects of group ($F_{1,120} = 28.81$, $p < 0.001$), ISI ($F_{2,120} = 21.71$, $p < 0.001$), and S1 intensity ($F_{5,120} = 11.14$, $p < 0.001$) with 2-way interactions of group $\times$ intensity ($F_{5,120} = 4.84$, $p < 0.001$), and ISI $\times$ intensity ($F_{10,120} = 7.75$, $p < 0.001$) but no group $\times$ ISI interaction or 3-way interaction. For the PD ON vs controls comparison, there were still main effects of group ($F_{1,120} = 5.55$, $p = 0.036$), ISI ($F_{2,120} = 20.02$, $p = 0.001$), intensity ($F_{5,120} = 20.31$, $p < 0.001$) with 2-way interactions of ISI $\times$ intensity ($F_{10,120} = 8.74$, $p < 0.001$), and trend for group $\times$ ISI interaction ($F_{2,120} = 2.15$, $p = 0.072$) but no group $\times$ intensity or 3-way interaction. Post hoc t test showed that SICF at SICF peak 1 in the PD OFF group was weaker than that in PD ON and control groups when SICF began to emerge. No difference was found between PD ON and controls. However, the decreased SICF at SICF trough 1 and 1-millisecond ISI was not completely normalized by medications.

Principal component analysis. The results are shown in table e-2. In controls, the first component was strongly related to SICF and ISI and the second component was strongly related to SICF with a weak correlation to SICF. In contrast, in PD OFF, the first component was strongly related to both SICF and SICF whereas the second component was related to SICF and ISI, similar to the first component of controls. For PD ON, only 1 component with eigenvalue of >1 was extracted. It showed strong correlation with SICF and ISI, with weak negative correlation with SICF, similar to the first component of controls. Thus, only the PD OFF group showed a principal

Figure 2 Effects of the second stimulus intensity on short-interval intracortical facilitation

Data obtained from 10 patients with PD and 10 healthy controls. The abscissa indicates S2 intensity expressed as a ratio of RMT, ranging from 0.6 to 1.1 RMT. The ordinate indicates the degree of SICF. It represents the MEP amplitude induced by S1 and S2. It is expressed as a percentage of the MEP amplitude induced by S1 alone. Values more than 100% indicate facilitation. Five different interstimulus intervals at 3 SICF peaks and 2 troughs (determined individually) were tested. Filled circles indicate SICF in patients with PD OFF medication. Triangles indicate SICF in patients with PD ON medication. Open circles indicate SICF in controls. * $p < 0.05$, ** $p < 0.01$, comparing PD OFF with control. # $p < 0.05$, ## $p < 0.01$, comparing PD OFF with PD ON, results of post hoc t tests. Error bars represent standard error. Note that there was greater facilitation for the PD OFF group compared with control and PD ON groups from low S2 intensities at SICF peak 1 (≥ 0.7 RMT for PD OFF vs control, unpaired t test; ≥ 0.8 RMT for PD OFF vs PD ON, paired t test). For SICF peaks 2 and 3, such difference only occurred at higher S2 intensities (≥ 0.9 RMT for peak 2, ≥ 1.0 RMT for peak 3, for both comparisons of PD OFF vs control and PD OFF vs PD ON). MEP = motor-evoked potential; PD = Parkinson disease; RMT = rest motor threshold; S1 = first stimulus; S2 = second stimulus; SICF = short-interval intracortical facilitation.

component that was strongly correlated to both SICI and SICF.

Correlations among SICI, SICF, and UPDRS score. SICI in the PD OFF group correlated with SICF at peak 1 ($R = 0.71$, $F_{1,10} = 9.94$, $p = 0.010$) and peak 2 ($R = 0.76$, $F_{1,10} = 13.24$, $p = 0.005$) with a trend at peak 3 ($R = 0.54$, $F_{1,10} = 4.02$, $p = 0.073$) but not at troughs or 1-millisecond ISI (figure 5A). The improvement in UPDRS scores with medications correlated with the changes in SICF at peak 1 ($R = 0.62$, $F_{1,10} = 6.11$, $p = 0.033$) and peak 2 ($R = 0.67$, $F_{1,10} = 8.11$, $p = 0.017$) but not at peak 3 or the 2 troughs (figure 5B). The improvement in UPDRS scores correlated with changes in SICI at SICF peak 1 ($R = 0.61$, $F_{1,10} = 5.79$, $p = 0.037$) with a trend at peak 2 ($R = 0.56$, $F_{1,10} = 4.58$, $p = 0.058$) but not at peak 3 or other ISIs (figure 5C).

DISCUSSION The paired-pulse TMS paradigms were used to examine the time courses of SICF and SICI, which overlap considerably. Our basic assumption is that the low-threshold SICI is superimposed on the high-threshold SICF,²⁻⁵ and the motor cortical output is determined by the complex interaction between them. We found that SICF is increased and SICI is decreased in PD.

SICF is of cortical origin because no facilitation is observed if S2 is replaced by transcranial electrical stimulation, which activates the corticospinal neurons directly.³ Epidural recordings showed that the amplitudes of corticospinal indirect waves (I-waves) generated by SICF were more than the sum of I-waves generated by S1 and S2 given separately.¹⁷ Because the effective ISIs for SICF coincide with the periods of I-wave generation, SICF is likely related to the summation of I-waves caused by activation of different sets of cortical interneurons. The occurrence of SICF at 3 distinct ISIs of approximately 1.4, 2.8, and 4.4 milliseconds (figure 1) in the control group is consistent with previous studies.^{3,4,18} We found that SICF occurred at the same ISIs in patients with PD as in controls in both ON and OFF medication states, suggesting that the timing of facilitatory inputs from cortical interneurons to corticospinal neurons is unaffected in PD. However, the degree of facilitation is clearly increased in PD compared with controls. This was revealed by a detailed study of the time course of SICF (figure 1), and was confirmed by the effects of different conditioning intensities on SICF (figure 2). Moreover, SICF was unchanged at the troughs of its time course where there was no significant facilitation, demonstrating that the increased facilitation was specific to SICF and was not due to a generalized increase in cortical excitability. Taken together, our results suggest that the summation of I-waves at

Figure 3 Short-interval intracortical inhibition and intracortical facilitation at different interstimulus intervals

(A) Recordings (average of 20 trials for S2 alone and 10 trials for paired-pulse) of SICI and ICF at different ISIs from representative subjects. The ISIs correspond to SICF peaks and troughs. An ISI of 1 millisecond was added for SICI. ISI of 10 milliseconds was used for ICF. There was decreased SICI at SICF peaks, troughs, and at ISI of 1 millisecond in the PD OFF medication state, and this was not completely normalized in the PD ON state. (B) and (C) show group data for SICI and ICF obtained from 12 patients with PD and 12 healthy controls. The abscissa indicates the ISI between S1 and S2. The ordinate indicates the degree of SICI and ICF. It represents the amplitude of paired-pulse (S1-S2) induced MEP expressed as a percentage of the MEP amplitude induced by S2 alone. Values more than 100% indicate facilitation and those less than 100% indicate inhibition. Filled circles indicate SICI and ICF in patients with PD OFF medication. Triangles indicate SICI and ICF in patients with PD ON medication. Open circles indicate SICI and ICF in controls. * $p < 0.05$, ** $p < 0.01$, comparing PD OFF with control. # $p < 0.05$, ## $p < 0.01$, comparing PD OFF with PD ON. S = $p < 0.05$, comparing PD ON with control, results of post hoc t tests. Error bars represent standard error. Note that SICI was reduced in PD OFF compared with controls at an ISI of 1 millisecond, at SICF peak 1, trough 1, peak 2, and peak 3 (unpaired t test). Reduced SICI in the PD OFF compared with PD ON group was only found at SICF peaks (paired t test). SICI for PD ON was still decreased compared with controls at ISI of 1 millisecond and at SICF trough 1 (unpaired t test). ICF = intracortical facilitation; ISI = interstimulus interval; MEP = motor-evoked potential; PD = Parkinson disease; S1 = first stimulus; S2 = second stimulus; SICF = short-interval intracortical facilitation; SICI = short-interval intracortical inhibition.

corticospinal neurons is exaggerated in patients with PD. In addition, the reduction of SICF in PD ON compared with OFF suggests that the exaggerated summation of I-waves can be reduced by dopaminergic medications.

Pharmacologic studies suggest that SICI is likely mediated by γ -aminobutyric acid type A (GABA_A) receptors.^{4,19,20} We found decreased SICI in PD both at SICF peaks and troughs (figure 3). In controls, principal component analysis showed that the variations in SICF and SICI were determined by 2 different principal components, suggesting that they are relatively independent measurements. In contrast, in the PD OFF group, the first principal component was strongly correlated to variations in both SICF and SICI. Furthermore, administration of dopaminergic medications in PD ON changed the relationship between SICI and SICF to similar to that of controls. These results support our hypothesis that in the OFF medication state, reduced SICI may be due to increased SICF in PD. Further testing of different S1 intensities (figure 4) found that decreased SICI at SICF peaks occurred over the entire range of S1 intensities that produced SICI. Our results may explain why previous studies found divergent results with decreased⁶ or normal SICI in PD.^{9,12} In particular, SICI at 3-millisecond ISI tested with TMS in the anterior-posterior current direction was normal whereas that tested in the posterior-anterior current direction was reduced in PD.²¹ Because TMS with anterior-posterior current predominantly activates late I-waves and SICF is less prominent for late I-waves compared with early I-waves,^{3,22} the contribution of increased SICF to SICI measurement is less with anterior-posterior current compared with the posterior-anterior current. However, the results of SICI tested in the posterior-anterior current²¹ are similar to our results with reduced SICI at SICF peak 2. SICI studies using a narrow range of ISIs and stimulus intensities where SICI and SICF overlap may lead to contradictory results.

An important finding in the present study was that SICI was decreased at SICF troughs and at 1-millisecond ISI in patients with PD. This is different from our hypothesis that abnormal SICI in PD is due to impairment in SICF. The detailed test of the effect of S1 intensities on SICI showed that at SICF trough 1, SICI in controls remained stable at high S1 intensities. However, SICI in patients with PD was still decreased at SICF trough 1 and dopaminergic medication only partly normalized this deficit. These results were similar to a previous study showing decreased SICI at 2 and 4 milliseconds (likely corresponding to SICF troughs 1 and 2) in PD, which was not completely normalized in the ON medication state.⁶ Therefore, decreased SICI at SICF troughs is likely related to impairment of

Figure 4 Effects of the first stimulus intensity on short-interval intracortical inhibition

Data obtained from 7 patients with PD and 7 healthy controls. The abscissa indicates S1 intensity expressed as a ratio of AMT, ranging from 0.4 to 1.4 AMT. The ordinate indicates the degree of SICI. It represents the MEP amplitude induced by S1 and S2. It is expressed as a percentage of the MEP amplitude induced by S2 alone. Values more than 100% indicate facilitation and those less than 100% indicate inhibition. Three different interstimulus intervals of 1 millisecond, at first peak and first trough of SICF, were tested. Filled circles indicate SICI in patients with PD OFF medication. Triangles indicate SICI in patients with PD ON medication. Open circles indicate SICI in controls. * $p < 0.05$, ** $p < 0.01$, comparing PD OFF with control. ## $p < 0.01$, comparing PD OFF with PD ON. S = $p < 0.05$, comparing PD ON with control, results of post hoc t tests. Error bars represent standard error. Note that SICI at an ISI of 1 millisecond increased with increasing S1 intensity and reached at plateau at higher S1 intensities in healthy controls. For PD OFF, SICI was reduced compared with controls at lower S1 intensities (0.6–1.2 AMT), but became normal at higher S1 intensities. For PD ON, reduced SICI compared with controls was significant at S1 intensities of 0.8 and 1.0 AMT. At SICF peak 1, the relationship between SICI and S1 intensities was U-shaped in healthy controls. Reduced SICI in the PD OFF group was significant when SICI began at 0.6 AMT and the difference between PD OFF and controls increased with higher S1 intensity. PD ON and PD OFF groups were different at similar range of S1 intensities (≥ 0.8 AMT). At SICF trough 1, SICI initially increased with increasing S1 intensity and slightly decreased at high S1 intensity in controls. For PD OFF, SICI was reduced compared with controls when the S1 intensity was 0.8 AMT as SICI began to emerge in controls, and continued up to 1.4 AMT. For PD ON, there was reduced SICI at S1 intensities of 1.0 to 1.4 AMT compared with controls. AMT = active motor threshold; MEP = motor-evoked potential; PD = Parkinson disease; S1 = first stimulus; S2 = second stimulus; SICF = short-interval intracortical facilitation; SICI = short-interval intracortical inhibition.

GABA_A-mediated synaptic inhibition and the impairment may represent a nondopaminergic feature of PD. Abnormalities in other cortical circuitry in PD, including decreased long latency afferent inhibition²³ and reduced interaction between SICI and long-interval intracortical inhibition,⁹ were also nonresponsive to dopaminergic medication. Interestingly,

SICI at 2 milliseconds²⁴ and afferent inhibition²⁵ were normalized by subthalamic nucleus deep brain stimulation in the ON medication state, suggesting that the effects of deep brain stimulation are different from that of levodopa, but that the 2 treatments interact. SICI at 1 millisecond in healthy controls initially increased and then saturated at higher S1 intensities (figure 4). It has been suggested that both the refractory period produced by S1¹⁶ and synaptic inhibition²⁶ contribute to this inhibition. SICI at 1 millisecond correlated with GABA concentration measured by magnetic resonance spectroscopy.²⁷ We found that there was decreased SICI at the mid-range of S1 intensities in patients with PD. The results were similar to the SICI tested at SICF trough 1, suggesting that impaired GABA-mediated inhibition may be responsible. Taken together, the mechanisms underlying abnormal SICI in PD at SICF peaks, troughs, and 1-millisecond ISI are different.

ICF was normal in our patients both ON and OFF medications, similar to a previous study.⁶ Although the mechanisms mediating ICF are still unclear,^{2,28} the results suggest that decreased SICI in PD is not caused by changes in ICF.

Abnormal neuronal activities in the basal ganglia–cortical pathways were reported both in a primate model of parkinsonism^{29,30} and in patients with PD.^{31,32} We found that improvement in both SICF and SICI with dopaminergic medications at SICF peaks 1 and 2 correlated with improvement in UPDRS scores (figure 5), whereas the measurements at SICF troughs and at 1-millisecond ISI did not show such correlations. The present findings support the notion that the abnormalities in motor cortical facilitation are related to the motor symptoms and the effects of treatment in PD.^{33,34} SICF peak 3 did not correlate with UPDRS scores likely because SICF peak 3 was weaker than SICF peaks 1 and 2.^{3,22}

A popular hypothesis to explain PD pathophysiology is that the loss of dopaminergic neurons in substantia nigra pars compacta reduces the activities in the direct pathway and increases activities in the indirect pathway, resulting in exaggerated inhibition from internal globus pallidus to the motor thalamus and leading to reduced excitatory input to the M1.^{1,35,36} Thus, increased excitability of corticospinal neurons in patients with PD may be a mechanism to compensate for decreased excitatory projection from the thalamus. If more corticospinal neurons are subliminally activated by excitatory inputs, this will facilitate the summation of S1 and S2 in the SICF protocol and result in observed increase of SICF in PD. Administration of dopaminergic medications restores the thalamocortical output, leading to the normalization of SICI and SICF measured at

Figure 5 Relationship between short-interval intracortical inhibition and facilitation and UPDRS scores in patients with PD

Red circles indicate measurements at SICF peak 1, green circles peak 2, and blue circles peak 3. SICF and SICI are expressed as a percentage of the amplitude of paired-pulse-induced MEP to the test MEP amplitude. (A) Relationship between SICI and SICF in patients with PD OFF medication state. The abscissa shows SICF and the ordinate shows SICI. The solid red and green lines indicate significant correlation between SICI and SICF at SICF peaks 1 and 2. The dashed blue line indicates a trend toward significant correlation between SICI and SICF at SICF peak 3. (B) and (C) Relationship between improvement in SICF (B) or SICI (C) and improvement in UPDRS scores by dopaminergic medication. The abscissa shows the improvement in SICF/SICI (difference between OFF and ON medication states). The ordinate shows the improvement in UPDRS scores (difference between OFF and ON medication states). The improvement in UPDRS scores correlated with the changes in SICF (B) at SICF peak 1 (solid red line) and peak 2 (solid green line). The improvement in UPDRS scores also showed significant correlation with changes in SICI (C) at SICF peak 1 (solid red line) and a trend toward significance at SICF peak 2 (dashed green line). MEP = motor-evoked potential; PD = Parkinson disease; SICF = short-interval intracortical facilitation; SICI = short-interval intracortical inhibition; UPDRS = Unified Parkinson's Disease Rating Scale.

SICF peaks. Decreased SICI in PD measured at SICF troughs and at 1-millisecond ISI may be caused by decreased GABA-mediated cortical inhibition.

AUTHOR CONTRIBUTIONS

Zhen Ni: drafting/revision of the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, statistical analysis. Nina

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