# Functional reorganization of sensorimotor cortex in early Parkinson disease

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## ABSTRACT

**Objective:** Compensatory reorganization of the nigrostriatal system is thought to delay the onset of symptoms in early Parkinson disease (PD). Here we sought evidence that compensation may be a part of a more widespread functional reorganization in sensorimotor networks, including primary motor cortex.

**Methods:** Several neurophysiologic measures known to be abnormal in the motor cortex (M1) of patients with advanced PD were tested on the more and less affected side of 16 newly diagnosed and drug-naive patients with PD and compared with 16 age-matched healthy participants. LTP-like effects were probed using a paired associative stimulation protocol. We also measured short interval intracortical inhibition, intracortical facilitation, cortical silent period, and input/output curves.

**Results:** The less affected side in patients with PD had preserved intracortical inhibition and a larger response to the plasticity protocol compared to healthy participants. On the more affected side, there was no response to the plasticity protocol and inhibition was reduced. There was no difference in input/output curves between sides or between patients with PD and healthy participants.

**Conclusions:** Increased motor cortical plasticity on the less affected side is consistent with a functional reorganization of sensorimotor cortex and may represent a compensatory change that contributes to delaying onset of clinical symptoms. Alternatively, it may reflect a maladaptive plasticity that provokes symptom onset. Plasticity deteriorates as the symptoms progress, as seen on the more affected side. The rate of change in paired associative stimulation response over time could be developed into a surrogate marker of disease progression in PD. *Neurology*® 2012;78:1441–1448

## GLOSSARY

**ADM** = abductor digiti minimi; **AMT** = active motor threshold; **APB** = abductor pollicis brevis; **CS** = conditioning stimulus; **CSP** = cortical silent period; **DaT** = dopamine transporter; **I/O** = input/output; **ICF** = intracortical facilitation; **ISI** = interstimulus interval; **LTP** = long-term potentiation; **MEP** = motor evoked potential; **PAS** = paired associative stimulation; **PD** = Parkinson disease; **RMT** = resting motor threshold; **SICI** = short-latency intracortical inhibition; **TMS** = transcranial magnetic stimulation; **UPDRS** = Unified Parkinson's Disease Rating Scale.

Motor signs in Parkinson disease (PD) appear when striatal dopamine is depleted beyond a critical threshold of ~60%–80%.[1] Neuropathologic and neuroimaging evidence suggests that presynaptic and synaptic changes in the nigrostriatal system compensate for dopamine deficiency.[1–6] Indeed, given the extent of preclinical dopaminergic denervation,[7] it is conceivable that compensatory changes extend also beyond the nigrostriatal portion of the motor circuit.

Patients with clinically asymmetric PD represent a valuable model to study compensatory reorganization within the motor system since functional changes that prevent motor symptom progression are likely to be more evident on the less affected side. A previous [$^{18}$F]-fluorodeoxyglucose PET study provided little evidence that this might be the case.[8] Asymmetric patients had an equally abnormal metabolic pattern in cortex and subcortical structures of both hemispheres (except within

Supplemental data at www.neurology.org

Supplemental Data

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**Table 1** Clinical and demographic characteristics of patients with Parkinson disease

| Patient | Age, y | Gender | Less affected side | Disease duration, mo | UPDRS less affected side | UPDRS more affected side | Motor UPDRS total |
|---|---|---|---|---|---|---|---|
| 1 | 34 | F | R | 28 | 1 | 20 | 24 |
| 2 | 71 | M | L | 28 | 1 | 9 | 18 |
| 3 | 44 | M | R | 24 | 0 | 8 | 12 |
| 4 | 66 | M | R | 9 | 1 | 6 | 9 |
| 5 | 62 | F | L | 10 | 0 | 12 | 12 |
| 6 | 67 | M | L | 28 | 1 | 4 | 9 |
| 7 | 64 | M | L | 24 | 2 | 13 | 26 |
| 8 | 50 | M | L | 48 | 7 | 18 | 32 |
| 9 | 63 | M | L | 36 | 2 | 4 | 6 |
| 10 | 58 | M | L | 5 | 2 | 3 | 6 |
| 11 | 62 | M | R | 6 | 0 | 9 | 9 |
| 12 | 73 | F | L | 60 | 1 | 13 | 19 |
| 13 | 61 | F | R | 3 | 2 | 4 | 7 |
| 14 | 52 | F | R | 8 | 1 | 6 | 8 |
| 15 | 65 | M | L | 10 | 1 | 6 | 12 |
| 16 | 48 | M | L | 24 | 3 | 23 | 33 |
| Mean ± SEM | 58.7 ± 2.6 | 11 M/5 F | 10 L/6 R | 22 ± 4.1 | 1.6 ± 0.4 | 9.9 ± 1.5 | 15.1 ± 2.3 |

Abbreviations: mo = months; y = years; UPDRS = Unified Parkinson's Disease Rating Scale.

the putamen).[8] However, an apparent absence of metabolic asymmetry in sensorimotor cortex, a major output of basal ganglia–cortical loops, could reflect insufficient sensitivity of metabolic measures.

In this study, using transcranial magnetic stimulation (TMS) techniques known to be sensitive to dopaminergic deficit, we measured the excitability of circuits in the sensorimotor cortex of clinically asymmetric drug-naive patients with PD with transcranial magnetic stimulation (TMS) techniques known to be sensitive to dopaminergic deficit. These involved paired associative stimulation (PAS), a method that assesses long-term potentiation (LTP)–like plasticity at cortical synapses[9] and which relies on sensorimotor integration of afferent input and motor output known to be impaired in PD.[10] In addition, we employed measures of intracortical inhibitory and excitatory function. We compared these measures between the less and more affected hemispheres in the patients and we contrasted them with those of healthy participants.

## METHODS

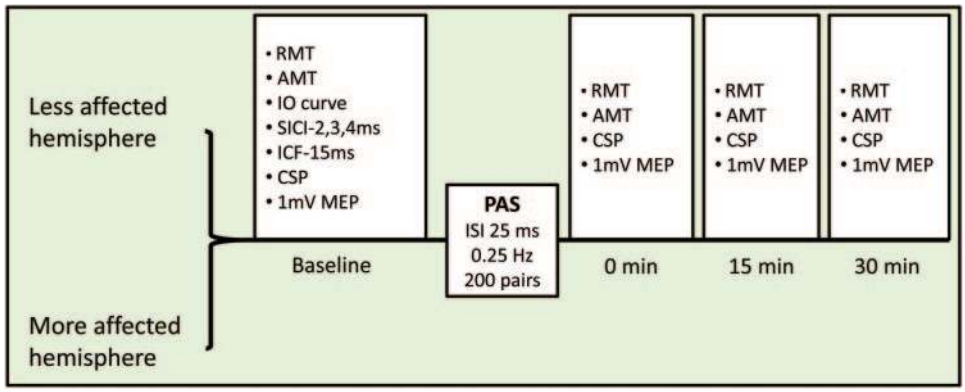
**Standard protocol approvals, registrations, and patient consents.** The study was approved by the local ethics committees at the collaborating institutions. Written informed consent was obtained from all participants.

**Participants.** Sixteen newly diagnosed, drug-naive patients with clinically asymmetric idiopathic PD (11 men, 5 women, mean age 59 years, range 34–73 years) (table 1) and 16 age-matched healthy participants (11 men, 5 women, mean age 60 years, range 35–73 years) were included in the study. Idiopathic PD was diagnosed according to the UK PD Society Brain Bank criteria[11] and further confirmed by abnormal dopamine transporter (DaT) SPECT in all patients. None of the patients had significant tremor that could interfere with EMG recording. Clinical disease severity was assessed with the motor section (items 3.1–3.18) of the Movement Disorder Society–sponsored revision of the Unified Parkinson's Disease Rating Scale (UPDRS).[12] For less and more affected side, the motor subscore was calculated from the sum of items 3.3 to 3.8 and 3.15 to 3.17 for each side (lateralized UPDRS score). None of the participants was on any medications that could affect the measurements performed. All participants were right-handed.

**Electromyographic recordings.** EMG recordings were made from the abductor pollicis brevis (APB) and abductor digiti minimi (ADM) muscles on the side contralateral to stimulated cortex with Ag-AgCl surface electrodes using a belly-tendon montage. The level of background EMG activity was monitored and trials with unwanted background EMG activity were rejected online. The background EMG area in at least 200 msec preceding the TMS pulse was measured in all trials and EMG root mean square amplitude calculated to ensure comparability of the baseline activity between groups.

**TMS: corticospinal excitability, intracortical excitability, and PAS technique.** Single and paired pulse TMS of the primary motor cortex was applied using Magstim 200[2] magnetic stimulators with a monophasic current waveform (Magstim Company, UK) connected to a standard figure-of-eight coil. The "hot spot" was defined as the optimal scalp position for eliciting

**Figure 1** Experimental design




Patients with Parkinson disease were studied over both hemispheres in 2 transcranial magnetic stimulation (TMS) sessions separated by 1 week. In each session we first measured baseline corticospinal excitability (resting motor threshold [RMT], active motor threshold [AMT], input/output [IO] curve, and 1 mV motor evoked potential [MEP]) and intracortical excitability (short-latency intracortical inhibition [SICI], intracortical facilitation [ICF], and cortical silent period [CSP]). We then applied conditioning paired associative stimulation (PAS) protocol and assessed the effect of PAS on RMT, AMT, 1 mV MEP, and CSP duration at 3 time points: 0 minutes, 15 minutes, and 30 minutes after PAS. For assessment of 1 mV MEP the TMS intensity was kept constant throughout the experiment. ISI = interstimulus interval.

motor evoked potentials (MEPs) of maximal amplitude in the contralateral APB muscle. The same hot spot was used for assessing the MEPs in ADM muscle.[9]

**Corticospinal excitability.** Active motor threshold (AMT) and resting motor threshold (RMT) were determined according to the standard definitions.[13] Single MEPs were recorded using a stimulus intensity adjusted to produce MEP amplitude of approximately 1 mV in the relaxed APB muscle (1 mV MEPs) and this intensity was kept constant for assessment of 1 mV MEPs after PAS.

Input/output curves (I/O curves) were assessed by recording 4 MEPs at each of 10 stimulation intensities, increasing in 10% steps from 80% to 170% of RMT.

**Intracortical excitability.** Short-latency intracortical inhibition (SICI) and intracortical facilitation (ICF) were assessed with paired-pulse paradigm.[14] The intensity of the test stimulus was adjusted to 1 mV MEPs while the intensity of the conditioning stimulus (CS) was 90% of RMT, an intensity known to produce a net loss of inhibition in PD.[15] SICI was assessed at rest, using interstimulus intervals (ISIs) of 2, 3, and 4 msec and ICF at ISI of 15 msec. For SICI and ICF 10 MEPs were collected for each ISI and for the test stimulus alone. For assessment of cortical silent period (CSP), 10 single TMS pulses were applied at an intensity of 120% RMT, while patients performed a constant contraction of APB at 20% of maximum voluntary contraction.

**PAS.** PAS consisted of 200 electrical stimuli to the median nerve at the wrist paired with TMS stimuli over the APB hot spot, given at the rate 0.25 Hz.[9,16] Each TMS stimulus was preceded by an electrical conditioning stimulus at an ISI of 25 msec. Intensity of electrical stimulus was 300% of the perceptual threshold; TMS intensity was adjusted to 1 mV MEP intensity. Subjects were instructed to look at their stimulated hand and to report every 20th peripheral electrical stimuli they perceived in order to ensure comparable attention levels between sessions.

**Experimental design.** Patients were tested on both hemispheres, corresponding to the more and less affected side in 2 different TMS sessions, separated by a week. The order of the tested hemisphere (affected vs unaffected) was randomized between subjects. Healthy participants were tested on the dominant hemisphere only.[17] In each session we measured RMT, AMT, 1 mV MEP, I/O curve, SICI, ICF, and CSP. We then delivered PAS and assessed the effect of this conditioning protocol on corticospinal excitability (RMT, AMT, and 1 mV MEPs) and CSP at 3 time points: 0, 15, and 30 minutes after PAS (figure 1).

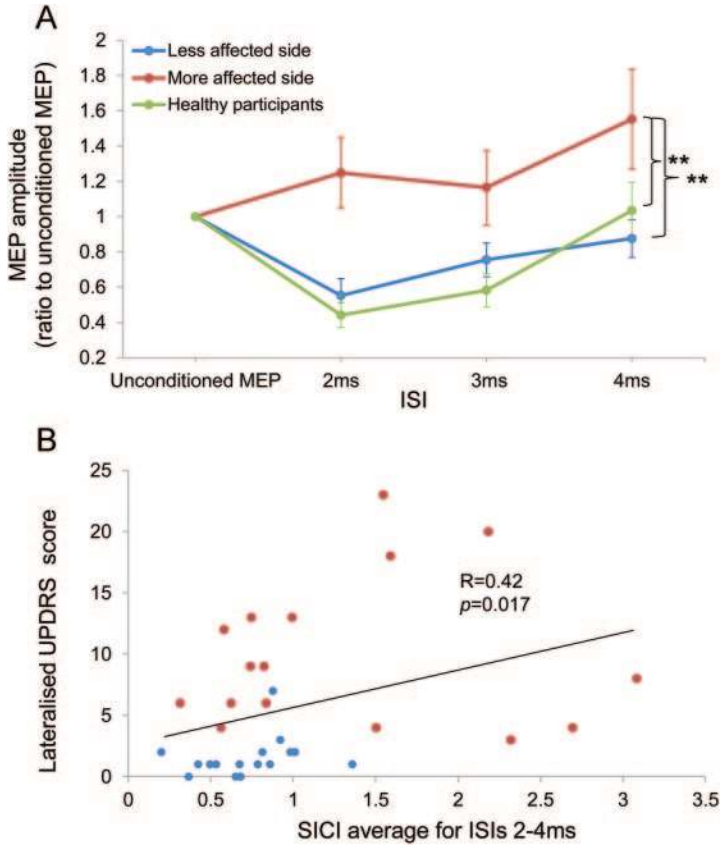
**Statistical analysis.** We used Wilcoxon *t* test to compare differences in the UPDRS scores between less and more affected side and to compare age between patients with PD and healthy participants. $\chi^2$ was used to compare gender distribution between patients with PD and healthy participants. TMS parameters between less and more affected side of patients with PD and healthy participants were compared using 2-way analysis of variance (ANOVA) with a factor group (less affected vs more affected vs healthy participants) as a between-subject factor. For I/O curves factor stimulus intensity (10 levels of stimulator output intensity) was used as within-subjects factor. For SICI, ISI (3 levels: normalized MEP size at 2, 3, and 4 msec) was used as a within-subject factor. PAS produced by stimulation of median nerve has different effects on MEPs evoked in median and nonmedian innervated muscles.[9] Thus the effects on MEPs in APB and ADM muscle were evaluated in separate 2-way ANOVAs for each muscle with time (4 levels: before PAS and 0, 15, and 30 minutes after PAS) as a within-subject factor. The effect of PAS on CSP was evaluated using time (3 levels: normalized CSP duration at 0, 15, and 30 minutes after PAS) as a within-subject factor. Conditional on a significant F value, to explore the strength of main effects and patterns of significant interactions we used post hoc Tukey HSD test and follow-up ANOVAs, respectively. Possible correlations between clinical and demographic data and TMS measures were evaluated with Spearman correlation analysis. The significance was preset at $p < 0.05$. Data are given as mean ± SEM. More details of the methods are given in appendix e-1 on the *Neurology*® Web site at www.neurology.org.

**RESULTS** **Clinical and demographic data.** No differences in age or gender distributions were found be-

tween patients with PD and healthy participants. As expected, there was a significant difference in lateralized UPDRS scores between less and more affected side in patients with PD (table 1), due to higher scores on more affected side (paired sample $t$ test, $p < 0.0001$).

**Corticospinal excitability and EMG root mean square amplitude.** At baseline, there was no difference in RMT, AMT, 1 mV MEPs, or resting EMG root mean square between less and more affected sides of patients with PD or patients and healthy participants. For I/O curves ANOVA showed an expected effect of stimulus intensity ($F_{9,423} = 73.4$; $p < 0.0001$). Factor group and the interaction group × stimulus intensity were nonsignificant, indicating no difference in baseline corticospinal excitability between groups (figure e-1).

**Figure 2** Short interval intracortical inhibition (SICI)




(A) In patients with Parkinson disease (PD), SICI is preserved on the less affected side and does not differ from SICI in healthy participants. On the more affected side SICI is reduced compared to less affected side ($p = 0.01$) and to healthy participants ($p = 0.007$). Data are plotted as a ratio to the unconditioned motor evoked potential (MEP) amplitude. ISI = interstimulus interval (**$p \leq 0.01$). (B) Correlation analysis between SICI and clinical severity of PD. Averaged SICI (for ISI 2, 3, and 4 msec, expressed as ratio to unconditioned MEP) positively correlates with lateralized Unified Parkinson's Disease Rating Scale (UPDRS) scores. Higher SICI ratio corresponds to less SICI and therefore positive correlation indicates that greater reduction in SICI is associated with more severe motor symptoms. Blue circles = less affected side; red circles = more affected side.

**SICI.** ANOVA revealed a difference in SICI between groups (factor group [2,45] = 6.28; $p = 0.004$), due to overall reduced SICI on the more affected side compared with the less affected side ($p = 0.01$) and with healthy participants ($p = 0.007$) (figure 2A). There was no difference in SICI between the less affected side and healthy participants. Factor ISI was also significant ($F_{2,90} = 14.8$; $p < 0.0001$), due to less SICI at 4 msec compared to 2 and 3 msec ($p = 0.0001$ and $p = 0.0003$, respectively) across all 3 groups (group × ISI interaction was not significant). The correlation analysis between lateralized UPDRS score and the averaged amount of SICI at 2, 3, and 4 msec (expressed as a ratio to unconditioned MEP) revealed that more severe symptoms were associated with greater reduction in SICI ($R = 0.42$; $p = 0.017$) (figure 2B).

**ICF.** For ICF, ANOVA revealed no group difference (figure e-2).

**CSP.** At baseline, ANOVA revealed differences in CSP duration between groups ($F_{2,45} = 5.73$; $p = 0.006$), due to a shorter CSP on the more affected side compared with the less affected side ($p = 0.02$) and healthy participants ($p = 0.001$). There was no difference in baseline CSP between the less affected side and healthy participants (figure e-3A).

**PAS.** Results are summarized in table 2 and figure 3, A and B. Separate 2-way ANOVAs for the APB and the ADM muscle with factors group and time revealed that the effect of PAS was different between groups in both APB (group × time interaction, $F_{6,135} = 2.6$; $p = 0.02$) and ADM (group and time, $F_{6,135} = 3.4$; $p = 0.004$). We explored these interactions further with follow-up ANOVAs in which we made separate comparisons between hemispheres in patients as well as comparisons of each hemisphere with the normal group. Less affected side had larger response to PAS than more affected side in both APB (group × time, $F_{3,90} = 5.44$; $p = 0.001$) and ADM (group × time, $F_{3,90} = 5.55$; $p = 0.001$) muscles. When the less affected side was compared to healthy participants there was no difference between the response to PAS in APB muscle; however, less affected side showed a spread of PAS effect to the ADM that was not present in healthy participants (group × time, $F_{3,90} = 4.36$; $p = 0.006$). Finally, comparison of the more affected side to healthy participants revealed that more affected side had less response to PAS in APB muscle. There was no spread of PAS response to ADM in more affected side or healthy participants. Within-group effects of PAS were further confirmed in separate ANOVAs for each group and muscle (figure 3, A and B).

**Table 2** Group comparisons of PAS effect in APB and ADM muscle[a]

| | APB | ADM |
|---|---|---|
| **Less affected side vs more affected side vs healthy participants** | | |
| Group | NS | NS |
| Time | $F_{3,135} = 10.1$ | NS |
| *p* | <0.0001 | |
| Group × time | $F_{6,135} = 2.6$ | $F_{6,135} = 3.4$ |
| *p* | 0.02 | 0.004 |
| **Less affected side vs more affected side** | | |
| Group | $F_{1,30} = 4.42$ | NS |
| *p* | 0.04 | |
| Time | $F_{3,90} = 6.05$ | NS |
| *p* | 0.0008 | |
| Group × time | $F_{3,90} = 5.44$ | $F_{3,90} = 5.55$ |
| *p* | 0.001 | 0.001 |
| **Less affected side vs healthy participants** | | |
| Group | NS | NS |
| Time | $F_{3,90} = 11.1$ | NS |
| *p* | 0.0001 | |
| Group × time | NS | $F_{3,90} = 4.36$ |
| *p* | | 0.006 |
| **More affected side vs healthy participants** | | |
| Group | $F_{1,30} = 5.17$ | NS |
| *p* | 0.03 | |
| Time | $F_{3,90} = 3.39$ | NS |
| *p* | 0.02 | |
| Group × time | $F_{3,90} = 2.89$ | NS |
| *p* | 0.04 | |

Abbreviations: ADM = abductor digiti minimi; APB = abductor pollicis brevis; PAS = paired associative stimulation.
[a] Each analysis of variance has main factor group (3 levels or 2 levels) and time (4 levels before PAS, 0 min, 15 min, and 30 min after PAS). For each main factor and interactions between main factors, *F* value and *p* value are given if significant or marked as NS if nonsignificant.

Correlation analysis between lateralized UPDRS score and average PAS response in APB disclosed that less severe motor symptoms were associated with a greater response to PAS ($R = -0.397$; $p = 0.025$) (figure 3C). There was no difference in our measure of attention during PAS between different TMS sessions or between groups.

Since baseline CSP was different between groups, to examine the effect of PAS on CSP, we expressed the duration of CSP at each point after PAS as a ratio to the baseline CSP and computed 2-way ANOVA with factors group (3 levels) and time (3 levels: normalized CSP duration at 0, 15, and 30 minutes after PAS). This analysis revealed a difference between groups (factor group, $F_{2,45} = 5.0$; $p = 0.01$) due to overall stronger effect of PAS on CSP duration on more affected side compared to healthy participants ($p = 0.01$). There was no difference between less and more affected side in patients with PD or between less affected side and healthy participants (figure e-3B).

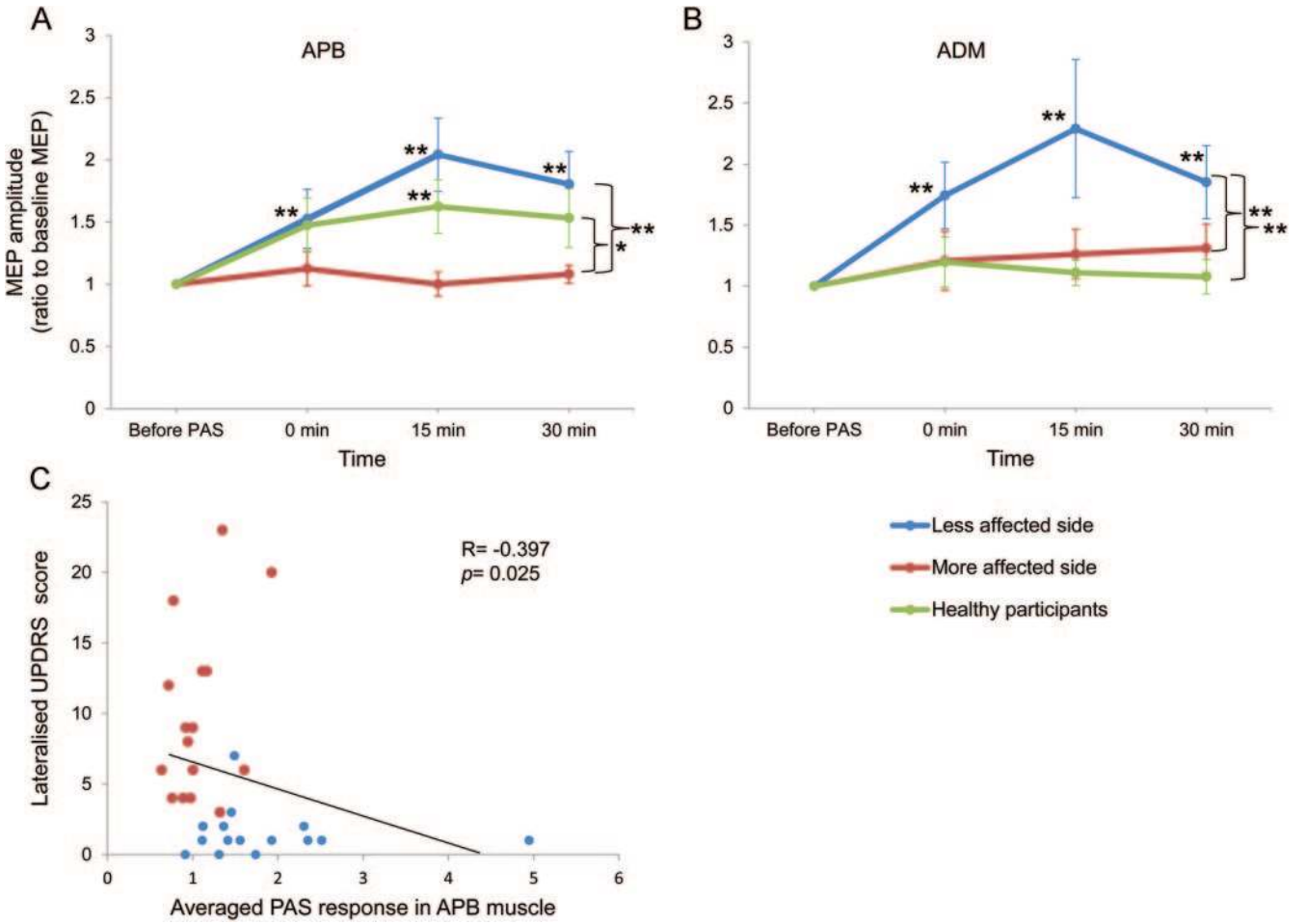
There was no change in RMT or AMT after PAS in patients with PD (neither side) or healthy participants.

**DISCUSSION** The main finding of the present study was that clinically asymmetric patients with PD had a heightened response to a plasticity protocol (PAS) in the less affected hemisphere, in contrast to absent PAS response in the more affected hemisphere. The asymmetry in electrophysiologic findings between hemispheres was also reflected in measures of intracortical inhibition; the less affected side showed preserved SICI and CSP, while on the more affected side SICI was reduced and CSP shortened. These asymmetries are not explained by differences in baseline corticospinal excitability, as there were no differences in I/O curves and motor thresholds between the 2 sides.

The absence of the PAS response on the more affected side is in line with previous studies in patients with more advanced PD,[18,19] who show decreased response to PAS in the "off" state that normalizes with L-dopa.[18] The reduced response to PAS is explained as being secondary to abnormal basal ganglia output[20] or to result from reduced dopamine at the cortical level.[21] Since there is major bilateral (albeit asymmetric) dopaminergic loss even in early clinically asymmetric PD[7] one might expect a similar reduction of PAS effect in both hemispheres in the present patients. On the contrary, we found an increased LTP-like plasticity with a loss of topographic specificity on the less affected side (compared with healthy age-matched subjects), suggesting that there is a functional reorganization of sensorimotor cortex in early PD. These findings may represent a compensatory change or they may reflect disease-related maladaptive plasticity. The negative correlation between severity of motor symptoms and the amount of response to PAS suggests that this is a compensatory change.

In health, basal ganglia neurons are highly "tuned" to fire in specific circumstances related to different parameters of movement and to contextual cues.[22] There is evidence to suggest that basal ganglia dysfunction in PD leads to a loss of specificity of surviving neurons and their connected structures.[23] Such changes could alter the precise coupling between sensory inputs and motor outputs that is characteristic of motor cortex. Since PAS relies on the interaction between sensory afferents and motor out-

**Figure 3** Paired associative stimulation (PAS) effect on corticospinal excitability, as measured by change in 1 mV motor evoked potential (MEP) amplitude in abductor pollicis brevis (APB) and abductor digiti minimi (ADM) muscle




(A) In the APB muscle on the less affected side, PAS increased 1 mV MEP amplitude ($F_{3,45}$ = 7.19; $p$ = 0.0004; one-way analysis of variance [ANOVA]) at all 3 time points: $p$ = 0.004 at 0 minutes, $p$ = 0.0006 at 15 minutes, and $p$ = 0.003 at 30 minutes. There was no significant effect of PAS in APB muscle on the more affected side. In healthy participants PAS increased 1 mV MEP amplitude in APB muscle ($F_{3,45}$ = 4.02; $p$ = 0.01; one-way ANOVA) only at the 15-minute timepoint: $p$ = 0.01. (B) In the ADM muscle, on the less affected side PAS increased 1 mV MEP amplitude at all 3 time points ($F_{3,45}$ = 6.23; $p$ = 0.001; one-way ANOVA), $p$ = 0.002 at 0 minutes, $p$ = 0.0009 at 15 minutes, and $p$ = 0.002 at 30 minutes. There was no significant effect of PAS in ADM muscle on the more affected side or in healthy participants. The data are plotted as a ratio to the baseline 1 mV MEP amplitude. Group differences (2-way ANOVAs; table 2) are marked with brackets (*$p < 0.05$, **$p \leq 0.01$). (C) Negative correlation between PAS-induced plasticity in APB muscle and clinical severity of PD shows that lower Unified Parkinson's Disease Rating Scale (UPDRS) score is associated with larger response to PAS. Blue circles: less affected side; red circles: more affected side.

put of the homologous muscle, loss of specificity could lead to spread of facilitation to the ADM muscle on the less affected side. The fact that the more affected side showed no response to PAS, even in the target APB muscle, might be explained by severe dopaminergic loss in the more affected hemisphere, as seen in more advanced disease. It has been shown that healthy subjects have an inverted "U"-shaped dopaminergic dose–plasticity response curve, in which low dopaminergic tone impairs plasticity, while moderate doses facilitate plasticity.[24,25] However, the nature of such nonlinear relationship has not been specifically investigated in PD.

Another novel finding of the present study is that patients with PD had normal SICI in the less affected hemisphere. SICI was absent in the more affected hemisphere, in line with previous findings of reduced SICI in more advanced PD.[26] We used CS intensity of 90% RMT to test SICI since this yields the clearest difference between PD and healthy individuals.[15] Detailed studies assessing SICI intensity curve or using different coil orientation indicate that GABAergic inhibitory circuits mediating SICI might be normal in PD and that decreased SICI possibly reflects a decreased threshold for intracortical facilitation at higher CS intensities.[15,27] Irrespective of underlying mechanism, impaired SICI in PD is thought to be related to dopaminergic deficiency since it is normalized with dopaminergic treatment.[26,28] Overall, our result implies that in early

PD, the dopaminergic deficit in the less affected hemisphere may still be under the critical threshold to trigger impairment of SICI. This would be consistent with the positive correlation between disease severity and reduced SICI. It should be noted that there is some debate in the literature over the best ISI to measure SICI.[29] Since we found similarly reduced SICI at all ISIs (2–4 msec) on the more affected side, we believe that this debate was not a confounding factor for the interpretation of the present results.

We found significantly shorter CSP on more affected side, and normal CSP on less affected side (figure e-2A), confirming previous reports.[30] In the present study, PAS effect on CSP was not statistically different between sides in patients with PD and was even stronger in more affected side compared to healthy participants (figure e-2B). This is in contrast with advanced patients with PD "off" dopaminergic treatment[19,31] and implies that circuits mediating PAS effect on CSP are preserved in early PD.

A critical question which is highlighted but unresolved by this current study is whether the alterations in plasticity response on the clinically less affected side represent a beneficial compensatory change that helps prevent motor symptoms evolving or a maladaptive change that reflects disease progression. With a follow-up of early asymmetric patients, it might be possible to determine if persistence of enhanced plasticity is associated with slower progression of motor signs on the less affected side, suggesting that this electrophysiologic change reflects a beneficial compensatory process, or the converse, which would suggest that it reflects a maladaptive process. The rate of change in PAS response over time could be developed into a surrogate marker of disease progression and deserves further investigation in longitudinal studies in patients with PD.

## AUTHOR CONTRIBUTIONS

Dr. Kojovic: design of the study, conceptualization of the study, data analysis, interpretation of data, drafting of the manuscript. Dr. Bologna: data analysis, interpretation of data, drafting of the manuscript. Dr. Kassavetis: data analysis, interpretation of data, revision of the manuscript for intellectual content. Dr. Murase: design of the study, revision of the manuscript for intellectual content. Dr. Palomar: data analysis, interpretation of data. Dr. Berardelli: design of the study, conceptualization of the study, revision of the manuscript for intellectual content. Dr. Rothwell: design of the study, conceptualization of the study, interpretation of data, revision of the manuscript for intellectual content. Dr. Edwards: design of the study, conceptualization of the study, interpretation of data, revision of the manuscript for intellectual content. Dr. Bhatia: design of the study, conceptualization of the study, interpretation of data, revision of the manuscript for intellectual content.

## DISCLOSURE

Dr. Kojovic received funding to attend congresses from MDS Society, Ipsen, and UCB Pharma. Dr. Bologna reports no disclosures. Dr. Kassavetis received funding to attend congresses from MDS Society, Ipsen, and UCB Pharma and is funded by Parkinson's UK (G-1009). Dr. Murase, Dr. Palomar, and Prof. Berardelli report no disclosures. Prof. Rothwell receives research support from Dystonia Medical Research Foundation, The Bachmann-Strauss Foundation, the Tourette Syndrome Association, and the Stroke Association, and is funded by FP7 Collaborative Project (222918) and (223524). He received financial support to speak at meetings organized by the Movement Disorders Society and the International Federation of Clinical Neurophysiology. Dr. Edwards received funding for conference travel and speaking engagements from Teva Pharmaceuticals and UCB. He has grant funding from the National Institute for Health Research (6187), Dystonia Society UK, and Parkinson's UK. Prof. Bhatia received funding for travel from GlaxoSmithKline, Orion Corporation, Ipsen, and Merz Pharmaceuticals, LLC; received speaker honoraria from GlaxoSmithKline, Ipsen, Merz Pharmaceuticals, LLC, and Sun Pharmaceutical Industries Ltd.; received personal compensation for scientific advisory board for GSK and Boehringer Ingelheim; received research support from Ipsen and from the Halley Stewart Trust through Dystonia Society UK; the Wellcome Trust MRC strategic neurodegenerative disease initiative award (ref. number WT089698); a grant from the Dystonia Coalition; and a grant from Parkinson's UK (ref. number G-1009). **Go to Neurology.org for full disclosures**.

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