Short and long latency afferent inhibition in Parkinson’s disease

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Summary
Sensory abnormalities have been reported in Parkinson’s disease and may contribute to the motor deficits. Peripheral sensory stimulation inhibits the motor cortex, and the effects depend on the interstimulus interval (ISI) between the sensory stimulus and transcranial magnetic stimulation (TMS) to the motor cortex. Short latency afferent inhibition (SAI) occurs at an ISI of ~20 ms, and long latency afferent inhibition (LAI) at an ISI of ~200 ms. We studied SAI and LAI in 10 Parkinson’s disease patients with the aim of assessing whether sensorimotor processing is altered in Parkinson’s disease. Patients were studied on and off medication, and the findings were compared with 10 age-matched controls. Median nerve and middle finger stimulation were delivered 20–600 ms before TMS to the contralateral motor cortex. The motor evoked potentials were recorded from the relaxed first dorsal interosseous (FDI) muscle. SAI was normal in Parkinson’s disease patients off dopaminergic medications, but it was reduced on the more affected side in Parkinson’s disease patients on medication. LAI was reduced in Parkinson’s disease patients compared with controls independent of their medication status. LAI reduced long interval intracortical inhibition in normal subjects but not in Parkinson’s disease patients. The different results for SAI and LAI indicate that it is likely that separate mechanisms mediate these two forms of afferent inhibition. SAI probably represents the direct interaction of a sensory signal with the motor cortex. This pathway is unaffected by Parkinson’s disease but is altered by dopaminergic medication in Parkinson’s disease patients and may contribute to the side effects of dopaminergic drugs. LAI probably involves other pathways such as the basal ganglia or cortical association areas. This defective sensorimotor integration may be a non-dopaminergic manifestation of Parkinson’s disease.

Keywords: Parkinson’s disease, motor cortex, magnetic stimulation, nerve stimulation

Abbreviations: CS = conditioned stimulus; DNS = digital nerve stimulation; FDI = first dorsal interosseous; ISI = interstimulus interval; LAI = long latency afferent inhibition; LICI = long interval intracortical inhibition; MEP = motor evoked potential; MNS = median nerve stimulation; SAI = short latency afferent inhibition; SEP = somatosensory evoked potential; TMS = transcranial magnetic stimulation; TS = test stimulus; UPDRS = Unified Parkinson’s Disease Rating Scale

Introduction
In addition to the well-known motor deficits in Parkinson’s disease, there is also evidence for sensory abnormalities. Sensory complaints have been reported in 20–43% of Parkinson’s disease patients (Snider et al., 1976; Koller, 1984; Hillen and Sage, 1996). They have been related to rigidity, bradykinesia and antiparkinsonian medications (Barbeau et al., 1971; Pallis, 1971), but a correlation between these features and sensory symptoms could not be found in larger studies (Snider et al., 1976; Hillen and Sage, 1996). Objective sensory deficits, especially diminished proprioception and kinaesthesia (Schneider et al., 1987; Klockgether et al., 1995; Demirci et al., 1997; Jobst et al., 1997; Zia et al., 2000), are well documented in Parkinson’s disease. It has been speculated that these sensory deficiencies may contribute to motor deficits and even to the development of dyskinesia (Moore, 1987; O’Suilleabhain et al., 2001).
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)/ gender</th>
<th>Disease duration (years)</th>
<th>More affected side</th>
<th>Medication* (LEs)</th>
<th>H&amp;Y+</th>
<th>UPDRS—total motor score§</th>
<th>UPDRS—more affected side¶</th>
<th>UPDRS—less affected side¶</th>
<th>Sensory symptoms³</th>
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<td>1</td>
<td>50 M</td>
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<td>901 (L-DOPA, ROP)</td>
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<td>35 22</td>
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<td>4 2</td>
<td>tingling and numbness</td>
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<td>2</td>
<td>60 M</td>
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<td>R</td>
<td>801 (L-DOPA, PRA)</td>
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<td>11 1</td>
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<td>numbness of R palm</td>
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<td>3</td>
<td>49 M</td>
<td>1</td>
<td>L</td>
<td>0 (no medication)</td>
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<td>10 –</td>
<td>0 –</td>
<td>tingling of L palm</td>
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<td>pain in L elbow</td>
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<td>4</td>
<td>60 F</td>
<td>17</td>
<td>L</td>
<td>1551 (L-DOPA, PRA)</td>
<td>2.5</td>
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<td>9 4</td>
<td>4 0</td>
<td>tingling of both (L&gt;R) hands</td>
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<td>5</td>
<td>51 F</td>
<td>4</td>
<td>R</td>
<td>334 (ROP)</td>
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<td>18 15</td>
<td>7 6</td>
<td>0 0</td>
<td>pain in L hand and knee</td>
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<tr>
<td>6</td>
<td>43 M</td>
<td>3</td>
<td>R</td>
<td>0 (AMA)</td>
<td>1.5</td>
<td>17 10</td>
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<td>7</td>
<td>73 M</td>
<td>3.5</td>
<td>L</td>
<td>1950 (L-DOPA, PER)</td>
<td>3.0</td>
<td>33 16</td>
<td>8 4</td>
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<tr>
<td>8</td>
<td>71 M</td>
<td>17</td>
<td>L</td>
<td>450 (L-DOPA)</td>
<td>1.5</td>
<td>17 7</td>
<td>5 3</td>
<td>2 0</td>
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<td>9</td>
<td>61 M</td>
<td>5</td>
<td>L</td>
<td>300 (L-DOPA, AMA)</td>
<td>2.5</td>
<td>30 19</td>
<td>10 4</td>
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<tr>
<td>10</td>
<td>64 F</td>
<td>8</td>
<td>R</td>
<td>396 (L-DOPA, ROP)</td>
<td>1.5</td>
<td>13 6</td>
<td>5 2</td>
<td>0 0</td>
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*The patients’ medication is converted into levodopa equivalents using the following formula: levodopa equivalent (LE) = total dose of regular levodopa (with peripheral decarboxylase inhibitor) + (0.75 x dose of controlled-release levodopa) + (100 x dose of pergolide) + (67 x dose of pramipexole) + (16.7 x dose of ropinirole). Medications are abbreviated as follows: L-DOPA = levodopa; ROP = ropinirole; PRA = pramipexole; PER = pergolide; AMA = amantadine; +modified Hoehn and Yahr scale; §Unified Parkinson’s Disease Rating Scale (UPDRS) motor section (items 18–31); ¶UPDRS—more and less affected side = items 20, 21, 22, 23, 24 and 25 of the UPDRS motor scale for the appropriate side; ³Sensory symptoms = item 17 of the UPDRS activities of daily living scale (‘sensory symptoms’) and subjective sensory symptoms reported by the patients. All patients who had sensory symptoms reported them to be worse in the off condition state and to be poorly localizable.
There is evidence that the central processing of sensory signals in Parkinson’s disease is abnormal. A PET study showed reduced activation of cortical areas and the basal ganglia in response to vibration (Boecker et al., 1999). Decreased amplitude of the N30 component of the somatosensory evoked potentials (SEPs) has been reported in Parkinson’s disease patients (Rossini et al., 1993; Ulivelli et al., 1999) and in primates rendered parkinsonian (Onofrj et al., 1990). Furthermore, abnormal neuronal responses in the basal ganglia after peripheral sensory stimulation have been found in animal models of Parkinson’s disease (Rothblat and Schneider, 1993; Aosaki et al., 1994).

Sensory stimulation can change motor cortex excitability. Motor cortex excitability in humans can be measured non-invasively using transcranial magnetic stimulation (TMS). A sensory conditioning stimulus, such as median nerve stimulation (MNS) or digital nerve stimulation (DNS), delivered to the contralateral hand can inhibit the motor cortex, resulting in decreased motor evoked potential (MEP) amplitude. This inhibitory effect depends on the interstimulus interval (ISI) between the conditioning sensory stimulation and the test TMS. Inhibitory effects occur at ISIs as short as 20 ms (Delwaide and Olivier, 1990; Tokimura et al., 2000), and we will refer to this as short latency afferent inhibition (SAI). At longer ISIs (>100 ms), a consistent inhibition was reported at an ISI of ~200 ms (Chen et al., 1999; Abruzzese et al., 2001), and we will refer to this as long latency afferent inhibition (LAI). In addition to the direct effects on MEP amplitude, LAI also interacts with other cortical inhibitory circuits such as long interval intracortical inhibition (LICI) (Sailer et al., 2002).

The aim of our study was to investigate whether cortical inhibition induced by peripheral sensory stimulation is altered in Parkinson’s disease and to examine the effect of dopaminergic medication on this inhibition. We studied the inhibitory effects of both MNS and DNS at different ISIs on motor cortex excitability and the effects of LAI on LICI.

Methods

Subjects

We studied 10 Parkinson’s disease patients without significant tremor (seven men and three women, aged 58.2 ± 9.8 years, mean ± SD; disease duration 7.4 ± 5.7 years) and 10 healthy, age-matched controls (six men and four women, aged 59.5 ± 10.7 years). All patients and controls were righthanded. All patients had asymmetric distribution of symptoms and were studied at least 12 h off medication in the ‘practically defined off state’ (‘off’ condition). Patients taking dopaminergic medication were also studied ~1 h after they took their usual doses of medication (‘on’ condition). All subjects gave written informed consent. The protocol was approved by the University Health Network Research Ethics Board in accordance with the Declaration of Helsinki on the use of human subjects in experiments.

Patients were assessed with the motor section (items 18–31) of the Unified Parkinson’s Disease Rating Scale (UPDRS) for both ‘off’ and ‘on’ conditions. Additionally, we obtained the Edinburgh Handedness score, the modified Hoehn and Yahr scale, the Schwab and England scale and a neurological examination including sensory examination. Sensory symptoms were assessed with a questionnaire that included item 17 of the UPDRS activities of daily living scale, the quality and location of sensory symptoms, and the differences between on and off medication states. The clinical information for the patients is listed in Table 1.

Experimental set-up

TMS

TMS was performed with a 7 cm figure-of-eight coil and two Magstim 200 stimulators connected via a Bistim module (The Magstim Company, Whitland, UK). The area for eliciting the best motor response for the right first dorsal interosseus muscle (FDI) was established over the left motor cortex with the coil held ~45° to the midsagittal line (approximately perpendicular to the central sulcus). The direction of the induced current was from posterior to anterior. The optimal position was marked on the scalp to ensure identical placement of the coil throughout the experiment. This procedure was then repeated for the right motor cortex and the left FDI.

EMG recording

A surface electromyogram (EMG) was recorded from the FDI muscles with Ag–AgCl electrodes placed over the belly of the muscle and near the metacarpal–phalangeal joint of the index finger. The EMG signal was monitored on a computer screen and via loudspeakers. The signal was amplified (Intronix Technologies Corporation Model 2024F, Bolton, Ontario, Canada), filtered (band pass 2 Hz–5 kHz), digitized at 5 kHz (Micro 1401, Cambridge Electronics Design, Cambridge, UK) and stored in a laboratory computer for off-line analysis. The subjects relaxed throughout the study. Trials contaminated with voluntary muscle activity were rejected.

MNS

The median nerve was stimulated at the wrist with standard bar electrodes (0.5 ms square wave constant current pulses), with the cathode positioned proximally. Stimulus intensity was adjusted to produce a slight thumb twitch (Chen et al., 1999; Abruzzese et al., 2001).

DNS

DNS was applied to the middle finger with ring electrodes (0.5 ms square wave constant current pulses), with the
cathode positioned proximally. Stimulus intensity was set at three times the sensory threshold. This stimulus intensity was chosen because it was not painful, and previous studies (Chen et al., 1999; Abbruzzese et al., 2001) showed that stronger stimuli did not increase the degree of inhibition.

**F-waves**

F-waves were elicited by supramaximal stimulation of the ulnar nerve at the wrist (0.2 ms constant current pulse). Surface EMG was recorded from the abductor digiti minimi muscle of the stimulated side.

**Study design**

We tested the effects of peripheral nerve stimulation (both MNS and DNS) at different ISIs on test MEPs induced by TMS. The intensity of the test stimulus (TS) was the minimum stimulator output that elicited MEPs of >1 mV in at least five out of 10 trials. The afferent inhibition induced by MNS was tested using the following pulse configurations: TS alone, and MNS preceding the TS by ISIs of 20, 40, 100, 200 and 600 ms. Since our previous study (Sailer et al., 2002) demonstrated that LAI inhibits LICI, we also tested LICI and the interactions between LAI and LICI. LICI was elicited by a suprathreshold conditioning stimulus (CS) set to evoke MEPs of ~1 mV and delivered 100 ms (CS 100) before the TS. LICI–LAI interaction was assessed by a triple pulse configuration consisting of a median nerve stimulus delivered 200 ms before the TS (MNS 200), a TMS CS (CS 100) and a TS (Sailer et al., 2002).

The afferent inhibition induced by DNS was tested using four different pulse configurations: TS alone, and DNS preceding the TS by 23, 43 and 203 ms. Three milliseconds were added for DNS to account for the extra peripheral conduction time, as a sensory volley takes ~2.8 ms to travel from the digit to the wrist (Kimura, 1989). Compared with MNS, several ISIs were omitted for DNS to reduce the recording time for Parkinson’s disease patients. The effects of MNS and DNS were studied on both sides.

The effects of MNS on spinal excitability were tested using F-waves. In Parkinson’s disease patients, the more affected side was tested in the ‘off’ state. Controls were tested randomly on either the left or the right side. MNS preceded the supramaximal ulnar nerve stimulation with the same ISIs as used in the TMS experiment (20, 40, 100, 200 and 600 ms). The same ISIs were used because the F-wave latency is similar to the MEP latency.

All the test conditions (eight for MNS, LICI and LICI–LAI, four for DNS, six for F-waves) were delivered in random order 6 s apart, and each condition was repeated 10 times.

**Data analysis**

The peak-to-peak MEP or F-wave amplitudes for each trial were measured off-line. The degree of test MEP inhibition was expressed as the ratio of the conditioned (with preceding MNS, DNS or CS100) to the unconditioned (TS alone) MEP amplitudes. Ratios <1 represent inhibition, and ratios >1 represent facilitation. For F-wave studies, the amplitude of F-waves elicited by ulnar nerve stimulation alone was compared with the amplitude of F-waves preceded by MNS. We also examined F-wave persistence, which is defined as the percentage of trials in which F-waves were elicited in each stimulus condition.

Background EMG area in a 600 ms period before the TMS TS was measured to look for differences in background EMG activity between patients and controls. LICI in the presence of LAI was computed by dividing the MEP amplitude resulting from the digit to the wrist (Kimura, 1989). Compared with MNS, several ISIs were omitted for DNS to reduce the recording time for Parkinson’s disease patients. The effects of MNS and DNS were studied on both sides.

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**Table 2. Motor threshold, test stimulus intensity used, test MEP amplitude and background EMG area for controls and Parkinson’s disease patients**

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>PD-off</th>
<th>PD-on</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Right hand</td>
<td>Left hand</td>
<td>More affected</td>
</tr>
<tr>
<td>Resting motor threshold (% of stimulator output)</td>
<td>49.7 ± 10.5</td>
<td>51.0 ± 12.5</td>
<td>44.4 ± 10.7</td>
</tr>
<tr>
<td>Test stimulus intensity used (% of stimulator output)</td>
<td>66.7 ± 20.0</td>
<td>69.7 ± 19.9</td>
<td>53.8 ± 14.7</td>
</tr>
<tr>
<td>Test MEP amplitude with MNS (mV)</td>
<td>0.91 ± 0.41</td>
<td>1.03 ± 0.43</td>
<td>1.14 ± 0.40</td>
</tr>
<tr>
<td>Background EMG area with MNS (mV × ms)</td>
<td>1.23 ± 0.55</td>
<td>1.35 ± 0.56</td>
<td>1.42 ± 0.70</td>
</tr>
<tr>
<td>Background EMG area with DNS (mV × ms)</td>
<td>5.62 ± 2.22</td>
<td>4.65 ± 1.21</td>
<td>4.87 ± 1.84</td>
</tr>
<tr>
<td>Background EMG area with DNS (mV × ms)</td>
<td>18.13 ± 18.69</td>
<td>21.14 ± 18.08</td>
<td>12.08 ± 5.67</td>
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from the triple pulse (MNS 200–CS 100–TS) condition by the MEP amplitude of the MNS 200–TS condition.

Statistical analysis

UPDRS scores in the ‘off’ and ‘on’ medication states were compared using the Wilcoxon signed rank test. For all other variables, Kolmogorov–Smirnov normality tests were performed. Non-parametric tests were used if the values were not normally distributed (P < 0.05, Kolmogorov–Smirnov test); otherwise parametric tests were used. Therefore, side differences for the TMS measures stated in Table 2 were assessed using the paired t test, and group differences using the unpaired t test, except for background EMG area which was not normally distributed and so the Wilcoxon signed rank and Mann–Whitney U tests were used.

The effects of MNS and DNS were examined by repeated-measures analysis of variance (ANOVA) with ISI as the repeated measure, side (left or right for controls; more or less affected for Parkinson’s disease) and medication status (patients only, on or off) as the between-group variables. If the effect of ISI was significant, changes at each ISI compared with the TS alone were assessed by the paired t test.

Differences between patients and controls were compared by repeated-measures ANOVA with ISI as the repeated measure, and group [control, Parkinson’s disease (PD)-on, PD-off] as the between-group variable. The more and less affected sides of patients were analysed separately. In order to account for any side differences in the control group, the average of the left and right hand results were compared with the patient groups. If the group effect was significant, Fisher’s protected least square difference post hoc test was calculated and the effect of group for each ISI was tested by factorial ANOVA.

SAI (ISI 20 ms) and LAI (ISI 200 ms) in the PD-off and PD-on states were correlated with the total UPDRS motor score, the sum of the upper extremity scores (items 20–25), item 17 (sensory symptoms) of the UPDRS activities of daily living section, and disease duration using Spearman’s correlation coefficient.

For LICI and LICI in the presence of LAI, the effects of side (right or left for controls; more or less affected for Parkinson’s disease) and medication status (on or off for Parkinson’s disease only) were assessed by factorial ANOVA. Patients and controls were compared using factorial ANOVA for group (control, PD-on, PD-off) separately for the more and less affected sides.

Changes in the F-wave between PD-off and control were compared by repeated-measures ANOVA with ISI as the repeated measure and group (control, PD-off) as the between-group variable.

Values were expressed as means ± SD. The threshold for significance was set at P < 0.05.

Results

The UPDRS scores for each patient are shown in Table 1. The UPDRS motor score was significantly higher (P = 0.008) in the ‘off’ (23.7 ± 11.1) compared with the ‘on’ (12.8 ± 6.3) state. The patient who was not taking medication and the patient on amantadine only were not included in the ‘on’ group. In one patient, only the more affected right side (both off and on medication) was studied due to discomfort. All the patients who reported sensory symptoms found them to be more prominent on the more affected side than the less affected side and in the ‘off’ compared with the ‘on’ state. Clinical sensory examination was normal in all patients, except patient 3 who reported hypoaesthesia of the more affected left hand. The mean and SD for rest motor threshold, TS intensity used, the MEP amplitude for the test pulse alone and the background EMG area are shown in Table 2. There were no significant side differences within the groups or group differences between controls and PD-off or PD-on, except for a higher background EMG in controls compared with the more affected side of PD-on for MNS (Mann–Whitney U test, P = 0.021).

Control subjects

MNS

The averaged MEPs of a control subject are shown in Fig. 1A. The afferent inhibition was significantly influenced by ISI (repeated-measures ANOVA; P < 0.001). There was no significant difference between the right and left hands and no significant side × ISI interaction.

Both sides showed significant inhibition for 20 ms (right P = 0.024, left P = 0.015), 100 ms (right P = 0.009, left P = 0.005) and 200 ms (right P = 0.0001, left P = 0.018) ISIs. At a 600 ms ISI, only the left FDI showed significant inhibition (P = 0.018). There was no inhibition at an ISI of 40 ms.

DNS

The afferent inhibition was dependent on ISI (repeated-measures ANOVA; P = 0.014). There was no significant difference between the right and left sides and no side × ISI interaction. Both sides showed significant inhibition only for an ISI of 200 ms (right P = 0.0001; left P = 0.027)

Parkinson’s disease patients

MNS

The averaged MEPs of a Parkinson’s disease patient (more affected side, off medication) are shown in Fig. 1B. The afferent inhibition was significantly influenced by the ISI (repeated-measures ANOVA; P = 0.001) and side (P = 0.014), but not medication status. The interactions between ISI, side and medication status were not significant. In the ‘off’ condition, there was significant inhibition
at an ISI of 20 ms (more affected, \( P = 0.002 \); less affected, \( P = 0.008 \)) and at an ISI of 100 ms for the less affected side (\( P = 0.014 \)).

The ‘on’ condition showed significant inhibition at an ISI of 20 ms (\( P = 0.017 \)) and 100 ms (\( P = 0.001 \)) only on the less affected side.

**DNS**
The degree of afferent inhibition was not significantly affected by ISI, side or medication status. The interactions between ISI, side and medication status were also not significant. In both the ‘off’ and ‘on’ conditions, there was no significant inhibition for any of the ISIs compared with the TS alone.

**Comparison between Parkinson’s disease patients and controls**

**MNS**
For the more affected side (Fig. 2A), afferent inhibition was significantly affected by ISI (repeated-measures ANOVA; \( P = 0.008 \)) and group (control, PD-on, PD-off; \( P = 0.012 \)), but the interaction between ISI and group was not significant. Controls had more inhibition than PD-off (\( P = 0.025 \)) and PD-on (\( P = 0.003 \)), but PD-off and PD-on were not significantly different from each other.

There were significant group differences for SAI (\( P = 0.010 \)), with less inhibition in PD-on compared with control (\( P = 0.016 \)) and PD-off (\( P = 0.004 \)). The groups also behaved differently for LAI at an ISI of 200 ms (\( P = 0.011 \)), where the inhibition was significantly reduced in PD-off.

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**Fig. 1** Examples of afferent inhibition in a control subject and a Parkinson’s disease patient. Averaged MEPs (10 trials) for the test stimulus (TS) alone and after median nerve stimulation (MNS) at different ISIs for (A) a control subject and (B) a Parkinson’s disease patient off medication. The TS was set to produce MEPs of ~1 mV. For short latency afferent inhibition (SAI) (ISI 20 ms), the MEPs for both the control subject and the Parkinson’s disease patient were inhibited compared with the TS alone. For long latency afferent inhibition (LAI) (ISIs 100–600 ms), there was MEP inhibition in the control subject, but in the Parkinson’s disease patient the MEPs were facilitated.
For the less affected side (Fig. 2B), the afferent inhibition was significantly affected by the ISI (repeated-measures ANOVA for ISI; \( P < 0.0001 \)), but there was no significant effect of group or group \( \times \) ISI interaction.

DNS

For the more affected side (Fig. 3A), the effects of ISI, group and group \( \times \) ISI interaction were not significant. For the less affected side (Fig. 3B), the effect of ISI was significant \( (P = 0.007) \) as well as PD-on \( (P = 0.013) \) compared with control.

For the less affected side (Fig. 2B), the afferent inhibition was significantly affected by the ISI (repeated-measures ANOVA for ISI; \( P < 0.0001 \)), but there was no significant effect of group or group \( \times \) ISI interaction.

**LICI**

LICI in the presence of LAI was assessed in nine patients, as one patient had to be excluded due to artefacts in the recording. LICI and LICI in the presence of LAI were not significantly different for the right and left sides in control subjects. For Parkinson’s disease patients, the effects of side (more affected or less affected), medication status (on or off) and the side \( \times \) medication interaction were not significant.
MNS inhibited the MEP produced by the CS 100 pulse in controls (MEP ratio 0.85 ± 0.62) and Parkinson’s disease patients (0.75 ± 0.29) to a similar degree. For both the more affected (Fig. 4A) and less affected sides (Fig. 4B), LICI alone did not differ between the groups (controls, PD-off, PD-on), but the group effect was significant for LICI in the presence of LAI (factorial ANOVA; P = 0.050 for the more affected side, P = 0.013 for the less affected side). LICI in the presence of LAI was reduced in controls compared with PD-off (P = 0.039 for the more affected side, P = 0.034 for the less affected side) and PD-on (P = 0.034 for the more affected side, P = 0.005 for the less affected side).

F-wave
Results were obtained in nine controls and nine patients. In one control subject, consistent F-waves could not be obtained, and one patient did not tolerate supramaximal ulnar nerve stimulation. The unconditioned F-wave amplitude showed no significant difference between patients (0.21 ± 0.13 mV) and...
controls (0.17 ± 0.08 mV). However, the unconditioned F-wave persistence was significantly higher ($P = 0.003$) in patients (96 ± 4%) than in controls (79 ± 12%). Repeated-measures ANOVA did not show any significant effect of ISI, group and ISI × group interaction.

**Correlation with clinical measurements**
SAI (ISI 20 ms) and LAI (ISI 200 ms) did not correlate with the total UPDRS motor score, the upper extremity score, the presence of sensory symptoms and the disease duration.

**Discussion**
In Parkinson’s disease patients, SAI is normal while off medication but is reduced in the on medication state. LAI is reduced in Parkinson’s disease patients off medication, and dopaminergic drugs do not normalize this effect. The inhibitory effect of LAI on LICI is also reduced in Parkinson’s disease patients. Since SAI and LAI are probably mediated by different mechanisms, they will be discussed separately.

**SAI**
Our findings of SAI from MNS are in accordance with a previous study in healthy subjects (Tokimura et al., 2000). SAI probably occurs at the cortical level because the corticospinal waves (I-waves) induced by TMS are decreased after MNS (Tokimura et al., 2000). As an afferent volley needs 18–20 ms to reach the cortex, the inhibitory information has to travel to the motor cortex with only a few
processing steps (Tokimura et al., 2000). Since SAI in the PD-off group is normal, the direct interaction of the median nerve sensory signal with motor output seems to be unaffected by Parkinson’s disease. However, the PD-on group showed deficient SAI. Although cholinergic circuits are likely to be involved in SAI (Di Lazzaro et al., 2000) and SAI is reduced in Alzheimer’s disease (Di Lazzaro et al., 2002), none of our patients were on anticholinergic medications and therefore cholinergic deficits cannot explain these results.

Dopaminergic medication decreased SAI on the more affected side but not on the less affected side (Fig. 2), suggesting that reduction of SAI in the PD-on groups occurs predominantly in more advanced Parkinson’s disease. Dopaminergic medications have been reported to worsen proprioception (O’Suilleabhain et al., 2001) and postural sway (Bronte-Stewart et al., 2002; Rocchi et al., 2002) in Parkinson’s disease patients. It has been speculated that this effect may contribute to dyskinesia (Moore, 1987; O’Suilleabhain et al., 2001). Moreover, patients often fail to recognize dyskinesias, and this may be related to disturbed processing of sensory input. However, whether changes in SAI are related to worsening of proprioception or dyskinesia remains to be established.

We found no significant SAI with middle finger stimulation at an ISI of 23 ms in either control subjects or Parkinson’s disease patients, similar to the results of Tamburin et al. (2002) with stimulation and recording sites from different digits (non-contiguous finger stimulation). Since dopaminergic medications change SAI from MNS, but do not affect the results digit stimulation, they may predominantly affect the processing of muscle afferent information. However, a cutaneous contribution cannot be ruled out because the effects of sensory stimulation in the hand are organized somatotopically (Classen et al., 2000; Tamburin et al., 2001, 2002). Abnormal MEP facilitation in Parkinson’s disease patients off medication has been reported if the stimulation site and the muscle being tested were from the same digit (contiguous finger) (Tamburin et al., 2002).

SAI

Our results indicate that LAI is reduced or absent in Parkinson’s disease patients. As the direct sensorimotor connection seems to be intact in Parkinson’s disease (normal SAI), the deficiency in LAI is most likely to be caused by other structures that are involved in sensory processing. One of these pathways could be the basal ganglia–thalamocortical loop. Animal studies and intraoperative recordings in humans have shown that neurons in the basal ganglia respond to cutaneous and proprioceptive stimuli (Rothblat and Schneider, 1993; Aosaki et al., 1994; Levy et al., 2001). Cats rendered parkinsonian with the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) showed reduced and abnormal activation in the striatum after peripheral sensory stimulation (Rothblat and Schneider, 1993). It has been hypothesized that the basal ganglia function as a sensory analyser, and abnormal afferent processing in the basal ganglia might contribute to motor manifestations in Parkinson’s disease (Brown et al., 1997).

Other areas may also be responsible for the deficient LAI in Parkinson’s disease. SEP and magnetoencephalographic studies have shown that at latencies longer than 40 ms after MNS, bilateral S1 and S2 (Hari et al., 1984; Allison et al., 1992) as well as the contralateral posterior parietal cortex are activated (Forss et al., 1994). A PET study using vibratory stimulation found reduced activation of the lateral premotor cortex, secondary somatosensory area and bilateral prefrontal cortices in Parkinson’s disease patients (Boecker et al., 1999). An altered distribution of proprioception-related evoked potentials at latencies of 170–180 ms has been found in Parkinson’s disease patients (Seiss et al., 2003).

As the deficiencies in LAI were not reversed with dopaminergic medications despite improvement in motor symptoms, our findings cannot be explained by dopaminergic deficit. In Parkinson’s disease, there is also degeneration of non-dopaminergic structures such as the nucleus basalis, locus coeruleus, raphe nuclei and the centromedian and parafascicular complex of the thalamus (Henderson et al., 2000) which send major glutamatergic inputs to the basal ganglia, but are also believed to influence sensorimotor and premotor cortices directly.

Whether changes in LAI are related to any particular symptom or sign in Parkinson’s disease is not known. Since LAI did not change with dopaminergic drugs and did not correlate with the UPDRS motor scores, reduction in LAI is probably not secondary to motor manifestations (Snider et al., 1976). The greater deficiency in LAI on the more affected side is consistent with sensory symptoms and deficiencies in proprioception occurring more frequently on the same side in Parkinson’s disease patients (Koller, 1984). Although no correlation was found between sensory symptoms and LAI, this may be related to the low sensitivity of the measure (item 17 of the UPDRS), and quantitative sensory testing was not performed. Since LAI is also reduced in dystonia (Abbruzzese et al., 2001), the finding may also be related to dystonic symptoms that are often present in Parkinson’s disease patients.

LAI

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Interactions between LAI and LICI

The marked reduction of LICI in the presence of LAI in control subjects is similar to the findings in a previous study (Sailer et al., 2002). The normal LICI in our patients is similar to the results of Berardelli et al. (1996) who found no significant difference between Parkinson’s disease and controls at ISIs of 100 ms although Parkinson’s disease patients had increased LICI at ISIs of 150 and 200 ms (Berardelli et al., 1996). We chose an ISI of 100 ms because our main interest was to examine the effects of LAI on LICI and previous studies in normal subjects were performed at this ISI (Sailer et al., 2002). Our results showed that the inhibitory effect of
LAI on LICI is deficient in Parkinson’s disease patients and is unaffected by dopaminergic medications, similar to the effect of LAI on MEP amplitudes. This effect cannot be explained by MNS-induced inhibition of the conditioning pulse (CS 100) because this inhibition was similar between Parkinson’s disease patients and controls, and a previous study demonstrated no relationship between inhibition of the conditioning pulse and the effects of LAI on LICI (Sailer et al., 2002).

Peripheral and spinal effects
Because muscle relaxation was monitored continuously and Parkinson's disease patients and controls had a similar background EMG area, it is unlikely that our findings are due to inability of the patients to relax. The higher F-wave persistence in Parkinson’s disease patients is consistent with previous observations (Abbruzzese et al., 1985). Since MNS had no effect on F-wave, the change in corticospinal excitability following MNS may occur predominantly at the cortical level, but changes at subcortical sites and spinal motor neuron populations not examined by F-waves cannot be ruled out.

Altered sensorimotor integration in Parkinson’s disease
Our findings suggest that the corticomotor output in response to sensory input is altered in Parkinson’s disease. A previous study has shown that in Parkinson’s disease patients on medication, the modulation of MEP amplitude in forearm muscles induced by changes in joint angle and passive movement was reduced (Lewis and Byblow, 2002). Whether these changes are related to altered SAI and LAI will require further study. Abnormalities in SAI and LAI could potentially lead to difficulty in determining joint positions during movement and consequently lead to errors in the scaling of movement amplitude (Berardelli et al., 1986) in Parkinson’s disease.

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