Altered sensorimotor integration in Parkinson’s disease

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Summary
Transcranial magnetic stimulation (TMS) was used to investigate sensorimotor integration in the upper limb of 10 patients with Parkinson’s disease and 10 age-matched controls. Non-conditioned and subthreshold conditioned (2 ms interstimulus interval) responses were recorded in the flexor and extensor carpi radialis muscles (FCR and ECR) of the more impaired (non-dominant) limb. Stimuli were delivered while the wrist joint was positioned statically at various joint angles as well as during different phases of passive movement of the wrist joint (90° amplitude, 0.2 Hz). The FCR and ECR muscles remained relaxed during all stimulation. In both groups, responses in the static condition were larger when the target muscle was in a shortened position. Responses were also facilitated in the muscle shortening phases of passive movement. In both static and dynamic conditions, the extent of modulations in response amplitude was significantly reduced in the patient group. The level of intracortical inhibition (ICI) was also significantly less in the Parkinson’s disease patients in static conditions. During passive movement, control subjects demonstrated a clear reduction in ICI compared with the static trials; however, the level of ICI was unchanged in the Parkinson’s disease group in the dynamic condition. The results suggest an abnormal influence of afference on corticomotor excitability in Parkinson’s disease. This may be related to abnormal sensory input, a defective integrative unit or an inappropriate motor response.

Keywords: Parkinson’s disease; sensorimotor integration; transcranial magnetic stimulation; Ia afferent; intracortical inhibition

Abbreviations: ECR = extensor carpi radialis; FCR = flexor carpi radialis; ICI = intracortical inhibition; ISI = interstimulus interval; MEP = motor evoked potential; r.m.s. = root mean square; RTh = rest threshold; TES = transcranial electrical stimulation; TMS = transcranial magnetic stimulation

Introduction
Parkinson’s disease patients have noted difficulties in regulating the amplitude of movements, particularly when visual information is absent and patients are reliant on kinaesthetic input for sensory feedback. Interestingly, conscious proprioception is usually intact and patients seldom report disturbances in joint position and movement sensation. However, in laboratory testing, deficiencies in sensorimotor integration tasks are detected routinely (e.g. Moore, 1987; Jobst et al., 1997).

The precise neural mechanisms associated with deficits in kinaesthesia and movement amplitude scaling in Parkinson’s disease are less certain, with conflicting hypotheses often published in the literature. An impaired ability in both static joint position sense (e.g. Zia et al., 2000) and movement perception (Schneider et al., 1987) has been reported in individuals with Parkinson’s disease, suggesting a degradation of afferent sensory information. Abnormalities in the performance of various limb positioning tasks (Klockgether et al., 1995; Rickards and Cody, 1997; Khudados et al., 1999) have also led others to implicate disturbed peripheral feedback and consequent impairments in sensory integration. In addition to this, some authors have implied deficits in the scaling of motor output and motor effort (Berardelli et al., 1986; Demirici et al., 1997), while the results of further studies have suggested that perceptions of motor effort are intact in Parkinson’s disease (Lewis et al., 2000).

Information from neurophysiological studies regarding afferent kinaesthetic input and its role in the sensory and motor disorders associated with Parkinson’s disease is also inconclusive. Alterations in fusimotor innervation may con-
tribute to defective sensory feedback in Parkinson’s disease patients; however, interpretations of Ia afferent microneurographic recordings are problematical in Parkinson’s disease as patients have difficulty completely relaxing their muscles, which can critically alter the degree of fusimotor activity (Burke, 1983). Studies examining the mechanoreceptor-evoked stretch reflex in the upper limb of Parkinson’s disease patients have demonstrated that the long latency segment (M2–3) is markedly potentiated compared with neurologically intact individuals (Tatton and Lee, 1975; Mortimer and Webster, 1979). It is now accepted that the M2–3 component of reflexes evoked in distal upper limb musculature includes a contribution from neurones within the motor cortex (Lenz et al., 1983; Tatton et al., 1983), suggesting an increased gain in the transcortical component of the feedback system in Parkinson’s disease. Abnormalities in basal ganglia output in response to passive movement have also been noted in monkeys rendered Parkinsonian by MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) treatment (Filion et al., 1988). This study revealed an increased magnitude of basal ganglia output and a loss of joint and directional specificity in the monkeys post-treatment, providing potential evidence of dysfunctional sensory processing in the basal ganglia.

In the current study, we further examined the neurophysiology of sensorimotor integration in Parkinson’s disease using an established upper limb movement paradigm (Lewis and Byblow, 2001) in conjunction with transcranial magnetic stimulation (TMS). In normals, we previously have demonstrated modulations in the excitability of the corticomotor pathway to forearm musculature during different phases of continuous passive wrist movement (Carson et al., 2000; Lewis et al., 2001). The pattern of response modulation throughout the movement cycle and the alterations in response modulation apparent at different movement frequencies strongly suggest that these modulations are mediated via Ia receptors, and are likely to include a cortical influence. The aim of the present investigation was to examine the modulations in responses evoked by TMS during passive upper limb movement in individuals with Parkinson’s disease versus matched control subjects. Modulations in intracortical excitability during passive movement were also examined by implementing a paired-pulse paradigm with subthreshold conditioning (Kujirai et al., 1993). At short interstimulus intervals (ISIs), this technique elicits inhibition of the motor evoked potential (MEP) that is thought to reflect the activity of GABA-mediated intracortical inhibitory circuits. Previous authors have demonstrated that this inhibition is deficient in individuals with Parkinson’s disease (Ridding et al., 1995a).

### Methods

#### Subjects

Ten individuals with idiopathic Parkinson’s disease and 10 age-matched, neurologically intact controls participated in the project. Details of patient and control subjects are

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>Sex</th>
<th>Impaired limb</th>
<th>Tested limb</th>
<th>Years diagnosed</th>
<th>H&amp;Y</th>
<th>Medication (mg/day)</th>
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<tr>
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<td>86</td>
<td>M</td>
<td>B</td>
<td>L</td>
<td>6</td>
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<td>L</td>
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<td>M</td>
<td>B</td>
<td>L</td>
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<td>1.5</td>
<td>Sinemet (800/200)</td>
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Average 65 ± 11 7.0 ± 3.6 2.1 ± 0.5

H&Y = Hoehn and Yahr rating, B = bilateral, R = right, L = left.

<table>
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<tr>
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<td>C10</td>
<td>48</td>
<td>M</td>
<td>L</td>
<td>L</td>
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</tbody>
</table>

Average 66 ± 12

L = left.
provided in Tables 1 and 2, respectively. Parkinson’s disease patients were required to be without marked tremor and rigidity. All individuals with Parkinson’s disease were tested when in a self-reported ‘on’ state of medication. All subjects were required to have no contraindications to TMS and to have a passive wrist joint range of motion of at least 100°. Informed consent was acquired prior to testing in accordance with the Declaration of Helsinki. Ethical approval for the study was obtained from the University of Auckland Human Subjects Ethics Committee.

Equipment
Subjects were seated in front of a custom-built manipulandum that generated passive flexion–extension movements of the wrist joint. The manipulandum consisted of a flat, vertically orientated hand piece mounted on a steel-framed table and top plate. The proximal end of the hand piece was mounted on a rotating shaft located coaxially with the wrist joint, enabling free rotation of the hand in the sagittal plane. The shaft was connected to a potentiometer to enable accurate specification and collection of displacement signals of the hand piece. Motion of the hand piece and wrist joint was induced by an AC servo motor (Baldor, Fort Smith, AR, USA) that was coupled to the shaft of the manipulandum and mounted underneath the unit. The motor generated sinusoidal motion of a programmable amplitude, frequency and duration.

The outer boundary of the top plate was drilled with holes corresponding to 5° increments of hand piece (wrist joint) angle, from −90 through to +90°. Zero degrees was defined as the angle at which the forearm and the palmar surface of the hand were aligned at 0°, with negative angles pertaining to wrist extension. The hand piece was able to be constrained statically to any angle by placing steel pins through the top plate holes on either side of the hand piece while located at the appropriate position.

Electromyography
Electromyographic (EMG) activity of the flexor- and extensor carpi radialis (FCR and ECR) muscles of the target limb was recorded using 10 mm Ag/AgCl surface electrodes (Hydrospot, Physiometrix Inc., MA, USA). Electrodes were placed 2 cm apart on the belly of each muscle in the proximal forearm. Triggering of EMG collection was initiated 20 ms prior to stimulus onset. EMG signals were amplified using Grass P511AC amplifiers (Grass Instrument Division, RI, USA) and bandpass filtered (30–1000 Hz). Signals were sampled at 4000 Hz using a MacLab A/D acquisition system (AD Instruments, Castle Hill, NSW) and stored to disc for further analysis.

Transcranial magnetic stimulation
Magnetic stimuli were delivered by two MagStim 200 stimulators (Magstim, Whitland, Dyfed, UK) with a BiStim unit via a figure-of-eight coil (diameter 70 mm each). The subjects wore a cotton cap with pre-marked grid coordinates that was securely fastened to the head with Velcro straps. The stimulating coil was positioned over the subject’s motor cortex contralateral to the test limb orientated at an angle 45° to the midline and tangential to the scalp, such that the induced current flow was in a posterior–anterior direction along the motor strip (Ziemann et al., 1998). To determine the optimal site of stimulation (hot spot), the coil was moved systematically around the grid locations until the site eliciting MEPs of the largest amplitude in the target FCR muscle was located. All further testing was carried out with the coil held over the hot spot by an experimenter. In all subjects, a discernible MEP in the ECR muscle was also obtainable with the stimulating coil at this location. Subjects were encouraged to affix their attention on a (blank) computer monitor located directly in front so that head position was maintained during testing. The location of the coil in relation to the subject’s head was checked repeatedly throughout the session to ensure that the site and angle of stimulation also remained constant.

Rest threshold (RTh) was determined for each subject with the coil held over the hot spot. Threshold was defined as the minimum intensity at which four of eight consecutive stimuli yielded a response of at least 50 μV in the relaxed FCR muscle. Test stimulus intensity was set to 110% of individual RTh, and conditioning stimulus intensity to 70% RTh. It was verified that potentials in the target muscles were not evoked in response to the conditioning stimulus alone. For conditioned trials, the ISI was set to 2 ms for all subjects. Conditioned responses were not examined in one patient (P5).

Protocol
The target limb for patients with unilateral deficits was the upper limb of the more impaired side (Table 1). For patients with bilateral deficits, and for control subjects, the non-dominant (Oldfield, 1971) limb was examined. MEPs were first evoked while the target limb was positioned statically at four wrist joint angles (−43, −18, +18 and +43°). These angles pertained to the position of the wrist when stimuli were evoked during passive movement. At each joint angle, eight non-conditioned and eight conditioned magnetic stimuli were delivered over the contralateral motor cortex. Subjects were instructed to maintain muscle quiescence during stimulation.

Stimuli were then delivered during continuous, sinusoidal passive movement of the wrist joint of 90° amplitude at 0.2 Hz. The movement cycle (peak flexion to peak flexion) was divided into eight temporally equal phases, with one stimulus delivered in each phase per passive movement trial. Each trial lasted ~60 s, and 16 trials were completed in the test session. In eight of these trials, non-conditioned stimuli were delivered, while conditioned stimuli were delivered in the remaining eight trials. This resulted in the collection of eight responses for each cycle phase and condition.
Transcranial electrical stimulation

In two neurologically intact subjects (age 21 and 37 years), corticospinal excitability at different static wrist joint angles was investigated further using transcranial electrical stimulation (TES). In contrast to TMS, TES preferentially activates neurones of the corticospinal tract directly (Day et al., 1989). Modulations in the size of the response to TES are therefore largely constrained to influences below the level of the cortex.

Electric stimuli were delivered by a Digitimer D185. Stimulating electrodes (Grass 6 mm) were adhered to the subject’s head and filled with conductive gel. The cathode was placed over the vertex, while the anode was positioned 7.0 cm distal from the cathode along the inter-aural line. Stimulus intensity was increased until a clearly discernible MEP was evident in the contralateral FCR and ECR muscles while quiescent.

Eight electric stimuli were delivered over the scalp while the wrist joint was constrained in each of the four target angles. The subjects were instructed to maintain their forearm muscles in a relaxed state during stimulation.

Data processing and analysis

Data were processed and analysed using custom-built routines on a Unix workstation. For each response collected, the root mean square (r.m.s.) amplitude of EMG activity 15 ms prior to the stimulus was determined, and responses were removed from further analysis if EMG silence was not maintained in this period (r.m.s. value comparable with that obtained during static trials). The peak-to-peak amplitude of all remaining responses was determined and averaged for each of the static wrist joint angles/cycle phases.

To examine the modulation of responses during the movement cycle in relation to static values, MEP amplitude in each passive movement phase was normalized to the corresponding value recorded in the relevant position and condition (non-conditioned or conditioned) during static trials. Therefore, all phase 1 and 8 conditioned responses were expressed relative to the value recorded in the conditioned static trial at +43°, phase 2 and 7 to +18°, phase 3 and 6 to −18°, and phase 4 and 5 to −43°. The extent of intracortical inhibition (ICI) was determined by expressing the amplitude of conditioned responses relative to the amplitude of the relevant non-conditioned response. For each group, values of ICI were averaged across wrist joint angles and cycle phases for the static and passive movement trials, respectively.

Statistical analysis

A two-way (group × joint angle) repeated measures ANOVA (analysis of variance) was conducted on MEP amplitudes from static trials to compare responses at the four wrist joint angles. Planned contrasts were made between the two flexed positions and the two extended positions (+43°, +18° versus −18°, −43°). MEPs obtained during passive movement were also analysed using a two-way repeated measures ANOVA (group × cycle phase). Significant main effects and interactions were explored using independent sample t tests which compared response amplitude between the patient and control groups. To investigate the phasic modulation of MEP amplitude in relation to responses obtained during static conditions, a further two-way repeated measures ANOVA (group × cycle phase) was implemented on the data normalized to static values. Effects of phase were examined using one-sample t tests that compared the value at each phase against unity, i.e. if static and passive responses were equivalent. For each group, paired t tests were also used to compare the level of ICI between static and passive movement conditions, while independent sample t tests were used to compare inhibition between the two groups.

An α level of 0.05 was used as a guide for establishing significant results. A Hunyh–Feldt correction factor was used for the repeated measures ANOVAs, and a Bonferroni correction factor was implemented to adjust the level of significance of t tests conducted (all two-tailed unless stated otherwise). Results are reported as mean ± standard deviation.

Fig. 1 Patient (open symbols) and control (closed symbols) MEP amplitudes during static conditions in the FCR (left) and ECR (right) muscles. * = significant difference between patient and control amplitudes. Club symbol indicates a significant difference in MEP amplitude between flexed and extended postures. Error bars represent 1 SEM.
Results

Magnetic stimulation

MEPs could not be obtained from one patient in the FCR muscle. Two control subjects were unable to maintain quiescence in the ECR muscle during static conditions at the most extended wrist joint angle, and data from this muscle of these two subjects were not included in the analysis. When the specified background EMG r.m.s. amplitude was exceeded consistently in any of the cycle phases, data from that muscle were excluded from the group analysis of passive movement responses. Sufficient data from the FCR muscle were obtained from eight patients and eight control subjects. For the ECR muscle, six of the 10 Parkinson’s disease patients were able to maintain muscle quiescence in all cycle phases; however, this was achieved by only one control subject. ECR results during passive movement were therefore only analysed for the patient group.

FCR muscle—static responses

Non-conditioned MEP amplitudes during static trials are illustrated in Fig. 1. Example MEPs from individual subjects are shown in Fig. 2. The main effect of joint angle \( [F(3,51) = 9.3; \ P = 0.001] \) and the group and joint angle interaction \( [F(3,51) = 4.0; \ P = 0.04] \) were significant. A planned comparison between the two flexed and two extended postures revealed a significantly larger response amplitude when the FCR muscle was in a shortened position (flexed = 211 ± 198 μV, extended = 90 ± 83 μV; \( P < 0.001 \)). MEP amplitude was also found to be larger in the control subjects than in Parkinson’s disease patients when the wrist was in a flexed posture (control = 283 ± 244 μV, Parkinson’s disease = 133 ± 83 μV; \( P = 0.02 \)). However, the difference between responses in the two groups was not significantly different when the wrist was at the extended joint angles (control = 101 ± 82 μV, Parkinson’s disease = 77 ± 40 μV; \( P = 0.3 \)).

ECR muscle—static responses

A significant effect of group indicated larger responses in the ECR muscle of the control subjects compared with the Parkinson’s disease patients \( [F(1,16) = 4.5; \ P = 0.05] \). Similar to the results in the FCR muscle, the main effect of joint angle \( [F(3,48) = 11.6; \ P < 0.001] \) and the group and joint angle interaction \( [F(3,48) = 5.0; \ P = 0.008] \) were also significant. Across both groups, MEPs again displayed a significantly greater amplitude when the ECR muscle was in a shortened position (wrist joint extended) compared with the two lengthened positions (flexed = 453 ± 373 μV, Parkinson’s disease = 2093 μV; \( P = 0.001 \)).
extended = 289 ± 205 μV; *P < 0.001). Comparisons between Parkinson’s disease and control groups at the flexed and extended postures revealed a significant difference in response amplitude when the wrist joint was extended (control = 658 ± 456 μV, Parkinson’s disease = 288 ± 166 μV; *P = 0.005). However, responses in the two groups were not significantly different when the wrist was in a flexed position (control = 358 ± 256 μV, Parkinson’s disease = 233 ± 137 μV; *P = 0.1).

**FCR muscle—passive movement responses**

A graph of Parkinson’s disease and control non-conditioned responses in the FCR muscle during passive movement is shown in Fig. 3A. The main effect of cycle phase was significant for these data [F(7, 98) = 7.7; *P = 0.002], indicating the expected phasic modulation of response amplitude during the movement cycle. From Fig. 3 it is evident that MEPs are potentiated in both groups when the FCR muscle is shortening. A prominent feature of the data is the reduced range of response amplitudes in the Parkinson’s disease patients, resulting in a much less marked pattern of modulation. This appears to be confirmed by a significant cycle phase and group interaction [F(7, 98) = 3.7; *P = 0.04]. However, *post hoc* tests failed to detect any significant differences between Parkinson’s disease and control MEP amplitudes at the individual cycle phases (all *P > 0.07*). When the two most potentiated phases (7 and 8) were combined, response amplitude was significantly greater in the control group (*P = 0.01*), whereas MEP amplitude in the groups at the two most inhibited phases (2 and 3) was not significantly different (*P = 0.5*).

To examine modulations in MEP amplitude compared with the responses obtained at the static wrist joint angles, MEPs from both groups during passive movement were normalized to the amplitude of the responses elicited in static trials (Fig. 3B). A significant main effect of phase for these data indicated the persistence of modulations in response amplitude during movement when taking alterations in static wrist joint angle into account [F(7, 98) = 4.6; *P = 0.001]. Following the results of similar studies, responses at cycle phases 6 and 7 were found to be significantly greater than unity (1), indicating a facilitated response compared with that obtained while the wrist was in the relevant static position (one-tailed; both *P < 0.005*). The heightened MEP amplitude at cycle phase 8 approached significance (*P = 0.01*, corrected *α = 0.006*). Both the main effect of group and the group

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**Fig. 3** Patient (open symbols) and control (closed symbols) FCR MEP amplitudes during passive movement. The top figure (A) shows raw MEP amplitudes, while results have been normalized to static values in the bottom figure (B). * = phases significantly facilitated above static values. Error bars represent 1 SEM.

**Fig. 4** Patient ECR MEP amplitudes during passive movement. The top figure (A) shows raw MEP amplitudes, while results have been normalized to static values in the bottom figure (B). Error bars represent 1 SEM.
During static conditions, in the FCR muscle of control inhibition was present, compared with the levels obtained control subjects (demonstrating significantly less inhibition in comparison with extensor muscle, with the Parkinson’s disease patients again was elicited (significantly less inhibition of the non-conditioned response the control group. In the Parkinson’s disease patients, to less than half the amplitude of non-conditioned values in static conditions, responses in the FCR muscle were inhibited (Fig. 5). During amplitude relative to non-conditioned and averaging across conditions was determined by expressing conditioned MEP The level of ICI during static and passive movement and cycle phase interaction were not significant for these data (both \( P > 0.1 \)).

**ECR muscle—passive movement responses**

As noted, MEPs obtained from the ECR muscle during passive movement were examined for the patient group only. A one-way ANOVA revealed an effect of phase for ECR MEP amplitude in this group \( F(7,35) = 3.5; P = 0.02 \). Similar to the results of the flexor muscle, responses in the ECR were facilitated during muscle shortening (wrist extension) and relatively inhibited during the phases of muscle lengthening (Fig. 4). When normalized to static values, the pattern of response modulation remained, confirmed by a significant phase effect for the normalized data \( F(7,35) = 3.9; P = 0.03 \).

**Intracortical inhibition**

The level of ICI during static and passive movement conditions was determined by expressing conditioned MEP amplitude relative to non-conditioned and averaging across joint angles and cycle phases, respectively (Fig. 5). During static conditions, responses in the FCR muscle were inhibited to less than half the amplitude of non-conditioned values in the control group. In the Parkinson’s disease patients, significantly less inhibition of the non-conditioned response was elicited \( (P = 0.01) \). Similar results were seen in the extensor muscle, with the Parkinson’s disease patients again demonstrating significantly less inhibition in comparison with control subjects \( (P = 0.05) \).

During passive movement, a significant reduction in inhibition was present, compared with the levels obtained during static conditions, in the FCR muscle of control subjects \( (P = 0.002) \). In contrast, the level of inhibition was comparable in the patient group between passive movement and static conditions \( (P = 0.2) \). This resulted in a non-significant difference in ICI in the FCR muscle between Parkinson’s disease patients and controls during passive movement \( (P = 0.6) \). Similar levels of inhibition were also evident in the ECR muscle of the patient group during passive movement and static conditions \( (P = 0.6) \).

It could be argued that the difference in non-conditioned MEP amplitude in the two groups may have contributed to the altered levels of inhibition seen. Most research indicates that ICI is less pronounced at larger test amplitudes \( (Ridding et al., 1995b; Ziemann et al., 1996; Abbruzzese et al., 1999) \), the opposite effect to that seen in our patient and control results. We decided to discount further possible influences of test MEP amplitude by only comparing ICI in conditions where non-conditioned MEP size was equivalent between patient and control groups. From Figs 1 and 3A, it is evident that this occurs in the static trials when the target muscle is in a lengthened posture \(-18^\circ, -43^\circ\) for FCR; \(+18^\circ, +43^\circ\) for ECR), and in phases 2–6 of passive movement (FCR only). \( t \) tests confirmed that non-conditioned MEP amplitude was not significantly different between the two groups during the selected static \( (P = 0.2) \) and passive movement \( (P = 0.9) \) conditions. Supporting the overall results, when test MEP size was matched, it was found that the extent of ICI was reduced in the patients during static trials \( (control 0.54 \pm 0.39, Parkinson’s disease 0.81 \pm 0.46; P = 0.01) \). However, there were no differences in the level of inhibition between the two groups during passive movement \( (control 0.79 \pm 0.29, patient 0.84 \pm 0.59; P = 0.7) \).

**Rest threshold**

Individual RTh in the FCR muscle did not differ between the control subjects \( (57 \pm 10\%) \) and Parkinson’s disease patients \( (57 \pm 11\%, P = 0.9) \).

**Electrical stimulation**

Figure 6 illustrates MEP amplitude in the FCR and ECR muscles in response to TES in the two control subjects. The results depict a similar finding to that seen with magnetic stimulation, i.e. response amplitude is greater when the target muscle is in a shortened position. \( t \) tests confirmed a significant difference between flexed and extended postures in the two subjects in both the FCR and ECR muscles (all \( P < 0.05 \)).

**Discussion**

**Responses in static conditions**

The results of the static trials follow those of previous studies that have indicated a heightened response amplitude when the target muscle is in a shortened position \( (Lewis et al., 2001) \).
The current study, however, demonstrated marked differences in the extent of MEP modulation between the controls and Parkinson’s disease patients. In the control subjects, FCR MEP amplitude was increased ~3-fold from the extended to the most flexed posture, while ECR response size in the extended postures was more than double that seen while the wrist was in a flexed position. Although the results of the patients mimicked this pattern of response modulation, the extent of facilitation was much less marked in comparison, particularly in the wrist extensor muscle.

There are several potential reasons that may account for the discrepancies in MEP facilitation between the two groups. Differences in resting corticospinal excitability between the two groups may have resulted in the use of a test stimulus intensity that was relatively reduced (or enlarged) in one of the groups. This is an unlikely possibility as, like many previous studies (Valls-Sole et al., 1994; Ellaway et al., 1995; Ridding et al., 1995c; Berardelli et al., 1996; Valzania et al., 1997), we found no difference in RTh between the two groups, and all subjects were tested at a stimulus intensity relative to threshold. A further possibility is that patients were simply incapable of eliciting an increased motor output in response to the cortical stimulus, such that response amplitude may have saturated. Similar suggestions have been made to account for the reduced facilitation of responses in Parkinson’s disease patients when undergoing muscle activation (Cantello et al., 1991; Valls-Solé et al., 1994). A notable difference in our study was the maintenance of muscle relaxation during all stimulation. Valls-Solé et al. (1994) found that, while relaxed, evoked responses in Parkinson’s disease patients were larger than those seen in controls, and increased in size with increments in stimulus intensity in an expected manner. Similar normal or larger-than-normal responses in relaxed muscle have been reported elsewhere in Parkinson’s disease patients (Cantello et al., 1991; Davey et al., 1991), suggesting that corticomotor excitability is intact, or slightly raised, during rest. The possibility of a saturated motor response in the static conditions in the current study also tends to be discounted by the enlargements in MEP amplitude during the facilitated phases of passive movement. Two further possibilities are that Parkinson’s disease patients have an altered sensory receptor function, or demonstrate altered sensorimotor integration. Previously, we have implicated muscle spindle afferents, from both homonymous and antagonist musculature, in the changes in corticomotor excitability evident at various joint angles, along with a possible involvement of Golgi tendon organ output through the slight alterations in muscle tension at different muscle lengths (Lewis et al., 2001).

Reduced sensory receptor function and, consequently, output would lead to deficits in the modulation of response amplitude with different joint postures. Likewise, a disturbed or less influential effect of sensory input on motor output would have the same consequence. An earlier study by Rossini et al. (1991) noted a reduced influence of peripheral conditioning on corticospinal excitability in Parkinson’s disease patients. They concluded that Parkinson’s disease was associated with abnormal processing of sensory input used in the generation and execution of movement. Our findings in the current study appear to be in accordance with this observation.

There is evidence to suggest that, in neurologically intact individuals, the modulatory effect of joint angle on corticomotor excitability in static conditions is mediated predominantly at the spinal level. Evidence for this includes the lack of alterations in the extent of ICI between the different wrist joint angles (Lewis et al., 2001), and the equivalence of response amplitude across joint angles during a constant level of muscle activation, which serves to stabilize the excitability of the motoneurone pool (Lewis and Byblow, 2002). Both of these findings imply the absence of alterations in cortical excitability while in different wrist postures. The TES findings in the present study provide further evidence that there is a substantial subcortical component to the modulations in response amplitude at different joint postures. As TES preferentially stimulates the corticospinal tract directly, alterations in pathway excitability are constrained.
to influences that are mediated below the level of the cortex. That the static responses were abnormal in the patient group strongly suggests an impairment present or arising at a subcortical level.

**Responses during passive movement**

MEPs elicited during passive movement demonstrated the normal pattern of facilitation when the target muscle was shortening and relative inhibition during muscle lengthening. In the patient group, this pattern of modulation was found in both the flexor and extensor muscles. In line with the results obtained in static conditions, the pattern of modulation throughout the movement cycle was comparable between the two groups, although the extent of MEP potentiation was much less distinct in the Parkinson’s disease patients. Response amplitude was equivalent between Parkinson’s disease and control subjects at the inhibited cycle phases (2–5); however, the patients demonstrated significantly less disinhibition during the facilitated cycle phases, particularly at phases 7 and 8. Interestingly, when normalized to static responses, there were no significant differences between response amplitudes of the two groups. This suggests that the extent of MEP modulation during passive movement is comparable based on the size of the responses in static conditions, i.e. Parkinson’s disease responses appear to be downregulated in amplitude overall, but still maintain an equivalent amount of facilitation during movement in relation to static responses.

It is prudent to consider whether or not the inability of the majority of control subjects to maintain the ECR muscle in a relaxed state during movement may have influenced the excitability of pathways to the FCR muscle. However, inappropriate activation of the ECR muscle was almost always restricted to the cycle phases corresponding to shortening of the muscle while in a shortened position, i.e. phases 3 and 4. Therefore, it is unlikely that this unwanted activation would have contributed to the reduced potentiation of responses in the FCR muscle during cycle phases 7 and 8.

**Intracortical inhibition**

The demonstration of a reduced level of ICI in Parkinson’s disease patients during static conditions supports the findings of Ridding et al. (1995a). These authors revealed a deficit in ICI at ISIs of 2, 4 and 5 ms in relaxed muscles of patients off medication. They proposed that the abnormalities in inhibition in Parkinson’s disease were due to a reduction in the excitability of GABA-dependent inhibitory pathways as a consequence of faulty basal ganglia output. More recent studies have indicated similar abnormalities in ICI in atypical Parkinsonism (Marchese et al., 2000) and other movement disorders (Ridding et al., 1995c; Abbuzzese et al., 1997), suggesting that this phenomenon may be related to a more general imbalance of cortical excitation and inhibition not specific to individuals with Parkinson’s disease. Interestingly, we were able to demonstrate reductions in ICI in patients while on their normal medication, whereas previously the intake of L-dopa has been seen to normalize responses in this population (Ridding et al., 1995a; Marchese et al., 2000).

A further irregularity between the groups was the significant reduction in inhibition during passive movement in the control group, which was not evident in the Parkinson’s disease patients. This resulted in comparable levels of inhibition between the two groups in the passive movement condition. A reduction in ICI during passive movement was also demonstrated in our previous experiments involving wrist joint movement (Carson et al., 2000; Lewis et al., 2001), most notable during the muscle shortening phases. It was suggested that the changes in muscle afference during movement may act to suppress the activity of inhibitory circuits within the cortex.

We suggest two possible explanations for the dissimilar ICI results in the patient group in the current study. First, the suppression of disinhibition with passive movement in the Parkinson’s disease group may be further evidence of an altered influence of movement-elicited afference on corticodorsal pathways. A reduced modulatory effect of afference on motor pathways was noted earlier in the non-conditioned responses; the results of the conditioned trials may be indicative of a similar effect involving intracortical circuits. An alternative view is that the abnormal activity of intracortical inhibitory circuits present during static conditions is normalized by the introduction of afference elicited by passive movement, as levels of inhibition were equivalent in the two groups in the dynamic condition. Further investigations obviously are required to distinguish the two possibilities.

How may these findings relate to deficits in kinaesthesia in Parkinson’s disease? The results of the static and passive movement conditions suggest a defective or reduced sensory receptor function, or a downregulation of corticodorsal output in response to an intact sensory input. Both of these possibilities would lead to difficulties in accurately determining joint position and movement and/or in the regulation and scaling of movement amplitude. The current experimental paradigm does not allow us to determine more precisely where kinaesthetic deficits in Parkinson’s disease arise; however, it does appear to confirm abnormalities in sensorimotor integration in this population. It is unknown whether these neuropsychological deficits are specific to individuals with Parkinson’s disease, or if other populations with disordered basal ganglia function may show similar patterns, e.g. focal dystonia, or Wilson’s disease, where there are known impairments of basal ganglia–thalamic outputs to the motor cortex. Similarly to the studies discussed in the Introduction (Tatton and Lee, 1975; Mortimer and Webster, 1979; Filion et al., 1988), we have provided evidence of an altered motor response to afferent input in pathways involving a cortical or subcortical loop. In the present study, abnormal responses were also noted in static conditions, in
what is very probably a spinally mediated effect. Our results may point towards a general deficit in sensory processing in Parkinson’s disease that is not necessarily constrained to circuits involving transcortical pathways.

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