Impaired Modulation of Intracortical Inhibition in Focal Hand Dystonia

Cathy M. Stinear and Winston D. Byblow

Human Motor Control Laboratory, Tamaki Campus, University of Auckland, Auckland, New Zealand 1005

Previous studies have shown that intracortical inhibition (ICI) plays an important role in shaping the output from primary motor cortex, and that ICI may be impaired in people with Focal Hand Dystonia (FHD). This study explored the muscle-specificity and temporal modulation of ICI during the performance of a phasic index finger flexion task. Eight control subjects and seven with FHD were asked to rest their dominant hand upon a computer mouse, and depress the mouse button using their index finger in time with a 1 Hz auditory metronome, while keeping the rest of their hand as relaxed as possible. Responses to single and paired-pulse transcranial magnetic stimulation were recorded from the first dorsal interosseous (FDI) and abductor pollicis brevis (APB) muscles while subjects were at rest and during ‘on’ and ‘off’ phases of the task. For control subjects during the movement (i) FDI motor evoked potential (MEP) amplitude and pretrigger EMG increased, and ICI decreased, as expected, and (ii) there was no significant facilitation of MEP amplitude or pretrigger EMG for APB, which was associated with a significant increase in ICI during the movement. This may have helped prevent the unwanted activation of this muscle. While FHD subjects demonstrated the same patterns of modulation of both MEP amplitude and pretrigger EMG for both FDI and APB, their levels of ICI were not modulated by task performance. This was despite no difference between subject groups in the level of ICI observed at rest. These findings suggest that FHD is associated with impaired modulation of ICI during performance of a precise manual task, which may contribute to a lack of specificity in the output from M1 and the development of dystonic symptoms.

Keywords: dystonia, intracortical inhibition, transcranial magnetic stimulation

Introduction

Intracortical inhibitory interneurons within the primary motor cortex (M1) produce inhibition of the corticospinal neurons, found in layer V (Di Lazzaro et al., 1998). They form a horizontal network of connections within the cortex, and seem to play an important role in shaping the output from M1 (Donoghue et al., 1996). Animal research has demonstrated that pharmacological blockade of intracortical inhibition (ICI) with a GABA_A antagonist (bicuculline methobromide) degrades the spatial selectivity of the output from M1 (Jacobs and Donoghue, 1991; Matsumura et al., 1991, 1992). This is thought to result from the disinhibition of horizontal intracortical connections between areas of M1, which promotes the recruitment of additional muscle or movement representations (Schneider et al., 2002). Schneider et al. (2002) have also provided evidence of a critical role for intracortical inhibitory processes in the prevention of co-activation of separate motor cortical points.

In humans, paired-pulse transcranial magnetic stimulation (TMS) provides a non-invasive means of studying intracortical inhibitory function. When a suprathreshold magnetic test stimulus is preceded by a subthreshold magnetic conditioning stimulus, the resulting motor evoked potential (MEP) may be inhibited or facilitated, depending upon the interstimulus interval (ISI) (Kujirai et al., 1993). Generally, short ISIs (1–5 ms) produce inhibition of the test MEP, while longer ISIs (10–15 ms) produce facilitation of the test MEP (Kujirai et al., 1993; Chen et al., 1998). The conditioning stimulus is thought to excite GABA-ergic intracortical inhibitory interneurons, which inhibit corticospinal cells with a latency of between 1 and 5 ms (Ziemann et al., 1996a,b). Other authors have shown that even minimal levels of voluntary activation of the target muscle significantly reduce the degree of inhibition produced by subthreshold conditioning stimuli delivered at ISIs between 1 and 6 ms (Ridding et al., 1995b; Hanajima et al., 1998). This is probably due to reduced excitability of the inhibitory interneurons that project to the corticospinal neurons responsible for activation of the target muscle (Ridding et al., 1995b).

Paired-pulse TMS has also been used to demonstrate the role of ICI in the prevention of unwanted muscle activation. Liepert et al. (1998) showed that ICI acting upon the M1 representations of different hand muscles can be differentially modulated and volitionally increased. However, these authors tested ICI while subjects were at rest, so the potentially differential modulation of ICI and its contribution to selective muscle activation during task performance was not examined. Sohn et al. (2002) provided evidence of a globalized increase in ICI during volitional inhibition of motor activity in the context of a Go–NoGo reaction time task (Sohn et al., 2002). However, this finding was based on a whole hand task, and it is perhaps unsurprising that the authors found a globalized, rather than muscle-specific, increase in ICI.

More recently, we demonstrated that the ICI acting upon the M1 representations of intrinsic hand muscles was temporally modulated in a muscle-specific way during the performance of a phasic manual task (Stinear and Byblow, 2003). This was achieved by recording MEPs in response to single and paired-pulse TMS while subjects were performing a phasic index finger flexion task paced at 1 Hz. Responses were recorded from first dorsal interosseous (FDI) as it was activated during index finger flexion, and abductor pollicis brevis (APB) as a control muscle. During task performance, stimuli were delivered during finger flexion (‘on’ phase) and between finger flexions (‘off’ phase). We found that those subjects who successfully maintained EMG quiescence in APB during task performance increased the ICI acting upon APB during the ‘on’ phase of the task, compared to resting levels of ICI (Stinear and
Impaired Modulation of ICI in FHD • Stinear and Byblow, 2003). This finding lends further support to the hypothesis that an increase in ICI acting upon a hand muscle’s representation in M1 may help to prevent its unwanted activation during the performance of a precise manual task.

Focal Hand Dystonia (FHD) is characterized by excessive and widespread involuntary contraction of the muscles controlling the hand during the performance of a specific task, leading to a loss of movement precision and selectivity (Sheehy et al., 1988; Marsden and Sheehy, 1990). Symptoms typically arise during the performance of specific tasks such as writing and playing a musical instrument, and have been linked to impaired sensorimotor integration at multiple levels of the central nervous system (Berardelli et al., 1998). Previous authors have also found evidence of impaired ICI at rest in FHD patients (Ridding et al., 1995a; Siebner et al., 1999b). A recent study by Giliio et al. (2003) has also demonstrated impaired pre-movement modulation of corticospinal excitability and ICI during the performance of a simple reaction time task by patients with upper limb dystonia. However, the modulation of ICI during task performance has not been explored in people with FHD. We hypothesized that impaired and/or inappropriate modulation of ICI may occur during manual task performance, thus contributing to the symptoms of FHD. To test this hypothesis, we recruited volunteers with FHD and carried out the experimental protocol that has previously allowed us to demonstrate muscle-specific temporal modulation of ICI in neurologically normal control subjects (Stinear and Byblow, 2003).

Materials and Methods

Subjects

Eight neurologically normal subjects and seven with FHD participated in this experiment (two women in each group, control subjects’ mean age 31 years, range 23–56 years, FHD subjects’ mean age 49 years, range 36–59 years). Two subjects with FHD were bilaterally affected and tested, giving a total of nine affected hands tested. See Table 1 for clinical details. Two subjects with FHD were undergoing treatment with botulinum toxin. Care was taken to ensure that they were tested at least 10 weeks after their last treatment, and immediately before their next. Using a handedness questionnaire (Oldfield, 1971), all were deemed right-handed (control subjects’ mean laterality quotient 88.7%, SD 9.7; FHD subjects’ mean laterality quotient 85.8%, SD 11.9). The Auckland Ethics Committee approved the procedure in accordance with the Declaration of Helsinki, and informed consent was obtained from all participants.

Preparation

Subjects were seated comfortably next to a table upon which they rested their dominant forearm and hand in a pronated position. Their dominant hand rested upon a computer mouse, with the middle and distal phalanges of their index finger resting on the mouse button. Their dominant thumb was supported by a foam block in a slightly abducted position, so that it did not contact the mouse. Their dominant wrist and forearm were supported by a large piece of foam so that the wrist joint was maintained in a neutral position. Subjects were instructed to keep their hand and forearm muscles as relaxed as possible, and apply downward pressure to the mouse button using only their index finger.

Depression of the mouse button activated a sound transducer, which emitted a high-pitched tone while the mouse button switch was closed. Subjects practiced depressing the switch and creating a tone in time with an auditory metronome that was emitting 800 Hz tones of 200 ms duration at a rate of 1 Hz. The output from the mouse button was collected at a 200 Hz sampling rate with a National Instruments 16 bit A/D converter (PCI-MIO-16XE-50) and PC LabView programme, and stored to disk for subsequent analysis. Electromyography (EMG) data were collected from the FDI and abductor pollicis brevis (APB) muscles of the dominant hand via a pair of 12 mm diameter surface Ag-AgCl Hydrospot electrodes (Physiometrix Inc., MA), using standard techniques. Signals were amplified by two Grass P511AC EMG amplifiers (Grass Instrument Division, RI). The EMG data were bandpass filtered at 30–1000 Hz, sampled at 4 kHz with a 12-bit MacLab A/D acquisition system and software, and stored to disk for subsequent analysis.

This experiment was conducted in two separate sessions, separated by at least 24 h. In the first session, the TMS variables were optimized for stimulation of APB, and in the second session the TMS variables were optimized for stimulation of FDI, or vice versa. The same procedure was followed for both sessions. A pair of MagStim 200 magnetic stimulators (MagStim Company, Dyfed, UK, maximum output intensity 2.0 T) connected by a Bitstim unit was used to stimulate the motor cortex via a figure-of-eight coil (7 cm coil diameter). The coil was held tangentially to the scalp and perpendicular to the central sulcus, so that the induced current flow was in a posterior to anterior direction. The optimal location for eliciting MEPs in the muscle of interest (APB or FDI) was determined by stimulating at sites over the contralateral motor cortex in a 1 cm grid pattern with the subject at rest. The location that produced the greatest peak-to-peak amplitudes in the muscle of interest was considered optimal. This was found to be 2–4 cm lateral to the vertex for all subjects.

Rest threshold for the muscle of interest was then established at the optimal locations by altering the stimulator output intensity initially in 5% and then in 1% increments. Rest threshold (RTh) was defined as the stimulator output intensity that produced MEPs with a peak-to-peak amplitude of ∼30% inhibition of the test response. This ISI was used for all subsequent paired-pulse trials, and was found to be between 2.3 and 2.8 ms for all subjects. Resting levels of ICI in FDI were determined using conditioning and test stimulus intensities of 80% and 120% RTh, respectively, and each subject’s optimal ISI, at the beginning of the FDI session. For FDI, conditioning stimulus intensity was then set to 90% RTh. For both muscles, the conditioning stimulus intensity was initially set to 80% RTh. The ISI was then altered in 0.1 ms steps to determine the ISI that produced peak-to-peak amplitude of ∼30% inhibition of the test response. This ISI was used for all subsequent paired-pulse trials, and was found to be between 2.3 and 2.8 ms for all subjects. Resting levels of ICI in FDI were determined using conditioning and test stimulus intensities of 80% and 120% RTh, respectively, and each subject’s optimal ISI, at the beginning of the FDI session. For FDI, conditioning stimulus intensity was then set to 90% RTh. For APB, the conditioning stimulus intensity was then reduced to a level that produced ∼50% inhibition of the test response (C50). This level was chosen to avoid the ‘floor effect’ (Fisher et al., 2002), and allow the detection of any increases in the level of inhibition acting upon the APB representation during task performance. The conditioning stimulus intensities for both FDI and APB most likely intersect the linear region of the stimulus–response curve for the intracortical inhibitory interneurons (Fisher et al., 2002), thus allowing the detection of changes in ICI that occur with changes in

<table>
<thead>
<tr>
<th>Table 1</th>
<th>FHD clinical data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject</td>
<td>Gender</td>
</tr>
<tr>
<td>1</td>
<td>M</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
</tr>
</tbody>
</table>
Experimental Protocol
Two types of trials were conducted: active task performance and rest. During active trials, an auditory metronome produced 800 Hz tones, of 200 ms duration, at a rate of 1 Hz. For active trials subjects were instructed to use their dominant index finger to depress the mouse button in time with the auditory metronome, while keeping the rest of their hand as relaxed as possible. Depressing the mouse button activated a sound transducer that provided auditory feedback to subjects. They were instructed to match the offset and onset of the tones they generated by depressing the mouse button with those of the auditory metronome. During rest trials, subjects were instructed to relax their dominant hand on the computer mouse. Single and paired TMS pulses were delivered during active and rest trials in blocks of eight stimuli, at a frequency of 0.2 Hz. During active trials, stimuli were delivered either 50 ms or 600 ms prior to the metronome beat. This meant that stimuli were delivered either during the FDI EMG burst (50 ms offset, ‘on’ phase) or while the FDI was at rest between EMG bursts (600 ms offset, ‘off’ phase). This protocol is depicted in Figure 1. Test stimulus intensity was initially maintained at 120% RTh during task performance, enabling the assessment of the modulation of corticospinal excitability by task performance. Test stimulus intensity was then adjusted to match non-conditioned MEP amplitude during the ‘on’ and ‘off’ phases with the non-conditioned MEP amplitude recorded at rest.

Prior to data collection, subjects completed active practice trials, and their FDI EMG activation and timing checked. Blocks of eight TMS stimuli were delivered in a pseudorandomized order such that a total of 16 MEPs were collected in response to TMS for each condition.

Data Analysis
The output from the mouse button was transformed and visually displayed so that the timing of mouse button depression with respect to the auditory metronome beep could be visually inspected. Trials were accepted if the onset of the mouse button depression occurred within a 200 ms window, extending from 150 ms before to 50 ms after the onset of the auditory metronome beep, and the release of the mouse button occurred within the 300 ms following the onset of the auditory metronome beep. If less than 60% of a subject’s data was accepted on the basis of these criteria, their entire data set was discarded.

The trials recorded under each combination of experimental conditions for each subject and muscle were ranked in ascending order of peak-to-peak MEP amplitude. The top 20% and bottom 20% of the ranked trials were then discarded. A mean was then calculated from the remaining trials, which gives an accurate representation of central tendency when the data are skewed (Wilcox, 2001). For the retained trials, the pretrigger level of EMG activity was determined by calculating the root mean square (r.m.s., mV) value for a 20 ms period ending 5 ms prior to the stimulus artefact.

For each subject, muscle and condition, the average non-conditioned MEP amplitude in response to the unadjusted test stimulus (120% RTh) was normalized to the maximum MEP amplitude recorded from that muscle which remained after trimming of the data. This scales each subject’s data within their own range of MEP amplitudes, compensating for interindividual differences in MEP amplitude. The degree of inhibition for each muscle under each condition was then calculated using the following formula:

\[
ICI (%) = 100 - \frac{\left( NC - C \right)}{C} \times 100
\]

where NC = average matched non-conditioned MEP amplitude and C = average conditioned MEP amplitude. This results in a number that represents the degree of inhibition as a percentage, which at least partly compensates for interindividual variability in MEP amplitudes.

The pretrigger EMG data were normalized using a log_{10} transformation. The normality and homoscedasticity of the data were confirmed prior to statistical analysis (Bruning and Kintz, 1987). For NC MEP amplitude and ICI data, a mixed repeated measures analysis of variance (ANOVA) was performed, with muscle (FDI, APB) and phase (rest, ‘on’, ‘off’) as the within-group factors. For pretrigger EMG data, a mixed repeated measures ANOVA was performed for each muscle, with phase (rest, ‘on’, ‘off’) as the within-group factor. Planned contrasts were used to test for temporal modulation of NC MEP amplitude and ICI were then carried out, using paired t-tests.

Results

Subject Variables
The control subjects’ data have been reported previously (‘Group 2’, Stinear and Byblow, 2003). This entire group of control subjects was chosen for comparison with the FHD subjects, as they exhibited the same patterns of corticospinal excitability and EMG activity modulation during task performance. There were no differences between the two groups of subjects in their handedness, or temporal accuracy of task performance (Table 2). However, the groups were not age-matched (control mean 31 years, range 23–56 years; FHD mean 49 years, range 36–58 years; P < 0.01), as the control group data were collected as part of a larger study conducted previously (Stinear and Byblow, 2003). Both groups depressed the mouse button switch ∼20 ms prior to the metronome beep (on average) and held the switch closed for ~180 ms. The percentage of trials discarded due to temporal accuracy was between 3 and 10% (on average) and held the switch closed for ~180 ms. The percentage of trials discarded due to temporal accuracy was between 3 and 10% (on average) for both groups, during both experimental sessions. The rest thresholds, active thresholds, and CS_{50} intensities were comparable, and not significantly different (all P > 0.05). The degree of ICI produced at rest by the 90% ATh conditioning stimulus for FDI and by the CS_{50} conditioning stimulus for APB were comparable between groups, and not significantly different (P > 0.08). The non-conditioned test MEP amplitudes during task performance were adequately matched to those recorded at rest for each muscle (Table 2).

Corticospinal Excitability
The modulation of corticospinal excitability by task performance was examined by comparing normalized MEP amplitude at rest and during the ‘on’ and ‘off’ phases in response to the 120% RTh test stimulus between groups (Fig. 2). The mixed repeated measures ANOVA revealed a significant interaction between Muscle and Phase (F_{2,15} = 27.854, P < 0.001). Planned contrasts revealed that for FDI mean MEP amplitude was significantly higher during the ‘on’ phase than the ‘off’ phase or at rest (‘on’ 72.0%, ‘off’ 55.1.0%, rest 26.5%, P < 0.001). In
contrast, for APB mean MEP amplitude was significantly higher during the ‘off’ phase than the ‘on’ phase or at rest (‘off’ 68.3%, ‘on’ 47.4%, rest 32.7%, \( P < 0.001 \)). There was no effect of Group \( (P > 0.05) \).

**Pretrigger EMG**

For FDI, the mixed repeated measures ANOVA revealed a main effect of Phase \( (F_{2,15} = 46.679, P < 0.001) \). Planned contrasts revealed significantly higher mean levels of pretrigger EMG during the ‘on’ phase than at rest or during the ‘off’ phase (‘on’ 0.0082 mV, rest 0.0026 mV, ‘off’ 0.0038 mV, \( P < 0.001 \)). There was no effect of Group \( (P > 0.05) \), indicating that in both groups this muscle remained quiescent throughout task performance (Fig. 3).

**Intracortical Inhibition**

For FDI, when the conditioning stimulus and test stimulus intensities were set to 80% and 120% RTh, respectively, there was no difference between the groups in the level of ICI at rest (control 84.2% \( \pm \) 21.1%, FHD 79.9% \( \pm \) 24.1%, \( P > 0.05 \)). The modulation of ICI by task performance was examined by comparing ICI at rest and during the ‘on’ and ‘off’ phases of the task between groups. The mixed repeated measures ANOVA revealed a significant interaction between Group, Muscle and Phase \( (F_{2,15} = 5.371, P < 0.05) \). For control subjects, the level of ICI acting upon FDI was significantly lower during the ‘on’ phase than at rest or during the ‘off’ phase (‘on’ 18.7%, rest 76.0%, ‘off’ 57.3%, \( P < 0.05 \)), while the level of ICI acting upon APB was significantly higher during the ‘on’ phase than at rest or during the ‘off’ phase (‘on’ 50.4%, rest 25.8%, ‘off’ 21.5%, \( P < 0.05 \)). In contrast, for FHD subjects there was no statistically significant modulation of ICI during task performance, in either muscle (Fig. 4).

**Discussion**

The findings from this study suggest that while the level of ICI at rest in FHD is comparable to control subjects, the modulation of ICI during the performance of a precise manual task is impaired in FHD subjects. This is a novel finding that extends the work of others (Ridding et al., 1995a; Siebner et al., 1999a; Gilio et al., 2003) and supports a more sophisticated perspective on the nature of the abnormal inhibitory function associated with FHD. These data suggest that while short-latency inhibitory function may be unimpaired while FHD patients are
at rest, the modulation of this inhibitory function is impaired during manual task performance.

Both control and FHD subjects demonstrated a significant facilitation of corticospinal excitability during the ‘on’ phase for FDI, and during the ‘off’ phase for APB (Fig. 2). In Figure 2 it can be seen that there is an increase in corticospinal excitability above resting levels during the ‘off’ phase of the task, for both FDI and APB, in both subject groups. This is probably due to a globalized increase in excitability above resting levels associated with the ongoing performance of the phasic task, which is associated with minimal levels of EMG activity during the ‘off’ phase. For FDI in both groups, the level of excitability is further increased during the ‘on’ phase of the task. In contrast, for APB in both groups the level of excitability is actually lower during the ‘on’ phase than the ‘off’ phase of the task. The differential changes in excitability observed in FDI and APB during the ‘on’ phase of the task are probably due to the modulation of both excitatory and inhibitory inputs to the corticospinal neurons.

Both groups also demonstrated a significant increase in FDI EMG activity during the ‘on’ phase, with no change in APB activity during task performance (Fig. 3). For FDI in control subjects, the temporally modulated increase in corticospinal excitability and activation of this muscle were associated with a significant decrease in the level of ICI acting upon the FDI representation during the ‘on’ phase. These findings are in agreement with those from previous studies (Flament et al., 1993b; Ridding et al., 1995b; Devanne et al., 1997) and support the hypothesis that there is a temporal pattern of ICI and corticospinal excitability modulation during phasic muscle activation.

For APB in control subjects, there was no significant facilitation of corticospinal excitability during the ‘on’ phase. This was associated with a significant increase in ICI, and no change in APB activity during the ‘on’ phase. The increase in ICI acting upon the APB representation may have helped to prevent the unwanted activation of this muscle, enhancing the selectivity of muscle activation during task performance.

FHD subjects demonstrated the same patterns of modulation of both corticospinal excitability and EMG activity as control subjects, for both muscles. However, this was not associated with any significant modulation of ICI in either muscle. That is, the level of ICI acting upon the M1 representations of both FDI and APB during task performance did not differ significantly from the levels of ICI recorded at rest. For FDI, there is a trend towards a release of ICI during the ‘on’ phase, but this did not reach significance. For APB, there is also a trend towards a release of ICI during the ‘on’ phase, which is in direct contrast to the significant increase in ICI observed during the ‘on’ phase in control subjects (Fig. 4). One interpretation of the FHD subjects’ data is that it represents a mild, globalized reduction in ICI during task performance, which lacks clear spatial and temporal resolution. Further work with a larger sample of the FHD population is required to confirm this hypothesis.

These findings suggest that the modulation of ICI during the performance of this task is impaired in those with FHD. However, there were no behavioural consequences of this impaired modulation. Performance of the task did not provoke dystonic symptoms in any of the FHD subjects, and the FHD group performed the task with the same level of temporal accuracy as the control group (Table 2). This raises two possibilities. One is that the modulation of ICI is not, in fact, necessary for the performance of precise manual tasks. This seems unlikely, given the wealth of evidence from both animal and human studies demonstrating a role for ICI in enhancing the selectivity of the output from M1 (Jacobs and Donoghue, 1991; Matsumura et al., 1991, 1992; Liepert et al., 1998; Schneider et al., 2002; Stinear and Byblow, 2003). Alternatively, it may be that the normal modulation of corticospinal excitability observed in the FHD subjects arose due to a compensatory enhancement in the modulation of excitatory inputs to the corticospinal cells. The excitability of the corticospinal pathway is determined by the net effects of both inhibitory and excitatory inputs to the corticospinal cells. It is possible, therefore, that the impaired modulation of inhibitory inputs was compensated for by the modulation of excitatory inputs to the corticospinal cells. In the context of this simple task, this compensation may have been sufficient to allow normal modulation of corticospinal excitability and normal task performance. However, when FHD subjects perform the task that triggers their symptoms, the modulation of excitatory inputs may be insufficient to fully compensate for the impaired modulation of inhibitory inputs. This may lead to a lack of temporal and spatial selectivity of the output from the corticospinal population, and contribute to the development of dystonic symptoms. Further work is required to address this hypothesis.

One of the limitations of this study is that the control subjects were not age-matched to the FHD subjects. This is because the control subject data were collected as part of an earlier study, using the same experimental protocol (Stinear and Byblow, 2003). As our previous study demonstrated that neurologically intact subjects utilized two different strategies for the performance of this task (Stinear and Byblow, 2003), it was important to compare FHD subjects with a control group that utilized the same strategy for task performance. There were no differences between the groups in any subject variables other than age, or any dependent variables other than modulation of ICI. Furthermore, the age ranges of the two groups overlap considerably, with the maximum age of the control subjects being 56 years, and the maximum age of the FHD subjects being 59 years. Given that there is currently no body of evidence supporting the hypothesis that age has a significant effect upon ICI function, we used the available control subject data that exhibited the same modulation of EMG activity and corticospinal excitability demonstrated by the FHD subjects.
The finding that the resting level of ICI in the FHD subjects was not significantly different to that observed in control subjects is in contrast to the evidence of reduced resting levels of ICI associated with FHD presented by previous authors (Ridding et al., 1995a; Siebner et al., 1999b). Ridding et al. (1995a) used a range of ISIs (1–6 ms) and pooled results across these intervals to demonstrate less ICI in people with FHD. Siebner et al. (1999b) report lower levels of ICI in FHD patients with ISIs of 1 and 3 ms. However, no data regarding the statistical significance of this effect are reported. Recently, Lourenço et al. (2003) reported no difference in ICI levels at rest between control subjects and those with FHD. It is apparent that further work is required to resolve this issue.

We speculate that the impaired modulation of ICI observed in these FHD patients may have arisen due to impaired function of the sources of input to the intracortical inhibitory network, such as the basal ganglia. Generally, basal ganglia dysfunction is considered to be an important feature common to the family of dystonia disorders (Berardelli et al., 1998). When voluntary movement occurs, motor cortical areas send corollary output to multiple nuclei of the basal ganglia. These areas subsequently send output back to the motor cortical areas via the thalamus (for review, see Alexander and Crutcher, 1990; Mink, 1996). The two features of these pathways that are particularly relevant to FHD are their somatotopic organization, and their inhibitory function. Mink (1996) and Nambu et al. (2002) have hypothesized that these features play a critical role in focusing the motor output from M1. Specifically, the basal ganglia and thalamus are thought to have two parallel functions: the specific selection of the desired motor activity, and the inhibition of unwanted motor activity, via a centre-surround pattern of excitation and inhibition in the somatotopically organized output from the globus pallidus internus and thalamus. The thalamocortical projection may therefore serve to enhance motor contrast and focus the output from the motor cortex (Mink, 1996; Nambu et al., 2002).

Applying this model to FHD, it seems that basal ganglia dysfunction may result in disordered output from the thalamus, contributing to the loss of selectivity and motor overflow that is characteristic of FHD. The clinical literature supports this hypothesis by demonstrating that focal lesions of these structures are associated with reduced cortical inhibitory function and the development of dystonia (Hanaajima and Ugawa, 2000; Minchau et al., 2002). These reports indicate that basal ganglia dysfunction is associated with impaired intracortical inhibitory interneuron function, probably due to derangement of the pallido-thalamo-cortical pathway. Therefore, we speculate that deranged input to intracortical inhibitory networks from a dysfunctional pallido-thalamo-cortical pathway may impair the modulation of ICI during the performance of precise manual tasks, such as that utilized in this study.

In conclusion, our results suggest that the muscle-specific temporal modulation of ICI observed in control subjects during the performance of a precise manual task is impaired in those with FHD. This impaired modulation may degrade motor contrast and the selectivity of muscle activation during the performance of specific manual tasks, contributing to the development of dystonic symptoms. Examination of any changes in the modulation of ICI produced by the various rehabilitative approaches to FHD, such as immobilization, botulinum toxin injection, and retraining, may provide a useful insight into their efficacy and modes of action.

Notes
C.M.S. is supported by the Foundation for Research, Science and Technology. This project was supported by grants from Mr P. Baines, the University of Auckland Graduate Research Fund, and the Neurological Foundation of New Zealand.

Address correspondence to C. M. Stinear, Human Motor Control Laboratory, Tamaki Campus, University of Auckland, Private Bag 92019, Auckland, New Zealand. Email: c.stinear@auckland.ac.nz.

References