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Deficits in sensorimotor control during precise hand movements in Huntington's disease

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Abstract

Objectives: To investigate the performance of patients with Huntington's disease (HD) while manipulating objects using a precision grip.

Methods: The grip forces developed by the fingers were studied while subjects lifted an object of unpredictable weight in the hand. The ability to stabilize grip force after externally imposed weight change was also studied.

Results: Patients used higher grip forces than the normal subjects in both the lifting and holding phases, particularly with a lighter weight. Lift timing was slowed in the patients, most markedly with a lighter weight. Increased levels of inter-trial variation were observed only with a light weight. This indicates that the slowing in HD differs from that in Parkinson's disease, which remains constant regardless of object load, and that the slowing in HD is not due to involuntary antagonist muscle activity resulting from an underlying chorea. The grip force response to sudden weight change was normal, but appeared after a delay which increased at lower rates of weight change.

Conclusions: Disturbances in precision grip timing and magnitude in HD may result from a reduced ability to process relevant tactile afferent input. The delay in the adaptive response suggests an increased threshold for detection of weight change in HD. Alternatively, this delay may arise from mediation of the response over an additional cerebellar pathway to compensate for damage to the basal ganglia.

Keywords: Huntington's disease; Sensorimotor; Precision grip; Basal ganglia; Cerebellum

1. Introduction

Of the spectrum of sensory afferent information available to cortical structures, only specific subsets of sensory input are relevant to the planning and execution of a specific voluntary motor act. The basal ganglia are thought to play a major role in the selection of this relevant sensory input (Lidsky et al., 1985). The integrity of basal ganglia structures is an important factor in the proper operation of the learning and memory aspects of motor tasks (Knowlton et al., 1996). In diseases in which the basal ganglia are damaged, such as Parkinson's disease (PD) and Huntington's disease (HD), there is often a disruption of serially ordered complex movements. This indicates that the basal ganglia are important for the automatic performance of complex movement sequences (Phillips et al., 1993). Such complex movement sequences often involve manipulative actions of the hand, usually under direct cortical control (Porter and Lemon, 1993). Hand function has been much studied in both PD and in HD, but the majority of studies up until now have been concerned with simple reaction time tasks or have been designed to study changes in cognitive processes in these diseases. Fewer studies have concerned themselves directly with the changes in a functional motor task resulting from damage to the basal ganglia. In recent studies (Fellows et al., 1997, 1998; Gordon et al., 1997; Ingvarsson et al., 1997) it has been demonstrated that one such task, the lifting with the hand of an object held in a precision grip, may be usefully applied to patient groups. Johansson and his co-workers (Johansson, 1996) have shown that, in normal subjects, lifting in a precision grip is achieved by a complex, but reproducible sequence of voluntary activity. This sequence involves arm positioning, preparation of the fingers for gripping the object, and then appropriate development of finger grip forces combined with lifting and bracing activity in wrist, elbow and shoulder musculature. Furthermore, it has been demonstrated that this task contains elements of memory related to object properties such as weight and surface friction. Grip force parameters are recalled by the subject as a 'set' on a predic-

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tive basis with the assumption that, for example, the weight of the lifted object will have remained unchanged from the last encounter (Johansson and Westling, 1988; Gordon et al., 1993). It has also been shown that when sensory information (predominantly cutaneous afferent information from the hand and lower arm (Johansson and Westling, 1984, 1987)) indicates a change in loading (Johansson, 1991), then such a parameter set can be modified automatically during an ongoing lift. From this it is apparent that the correct functioning of such hand movements is highly dependent on sensorimotor processing. It is exactly such processes, however, that may be disrupted in basal ganglia disorders such as HD. Much evidence exists that sensorimotor activity is abnormally reduced in this condition (Noth et al., 1984; Bollen et al., 1985; Abbruzzese et al., 1990) and that this reduction results from abnormal gating by damaged basal ganglia structures (Schwarz et al., 1992). The present study addresses, therefore, the ability of patients with HD to plan and execute lifting of an object using the precision grip and to adapt their lifting strategy when faced with externally imposed changes in object loading.

2. Methods

2.1. Subjects

Fifteen patients with HD were recruited for the present study while being treated as in or out-patients of the neurological clinic of the University of Aachen, or while resident in a local hostel. Ten were male, 5 female, aged 27–63 (mean 46). Clinical details are given in Table 1. Sixteen age-matched subjects (aged 27–64, mean 46; 10 male, 6 female) with no neurological abnormalities acted as a control group. All subjects gave their informed consent to the procedures, which had previously been approved by the Local Ethics Committee.

2.2. Apparatus

The experiments were performed in a quiet room with subdued lighting. The subjects were seated in a stable chair before a table on which the lifting apparatus was placed. This has been fully described elsewhere (Fellows et al., 1998). A curtain was drawn between the subject and the apparatus in order to remove visual cues concerning hand position. The device consisted of an aluminium block that was free to move in the vertical plane on a low-friction track. The block was in two parts, on each of which was attached a plastic disk. These were contacted by the tip of the fully extended thumb or forefinger, respectively. These disks were interchangeable in order to allow varying of the frictional properties of the grip surface: in the present study two sets were used, one set covered with sandpaper (for lifting), the other with silk (for unexpected loading during holding). The subjects were required to keep their other fingers away from the apparatus while lifting the block and to rest the elbow of the active arm on a padded support. A force transducer (9301B, Kistler, Winterthur, Switzerland), mounted between the two halves of the block, registered the grip force exerted on the block by the subject. The block was also connected, via a non-elastic band, to a servo-controlled torque motor, which could vary, without forewarning, the weight the subject was required to lift. With no extra torque from the motor, the block and transducers represented a weight of 3.3 N when lifted. Between lifts the block was supported on a stop. A laboratory computer (Macintosh IIvx, Apple, Cupertino, CA, USA) controlled

Table 1
Clinical details of the patients

Patient	Sex (M/F)	Age (years)	Age at onset (years)	Duration of symptoms (years)	UHDRS motor score[a]	CAG[b]
1	F	27	26	1	17	56
2	M	33	24	9	49	*
3	F	36	30	7	17	*
4	F	37	32	5	64	55
5	M	40	38	2	34	49
6	M	43	38	5	72	*
7	F	43	35	7	32	49
8	M	45	[c]	0	0	40
9	F	45	32	13	31	46
10	M	48	43	6	28	42
11	M	50	49	1	63	44
12	M	56	52	5	26	42
13	M	60	57	3	31	43
14	M	60	40	20	59	41
15	M	63	53	10	49	41

[a] United Huntington's disease rating scale; motor assessment (items 1–20), maximum score 124 (Huntington Study Group, 1996).
[b] Size of trinucleatide repeat sequence on the Huntington gene: * indicates that no genetic testing was performed.
[c] Patient asymptomatic at time of testing.

the output of the motor via the analogue outputs of an ADC board (NB-MIO-16H, National Instruments, Austin, TX, USA) and a servo device. It was possible either to vary the weight of the device between lifting trials, or to apply rapid step increases in the object's weight during a maintained lift. This computer also generated trigger events to initiate sampling. A position signal was provided by a linear potentiometer (T60500, VAC, München, Germany) mounted as part of the track. Trigger, grip force, and position signals were then passed to the ADC board (NI-PCI-MIO-16XE, National Instruments) of a second computer (Power Macintosh 7600/132, Apple). This computer, using the LabView 4 analysis package (National Instruments), sampled each channel at 2.5 kHz, displaying the data on-line and saving it to disk for later analysis.

2.3. Procedures

The total experimental time was between 35 and 55 min, depending on the attention span and stamina of the subjects. The study period was divided into two sections. The first examined the responses of the subjects to unexpected changes in the weight of the object between two successive self-initiated lifts. Under such conditions it has been demonstrated that a subject initiates a lift using the parameters (for example, the grip force profile) appropriate to the weight encountered in the previous lift (Johansson and Westling, 1988). Should the weight encountered differ from that expected, normal subjects are able to adjust their lifting parameters to appropriate values within the course of a lift (Johansson and Westling, 1988). In order to examine the extent to which this predictive and adaptive behaviour is preserved in HD, the following protocol was employed: the subjects were requested to grip and lift the block 4–8 cm above the table in one smooth action, hold the end position for 5–6 s, then to let the block fall back onto the stops. The subject was unable to see the hand, which caused excessive fumbling in search of the object in several of the patients. Accordingly all subjects were allowed to rest the tip of the finger and the thumb against the grip surfaces between lifts, but were requested to first exert grip force on the object when instructed to lift it. The weight of the block was changed between 3.3 and 7.3 N between lifting trials on a pseudo-random basis. The grip surfaces were of sandpaper. A total of 21 lifts were performed, so that, discarding the first trial, which had no pre-history, 5 trials were obtained for each of the 4 conditions: light weight follows light weight ('light'); light weight follows heavy weight ('unload'); heavy weight follows light weight ('load'); heavy weight follows heavy weight ('heavy'). Each lift was separated by a 15–20 s pause.

The second part of the study examined the grip force adjustments evoked by a sudden change in weight of an object held in a precision grip. For this series the subjects were required to maintain the block (3.3 N) at a steady height 4–6 cm above the table without visual control. The grip surfaces for this section were of silk. Step increases in the load (2 N at 200 N/s) were then randomly applied at intervals of 15–20 s. Subjects were required to retain the object in their hand and above the table, but were instructed not to use more force than felt natural to achieve this. Ten such trials were applied with and without visual control of the hand. A further series of 10 loading trials was applied subsequently at each of two other loading rates, in both cases without visual feedback of hand position. These were applied as linear ramp loading at rates of 32 and 8 N/s. Any trial in which the block escaped the patient's grasp was eliminated from later analysis and repeated, but this was a rare occurrence.

2.4. Analysis

For lifting trials a series of parameters was obtained for each lift, as shown in Fig. 1A, which represents the grip force and object position curves obtained from a typical normal subject lifting the lighter weight (3.3 N). The starting point for the analysis was the first increase in the grip force signal (vertical line). Two timings were made from this point: that to the first increase in the position signal (initial grip to lift (a)); and that to the peak value in the grip force signal (time to peak grip force (d)). The magnitude of the peak grip force developed up to the attainment of a stable end position (peak grip force (e)) and the static grip force 4 s after initial contact, when grip force and object position had stabilized (f), were also measured. In addition the duration of the lifting phase (b) and the height above the table of the final hold position (c) were measured.

For the sudden weight changes during holding each sequence of 10 unexpected weight changes was checked to ensure stability of grip force and object height over a period of 200 ms before the onset of the weight change. Any sweeps where variations in grip force of greater than ± 0.2 N occurred in this period were eliminated from the analysis. Fig. 1B shows the 5 parameters that were measured from the remaining trials. These were: (a) the grip force level in the 200 ms before the weight change; (b) the time between onset of the weight change and the increase in grip force marking the onset of the grip force response; (c) the time between onset of the grip force response and the development of peak grip force; (d) the peak grip force developed in the grip force response; (e) the 'adjusted' grip force in the hold phase of the response.

2.5. Statistics

Non-parametric statistical analysis of the data was performed using the StatView 4.5 package (Abacus, Berkeley, USA). Group averages for the lifting section were obtained by combining the median value under a given condition of each subject. Data were evaluated using the Kruskal–Wallis test and Mann–Whitney *U* test. Second order polynomial regression modelling was performed using the same package. Statistical significance was

assessed at the 5, 1 and 0.1% levels ($P < 0.05$; $P < 0.01$; $P < 0.001$).

3. Results

3.1. Lifting the object

When normal subjects expected and encountered the lighter load, they demonstrated a high degree of consistency over a series of lifts. This is illustrated in the upper traces of Fig. 2A. It may be seen that a typical normal subject employed largely the same timing in the early stages of grip force development over the sequence of 5 lifts. Similarly the peak grip force generated and the grip force in the holding phase were also rather reproducible. The lower traces in Fig. 2A shows a sequence of 5 lifts under the same conditions performed by a representative patient with HD (#11). The dotted line represents the grip force employed in the holding phase by the normal subject illustrated in the upper traces. It is apparent that the patient showed increased variability in the timing of grip force development, sometimes achieving normal values, but more generally showing a slowing of grip force development. Furthermore the peak grip force developed and the grip force level adopted in the holding phase were both elevated over normal values. Fig. 2B shows the group means for the magnitude of the grip forces employed in the early phases while lifting a light (3.3 N) or heavy (7.8 N) weight. The peak grip force employed by patients with HD was significantly higher than normal values for both weights (Mann–Whitney U, $P < 0.01$). Fig. 2C shows the corresponding values obtained in the holding phase. It may be seen that the grip force in this phase was also significantly exaggerated over normal values (Mann–Whitney U, $P < 0.01$). This exaggeration was more marked with the lighter weight (85% increase over normal) than for the heavy weight (49% increase). Thus while normal subjects holding the light weight used less than half of the grip force they required with the heavy weight (Fig. 2C), patients with HD used significantly more (almost two-thirds of the level they employed for the heavy weight (Fig. 2D)) while holding the light weight. This difference was significant (Mann–Whitney U, $P < 0.05$).

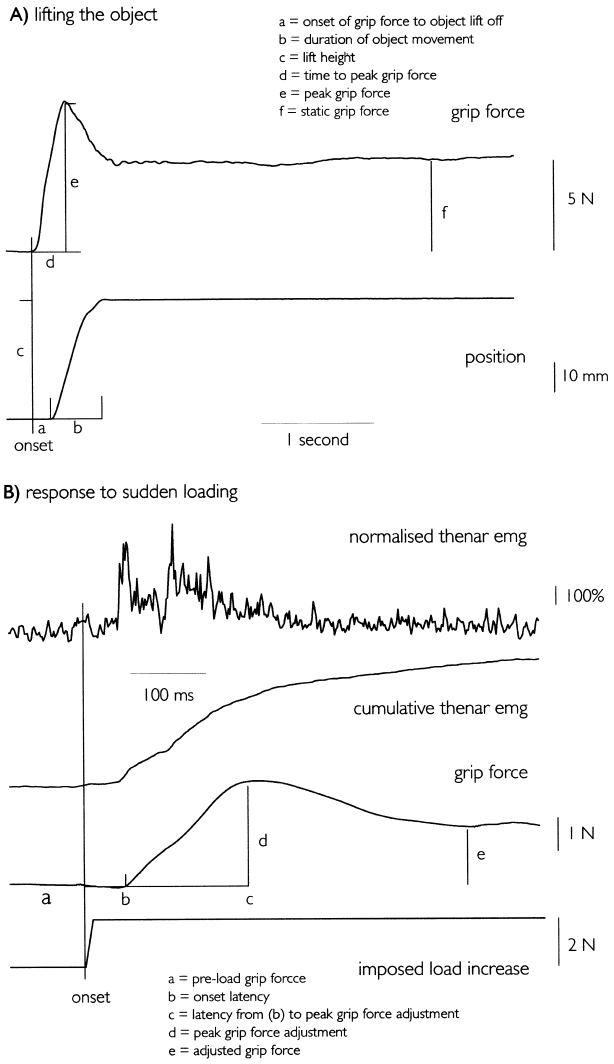

Fig. 1. (A) Grip force and position traces from a normal subject lifting the lighter weight (3.3 N), illustrating the parameters measured for each lift. (B) The thenar EMG, grip force and load change curves for the grip force response to a sudden weight change, illustrating the parameters measured for each trial.

As mentioned above, grip force development in the patients with HD was significantly slowed relative to normal values. A clear increase in the time taken to reach peak grip force was seen with both weights (Mann–Whitney U, $P < 0.01$), but particularly when lifting a light object (Fig. 3A). It may be seen that HD patients required 60–70% longer than normal subjects to reach peak grip force lifting the light object but only 25–45% longer than normal with a heavy weight. If the early stages of grip force development while lifting the light load are examined (Fig. 3B), a slowing of grip force development is apparent in almost all of the patients with HD. It should be noted, however, that the divergence from normal values was not apparent from the onset of grip force development, but rather became apparent some 70 ms later. When lifting the heavy weight (Fig. 3C), however, many of the patients were able to generate force at normal rates. As has been shown by Fellows et al. (1998), the early stages of the grip force curve may be closely modelled using a 2nd order polynomial regression. If this model is used to obtain predicted grip force values at a given point in time, it allows quantitative comparison of the rate of grip force development in different subjects while taking into account intra-subject variability. Fig. 3D shows the group means obtained for the predicted grip force 70 and 140 ms after lift onset with the light load. There was no significant difference from normal values after 70 ms, a point at which the force curve is determined by memory of the force co-ordination used in the previous lift. By a point 140 ms after the onset of lift, however, when sensory input concerning the object

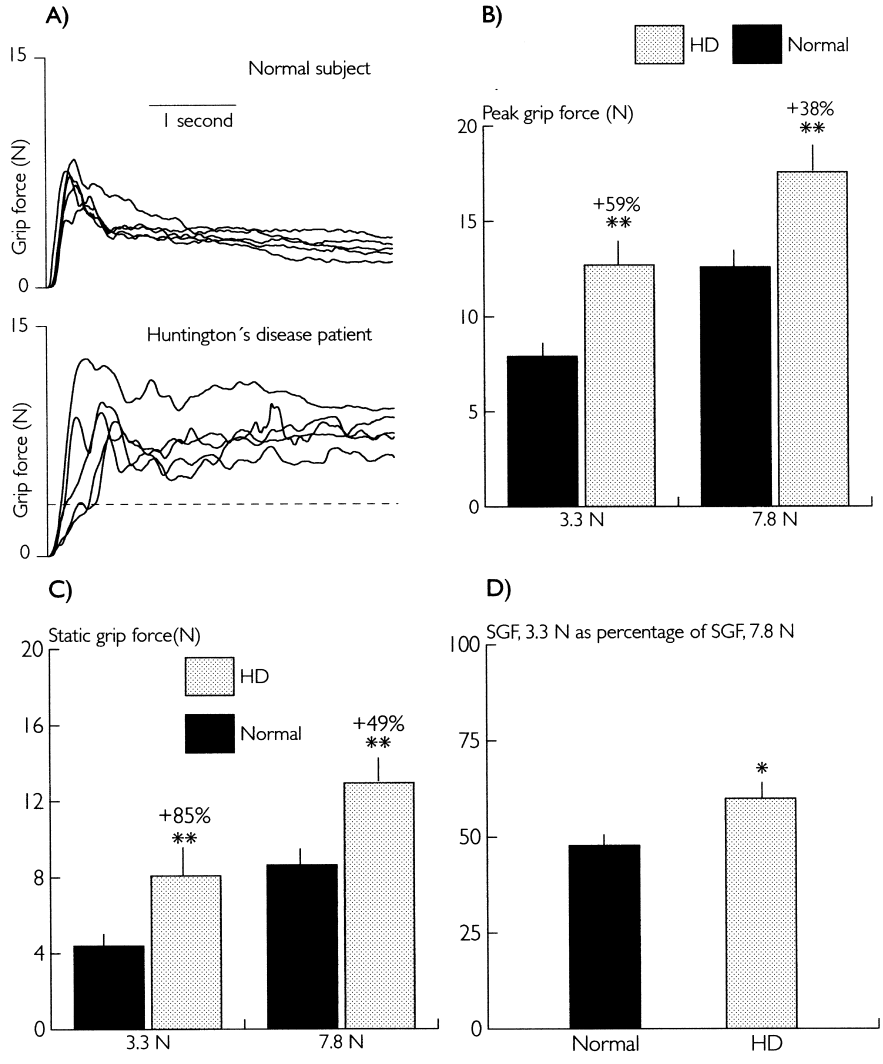

Fig. 2. (A) The upper panel shows grip force profiles from the first 4 s of 5 trials with a light weight (3.3 N) performed by a typical normal subject under 'light' conditions. Note the reproducibility of both the timing and the magnitude of the grip force curve. The lower panel shows similar grip forces curves obtained from a patient with HD (#11). Note the variability over the series in grip force magnitude and, in particular, in the timing of grip force development. (B) Group means for peak grip force attained during while lifting the light (3.3 N) and heavy (7.8 N) weight in the normal subjects (black) and HD patients (grey). The percentages represent the relative increase seen in HD patients over normal values. Error bars indicate SEM. $^{**}P < 0.01$. (C) Group means for static grip force maintained in the hold phase while lifting the light (3.3 N) and heavy (7.8 N) weight in the normal subjects (black) and HD patients (grey). Error bars indicate SEM. $^{**}P < 0.01$. (D) Group means for static grip force exerted while lifting the light weight expressed as a percentage of the static grip force exerted while lifting the heavy weight. Normal subjects are shown in black, HD patients in grey. Error bars indicate SEM. $^{*}P < 0.05$.

would be expected to have reached and influenced the motor cortex (Jenmalm and Johansson, 1997), the HD patients had developed significantly less force than the normal subjects (Mann–Whitney $U, P < 0.05$). With the heavier weight (Fig. 3E), however, no differences from normal values were apparent in the group means either at the onset or in the later stages of the lift.

Unsurprisingly, given the slowness of grip force development, the time taken from the start of the grip force increase until the object left the table was significantly prolonged in the HD patients when lifting the lighter weight (Mann–Whitney U, $P < 0.01$). This time was also significantly prolonged with the heavier weight (Mann–Whitney U, $P < 0.01$). Grip force rate, however, was normal with the heavier weight. Thus the persistence of the slowing in the time taken from the start of the grip force increase until the object left the table may indicate a breakdown of the co-ordination between the fingers and the wrist muscles which were responsible for the actual lifting phase.

Lift duration was significantly prolonged by 75–85% over normal values in the patients with HD under all conditions (Mann–Whitney U, $P < 0.001$). Part of this increase in lift time could be attributed to extreme lifting heights adopted, despite warning, by 6 of the 15 patients.

When a normal subject, expecting to lift a heavy object, instead encounters a lighter weight, the peak grip force

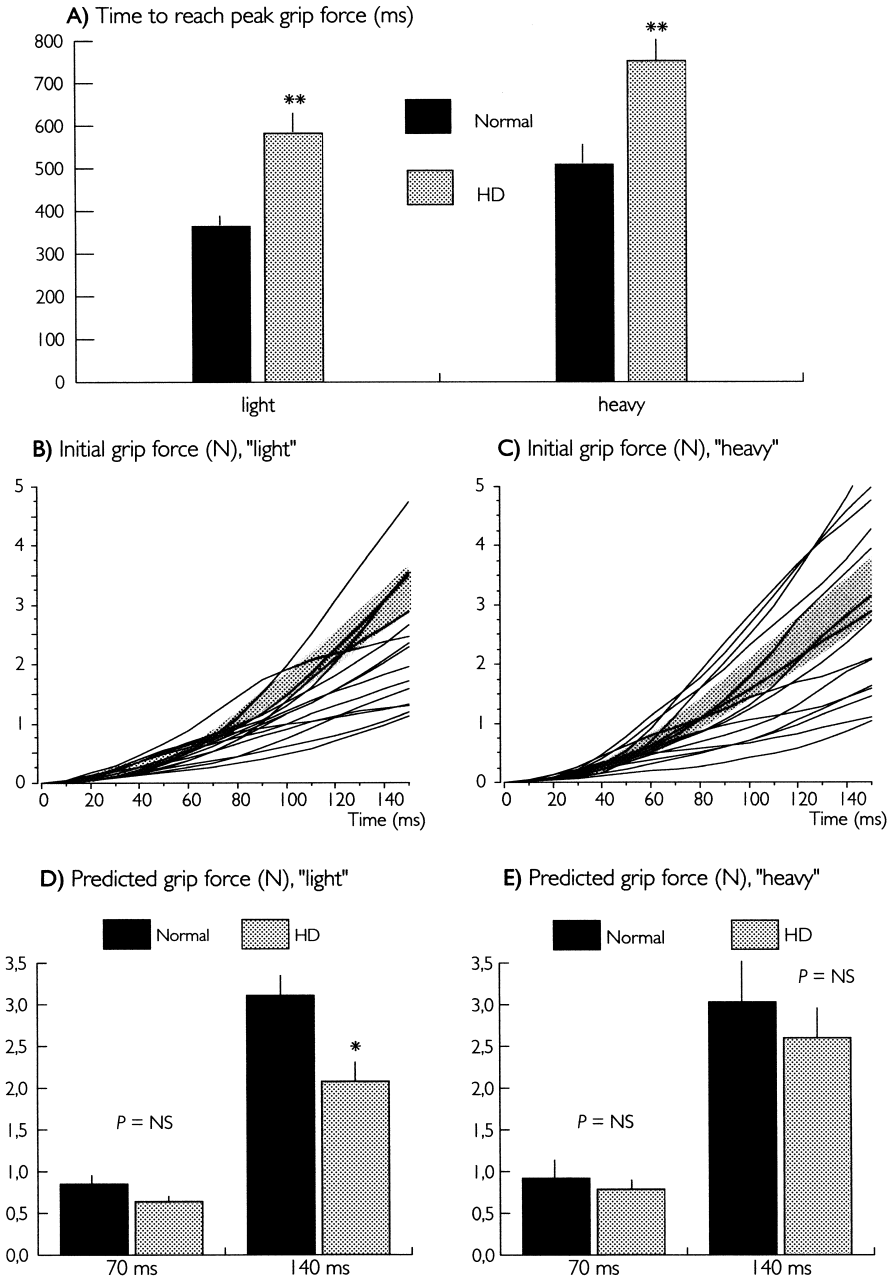

Fig. 3. (A) Group means for the time taken between the onset of grip force increase to the attainment of the peak grip force while lifting the light (3.3 N) and heavy (7.8 N) weight in normal subjects (black) and HD patients (grey). Error bars indicate SEM. $^{**}P < 0.01$. (B) Initial segments (up to 150 ms) of the grip force curves obtained from the HD patients while lifting under the 'light' condition superimposed on the shadowed curve representing the normal mean value (±SEM). Note that divergence of the patients curves from the shadowed area was first apparent between 70 and 90 ms after onset of the lift. (C) The corresponding curves obtained under the 'heavy' condition. Note that a significant proportion of the patients were able to reach normal values under this condition. (D) Group means (±SEM) 'light' conditions for the predicted grip force after 70 and 140 ms of grip force development obtained from a 2nd order polynomial model applied to the first 150 ms of the actual grip force curves. The normal mean is displayed in black, that of the HD group in grey. Note the largely normal response after 70 ms, but the significant reduction in the force achieved after 140 ms ($^{*}P < 0.05$). (E) The comparable values obtained under the 'heavy' condition. Note that the HD patients now show normal values at both stages of the lift.

developed, while lower than that reached with the heavy object, is nevertheless reproducibly greater than that seen when the subject expects to lift a lighter weight. This is illustrated in Fig. 4A. The quantitative data for the normal group is illustrated on the left in Fig. 4B. It may be seen that normal subjects are able to modify grip force development erroneously programmed for a heavier weight and limit peak grip force to 80% of that seen while lifting a heavy weight. Comparison of the group data for the patients with HD shows that this ability remains intact in these patients.

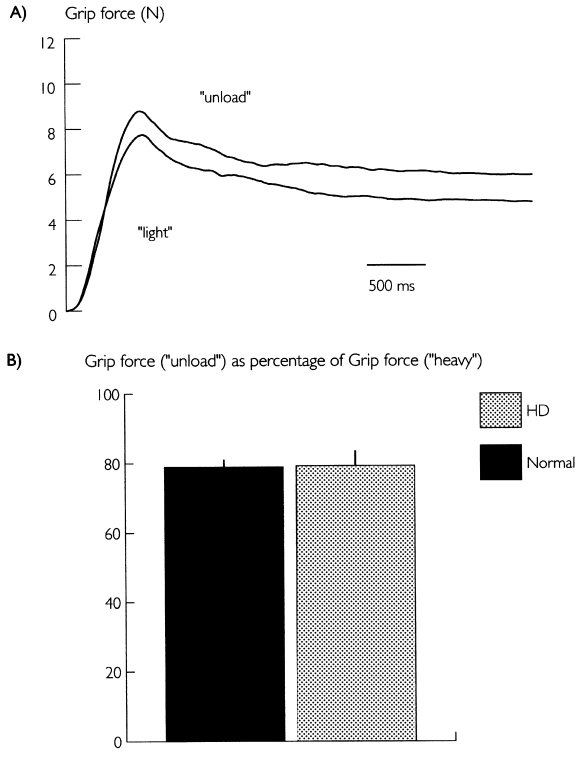

Fig. 4. (A) The mean grip force curves obtained from a normal subject lifting the 3.3 N weight under 'light' and 'unload' conditions. Note the overshoot of the grip force curve in the 'unload' condition. (B) Group means for the peak grip force reached in the 'unload' condition expressed as a percentage of the peak grip force reached in the 'heavy' condition. Normal subjects are shown in black, HD patients in grey. Error bars indicate SEM. Note the unimpaired ability to terminate an erroneously generated grip force.

3.2. Unexpected weight change during holding

When an object held in a precision grip is subjected to a sudden, unexpected increase in weight, the grip force used to hold the object is automatically increased to match the higher weight (Cole and Abbs, 1988; Johansson et al., 1992c). A series of such grip force responses to an unexpected weight change are shown in Fig. 5A for a representative normal subject and a patient with HD at 3 rates of weight change. The grip force levels exerted by the patients with HD over the 200 ms before the onset of the weight change did not differ significantly from normal values. At the fastest rate (200 N/s) the grip force curve of the normal subject began to adapt at about 60 ms after the onset of the weight change. With slower rates (32 & 8 N/s) the onset of the grip force response occurred progressively later (97 and 142 ms, respectively), reflecting the less dynamic nature of the weight change. From the curves of the HD patient it can be seen that the onset of the grip force response was abnormally prolonged at all 3 loading rates.

The quantitative analysis for the magnitude of the peak grip force and of the stabilized force in the holding phase is given in Table 2. Although a tendency towards exaggerated peak grip forces was observed at both these points in time in the patients with HD, no significant differences from normal values were found. The group means for the timing parameters are shown in Fig. 5B,C. It may be seen that at the fastest rate of loading the grip force response of the HD patients began, on average, 26 ms later than that of the normal subjects (Mann–Whitney U, $P < 0.01$). This confirms the findings with a smaller group of patients by Fellows et al. (1997). An additional finding was that this significant delay in the onset of the grip response was also apparent with slower rates of weight change, increasing to 28 ms at a rate of 32 N/s (Mann–Whitney U, $P < 0.001$) and 45 ms at a rate of 8 N/s (Mann–Whitney U, $P < 0.05$). This suggests that the threshold for the weight increase capable of eliciting the grip force reaction may be increased in HD. However, the delayed onset of the response was fully compensated for by a faster development of grip force within the response (Fig. 5C), so that peak grip force values were achieved with normal timings at all loading rates.

4. Discussion

4.1. Exaggerated grip forces during object lifting

The results of the present study show that patients with HD employ abnormally high grip forces at all stages of a lifting task. This abnormality was particularly marked while lifting the lighter weight. Under this condition relatively less sensory input is available to the patient. Under normal conditions this sensory input will, for the most part, be of cutaneous origin (Rossi et al., 1998). It is known that an increase in magnitude of grip force at all stages of the lifting task is a feature of normal subjects when cutaneous afferent input is attenuated through the application of local anaesthesia (Westling and Johansson, 1984). Thus a reduction in sensory input reaching the cortical structures responsible for planning and execution of the lifts may result in the disturbances of the precision grip in HD. This could be due to reduced perception of sensory cues, reduced processing, or some combination of both. Direct demonstrations of reduced cutaneous sensory discrimination have been made in PD (Sathian et al., 1997), but evidence for reduced sensorimotor capability in HD is more indirect. A recent study reported that patients with HD were often unaware of their choreatic movements, although they remained aware of their consequences (Snowden et al., 1998). The reduction in the startle response normally obtained using by a tactile warning cue, the so-called 'pre-pulse inhibition', is absent in HD (Swerdlow et al., 1995), indicating a failure of the patients to identify the tactile cue. Furthermore, Heindel et al. (1991) found that previous exposure to a light or a heavy weight influenced a subsequent weight judgement made by normal subjects. A preceding series of heavy weights led to underestimation and a series of light weights to overestimation of a test weight. This bias effect, however,

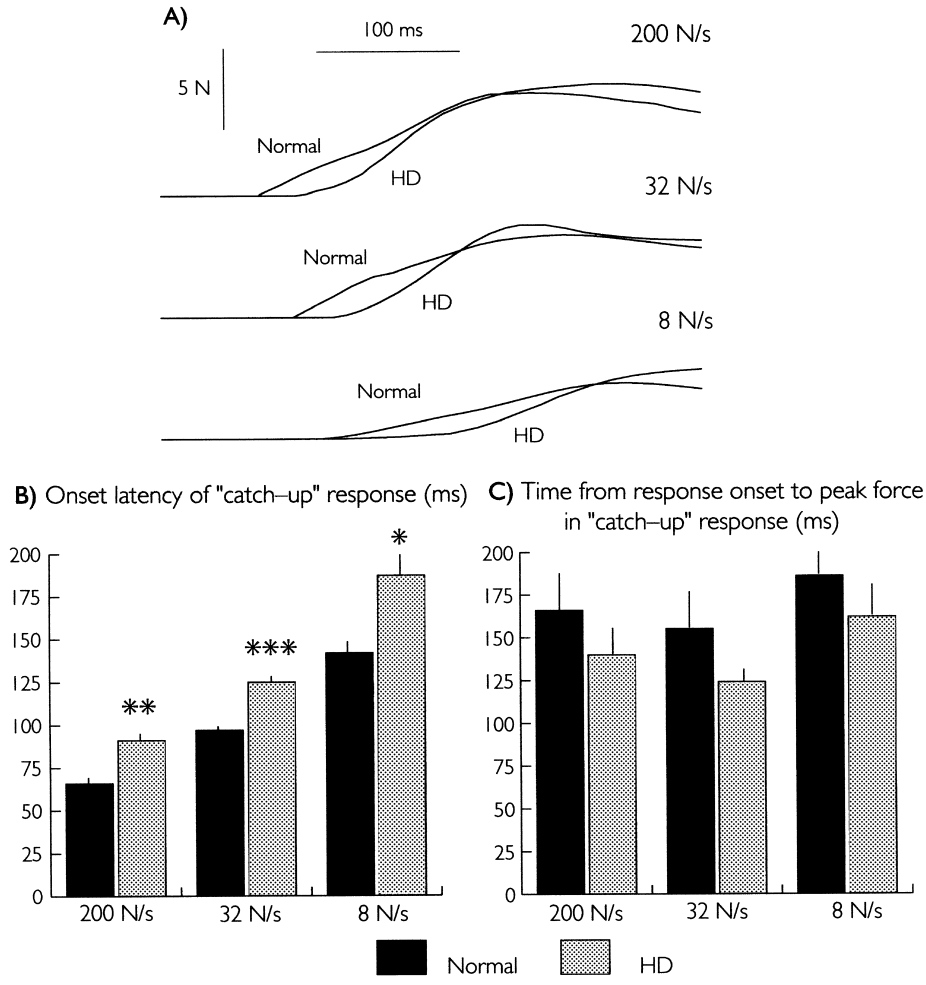

Fig. 5. (A) The mean grip force curves obtained following sudden weight increase (2 N) while holding an object at a stable height from a normal subject and a patient with HD (#9). Three rates of weight change are shown: 200, 32 and 8 N/s. Note the clearly delayed onset latency of the response of the patient at all 3 loading rates. (B) Group means (±SEM) for the onset latency of the grip force adjustment at each of the 3 loading rates. The normal mean is displayed in black, that of the HD group in grey. $*P < 0.05$; $**P < 0.01$; $***P < 0.001$. (C) Corresponding values for the time taken to reach the maximal value of the grip force adjustment at each of the 3 loading rates.

was reduced or absent in a group of patients with HD. A reduction in the amplitude of somatosensory evoked potentials obtained by peripheral nerve stimulation in patients with HD is now an established finding (Noth et al., 1984; Bollen et al., 1985; Kanda et al., 1989; Abbruzzese et al., 1990; Töpper et al., 1993). This attenuation correlates with the reduction in the long-latency stretch reflexes of the finger muscles (Meyer et al., 1992), which are known to be mediated over a transcortical pathway (Noth et al., 1985). It must be borne in mind, however, that this attenuation has also been reported in PD (Cheron et al., 1994; Rossini et al., 1989, 1993, 1995). The universal nature of these findings, however, has been called into doubt by studies which were unable to discover such attenuation (Garcia et al., 1995; Huttunen and Teräväinen, 1993; Mauguière et al., 1993). Thus it would seem justified to say that the attenuation in the amplitude of somatosensory evoked potentials is a more robust finding in HD than is the case in PD. It has been demonstrated (Töpper et al., 1993) that sensory afferent input is normal up to the level of the

Table 2
Mean values (±SEM) for peak and stabilized grip forces during the compensatory response

	Peak grip force (N)			Hold phase grip force (N)		
	200 N/s	32 N/s	8 N/s	200 N/s	32 N/s	8 N/s
HD	6.10 ± 1.31	5.11 ± 0.68	4.71 ± 0.92	3.77 ± 0.97	2.86 ± 0.36	2.53 ± 0.45
Normal	5.16 ± 1.59	3.40 ± 0.79	2.79 ± 0.63	2.90 ± 0.86	1.94 ± 0.42	1.97 ± 0.61

thalamus in HD. The transmission in sub-cortical afferent projection systems in the mid-brain and brain stem (Mann, 1989), the conduction time in the cortex itself (Thompson et al., 1986; Hömberg and Lange, 1990) and transmission in descending motor tracts (Eisen et al., 1989) are all known to be normal in HD. However, the silent period following transcortical magnetic stimulation is prolonged in some patients with HD (Tegenthoff et al., 1996), indicating a possible change in the balance between excitation and inhibition in the cortex. A recent PET study (Boeker et al., 1999) also found reduced activity in cortical areas. Even more marked changes, however, were found in basal ganglia structures closely connected with these cortical areas. Thus it is difficult to assess if the latter changes are due to changes in the cortex itself or result from damage to other structures. Clearly damage to a variety of structures outside the basal ganglia plays an important role in HD, particularly in the later stages of the disease, and might contribute to these deficits. Nevertheless it is true that in the early stages of HD damage is largely limited to basal ganglia structures (Albin et al., 1990), and the abnormalities described in the present study were clearly visible in patients in the early stages of the disease (including the asymptomatic subject). In addition, a recent study of reaching movements in asymptomatic carriers of the gene for HD (Smith et al., 2000) found marked increases in the variability of performance which they ascribed to deficient error correction. Thus it would appear that our findings point to disturbed sensorimotor processing resulting from a gating effect on sensory input to cortical structures caused by damage to basal ganglia structures, as has been demonstrated in an animal model of HD (Schwarz et al., 1992).

As will be subsequently discussed, selection of grip force magnitude in the initial stages of lifting an object of uncertain weight operates on a predictive basis (Johansson and Westling, 1988). Excessive peak grip forces could be caused by a failure in the 'motor memory' underlying this predictive behaviour. The grip force in the holding phase of the lift, however, remained abnormally high, long after sensory input about the actual object weight should have been available. Thus it is not implausible to attribute the difficulties HD patients experienced in the lifting task to a failure to identify the lighter weight because of a reduced ability to utilize relevant sensory input.

Another cause of excessive grip forces might lie in the choreatic movements associated with HD: it is possible that the subjects increased contraction levels in a range of muscles in order to increase joint stiffness and thus minimize the disruptive effects of choreatic movements. If this were the case, however, one might expect the excursion of the wrist caused by imposed loading to be reduced in HD patients. The opposite, however, is the case (see the position curves in Fig. 2; Fellows et al., 1997). This indicates that increased joint stiffness as a strategy to offset the effects of the choreatic movements did not play a large role in the present study, possibly due the reduced influence of upper arm and shoulder muscles resulting from the elbow support provided.

4.2. Timing deficits during object lifting

A striking feature of the performance of the patients with HD whilst lifting the lighter weight was the large variability shown between individual lifts, both in the magnitude and, more markedly, in the timing of the grip force developed by the fingers. While lifting the light weight an individual HD patient might show grip force timing ranging from the fastest achieved by the normal subjects to the profoundly slowed timing characteristic of a severely bradykinetic patient with PD (Fellows et al., 1998). Normal subjects and PD patients show little variation between successive lifts under similar conditions, either in the time course of grip force development or in grip force magnitude (Fellows et al., 1998). This was also the case in patients suffering from a variety of clinical conditions affecting the cerebellum (Schwarz et al., 1998). Inter-trial variability would thus seem to be a specific feature of the motor abnormalities associated with HD. Thompson et al. (1988) observed an abnormal variability in movement velocity and amplitude during self-paced wrist flexion movements. Phillips et al. (1996) reported a greater inconsistency of movement duration during precise drawing movements performed by patients with HD than was the case for normal subjects. They attributed these abnormalities both to a failure of the basal ganglia to provide adequate cues to initiate movement phases and to the intrusion of unnecessary (choreiform) activity into the motor program. Some of this variability might also be attributed to abnormal variability in the profiles associated with grip force production. Hefter et al. (1987) found slowing of isometric force production in the finger muscles of HD patients. They suggested that this reflected a generalized bradykinesia associated with damage to structures in the basal ganglia. However, as the results of the present study demonstrate, this slowing of force development was not invariably shown by an individual patient in each lift, nor was it nearly so apparent whilst lifting the heavier weight. Neither of these characteristics are features of the bradykinesia shown by PD patients while lifting an object under similar conditions (Fellows et al., 1998). Furthermore, comparison of the initial grip force curves of HD patients with those of normal subjects shows that deviation from normal values under 'light' conditions first becomes significant some 140 ms after the onset of force production, when sensory cues could have begun to influence lifting dynamics (Jenmalm and Johansson, 1997), and not from the onset, as is the case in PD. Indeed, some of the patients in the study of Hefter et al. (see their Fig. 7) showed clear variation in the profiles of force development, and were capable of developing force rapidly on at least some occasions. Thus a variability of central timing, rather than a general deficit of force production underlies the slowing in grip force development observed in HD. A possible cause of

this variability can be found in results obtained from a functional magnetic resonance imaging (fMRI) study in patients with schizophrenia (Schröder et al., 1999). This study found significantly increased levels of variability in the velocity of finger movements performed by schizophrenic patients. This variability was more pronounced for slower movements (i.e. with less afferent feedback) and in untreated patients or those on low levels of medication (i.e. variability was not neuroleptic-induced) and was associated with significantly lower activation of the sensorimotor cortex and SMA. Given that the variability shown by the HD patients was much less marked when lifting the heavier weight (which might be expected to generate more sensory input), this disturbance may, therefore, reflect a reduced effectiveness of sensorimotor processing. It must also be considered, however, that HD is associated with significant cognitive deterioration over its course. It is thus possible that the variability in lifting performance observed in the HD patients might arise from cognitive difficulties, which were certainly apparent in those patients with the longest disease duration. These patients were not, however, those showing the greatest deterioration in motor performance. Indeed, the variability was pronounced in 3 patients (# 5, 8 and 10) who showed no cognitive deficit on testing, and who were all active in professional life. Also, as mentioned above, a recent study involving asymptomatic gene carriers with no cognitive dysfunction found a marked increase in the variability of reaching movements (Smith et al., 2000). Thus cognitive changes would not seem to be a major source of the variability in lifting performance.

Another possible source of this variation is the disturbing influence of 'motor system noise' associated with choreiform activity (Phillips et al., 1996), or of choreatic movements per se. Against such an interpretation, however, is the finding that no variation in timing was apparent in the grip force responses to imposed loading, which are reflex in nature but nevertheless open to disturbance by a choreatic movement.. The variation may also arise from additional, normally uninvolved motor pathways: PET studies during finger movement tasks performed by patients with HD have revealed additional activation, particularly in the parietal cortex (Bartenstein et al., 1997). This additional activation has been suggested to compensate for an impairment of the normal output stages of the basal ganglia-thalamo-cortical motor circuit.

4.3. Memory of object weight during object lifting

When lifting an object of unpredictable weight, normal subjects select grip force parameters appropriate to the load last encountered: i.e. on the assumption that load will remain unchanged (Johansson and Westling, 1988). This strategy requires a simple motor memory, and its effective operation is reflected in the significant modulation in grip force magnitudes seen in normal subjects when lifting a light or a heavy load. Deficits have been observed in a range of memory tasks in HD (Butters et al., 1994). HD patients showed an increasing deficit when the time between two movements was prolonged in a task requiring reproduction of a previously executed linear hand movement, in contrast to both normal subjects and PD patients (Pasquier et al., 1994). Furthermore, progressively decreasing the external cues associated with a sequential button pushing task, thus causing an increasing reliance on internal representation of the required movement, also caused increasing deterioration in the performance of HD patients (Georgiou et al., 1995). It should be emphasized that 'motor memory' can only develop as the result of experience, i.e. from exposure to sensory input. A reduced sensitivity to or an inability to process this factor would lead to an impairment in the development and utilization of 'motor memory'. As evidenced by the erroneous programming of grip force in a lift where a heavy weight was expected but a light weight was encountered (see Fig. 4), this 'motor memory' can function correctly under certain conditions in HD. It remains possible, however, that the high variability in grip force generation observed when lifting the light weight reflects the failure to generate an appropriate 'motor set' for this weight due to reduced effectiveness of sensorimotor processing.

4.4. Grip force responses to sudden weight changes

The latency of the grip force responses to an imposed weight change during object holding was prolonged in normal subjects as slower rates of weight change were applied. This extends previous finding in the literature for a more restricted range of rates of change (Johansson et al., 1992b) and supports the suggestion made there that a threshold weight change exists which must be crossed before the grip force response appears. The consistently later appearance of the response in HD patients over the range of rates of change in the weight of the object may represent an increase in this threshold, perhaps due to a shift in sensory perception. Indeed, such a delay in the appearance of the grip force response was observed under conditions of digital anaesthesia in normal subjects (Johansson et al., 1992a). This supports the idea that the delay in the appearance of the grip force response in HD arises from a deficit in sensory processing. However, Johansson et al. (1992a) also observed increased variability in the grip force response following digital anaesthesia, particularly in the level of adjusted grip force at the end of the response. Such variation was not apparent in the responses of HD patients in the present study, however, indicating that the condition of the patients is not simply comparable to that of normal subjects experiencing digital anaesthesia.

The hypothesis of a threshold shift for perception of afferent input (in particular that from cutaneous receptors) remains attractive, however, and also explains the striking difference between the results of the present study and earlier studies on long-latency reflex responses in the finger muscles of HD patients. These studies found an absence or

marked reduction in the long-latency responses of the intrinsic hand muscles in HD. This was the case whether these responses were elicited by mechanical perturbations of the finger (Noth et al., 1985), of a mixed motor and cutaneous nerve (Noth et al., 1985; Deuschl et al., 1989), or electrical stimulation of a purely cutaneous nerve (Deuschl et al., 1989). In the present study, however, the grip force response showed no evidence of a reduction in amplitude, and, indeed, showed a tendency towards an increase over normal values. It must be noted, however, that the earlier studies cited all used a more or less artificial stimulus; that the responses obtained required averaging over many trials before achieving a stable form; and that the responses themselves have little or no functional role. The grip force response, in contrast, was elicited by a much more natural stimulus, was visible in single trials and played a important role in a functional task. Should a threshold shift in the effective level of afferent input exist in HD, then it might be expected that the afferent information associated with the weaker, functionally unimportant stimuli simply fails to traverse the gating mechanisms of the basal ganglia. These same gating mechanisms in normal circumstances would be optimized for selection of the afferent inflow underlying the grip force response. Thus this afferent inflow would have a much better chance of passing these gating mechanisms, even when these mechanisms are disordered.

The delayed onset of the automatic compensation for sudden changes in object loading can be explained in terms of a reduced effectiveness of afferent input to cortical structures due to abnormal gating by structures in the basal ganglia. But this is not the only possible explanation. It is now well established that the cerebellum receives a copy of most, if not all, of the afferent information passed to the sensorimotor cortex. In the cat forelimb, separate, somatotopically organized pathways exist to the 'forelimb areas' of the cerebellar cortex. One carries cutaneous afferent input, over the rostral part of the main cuneate nucleus and the exteroceptive cuneocerebellar tract, while the second carries information from muscle receptors over the external cuneate nucleus and the proprioceptive cuneocerebellar tract (Cooke et al., 1971a,b). It is equally well established that such afferent input, albeit in a highly processed form, is passed from the cerebellar cortex to the primary motor area of the cerebral cortex. Additionally, the connections of the cerebellum are organized in a fashion similar to that observed in the basal ganglia, with a strict division of afferent inputs from different modalities. There exists, therefore, a potential side-loop, avoiding the abnormal gating exerted by the basal ganglia on more direct pathways over the sensorimotor cortex. Thus in circumstances, such as in HD, in which the transmission over the direct route is disturbed, some of the function of the latter may be taken over by this cerebellar side-loop. This would preserve the automatic compensation for sudden changes in object, but, as observed, lead to the delayed appearance of this response due to the longer central transmission over the cerebellar side-loop.

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