Correlation between impaired dexterity and corticospinal tract dysgenesis in congenital hemiplegia

Julie Duque,1 Jean-Louis Thonnard,2 Yves Vandermeeren,1 Guillaume Sébire,3 Guy Cosnard4 and Etienne Olivier1

1Laboratory of Neurophysiology, 2Physical Medicine and Rehabilitation Unit, 3Department of Neuropediatrics and 4Neuroradiology Department, School of Medicine, Université catholique de Louvain, Brussels, Belgium

Summary
One of the most devastating consequences of early corticospinal lesions is the impaired dexterity that results in a noticeable deficit while manipulating small objects. One purpose of the present study was to investigate the extent to which a deficit in the coordination of fingertip forces when grasping and lifting an object between the thumb and index finger could account for the impaired dexterity in patients with congenital hemiplegia (CH). A second objective was to examine whether, in these patients, deficits in skilled hand movements are correlated with the importance of structural damage to the corticospinal tract. The scaling and coordination of fingertip forces during precision grip was investigated in 16 CH patients (aged 8–19 years) and 16 age- and sex-matched control subjects. Proprioception, stereognosis, pressure sensitivity and motor upper limb function (including digital and manual dexterity) were also assessed quantitatively. The structural damage of the corticospinal tract was estimated by measuring the cross-sectional area of cerebral peduncles with MRI and by calculating an index of symmetry between the two peduncles. In CH patients, a large number of parameters measured during the grip-lift task were significantly different when compared with those found in control subjects. Among those, the duration of the pre-loading and loading phases was significantly longer in CH patients. In addition, both the dissimilarity and time-shift between the profiles of the grip and load force rates, quantified with the cross-correlation method, were also significantly larger in CH patients; the time-shift was strongly correlated with impaired dexterity. These findings suggest that impaired dextrous finger movements in CH patients may specifically result from their inability to ensure a precise synergy between fingertip forces while manipulating an object. Finally, the finding that the time-shift also correlated with the corticospinal tract dysgenesis, as estimated with the cerebral peduncle asymmetry, argues in favour of a critical role of the corticospinal system in the temporal coordination between different muscles involved in dextrous hand movements. Both digital and manual dexterity were also altered in the non-paretic hand of CH patients. This deficit may reveal the contribution of the lesioned hemisphere to the control of ipsilateral skilled finger movements.

Keywords: cerebral palsy; pyramidal tract; finger movement; grip-lift synergy

Abbreviations: CH = congenital hemiplegia; GF = grip force; LF = loading force

Introduction
Manipulating small objects, and exploring their shape and texture, require highly skilled hand and finger movements. Although the biomechanical conditions for independent finger movements are present in many primates, the neural circuitry necessary for controlling these movements is most developed in higher primates, especially in man (Nakajima et al., 2000). A substantial amount of anatomical, electrophysiological and clinical evidence suggests that the principal constituent of the motor system underlying the performance of highly skilled finger movements is the corticospinal pathway and, more specifically, its corticomotoneuronal component (see Porter and Lemon, 1993). The portion of
the corticospinal tract originating from the primary motor cortex is largely concerned with the control of muscles acting on the wrist and fingers, and earlier studies have suggested that the primary motor cortex is necessary, and largely sufficient, to control skilled hand movements. However, recent functional imaging studies have shown that a large network including several other contralateral and ipsilateral cortical areas is also involved in the control of fine finger movements (Forssberg et al., 1999; Ehrsson et al., 2000, 2001). These observations suggest that, although the primary motor cortex is a prerequisite for the execution of skilled finger movements, their precise programming and control involve highly specialized brain structures.

The manipulation of small objects between the tips of the thumb and index finger requires a precise coordination between the grip force (normal to the grip surface) and load force (tangential to the grip surface). This so-called ‘grip-lift synergy’ is characterized by a smooth and parallel increase in both the grip and load forces, suggesting they are controlled in a predictive way (Westling and Johansson, 1984; Johansson and Westling, 1988). This anticipatory control was regarded as evidence for the existence of an internal representation of both the mechanical characteristics of the limbs and the object’s physical properties in order to predict the consequences of voluntary movements; this process is thought to rely on an ‘internal forward model’ (Flanagan and Wing, 1997; Witney et al., 2001a; Wolpert and Flanagan, 2001). After movement onset, the nervous system can optimally estimate the current state of the motor system by combining actual sensory feedback with the predictions of the forward model in order to update these internal representations (Wolpert et al., 2001). Therefore, even a simple movement such as grasping and loading an object involves subtle interplay between feed-forward and feedback mechanisms in order to generate a smooth vertical acceleration of the object (Witney et al., 2001b).

The complexity of the grip-lift task was further revealed by developmental studies. Before the age of two, children use a pure feedback strategy while performing a grip-lift task, as shown by multiple successive increments in both grip and load force rates (Forssberg et al., 1992; Gordon et al., 1992). First signs of an anticipatory control of grip and load forces appear around the age of two and develop throughout childhood to reach adult performance at the age of eight years (Forssberg et al., 1991). This evolution of the grip-lift synergy parallels the development of manual skills (Forssberg et al., 1991) and may reflect the protracted maturation of the corticospinal tract in primates (Olivier et al., 1997; Paus et al., 1999) and the progressive implementation of the cortical circuitry responsible for the control of skilled finger movements (Forssberg et al., 1999; Ehrsson et al., 2000, 2001).

Congenital hemiplegic (CH) patients do not usually acquire normal skilled hand movements. Although their impaired dexterity is partly due to spasticity and associated musculo-skeletal malformations, the neural control of finger movements is known to be specifically altered in these patients (Forssberg, 1999). In CH patients, the grip-lift movement is characterized by an asynchronous onset of both grip and load forces, and by multiple successive increments in grip and load force rates (Eliasson et al., 1991, 1992, 1995; Gordon and Duff, 1999a; Gordon et al., 1999; Forssberg et al., 1999). This pattern of movement is reminiscent of that observed in normal children younger than 2 years.

The aim of the present study was to investigate the extent to which a deficit in the coordination of fingertip forces during precision lifting could account for the impaired dexterity in CH patients. Whereas Gordon and Duff (1999b) failed to find a relationship between dexterity and performance in a grip-lift task, a correlation between a global index of grip-lift synergy and impaired dexterity in CH children was shown by Forssberg et al. (1999). In the current study, several individual temporal and dynamic parameters were measured during a grip-lift task in 16 CH patients and were correlated with manual and digital dexterity and with a global score of upper limb function. These results were compared with those gathered from a group of 16 age- and sex-matched control subjects. In addition, in order to investigate the specific contribution of the corticospinal pathway to skilled hand movements, both grip-lift task parameters and functional scores were correlated with the corticospinal tract dysgenesis. This was estimated by measuring the cross-sectional area of cerebral peduncles with MRI and by calculating an index of symmetry between the two peduncles. This measure proved to be a reliable index to estimate the degeneration of the corticospinal tract in CH patients (Bouza et al., 1994; Staudt et al., 2000).

Methods
All experimental procedures were approved by the Ethical Committee of the Université catholique de Louvain. Subjects and parents gave their written informed consent.

Subjects
Sixteen patients (age 12.6 ± 3.4 years, mean ± SD) with a congenital hemiplegia and 16 age- and sex-matched control subjects (12.8 ± 3.2 years, mean ± SD) were selected to participate in this study. A standard clinical evaluation showed hemiplegia with a predominantly upper limb distribution. The severity of the hemiplegia varied, according to Claesys et al. (1983), from mild, in most patients, to moderate. This was confirmed by scores on different functional tests (see below). All patients and control subjects had a normal, or nearly normal, school level for their age, suggesting that none of them had major cognitive deficits. A brief description of each patient is given in Table 1.
Table 1 Clinical description, scores on functional tests for the contralesional upper limb, lesion description and peduncular symmetry for CH patients

<table>
<thead>
<tr>
<th>Patient (sex)</th>
<th>Age (years)</th>
<th>Clinical description</th>
<th>Pressure sensitivity (mg)</th>
<th>Stereognosis /10</th>
<th>Proprioception/5</th>
<th>Melbourne (%)</th>
<th>Lesion description (MRI)</th>
<th>Lesion group*</th>
<th>PSym (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (F)</td>
<td>8</td>
<td>R hemiparesis, R hand disuse</td>
<td>NA</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>73</td>
<td>L central macrocystic encephalomalacy, L ventriculomegaly, L hemispheric hypotrophy, R ventriculomegaly</td>
<td>1</td>
</tr>
<tr>
<td>2 (M)</td>
<td>8</td>
<td>R hemiparesis</td>
<td>27.5</td>
<td>10</td>
<td>5</td>
<td>5</td>
<td>99</td>
<td>L white matter ASI (periventricular and centrum semiovale), L ventriculomegaly, internal capsule atrophy (both ant and post limbs)</td>
<td>1</td>
</tr>
<tr>
<td>3 (M)</td>
<td>9</td>
<td>R hemiparesis, R hand disuse</td>
<td>27.5</td>
<td>10</td>
<td>5</td>
<td>5</td>
<td>55</td>
<td>L deep sylvian artery stroke, L ventriculomegaly</td>
<td>4</td>
</tr>
<tr>
<td>4 (M)</td>
<td>10</td>
<td>R hemiparesis</td>
<td>27.5</td>
<td>10</td>
<td>5</td>
<td>5</td>
<td>70.5</td>
<td>L frontal closed-lip schizencephaly, L cerebral and cerebellar hemispheric hypotrophy, mild L ventriculomegaly</td>
<td>1</td>
</tr>
<tr>
<td>5 (M)</td>
<td>10</td>
<td>R hemiparesis, R hand disuse</td>
<td>166</td>
<td>10</td>
<td>0</td>
<td>3</td>
<td>NA</td>
<td>L widespread cavity in frontoparietal cortex, internal capsule hypoplasia, mild L ventriculomegaly</td>
<td>1</td>
</tr>
<tr>
<td>6 (M)</td>
<td>10</td>
<td>R hemiparesis</td>
<td>27.5</td>
<td>10</td>
<td>5</td>
<td>5</td>
<td>88.5</td>
<td>L white matter ASI (centrum semiovale), L ventriculomegaly</td>
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</tr>
<tr>
<td>7 (M)</td>
<td>11</td>
<td>R hemiparesis</td>
<td>27.5</td>
<td>10</td>
<td>5</td>
<td>5</td>
<td>96</td>
<td>L white matter ASI (corona radiata) consistent with remote cerebral infarction, L ventriculomegaly, R parietal microlesions</td>
<td>3</td>
</tr>
<tr>
<td>8 (F)</td>
<td>12</td>
<td>R hemiparesis, R hand disuse</td>
<td>3632</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>NA</td>
<td>L hemispheric atrophy with micro and macrocystic lesion in the rolandic cortex, mild L ventriculomegaly, R discrete white matter ASI (corona radiata)</td>
<td>1</td>
</tr>
<tr>
<td>9 (M)</td>
<td>12</td>
<td>L hemiparesis, L hand disuse</td>
<td>67.7</td>
<td>7</td>
<td>2</td>
<td>5</td>
<td>51</td>
<td>Large R white matter ASI with R hemispheric hypotrophy</td>
<td>1</td>
</tr>
<tr>
<td>10 (F)</td>
<td>13</td>
<td>L mild equinus, no evident Impairment of the L upper limb</td>
<td>27.5</td>
<td>10</td>
<td>5</td>
<td>5</td>
<td>98</td>
<td>No visible lesion</td>
<td>0</td>
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<tr>
<td>11 (M)</td>
<td>13</td>
<td>R hemiparesis</td>
<td>23</td>
<td>10</td>
<td>5</td>
<td>5</td>
<td>93</td>
<td>L white matter ASI (corona radiata), L ventriculomegaly, small L paraventricular cyst</td>
<td>3</td>
</tr>
<tr>
<td>12 (F)</td>
<td>16</td>
<td>R hemiparesis</td>
<td>408.2</td>
<td>9</td>
<td>5</td>
<td>5</td>
<td>84</td>
<td>L cortico-subcortical ASI (rolandic operculae and premotor cortex lower part of the prefrontal gyrus), L hemispheric hypotrophy</td>
<td>2</td>
</tr>
<tr>
<td>13 (F)</td>
<td>16</td>
<td>R hemiparesis</td>
<td>27.5</td>
<td>10</td>
<td>5</td>
<td>5</td>
<td>98</td>
<td>L precentral cortico-subcortical ASI (hand knob), L paraventricular (deep parietal) ASI</td>
<td>3</td>
</tr>
<tr>
<td>14 (F)</td>
<td>17</td>
<td>R hemiparesis</td>
<td>27.5</td>
<td>9</td>
<td>5</td>
<td>5</td>
<td>100</td>
<td>L postcentral cortical ASI, small L posterior parietal cyst, R ventriculomegaly</td>
<td>2</td>
</tr>
</tbody>
</table>
Morphologic MRI were acquired for each CH patient and for 13 control subjects on a 1.5 T MRI system (Signa Horizon Echospeed, General Electric Medical Systems, Milwaukee, Wisconsin, USA) using the 3D gradient echo T1-weighted sequence: TR (repetition time) = 23 ms; TE (echo time) = 3 ms; flip angle 30°; 124 contiguous axial slices (1.5 mm thick); FOV (field of view) = 24 cm and rectangular FOV = 75%; matrix = 256 × 256; 1 Nex. Individual MRI scans were realigned on the anterior and posterior commissural (AC–PC) plane (Talairach and Tournoux, 1988).

CH patients were classified into five groups according to the location and the extent of their lesion (see Table 1). One patient had no visible lesion on MRI (group 0). Six patients had extensive hemispheric lesions (group 1), three patients had focal cortical lesions (group 2) and five had subcortical lesions (group 3). One patient had a focal internal capsule lesion (group 4). In addition, detailed MRI analysis also showed minor lesions in the contralesional hemisphere in three patients (Patients 7, 8, 15) and ventricular dilatation in two patients (Patients 1 and 14) (see Table 1).

Upper limb assessment

Upper limb function was assessed in both CH and control subjects by means of different tests and functional scales. Both hands were systematically tested in the two groups starting with the dominant, or non-paretic, hand.

The Melbourne assessment of unilateral upper limb function is a clinical test specifically developed for children with neurological impairment (Johnson et al., 1994). It consists of 16 items scored on an ordinal scale of two to four levels depending on the item; each item involved reaching, grasping, releasing or manipulating small objects. Each child was videotaped during the test performance for subsequent analysis according to the criteria described by Randall et al. (1999). The total raw score was expressed as a percentage of the maximal score.

Strength

The grip strength was evaluated by means of a Jamar dynamometer (Therapeutic Equipment Corporation, Clifton, New Jersey, USA) adjusted at the second smaller setting; a pinch gauge was used to measure the key pinch force (Mathiowetz et al., 1986b). The tip pinch force was evaluated by means of the grip-lift apparatus (see below) (Eliasson et al., 1991). The subjects were asked to squeeze the apparatus as hard as possible for 3–5 s. This method allowed us to compare the maximum tip pinch force the subject could apply on the apparatus with the static grip force. It is noteworthy that the result of this measurement is likely to be underestimated when compared with the measure proposed by Mathiowetz et al. (1986b). For these three strength measures, each hand was tested three times, alternately, with a rest period of 30 s in
between each trial. The final score was expressed as the mean value of the three trials.

**Dexterity**

The digital dexterity was measured by means of the Purdue pegboard test (Backman *et al*., 1992; Mathiowetz *et al*., 1986a). The score was defined as the maximum number of pegs picked up from a cup and inserted into the holes of the board, within a 30 s period of time. Each subject performed this test three times with each hand, alternating the dominant (or non-paretic) and the non-dominant (or paretic) hand. The total score was the mean value of the three trials for each hand. The manual dexterity was assessed with the box and block test (Cromwell, 1965). In this test, the score was defined as the maximum number of blocks transported individually from one compartment of a box to the other, within a 60 s period.

**Pressure sensitivity**

The pressure detection threshold was measured at the tip of the index finger using a Semmes-Weinstein aesthesiometer (Lafayette Instrument Company, Loughborough, UK) according to the procedure described by Bell-Krotosky (1990). This instrument consists of a set of 20 monofilaments of progressively smaller diameters, calibrated to exert a decreasing peak force when pressed and bent against the skin. With vision occluded, subjects had to report when they felt the pressure of the filament applied briefly (<1 s) perpendicularly to the finger pulp. The score was the weight (expressed in mg) required to bend the thinnest monofilament the subject could feel.

**Stereognosis**

Stereognosis was assessed using a version of the manual form perception test (Ayres, 1989), as modified by Cooper *et al*. (1995). Five shapes (circle, triangle, square, diamond and octagon) and five objects of daily use (toothbrush, tennis ball, comb, large cup and a sweet in wrapper) were presented to the subjects in a random order, with vision occluded. The subject was then asked to point to the object from a selection of drawings representing the ten objects. The number of objects matched correctly was taken as the stereognosis score.

**Proprioception**

With eyes occluded, the metacarpo-phalangeal joints of the thumb and index finger were passively moved, with a maximum of 30°. The subject was asked to identify the direction of passive joint displacements; the number of correct responses out of five trials performed for each finger was scored.

**The grip-lift task**

The apparatus used to measure fingertip forces while lifting an object was similar to that described originally by Westling and Johansson (1984) (Fig. 1A). This apparatus weighted 280 g and the two parallel vertical grip surfaces were covered with smooth brass. The force perpendicular to the grip surface (grip force, GF) and the vertical force tangential to the surface (load force, LF) were measured with strain gauge transducers.
Signals were sampled at 400 Hz with a 12-bit resolution analogue-to-digital converter (National Instruments, Austin, Texas, USA).

Subjects sat on a chair in front of a table; the chair was adjusted so that the table was just above the thighs. The task was explained carefully and demonstrated to each subject; they had a chance to practise the task a few times with each hand before data collection began. Subjects had to grasp the apparatus between the tips of the index finger and thumb, to lift it ~5 cm above the table and to maintain it in the air for ~10 s. CH patients often used an additional finger for extra support when lifting the apparatus with their paretic hand. Each subject performed 10 trials with each hand, starting always with the dominant (or non-paretic) hand. Three patients (1, 8 and 9) were unable to perform this task because their impairment was so severe they could not grasp the apparatus properly.

The following temporal parameters were measured: (i) T₀–T₁, the delay between the contact of the two fingers with the manipulandum; (ii) T₂–T₃, the delay between the onset of GF and that of LF; (iii) T₀–T₃, the preloading phase i.e. the delay between the contact of the first finger and the onset of LF; and (iv) T₃–T₄, the loading phase during which both GF and LF increase until LF becomes equal to the weight of the object (see Fig. 1B).

The loading phase is followed by a static phase, during which the object is held stationary.

We also measured the following dynamic parameters: (i) the first derivative of both LF and GF i.e. the grip force rate (dGF/dt) and load force rate (dLF/dt); (ii) the peak GF i.e. the maximal value of GF reached during the loading phase; (iii) the value of GF at LF onset (i.e. at T₃) expressed as a percentage of peak GF; (iv) the static GF expressed with respect to the static LF (GF/LF); and (v) the average value of dGF/dt calculated between the onset and the peak of GF.

The precise synergy between GF and LF was assessed by computing, for each trial, a cross-correlation function between dLF/dt and dGF/dt. This method consists in searching for the larger coefficient of correlation between the two signals by shifting one signal with respect to the other one in order to cancel out the effect of a possible asynchrony. In the example illustrated in Fig. 2A, both dLF/dt and dGF/dt had a very similar profile but were slightly asynchronous and the maximum correlation was searched by systematically shifting, by steps of 2.5 ms, dGF/dt with respect to dLF/dt (Fig. 2B). In this example, the shift of dGF/dt required to maximize the coefficient of correlation was 20 ms, indicating that GF increase led LF increase. Therefore, for each trial, this method provides us with two values: the maximum coefficient of correlation, which indicates the similarity between the profiles of the two force rates, and the time-shift, which provides an objective measure of the asynchrony between dGF/dt and dLF/dt. A positive value for the time-shift indicates that GF leads LF, whereas a negative time-shift value indicates that GF lags LF. We also computed the absolute value of this time-shift to obtain a global estimate of the asynchrony between the two force rates.

**Index of peduncular symmetry**

Cross-sectional area of the cerebral peduncles in the mesencephalon was measured in order to estimate the dysgenesis of the corticofugal pathways (Bouza et al., 1994; Staudt et al., 2000). The area of the left and right cerebral peduncles was measured in a transverse plane passing through the mammillary bodies, five or six slices below the AC–PC plane. Because it was not always possible to dissociate the substantia nigra from the cerebral peduncles, the substantia nigra was also included in our measurements (see Fig. 6). In 15 CH patients, the absolute value of the peduncle area was expressed in mm²; in one CH patient,
the peduncular area was only available as a pixel number. The index of symmetry was defined as follows: (ipsilesional peduncular area/contralesional peduncular area) \times 100\%. In 13 out of 16 control subjects, the index of symmetry was defined as follows: (non-dominant side peduncular area/dominant side peduncular area) \times 100\%.

**Statistics**

Paired *t*-tests were used to compare: (i) the performance of both hands in control subjects and CH patients; and (ii) the performance of the paretic and non-paretic hands of each CH patient with the non-dominant and dominant hands, respectively, of his/her age-matched control. Non-parametric statistics were applied when normality test failed (Kolmogorov-Smirnov, \(P < 0.001\)) or when statistics were performed on ordinal-level data. Hence, a Friedman repeated measure analysis of variance on ranks was performed in control subjects and CH patients to search for a possible effect of repetition over the ten trials of the grip-lift task. A Spearman rank order correlation was used to determine the correlation between the grip-lift parameters, the upper limb function, the index of peduncular symmetry and the location, or the existence, of a lesion on any side. Given the large number of tests, the level of significance for the *P* value was set to 0.005 in order to minimize type 1 statistical errors.

**Results**

**Upper limb assessment**

The scores of CH patients on the functional and clinical tests performed on the paretic hand are listed in Table 1. Four patients had a deficit in pressure sensitivity (>67.7 mg) and three in proprioception; a deficit in stereognosis was found in six patients. When the non-paretic hand was assessed, all CH patients had a maximal score on all these tests, except for Patients 1 and 12, who had a deficit in pressure sensitivity. The scores of CH patients on the Melbourne test ranged from 51 to 100\%; two patients (14 and 15) and all control subjects had a maximum score on this test (see Table 1).

Table 2 presents the results of dexterity and strength tests performed in both CH patients and control subjects. In control subjects, the score on the Purdue pegboard test revealed a better digital dexterity in the dominant hand (CTRL\_dom) than in the non-dominant hand (CTRL\_ndom) \((t = 3.295, P = 0.005)\). The fingertip strength was also significantly larger in the dominant hand than in the non-dominant hand of control subjects \((t = 3.381, P = 0.004)\). In CH patients, as expected, the results of dexterity and strength tests disclosed a statistically significant difference between the paretic (CH\_paretic) and non-paretic hand (CH\_non-par) \((P < 0.001\) in all five tests; not shown in Table 2). When the paretic hand of CH patients was compared with the non-dominant hand of control subjects, both the dexterity and strength were significantly reduced in patients \((P < 0.001\) on all five tests). CH patients also showed a worse digital \((t = -5.41, P < 0.001)\) and manual \((t = -7.76, P = 0.001)\) dexterity when their non-paretic hand was compared with the dominant hand of control subjects; they also had a lower grip strength \((t = -3.4, P = 0.004)\) (see Table 2).

**The grip-lift task**

The performance of CH patients in the grip-lift task was strikingly different from that observed in control subjects. As shown in the example illustrated in Fig. 3B for a CH patient, the preloading phase (i.e. the delay before LF started to increase, T0-T3) was much longer than in the control subject. Then, both GF and LF increased in a less synchronous and less harmonious manner, as indicated by the noisier profiles of GF and LF rates. Altogether, this led to an overall increase in the duration of the initial phases of the grip-lift task in CH patients when compared with controls. This strategy contrasts with that observed in control subjects, namely a nearly simultaneous onset and parallel increase of GF and LF and a synchronous occurrence of the peaks of GF rate and LF rate, by the middle of the loading phase (T3-T4) (Fig. 3A).

The difference between the performance of CH patients and controls in the grip-lift task was further evidenced by the cross-correlation method. As shown in Fig. 3C, in the control subject, the correlation between dGF/dt and dLF/dt was rather high, attesting a close similarity between the profiles of GF and LF.
and LF rates. In addition, the finding that this correlation was found for a 0 ms time-shift proved that, in this example, both GF and LF increased synchronously. In contrast, in the CH patient we found both a lower correlation between GF and LF rates and a longer time-shift that indicate, respectively, the dissimilarity and the asynchrony between GF and LF rates (Fig. 3D). In this particular example, the peak of GF rate led that of LF by 102 ms.

These results were representative of those found for the whole population of patients and controls. As shown in Fig. 4A and B, the time-shift found in controls was shorter (median: 15 ms) than in CH patients (median: 35 ms). Moreover, although the dispersion of time-shift values in controls was far from being negligible, the time-shift distribution in CH patients was found much wider, ranging between ~20 ms and ~200 ms (Fig. 4A). In both groups, only a few cases of negative time-shift values were found. The mean time-shift was not statistically different in CH patients (54 ± 44.4 ms, mean ± SD) when compared with controls (23 ± 15.4 ms) (t = 2.43; P = 0.032); however, when the absolute value of the time-shift was computed, it showed a significant difference between patients (72 ± 39.1 ms) and controls (29 ± 13.1 ms) (t = 3.48; P = 0.005) (see Table 3). The distributions of correlation values gathered in CH patients (Fig. 4C) and in control (Fig. 4D) were also clearly dissimilar. We found a significantly lower correlation between the first derivatives of GF and LF in the paretic hand of CH patients (0.56 ± 0.14, mean ± SD) than in the non-dominant hand of controls (0.71 ± 0.10) (t = −3.74; P = 0.003). These observations further support our conclusion that the synergy between LF and GF was specifically impaired in CH patients.
Table 3 gives the mean values of the different temporal and dynamic parameters measured during the grip-lift task for the whole population of CH patients and control subjects. In control subjects, the performance of the non-dominant hand was indistinguishable from that of the dominant hand during the grip-lift task. In contrast, as expected, a significant

![Table 3 Grip-lift parameters in CH patients and control subjects](image)

*P ≤ 0.005; CTRLndom = non-dominant hand of control subjects; CTRLdom = dominant hand of control subjects; CHparetic = paretic hand of CH patients; CHnon-par = non-paretic hand of CH patients; Delay thumb–index, T0–T1 = delay between the contact of the thumb and index finger; GFonset–LFonset, T2–T3 = delay between the grip force (GF) onset and load force (LF) onset; Preloading (T0–T3) = preloading phase; Loading, T3–T4 = loading phase; GF at LF>0 = GF at LF onset (T3), expressed in percentage of the peak GF; Mean GFr = mean GF rate; Cross-correlation = r value obtained by the cross-correlation method (see Methods); Abs-shift = absolute value of the shift obtained by the cross-correlation method (see Methods).
difference was observed between a large number of grip-lift parameters when the paretic hand of CH patients was compared with the non-dominant hand of control subjects. Both the preloading and loading phases were significantly longer in CH patients (see Table 3). Within the preloading phase, the delay between the onset of GF and LF (T2–T3) was significantly prolonged whereas the delay between the contact of the two fingers with the object (T0–T1), although longer in CH patients, did not reach the significance level. There was a clear trend for a higher value of GF at LF onset and for a lower mean GF rate in CH patients, but these differences were not statistically significant. When the non-paretic hand of the CH patients was compared with the dominant hand of the control subjects, the delay between the thumb and index finger contact (T0–T1) was also found longer in CH patients (see Table 3), suggesting that the non-paretic hand was also somewhat impaired.

In both control subjects and CH patients, the Friedman repeated measure analysis of variance on ranks failed to disclose an influence of repetition on parameters measured during the grip-lift task.

Correlation between the grip-lift parameters and dexterity
There was a significant negative correlation between the preloading phase duration and digital and manual dexterity and the Melbourne score (see Table 4); the negative correlation between the preloading phase duration and digital dexterity ($r = -0.89$, $P < 0.001$) is illustrated in Fig. 5A. The digital dexterity also correlated significantly with the absolute value of the time-shift between GF and LF rate ($r = -0.77$, $P < 0.001$). None of the dynamic grip-lift parameters correlated with the dexterity or the Melbourne score.

Index of peduncular symmetry
As illustrated in Fig. 6, one consistent feature of CH patients was a distinct peduncular asymmetry (see Table 1 for individual values in CH patients). On average, in CH patients, the area of the ipsilesional peduncle was $137.6 \pm 27.2$ mm$^2$. 

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**Table 4** Correlation coefficients ($r$) between the grip-lift parameters and upper limb motor function

<table>
<thead>
<tr>
<th>Grip-lift parameters</th>
<th>Delay thumb–index (T0–T1)</th>
<th>GF$<em>{onset}$–LF$</em>{onset}$ (T2–T3)</th>
<th>Preloading (T0–T3)</th>
<th>Loading (T3–T4)</th>
<th>GF at LF&gt;0</th>
<th>Mean GFr</th>
<th>GF/LF Cross–corr</th>
<th>Abs–shift</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melbourne</td>
<td>-0.68</td>
<td>-0.63</td>
<td>-0.82*</td>
<td>-0.41</td>
<td>-0.66</td>
<td>0.43</td>
<td>0.42</td>
<td>0.50</td>
</tr>
<tr>
<td>Digital dexterity†</td>
<td>-0.58</td>
<td>-0.58</td>
<td>-0.89*</td>
<td>-0.48</td>
<td>-0.69</td>
<td>0.65</td>
<td>0.62</td>
<td>0.60</td>
</tr>
<tr>
<td>Manual dexterity‡</td>
<td>-0.36</td>
<td>-0.55</td>
<td>-0.79*</td>
<td>-0.69</td>
<td>-0.50</td>
<td>0.46</td>
<td>0.46</td>
<td>0.56</td>
</tr>
</tbody>
</table>

*P < 0.001; †As measured by the Purdue pegboard test. ‡As measured by the box and block test. Delay thumb–index (T0–T1) = delay between the contact of the thumb and index finger on the apparatus; GF$_{onset}$–LF$_{onset}$ (T2–T3) = delay between the grip force (GF) onset and load force (LF) onset; Preloading (T0–T3) = preloading phase; Loading (T3–T4) = loading phase; GF at LF>0 = GF at LF onset (T3), expressed in percentage of the peak GF; Mean GFr = mean GF rate (see Methods); Cross-corr = maximum $r$ value obtained by the cross-correlation method (see Methods); Abs-shift = absolute value of the shift obtained by the cross-correlation method (see Methods).
(mean ± SD, n = 15); it was significantly smaller than the peduncular area measured on the non-dominant side in controls (180.5 ± 17.8 mm², n = 13) (t = 4.04, P = 0.002). In contrast, the area of the contralesional peduncle in patients (181.7 ± 18.6 mm², n = 15) was not significantly different from the peduncular area measured on the dominant side in control subjects (179.4 ± 22.5 mm², n = 13) (t = 0.167, P = 0.871).

In CH patients, the area of the ipsilesional peduncle (mean ± SD: 137.6 ± 27.2 mm², n = 15) was significantly smaller than that of the contralesional peduncle (181.7 ± 18.6 mm², n = 15) (t = 7.054, P < 0.001). It is interesting to note that the cross-sectional area of the contralesional peduncle in CH patients was identical to values found in controls. The index of peduncular symmetry in patients ranged from 54.7 to 95.3% (mean ± SD: 76.2 ± 12.6%, n = 16) (see Table 1). In control subjects, the index of peduncular symmetry varied between 91.3% and 109.2% (mean ± SD: 100.8 ± 5.1%, n = 13).

Correlation between the dexterity and the peduncular symmetry

The index of peduncular symmetry was highly correlated with the Melbourne score (r = 0.81) and with both manual (r = 0.86) and digital dexterity (r = 0.84; P < 0.001 for all tests); the correlation between the digital dexterity and the index of peduncular symmetry is illustrated in Fig. 5B. The index of peduncular symmetry was also found to be negatively correlated with preloading phase duration (r = −0.76, P < 0.001), the GF at LF onset (r = −0.64, P = 0.005) and the absolute time-shift value (r = −0.71, P = 0.005).

No correlation was found between the anatomical location of the lesion (see Methods), and grip-lift synergy and functional parameters for the paretic hand. In the non-paretic hand, no correlation was found between the motor deficits, the presence of a minor lesion in the undamaged hemisphere (Patients 1, 7, 8, 14, 15) and the index of peduncular symmetry.

Discussion

Deficits in dextrous finger movements, which require accurate opposition of the thumb and index finger, were investigated in CH patients by quantifying the scaling and coordination of fingertip forces while lifting an object. This so-called ‘grip-lift task’ has proved to be very sensitive to reveal subtle deficits in skilled hand movements (Eliasson et al., 1991; Forssberg et al., 1999, 2000; Pereira et al., 2001).

Fig. 6 Axial (~10 mm AC–PC plane) T1-weighted MRI at the level of mesencephalon showing the cerebral peduncles (CP) in one CH and one control subject. Cross-sectional area of the left and right CP was measured in a transverse plane passing through the mammillary bodies and because of the difficulty to dissociate the substantia nigra from the cerebral peduncles; it was also included in our measurements. An index of peduncular symmetry was used to quantify dysgenesis and/or degeneration of the corticospinal tract. (A) Symmetry between the right (194 mm²) and left (193 mm²) cerebral peduncles in a control subject (Subject 16); in this subject, the index of peduncular symmetry equals 101%. (B) In Patient 9, with a large right matter infarct, cerebral peduncles were clearly asymmetrical. The cross-sectional area of the right and left peduncles was 115 mm² and 176 mm², respectively; the index of symmetry was 65% and was associated with severe motor deficits.
This approach provides further insight into the mechanisms responsible for motor deficits of the hand and a better understanding of the computational principles underlying motor control (Flanagan and Wing, 1997; Wolpert and Flanagan, 2001).

**Deficit in grip-lift movements in CH patients**

Earlier studies have shown that CH patients have a distinct deficit in scaling and coordinating fingertip forces while lifting an object between the thumb and index finger (Eliasson et al., 1991, 1992, 1995; Gordon and Duff, 1999a; Forssberg et al., 1999). The present study both supports and extends these results with the finding that mainly temporal parameters of the grip-lift task were altered in CH patients.

In agreement with previous studies (Eliasson et al., 1991, 1992, 1995; Gordon and Duff, 1999a), we found a significant increase in the duration of both the preloading (T0–T3) and loading phases (T3–T4) in CH patients. A longer preloading phase in patients could, at least partly, be explained by a significant increase of the T2–T3 delay (i.e. the delay between the onset of GF and LF). This observation confirms that, in CH patients, GF and LF increase in a more serial manner than in controls (Eliasson et al., 1991). The asynchrony between GF and LF increase was further investigated by computing the cross-correlation function between the first derivatives of GF and LF; this method provided us with a reliable measurement of the time-shift between both force rates. Interestingly, even in control subjects, the time-shift between GF and LF was far from being negligible and ranged between about –10 to 50 ms, indicating that GF and LF rates were not absolutely synchronous. In CH patients, the time-shift was found significantly longer and more widely distributed than in control subjects, confirming the inability of CH patients to ensure a precise synergy between fingertip forces while manipulating an object.

In addition to a larger asynchrony between GF and LF rates, profiles of both force rates were found more dissimilar in CH patients than in controls. Indeed, even when the GF rate profile was realigned with the LF rate profile in order to compensate for the time-shift, the coefficient of correlation remained, on average, significantly smaller in patients than in control subjects. This confirms the finding that in CH patients one consistent feature of grip-lift movements is the large number of small irregular increments in grip and load force rates (Eliasson et al., 1991) that contrast with the unimodal and smooth bell-shaped profiles of GF and LF rates found in control subjects (Johansson and Westling, 1988; Forssberg et al., 1991). This measurement is the first attempt to quantify the degree of dissimilarity between both grip and load force rates found in CH patients. In CH patients, these multi-peaked GF and LF rates may reflect the use of a probing strategy comparable to that described in very young children (Forssberg et al., 1991) and in adults who lack confidence about object’s physical properties (Gordon et al., 1993). However, it cannot be excluded that other factors such as co-contraction (Gibbs et al., 1999) or spasticity had a negative influence on this correlation.

In normal subjects, the finding that force rate profiles are synchronous and unimodal has been regarded as evidence for an anticipatory scaling of force output (Forssberg et al., 1991, 1992; Gordon, 1992; Gordon et al., 1992). The current results confirm that CH patients lack this ability to programme the different components of grip-lift movements in advance and that they are unable to ensure a precise temporal coordination between the different muscles involved in dextrous hand movements.

**Correlation between the grip-lift parameters and dexterity**

A correlation between a global index of grip-lift synergy and impaired dexterity has already been shown in CH patients by Forssberg et al. (1999); however, a correlation between individual grip-lift parameters and dexterity has never been reported. In the present study, we found that, in CH patients, the preloading phase duration was significantly correlated with manual and digital dexterity but also with the score on the Melbourne test. These correlations are difficult to interpret because the preloading phase consists of a large number of different processes taking place successively (Steenbergen et al., 1998). However, the time-shift between the profile of GF and LF rates was found correlated with digital dexterity. This further emphasizes that a tight temporal relationship between fingertip forces is of critical importance when manipulating small objects between the thumb and index finger, and that altering this synergy may dramatically impair dextrous finger movements. On the other hand, the absence of correlation between dexterity and GF and LF rate correlation suggests that, in CH patients, the presence of multiple irregular increments in both grip and load force rates is not synonymous with a poorer performance in skilled finger movements.

**Peduncular asymmetry and impaired dexterity in CH patients**

The present study confirms that most CH patients had a significant asymmetry of the cerebral peduncles when compared with control subjects (Bouza et al., 1994; Niemann et al., 1996; Staudt et al., 2000); similar findings have been reported in adult stroke patients (Fukui et al., 1994). Although several other corticofugal pathways are included in this measurement (Lemon, 1999), the asymmetry of the brainstem, or peduncle, has been regarded as a reliable estimate of the corticospinal tract degeneration (Bouza et al., 1994; Staudt et al., 2000). It is noteworthy that, in the present study, the cross-sectional area of the contralesional peduncle in CH patients was found identical to that of age-matched controls; therefore, the smaller index of peduncular symmetry found in CH patients was exclusively due to an atrophy of the...
damaged corticospinal tract and not to a compensatory overgrowth of the undamaged corticospinal tract. This observation indicates that, although transcranial magnetic stimulation studies have suggested that, after early brain injury, the contralesional corticospinal tract may play a crucial role in motor recovery (Carr et al., 1993; Vandermeeren et al., 2002), it does not result in macroscopically visible structural changes. This is in agreement with studies in monkeys showing that an early unilateral section of the corticospinal tract at birth does not yield a demonstrable structural reorganization of the corticospinal projections originating from the undamaged hemisphere (Galea and Darian-Smith, 1997a).

The present study confirmed the relationship between the degeneration of corticospinal tract and the severity of motor deficits (Bouza et al., 1994; Fukui et al., 1994; Sawlani et al., 1997), although this view has been questioned in adult stroke patients (Miyai et al., 1998). We further extended these previous results with the finding that the peduncular asymmetry correlated strongly with the deficits in dextrous finger movements found in CH patients. This observation is in agreement with results from monkey experiments showing that, after an early lesion of the corticospinal tract, although a remarkable recovery of manual dexterity may be observed, dextrous movements essential to grasp a small piece of food between the thumb and index finger remained irremediably impaired (Passingham et al., 1983; Galea and Darian-Smith, 1997b; Rouiller et al., 1998). In CH patients, a correlation between the grip-lift synergy and the structural damage of the brain, as estimated by measuring the total lesion extent in the damaged hemisphere, has already been reported by Forssberg et al. (1999). However, as repeatedly observed, the correlation between the lesion extent and functional outcome is usually rather poor or even absent (Bouza et al., 1994; Staudt et al., 2000); the measure of the brainstem asymmetry is probably a more reliable index because it provides an estimate of the corticospinal damage consequent on the lesion, irrespective of its size or location. In addition, because it is possible to evidence an asymmetry of the brainstem as early as 3 months after birth (Bouza et al., 1994; Pennock et al., 1993), i.e. much before deficits in skilled hand movements become evident clinically, this index also has a distinct prognostic relevance.

The correlation between such a global estimate of the corticospinal tract degeneration and rather subtle deficits in motor programming evidenced by the grip-lift task may appear somewhat puzzling. It is, however, important to keep in mind that, in addition to the primary motor cortex, a large number of cortical areas contribute efferent axons to the corticospinal tract (He et al., 1993, 1995; Galea and Darian-Smith, 1994) and that recent functional MRI studies have suggested that the control of the precision grip is distributed among the same network of cortical areas (Ehrsson et al., 2000, 2001; Kuhtz-Buschbeck et al., 2001). The peduncular asymmetry may therefore reflect the extent to which the development of these different cortical areas was affected by an early lesion (Marin-Padilla, 1997; Vandermeeren et al., 2002); the correlation between dexterity and peduncular asymmetry further supports the distributed nature of the control of the precise coordination of fingertip forces (Lemon, 1999; Ehrsson et al., 2000, 2001; Kuhtz-Buschbeck et al., 2001). Alternatively, it may be argued that the peduncular asymmetry reflects mainly the damage of larger corticospinal axons originating from the primary motor cortex.

**Deficits in the non-paretic hand**

In agreement with previous studies, we found that the non-paretic hand of CH patients also shows some discrete motor impairments (Gordon et al., 1999; Mercuri et al., 1999); similar results have been reported in adult stroke patients (Jones et al., 1989; Thilmann et al., 1990; Marque et al., 1997; Debaere et al., 2001). In the present study, we found a significant deficit in the digital and manual dexterity in the non-paretic hand of CH patients when compared with the non-dominant hand of controls. However, it is noteworthy that, except for T0–T1, the grip-lift task failed to disclose a significant difference between the performance of controls and that of CH patients when they used their non-paretic hand. This may question the sensitivity of the grip-lift task to detect subtle motor deficits. However, it may be argued that the two tests we used to assess digital and manual dexterity are more complex than the grip-lift task because they comprise other movement components such as the prehapping of the hand (Jeannerod et al., 1995) and the precise manipulation of the objects. It is probable that, at least in some patients, these components were affected leading to a lower score on these two tasks.

Mercuri et al. (1999) suggested that an impairment of the non-paretic hand invariably reveals the existence of a discrete lesion involving the contralesional hemisphere. In the present study, although detailed MRI analysis showed discrete lesions to the contralesional hemisphere in three patients and a ventricular dilatation in two others, those subjects did not have more severe deficits in the non-paretic hand than the other patients; contralesional lesions are therefore unlikely to explain the impairment observed in the ipsilesional hand of all CH patients. Recent functional imagery studies have stressed the important contribution of the ipsilateral motor areas during precision grip tasks, particularly when the demand on dextrous control increases i.e. when the task becomes more difficult (Ehrsson 2000, 2001; Kuhtz-Buschbeck et al., 2001). The motor deficit observed in the non-paretic hand of CH patients may, therefore, reveal the loss of the contribution of the damaged hemisphere to the control of the non-paretic, ipsilateral hand movements.

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