The aim of the study was to reveal specific aspects of impaired hand function in mildly affected multiple sclerosis (MS) patients. Static manipulation tasks were tested in 13 mildly impaired (EDSS 1.5-4) MS patients and 13 age and gender matched controls. The tasks were based either on presumably visually (i.e., feedback) controlled tracing of depicted patterns of load force (LF; produced by symmetric bimanual tension and/or compression applied against an externally fixed device) or on predominantly feed-forward controlled amplitudes of sinusoidal patterns of LF. The task variables (based on accuracy of exerting the required LF pattern) suggested poor performance of MS subjects in feedback, but not in the feed-forward controlled tasks. The patients also revealed higher GF/LF ratio in all tasks. However, the coordination of GF and LF appeared to be comparable in the two groups. These results continue to support the chosen experimental paradigm and suggest that in mildly affected MS patients, sensorimotor deficits and overgripping precede the decoupling of grip and load forces observed in more severely affected patients.

**Key Words:** hand, control, test, performance, EDSS

Multiple sclerosis (MS) is the most common demyelinating disease of the central nervous system (CNS), affecting more than 2.5 million individuals worldwide. MS is characterized by inflammatory loss of myelin in the CNS (brain and spinal cord), and presents with neurological deficits resulting in impaired vision, sensory disturbances, motor weakness, intention tremor, ataxia, etc. The clinical symptoms of MS are highly variable depending upon the site and extent of CNS involvement. One clinical feature that affects the functional independence of subjects with MS is reduced hand dexterity, i.e., the skill and ease of performing manipulation tasks (Feys, Duportail, Kos, Van Asch, & Ketelaer, 2002).

Manipulation of objects in daily living requires accurate control of load force (LF) exerted by arm muscles required to reach external objects, replace them, or use external supports when maintaining body posture (Flanagan & Wing, 1995;
Johansson & Westling, 1988). In addition to LF, manipulation tasks also require controlling hand grip force (GF) that not only prevents slippage of the hand-held object, but also avoids excessive forces that could cause unnecessary fatigue or crush the object (Flanagan, Tresilian, & Wing, 1993; Johansson & Westling, 1984; Scholz & Latash, 1998). Recent studies performed on various manipulation tasks of healthy participants have revealed a close coupling of GF with LF with no time lag between them in both dynamic (Flanagan & Wing, 1995; Gysin, Kaminski, & Gordon, 2003; Scholz & Latash, 1998) and static tasks (Scholz & Latash, 1998) suggesting predictive feed-forward control mechanisms (Blank et al., 2001; Bracewell, Wing, Soper, & Clark, 2003). The main outcome represents a stable grip-to-load force ratio (Bracewell, Wing, Soper, & Clark, 2003; Serrien & Wiesendanger, 2001), which is highly adjusted to the friction between the contact surface and, therefore, provides a relatively small safety margin that prevents slippage (Flanagan & Wing, 1995; Johansson & Westling, 1984). However, conditions involving either an increase in the frequency of vertical shaking or producing sinusoidal static LF against a hand-held object at greater than approximately 1.5–2 Hz lead to a deteriorated coordination of GF and LF, as well as to a higher GF/LF ratio (Blank et al., 2001; Flanagan & Wing, 1995; Jaric, Russell, Collins, & Marwaha, 2005; Zatsiorsky, Gao, & Latash, 2004).

Some recent studies, however, have showed that certain populations do not demonstrate such a fine coordination of the GF with LF. For example, the elderly exert longer and stronger than necessary grip forces with excessive fluctuations when manipulating external loads (Kinoshita & Francis, 1996), while young children demonstrate a prominent phase lag and a relatively low level of coordination between GF and LF (Blank et al., 2001). Regarding the GF control, neurological patients demonstrate either elevated grip, or poorly coordinated GF and LF, or both (see Nowak & Hermsdorfer, 2005, for review). In particular, Parkinson’s patients demonstrate excessive GF and a long period of force adjustment when dealing with unpredictable changes in LF (Fellows, Noth, & Schwarz, 1998; Ingvarsson, Gordon, & Forssberg, 1997) and the indices of hand grip coordination are strongly related with medication both on and off and stage of the disease (Ingvarsson, Gordon, & Forssberg, 1997). Stroke patients also demonstrate GF that is usually both higher than necessary and poorly coordinated in time with LF (Nowak, Hermsdorfer, & Topka, 2003). Similar findings were observed by Serrien and co-workers with Huntington's disease patients performing rhythmic unimanual and bimanual tasks of lifting (Serrien, Burgunder, & Wiesendanger, 2002), while cerebral lesions caused by stroke were associated with elevated GF, while the coordination of GF and LF remained mainly preserved (Hermsdorfer, Hagl, Nowak, & Marquardt, 2003). Regarding MS patients, recent studies of Feys and co-workers revealed that both the intention tremor and aiming accuracy increase with the availability of visual feedback (Feys, Helsen, Lavrysen, Nuttin, & Ketelaer, 2003; Feys et al., 2003; Feys et al., 2005). However, there is still a general lack of data regarding hand function in a number of neurological diseases. For example, in addition to the poorly understood relationship between general severity of neurological symptoms and ability to use hands in everyday tasks, little is known about specific effects of different manipulation conditions (e.g., uni-manual versus bimanual tasks, static versus dynamic conditions, etc.).
We recently evaluated a novel method that allows for comprehensive bimanual testing of hand function in uni- and bimanual static manipulation tasks (Jaric, Knight, Collins, & Marwaha, 2005). The method not only provided a number of reliable indices of coordination of GF and LF, but also proved to be sensitive enough to detect differences between various tasks based on specific LF profiles (Jaric, Russell, Collins, & Marwaha, 2005) and suggested prominent differences in hand control between static and dynamic manipulation (Jaric, Collins, Marwaha, & Russell, 2006). Note also that, in addition to the control of GF explored in most of the above cited studies, the method applied enabled accurate and reliable assessment of the subject’s ability to exert the required pattern of LF, which also represents a functionally important aspect of hand function. Within the present study, we applied a similar methodological approach to test hand function in mildly affected MS patients and healthy controls during performance of a variety of bimanual manipulation tasks. The main aim of the study was to reveal specific aspects of hand function impairment in MS. In particular, we hypothesized that the applied methodology would be sensitive enough to reveal impaired ability of mildly affected MS patients to accurately produce prescribed LF profiles, to produce a sufficient but not excessive GF/LF ratio, as well as to coordinate GF with respect to the prescribed changes in LF.

Methods

Subjects

Thirteen MS patients (9 females, 4 males) between 35 and 56 years of age (mean ± SD, 43.8 ± 10.6 years) participated in the study. This proportion of males and females was selected because MS has exceptionally higher prevalence in females (60–75%; Whitacre, 2001). The patients were recruited from the MS Clinic at the University of Delaware Physical Therapy Department, as well as through the Delaware chapter of the National Multiple Sclerosis Society. To control for the heterogeneity of expression and symptomatology of the disease, several inclusion criteria were applied. In particular, all 13 MS patients recruited for the study had the relapsing-remitting form of the disease. Patients were also without signs of cognitive impairment (i.e., “normal” that corresponds to a score of 24 or higher on the Mini Mental State Exam; Folstein, Folstein, & McHugh, 1975) and all were capable of independent living. An experienced neurologist screened the MS patients using the Expanded Disability Status Scale (EDSS; ranging from 0 that corresponds to normal neurological examination, to 10; Kurtzke, 1983), upper portion of Fugl-Meyer Scale (FM ranging from 1 to 4 [normal function]; Fugl-Meyer, Jaasko, Leyman, Olsson, & Steglind, 1975) and nine-hole peg test (Oxford Grice et al., 2003). Only the subjects with an EDSS score of 4 or less, and a nine-hole peg test time of 45 s or less were included. Table 1 provides a summary of all MS subjects.

An equal number ($N = 13$) of age (range 31–49, mean ± SD, 41.9 ± 6.3 years) and gender matched (9 females, 4 males) healthy control subjects also participated in the study. None had a history of neurological pathology or any recent injury to the upper extremities. Finally, all subjects selected were right handed (as assessed by the Edinburgh scale; Oldfield, 1971), and had normal or corrected-to-normal
vision. The subjects provided their informed consent to the procedures approved by the Human Subjects Review Board of the University of Delaware.

**Apparatus**

An experimental device developed at the University of Delaware was used (Figure 1; see Jaric, Knight, Collins, & Marwaha, 2005, for details). The device consists of two coupled handles (width ~ 4.5 cm) positioned horizontally and four force transducers (miniature strain gauge load cells; model WMC-50, Interface, Inc., Atlanta, GA). The design of the device allows for simultaneous recording of two independent compression/tension forces (LF) exerted along the long axis of the device and grip forces (GF) of each hand exerted perpendicularly. The height of the device can be individually adjusted for each subject to have a “comfortable position” while sitting in a chair and keeping vertically oriented forearms supported by pads positioned on the top of the table. This position has been suggested to provide a better standardization across subjects, as well as to limit the amount of bending and shearing forces produced during task performance (Jaric, Collins, Marwaha, & Russell, 2006; Jaric, Knight, Collins, & Marwaha, 2005).

The subjects held the device in the previously described position using the tips of all five fingers (“pinch grip”). A computer monitor in front of the subjects was used to display the task parameters and the feedback signals (the current average of

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Sex</th>
<th>Age (y)</th>
<th>FM score (R)</th>
<th>FM score (L)</th>
<th>9-hole peg test R (s)</th>
<th>9-hole peg test L (s)</th>
<th>EDSS score</th>
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<td>2.53</td>
<td>2.42</td>
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*Note:* The results of the upper extremity portion of Fugl-Meyer (FM) and the 9-hole peg test are reported for two hands separately. All subjects were right handed and had “relapsing-remitting” form of MS. (M, male; F, female; R, right hand; L, left hand; EDSS, Expanded Disability Status Scale)
two LFs exerted by subject’s right and left hands). Testing sessions were performed in the morning to minimize the effects of fatigue that are commonly reported later in the day in MS subjects. Custom written software (DASYLab, version 6.0, National Instruments, Austin, TX) was used for data acquisition and biofeedback.

The testing session consisted of five consecutive steps: neurological testing, test of maximum pinch force, familiarization procedure, assessment of the slip point, and experimental testing. The neurological testing consisted of evaluation on EDSS, upper extremity portion of the Fugl-Meyer questionnaire, and the nine-hole peg test for MS subjects. Only the nine-hole peg test was conducted on the healthy subjects. Following the neurological examination, the subjects’ peak pinch grip strength was tested using a pinch dynamometer (Jamar, range 200 N). The measured maximum pinch grip strength of the weaker hand of each subject was used to determine the magnitude of peak target level force for experimental testing (target peak force ~ 25% maximum pinch grip strength). This was done to account for strength differences among subjects. The rationale for using the maximum pinch grip strength was that in the experimental position (LF applied horizontally), the maximum amount of LF produced by large muscles of the arm is limited by the

**Figure 1**—A schematic representation of the device. Subject bimanually exerts load force (LF) in the direction of compression tension, while grip forces (GF) are also measured.
maximum GF that can be produced by small muscles of the hand and forearm to prevent slippage. In addition, pilot experiments suggested that exerting LF below 30% of the maximum pinch grip strength did not cause fatigue (Jaric, Knight, Collins, & Marwaha, 2005). Following the pinch grip strength testing, subjects performed a 15 min familiarization protocol that included all experimental tasks (see below for details).

The minimum G/L ratio that prevents slippage (“slip point”) was assessed prior to the main experiment according to methods applied in previous studies (Flanagan & Wing, 1995; Serrien, Burgunder, & Wiesendanger, 2002). In short, subjects were holding the device (released from the fixation and hanging vertically) stationary with one hand while gradually reducing their grip force. The ratio between GF at the moment slippage began and the weight of the device (corresponding to LF) was calculated as the slip point. Note that the slip point depends on the friction coefficient between the skin and surface of the device.

During the experimental testing, subjects were asked to exert a laterally symmetric LF along the long axis of the device using both hands (“pull out” or “push in”) according to the specific instructions for each task. Subjects remained naïve of GF, as it was not mentioned or displayed throughout the entire session. The following six tasks based on different LF profiles were tested in randomized sequence:

1. **Constant force task.** The subjects applied a tensile force (pulling out) to match a horizontal line shown on the computer monitor over 12 s.
2. **Ramp force task.** Subject matched a pulling out force pattern of six consecutive 2.5 s ramps on the monitor (Jaric, Knight, Collins, & Marwaha, 2005).
3. **Unidirectional 0.67 Hz oscillatory force task.** Subjects produced sinusoidal oscillation by consecutive pulling out and relaxing their LF over 12 s. They were instructed to match two depicted horizontal lines with the peaks of their pulling force and zero force. The frequency was paced by a metronome.
4. **Unidirectional 1.67 Hz oscillatory force task.** The only difference from the previous task was that the oscillation frequency was 1.67 Hz.
5. **Bidirectional 0.67 Hz oscillatory force task.** The task was identical to the unidirectional oscillatory force tasks except that instead of pulling out and relaxing, it required alternating pulling out and pushing in. Therefore, target lines depicted on the computer monitor corresponded to the prescribed peaks of the pulling and pushing force.
6. **Bidirectional 1.67 Hz oscillatory force task.** The only difference from the previous task was that the oscillation frequency was 1.67 Hz.

The rest intervals between two consecutive tasks was 1 min.

An important consideration could be the presumed “types of force control” in the applied six tasks. Regarding the constant and ramp force task, the subjects were tracing the prescribed constant or ramp force pattern depicted on the computer monitor. Thus, they were able to apply on-line corrections based on visual feedback mechanisms. Regarding the oscillatory force tasks, preliminary experiments revealed that most of the subjects were able to “draw” a low frequency sinusoidal LF profile by applying similar visual feedback based control mechanisms to those applied in the constant and ramp force task. However, as the frequency approached
approximately 0.5 Hz and went beyond, all subjects reported that they were switching from “drawing the entire cycle of the force” to “only adjusting LF peaks” relying on previous LF peaks for correcting the forthcoming ones. Therefore, while the constant and ramp force tasks presumably provided conditions for applying feedback control mechanisms, the control of all four oscillation force tasks could be predominantly based on feed-forward neural mechanisms.

Regarding the applied frequencies of the oscillatory force tasks, the lower one (i.e., 0.67 Hz) was selected to be relatively low, but still above the level that enables “drawing the entire circle” (see previous paragraph). The selection of the higher one (1.67 Hz) was based on both the pilot measurements performed on MS patients (Jaric, Knight, Collins, & Marwaha, 2005) and our recent results obtained from healthy subjects (Jaric, Collins, Marwaha, & Russell, 2006). The results suggest that while healthy controls can perform oscillatory tasks at as high as 3.33 Hz, some MS patients can have problems with frequencies of 2 Hz and higher.

**Data Processing**

Force signals were recorded from the four transducers at a rate of 200 samples per second and stored on a computer for further analysis. Custom written software (LabVIEW version 6i, National Instruments, Austin, TX) was used for data processing. The data were low pass filtered online at 10 Hz with a fourth order Butterworth filter to free the data from interfering high frequency noise. The duration of each trial was 12 s, but only the last 9 s (or last three out of six ramps) were used for data analysis to avoid the inevitable variability originating from initial adjustment of LF. In addition, since little coordination between GF and LF is necessary when LF is low, only the intervals where LF was higher than 20% of the peak LF were used for analysis (see Flanagan & Wing, 1995, for similar approach).

Since the tasks required the exertion of the averaged LF produced across both hands to reach the prescribed force level, the task performance was assessed from the difference between the prescribed and actual LF averaged across hands. Due to the nature of the tasks (i.e., tracing a prescribed force pattern), the root mean square errors (RMSE) were calculated to assess task performance observed in the constant and ramp force tasks. Since the oscillatory force tasks required reaching the prescribed levels of the peak LF, the respective task performance was assessed through constant errors (CE) and variable errors (VE). Specifically, CE was calculated as a difference between the average peaks of LF and the prescribed force levels, while VE was calculated as standard deviations of peaks of LFs. Note that the selected variables of task performance reveal important aspects of hand function. From the “ecological aspect” they could reflect the ability to precisely manipulate hand-held objects or provide an accurate pattern of reaction force from external supports.

To evaluate the magnitude of applied GF relative to the magnitude of LF during a particular task, the average GF-to-LF ratios (GF/LF ratio) were calculated from the time series of force profiles of all tasks. The GF/LF ratio was used because it represents a load independent index which permits evaluation of GF across movement cycles when the LF is continuously varying.

The coordination of GF and LF was initially assessed through the cross correlation. However, since the time lags observed between GF and LF appeared to
be relatively small and inconsistent (see the Results section for details), Pearson’s correlations were calculated instead (see Jaric, Collins, Marwaha, & Russell, 2006, for similar approach). This calculation was performed on all data sets except the constant force task due to exceptionally steady force profiles.

Descriptive statistics were calculated for all dependent variables. Initially, mixed three-way ANOVAs were used that included the effect of hand. However, none of the data revealed significant effect of hand except somewhat higher left hand GF/LF ratio in healthy subjects (but not in MS patients). Moreover, clinical assessment also showed no difference between hands in MS patients (see Results), as well as no differences between the maximum pinch grip strength between the left and right hand in either of the two groups recorded. Therefore, we pooled the data for the right and left hands in further analysis. Finally, mixed two-way ANOVAs (significance: $p < .05$) were used to test the effects of group (between subjects factor—MS patients versus healthy controls) and task (within subject factor—constant, ramp, and four oscillatory force tasks) on each dependant variable. Simple main effects were evaluated wherever significant interactions were present.

Results

The pinch grip strength recorded in MS patients and healthy controls was (mean ± SD) 23.0 ± 5.8 and 30.0 ± 12.9 N, respectively ($p < .05$; independent samples t-test). The EDSS, the upper extremity portion of Fugl-Meyer test, and nine-hole peg test were performed on the MS patients, while only the nine-hole test was performed on healthy controls. The EDSS scores of MS patients were 3.0 ± 0.9 (range, 1.5–4), while the Fugl-Meyer scores for the right and left upper extremity were 2.68 ± 0.3 (range, 1.9–3) and 2.77 ± 0.2 (range, 2.4–3), respectively. The later results suggested no difference between the right and left arm ($p > .05$). The nine-hole peg test scores obtained from MS patients were 23.3 ± 6.1 s and 23.1 ± 6.7 s, while the same scores obtained from healthy controls were 16.7 ± 1.7 s and 17.7 ± 1.3 s for the right and left hands, respectively. The differences between the left and right hand in both groups were non-significant (paired t-test; $p > .05$). Comparison of the nine-hole peg test scores revealed significantly better scores in healthy controls than in MS subjects ($t = 4.7, p < .01$; independent samples t-test).

Figures 2, 3, and 4 illustrate the time series of GF and LF profiles obtained from a representative MS patient and healthy subject. These two subjects appeared to have similar maximum pinch force and, therefore, the instructed maximum LF was about 5 N for both of them. In general, visual inspection suggests that both subjects were able to produce the required LF profiles, and that GF were highly modulated with respect with LF in all tasks except for the two bidirectional oscillation tasks. Comparison of the average levels of the recorded forces suggests that the involvement of two hands regarding exertion of both GF and LF was similar. However, the MS patient demonstrated a somewhat irregular pattern of LF (as compared to the healthy subject), particularly in the constant and ramp force tasks (Figure 2). In addition, the overall GF in the MS patient appears to be higher than in the healthy subjects. This difference appears to be particularly prominent in the constant and ramp force task (Figure 2) and, to a lesser extent, in the unidirectional and bidirectional 0.67 Hz oscillatory tasks (Figures 3 and 4).
Figure 2—Force patterns recorded over last 9 s of the constant and ramp force tasks recorded from a representative MS patient (left hand graphs) and healthy control (right hand graphs). For illustrative purposes, grip forces (GF) are depicted as positive, while load forces (LF) in the direction of tension as negative (r, right hand; l, left hand; TGT, target force level).

Figure 3—Force patterns recorded from unidirectional oscillation tasks. Data are obtained from the same subjects as shown in Figure 2.
Tasks

Figure 5 depicts the task performance variables which describe the success in exerting the required LF profiles. The two-way ANOVA (group × task) applied on RMSE obtained from the constant and ramp force task (see Figure 5A) revealed significant effect of group \(F(1, 24) = 9.5, p < .01\) and task \(F(1, 24) = 130, p < .001\) and no interactions \((p > .05)\). In general, the RMSE was less for the constant as compared to the ramp tasks across both groups, and greater in MS patients than in healthy subjects.

The same ANOVA applied on VE obtained from four oscillatory tasks (see Figure 5B) suggested a significant effect of task \(F(3, 72) = 27.5, p < .01\), but no effect of group \(F(1, 24) = 0.4, p = .85\) and no interaction \(F(3, 72) = 0.4, p = .78\). The VE of bidirectional 1.67 Hz task was greater than in the remaining three oscillation tasks \((p < .01)\). In addition, VE of the bidirectional 0.67 Hz oscillation task was significantly greater than VE of the unidirectional 0.67 Hz task \((p < .05)\).

Similar to VE, CE revealed a significant effect of task \(F(3, 72) = 19.4, p < .01\), but no effect of group \(F(1, 24) = 0.0, p = .96\) and no interaction \(F(3, 72) = 0.3, p = .80\); see Figure 5C. CE of the bidirectional 1.67 Hz task was greater than CE of all other tasks. In addition, the CE of the unidirectional 1.67 Hz task was significantly greater than for the 0.67 Hz unidirectional task \((p < .05)\).
Figure 5—Task performance (averaged across the subjects and hands; MS, multiple sclerosis patients; HS, healthy subjects; means with SE bars) assessed by (A) RMSE calculated from the constant and ramp force tasks, and (B) variable (VE), and (C) constant error (CE) calculated from the oscillation force tasks (* indicates significant differences between groups).
Figure 6A depicts the GF/LF ratio of two subject groups obtained from all six tasks. Since a two-way ANOVA (group × task) revealed a significant interaction of the two main factors \(F(5, 120) = 2.34, p < .05\), we looked at the simple main effects. The GF/LF ratio was greater in MS than in healthy controls in the ramp task, as well as in both the 0.67 and 1.67 Hz bidirectional oscillation tasks \(p < .01\). For the MS patients, the GF/LF ratio of the bidirectional 1.67 Hz task was significantly greater than in all other tasks \(p < .01\) except the bidirectional 0.67 Hz task. The GF/LF ratio of the bidirectional 0.67 Hz task was also significantly greater than in the constant and in the 0.67 Hz and 1.67 Hz unidirectional tasks \(p < .05\). In the healthy subjects, the GF/LF ratio of the constant task was significantly less than the same ratio of the bidirectional 0.67 and 1.67 Hz oscillation tasks \(p < .05\). Finally, since the slip point revealed 0.64 ± 0.06 and 0.67 ± 0.05 (for the right and left hand, respectively; data averaged across the subjects and hands; mean ± SD), note that the results depicted at Figure 6A suggest that the average GF/LF ratio was between 1.5 (constant force task in healthy subjects) and three times (1.67 Hz bidirectional task in MS patients) higher than the minimum ratio that prevents slippage.

Preliminary statistical analysis of the time lags was obtained from the cross correlations calculated between LF and GF. When averaged across the subjects within each group separately, the results show that GF lead the LF in five analyzed tasks. However, the time lags were exceptionally short and inconsistent (see Figure 6B for the data). As a consequence, the results revealed neither the effect of group, nor task. Therefore, the Pearson’s correlations were calculated to assess the coordination of GF with LF (see Figure 6C). The two-way ANOVA applied on the Z-transformed Pearson’s correlation coefficients showed a significant main effect of task \(F(4, 96) = 114, p < .01\), but not of the group \(F(1, 24) = 0.8, p = .38\) and no interactions \(F(4, 96) = 1.2, p = .30\). Post hoc analysis revealed that the unidirectional 0.67 Hz task showed higher correlation between GF and LF than the remaining four analyzed tasks \(p < .05\). Also, the bidirectional task at 1.67 Hz suggested the lowest correlation among all tasks \(p < .05\); see Figure 6C). There were significant differences for all pairwise comparisons \(p < .05\) among the five tasks, except between unidirectional 1.67 Hz and ramp tasks.

Discussion

Regarding the hypothesized outcomes, the main findings of the present study were that mildly affected MS patients (as compared to healthy controls) revealed (a) impaired ability to exert prescribed LF profiles in visually traced (i.e., constant and ramp force) tasks and (b) higher GF/LF ratio, while (c) the coordination of GF and LF appears to be unaffected. However, before interpreting the main findings, some general methodological aspects of the study need to be addressed.

General Considerations

Before interpreting the observed differences in hand function between two groups of subjects, one must take into account the general level of neurological impairment of the tested MS patients. The inclusion criteria enabled only those with mild
Figure 6—(A) Grip-to-load (GF/LF) force ratio averaged across the subjects and hands (means with SE error bars; MS, multiple sclerosis patients; HS, healthy subjects; (B) Time lags between GF and LF averaged across the subjects and hands. (C) Median correlation coefficients between GF and LF averaged across the subjects and hands; (*) indicates significant differences between groups).
motor impairment (according to EDSS), without cognitive deficits, and capable of independent living to participate in the study. As a result, all patients reported a fully active professional life and little impairment of motor function according to the upper portion of the Fugl-Meyer test. Interestingly, despite having on average a score almost 40% lower in the nine-hole peg test, most of the patients claimed no problems regarding hand function in their professional and everyday life except somewhat pronounced fatigue. Conversely, “moderately affected” MS patients tested in several recent studies (Fays et al., 2003; Feys et al., 2005; see text below for details) revealed EDSS scores within the range of 6–8, while their time to complete the nine-hole peg test was more than three times longer than the same time recorded for the patients tested in the present study. All these findings suggest that the evaluated sample of MS patients represent a group of mildly impaired individuals.

Prior to comparison of MS patients and healthy subjects, the observed effects of tasks regarding each assessed variable depicting particular aspects of force control needs to be discussed. The results appeared to be in line with our recent studies which used a similar experimental approach. The task performance revealed higher errors in production of the prescribed LF patterns in ramp than in constant force profiles (Jaric, Knight, Collins, & Marwaha, 2005) as well as higher variable errors in high than in low frequency and in bidirectional than in unidirectional tasks (Jaric, Russell, Collins, & Marwaha, 2005). GF/LF ratio was also higher in ramp than in constant force tasks (Jaric, Knight, Collins, & Marwaha, 2005), and in bidirectional than in unidirectional tasks (Jaric, Russell, Collins, & Marwaha, 2005). Finally, the coordination of GF with LF assessed through the correlation coefficients between them also revealed lower indices for bidirectional than for unidirectional oscillation force tasks (Jaric, Russell, Collins, & Marwaha, 2005).

Although some of these findings could be based on distinctive mechanisms of force control in static (as compared to dynamic) manipulation tasks (Jaric, Collins, Marwaha, & Russell, 2006) of considerable interest for further discussion could be the subject-specific effects of task on the assessed indices of hand function. However, except for the indices of task performance (RMSE versus VE; see below for details), both the visual inspection of the depicted data (Figures 5 and 6) and the post hoc tests suggest that neither the presumed control mechanisms (i.e., feed-back versus feed-forward) nor task complexity (e.g., high versus low frequency or uni- versus bimanual oscillations; (Blank et al., 2001; Jaric, Russell, Collins, & Marwaha, 2005; Zatsiorsky, Gao, & Latash, 2004) have different effects on hand control in the tested MS patients and healthy controls. Therefore, further discussion will focus on the differences in hand coordination between these two groups.

**Differences Between MS Patients and Healthy Controls**

An important aspect of hand function in everyday living is the production of accurate temporal patterns of LF against manipulated external objects. When compared to healthy subjects, neurological patients are generally expected to display deteriorated performance in manipulation tasks (see above for details), while MS patients in particular are expected to demonstrate a delayed onset, slower execution, and aiming
inaccuracies when performing reaching movements (Feys, Helsen, Lavrysen, Nuttin, & Ketelaer, 2003; Nowak & Hermsdorfer, 2005). Therefore, we hypothesized that MS patients would reveal deteriorated task performance, as compared to healthy controls. However, in the applied static force production task of the present study, the tested MS patients only failed to produce the required pattern of LF in the constant and ramp force task (as compared to the healthy subjects), but not in the remaining oscillation tasks. A possible interpretation of this finding could be based on the presumed differences in neural control of these two groups of tasks. In short, while the constant and ramp force tasks were based on visual tracing of depicted lines on the computer monitor (i.e., “feed-back control”), the oscillatory force tasks were presumably based on feed-forward mechanisms (see the Methods section for details). Therefore, one could conclude that controlling an accurate exertion of LF based on visual feedback could represent a specific aspect of motor impairment in mildly affected MS patients. This finding is in line with previous results suggesting a relatively high level of impairment in visually guided movements when compared to the same tasks performed without visual feedback (Feys et al., 2003; Schenk, Walther, & Mai, 2000) which could be partly caused by intention tremor typical for MS patients (Feys et al., 2005). However, it should be noted that the above-mentioned studies were performed on MS patients with a considerably more severe level of general motor impairment including the ocular system (see previous paragraph for details). Impairment of this system not only deteriorates performance of visually guided movements in general, but could also trigger intention tremor in MS patients (Feys et al., 2005). Note that impaired vision was one of the exclusion criteria in the present study. Another potential problem in our interpretation could be the auditory signal used for cuing the oscillatory tasks which could be also considered as feed-back information. Therefore, further research is needed to interpret the differences in controlling LF under various feed-forward and feed-back (i.e., not only visually guided) conditions observed in the tested patients.

Another aspect of hand function that revealed a prominent difference between the MS patients and healthy controls is the recorded overall GF/LF ratio. In particular the greater GF/LF ratio and lack of a group-task interaction suggests that MS patients use a greater safety factor to prevent slippage and that this behavior is not task specific, which is in line with our hypothesis regarding the GF/LF ratio. A number of studies have reported excessive GF in neurological patients (Fellows, Noth, & Schwarz, 1998; Nowak, Hermsdorfer, & Topka, 2003) and elderly (Kinoshita & Francis, 1996) as compared to healthy subjects. This observation has been interpreted as an indication that hand function impairment could be caused by either central (Fellows, Noth, & Schwarz, 1998; Schenk, Walther, & Mai, 2000; Serrien, Burgunder, & Wiesendanger, 2002) or sensory dysfunction (Augurelle, Smith, Lejeune, & Thonnard, 2003; Johansson & Westling, 1984). However, our data do not allow us to speculate as to which of these two causes might play a dominant role in the observed phenomenon.

Although the results revealed differences between MS patients and healthy subjects regarding their ability to exert specific LF pattern while minimizing the GF/LF ratio, the results did not support the hypothesized differences in correlation coefficients between GF and LF. These correlations have been considered an important index of coordination in manipulation tasks, allowing a stable and relatively low safety margin (Flanagan & Wing, 1995; Johansson & Westling, 1988; Zatsiorsky,
Gao, & Latash, 2004). Therefore, from the perspective of general impairment of hand function in neurological patients, the observed lack of differences in force coordination between the tested patients and healthy controls could be considered somewhat surprising. Moreover, our recent study (Jaric, Knight, Collins, & Marwaha, 2005) revealed a prominent difference in the correlation coefficients in GF and LF between a group of healthy subjects and two selected MS patients. However, one should also take into account the relative severity of the motor impairment of the tested patients. These two MS patients showed EDSS scores of 3 and 4.5 (as compared to the range 1.5–4 observed in the present study), while our recent set of pilot data obtained from three moderately impaired MS patients (EDSS scores between 6 and 7.5) suggests virtually no coordination of GF and LF. Therefore, it is possible that the disruption of GF-LF coordination in MS is a phenomenon associated with higher levels of motor impairment.

Conclusions and Recommendations for Future Research

In general, our study revealed a part of the hypothesized specific aspects of motor impairment in MS patients while performing static manipulation tasks. Despite being mildly impaired and, therefore, able to live an independent and fully active professional life, the tested patients demonstrated deteriorated ability to exert required patterns of LF (i.e., to exert accurate forces against external objects) when visual feedback was available, while their performance in the absence of that feedback was comparable to healthy controls. In addition, despite showing a normal level of coordination of GF and LF, the GF/LF ratio was higher, suggesting use of somewhat excessive grip forces while controlling hand-held objects. Future research needs to address a number of questions, such as whether a similar approach could be applied to MS patients (and other neurological patients as well) with more severe motor symptoms. Evaluation of other experimental conditions could also deserve attention, such as testing a uni-manual task to assess laterality of symptoms (strongly recommended by De Souza, 1999, for testing MS patients), or comparison of long lasting (as tested in the present study) with short lasting discrete tasks that could reveal transient neural phenomena characterizing coordination of GF and LF (Ohki & Johansson, 1999). Taking into account the role of manipulation tasks in everyday life, as well as the lack of quantitative clinical tests of hand function (Jaric, Knight, Collins, & Marwaha, 2005), concurrent validity of the variables derived from the applied methodological approach with the standard clinical assessments could deserve particular attention. If experimentally supported, this validity could motivate further research in the development of both a simpler version of the applied device and a simpler experimental protocol that could serve as a standard clinical test of hand function in neurological patients.

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