

Ordered Motor-Unit Firing Behavior in Acute Cerebellar Stroke

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Sauvage, Chloe, Mario Manto, Alexander Adam, Rick Roark, Patrice Jissendi, and Carlo J. De Luca. Ordered motor-unit firing behavior in acute cerebellar stroke. *J Neurophysiol* 96: 2769–2774, 2006. First published June 21, 2006; doi:10.1152/jn.00268.2006. It is known that at any given force level, the lower-threshold motor units generally fire at greater rates than the higher-threshold units during isometric tasks of extremity muscles. In addition to this hierarchical arrangement, firing rates of motor units fluctuate in unison with nearly no time delay; an observation that has led to the concept of common drive, a basic motoneuronal rule. Although it is established that the cerebellum plays a critical function in motor control, its role in the genesis, triggering, selection, and monitoring of motor-unit firing pattern discharges during isometric tasks is unknown. We applied an electromyographic (EMG) decomposition technique, known as precision decomposition, to accurately identify motor-unit firing times from the EMG signal recorded from the first dorsal interosseous muscle to unravel the features of motor-unit firings in three patients presenting a unilateral cerebellar stroke and exhibiting an acute cerebellar syndrome. We observed ataxic isometric force during visually guided abduction of the index finger on the affected side. However, the hierarchical response of individual motor units was spared. Furthermore, acute cerebellar ataxia was not associated with a loss of the common drive.

INTRODUCTION

Patients presenting an acute cerebellar lesion such as a stroke exhibit oculomotor disturbances, ataxic speech, dysmetria, kinetic tremor, and ataxic gait (Gilman et al. 1981; Holmes 1917; Trouillas et al. 1997). During the task of visually guided isometric force production, ataxic patients are unable to produce constant forces (Mai et al. 1989). This impairment for producing sustained forces is a major component of the difficulties associated with skilled tasks requiring hand or finger use (Mai et al. 1989; Manto 2002).

Although our understanding of cerebellar roles in motor control has improved in recent years, the contribution of cerebellar pathways to the control of firings of motoneurons in human is unknown. Because the motoneurons are the end effectors of the motor system, it is presumed that their firing pattern discharges are disturbed in cerebellar stroke patients. These patterns might be used as objective, quantitative means for monitoring the progression or regression of cerebellar deficits. In particular, the unraveling of these patterns could lead to new strategies of rehabilitation in cerebellar disorders.

Our technology, called precision decomposition, identifies the individual action potentials that contribute to motor unit potentials, allowing the detailed investigation of firing rates of

motor units (De Luca and Adam 1999; De Luca et al. 1982). Recruitment thresholds, firing rates and firing variability of motor units can be unraveled. Several studies have demonstrated that in healthy, young adults the average firing rates of motor units during force-varying contractions have a hierarchical organization, with higher firing rates for earlier recruited units (De Luca and Erim 1994; De Luca et al. 1982; Erim et al. 1996, 1999; among others). For contractions with a trapezoidal force profile, plots of mean firing rate signals of motor units take the appearance of an “onion skin.” Also, the observation that the firing rates of motor units fluctuate in unison with essentially no time delay between them has led to the concept of common drive, a basic rule of the motoneuronal code (De Luca and Erim 1994; De Luca et al. 1982). The common drive received by all the motor units in the pool is translated into individual firing patterns by the input/output characteristics of the motoneuron (Erim et al. 1996). Fluctuations in the common drive are reflected in concurrent fluctuations in the firing rates of motor units of the same pool. Common drive has been found in all muscles tested by our group, ranging from small distal muscles such as the first dorsal interosseous to large proximal muscles such as the deltoid muscle (De Luca and Mambrito 1987; De Luca et al. 1982, 1996; Erim et al. 1996, 1999).

In this report, we investigated three patients presenting acute, unilateral cerebellar stroke using the precision decomposition technique (the number of subjects was limited due to the rarity of finding 3 acute cerebellar stroke patients willing to participate). We tested the hypothesis that cerebellar stroke causes disorganized firing behavior of motor units during a visually guided isometric task. We presumed that the ataxic isometric motor behavior distally in upper limb was associated with a compromised recruitment rank.

METHODS

The patients were admitted in the Department of Neurology of the Free University of Brussels. They were examined on a daily basis. They gave a written informed consent for the participation in the study, which received prior approval from the Ethical Review Board of the Free University of Brussels. The project was also approved by the Institutional Review Board of Boston University.

Clinical description

The three patients were all right-handed and exhibited an acute cerebellar syndrome associated with a cerebellar stroke. *Patient 1* was a 70-yr-old man, who presented sudden vertigo associated with nausea and vomiting. He developed clumsiness in left-upper limb. He had a

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personal history of hypertension and used to smoke 20 cigarettes per day for 25 yr. He was taking amlodipine (5 mg/day) and bisoprolol (10 mg)/hydrochlorothiazide (25 mg). He exhibited a horizontal nystagmus and saccadic pursuit in absence of skew deviation with a scanning speech. Horner sign was absent. There was a decreased perception of light touch in the territory of nerve V on the left side as well as a slight facial asymmetry. He did not present fasciculations. Muscle tone was normal. Gait was broad-based and ataxic. Finger-to-nose and heel-to-chin tests were ataxic on the left side. He exhibited dysidiadochokinesia on the left side. Plantar reflexes were indifferent. Tendon reflexes were 2/4 in four limbs. There was no clinical evidence of force deficit in upper and lower limbs. The sense of position was normal. Ataxia Rating Score was (0: no deficit, 4: severe deficit): Dysarthria D 1/4, Tremor T 3/4, Ataxia of Stance Gait A 3/4, Hypotonia H 0/4 (day of recording). Brain MRI revealed an extensive ischemic stroke in the territory of left posterior-inferior cerebellar artery (PICA; inflow lesion with a large vessel infarct involving both medial and lateral branches of PICA (see Kumral et al. 2005) with a lesion on the left side at the origin of the inferior cerebellar peduncle, involving lobules VIIIB and VIIIA and adjacent lobules Crus II and VIIIB (Gerwig et al. 2003; nomenclature of Larsell as adapted by Schmahmann). Only part of the inferior and posterior dentate nucleus was affected as described previously in posterior inferior cerebellar lesions (Gerwig et al. 2003). Lobules III–IV, V, and VI were spared bilaterally.

Patient 2 was a 75-yr-old right-handed woman who presented a sudden difficulty for standing up and for speaking, associated with nausea and vomiting. She developed clumsiness in left-upper limb. She exhibited a horizontal nystagmus and saccadic pursuit. Speech and gait were ataxic. Finger-to-nose test was dysmetric on the left side and she exhibited a kinetic tremor on the left arm. Plantar reflexes were flexor. Sense of position was normal. There was no sign of extra-cerebellar lesion. Ataxia Rating Score was: D 2/4, T 3/4, A 3/4, H 0/4. Brain CT-scan revealed an ischemic cerebellar stroke on left side (territory of the superior cerebellar artery SCA; outflow lesion).

Patient 3 was a 76-yr-old woman presenting an acute cerebellar syndrome 10 days after placement of a pacemaker for heart disease. She exhibited a horizontal nystagmus. Gait was ataxic and impossible without external aid. Finger-to-nose test was dysmetric on the left side. She presented dysidiachokinesia on the left side. Plantar reflexes were indifferent. Sense of position was normal. There was no sign of extra-cerebellar lesion. Ataxia Rating Score was: D 0/4, T 2/4, A 3/4, H 0/4. Brain MRI revealed a cerebellar stroke in the territory of left PICA (inflow lesion). The lesion did not extend to the contralateral side and there was no brain stem involvement.

Data collection

Patients were seated comfortably in front of a computer screen displaying the force recorded by a transducer located on a table. They were asked to produce an isometric force with the first dorsal interosseous (FDI) muscle. To ensure isometric contractions, the hand and forearm were immobilized in a restraining device (finger mold with straps) and the index finger was coupled to the transducer measuring forces in the abduction direction. Maximal voluntary contraction (MVC) strength for index finger abduction was determined, and specially designed sterile quadrifilar needle electrodes (De Luca and Adam 1999) were inserted into each of the FDI muscles. The affected hand was tested first. The electrodes provided four selective pickup surfaces from which three differential pairs of intramuscular EMG signals were selected and amplified (band-pass: 1–10 kHz). A self-adhering electrode (Dermatode, American Imex) positioned on the hand functioned as reference electrode. Intramuscular EMG signals from the muscles were recorded while the subjects traced specified force trajectories with the aid of real-time visual feedback. The trapezoidal trajectories had 20 and 15 s plateaus at 20 and 50% of the subject's MVC, and the up and down ramps had slopes of 10%

MVC/s. These values were selected because of the stable and reliable EMG data obtained from the same muscle in prior studies.

Data analysis

We used the precision decomposition technology to decompose the EMG signals into the constituent action potentials. This technology has been under development for more than two decades at the NeuroMuscular Research Center at Boston University (De Luca and Adam 1999; De Luca et al. 1982; LeFever and De Luca 1982) and has recently undergone substantial improvements (Nawab et al. 2002, 2004). Briefly, the precision decomposition technology utilizes time-adapting-template matching algorithms and firing rate statistics with resolution of superpositions to reliably identify motor unit action potentials of concurrently active motor units, yielding a time series representation of motor unit firings. The accuracy of the decomposition is >96%. We studied the force/EMG data for the affected/unaffected hand at a target force level of 20% MVC. For force curves, we visually assessed the presence of target undershoot or overshoot and analyzed, for each hand, the coefficient of variation ($CV = SD/mean$) during the attempted target plateau (Adam et al. 1998). The following motor-unit firing parameters were calculated: derecruitment threshold, time-varying firing rate, average firing rate at target force, and cross-correlation among firing rates. The derecruitment threshold of a motor unit was estimated as the level of voluntary force at the time of the last firing. Measurement of motor unit recruitment threshold could not be used in these patients because the initial force rise was too unstable to provide useful data. The average firing rates at target force and the firing rate cross-correlation function were calculated from the time-varying firing rates over a 5-s interval in the midpoint of the contraction (Adam et al. 1998). The time-varying firing rates were obtained by passing impulse trains corresponding to the motor unit firing times through a unit area Hanning window of 400-ms duration (De Luca et al. 1982). The length of the window is convenient for presenting the behavior of the cross-correlation functions and was used for analyzing data from healthy subjects in our previous studies (Adam et al. 1998; Erim et al. 1999). These firing rates were then high-pass filtered at 0.75 Hz before computing the firing rate cross-correlation between all possible pairs of concurrently active motor units (De Luca et al. 1982). The maximum of the cross-correlation function for each pair within the time lag interval of -1 to 1 ms was used as a measure of the strength of the common drive.

RESULTS

The MVC forces for the three patients were 28.6, 21.5, and 10.7 N on the unaffected side and 18.0, 23.9, and 11.5 N, respectively, on the affected side. Patients exhibited obvious difficulties in tracking the target trajectories, which were more pronounced on the affected side in 2/3 subjects. Classical overshooting and undershooting of the target force were found in both hands as well as the inability to maintain an isometric contraction.

Figure 1 shows the force output and the underlying firing pattern of motor units for one patient (*patient 2*) in the affected and unaffected side. The figure also illustrates the processing steps in the analysis of the data. The top graphs (*A* and *B*) present the results of the EMG signal decomposition process, i.e., the complete firing time records of motor units concurrently active during the attempted isometric contraction on each side. The time-varying firing rates for each of the motor units are shown below (*C* and *D*). Details of the firing pattern in the expanded sections illustrate ordered activation of motor units (*E* and *F*) and layering of firing rates (*G* and *H*). Note that

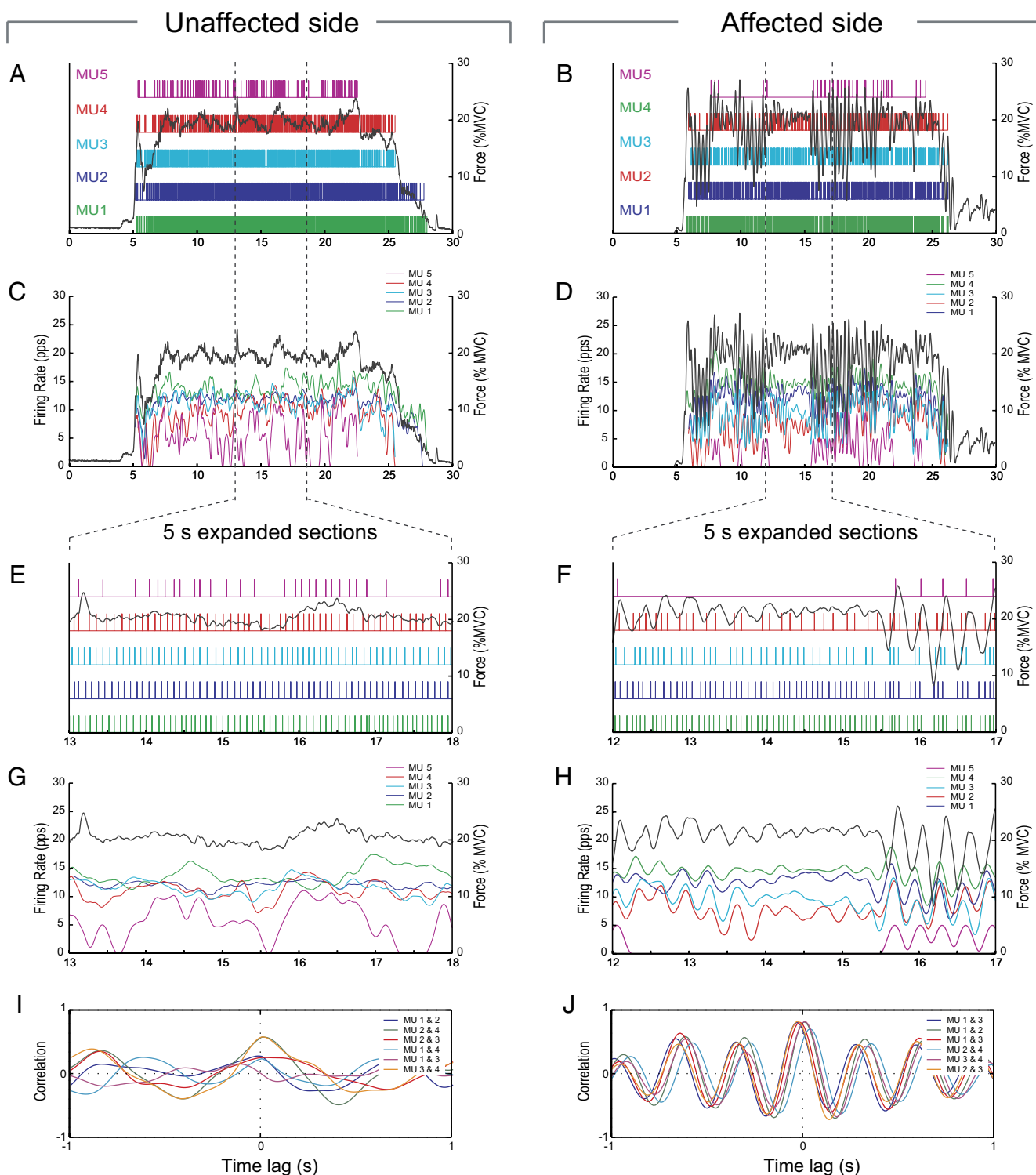


FIG. 1. Decomposition, force, and correlation results for the unaffected and affected 1st dorsal interosseus muscles of *patient 2* when performing 20% maximal voluntary contraction (MVC) target contractions. *A* and *B*: decomposition bar plots of 5 motor-unit (MU) firings that were identified for each muscle, and the measured muscle force curves (in black). *C* and *D*: time-varying firing rate plots in pulses per second (pps), indicating preservation of ordered recruitment and firing rate behavior (onion skin phenomenon) in spite of tremor in the affected muscle. *E–H*: expanded 5-s sections of the bar plots (*E* and *F*) and the firing rate plots (*G* and *H*). *I* and *J*: pair wise cross-correlation functions for the 4 most-active MUs. The low degree of correlation in the unaffected side is similar to that found in normal subjects for this age group, whereas the high degree of correlation of all 4 MUs is evidenced in the affected muscle.

in both sides, the highest threshold motor unit (MU 5) was only intermittently active. For motor units that discharged continuously (MUs 1–4), the assessment of the strength of the common drive was accomplished by high-pass filtering the firing

rates and computing the cross-correlation among all pairs, yielding six cross-correlation functions (*I* and *J*). On the affected side of *patient 2*, cross-correlation pairs showed high peak values (0.79 ± 0.05) in a narrow range around zero

TABLE 1. Results of the cross-correlation analysis between the time-varying firing rates of pairs of motor units at the target force of 20% maximal voluntary contraction

Patient	Unaffected Side				Affected Side			
	1	2	3	All	1	2	3	All
Peak	0.38 ± 0.16	0.38 ± 0.16	0.62 ± 0.16	0.44 ± 0.18	0.68 ± 0.19	0.79 ± 0.05	0.77 ± 0.04	0.74 ± 0.13
Lag, s	0.27 ± 0.25	-0.11 ± 0.56	0.00 ± 0.02	0.01 ± 0.42	0.02 ± 0.01	0.01 ± 0.03	-0.02 ± 0.02	0.01 ± 0.02
n	3	6	3	12	6	6	3	15

Values are means ± SD.

lag-time (0.01 ± 0.03 ms), indicative of a high degree of common drive to these motor units. In contrast, the cross-correlation results on the unaffected side were more variable, with lower peak values (0.38 ± 0.16) and nonzero time lag (-0.11 ± 0.56 ms). Cross-correlation analysis on all subjects (Table 1) revealed that the average peak was higher in the affected side, especially in *patients 1* and *2*.

The target overshoot and force transients at the beginning of the contractions were associated with near simultaneous recruitment of motor units (cf. Fig. 1, *A* and *B*) precluding a reliable estimation of recruitment thresholds. However, ordered recruitment/derecruitment was seen during fluctuations in force output (cf. Fig. 1*F*), when motor units were repeatedly recruited in the same order after temporary cessations of firing. Furthermore, in most cases, patients produced smoother force gradation during the down ramp (Figs. 1*A* and 2*A*), and in these situations, an ordered motor-unit derecruitment pattern was clearly observed. The relation between firing rate and dere-

ruitment threshold was explored by plotting the average firing rate for each motor unit as a function of its estimated recruitment threshold (Fig. 2*B*). On the unaffected (\blacklozenge , \blacksquare , \blacktriangle) and the affected side (\diamond , \square , \triangle), a trend toward lower firing rates at higher thresholds was apparent.

DISCUSSION

Despite the key roles of motoneurons in motor execution and the well-known motor deficits in cerebellar patients, a detailed analysis of their firing behavior has never been investigated in patients presenting with an acute cerebellar stroke. As anticipated from the work of Mai et al. (1989), our patients were unable to produce constant isometric force. However, unexpectedly, the onion skin motor control behavior, which refers to the inverse relation between firing rate and firing threshold (cf. Fig. 2), was preserved in all three patients with acute cerebellar ataxia despite an isometric tremor or irregularities in

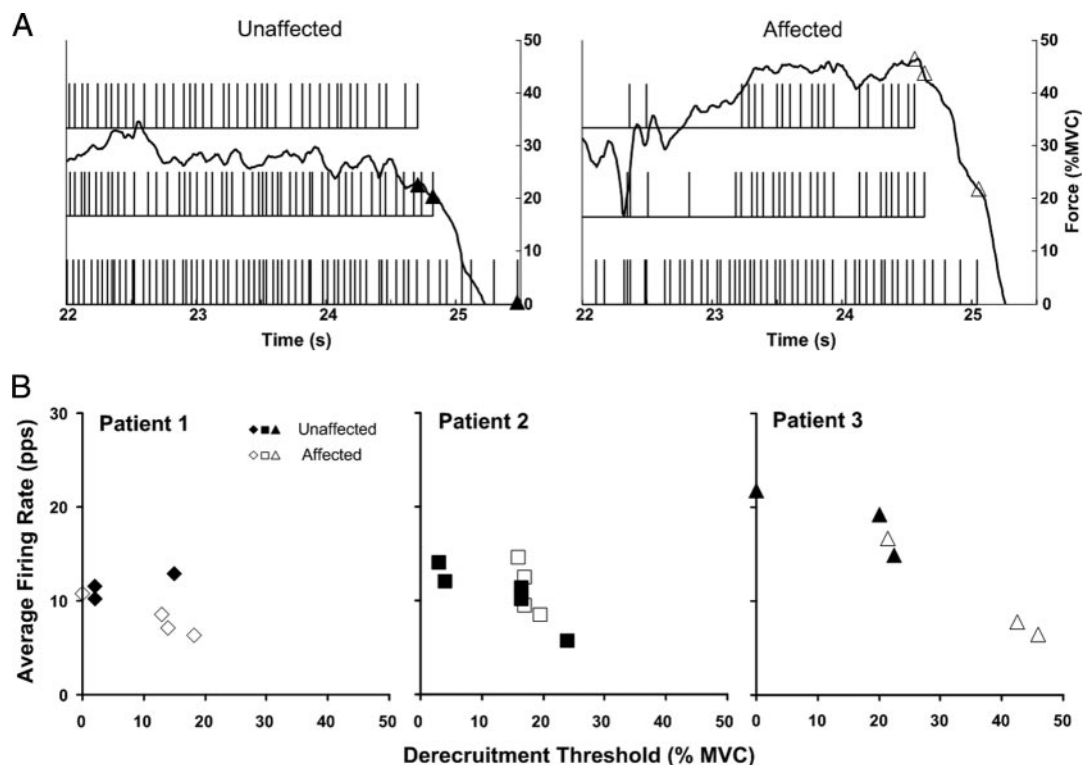


FIG. 2. *A*: example of orderly motor-unit derecruitment on the unaffected and the affected side for *patient 3*. Derecruitment thresholds for each motor unit indicated by symbols on the force trace. Note the variation in force output on the affected side (18–44% MVC) during the attempted constant target force of 20% MVC. *B*: scatter plot of the average firing rate of motor units plotted as a function of their estimated derecruitment threshold in each of the 3 patients. On the unaffected (\blacklozenge , \blacksquare , \blacktriangle) and the affected (\diamond , \square , \triangle) sides, a trend toward lower firing rates at higher derecruitment threshold was apparent. The inverse relationship between firing rate and derecruitment threshold is indicative of onion skin phenomenon found in healthy subjects. Average firing rate, calculated over a 5-s interval (see *Analysis*), is measured in pps; recruitment threshold is plotted as %MVC force.

the production of force. A noticeable finding came from the study of time-varying firing rates of pairs of motor units. Investigation of the common drive, which refers to in-phase common fluctuations in the mean firing rate signals of pairs of consistently discharging motor units, showed that the fluctuation in unison was preserved on the affected side. We observed a trend toward increased commonality when compared with the unaffected side, which showed low common drive. The low common drive on the unaffected side is in agreement with our previous report on the motor-unit firing behavior in the FDI muscle of 10 healthy subjects in an age group (76 ± 6.6 yr) closely matching that of the current study and using an identical protocol (Erim et al. 1999). A relationship between heightened common drive on the affected side and the ataxic force tracking exhibited by our patients is very likely. It could be due to rhythmic modulation of the premotoneuronal cells driving motor units. Brain functions are heavily contingent on neural interactions both at the single neuron and the neural population or system level (Schnitzler et al. 2006). Oscillatory firing behavior in the premotor cortex has been widely demonstrated (Lebedev and Wise 2000; Schnitzler et al. 2006; Volkman et al. 1996). In the normal case, these cells might not tend to oscillate together so strongly because they are regulated by an intact cerebellum such as through the inhibitory action of the Purkinje cells. A study of single-cell and EMG recordings in primates concluded that “the apparent function of this inhibition is to restrain activity in the limb premotor network, shaping it into a spatiotemporal pattern that is appropriate for controlling the many muscles that participate in this task” (Miller et al. 2002). Loss of the Purkinje cell inhibition would then result in less-refined descending motor commands, a hypothesis supported by recent data on the essential role of the intrinsic precision of Purkinje cell pace-making for motor coordination in a mouse model of ataxia (Walter et al. 2006). In the unaffected side, the correlation might be primarily sensitive to the divergent input from a ‘single’ premotoneuronal cell to multiple motor units, whereas in the affected side both this mechanism and the common modulation of the input could lead to the high correlation values.

It is known that the cerebellum: acts as a comparator compensating for errors by evaluating the intended motor act with actual performance, corrects ongoing actions through comparisons of internal and external feedback signals, and is critical for planning motor activity by shaping the commands (Kandel et al. 2000). But the effect of these functions on the control of motor units has never been observed previously. During the past two decades, several mechanisms have been suggested to explain the effect of cerebellar ataxia on motor control of upper limbs. For example, Hore et al. (1991) and Wild et al. (1996) have shown that dysmetria is associated with decreased phasic muscle strength, delayed antagonist activities, and decreased rate of rise in the antagonist activities. Convergent studies by Topka et al. (1998) provide support for the hypothesis that deficits in generating normal magnitudes of phasic muscle forces contribute to the lack of coordination in multijoint movements with the cerebellum playing a key role in tuning of dynamic joint interactions. It is assumed that this modulation is the result of a close interaction with the motor cortex and the spinal motoneuronal pool because cerebellar output exerts an excitatory effect on the contralateral motor

cortex via the cerebellothalamocortical pathway. Cerebellar information is guided to the primary motor cortex via the ventrolateral thalamic group that projects mainly to layers IV and V (Sanes and Donoghue 2000). Cerebellar lesions impair the excitability of the motor cortex and have also direct effects on spinal cord function, altering the H-reflex recruitment and decreasing the F-wave excitability ipsilaterally (Oulad Ben Taib et al. 2005).

In the present study, we addressed the possibility that a fundamental deficit underlying ataxia could be the inability to generate appropriate patterns of motor unit discharges. Because the decomposition of intramuscular EMG signals during dynamic contractions is currently a major challenge, we restricted the assessment of motor units to isometric contractions. The severity of isometratxia is correlated with the degree of dysmetria in cerebellar patients (Manto 2002). Both deficits follow a similar time course during the recovery of a cerebellar syndrome resulting from a stroke. Therefore the follow up of the isometric force could be used as an indicator of the level of cerebellar dysfunction.

Our study indicates that the source of the onion skin phenomenon is independent of the cerebellum and that motor codes for ordered motor-unit firing are not located or initiated in the cerebellum. Surprisingly, although the cerebellum is the main actor for planning motor activity, cerebellar pathways do not appear to deal with the hierarchical motoneuronal control.

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