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A Kinematic And Electromyographic Study Of The Mechanisms Contributing To Cerebellar Intention Tremor And Dysmetria

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A KINEMATIC AND ELECTROMYOGRAPHIC STUDY OF THE MECHANISMS CONTRIBUTING TO CEREBELLAR INTENTION TREMOR AND DYSMETRIA

by

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ABSTRACT

The aim of this study was to investigate, in six Cebus monkeys, the characteristics of the movement parameter and electromyographic (EMG) disorders that occur in elbow movements during cerebellar dysfunction produced by reversibly cooling the dentate and interposed nuclei. These disorders include 1) an intention tremor that occurs during voluntary limb movement (kinetic tremor), 2) an intention tremor that occurs at the end of voluntary limb movement (terminal or static tremor) and 3) dysmetria. The extent to which these disorders might result from inappropriate central commands or from disordered activity in proprioceptive reflex loops was also investigated.

In tremulous movements during cerebellar dysfunction with two or more peaks in velocity (kinetic tremor) the first deflection from the normal trajectory was associated with abnormally early or larger EMG activity in the antagonist muscle. The inverse relation between the initial velocity of the movement and the latency of the antagonist burst, characteristic of control movements, was not seen in tremulous movements. This suggests that the antagonist burst was no longer accurately programmed during cerebellar cooling. The deflection from the movement trajectory was opposed by a second burst of activity in the agonist muscle which had the properties of a servo-like response. The response occurred at a relatively short latency (50-80 ms)

and was proportional to the size of the deflection. Furthermore, this response occurred in the absence of visual feedback. This response did not, however, return the limb accurately to the control trajectory, suggesting that cerebellar nuclear cooling impairs its function. Impaired function of the servo response is also suggested by the finding that an external perturbation applied during a voluntary movement resulted in a longer EMG burst during cerebellar cooling than under control conditions.

It was found that the cerebellar intention tremor that followed goal-directed, voluntary movements had the same characteristics as the tremor that occurred following a torque perturbation. For example, in both situations loading the limb with a constant torque increased the frequency and amplitude of the tremor, whereas increasing the inertial load decreased tremor frequency. Furthermore, the tremor in both situations was unaffected by removing visual feedback of limb position. The latter finding indicates that the tremor could not have been the result of a series of voluntary corrections based on visual recognition of a positional error. The dependence of tremor frequency on the load applied to the limb is evidence for tremor being driven, at least in part, by proprioceptive feedback from stretched muscles. Further evidence for this mechanism is that the characteristics of the oscillations were markedly altered in an isometric tracking task, where

stretch-driven afferent activity was greatly reduced or eliminated.

Hypometria was not a prominent feature of movements in this study. However, hypermetria was observed during cerebellar nuclear cooling, particularly in smooth movements with only one peak in velocity. These disordered movements had asymmetric acceleration and deceleration phases. Compared to control movements of the same amplitude and peak velocity they had accelerations that were of longer duration and smaller peak magnitude and decelerations that were of shorter duration and larger peak magnitude. Hypermetric movements were associated with prolonged agonist EMG activity and delayed antagonist activity. This EMG pattern appears to be a fundamental disorder of cerebellar dysfunction.

The evidence suggests that the cerebellar intention tremor that occurred during and following voluntary movements was driven, at least in part, by abnormal activity in stretch reflex pathways in agonist and antagonist muscles. Dysmetric movements made during cerebellar dysfunction were asymmetric and this was associated with prolonged agonist activity and delayed antagonist activity. It is concluded that cerebellar motor disorders result from inappropriate stretch-evoked activity and from disordered descending central commands.

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INTRODUCTION

It has been known since Rolando's (1809; cited in Dow and Moruzzi, 1958) cerebellar ablation experiments on goats, rabbits, guinea pigs, turtles and birds that damage to the cerebellum results in impaired motor function. The nature of the role played by the cerebellum in motor activity is still, however, far from clear. Part of the difficulty in elucidating the mechanism(s) by which the cerebellum regulates movement performance is undoubtedly related to the complex input-output organization of this organ. Because the cerebellum receives afferents from several cortical areas and spinal pathways and because it sends projections to cortical and subcortical structures that can have widely differing functions, it is often difficult to identify the cause of a particular cerebellar disorder. For example, cerebellar intention tremor has been attributed to voluntary corrections for an initial position error (Goldberger and Growdon, 1973) and to abnormalities in proprioceptive transcortical reflex loops (Meyer-Lohmann et al., 1975). Part of the reason for the different interpretations may be that different experimenters have studied the effects of cerebellar lesions that differed in severity and locus. Another possibility is that the nature of the disorders studied differed because they were studied in paradigms that differed. This possibility is suggested by Holmes' (1922)

remark that "all tremors occurring in cerebellar disease are not of the same nature." Thus to reveal the role of the cerebellum in motor control, ideally one should attempt to study a number of disorders under a variety of conditions in subjects with similar lesions.

While studies of humans can provide some insight into the cerebellar mechanisms involved in controlling goal-directed movements, animal experiments make possible the study of specific lesions and permit recording of single unit activity from the brain. In this study monkeys were used because they are relatively easy to train and because the central nervous system control of their limb movements can be expected to be similar to that in humans. Thus monkeys act as an appropriate model for understanding human motor control. Furthermore, it was intended to complement the present study with single unit recordings from motor cortex.

The first step in a comprehensive approach to understanding the cerebellar contribution to a particular limb movement is to analyze and compare the kinematic characteristics of normal and disordered movements. The second step is to relate these parameters to electromyographic (EMG) activity which indirectly represents the neural commands sent to the muscles moving the limb. Thus timing and magnitude changes of EMG activity can provide clues into central nervous system function. A third step would be to

relate single unit activity in central structures to these kinematic and EMG parameters with the expectation of establishing correlational relationships.

The aim of the present study was to perform an analysis of kinematic and EMG characteristics of movements disordered by reversible cooling lesions of the cerebellum. Three cerebellar disorders were studied: intention tremor following movements (static tremor), dysmetria and tremor during movement (kinetic tremor). These particular disorders where chosen because they are clearly evident in our monkeys and they can easily be manipulated by changing the mechanical state of the limb. These experiments provided the basis of a later study of motor cortex single unit activity.

HISTORICAL REVIEW

I. The Generation of Voluntary Limb Movements

i) Patterns of muscle activity

Simple limb movements made accurately between two targets have a characteristic pattern of muscle activity associated with them. This pattern is dependent on the speed of the movement and on the mechanical forces to be overcome during the movement.

Slow movements can be made with co-contraction of antagonist muscle pairs (Levine and Kabat, 1952; Stetson and Bouman, 1935; Tilney and Pike, 1925; Wachholder and Altenburger, 1926; Wilkie, 1950) but they have also been reported to be generated using continuous agonist muscle activity alone (Hallett et al., 1975a).

Fast movements are made with a triphasic pattern of muscle activity, first described by Wachholder and Altenburger (1926). A burst of activity in the agonist muscle, whose onset precedes movement onset, is followed by a burst of activity in the antagonist muscle, which is in turn followed by a second burst of activity in the agonist muscle. This pattern is now well established in both man and experimental animals (Angel et al., 1965, Flament et al., 1984a; Garland and Angel, 1971; Ghez, 1979; Hallett and Marsden, 1979; Hallett et al., 1975a; Marsden et al., 1977; Wiesendanger and Ruegg, 1978). When there is tonic activity

of the antagonist muscle, as for example when a force is applied opposing that muscle, the first agonist activation is often preceded by an inhibition of antagonist activity (Hopf et al., 1973; Hufschmidt and Hufschmidt, 1954; Stetson and Bouman, 1935). Inhibition of triceps shortly before biceps onset (of the order of 50ms) has been shown for human flexion movements (Gottlieb et al., 1970; Hallett et al., 1975; Hufschmidt and Hufschmidt, 1954) and in the monkey (Evarts, 1974; Flament et al., 1984a). Premovement periods of electromyographic (EMG) silence can occur simultaneously in agonist and antagonist muscles (Conrad et al., 1983; Ikai, 1955; Kawahats and Miyashita, 1983; Yabe, 1976).

The fastest class of voluntary limb movements, which have sometimes been called ballistic, fall into different categories. Brooks (1979a) has defined ballistic movements as brief, of high velocity, launched without peripheral sensory guidance and not requiring active braking of the limb to stop them, as this is achieved by a mechanical obstacle. Others have termed movements ballistic simply for being launched without peripheral guidance even if they did require active braking (Desmedt and Godaux, 1979). In both cases the agonist activity is represented by one large burst of activity. The term ballistic has also been used to describe any movement made as fast as possible but accurately (e.g. Berardelli et al., 1984; Hallett and Marsden, 1979; Lamarre et al., 1980). These are movements that

exhibit the triphasic pattern of muscle activity described above and will therefore be termed "fast" in the discussions that follow.

Exceptions to the triphasic pattern do occur in some fast movements. Human ankle movements (Gotttlieb et al., 1970) and monkey head movements (Bizzi et al., 1971) were reported to have only two bursts of agonist activity and no phasic antagonist burst. Another common observation is that the second agonist burst is replaced by tonic activity. This pattern has been seen in man (Lestienne, 1979) and monkey (Meyer-Lohmann et al., 1977). Deviations from the classic triphasic pattern can be produced by applying mechanical forces to the limb.

Thus movement velocity is clearly related to the pattern of muscle activity generated during a movement. For a given pattern, the duration and magnitude of EMG bursts can be affected by the load exerted on the limb. Changes in EMG burst duration and amplitude are also associated with the movement amplitude and, again, the velocity of the movement.

ii) Factors influencing EMG burst duration and amplitude

a) Effect of mechanical load

The duration and magnitude of the first agonist burst are increased by increasing the inertial load to be moved (Flament et al., 1984a; Lestienne, 1979). It is a common

observation that movements made with increased inertia are generally of lower peak velocity and acceleration. Could the changes in agonist EMG then be a consequence of these kinematic changes? For a given velocity the duration of the first agonist burst was found to be no different than in movements made without added inertia (Lestienne, 1979). Therefore, changes in agonist burst duration were associated with the decreased acceleration and mean velocity of movements with inertia (Angel, 1974; Lestienne, 1979), while the magnitude changes of the agonist burst could be interpreted as being direct consequences of the inertial load. The antagonist burst has also been demonstrated to be increased in amplitude for movements of a given amplitude and peak velocity with added inertia (Lestienne, 1979).

Torque loads were found to have a profound influence on EMG magnitude and duration of agonist and antagonist muscles in monkeys (Flament, 1983). Loading the agonist muscle increased the magnitude and duration of the phasic agonist bursts, superimposed on a raised tonic discharge level. Antagonist EMG activity was decreased. Loading the antagonist produced reciprocal changes in these muscles. In human subjects Hallett and Marsden (1979) reported an invariance of the first agonist burst duration for flexions of the thumb under a series of torques. It has recently been shown, however, that agonist burst duration of wrist flexors

increases as a load opposes their contraction (Berardelli et al., 1984).

b) Effect of movement amplitude

Different movement amplitudes can be produced by changing the magnitude and duration of the first agonist burst. In humans, increasing movement amplitude is associated with an increase in agonist burst duration (Angel, 1974; Berardelli et al., 1984, Brown and Cooke, 1984; Wadman et al., 1979) and an increase in agonist burst magnitude (Brown and Cooke, 1981; Freund and Budingen, 1978; Ghez, 1979; Hallett and Marsden, 1979; Marsden et al., 1977). The magnitude of the second agonist burst has also been shown to vary directly with movement amplitude (Brown and Cooke, 1981). In monkeys, the influence of movement amplitude has been demonstrated for neck muscles by Bizzi et al. (1971) who showed that both the duration and magnitude of the first agonist burst were directly related to the amplitude of the movement. For limb movements of different amplitudes but of the same peak velocity the large amplitude movements had longer first agonist bursts that were of smaller magnitude (Flament, 1983; Flament et al., 1984a).

The antagonist burst is also related to movement amplitude. It is now clear that for large and small movements of the same peak velocity, the antagonist burst is of greater magnitude in the small amplitude movements (Flament et al., 1984a; Hoffman and Strick, 1981; Marsden et

al., 1981, 1983). The duration of the antagonist burst has been reported to be longer in larger amplitude movements (Brown and Cooke, 1981).

c) Effect of velocity

Lestienne (1979) has shown that agonist burst duration and magnitude were both related to the peak velocity of movement. The duration of the first agonist burst had an inverse relation with peak velocity while the magnitude of the burst increased in a near-linear fashion. This latter relation has been confirmed by Brown and Cooke (1981), but their study found no relation between burst duration and movement velocity. This difference may result from variations in instructions given to their subjects and their level of training.

The antagonist burst magnitude has been found to vary directly with peak velocity for limb movements made in humans (Lestienne, 1979; Marsden et al., 1983a) and monkeys (Flament et al., 1984a; Soechting et al., 1976). The latency of the antagonist burst, however, is shorter for high velocity movements than for low velocity movements (Lestienne, 1979).

iii) Central origin of learned movements

In spite of the numerous studies of movements of the limbs that have been done to date, one question which still remains unanswered is whether the EMG pattern characteristic of accurate movements is dependent on peripheral feedback.

Clearly, the first agonist burst of a voluntary, goal-directed movement must be generated centrally, but some uncertainty exists as to whether the antagonist muscle activity is generated via stretch reflexes (as the muscle is stretched) or by central commands.

That sensory feedback is not necessary for a centrally initiated movement to be executed accurately was demonstrated in humans by Lashley (1917). More recently, deafferentation by disease processes (pansensory neuropathy) (Forget and Lamarre, 1983; Hallett et al., 1975a; Rothwell et al., 1982) or by ischemic block (Jennings and Sanes, 1982; Sanes and Jennings, 1984) was shown to produce no major alterations of the EMG pattern characteristic of fast movements. Similar findings have been made in monkeys deafferented by dorsal rhizotomy (Lamarre et al., 1978, 1980). Hoffman and Strick (1982) further showed that antagonist burst amplitude could be varied independently of initial movement parameters, suggesting a central origin for this muscle activity.

Movement accuracy, as judged by the attainment of desired end point, was not affected by deafferentation in monkeys making head rotations (Bizzi et al., 1976; Polit and Bizzi, 1979) or pointing movements of the limbs (Taub et al., 1975), indicating that appropriate muscle patterns can be generated in the absence of proprioceptive feedback.

The performance of accurate movements in the absence of proprioceptive feedback naturally requires some practice.

These movements, once thoroughly learned, become highly stereotyped and have particular kinematic characteristics.

iv) Kinematic characteristics of learned movements

Highly practiced simple movements about one joint can be made smoothly and accurately. The velocity profile is bell-shaped and continuous (Brooks, 1979b, 1983, 1984a; Brooks et al., 1973b; Brooks and Thach, 1981; Flament et al., 1984a; Kozlovskaya et al., 1970). Continuous movements have been defined by Brooks et al. (1973a) as those whose acceleration traces cross the zero line only once. This is in contradistinction to slower discontinuous movements that have a jerky or tremulous appearance, with two or more velocity maxima and two or more zero-crossings of acceleration traces. Compound movements requiring the coordinated action of several joints can also be made with smooth single-peaked velocity profiles (Abend et al., 1982; Atkeson and Hollerbach, 1985; Flash and Hogan, 1985; Georgopoulos et al., 1981; Morasso, 1981). Discontinuous movements occur during motor learning (Brooks et al., 1983) and can also occur as a result of cerebellar dysfunction (Brooks et al., 1983; Brooks and Thach, 1981; Flament and Hore, 1986; Hore and Flament, 1986).

One feature of smooth, fast elbow movements in humans is the near symmetry of the acceleration and deceleration phases (Ostry et al., 1986; Wiegner and Wierzbicka, 1986). Studies on humans performing arm movements have shown that

in naive subjects acceleration and deceleration phases were symmetric (Beggs and Howarth, 1972a,b; Howarth et al., 1971) but that as the subjects acquired practice movement symmetry changed and movements had shorter accelerations and longer decelerations (Beggs and Howarth, 1972a).

Studies on monkeys, however, have yielded quite different results: unpracticed movements are more likely to be irregular with symmetry developing as practice progresses (Brooks et al., 1973; Flament et al., 1984a). Although symmetry appears, on average, to be a characteristic of learned movements (Flament et al., 1983, 1984a), there is a certain amount of variability from trial to trial for movements of the same peak velocity and amplitude such that movements with shorter durations of acceleration have longer decelerations and vice versa (Flament, 1983; Flament et al., 1982).

Because energy expenditure is minimized by symmetry of acceleration and deceleration phases (Nelson, 1983) it has been suggested that this symmetry may occur to minimize energy expenditure (Flament, 1983; Flament et al., 1983, 1984a) and that it may also simplify the way in which movements are generated by permitting the command sent to the antagonist muscle to be generated from an efference copy of the agonist command (Flament et al., 1984a). Mathematical models of arm movements have demonstrated that smooth symmetric movements can be made by minimization of mean-

squared jerk, the third time derivative of displacement (Flash 1983; Flash and Hogan, 1985; Hogan 1982, 1984), or by minimization of snap, the fourth time derivative of displacement (Flash, 1983). They have suggested that possible objectives of this strategy may be to reduce abrupt force changes to objects carried by the hand or to maximize trajectory predictability.

A recent model of limb movement in which sense of effort is minimized by specifying a particular trajectory and joint stiffness has yielded the result that this is best achieved by smooth, bell-shaped velocity profiles (Hasan, 1986).

Not all voluntary movements, of course, are made smoothly. Obstacles are sometimes encountered which perturb the intended movement. The response of the motor system to disturbances introduced into movements has been studied experimentally and the results have led to the suggestion that a servo mechanism may be operating to compensate for these disturbances.

v) Servo-controlled mechanism in movements

A servo mechanism is one in which a strong effector does work under the direction of a controller which in turn is directed by feedback from the effector. The forces developed in the effector are produced as the result of a comparison made by the controller between the desired and achieved states (Houk, 1980; Roberts, 1965). Servos may be

used for controlling a wide variety of parameters--length, tension, velocity, stiffness and so on.

A servo mechanism is usually designed to respond to a small error signal (difference between desired and achieved state) with a strong correcting signal; such a mechanism needs a high loop gain (Rack, 1981). Loop gain is an index of the system's ability to deal with error and, in systems with time lags, directly affects the system's stability. Stability is also affected by feedback delays which may constitute an intrinsic part of the system as simple transport delays or they may appear as phase lags involved in low-pass filtering (Rack, 1981).

a) The motor servo

The stretch reflex can be regarded as a servo-control mechanism through which muscle receptor signals influence muscular control. This system, sometimes called the motor servo, contains many elements: intrafusal and extrafusal muscle fibers, primary and secondary spindle receptors, golgi tendon organs, alpha and gamma motoneurons (Houk, 1978; Houk and Rymer, 1981) all under the direction of a supraspinal controller. The basis for the operation of this system is the more or less simultaneous activation of alpha and gamma motoneurons--a process which has been called alpha-gamma linkage (Granit, 1955) or alpha-gamma coactivation (Phillips, 1969). In this scheme movements are produced by sending commands to both the alpha and gamma

motoneurons. If the resulting intrafusal and extrafusal shortening are equal, discharge rate of spindle afferents should not change. If a load should interfere with the desired contraction of the main muscle, an "error" will be detected by the spindle and afferent discharge will increase or decrease as the case may be. Thus the servo loop will remain inoperative if the movement proceeds as expected and become operative in response to an error (Houk and Rymer, 1981). This constitutes servo assistance (Matthews, 1964).

b) Servo assistance in voluntary movements

Since servo assistance is based on alpha-gamma coactivation a question of prime importance is whether alpha-gamma coactivation occurs in voluntary movements. A number of studies have shown that spindle afferent discharge rate increases with the onset of muscle activity during isometric contractions of human forearm (Vallbo, 1970a,b, 1971, 1974) and leg muscles (Burke and Eklund, 1977; Burke et al., 1978a,b). Similar findings have been made during slow shortening of finger flexors in humans (Vallbo, 1973), hindlimb muscles during locomotion in the cat (Loeb and Duysens, 1978; Prochazka et al., 1976, 1977) and jaw-closing muscles in the monkey (Lund et al., 1979). These findings have been interpreted as evidence for coactivation of alpha- and gamma-motoneurons.

Some studies, however, have shown that spindle discharge may be decreased independently of extrafusal muscle

fiber activity (Cody et al., 1975; Loeb and Duysens, 1978; Prochazka et al., 1976, 1977) or increased (Lund et al., 1979; Rymer et al., 1981; Schieber and Thach, 1980; Vallbo and Hulliger, 1981). Thus although alpha-gamma coactivation is common, fusimotor activity can be dissociated from skeletomotor activity (Prochazka et al., 1985; Prochazka and Wand, 1981).

Servo assistance could also operate through a third type of motor fiber, the skeletofusimotor or beta-fiber, whose axons branch to innervate both intra and extrafusal muscle fibers (Laporte et al., 1981; Matthews, 1981; Houk and Rymer, 1981). Consequently, alpha-gamma coactivation invariably occurs with beta-excitation. Although there is currently little known about the functional importance of these fibers they have been identified in mammalian muscles and implicated in the augmentation of spindle afferent activity in isometric contractions and during stretch of muscles in the cat (Emonet-Denand et al., 1975; Emonet-Denand and Laporte, 1983; Post et al., 1980; Rymer et al., 1981).

Given that a mechanism that theoretically could contribute to servo assistance apparently exists, does it function as a load-compensator during voluntary movements? This question has been addressed in a number of studies of human forelimb (Desmedt and Godaux, 1978; Dietz and Noth, 1978; Dietz et al., 1979; Dufresne et al., 1978, 1980),

wrist (Lee et al., 1986), ankle (Gottlieb and Agarwal, 1979, 1980a,b; Gottlieb et al., 1981, 1983), jaw (Lamarre and Lund, 1975) and thumb movements (Marsden et al., 1972, 1976a,b), in monkey neck (Bizzi et al., 1978) and forelimb movements (Conrad et al., 1974) and in cat hindlimb movements (Appenteng et al., 1982; Prochazka et al., 1979). The outcome of these studies was that perturbations introduced during voluntary movements could produce clear EMG responses that appeared at latencies comparable to those of spinal and transcortical stretch reflexes with the limb stationary. Different interpretations regarding the relative contribution of these responses to load compensation have, however, been made. Marsden and his colleagues concluded "(1) that there is servo action, sensitive, brisk and so early as clearly to be automatic, in voluntary movements of the thumb, (2) that the gain of the servo loop is proportional to the force exerted," (Marsden et al., 1972, p. 143). Bizzi and his colleagues (1978), however, estimated reflex action to contribute only one third of the force output resulting from head displacements and the remainder as coming from mechanical properties of head and neck musculoskeletal elements. Melvill-Jones and Watt (1971a,b) detected no useful contribution from the stretch reflex response following unexpected falls in man. Similarly, Allum (1975) showed that reflex responses to load disturbances in human shoulder muscles at best provided 15%

of the force required to resist the disturbance. Prochazka and colleagues (1979) demonstrated that spindle afferent discharge could not be maintained when velocity of muscle shortening exceeded .2 resting-lengths/s even under fusimotor activity. However, Appenteng et al. (1982) later showed that the simultaneous electrical stimulation of several fusimotor fibers could maintain Ia spindle discharge during muscle shortening at speeds up to 2 resting-lengths/s. It thus appears that while servo assistance, under most conditions studied, may not be strong enough to provide adequate load-compensation it may, however, play an effective load-compensating role in slow movements about certain joints. The inability of servo-assistance to load-compensate under all conditions has led to the suggestion that the stretch reflex pathway can be used to regulate parameters other than limb position, such as joint stiffness (Houk, 1976, 1979) or that it may function to return the limb to an intended trajectory following a perturbation (Cooke, 1979, 1980a,b).

While the supposed function of the servo system is to provide some benefit to the motor system, its intrinsic properties (e.g. time delays) can sometimes add instability to the system and result in tremor.

c) Tremor and the servo system

Tremor is an involuntary movement characterized by a rhythmic oscillation about a fixed point or trajectory

(Stein and Lee, 1981). These oscillations may occur as a result of (1) mechanical properties of the limb itself (provided there is some source of energy to maintain them), (2) rhythmic activity in spinal or supraspinal structures (i.e. central oscillator), or (3) from instability of the servomechanism associated with the spinal or supraspinal stretch reflex (Henatsch, 1967; Lippold, 1970; Stein and Lee, 1981). These mechanisms are not mutually exclusive and may act together to produce tremor. One property that distinguishes reflex and mechanical tremor from that of central origin is its sensitivity to resetting by external stimuli (Stein and Lee, 1981). Tremor of reflex or mechanical origin is completely reset by an external stimulus whereas that of purely central origin is not (Stein et al., 1978).

Tremor produced by the servomechanism occurs as a result of inherent delays in the feedback pathway. The amplitude and frequency of the oscillations are dependent on loop gain and latency. The gain of the reflex pathway, and thus its susceptibility to tremor, is increased in parallel with force during voluntary contraction (Gottlieb and Agarwal, 1973). Increasing force, by increasing muscle stiffness, also has the effect of increasing tremor frequency (Joyce et al., 1974). The latency of the reflex pathway is thought to influence tremor frequency (Oguztoreli and Stein, 1975) and the loop delays, as already stated, are

responsible for the tendency to oscillate (Rack, 1981; Stein and Lee, 1981).

Stabilization, the reduced tendency to oscillate, results primarily from muscle low-pass filter properties which prevents it from following high-frequency changes (Stein and Oguztoreli, 1976). Increasing low-pass properties by cooling can further reduce tremor amplitude (Lippold, 1970). It has also been suggested that the velocity-sensitivity of spindles could contribute to stabilization by providing a phase-advanced signal of limb position (Matthews, 1964, 1981). This mechanism does seem effective in reducing low frequency oscillations but at higher frequencies it contributes to the tremor (Goodwin et al., 1978; Stein and Oguztoreli, 1976).

While the above discussion has focused on the many factors involved in the generation of isotonic limb movements, not all motor activity is of this nature. Many voluntary motor acts do not involve movement but rather they require the exertion of static force. These are produced by isometric muscle contractions.

II. The Generation of Goal-Directed Isometric Contractions

i) Isometric force tracking

Isometric force tracking is a paradigm which requires the subject to contract muscles isometrically (or very nearly so) to match a preset force level. The duration of

contraction to reach a given force level can be varied, analogously to changing movement duration between two positional targets. In the description of muscle activity patterns that follows, two types of isometric tasks are considered. One is the "pulse" type: a brief phasic isometric contraction to a given force level immediately followed by a return to the prepulse level. The other is the "step" type: a sustained contraction to a new force level.

ii) Patterns of muscle activity

For isometric contractions made as fast as possible, the duration of the contractions are approximately constant for all amplitudes of target force studied (Freund, 1983; Freund and Budingen, 1978; Ghez and Vicario, 1978; Gordon and Ghez, 1984). The duration of the EMG burst in the contracting muscle is similar to the duration from contraction onset to peak contraction (Freund and Budingen, 1978; Ghez and Vicario, 1978). Since contraction time is fixed and EMG burst duration is equal to the contraction time the EMG burst magnitude is proportional to the rate of rise of the contraction and the integrated muscle activity is proportional to the force exerted (Ghez and Vicario, 1978). Tonic EMG activity covaries with the level of tonic force exerted (Ghez and Martin, 1982).

The usual EMG pattern associated with rapid, accurate limb movements is bi- or triphasic. One question of

interest is whether these patterns occur for isometric contractions and, if so, under what circumstances. The biphasic and triphasic patterns have been found in human subjects making "pulse" type isometric contractions of the elbow (Gordon and Ghez, 1984), wrist (Sanes and Jennings, 1984) or index finger (Meinck et al., 1984). "Step" type contractions were associated with a phasic burst of activity in the agonist muscle that was followed by sustained tonic activity (Meinck et al., 1984; Sanes and Jennings, 1984). A burst of antagonist activity or a second agonist burst was rarely seen. Similar results were reported in the cat making "step" type isometric contractions (Ghez and Martin, 1982).

Although a triphasic pattern was observed in "pulse" contractions the characteristics of this activity were different to that observed during rapid movements (Sanes and Jennings, 1984). The first agonist burst was prolonged, the antagonist burst had a decreased latency and the second agonist tended to have an increased latency. Thus the EMG pattern of isometric contractions was more of a cocontraction than the reciprocal pattern of isotonic movements.

Voluntary, goal-directed movements and isometric muscle contractions are produced by the concerted activity of many parts of the nervous system. One of these, the cerebellum, plays a major role in the regulation and performance of motor activity.

III. Cerebellar Control of Movement

1) Overview of cerebellar function

The cerebellum is intimately involved in the initiation and execution of movements and in the maintenance of postures. It also appears to be responsible for learning to make these motor acts in a stereotyped, accurate and task-appropriate manner (Brooks, 1984b; Brooks and Thach, 1981). The cerebellum is also involved in basic associative learning, such as the classically conditioned nictitating membrane-eyelid response (McCormick et al., 1981; McCormick and Thompson, 1984) and, recently, was postulated to contribute to mental skills in humans and anthropoid apes (Leiner et al., 1986).

The cerebellar output responsible for these functions can, in greatly simplified form, be divided into three main components. The medial component, that comprises the vermis and flocculonodular lobes which act upon the fastigial and vestibular nuclei, regulates muscle tone, posture and movements of the eyes (Ito, 1972; Lisberger and Fuchs, 1978a,b). The intermediate component, that projects to the interposed nuclei, is primarily involved in the ongoing control of voluntary movements (Murphy et al., 1975). Its projections to the red nucleus and motor cortex and its rich peripheral afferent and motor cortical input make it ideally suited for this function. The lateral component, receiving input from frontal and parietal association areas and

projecting to the dentate nucleus and from there to the motor cortex by way of the thalamus, is thought to influence movement planning and initiation (Allen and Tsukahara, 1974). Together, these cerebellar components interact to produce smooth, coordinated movements.

ii) The cerebellum and control of limb movement

Although there is general agreement that the cerebellum plays a major role in the control of limb movement, different workers have emphasized different facets of this control. The different motor functions attributed to the cerebellum need not be seen as mutually exclusive; in fact, given the complex input-output relations of the cerebellar system and its compartmentalization into saggital zones, it should not come as a surprise to find that it can perform a number of complementary functions. Some of these are described below.

a) Cerebellar control of movement initiation

Since Gordon Holmes (1917, 1922, 1939) first reported increased reaction time as a symptom of cerebellar injury, it has been concluded that the cerebellum in some way influences movement initiation. The effect of cerebellar lesions in increasing reaction times as much as 150ms have been confirmed in more recent studies of cerebellar patients (Beppu et al., 1984; Hallett et al., 1975b; Marsden et al., 1977) and in monkeys with permanent (Beaubaton et al., 1980; Lamarre and Jacks, 1978; Lamarre et al., 1978; Trouche and

Beaubaton, 1980) or reversible cooling lesions (Beaubaton et al., 1980; Meyer-Lohmann et al., 1977; Miller and Brooks, 1982; Miller et al., 1974; Trouche et al., 1979) of the cerebellum. Some of these studies have emphasized the role of the dentate nucleus in producing this increase in reaction time (Beaubaton et al., 1980; Meyer-Lohmann et al., 1977; Miller et al., 1974; Trouche and Beaubaton, 1980; Trouche et al., 1979).

Evidence obtained in monkeys indicates that the increase in reaction time associated with cerebellar lesions results from a delay in motor cortex neural discharge. Meyer-Lohmann et al. (1977) reported that, following cerebellar dysfunction produced by cooling through probes implanted lateral and medial to the dentate nucleus, movement-related single units in motor cortex had a delayed onset of discharge. Lamarre and colleagues reported a similar delay in motor cortex neural discharge following cerebellectomy (Lamarre et al., 1978; Lamarre and Jacks, 1978; Spidalieri et al., 1983). This delay may have been the result of a loss of a phasic movement instruction from the cerebellum to the motor cortex (Meyer-Lohmann et al., 1977). This is supported by the finding of Thach (1970a, 1975) that some neurons in dentate fire before movement onset and before neurons in motor cortex. It would appear, however, that the pathway responsible for the reaction time increase does not include the VL nucleus of the thalamus, as

cooling lesions of this nucleus did not produce a reaction time increase (Miller and Brooks, 1982).

More recently it has been shown that of neurons in dentate whose firing rate changed before movement onset roughly 70% of them were related to the stimulus and 20% to the movement (Chapman et al., 1986). These authors suggested that the neural response of the stimulus-related neurons may represent a triggering mechanism for the initiation of reaction time movements in response to visual and auditory stimuli; the movement-related neurons were suggested to play a role in controlling movement execution.

b) Cerebellar control of movement execution

Implicit in the cerebellum's function as a controller of movement execution is its ability to act as a comparator of how the movement is proceeding and how it is intended to proceed. Oscarsson (1971, 1973) has postulated that the anterior lobe of the cerebellum is important for correcting errors in motor behaviours elicited from the cerebral cortex. The movement command signals may be monitored by the anterior lobe through cerebrocerebellar paths relayed in the pontine nuclei, the lateral reticular nucleus and inferior olive (reviewed in Evarts and Thach, 1969). Afferent activity from the evolving movement and from the effects of command signals on spinal motor centres can be relayed via spinocerebellar paths (Lundberg, 1971). The results of a comparison between the original commands, the

evolving movement and activity in lower motor centres could result in any necessary corrections. Visual and auditory inputs to the medial and intermediate regions of the posterior lobe can also provide the cerebellum with the visual and auditory representation of the movement goal and compare this to the command input and peripheral feedback of the moving limb (Ruch, 1951). These corrections could be carried out through cerebellar efferent paths to motor cortex and brain stem. These suggestions are consistant with Thach's (1968, 1970b) reports of changes in Purkinje cell activity in the anterior lobe of conscious monkeys immediately before and after the initiation of a voluntary hand movement. Activity changes occuring before the movement might be due to signals either from the motor cortex or from lower motor centres; changes occuring after movement onset might be due to proprioceptive and exteroceptive feedback (Oscarsson, 1973).

As the anterior lobe projects to the fastigial and interposed nuclei the cerebellar corrective function is one which may primarily involve the medial and intermediate cerebellum. Bava et al. (1983; Bava and Grimm, 1978) have shown that fastigial neurons are recruited before and, predominantly, after a movement begins, processing force-velocity information. They concluded that the fastigial nucleus, with its afferent and efferent systems, could provide a fast feedback pathway to the thalamus and motor

cortex for information regarding movement performance and thus provide a 'correction' signal for motor performance.

A number of facts point to the nucleus interpositus as being involved in the control of movement execution. For example, neurons in this nucleus respond quickly (of the order of 20ms) to a perturbation applied to the limb of a monkey (Strick, 1978; Thach, 1978). Furthermore, in a visual reaction time task the change in frequency of discharge of interpositus neurons follows that of motor cortex (Thach, 1970a, 1978).

A role for interpositus in movement braking is suggested by the late red nucleus discharge (which may be related to the braking of movement) because the interpositus sends projections to the red nucleus (Otero, 1976). A braking function for interpositus has also been suggested by Thach (1978) who reported that interpositus neurons were highly related to holding still at a given position. Following lesions of the deep cerebellar nuclei in monkeys, Goldberger and Growdon (1973) also arrived at the conclusion that interpositus may be preferentially concerned with the control of posture. Thach and colleagues (Elble et al., 1984; Thach et al., 1985) have recently proposed that the interpositus plays a direct role in tremor suppression. They suggest that one mechanism by which it could exert this effect is by stopping the EMG bursts associated with the

tremor, and thus limit tremor amplitude within tolerable limits.

Although the dentate nucleus has generally been assigned a function in planning or programming of movements (Allen and Tsukahara, 1974) some evidence indicates that it too may contribute to the moment-to-moment control of voluntary movement. Strick (1978) found that neurons in dentate fired at a latency of 30-50ms to a load change and that this response was strongly influenced by the animal's motor set. From this he suggested that the dentate may be involved in the generation of the 'intended' component of motor cortex discharge and muscle activity (Evarts and Tanji, 1976).

Chapman et al. (1986) found neurons in the dentate nucleus that were time-locked to movement onset; some of these showed directionality before and/or during the movement and some were velocity-related. They suggested that the discharge characteristics linked to the final execution phase of movement made these cells likely candidates for the control of ongoing movements. Other dentate neurons had early responses time-locked to the presentation of the stimulus initiating the movement. Most of these cells also showed a later 'secondary' response related to the movement that was timed such that it could have contributed to some aspect of the control of movement execution. Although the observations of Chapman et al. (1986) and

Strick (1978) do not constitute proof of a dentate role in the moment-to-moment control of movement execution, they do indicate that the lateral cerebellum does more than organize or trigger voluntary movement.

c) Cerebellar control of reciprocal and co-active patterns of muscle activity

Two modes of muscular activation are reciprocal inhibition and coactivation of antagonist muscle pairs. The type of mode used depends on the nature of the task being performed. For example, an isometric grip of thumb and forefinger elicits cocontraction of antagonist forearm muscles whereas flexion or extension movement of the wrist produces reciprocal activity in forearm flexors and extensors (Smith et al., 1983). The neural circuits directly responsible for these modes of muscle activity probably reside within the spinal cord (Hultborn, 1972, 1976). It has been suggested, however, that the cerebellum may be responsible for switching between these two modes of motor control (Frysinger et al., 1984; Smith and Bourbonnais, 1981; Smith et al., 1983; Wetts et al., 1985).

This suggestion came after finding that in the coactivation task, the majority of Purkinje cells decreased their activity whereas, in contrast, most non-Purkinje cells of the cerebellar cortex increased firing (Smith and Bourbonnais, 1981). Subsequent experiments showed that in a task eliciting reciprocal muscle activity Purkinje cell activity

was directionally related (Frysinger et al., 1984; Smith and Bourbonnais, 1983). That is, the discharge frequency decreased for one direction of movement or isometric wrist torque and increased for the other direction. Thus the discharge of these Purkinje cells related to forearm muscles may have been dependent on whether antagonist muscles were activated reciprocally or coactively (Frysinger et al., 1984). Dentate and interpositus neurons discharged with similar patterns as Purkinje cells in these two tasks, but with opposite sign (Wetts et al., 1985). Thus, whereas in the coactivation task Purkinje cell discharge frequency decreased, dentate and interpositus discharge increased. It was thought possible, but clearly uncertain, that the increased nuclear activity resulted from a release from Purkinje cell inhibition due to the decreased Purkinje cell activity. Taken together, these observations provide support for the hypothesis that the cerebellum plays a functional role in switching excitation and inhibition between antagonist muscle pairs.

Hore and Vilis (1984), using a totally different paradigm, reached a similar conclusion. Monkeys trained to return their arm to a target following perturbations generated different patterns of muscle activity depending on whether the perturbations were brief (40ms) or long (2000ms). Brief torque pulses were associated with a burst of activity in the antagonist muscle at a latency of 60ms;

long torque steps had enhanced 50-60ms and 70-80ms responses in the agonist muscle. These responses only occurred when the monkey was expecting the particular perturbation and were therefore attributed to motor set. During cerebellar dysfunction the early antagonist response disappeared and the M2 and M3 agonist responses decreased in size, even when the monkey was expecting, and therefore set for, the given perturbation. It was suggested that the cerebellum enabled activity after a latency of 60ms (i.e. the 70-80ms agonist response and early antagonist response) to be switched to the elbow-flexor or extensor muscles as appropriate, regardless of which muscle was being stretched (Hore and Vilis, 1984).

d) Cerebellar control of fusimotor bias.

Holmes (1922) described decreased muscle tone (defined as the resistance of a limb to passive displacement) as a symptom of cerebellar injury in the human. This disorder, termed hypotonia, is also seen following ablations of the cerebellum in experimental animals. Luciani (1891 cited in Dow and Moruzzi, 1958) described a decreased supporting reaction of the limb extensor muscles, which he called "atonia", in dog and monkey. Hypotonia, in the sense used by Holmes, occurs most clearly after neocerebellar lesions in the subprimate (Bremer, 1935) and in the monkey and baboon (Botterell and Fulton, 1936, 1938c). Hypotonia is greatest in the chimpanzee (Fulton and Dow, 1937).

Granit, Holmgren and Merton (1955) were the first to provide a clue as to the physiological mechanism underlying hypotonia when they showed that cooling the anterior cerebellar lobe of a decerebrate cat decreased the response of soleus spindle afferents to maintained extension. It was subsequently shown that acute total cerebellectomy in decerebrate cats decreased spindle sensitivity in both flexor and extensor muscles (Van Der Meulen and Gilman, 1965). The disorder of spindle sensitivity affects primary afferents to a greater degree than secondaries, depressing their threshold, adaptation and frequency response (Gilman, 1968, 1969b; Gilman and McDonald, 1967). The maximum reaction of spindle endings to natural cutaneous, labyrinthine and proprioceptive stimuli was, however, not affected by cerebellectomy. These changes in spindle response can be the result of decreased background discharge rate of fusimotor fibers (Gilman 1969a; Gilman and Ebel, 1970).

A number of impaired stretch reflex responses associated with cerebellar lesions may reflect the above fusimotor/spindle disorders. For example, cerebellar dysfunction in man results in a diminished tonic vibration reflex (Lance et al., 1966; Gemba and Sasaki, 1978) and reduces the sensitivity of the tonic stretch reflex, potentially making effective damping of mechanical oscillations impossible (Hufschmidt and Linke, 1977; Neilson and Lance, 1978). Cerebellar lesions in cats are also known to produce phase

lags in the stretch reflex (Glaser and Higgins, 1965; Higgins and Glaser, 1964).

Lesions of the cerebellum have not only been associated with decreased reflex activity; some studies have shown that stretch reflexes can be enhanced in cerebellar disease. Mauritz et al. (1981) reported both delayed and enhanced long-latency reflexes in patients with late cerebellar atrophy. However, Diener et al. (1984) found only prolonged and enhanced reflex EMG responses in cerebellar patients with no change in latency. Two possible reasons for the differences in reflex excitability reported by these studies are that 1) the paradigms used differed widely (ie. tibial nerve stimulation causing contraction of triceps surae (Mauritz et al., 1981), platform tilt stretching triceps surae (Diener et al., 1984), sinusoidal stretches of forearm (Neilson and Lance, 1978)) and 2) the severity and locus of cerebellar lesions in patients undoubtedly varied between studies. For example, patients with anterior vermal lesions displayed a prominent medium latency response in leg muscles (gastrocnemius and tibialis) which could not be suppressed when it was inappropriate (Nasher, 1976; Nashner and Grimm, 1978) whereas patients with dentate, and probably interpositus, damage had a reduced medium latency reflex in arm muscles (biceps and triceps) (MacKay and Murphy, 1979a).

Disordered reflex loop function produced by cerebellar lesions has led to the hypothesis that the cerebellum

functions as an accessory structure adjusting gain and phase relationships in reflex loops (MacKay and Murphy, 1979a,b). Bidirectional responses of neurons in dentate, interpositus, motor cortex and spindle afferents during slow tracking wrist movements in monkeys has been interpreted as indicating a functional relation between motor cortex, cerebellar neurons and spindles (Schieber and Thach, 1985). It also led to the suggestion that the cerebellum (particularly the lateral zone) may function to help set appropriate levels of fusimotor activity prior to an intended movement. This suggestion, however, contradicts the finding of Burke et al. (1980) who showed that the change in stretch reflex gain that occurs in preparation for a muscle contraction occurs through a central process that is independent of the fusimotor system.

Because of the cerebellar involvement in the control of movement initiation and execution and its role in regulating muscle patterns and fusimotor activity, it is not surprising that dysfunction of the cerebellum produces severe motor impairments.

iii) Disorders associated with cerebellar dysfunction

Holmes (1917, 1922, 1939) identified a number of deficits associated with lesions of the cerebellum in man. These were delays in the initiation and termination of a voluntary movement, error in movement direction and lack of uniformity of speed. Multi-joint movements were decomposed

into a series of simple movements and rapidly alternating movements were made with great difficulty. There was a general weakness of the limbs making maintenance of fixed postures difficult. Perturbations that stretched muscles of an affected limb elicited weaker responses than in a non-affected one. These disorders can be reproduced in experimental animals by complete cerebellectomy as well as by smaller lesions restricted to the cerebellar nuclei. Some of the above disorders have already been discussed in relation to the cerebellar control of movements (see section IIIii). Below is a description of some other major cerebellar deficits.

a) Disorders of movement trajectory

Holmes (1939) recognized that movements made by cerebellar patients were "jerky and discontinuous" and lacked "uniformity in their velocity." The irregular velocity of movement sometimes appeared as a frank tremor. Reversible, localized cooling lesions of the dentate nucleus in monkeys resulted in an increased prevalence of discontinuous movements in a step-tracking task (Brooks et al., 1973b). Smooth movements did still occur during cerebellar cooling but peak velocity occurred later in the movement and movements were often terminated by an abrupt deceleration. This produced an asymmetric velocity profile. Cooling of the interposed nucleus produced very little disorder other

than a general tendency to decrease movement amplitudes and peak velocities (Uno et al., 1973).

b) Dysmetria

Cerebellar patients making goal-directed movements often overshot (hypermetria) or undershot (hypometria) the aimed target (Holmes, 1939). Holmes suggested that hypermetric movements were due to a "delay in starting their arrest and slowness in completing it." Hypometria results from the premature arrest of movements and "occurs particularly in patients who have experienced the risk of overshooting the mark" (Holmes, 1939).

Cerebellar patients making rapid elbow (Hallett et al., 1975b) or thumb (Marsden et al., 1977) movements can have agonist and antagonist EMG bursts that are of more prolonged duration than those of normal subjects. Hallett et al. (1975b) have suggested that this could result in inappropriate accelerative and decelerative forces and could, therefore, be responsible for dysmetria. These EMG abnormalities could also disrupt the ability to perform rapid altenating movements (dysdiodokokinesis) as confirmed by Conrad and Brooks (1974) in the monkey.

Slow ramp movements of the elbow and thumb were made relatively accurately by cerebellar patients (Hallett et al., 1975b; Marsden et al., 1977). However Beppu et al. (1984) found that cerebellar patients tracking ramp displacements with velocities as low as 7.5 deg/s had

markedly discontinuous trajectories and had distorted EMG patterns. Fifty percent of the patients cocontracted biceps and triceps, a pattern which never appeared in control subjects. Thus, even slow ramp movements can be affected by cerebellar dysfunction.

Dysmetria has also been produced in the cat and dog (Bremer, 1935), in the monkey (Botterell and Fulton, 1938a; Fulton and Connor, 1939; Luciani, 1891 cited in Dow and Moruzzi, 1958) and in the baboon (Botterell and Fulton, 1938a).

More recently, hypermetria and some hypometria was produced in monkeys with dentate lesions (Brooks et al., 1973b); lesions of interpositus produced hypometric movements (Uno et al., 1973). In contrast, Chambers et al. (1972) found reaching movements to be hypermetric following interpositus lesions in cats.

c) Intention tremor

Tremor and movement oscillations as a consequence of cerebellar lesions have been described in several species. Cats and dogs with partial or total ablation of the cerebellum display varying degrees of tremor, which is particularly evident when an attempt is made to feed (Bremer, 1935; Dusser de Barenne, 1922; Luciani, 1915; Rademaker, 1931 cited in Dow and Moruzzi, 1958; Zatti, 1953; Thomas, 1897). Lesion of the interposed nucleus in rabbit produces a similar disorder (Snider, 1940). In primates, tremor and

other rhythmic oscillations also occur following lesions of the cerebellum (Botterell and Fulton, 1938a; Bremer, 1935; Ferrier and Turner, 1894; Fulton and Connor, 1939; Fulton and Dow, 1937; Luciani, 1891 cited in Dow and Moruzzi, 1958). Lesion of the dentate nucleus and also, to some extent, the interposed nucleus is a particularly potent cause of tremor (Botterell and Fulton, 1938c; Carrea and Mettler, 1947; Fulton and Dow, 1937). Cerebellar tremor is more marked in monkeys than in dogs, perhaps because of the more complex movements that can be made by primates (Bremer, 1935).

Cerebellar tremor also occurs in man and can occur during the entire range of movement (kinetic tremor), giving it an irregular, jerky appearance but it is usually more prominent at the end of the movement (static tremor) (Holmes, 1917, 1939; Thomas, 1897). Holmes (1939) viewed cerebellar tremor as a consequence of voluntary corrections for defective postural fixation. This view was also expressed by Growdon and colleagues (Goldberger and Growdon, 1973; Growdon et al., 1967) for tremor induced in monkeys by dentate and interpositus lesions. Their evidence for this was that lesions which destroyed the animal's ability to make rapid error corrections abolished tremor and only when the ability to make purposeful movements was regained through training did tremor reappear (Growdon et al., 1967).

Another possibility is that cerebellar intention tremor, like Parkinsonian and physiological tremor for example, is involuntary in nature (Stein and Lee, 1981). It could result from, among other possibilities, an abnormality in proprioceptive transcortical reflex loops (Meyer-Lohmann et al., 1975; Murphy et al., 1975; Vilis and Hore, 1980). Cerebellar tremor produced by perturbations applied to a limb held stationary in target was suggested to result from loss of a predictive cortical signal replaced by stretch-driven activity (Vilis and Hore, 1980). The stretch-driven cortical discharge was thought to arrive at the muscle too late to arrest the movement returning the limb to target. Consequently the limb overshot the aimed target, initiating the second cycle in a series of maintained oscillations. Perturbations applied during a self-initiated movement produced a smaller 'late' motor cortical response during dentate cooling (Meyer-Lohmann et al., 1975). It was concluded therefore that tremor resulted from the altered gain of the cortical response to the perturbation. The reflex origin of cerebellar tremor was further supported by the finding that tremor frequency and amplitude could be altered by the mechanical state of the limb (Chase et al., 1965; Hewer et al., 1972; Vilis and Hore, 1977).

If cerebellar tremor is indeed of peripheral origin one might expect that it could be abolished by section of the dorsal roots, thus effectively eliminating all stretch

reflex input. Liu and Chambers (1971) found that deafferented monkeys with lesions of the dentate and interposed nuclei made frequent errors of overshoot in goal-directed acts and proposed that attempts to correct for the errors were responsible for producing tremor. However, since "recovered movements in the deafferent cerebellar animals were essentially unaltered by exclusion of vision" continuous central feedback monitoring was presented as the mechanism by which errors were detected (Liu and Chambers, 1971). Complete cerebellar ablation in a deafferented monkey also produced a worsening of motor performance (Gilman et al., 1976a,b). It must be concluded therefore that there are mechanisms of cerebellar tremor independent of the reflex arc. However, since none of the above studies directly assessed the characteristics of cerebellar tremor in the rhizotomized and dorsal root-intact animal one cannot rule out the possibility that stretch reflexes contribute to cerebellar intention tremor.

IV. Rationale

This brief review illustrates that the cerebellum plays a major role in the performance of voluntary, goal-directed movements. However, a clear understanding of the nature of its contribution to movement performance is lacking and may remain so for some years. The first step in understanding

cerebellar function is to study the disorders that occur in simple movements.

One of the more prominent and debilitating disorders associated with lesions of the cerebellum is tremor. Tremor can occur both during (kinetic tremor) and after the movement (static or terminal tremor). Dysmetria is another common cerebellar disorder and it can be a feature of ataxic movements. In hypermetria the overshoot often appears as part of the first cycle of the intention tremor, suggesting a link between this disorder and tremor. Thus, in theory, an understanding of tremor and dysmetria can provide important information into cerebellar function.

A positive feature of the present study was that cerebellar lesions were produced by local, reversible cooling. This permitted repeated comparison of normal and disordered movements in the same animal over extended periods of time. Thus adaptation to the cerebellar lesion did not occur to the extent that it does with surgical ablation.

The experiments on the disorders that occur following torque pulse perturbations, performed in this laboratory by Drs. Hore and Vilis, provided a broad data base for the present study and contributed to the decision to study intention tremor.

The objectives of this study were 1) to determine if the tremor that occurs following torque pulse perturbations

has the same characteristics as that which occurs following a voluntary movement, 2) to determine the extent to which stretch-evoked proprioceptive activity contributes to intention tremor, 3) to describe the characteristics of smooth, dysmetric movements and 4) to study the nature of the oscillations that occurs in ataxic, tremulous movements. These objectives were investigated by analyzing the kinematic (position, velocity, acceleration and phase-plane trajectory) and EMG characteristics of normal movements and movements made during cerebellar dysfunction.

METHODS

I. Paradigm

i) Step-tracking limb movements

Six Cebus monkeys seated in a primate chair were thoroughly trained to make fast and accurate step-tracking movements about the elbow joint. With the elbow resting on a pivot, monkeys holding a manipulandum made flexion and extension movements between targets presented singly on an oscilloscope positioned 40 cm in front of them. Target width and separation was varied from 8-15° and 30-60° of elbow arc, respectively. Limb position (elbow angle) was measured with a potentiometer (Beckman Instruments, Inc., Missisauga, Ont.; model 6673-R10K-L.25-RS) and was displayed on the oscilloscope as a thin vertical cursor. Monkeys were prevented from seeing their arm by an opaque plate positioned at neck level. Monkeys were rewarded with fluid (water or grape drink) if they reached the aimed target within 500ms of a 'go' signal and remained in target for a further 150ms. An auditory signal supplemented the visual one when the handle cursor was within the target zone.

While it is recognized that these limb movements are not strictly isotonic, in the sense that non-constant forces produced accelerations and decelerations during the movements, the term isotonic will be used hereafter to differentiate these movements from isometric contractions (see below.

ii) Torque pulse perturbations

Monkeys were also trained to hold their arm in target and to return their arm to target when displaced by a torque pulse. The duration and magnitude of the pulses could be varied to obtain a range of limb displacements. Torques were generated by a precision, brushless, DC torque motor coupled to the manipulandum (Aeroflex Laboratories Inc., Long Island, N.Y.; model TQ34W-20H, rotor inertia: 84 x 10^{-4} oz/inch/s^2).

Some experiments were performed in which a torque pulse perturbation was administered early in a voluntary movement at a time prior to the deflections that occurred during cerebellar nuclear cooling. The torque pulses opposed the intended movement. Torque pulse duration or magnitude was varied to obtain a range of deflection amplitudes during the movement.

iii) Isometric force-tracking

Some monkeys were further trained to make isometric contractions in a force-tracking task. A strain gage (Micro Measurements Group, Raleigh, N.C.; model CEA-06-125UN-350) measured the force exerted on the manipulandum which was held immobilized by a clamp. Bias on the strain gage was adjusted such that some active force had to be generated to align the handle cursor and the target before each trial (i.e. before target jump). The force of contraction necessary to displace the cursor from one target zone to the

other was made approximately the same as that in the isotonic paradigm by matching EMG amplitudes.

iv) Paradigm manipulation

In some experiments constant torques were applied by the motor to load either agonist or antagonist muscles. The mechanical state of the manipulandum was also altered by feeding back a voltage proportional to handle velocity to the motor to produce a viscous force or by fixing weights to the end of the manipulandum shaft, 10cm from its center of rotation, to increase inertia. The viscous load was set such that, at peak movement velocity, it opposed movements to approximately the same extent that a triceps torque opposed extension movements, by matching the current driving the motor in both situations.

In other experiments the limb position cursor was removed to eliminate visual feedback of arm position. In these experiments the auditory tone that signalled the presence of the manipulandum cursor in the target zone was also removed, thus eliminating all teleceptive cues.

II. Cerebellar Cooling

i) Evaluation of cooling technique

The greatest advantages of the cooling method are that it permits tissue inactivation to be brief, highly localized and reversible. Furthermore it is produced without the compensatory neural reorganization that occurs after

surgical lesions (Brooks, 1983b). A serious limitation of the technique is the uncertainty of the extent of inactivated brain tissue. As cooling first raises and then lowers neural excitability mixed effects may, in theory, occur at a particular locus or there may be a shell of facilitated neurons surrounding a core of inactivated tissue (Brooks, 1983b).

ii) Cryoprobe sheath implantation

Monkeys were implanted under pentobarbital anesthesia (35 mg/Kg ip) with two epoxy-coated stainless steel cryoprobe sheaths (1.3 mm diameter) ipsilateral to the operational arm. One sheath was placed lateral to the dentate nucleus (P 5.5, L 7.0, V -5.0 in monkeys MI and MO; P 6.5, L 7.0, V -5.0 in monkeys BZ, DU and JO) at a rostrocaudal angle of 40° from the vertical. A second sheath was placed medial to dentate (P 8.5, L 4.0, V -4.0 in monkeys MI and MO; P 8.0, L 3.0, V -4.0 in monkeys BZ, DU and JO) at an angle of 20° from the vertical. Both sheaths were then advanced 2 mm past the aimed vertical coordinate. Cooling was produced by flow of pressurized cooled methanol through probes inserted into the sheaths at the beginning of each experiment. Brain temperature was measured by a copper-constantan thermocouple attached to the outer sheath surface, 4 mm from its tip. Implantation of the cooling sheaths did not produce any observable disorder in limb

performance as the monkeys moved in their cages, groomed themselves or reached for food.

iii) Verification of cooling effect

As one limitation of the cooling technique is knowing the extent of tissue being inactivated, an important control is determining target specificity. To confirm that the effects of cooling described below were due to a reversible lesion of the nuclei and not to cooling of the overlying cerebro-cortical tissue, the cryoprobes were withdrawn approximately 5 mm within the implanted sheaths while a constant cooling was maintained. This procedure raised the temperature at the approximate locus of the dentate and interposed nuclei to 33°C and returned EMG patterns and movement parameters to those of control movements.

A second essential control is post-mortem histological identification of cooling sheath location followed by reconstruction of tissue isotherms.

iv) Histology

Histological verification of cryoprobe sheath location was performed for monkeys BZ, JO and MO (Fig. 1). Animals were perfused intracardially with normal saline at about 37°C and then with 10% formalin. The brain was transected to the brain stem at antero-posterior coordinate 0.0 in the vertical plane. The brainstem, cerebellum and rostral segments of the spinal cord (C1 to C3) were removed and stored in 10% formalin for at least 30 days to ensure

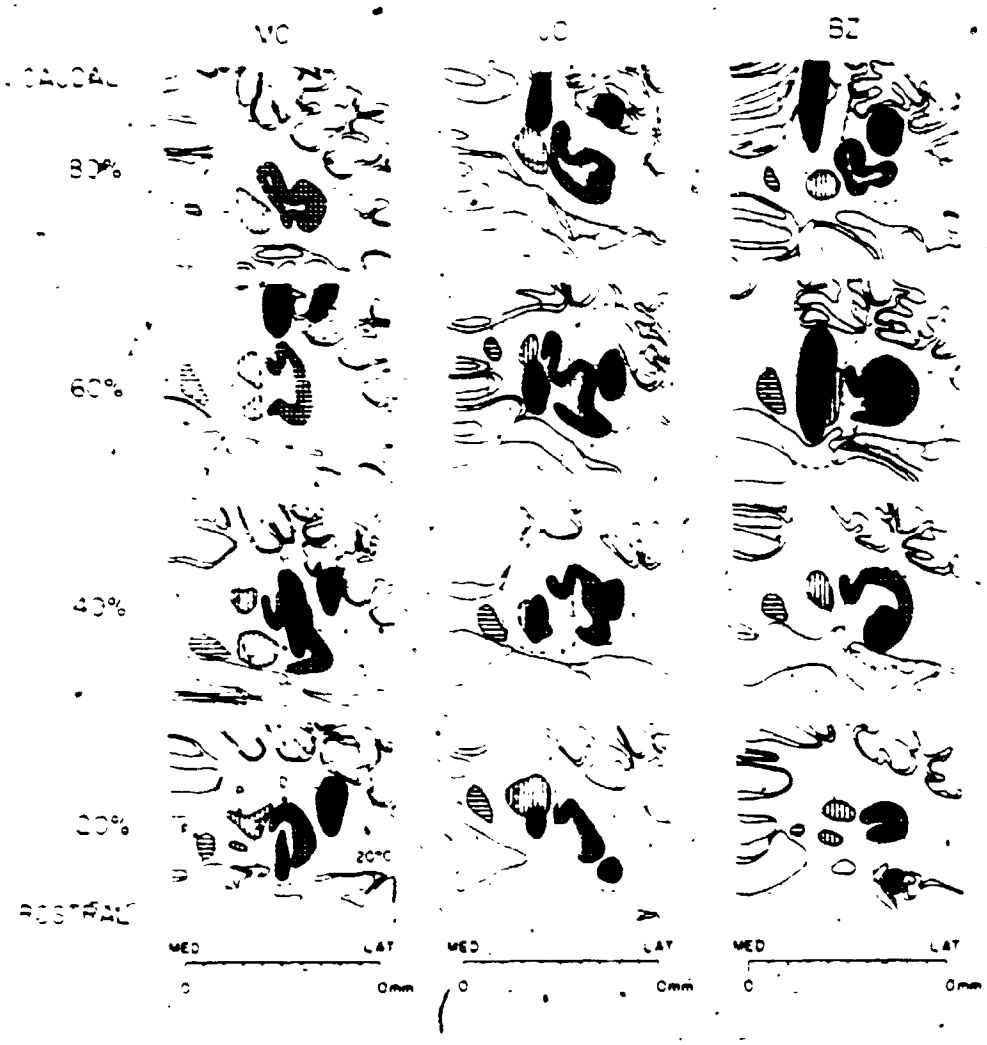

Fig. 1. Position of lateral and medial cryoprobe sheaths in monkeys MO, JO and BZ. Frontal sections are shown at 20, 40, 60 and 80% of the rostrocaudal extent ofthe dentate nucleus. Dotted lines are estimated 20°C tissue isotherms for a sheath reference temperature of 10°C. Midline is at 0mm. D, dentate nucleus (crosshatching); IP, interposed nucleus (vertical hatching); F, fastigial nucleus (horizontal hatching); LV, lateral vestibular nucleus (unshaded). Cryoprobe position indicated in solid black.

complete fixation of tissue. Formalin is categorized as a non-coagulant fixative and has been shown not to distort the form of gelatin/albumin gels (which serve as a model of protoplasm) soaked in it for several hours (Baker, 1970). Embedding tissue in paraffin or celloidin after formalin fixation is the method of choice when preservation of cytological detail is essential. This method however is associated with marked shrinkage of tissue. The purpose of doing histology in this study was to verify cooling sheath position and to calculate tissue isotherms. For the latter, it is essential that tissue shrinkage be kept to an absolute minimum. This can be achieved by freeze-sectioning the fixed tissue thus avoiding embedding altogetner. This method is extensively used in the production of stereotaxic atlases (e.g. Manocha et al., 1968; Olszewski, 1952; Snider and Lee, 1961). It is claimed that no appreciable shrinkage or distortion of tissue is present in frozen sections (Olszewski, 1952).

Sections through the region of the implanted sheaths were cut every 100 microns and stained with thionine. Every fifth section was mounted on a slide. Reconstruction of 20°C isotherms was based on the isotherms derived by Brooks et al., (1973b) using similar cooling probes and sheaths. These isotherms were double-checked in each monkey by cooling through one probe only and recording temperature at the other sheath. The exact distance between sheaths was

measured from the brain sections and the isotherm measured at that distance was compared to the complete isotherms of Brooks et al. (1973b). Good agreement was found between the two.

The 20°C isotherms (Fig. 1, dashed line) were chosen because this is the temperature at which synaptic transmission is first blocked (Benita and Conde, 1972; Brooks, 1983b). It can be seen that most of the dentate and interposed nuclei were within the 20°C isotherms when sheath reference temperature was held between 5-10°C.

III. Data Acquisition and Analysis

Up to four parameters were monitored in these experiments: 1) forearm position (elbow angle), by means of a potentiometer attached to the shaft of the manipulandum, 2) isometric force by means of a strain gage and 3) EMG activity of biceps and 4) triceps brachii muscles by means of fine Teflon-coated stainless steel wires (Medwire Corp., Mount Vernon, N.Y.; part #316SS3T) inserted into the muscle at the beginning of each experimental session. The wires were bared 1-2 mm at the tips and these were separated by 2-3 mm before being inserted into the muscle using a 23 gage hypodermic needle.

After amplification, the EMG signal was notch-filtered at 60 Hz to eliminate the primary component of the power main interference frequency. It was also band-pass filtered

at 30-1000 Hz to eliminate both low frequency hum and high frequency hiss. This range was used as it was not expected to greatly attenuate the EMG signal whose power spectrum, recorded with intramuscular fine wires, peaks at 500 Hz (Basmajian et al., 1975). The signal was then full-wave rectified and smoothed by a low-pass filter (0-100 Hz). This procedure is recognized as necessary to relate dynamic temporal details in the EMG to other measurements such as, for example, force of contraction (Basmajian et al., 1975, p. 87). These data were then digitized at 1000 Hz or 500 Hz. for 1s and 2s. records, respectively, on a PDP 11/44 computer (Digital Equipment Corp.). Further smoothing of the data was produced by block-averaging into 5ms or 2ms bins, for the data sampled at 1000 and 500 Hz, respectively. It is recognized that this procedure may introduce slight phase shifts (no greater than 2 or 5ms, depending on the bin width) into the EMG data. However, since all data were handled in the same way, valid comparisons of EMG burst latency, duration and amplitude could be made between control responses and responses made during cerebellar nuclear cooling.

Kinematic parameters (position and torque) were filtered (0-1000 Hz) and digitized at 1000 Hz or 500 Hz (for 1 and 2s records, respectively) and block averaged into 5ms or 2ms bins, respectively. Block averaging produced smoothing and slight phase-shifts in the data. Since

kinematic information of interest in this study was well below 100 Hz hence the lowest effective sampling rate of 200 data points/s (1000 Hz/5ms bins) was more than adequate.

Differentiation of the kinematic parameters was done off-line by taking the difference between points sampled 30ms or 24ms apart, for the 1s and 2s records, respectively (i.e. 6 point moving difference). This method overestimates start of movement and underestimates end of movement (i.e. velocity or acceleration start appears to begin before the actual start of movement and appears to end after the actual end of movement). Timing of peaks in velocity, acceleration and derivative of force are not affected by this method. Since control records and records of movements or isometric contractions made during cerebellar cooling were handled in the same way, comparisons of kinematic parameters for these conditions could be made in all confidence. All data were archived on magnetic tape for later retrieval.

Differentiated position and torque were used to obtain an estimate of movement start and end and contraction start and end, respectively. For example, movement onset was defined as the time when velocity first reached 25°/s and movement end as the time when it returned to the same velocity, before crossing zero as described previously (Flament et al., 1984a).

RESULTS

I. Kinematic Characteristics of Normal and Disordered Movements

Following extensive training all monkeys made fast and accurate elbow movements of 40-50° in approximately 300 ms (range 200-400ms), reaching peak velocities of 200-400°/s. Movements were smooth with only one peak in velocity and had nearly symmetric acceleratory and deceleratory phases (Fig. 2, A and C), as previously described (Flament, 1983; Flament et al., 1984a). Cooling the cerebellar nuclei through both probes caused the movements to become ataxic in all monkeys. Some movements were tremulous and had two or three peaks in velocity (Fig. 2B). These movements have been described as discontinuous (Brooks et al., 1973b; Holmes, 1922; Rondot et al., 1979). Others were smooth or continuous but were hypermetric (Fig. 2D). In both types of movements a terminal tremor occurred when attempting to hold in the new target (Fig. 2, B and D).

During cooling, smooth and tremulous movements could be obtained in the same monkey depending on the mechanical state of the manipulandum. This is illustrated in Fig. 3 for the same monkey as shown in Fig. 2, A and B. Figure 3A illustrates position, velocity and phase-plane trajectory (plot of position vs. velocity) for a representative control movement. During cerebellar nuclear cooling approximately 10% of movements were smooth but asymmetric (Fig. 3B),

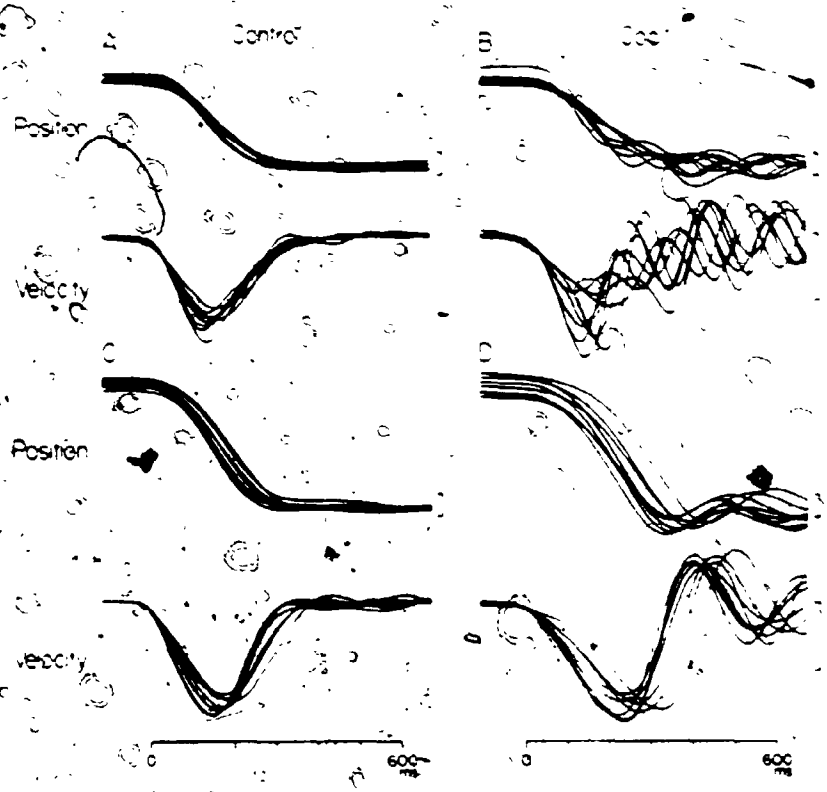

Fig. 2. Two types of ataxic elbow flexions. Superimposed individual records of position and velocity for 8 control movements (A,C) and 8 flexions made during cerebellar nuclear cooling (B,D) in monkeys DU (A,B) and MO (C,D). Torques of .014 Nm and .010 Nm loaded triceps (ie. assisted flexions) in A,B and C,D, respectively. Time 0ms indicates movement onset defined as when velocity reached a threshold value of 15°/s. Calibrations: position (target), 12°; velocity, 200°/s.

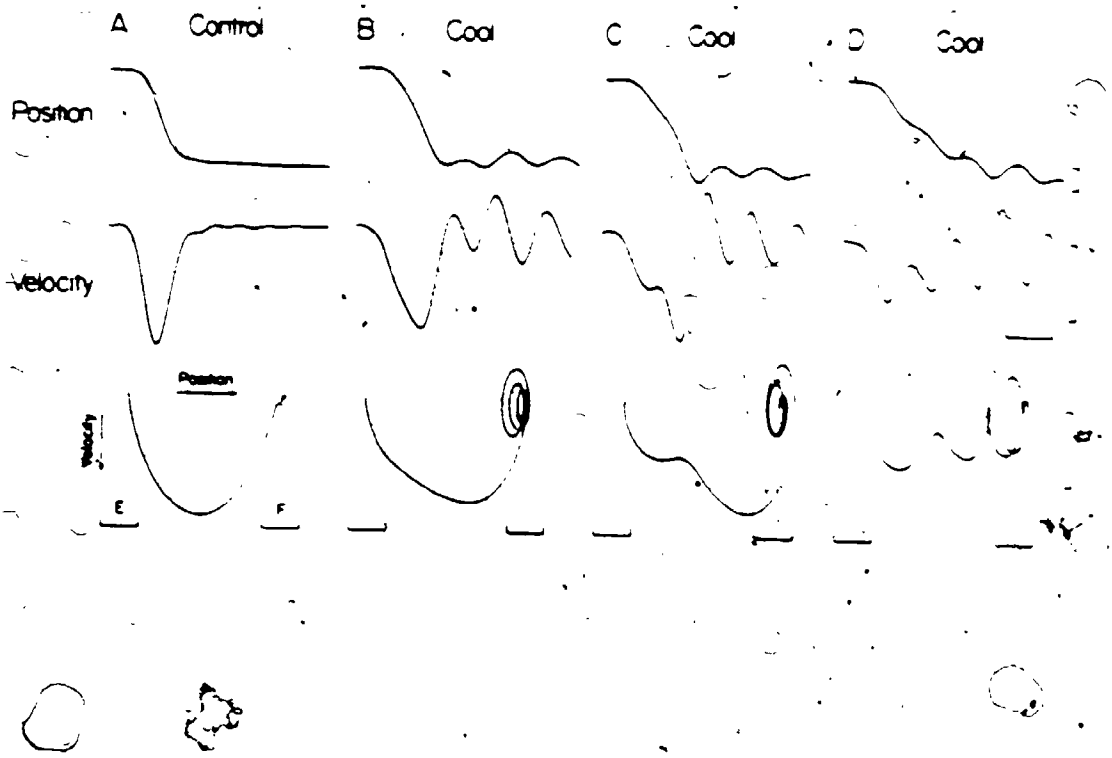

Fig. 3. Disorders in elbow flexions produced by cerebellar nuclear cooling. Position, velocity and phase plane trajectory for 4 representative single movements. A: control; B,C,D: during cerebellar nuclear cooling. Movements were made with a torque of .05 Nm loading triceps (i.e. assisting flexions). Calibrations: position (targets), 1l°; velocity, 200°/s; time, 200 ms. Monkey DU.

having longer durations of acceleration (time from movement onset to peak velocity) and shorter decelerations (time from peak velocity to end of movement). The asymmetry during cooling is also evident from the phase-plane records; whereas under control conditions the trajectory was bell-shaped (Fig. 3A) during cooling it was markedly skewed (Fig. 3B). This means that at peak velocity more displacement had taken place in the movement made during cooling than in the control movement. Other movements were jerky in appearance and had two (Fig. 3C) or three peaks in velocity (Fig. 3D), depending on the speed of the movement.

Thus four distinct disorders were identified in all monkeys as a result of cerebellar nuclear cooling: 1) tremor during the movement (kinetic tremor), 2) asymmetric movement trajectory, 3) dysmetria and 4) terminal tremor following the movement (static tremor). The first three may be viewed as disorders that occur during the intended movement and the fourth as a disorder occurring after the intended movement.

II. Cerebellar Disorder Following the Movement

1) Intention tremor following isotonic movements

A previous study by Vilis and Hore (1977) showed that the cerebellar tremor that occurs following torque pulse perturbations increased in frequency when a constant force loaded the limb and decreased in frequency when a mass was

added, while the tremor amplitude increased with constant forces and decreased with an increase in viscous resistance. In view of the opinion of Holmes (1922) that all tremors occurring in cerebellar disease are not of the same nature, the first aim of this study was to determine whether cerebellar tremor that occurred at the new intended position after movements had the same characteristics as that following perturbations. Figure 4 illustrates the effects of torque, viscous and inertial loads on tremor following voluntary movements. The changes in tremor frequency and amplitude were similar to those seen following torque perturbations (Flament et al., 1984b; Vilis and Hore, 1977). The frequency of tremor was increased by a torque load (Fig. 4, A and B) and decreased by addition of mass (inertia) (Fig. 4C). This finding was later confirmed statistically (Fig. 20). The amplitude of the tremor was decreased by an increase in viscous resistance (Fig. 4D). This indicates that the same mechanism could have generated the tremor in both situations (i.e. after a torque pulse and after a voluntary movement).

Previous work also demonstrated that during cerebellar nuclear cooling EMG activity in biceps and triceps follows stretch of each muscle during tremor that occurs following a limb perturbation (Vilis and Hore, 1977, 1980). To compare the EMG characteristics of tremor after voluntary movements with those of tremor after perturbations it was necessary to

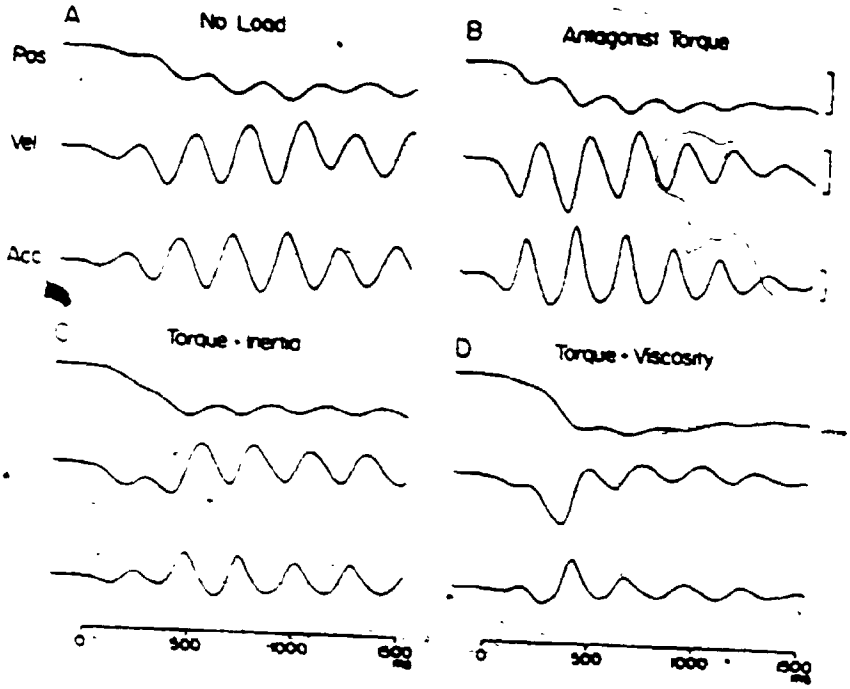

Fig. 4. Cerebellar tremor that followed voluntary goal-directed movements for four different mechanical load conditions. Single trials of manipulandum position. Calibration: Pos--position, 50°; Vel--velocity, 200°/s; Acc--acceleration, 4000°/s2. Antagonist torque: .05Nm; inertial load: 72g. The viscous load was set such that, at peak movement velocity, it opposed movements to approximately the same extent that the antagonist torque opposed extention movements (see methods). Monkey MI.

find some point on which to synchronize individual trials to enable averaging of EMG activity. Synchronizing records to movement onset did not yield a clear resynchronization of tremor occurring after movement (Fig. 5A). However, synchronizing records to the end of movement (defined as when velocity first crossed zero) resulted in a closer phase-matching of the cycles of tremor (Fig. 5B). This technique thus permited comparisons of averaged records of tremor following movements with that following perturbations and averages of tremor following movements made under a variety of mechanical states.

The EMG characteristics of tremor after movements made with a normal (not loaded) manipulandum and with increased inertia were studied. Figure 6 illustrates that, when traces were synchronized to end of movement and averaged, EMG activity in biceps and triceps followed stretch of its muscle for both mechanical conditions. Thus EMG activity in tremor following voluntary movements had the same characteristics as that following perturbations (Vilis and Hore, 1977, 1980).

The role played by visual feedback in the generation of cerebellar tremor was investigated by comparing tremor in the presence and absence of visual feedback of manipulandum position. Visual display of handle position was eliminated in 25 to 50% of the trials by removing the handle cursor from the oscilloscope screen at the time of the perturbation

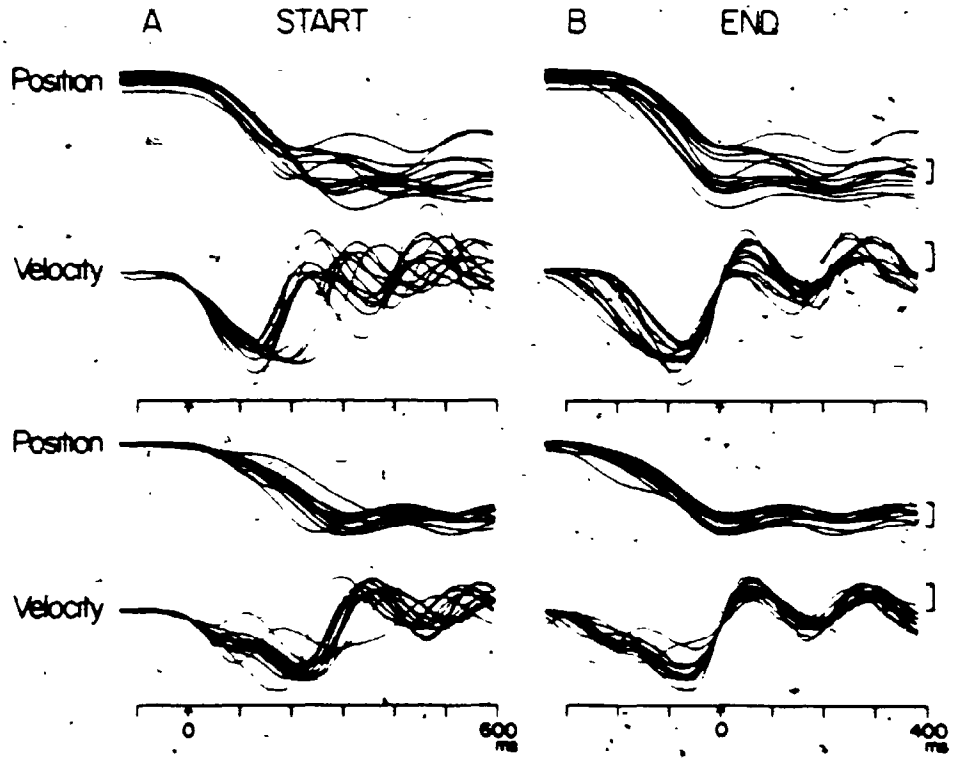

Fig. 5. Superimposed position and velocity records of individual flexion movements during cerebellar nuclear cooling synchronized to A--start of movement, B--end of the movement. Arrow at 0 indicates synchronization point. Calibrations: target, 12°; velocity, 100°/s. Upper four series of traces, monkey BZ; lower four series of traces, monkey JO.

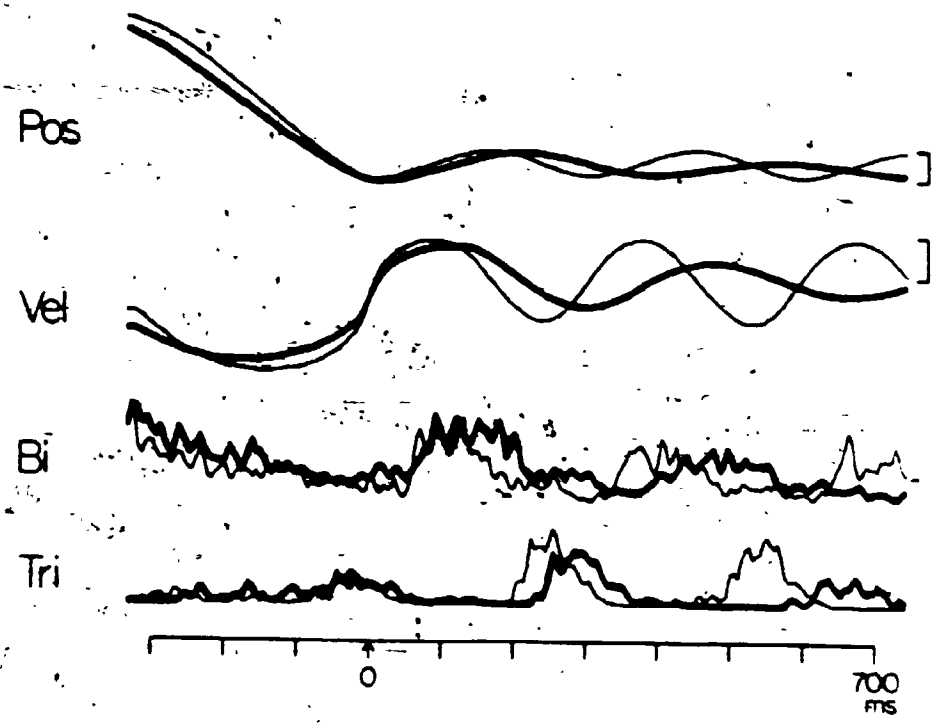

Fig. 6. Effect of inertial load on EMG activity during cerebellar tremor following movements. Thin line, normal manipulandum; thick line, 100g mass added to manipulandum. Averages of 15 movements. Movements synchronized to end of movement (when velocity equalled zero). Arrow at 0 indicates synchronization point. Pos--position, Vel--velocity, Bi--biceps, Tri--triceps. Calibrations: target, 12°; velocity, 100°/s. Monkey BZ.

or target jump. This is illustrated in Figure 7 where the top trace of each pair of records is with visual feedback of limb position (Vision) and the lower trace is in the absence of visual feedback (No Vision). Visual inspection of the data revealed that tremor amplitude and frequency and the associated EMG activity in biceps and triceps were not affected by removal of visual feedback for tremor occurring following limb perturbations (Fig. 7A) or following voluntary movements (Fig. 7B).

The above results indicate 1) that cerebellar intention tremor is influenced by peripheral feedback and 2) it is not the result of a series of visually guided voluntary corrections for an initial error. One way to test how strongly cerebellar tremor is dependent on peripheral feedback would be to section the dorsal roots containing afferents from the forelimb. The disadvantages of this procedure are that it is irreversible, thus prohibiting the use of animals that have been rhizotomized in other experiments, and it is associated with behavioural modifications such as self-mutilation that endanger the animals' well-being. Another method of preventing proprioceptive input from reaching the CNS is peripheral nerve block. It was felt, however, that the anesthesia associated with this procedure would disrupt the monkeys' performance to such an extent as to make meaningful results impossible. The simplest way to test the influence of proprioceptive feedback on tremor is to

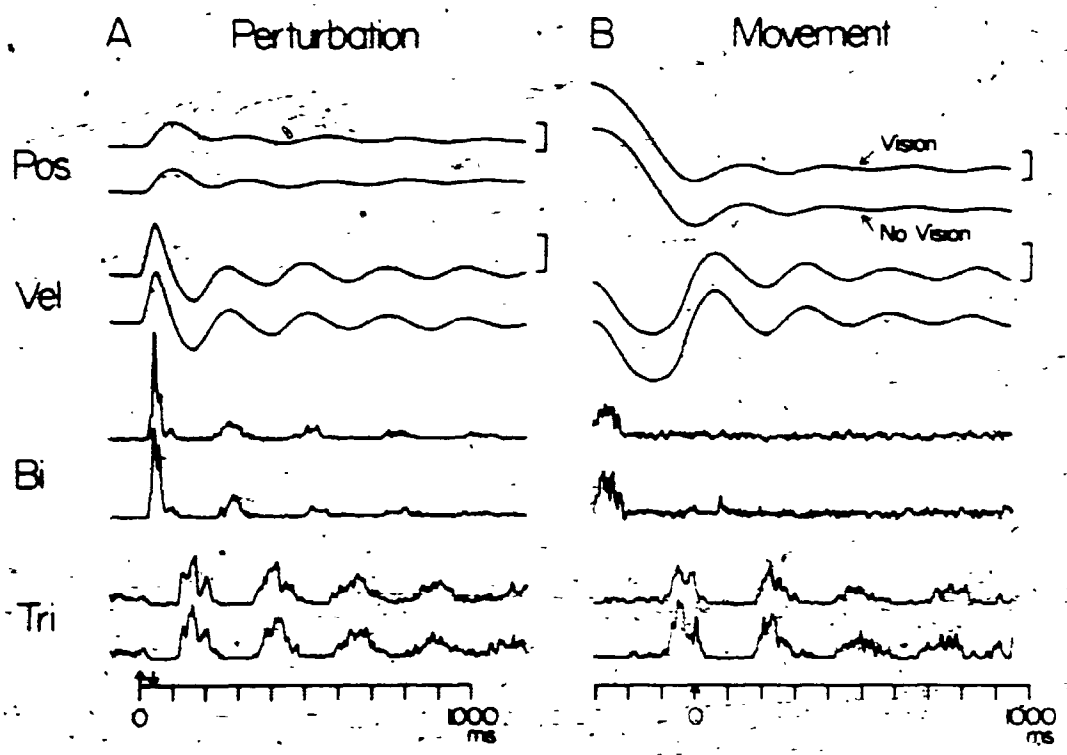

Fig. 7. Effect of removal of vision on cerebellar intention tremor. A--averages of tremors after perturbations; B--averages of tremors after movements. All traces during cooling of the cerebellar nuclei. Upper trace of each pair is with handle cursor displayed (vision), lower trace of each pair is with handle cursor removed (no vision). Movement traces were synchronized to end of movement (when velocity first equalled zero). Averages of 22 trials (perturbation with vision), 18 trials (perturbation with no vision), 29 trials (movement with vision) and 17 trials (movement with no vision). Arrows on time axis indicate onset and offset of 40ms perturbation (A) and synchronization point (B). Pos--position, Vel--velocity, Bi--biceps, Tri--triceps. Calibrations: target, 12°, velocity, 100°/s. A--monkey MO, B--monkey JO.

minimize or eliminate stretch-evoked afferent activity by using an isometric tracking paradigm.

ii) Cerebellar tremor following isometric contractions

Before addressing the question of what would happen to cerebellar tremor when stretch-driven proprioceptive feedback is reduced or abolished a comparison was made of normal isotonic movements and isometric contractions using step-tracking paradigms requiring similar levels of muscle activity (see Methods Iii). The force records of isometric contractions showed some similarity to the position records of isotonic movements, but were not as smooth and had greater variability (i.e. standard deviations) (Fig. 8). The difference in variability was greatest for flexion directed movements and isometric contractions, as judged by the standard deviation of the averaged force records (Fig. 8B, dashed line). Isometric contractions in this paradigm were made with agonist activity only (Triceps, Fig. 8A; Biceps, Fig. 8B). This EMG pattern was also observed in isotonic movements made against torques that loaded the agonist muscle. The classic triphasic EMG pattern of muscle activity was never observed in isometric contractions. This may be a consequence of the task, which required that agonist activity be maintained to hold the force-cursor within the target zone (i.e. "step" type task as defined in section IIi of historical review).

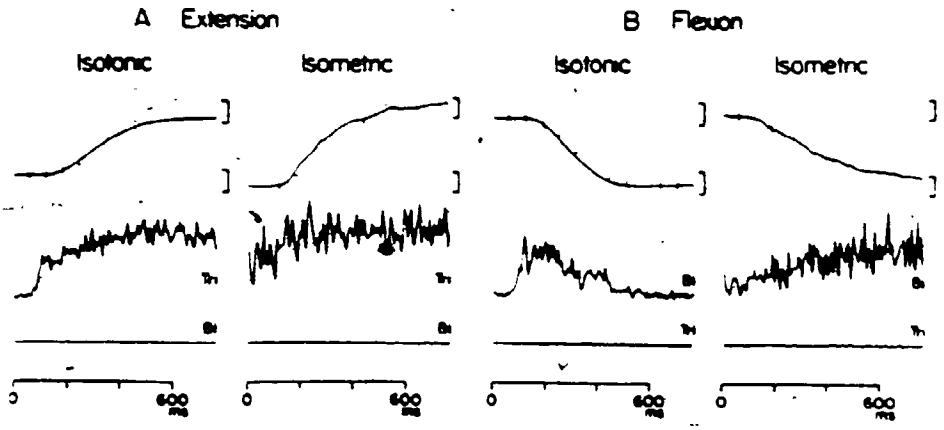

Fig. 8. Performance of normal isotonic and isometric contractions and the associated EMG activity in triceps (Tri) and biceps (Bi) brachii muscles. Averages and standard deviations of 15 contractions in the extension direction (A) and flexion direction (B). A constant torque of .03 Nm loaded extension and flexion movements. All records were synchronized to either movement onset (isotonic) or start of force increase (isometric). Calibrations: position (targets), 12°; torque (targets), .04 Nm. Monkey MI.

Cooling the cerebellar nuclei produced a clear disorder in the isotonic goal-directed movements and in isometric contractions (Fig. 9). Whereas control isometric contractions were made in a step-like fashion and were maintained near the target zone, during cerebellar cooling the initial step to the target zone was often inappropriate (see esp. monkey MI, Fig. 9) and the hold phase was characterized by large, irregular oscillations in maintained force. A regular tremor at a frequency of 3-4 Hz was observed following isotonic movements (Fig. 10A) whereas the force oscillations of the isometric contractions were irregular in amplitude, frequency and shape (Fig. 10B). The force oscillations associated with flexion directed isometric contractions were often of lower frequency (2-3 Hz). Furthermore, while isotonic terminal tremor was synchronized to the first peak in velocity after the end of the movement (Fig. 11A), isometric oscillations were not brought into phase by resynchronization to the first peak in torque following the point at which the derivative of torque (dT/dt) reached zero after it had entered the target area (Fig. 11B).

For the elbow torque to be transmitted to the manipulandum there has to be a comparable torque about the wrist joint that is maintained by the muscles acting across that joint. It is, in theory, possible that at least some of the force measured in our experiments may have been due

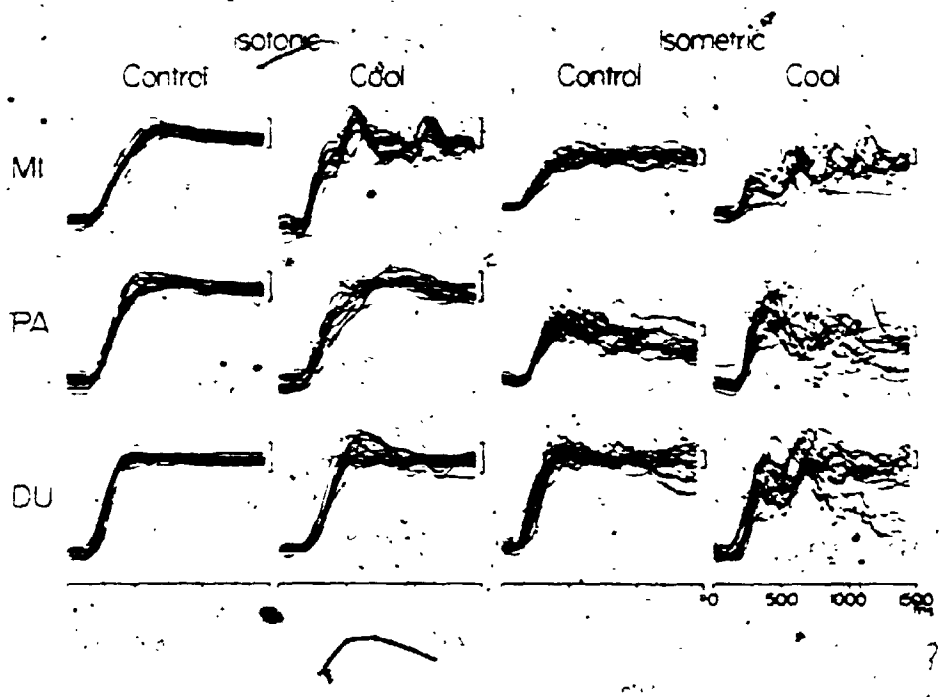

Fig. 9. Effect of cerebellar nuclear cooling on tracking task performance in the isotonic and isometric paradigms for three monkeys (MI, PA and DU). Superimposed individual position (2 left columns) and force (2 right columns) records under control conditions and during cooling. Control movements and contractions for MI were from same experiment as averages shown in Fig. 8. A torque of .026 Nm opposed the isotonic movements in MI and PA and a torque of .056 Nm was present in DU. Calibrations: position, 15°; torque, .027 Nm in monkey MI, .033 Nm in PA, .061 Nm in DU.

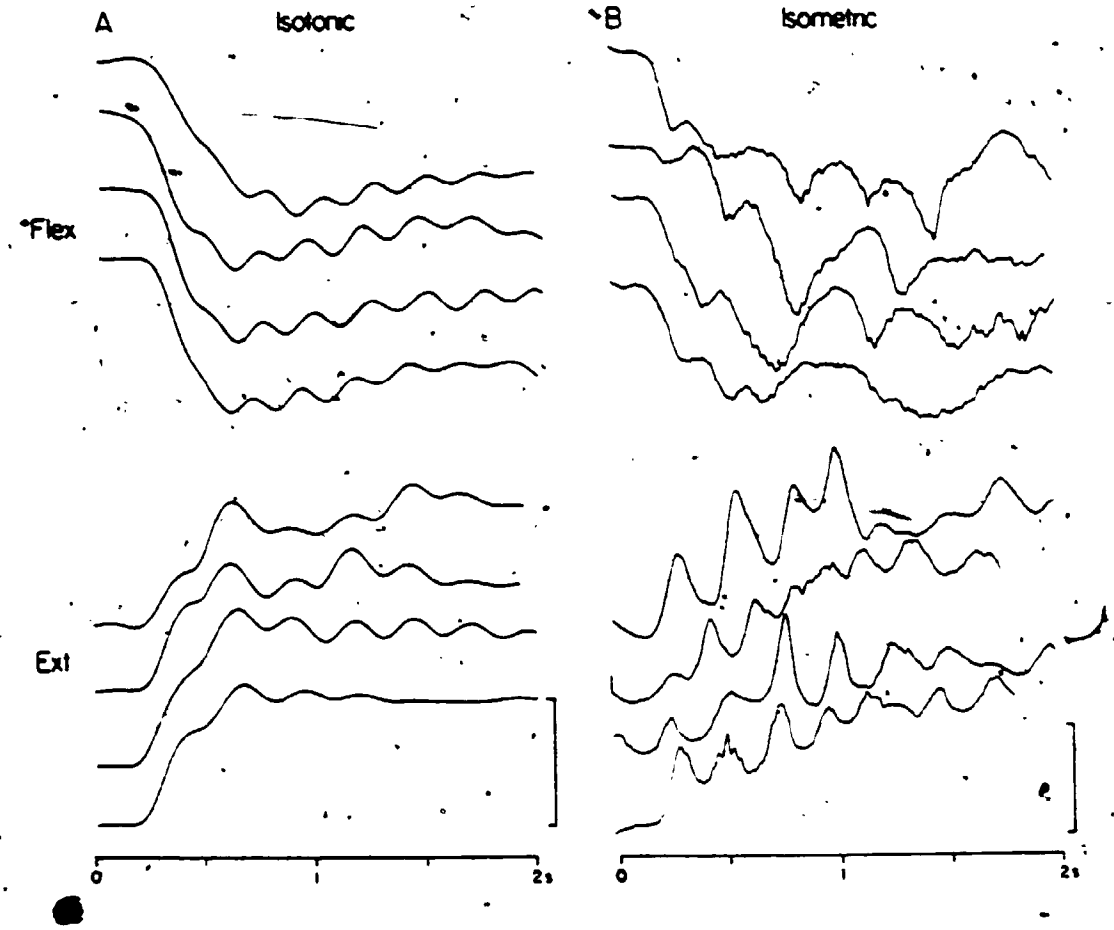

Fig. 10. Tremor characteristics of isotonic (A) and isometric (B) contractions during cerebellar nuclear cooling. Individual records of position and force for tracking in the flexion (Flex) and extension (Ext) direction. Calibrations: position, 40°; torque, 0.2 Nm. Monkey MI.

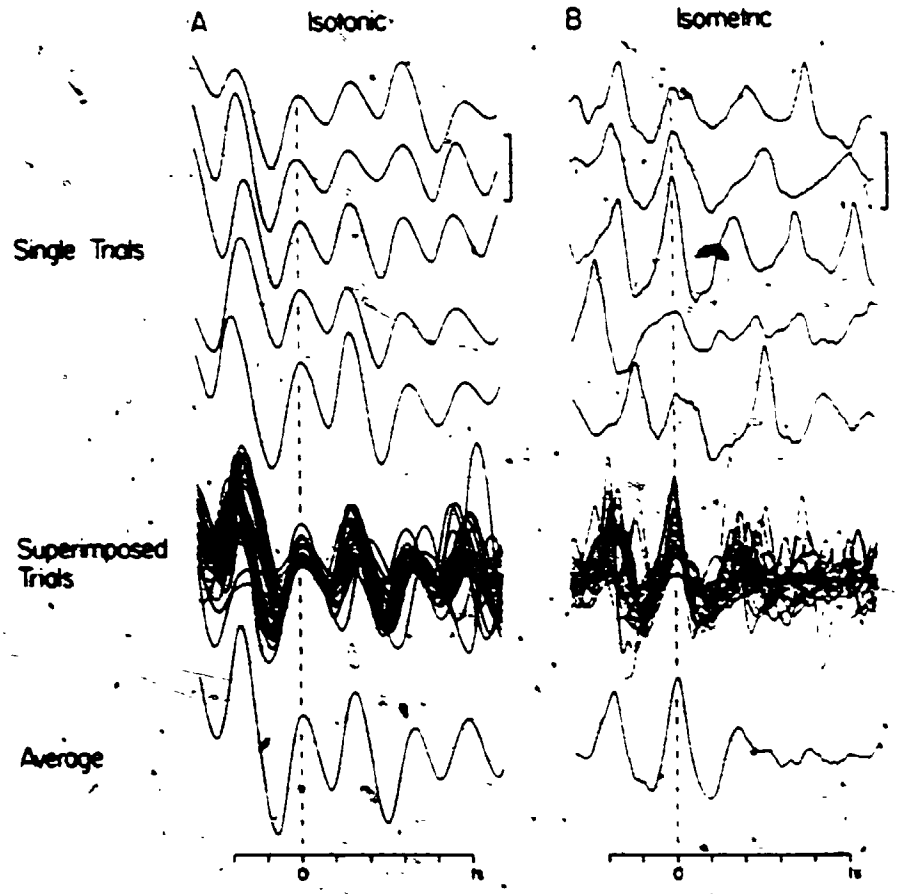

Fig. 11. Isometric tremor does not resynchronize. Records of velocity (A) and the first derivative of torque (B) synchronized to the first peak in velocity or rate of change of force (at dashed line) after end of movement (in the isotonic task) or after dT/dt reached zero once force reached the target area (in the isometric task). The single trials (top 5 records in A and B) were taken from the group displayed in the superimposed trials. The averages (lower records in A and B) are of the above superimposed trials. Calibrations: velocity, 400°/s; dT/dt, 4.0 Nm/s. Monkey MI.

to contraction of wrist musculature. However, the EMG data provide strong evidence that force changes observed isometrically were due to muscle activity acting about the elbow. This is illustrated for two monkeys in Fig. 12. Increments and decrements in isometric force during cerebellar cooling were closely related to EMG activity in the agonist muscle (triceps). Peaks in force were preceded by peaks in EMG activity and periods of low force output were associated with periods of muscle silence or low levels of tonic activity.

It is thus concluded that some form of cerebellar intention tremor can be produced isometrically (i.e. with reduced or absent stretch-driven spindle activity). This tremor, however, is irregular and quite different from that observed isotonically. Stretch of antagonist muscle pairs was associated with a rhythmic tremor.

III. Cerebellar Disorders During the Movement

i) Dysmetria

As described in section I of results, cerebellar nuclear cooling may lead to two types of ataxic movements: 1) smooth movements with only one peak in velocity and 2) tremulous movements with two or more peaks in velocity. One factor that determined the prevalence of one or the other type was the mechanical state of the manipulandum held by the monkey. Oscillations in movements (e.g. Fig. 2B) were

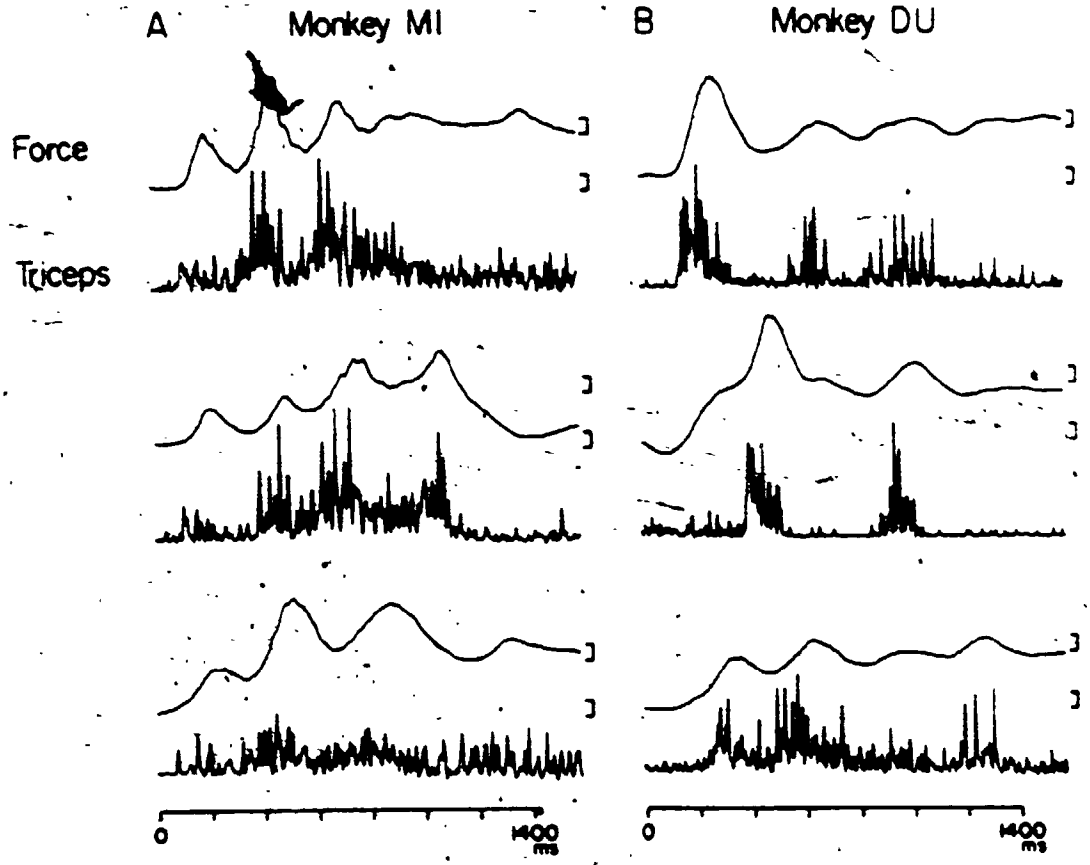

Fig. 12. Relation between measured force and agonist EMG activity during cooling. Three individual records of force and their associated triceps EMG activity for monkeys MI (A) and DU (B). Calibrations: torque, .033 Nm (in A), .041 Nm (in B).

more likely to occur when a constant torque loaded the antagonist muscle (Fig. 13A). In contrast, increasing the inertial load by fixing weights to the end of the manipulandum reduced or abolished the oscillation (Fig. 13B). When a torque loaded triceps (the antagonist muscle) movements made during cerebellar cooling were of lower peak velocity than control movements (Fig. 13A). This was due to the earlier and larger magnitude of triceps activity. Addition of a 98g mass to the end of the manipulandum abolished the early triceps activity and the oscillation during cerebellar cooling (Fig. 13B).

Movements made during cerebellar dysfunction classically were described as being either hypometric or hypermetric (Dow and Moruzzi, 1958; Holmes, 1922). However, in the present study hypometria was not a major feature of movements made during cerebellar cooling. This could arise as a result of differences in the definition of the end of movement. In the present experiments end position was defined as the point when velocity first reached zero, 250ms after movement onset. This value was chosen because all control movements were of at least this duration and because movements made during cerebellar cooling had slower, rather than faster, initial velocities than control movements. Figure 14A shows three individual movements (taken from those illustrated in Fig. 2B) that were tremulous and that reached the target zone and then oscillated within it. It

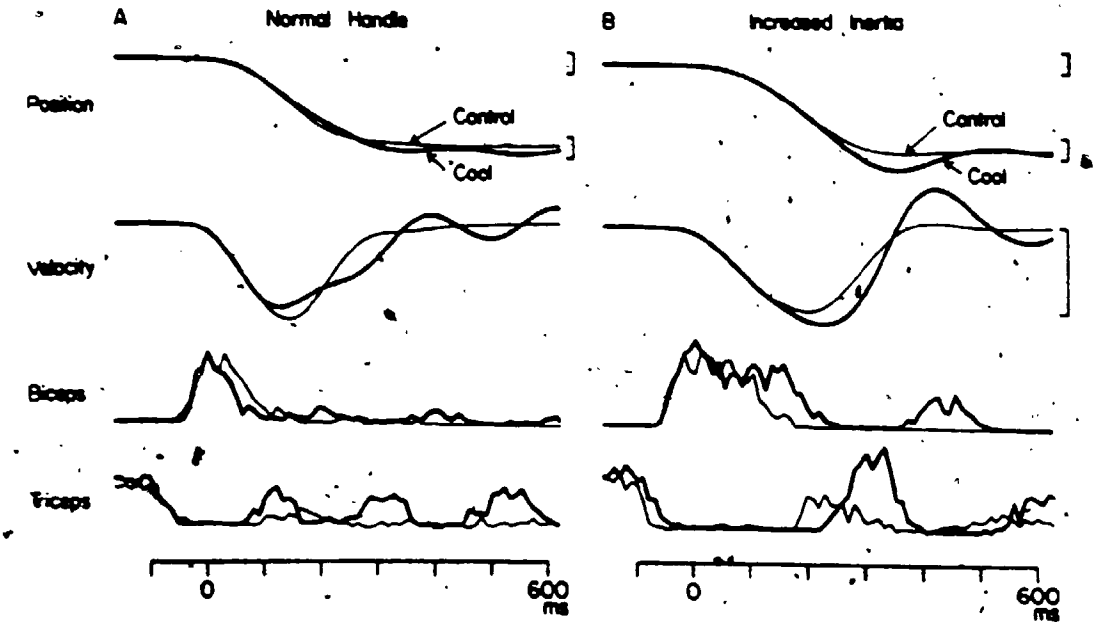

Fig. 13. Effect of increased inertial load on movements and EMG pattern. A: averages of 20 control movements (thin line) and 15 movements made during cerebellar nuclear cooling (thick line); B: averages of 20 control and 17 movements during cooling with a 98g mass added to the manipulandum. A torque of .020 Nm loaded triceps. Calibrations: position (target), 12°; velocity, 200°/s. Monkey JO.

was not considered meaningful to define as hypometric those movements in which velocity crossed zero very early in the movement because there was a continuum of velocity deflections in different movements, some of which reached zero velocity (Fig. 14A, lower movement) and some of which did not (Fig. 14A, upper 2 movements). Furthermore, these movements with oscillations eventually reached the target (arrow indicates defined end position). With end position defined this way, movements from this experiment were found on average to be normetric during cerebellar cooling but with increased standard deviation of end position compared to controls (Fig. 14B).

Movements without oscillations were on average normetric or slightly hypermetric. Figure 14D shows the average start (E-extension) and end (F-flexion) position for all the control (CON) and all the smooth movements made during cooling (COOL) from the experiment shown in Fig. 2, C and D. With targets separated by approximately 50°, movements were on average 11% larger during cooling than under control conditions and frequently overshot the aimed target (Fig. 14D). When targets were only 20° apart no hypermetria or hypometria was seen, but there was greater variability in end position (Fig. 14C).

Thus while hypometria was seldom seen, hypermetria did occur and was most often a feature of smooth, continuous movements. The prevalence of smooth and tremulous movements

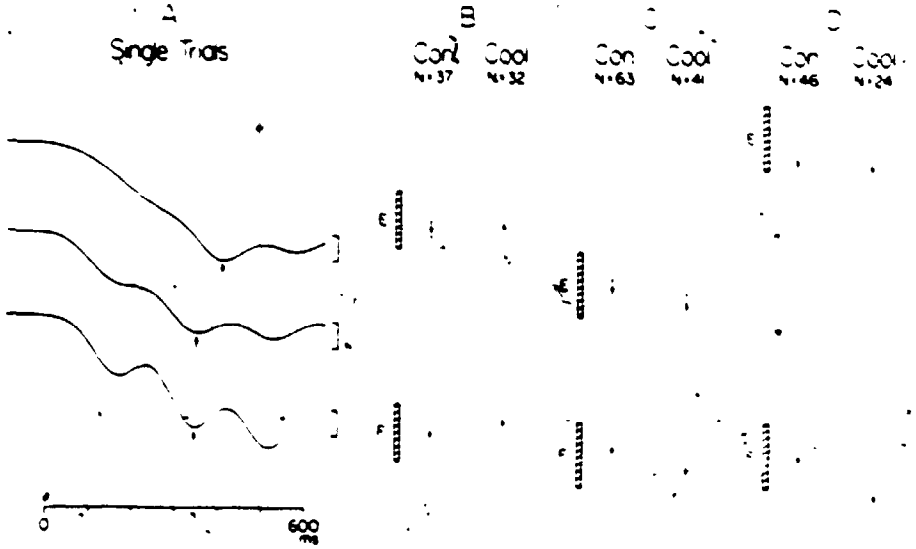

Fig. 14. Effect of cerebellar cooling on end position of elbow flexions. A: individual position records showing end position (at arrows) as defined when velocity first reached zero, 250ms after movement onset (at time 0ms). These movements were selected from Fig. 2B to demonstrate the continuum of deflections obtained during cerebellar cooling. A: position (target), 12°. B,C,D: mean + s.d. of starting (E-extension target) and end position (F-flexion target). A,B: Monkey DU; C,D: Monkey MO. CON-control movements, COOL-movements made during cerebellar nuclear cooling, N-number of movements used in average. Mean amplitude of control movements and movements during cooling, respectively, was B: 43°, 41°; C: 34°, 34°; D: 62°, 69°.

was affected by the type and strength of load applied to the manipulandum.

ii) Disorders of acceleration and deceleration: movement asymmetry

Two features of movements made by humans with lesions of the cerebellum are an increase in reaction time and a slow build-up of force (i.e. decreased acceleration) when starting movements (Holmes, 1922). While the former disorder has been well documented in animals with experimental cerebellar lesions (Lamarre and Jacks, 1978; Meyer-Lohmann et al., 1977; Spidalieri et al., 1983; Trouche and Beaubaton, 1980), the disorder in acceleration has not received as much attention. In the present study movements were made under a variety of mechanical conditions in an attempt to reveal this disorder in acceleration. When movements made during cerebellar nuclear cooling were compared with control movements of the same peak velocity, a clear decrease in peak acceleration was observed during cooling in monkeys BZ and MO; a marginal decrease in DU and MI and no decrease in JO. Even in the most extreme cases this disorder was relatively minor and was only obvious after quantitative analysis.

A marked example of this disorder is shown in Fig. 15. Figure 15A shows averaged records of six control movements and six movements made during cooling. All movements were selected from a narrow peak velocity range (310-340°/s) and

were synchronized to the time of peak velocity (at 0ms). During cooling there was a decrease in peak acceleration which was associated with EMG activity in biceps that was of smaller magnitude and longer duration than that of control movements. This disorder in EMG activity is illustrated for single trials now synchronized to movement onset (time 0ms) in Fig. 15B. The controls were from movements made over a range of peak velocities (255-340°/s) and each paired record was from a movement, made during cooling, of approximately the same peak velocity as the corresponding control. Biceps activity of controls was phasic, abrupt in onset and of a fairly constant duration. During cooling EMG activity was less abrupt in onset and was more prolonged and variable in duration than matched control records.

Previous work from this laboratory has shown that for control movements of a given amplitude there is a linear relationship between peak velocity and the magnitude of peak acceleration and between peak velocity and the integrated agonist activity (Flament, 1983; Flament et al., 1984a). These relationships were now investigated for movements made during cerebellar nuclear cooling. Figure 16 shows scatter plots of peak velocity as a function of peak acceleration and peak velocity as a function of agonist (biceps) activity integrated over a 100ms interval for all smooth movements from this experiment. The 100ms interval was chosen to give a measure of the amplitude (phasic nature) of the agonist

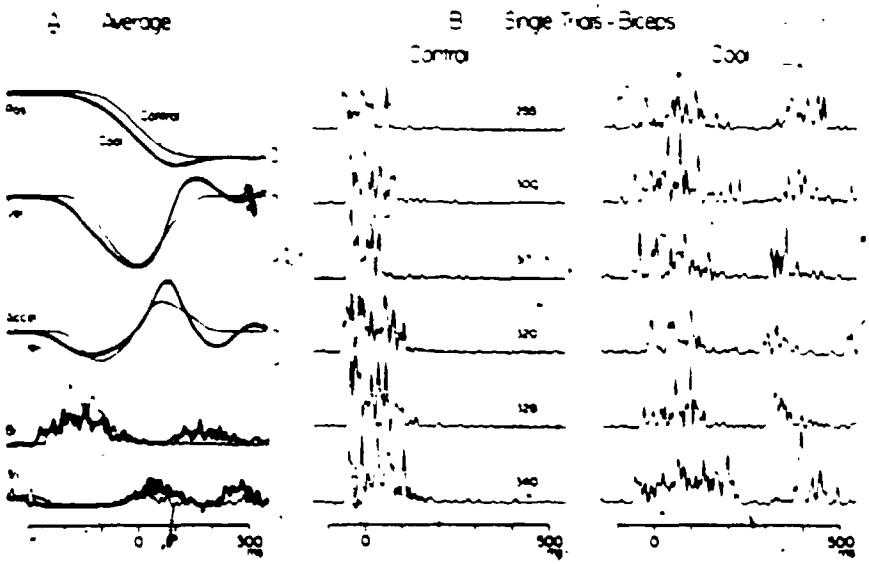

Fig. 15. Effect of cerebellar nuclear cooling on acceleration and on agonist EMG activity. A: averages of position (Pos), velocity (Vel), acceleration (Accel), biceps (Bi) and triceps (Tri) activity for 6 control (thin line) and 6 movements during cerebellar cooling (thick line) resynchronized to peak velocity (time 0ms). Movements were all of similar peak velocities. B: records of biceps (agonist) activity for single control movements made over a range of peak velocities (255-340°/s) and records from movements made during cerebellar cooling of corresponding peak velocities. Time 0ms indicates movement onset. Calibrations: position (target), 12°; velocity, 300°/s; acceleration, 3000°/s^2. Monkey BZ.

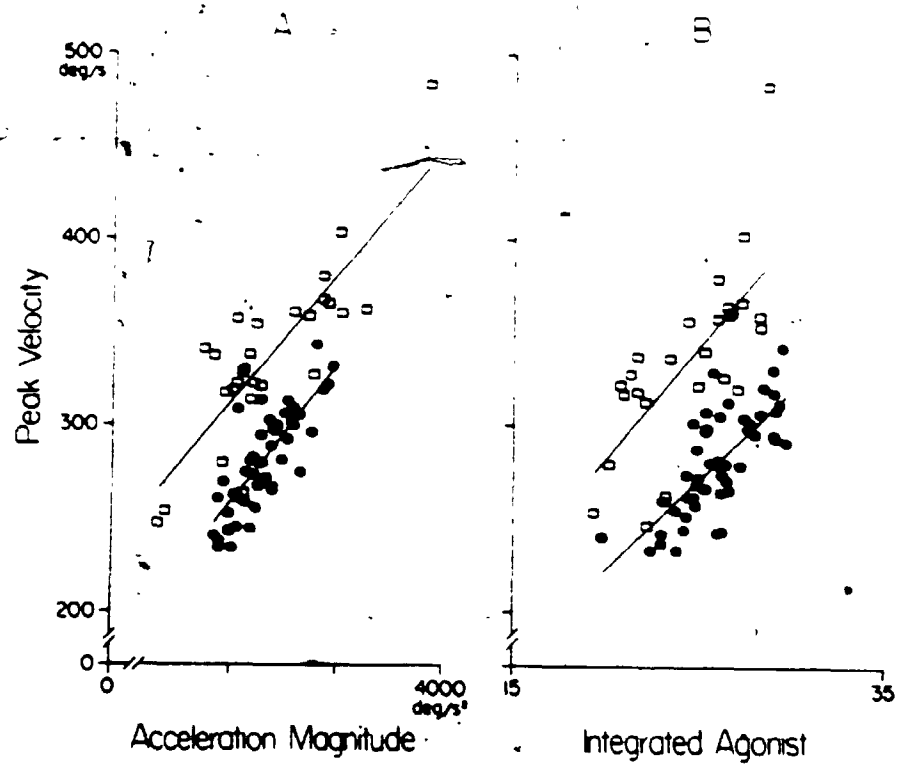

Fig. 16. Relations between peak velocity and magnitude of peak acceleration (A) and integrated agonist activity (B). Filled symbols: from movements under control conditions; open symbols: during cerebellar nuclear cooling. Agonist (biceps) activity was integrated over a 100ms interval ending at peak acceleration. Points during cerebellar cooling are from all movements without oscillations from the experiment shown in Fig. 15. Regression line equations and correlation coefficients (R) were A: y=.08x+110, R=.77 filled symbols; y=.07x+180, R=.84 open symbols, B: y=9.8x+34, R=.74 filled symbols; y=12.5x+42, R=.71 open symbols. T-test analysis showed all regression line slopes to differ significantly from zero.

burst. For control movements (filled symbols) and movements made during cerebellar cooling (open symbols) of the same peak velocity, there was a decrease in acceleration magnitude (Fig. 16A) and a decrease in integrated agonist activity (Fig. 16B) during cooling. Analysis of covariance showed these decreases to be highly significant ($P<.0001$).

A more prominent disorder observed in all monkeys was an increase in peak deceleration during cerebellar nuclear cooling. This was associated with a delay in onset of EMG activity in the antagonist muscle (triceps) (Fig. 17). Synchronizing the averages to the start of movement revealed that there was a prolongation of agonist activity and a delayed onset of antagonist activity during cooling (Fig. 17A). The delayed antagonist onset was also clear when averages were synchronized to the time of peak velocity (Fig. 17B). This delay was associated with the increased peak deceleration seen during cooling and was, therefore, considered abnormal. These findings are illustrated for all trials from this experiment in the form of scatter plots (Fig. 18). For control movements (filled symbols) and movements made during cerebellar dysfunction (open symbols) of the same peak velocity, there was a decrease in peak acceleration (Fig. 18A) and an increase in peak deceleration (Fig. 18B) during cooling. Analysis of covariance showed the latter increase to be highly significant ($P<.001$). The decrease in peak acceleration could not be tested in this

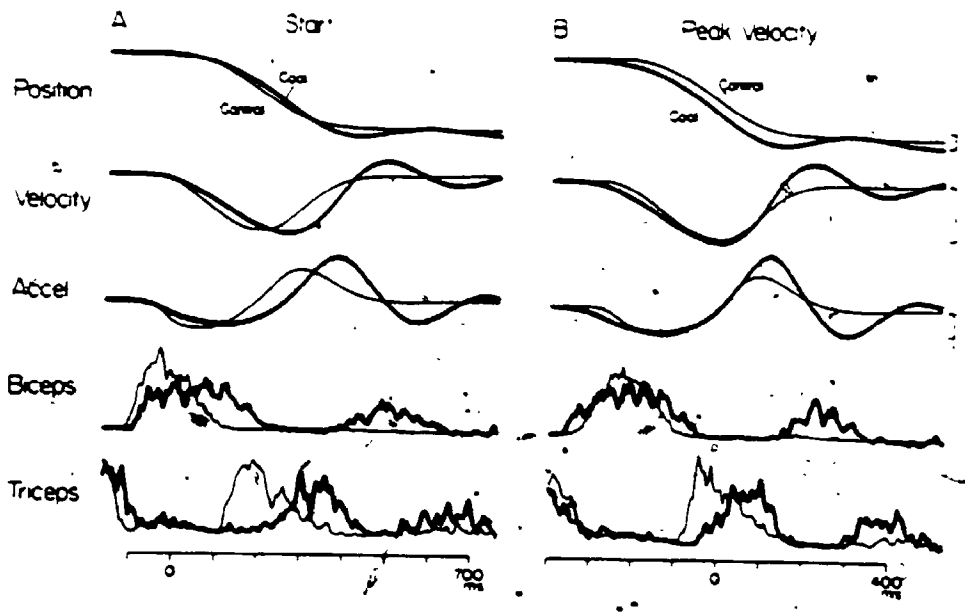

Fig. 17. Disorder of deceleration and antagonist (triceps) EMG activity during cerebellar nuclear cooling. Averages of 39 control movements (thin line) and 34 movements made during cereoellar nuclear cooling (thick line) synchronized to movement onset (A) and peak velocity (B). Calibrations: position (target), 12°; velocity, 300°/s; acceleration, 2000°/s^2. A torque of .010 Nm loaded triceps. Monkey MO.

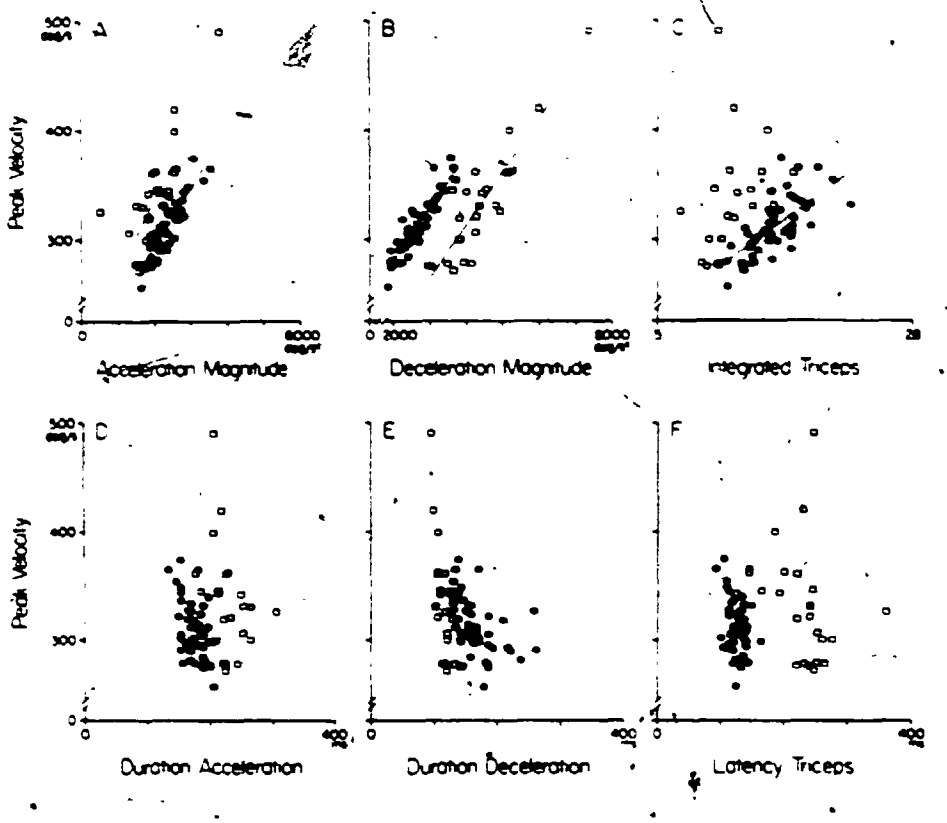

Fig. 18. Relations between peak velocity and acceleration magnitude (A), deceleration magnitude (B), integrated triceps activity (C), acceleration duration (D), deceleration duration (E) and triceps latency (F). Filled symbols: control movements; open symbols: during cerebellar nuclear cooling. Regression line equations and correlation coefficients for filled symbols and open symbols, respectively, were A: y=.055x+166, R=.84, y=.066x+170, R=.76; B: y=.05x+143, R=.89, y=.05x+88, R=.91; C: y=7.6x+100, R=.91. T-test analysis showed all regression line slopes to differ significantly from zero. Integrated triceps in arbitrary units. Triceps was integrated over a 100ms interval ending at peak deceleration. From same experiment as Fig. 17.

way because the slopes of the regression lines were statistically different. Correspondingly, acceleration duration was increased (Fig. 18D) and deceleration duration was decreased (Fig. 18E). The increase in peak deceleration during cooling was not, in this experiment, associated with larger bursts of antagonist activity (Fig. 18C). Rather, it was associated with a delay in antagonist onset (Fig. 18F). The delay may have resulted in the greater deceleration because antagonist onset now occurred when acceleration was lower and the inertial force to be overcome by antagonist activity was less. While in some experiments (e.g. Fig. 15A) antagonist activity was greater during cerebellar cooling than during control conditions, in most cases the increased deceleration was only related to the triceps delay.

It thus appears that one fundamental disorder observed in movements without oscillations during cerebellar cooling was that deceleration magnitude was greater for a given acceleration magnitude. This large deceleration was abnormal because it was associated with the overshoot of velocity that initiated the terminal tremor. Examples of the changed relationship between acceleration and deceleration are shown in Fig. 19 for the five monkeys in which this was studied. In all monkeys, for a given acceleration magnitude, the deceleration magnitude was, on average,

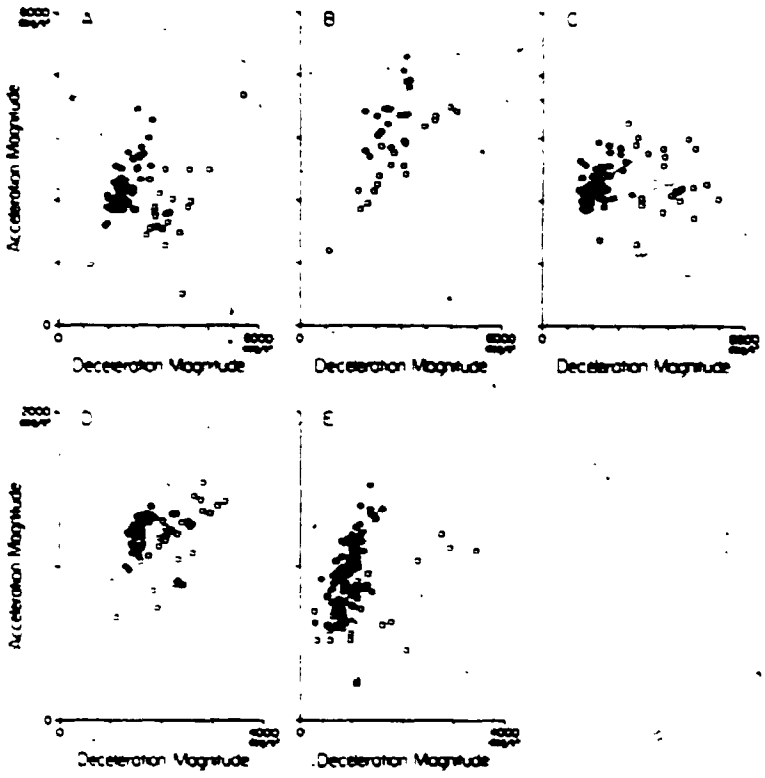

Fig. 19. Relation between peak acceleration and peak deceleration for all monkeys for movements made over a range of peak velocities. Filled symbols: control conditions; open symbols: during cerebellar nuclear cooling. Regression line equations and correlation coefficients for filled symbols were A: y=.61x+667, R=.75; B: y=.5x+611, R=.72; C: y=.26x+722, R=.45; D: y=.47x+500, R=.61; E: y=.56x+522, R=.78. T-test analysis showed all regression line slopes to differ significantly from zero. Monkeys were A: MO (same experiment as Fig. 9); B: DU; C: BZ; D: JO; E: MI. Note different scales for upper and lower graphs.

greater during cerebellar cooling (open symbols) than in the control situation (filled symbols).

iii) Cerebellar tremor occurring during movement

It has been shown that the terminal tremor following a voluntary movement and that following a limb perturbation are affected in a similar way by the mechanical state of the manipulandum held by the monkey. Similarly, tremor that occurred in voluntary movements during cerebellar cooling was also affected by the mechanical state of the handle. When a constant torque loaded triceps (ie. assisted flexions) rhythmic unstable oscillations or tremor appeared in acceleration records during the movement (Fig. 20A, before dashed line). These oscillations during the movement had similar properties to those that occurred after the movement. For example, they increased in frequency by addition of a torque loading the antagonist (Fig. 20B) and they decreased in frequency by adding mass to the handle (Fig. 20C). The change in frequency is shown quantitatively for all the movements from this experiment, under the different load conditions for the last cycle of oscillation during the movement (Fig. 20, Frequency-Move) and for the first cycle after the movement (Fig. 20, Frequency-Hold). Loading the antagonist muscle increased mean tremor frequency by .4 and .5 Hz in the move and hold phases, respectively. Adding a 72g mass to this load decreased the mean tremor frequency by [redacted] and .8 Hz in the move and hold

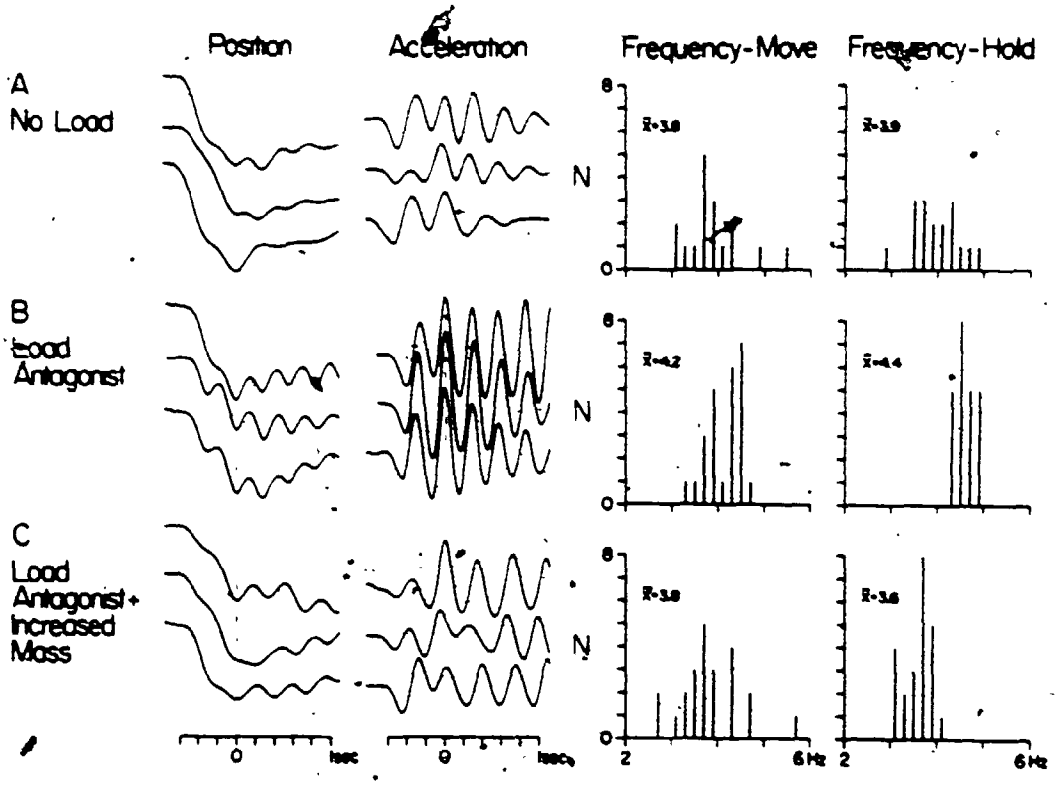

Fig. 20. Effect of mechanical load on tremor characteristics during cerebellar nuclear cooling. A: records of position and acceleration for 3 movements with no extra load added to the manipulandum. Frequency-Move: Histograms show frequency of last cycle of tremor that occurred during the movement (before dashed line) for all movements with tremor from this experiment. Frequency-Hold: frequency of first cycle of tremor after end of movement (dashed line). B: as for A but with a torque of .05 Nm that loaded the antagonist; C: a torque of .05 Nm loaded the antagonist plus a 72g mass was added to the end of the manipulandum. Values in upper left of each histogram indicate mean tremor frequency. The medians of tremor frequency are: A, 3.8 and 3.9; B, 4.3 and 4.4; C, 3.7 and 3.6 for Move and Hold, respectively. Movements synchronized to end of movement, at time 0ms, defined as the point when velocity first reached zero after the limb had entered the area of the aimed target. This definition, slightly modified from that used in Fig. 14, was necessary because movement durations were shorter due to the greater load assisting the movements in B. Monkey MI.

phases. Thus increased inertia reversed the effect of increased torque. The effects of load on tremor frequency during and after movement were found to be significant at the 5% level by the Rank Sum test (Appendix 1).

The initial decrease in velocity that initiated the oscillation during the movement was associated with earlier onset or increased magnitude of antagonist (triceps) EMG activity. Figure 21A shows superimposed averages of control movements (thin line) from monkey MO and movements made during cerebellar cooling (thick line) when a small constant force loaded the antagonist. During cerebellar nuclear cooling onset of triceps activity and corresponding inhibition of biceps activity was earlier. This resulted in the initial decrease in velocity that initiated the rhythmic oscillations seen in acceleration records of individual movements (Fig. 21B).

A characteristic of normal human elbow movements is that, for a given amplitude, there is an inverse relation between peak velocity and the latency of the antagonist EMG burst (Lestienne, 1979). A similar inverse relation was found for normal elbow flexions in the monkey when triceps onset latency (measured from movement onset) was plotted against initial velocity measured 80 ms after start of movement (Fig. 22A). Initial velocity, rather than peak velocity, was used because it was more variable in these highly trained movements and, consequently, provided a

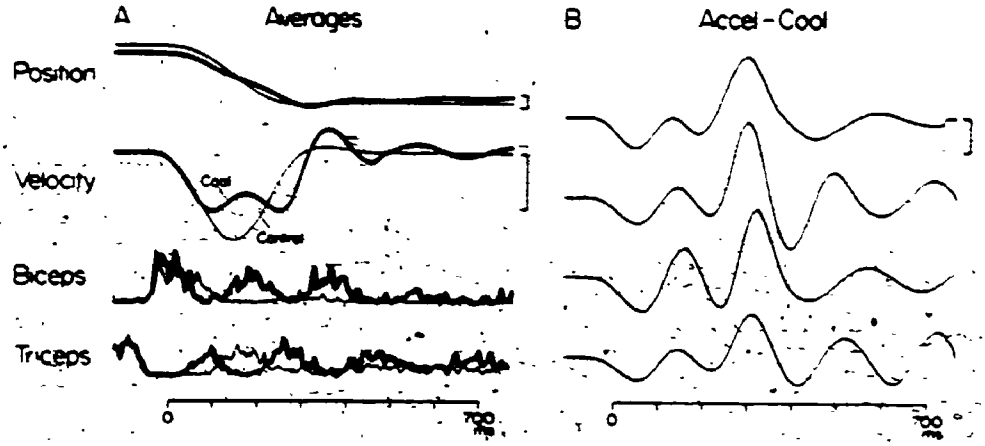

Fig. 21. Changes in the triphasic EMG pattern during cerebellar nuclear cooling. A: averages of 14 control movements (thin line) and 13 movements made during cooling (thick line) synchronized to start of movement (at time 0ms); B: acceleration (Accel) records of 4 single movements during cerebellar cooling that contributed to the average in A. A constant torque of .01 Nm loaded triceps. Calibrations: position (target), 12°; velocity, 200°/s; acceleration, 3000°/s^2. Monkey MO.

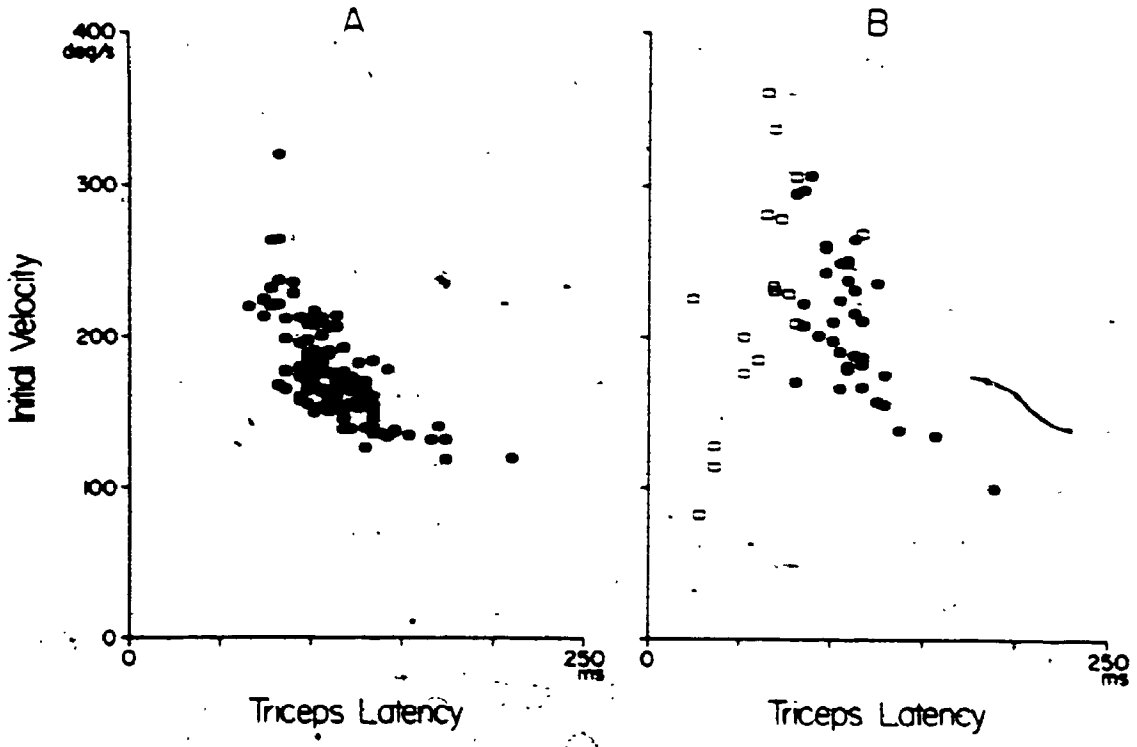

Fig. 22. Relations between initial velocity and latency of triceps EMG activity. Filled symbols: control movements; open symbols: movements during cerebellar nuclear cooling. A: from a control experiment in monkey MO; B: from same experiment as in Fig. 21. Triceps latency was measured from start of movement; initial velocity was measured 80ms after start of movement.

greater range of values over which to study triceps latency. This same relation did not hold during cerebellar dysfunction (Fig. 22B). This is illustrated for 34 control movements (filled symbols) and 16 movements with oscillations made during cooling (open symbols) from the experiment shown in Fig. 21. Figure 22B shows that during cerebellar cooling the antagonist latency was no longer inversely related to the initial velocity of the movement. Thus, during cerebellar dysfunction antagonist onset was no longer programmed accurately.

All monkeys showed abnormally short latencies of triceps onset during cerebellar nuclear cooling when a strong torque loaded triceps. The most extreme case was monkey JO, who consistently had triceps latencies of 30-50ms from movement onset during cooling (Fig. 23A). Because of the difficulty of measuring movement onset precisely, these latencies were also measured from biceps onset (Fig. 23B) and from the offset of the tonic triceps activity that preceded the movement (Fig. 23C). The earliest consistent latency from biceps onset was approximately 70ms, which is compatible with the latency measured from start of movement given an electromechanical coupling time of 40ms (Lestienne, 1979). The earliest consistent latency from triceps offset was approximately 120ms. The means of triceps latency for each of these parameters for all tremulous movements from this experiment are shown in Table 1. This table also gives

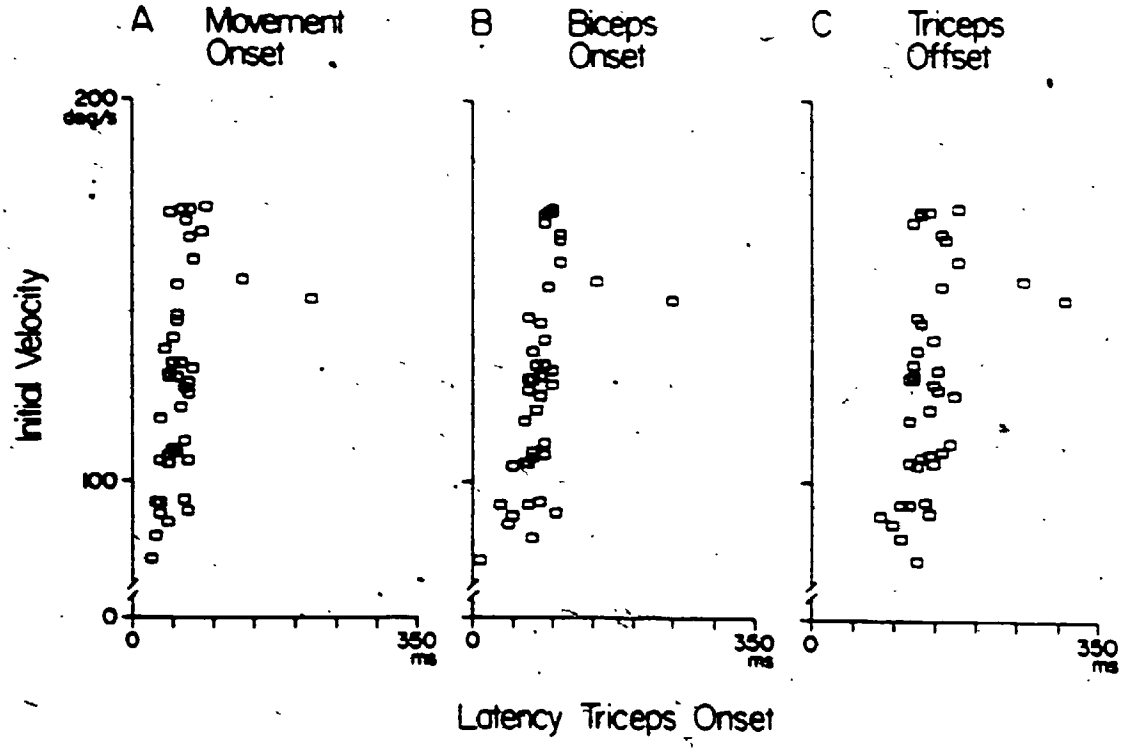

Fig. 23. Latency of triceps activity for flexions made during cerebellar nuclear cooling. A: triceps EMG latency measured from start of movement as a function of initial velocity (80ms after start of movement); B: triceps latency measured from onset of biceps activity; C: triceps latency measured from offset of tonic triceps activity preceding the movement. A torque of .02 Nm loaded triceps. Note the two points at the right of each graph are from movements without oscillations. Monkey JO.

Table 1

Latency of Triceps Onset during Cerebellar Nuclear Cooling (means and standard deviations, ms)

Monkey	JO	MO	DU	MI	BZ
Latency from Start of Movement	54 (15)	65 (21)	70 (29)	71 (19)	78 (53)
Latency from Biceps Onset	79 (21)	99 (22)	109 (31)	117 (24)	150 (60)
Latency from Triceps Offset	137 (20)	133 (23)	136 (36)	148 (23)	183 (83)
Number of Movements	38	14	31	29	20
Constant Torque Loading Triceps (Nm)	.045	.025	.035	.025	.025

equivalent latency measurements for tremulous movements from representative experiments in four other monkeys.

iv) Servo-like responses in movement

The initial decrease in velocity, or perturbation in the movement, was opposed by a second burst of EMG activity in the agonist (biceps) muscle (Fig. 21A). This biceps contraction contributed to the second increase in velocity. It can be seen from the phase-plane trajectories illustrated in Fig. 3 that this second increase in velocity returned the movement toward the trajectory it would have been on had it not been perturbed by the inappropriate burst of antagonist activity.

What was the mechanism responsible for the generation of the second agonist burst of agonist activity that returned the limb in the direction of the original trajectory? One possibility is that it was caused by a voluntary correction (Beppu et al., 1984; Dejong, 1979; Growdon et al., 1967; Holmes, 1917). This correction could have been based on visual feedback. This possibility was investigated by eliminating all visual information about manipulandum position as described in methods. In the absence of visual cues, discontinuities and tremor still occurred in movements during cerebellar cooling. In Fig. 24 are shown three representative position records and their corresponding biceps and triceps activity and phase-plane trajectories during cerebellar cooling in the absence of visual informa-

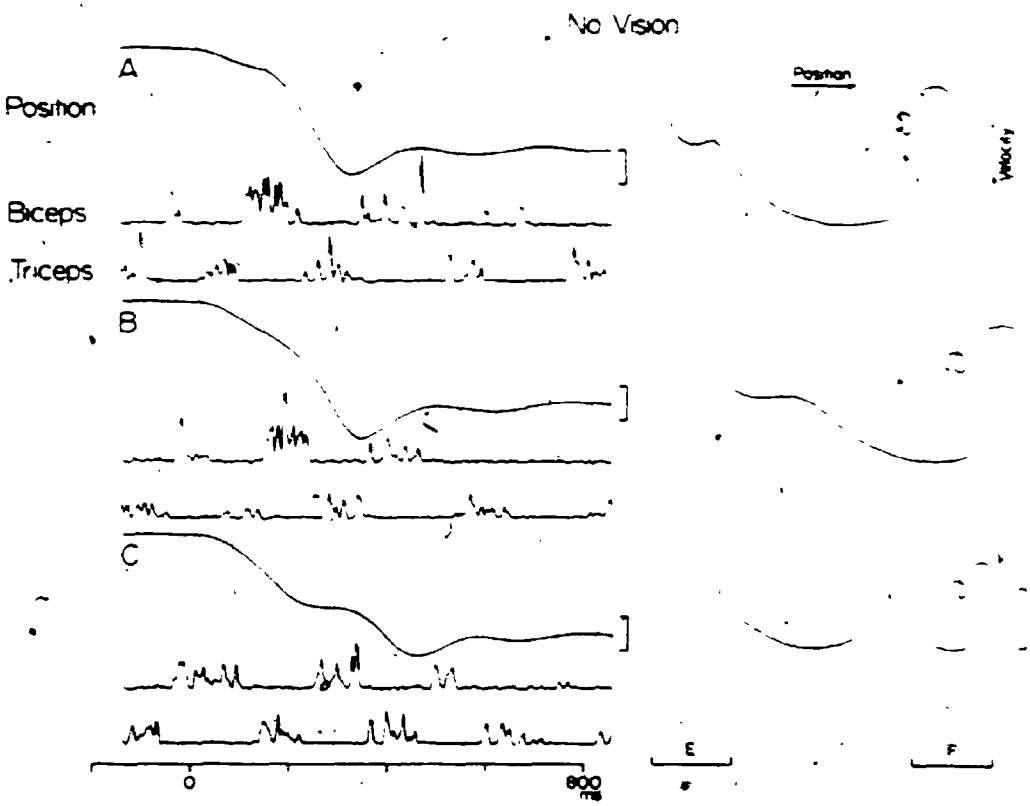

Fig. 24. Return towards correct trajectory in the absence of visual feedback. Three flexions made during cerebellar cooling. Left side: position, biceps and triceps activity; right side: phase plane trajectories for the movements on the left. Calibrations: position (targets), 14°; velocity, 200°/s. Time 0ms is at movement onset. E--extension target; F--flexion target. Monkey MO.

tion regarding handle position. In all movements, following the initial abnormal decrease in velocity, movement toward the target continued. The continuation of the movement was associated with a second agonist EMG burst. Thus the generation of the second agonist burst and the return toward the correct trajectory did not involve a correction based on vision.

Another possible origin of the second agonist burst was that the phasic agonist burst of activity that normally initiated control movements was replaced by a prolonged step of activity during cerebellar dysfunction. In this case the second agonist burst could simply be the continuation of the step following a period of inhibition produced by reciprocal inhibition from the abnormal antagonist activity. However, the second agonist burst was often larger in amplitude than the first (Fig. 24; Fig. 25; A and B, record 3), so this cannot be the only explanation.

From examination of individual records it appeared that the size of the second agonist burst was proportional to the magnitude by which velocity was deflected (perturbed) from the expected velocity (Fig. 25). This relation appeared to hold for movements in which the velocity deflection occurred at about the same time in the movement. The expected velocity (dashed line) was obtained from a control movement that had the same initial velocity measured 80ms after movement onset. This value was chosen because the abnormal

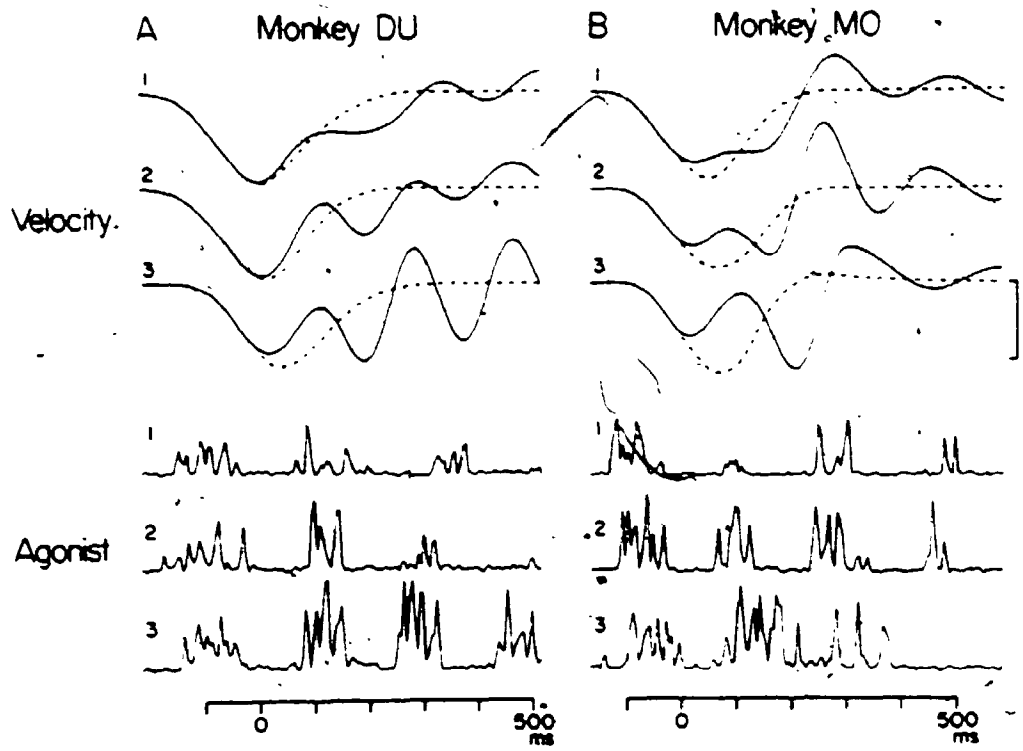

Fig. 25. Size of second agonist (biceps) burst for 3 movements during cerebellar nuclear cooling with different sized velocity deflections. Solid lines: velocities of movements during cerebellar nuclear cooling; dashed lines: velocities of control movements with the same initial velocity (80ms after movement onset). A: Monkey DU, no load on manipulandum; B: Monkey MO, same experiment as in Fig. 21. Records synchronized to point at which velocities diverged (time 0ms). Calibration: velocity, 200°/s.

decrease in velocity during cerebellar dysfunction occurred after this time. Figure 25 shows this relation between velocity deflection and second agonist burst for three representative movements from experiments in two monkeys. In both monkeys, although there was considerable variability from trial to trial, small velocity deflections were associated with small second agonist bursts (movement 1) and large deflections with large second agonist bursts (movement 3). The second agonist burst had a latency of 50-80ms from the onset of the abnormal velocity deflection (Fig. 25, time 0ms).

Since the deflection in movement was followed by a return toward the correct trajectory (e.g. Fig. 24) and that the second agonist burst was proportional to the velocity deflection (Fig. 25) it was reasoned that the second agonist burst might also be proportional to the trajectory deflection. Consequently, the relation between velocity deflection and second agonist burst magnitude was studied quantitatively by determining the maximum deflection in velocity from the expected trajectory as measured from phase-plane trajectory records. This is indicated by an arrow in the lower record of Fig. 26B. Figure 26 shows phase-plane plots of the same movements illustrated in Fig. 25. The amplitude of this velocity deflection was plotted as a function of the second agonist EMG burst magnitude (Fig. 27). Although scatter of points was

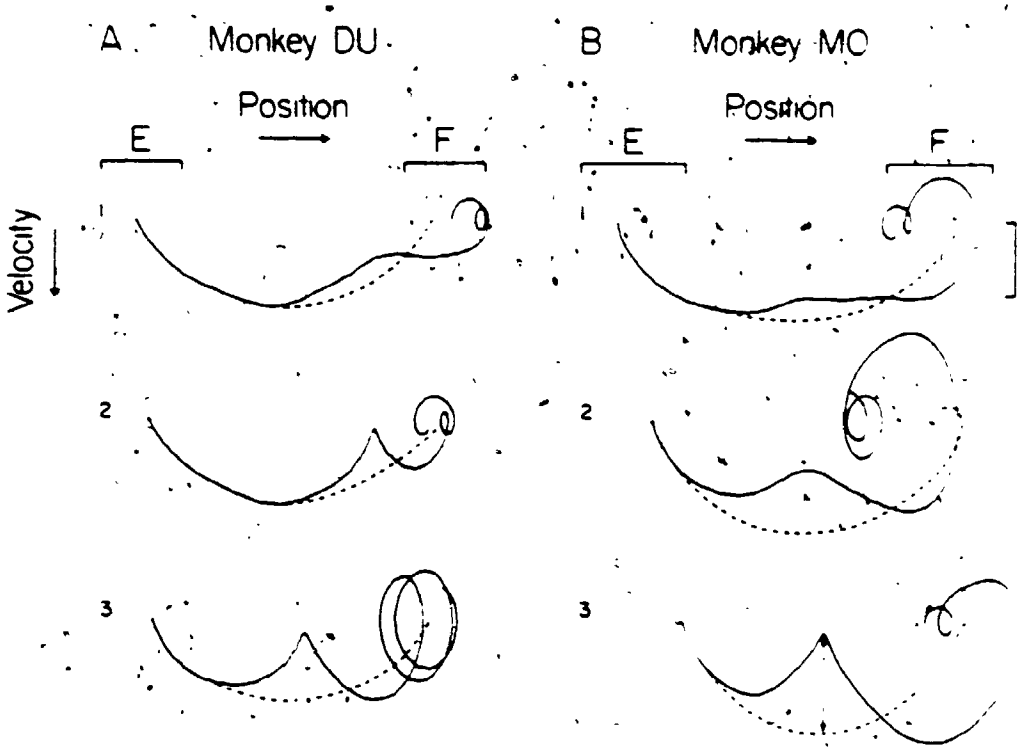

Fig. 26. Phase planes for flexions made during cerebellar nuclear cooling (solid lines) and matched controls (dashed line). Plots are for movements shown in Fig. 24. Calibrations: A: targets, 10°; B: targets, 12°. E--extension target; F--flexion target.

considerable, a positive relation was found for all the movements from the experiment illustrated in Figs. 25 and 26 (Fig. 27, A and B) and from an experiment in a third monkey (Fig. 27C). Although the agonist responses were plotted against the magnitude of the velocity deflection, one cannot rule out the possibility that they may also be related to other kinematic parameters.

Electromyographic responses to perturbations applied during a voluntary movement in normal humans have been shown to return the limb onto the control (expected) trajectory (Cooke, 1980a,b). However, in the present experiments the return to trajectory was not very accurate during cerebellar cooling: the return was variable, sometimes undershooting and sometimes overshooting the correct trajectory. When a constant torque loaded the antagonist muscle (ie. assisted flexions) the second increase in velocity often overshot the expected trajectory (Fig. 26). This overshoot could have been the result of inappropriately large or prolonged agonist activity and a correspondingly delayed onset of antagonist activity.

To investigate these possibilities it was necessary to know what the normal responses to an equivalent perturbation would be in a normal animal. Because our well-trained monkeys did not show oscillations in normal movements, external perturbations were applied by means of the torque motor. Perturbations were applied that opposed flexion

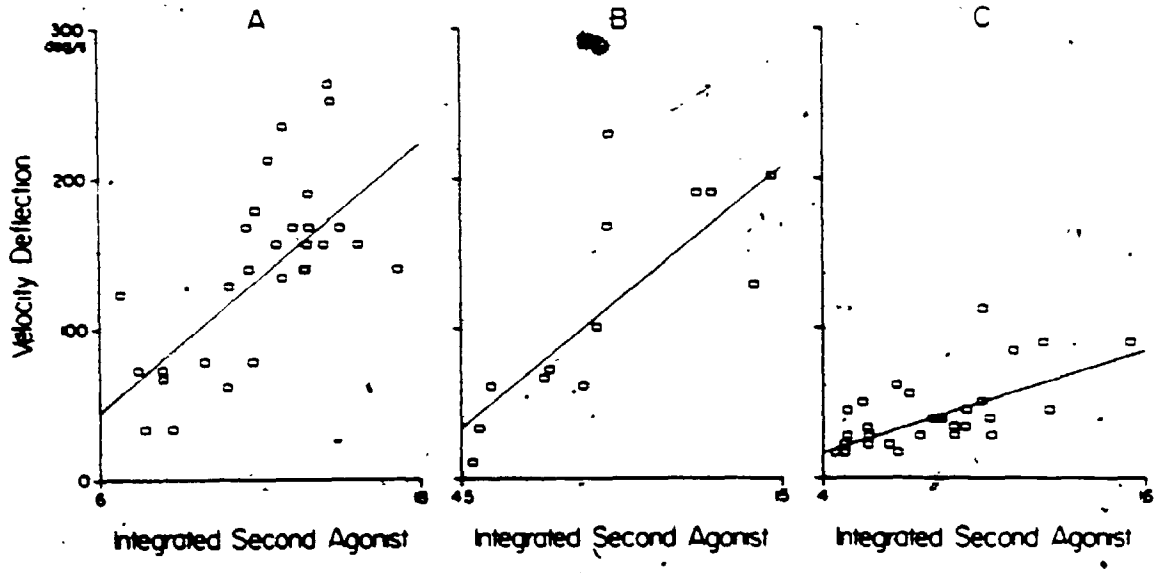

Fig. 27. Relation between integrated agonist activity and magnitude of velocity deflection for flexions made during cerebellar nuclear cooling. A: all movements with oscillations from the same experiment as Fig. 25A (monkey DU), Regression line equation: y=15.0x-6, correlation coefficient (R) = .68; B:. all movements from same experiment as Fig. 25B (monkey MO), y=17.1x-5, R = .78; C: movements from an experiment in monkey JO, y=5.9x+4, R = .64. T-test analysis showed all regression line slopes to differ significantly from zero. Second agonist burst was integrated over a fixed interval and is in arbitrary units; magnitude of velocity deflection was determined from phase plane trajectories as illustrated in Fig. 26B, record 3.

movements under control conditions and during cerebellar nuclear cooling. The perturbations were applied early in the movement, before the abnormal antagonist activity that occurred during cerebellar cooling could manifest itself.

One result of these experiments was that the magnitude of the agonist response to the perturbation was proportional to the magnitude of the velocity deflection produced by the perturbation, both under control conditions and during cooling. Figure 28 illustrates this result in two monkeys for superimposed averages of responses to three magnitudes of perturbations (duration of perturbation: 120ms, A and B; 60ms, C and D). For both control and nuclear cooling conditions small velocity deflections were associated with small biceps EMG responses and large deflections with large biceps responses. The proportional increase in agonist response occurred even when this muscle was not stretched (ie. velocity did not return to zero).

The other result was that during cerebellar cooling the agonist response was prolonged and the antagonist was delayed. For example, whereas the agonist response in the control situation ended 200ms after torque pulse onset (Fig. 28A, dashed line), during cooling it was extended to approximately 260ms (Fig. 28B). A similar prolongation occurred in a second monkey (Fig. 28, C and D) and antagonist activity was delayed during cerebellar cooling. No marked or consistent difference in the magnitude of the

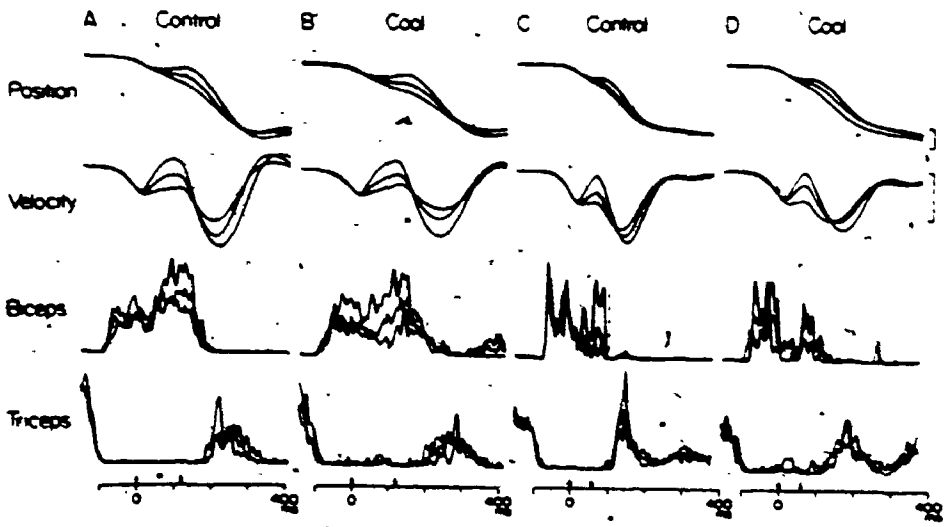

Fig. 28. Average movement and EMG responses to torque pulses injected into elbow flexions. A,B: Monkey MI; C,D: Monkey DU. Each trace is the average of 15 trials. Three different magnitudes of torque pulses were applied under control conditions (A,C) and during cerebellar nuclear cooling (B,D). Duration of torque pulses were 120ms (A,B) and 60ms (C,D). Averages were synchronized to torque pulse onset (upwards arrow, time 0ms). Dashed line: 200ms after torque pulse onset (A,B); 100ms after torque pulse onset (C,D). A constant torque of .05Nm loaded triceps.

agonist response for a given velocity deflection was observed between control and cool conditions in these experiments.

IV. Summary

Reversible cooling lesions of the cerebellar dentate and interposed nuclei produced an intention tremor following movement. Oscillations were also produced in isometric, goal-directed contractions and, under some conditions, during voluntary isotonic movements. Other movements, with some mechanical states, were dysmetric.

Cerebellar intention tremor following movements had the same characteristics as the tremor that followed limb perturbations. The tremor frequency and amplitude were affected by torque, viscous and inertial loads in a similar way regardless of whether the tremor followed a perturbation or a voluntary movement. The oscillations that occurred in isometric contractions were, however, irregular in shape and sometimes occurred at a lower frequency than isotonic tremor. These results suggest that tremor is influenced by proprioceptive feedback, but they do not rule out the possibility of a central component in its production.

Dysmetria did occur in some experiments during cerebellar cooling. Hypometria was not a prominent feature of the movements made in these experiments, but hypermetria did occur, particularly when the inertial load to be moved was

increased. In spite of an initial overshoot of the target, the region of the aimed target was eventually reached. Thus movement accuracy was not severely impaired by cerebellar cooling.

Smooth movements made during cerebellar dysfunction, of which hypermetric movements were a subset, were often markedly asymmetric. This disorder was characterized by a prolonged duration of acceleration which was associated with prolonged, and less phasic, agonist muscle activity. For any given acceleration magnitude the magnitude of the deceleration phase of the movement was greater during cooling than under control conditions. The greater deceleration appeared to be related to a delayed antagonist muscle activity.

Cerebellar nuclear cooling also resulted in tremor occurring during a voluntary movement, especially when torques were applied which loaded the antagonist muscle. The first deflection from the normal trajectory was produced by an early, and often large, burst of antagonist muscle activity. The antagonist activity was followed by a second burst of agonist activity which tended to return the limb to the desired trajectory. The return was inaccurate, however, suggesting that the servo-like mechanism responsible for this burst was disordered by cerebellar dysfunction.

DISCUSSION

The overall problem for cerebellar motor neurophysiology is to determine how the cerebellum controls movements. One can approach an answer to this problem by first posing some simpler questions. One such question is what are the kinematic and EMG characteristics of the disorders that occur in simple elbow movements? An understanding of these characteristics and of how they might change under different conditions can provide some insight into cerebellar function.

Cerebellar tremor, for example, could, in theory, occur as a result of voluntary corrections for an initial error, from activity in a supraspinal oscillator or from alternating stretch reflexes in antagonist muscle pairs. These mechanisms are not mutually exclusive and, furthermore, may be influenced by the mechanical resonant properties of the limb. A study of tremor under conditions of different proprioceptive drive may provide evidence in favour of one or more of these possible mechanisms.

Similarly, a study of the EMG and kinematic disorders that are associated with dysmetria may point to the role played by an intact cerebellum in producing movements of the correct amplitude.

The use of an animal model in these experiments has allowed the present results to serve as a framework for further experiments on cerebellar function that investigated

the activity of motor cortex single neurons. Such experiments are not normally possible in human subjects.

I. Cerebellar Intention Tremor

i) Static tremor

Lesions of the cerebellum in man are known to produce an intention tremor when voluntary effort is made to hold a limb steady at a given position and when attempting to perform accurate goal-directed movements (Holmes, 1917, 1922, 1939; Thomas, 1897). This disorder also occurs in monkeys that have had experimental lesions of the deep cerebellar nuclei (Aring and Fulton, 1936; Botterell and Fulton, 1938a; Carrea and Mettler, 1947; Goldberger and Growdon, 1973; Vilis and Hore, 1977). Holmes (1922) was of the opinion that not all tremors that occur in cerebellar dysfunction are of the same nature. Consequently the tremor that occurred following voluntary movements and following torque perturbations could have been produced by different mechanisms. Similarly, the tremor that occurred during the movement (kinetic tremor) could differ from that which occurred following the movement (static tremor). The finding in the present study that terminal tremor that occurred following voluntary movements and when attempting to hold steady in target following a torque perturbation was affected in a similar way by a number of mechanical condi-

tions, indicates that the mechanism responsible for the tremor is likely to be the same in both situations.

Holmes (1922) suggested that the cause of cerebellar tremor was a series of voluntary corrections for errors detected in the movement. This mechanism was also given as being responsible for the tremor seen in experimental animals by Growdon and colleagues (1967). Error recognition could be based on either visual or kinesthetic information or both. It has also been suggested that corrections are based on continuous central monitoring of motor discharges (Liu and Chambers, 1971).

Theoretically, visually guided corrections could account for the terminal oscillations seen in cerebellar dysfunction. The finding of Liu and Chambers (1971) and of the present study (Fig. 7) that tremor was still present and, indeed, unaltered by exclusion of the visual display of limb position indicates that visual feedback is not essential in sustaining tremor. It has, however, recently been reported that in the absence of visual display of joint position or target position, intention tremor is reduced or abolished in cerebellar patients (Sanes and Mauritz, 1986). The difference in result between these findings and those of this study on monkeys may be due to differences in lesion sites or to species differences. It is impossible, at this stage, to distinguish between these possibilities.

A role for proprioceptive feedback in cerebellar tremor was suggested by Denny-Brown's (1966) observation that a deafferented limb in cerebellectomized monkey failed to show ataxia and tremor. However, the movements in this study were not goal-directed, which may be part of the reason for the absence of tremor. Deafferented monkeys with cerebellar lesions did tremor when making movements that were purposeful and goal-directed (Liu and Chambers, 1971), indicating that if corrections for a positional error are responsible for tremor these corrections cannot solely be dependent on proprioceptive information. Since the tremor was also unaffected by eliminating vision, the suggestion was made that corrections were based on central monitoring of motor discharges. Such a mechanism may constitute a central oscillator.

Rhythmic activity in a central oscillator, together with peripheral reflex influences, was suggested as a possible mechanism of cerebellar tremor by Stein and Lee (1981). Their suggestion was made because evidence indicates that rhythmic activity in supraspinal structures can entrain tremor of the limbs. For example, harmaline-induced rhythmic activity of the inferior olive produced tremor of the limb of the same frequency as the oscillating olivary discharge (DeMontigny and Lamarre, 1973).

One property that distinguishes reflex and mechanical oscillations from those purely generated centrally is the

former's sensitivity to resetting by an external stimulus (Stein and Lee, 1981). Tremor of pure central origin, if sensory inputs do not affect the tremor generator, is not reset by external stimuli. Tremor generated by reflex pathways alone should completely reset with adequate reflex stimulation. Therefore the finding of Vilis and Hore (1977) that tremor could be reset by applying torque pulses to a limb is strong evidence for a peripheral involvement in experimental cerebellar tremor.

Further evidence for a peripheral role in the generation of cerebellar tremor comes from the finding that tremor characteristics (i.e. frequency and amplitude) were affected by the mechanical load acting on the limb. A torque load increased the velocity of stretch of the muscle in each cycle of tremor and increased tremor frequency (Fig. 4 and also Fig. 20). Adding mass to the manipulandum (i.e. increasing inertial load) decreased the velocity of muscle stretch in each cycle of tremor and the tremor frequency (Figs. 4,6,20). If cerebellar tremor was driven entirely by a central oscillator the amplitude of the tremor might be affected by these loads, but not the frequency.

The finding that the nature of cerebellar tremor was changed when proprioceptive feedback due to stretch was presumably reduced in the isometric tracking task lends further support to the notion that tremor results, at least in part, from reflex activity in proprioceptive loops. The

regular, 3-4 Hz tremor normally observed following voluntary movements was replaced by an irregular oscillation in the isometric task which, in the flexion directed contractions, was of lower frequency (Fig. 10). Intention tremor in cerebellar patients has also been found to be reduced, or even abolished, in isometric contractions of the wrist musculature (Sanes and Mauritz, 1986).

The absence of muscle stretch in the isometric task does not, however, necessarily mean that all proprioceptive input is eliminated. Spindles may be very sensitive to small tension fluctuations that occur in human isometric contractions (Vallbo, 1974) and Golgi tendon organs, whose discharge rate increases with increasing tension in a contracting muscle, send weak connections to motoneurons of antagonist muscles (Watt et al., 1976). Thus a potential for some proprioceptive activity to influence isometric contractions still exists in the isometric task.

A possible cause of cerebellar tremor is that it results from disordered activity in proprioceptive feedback loops through motor cortex (Goldberger and Growdon, 1973; Meyer-Lohmann et al., 1975; Murphy et al., 1975; Vilis and Hore, 1980). Discharge of some motor cortex neurons in monkeys during dentate cooling was oscillatory and at the same frequency as the limb tremor (Meyer-Lohmann et al., 1975). The units lead acceleration by about 60ms, suggesting that they were driving one direction of the limb

oscillations. Unit activity also changed in parallel with movement parameters in movements perturbed by loading or unloading torque pulses, during dentate cooling.

In monkeys trained to return the arm to a stationary target following torque pulse perturbations, cooling of the dentate and interposed nuclei also caused some neurons in motor cortex to discharge in rhythm with the intention tremor (Vilis and Hore, 1980). The firing of some of these neurons, during cerebellar nuclear cooling, followed stretch of the muscle to which they were related and could, therefore, be part of a trans-cortical stretch reflex contributing to the tremor.

An increase in the gain of supraspinal reflex loops could, in theory, result in tremor (Stein and Oguztoreli, 1978). This mechanism has been suggested to be responsible for the postural tremor seen in standing patients suffering from late cerebellar atrophy (Mauritz et al., 1981).

An increase in supraspinal loop time (i.e. increased phase lag) could also result in tremor (Stein and Oguztoreli, 1976; Vilis and Hore, 1977). Vilis and Hore (1980) proposed that such a mechanism was responsible for the tremor observed following limb perturbations: they suggested that during cerebellar cooling the second cortical component of the response to a limb perturbation (predictive component of Evarts and Tanji, 1976) was lost, causing EMG responses that were normally phase-advanced to be delayed as

they were now driven only by spinal and trans-cortical stretch reflexes. In the absence of phase-advanced antagonist EMG activity overshoot of the target occurred, producing greater stretch of the antagonist muscle and thus initiating a series of stretch reflexes in agonist and antagonist muscles. As the present results showed that the cerebellar tremor that follows goal-directed movements had the same characteristics as the tremor after limb perturbations, it is suggested that the former could also be caused, at least in part, by the loss of an appropriate programmed (predictive) mechanism and occurs as a consequence of alternating stretch reflexes (spinal and supraspinal) in the moving muscles.

Thus the tremor that occurs following cerebellar dysfunction probably results from a basic central instability (which may act as an oscillator) because tremor can still occur in a deafferented limb. Superimposed on this mechanism is a strong influence from peripheral feedback which may be responsible for the rhythmic, sinusoidal nature of intention tremor and for the sensitivity and responsiveness of the tremor to the prevailing mechanical conditions. This scheme is in agreement with the hypothesis of Stein and Lee (1981) that cerebellar tremor results from activity in supraspinal oscillators which can be influenced by peripheral factors.

ii) Kinetic tremor

One of the more obvious disorders associated with cerebellar lesions is that movements become jerky, discontinuous or tremulous. Holmes (1922, 1939) found that these discontinuities which occurred in simple movements about a single joint, were more obvious in slower movements and sometimes developed into what appeared to be a tremor, which he termed kinetic tremor because it occurs during active movement. The present result on simple elbow movements in monkeys agree with those observations. The tremulous nature of the disorder becomes particularly evident in acceleration records (Figs. 20, 21).

A number of theories of cerebellar tremor have been proposed and were described above, in reference to static tremor. Briefly, the three major arguments are 1) that tremor results from a series of voluntary corrections, 2) that tremor is caused by activity in a central oscillator and 3) that tremor results from disordered reflex loops. One theory of the latter argument is that tremor is produced by alternating activity of transcortical reflexes in antagonist muscle pairs (Vilis and Hore, 1980, 1986). Four lines of evidence support this theory: 1) the tremor can be resynchronized by an external perturbation (Vilis and Hore, 1977), 2) the tremor is influenced by the mechanical state of the limb (Chase et al., 1965; Flament et al., 1984b; Hewer et al., 1972; Vilis and Hore, 1977), 3) EMG activity

of a muscle follows stretch of that muscle during tremor (Flament et al., 1984b) and 4) motor cortex neurons fire at the tremor frequency (Meyer-Lohmann et al., 1975; Vilis and Hore, 1980). The latter point also supports the first two arguments.

Of these theories, which best explains the kinetic tremor observed in the present experiments? Clearly, corrections for an initial error recognized visually cannot explain the results because the tremor in movements was not altered by elimination of visual feedback (Fig. 24). Similarly, ataxic movements in cerebellar patients were not affected by closing the eyes during the performance of a movement (Holmes, 1917). Much evidence does, however, suggest an influence of proprioceptive feedback. The tremor frequency was influenced by the mechanical condition applied to the limb and changed in the same way as did the cerebellar tremor following the movement (Fig. 20) and the tremor that occured after an external perturbation (Flament et al., 1984b; Vilis and Hore, 1977). The tremor that occurred during and after the movement did not have identical frequencies and magnitudes, but this is to be expected as the movement command may influence the tremor during the movement. The differences do not, therefore, mean that the tremors are produced by different mechanisms. The relatively fixed latency of antagonist onset (Fig. 23 and Table 1) during cerebellar nuclear cooling when a torque loaded the

antagonist muscle is further evidence for a proprioceptive role in the generation of tremor. This could have resulted from abnormal reflex activity triggered by stretch of the antagonist muscle shortly after movement initiation.

One finding of the present study was that the perturbation (deflection) that occurred in the movement during cerebellar dysfunction, and was responsible for producing tremor during the movement, was followed by a burst of activity in the agonist muscle. This agonist burst had a latency of 50-80 ms from the onset of the velocity deflection (Fig. 25) and its magnitude was proportional to the magnitude of the deflection. This occurred whether the perturbation was self-generated (Figs. 25, 26) or generated externally by the torque motor (Fig. 28). Furthermore, the agonist response was not dependent on vision (Fig. 24) and it could not have resulted exclusively from continuation of an original long, step-like, agonist command (Fig. 25). These pieces of evidence indicate that the agonist burst had the properties of a servo-like response.

The importance of the role played by servo-assistance in voluntary movements is open to question. For servo-assistance to act effectively during a movement the spindles in the contracting muscle should not fall silent as the muscle shortens (Matthews, 1981). However, spindle unloading appears to occur when the muscle shortens at a rate greater than 20% of the muscle's resting length per second

(Prochazka et al., 1979; Prochazka and Wand, 1981). However, even if agonist spindles become unloaded, information that could correct deviations in trajectory could come from antagonist muscle spindles (Capaday and Cooke, 1981). The effectiveness of servo-assistance was questioned further when it was found that long-latency reflexes were inadequate to control limb or head position (Allum, 1975; Bizzi et al., 1978; Gottlieb and Agarwal, 1980a; Kwan et al., 1979).

However, the study of single motor unit responses to perturbations has provided evidence in support of the servo-assistance theory. Tatton and Bawa (1979) found that the motor units discharged in a graded fashion along with the initial velocity of the displacement and thus had servo-like responses. Many precentral neurons also have discharge properties compatible with a servo-assistance function (Cheney and Fetz, 1984; Conrad et al., 1974, 1975; Evarts, 1973; Evarts and Tanji, 1976; Sakai and Preston, 1978; Vilis and Hore, 1980). Marsden and colleagues have provided extensive evidence of a role for servo-assistance in human subjects making thumb movements (Marsden et al., 1972, 1976a, 1976b, 1983). The servo actions were effective in maintaining accuracy for small perturbations, but not for large perturbations where the long-latency reflex may saturate (Marsden et al., 1983b). Similarly, for brief perturbations applied during elbow movements, servo-assistance may have returned the limb to its intended trajectory

(Cooke, 1979, 1980a, 1980b). These results support the suggestion that a servo-like mechanism continues to operate during cerebellar dysfunction to compensate for deflections that occur during the movement. However, this servo, during cerebellar dysfunction, does not appear to operate properly.

The servo-like responses that occurred during cerebellar dysfunction may have been disordered because they did not return the limb accurately to the intended trajectory (Fig. 26). Furthermore, the response to an externally applied perturbation during a voluntary movement was prolonged (Fig. 28). This is similar to the finding for EMG responses to limb perturbations applied when holding steady in target during cerebellar cooling (Flament et al., 1984b; Hore and Vilis, 1984a). These responses were prolonged in the agonist and delayed in the antagonist.

How might servo-assistance operate and what role would the cerebellum play in this operation? Phillips (1969) originally proposed that any mismatch between actual and intended movements is computed by the cerebellum and a corrective signal is generated to reduce the mismatch to zero. If this was the only pathway, servo-assistance would be abolished by cerebellar lesion. The partial lesions produced in this study did not abolish servo-assistance. Another suggestion is that for servo-assistance to occur, fusimotor drive would represent an internal copy of the intended movement (Matthews, 1981). Unlike the alpha-

motoneuronal activity, it would be independent of load. Granit et al. (1955) suggested that the computation of the appropriate gamma activity involves the cerebellum. This is consistent with the disordered fusimotor drive seen to occur following lesions of the cerebellum (Gilman 1968, 1969a, 1969b, 1969c). Thus in this model cerebellar dysfunction would impair the ability to match the alpha:gamma ratio to the prevailing load condition. At slow contraction speeds the incorrect alpha:gamma ratio could result in abnormal agonist activity. At faster speeds, during which agonist muscle spindles are unloaded, improper fusimotor drive to the antagonist muscle could also result in inappropriate activity levels. For example, during cerebellar dysfunction a torque loading the antagonist muscle may inappropriately increase gamma drive to that muscle and thus increase stretch-evoked activity, leading to an abnormally early or large burst of activity in the antagonist muscle. This burst of activity could produce an abnormal decrease in velocity, unloading the antagonist spindles and causing a reflex agonist excitation. This may explain why kinetic tremor was more prevalent when a load opposed the antagonist muscle.

Thus kinetic tremor, like static tremor, appears to result from inappropriate activity in reflex loops but may also be dependent on the activity of a central oscillator. Kinetic tremor is further influenced by the operation of a

servo-like mechanism which, during cerebellar dysfunction, is unable to accurately correct for deflections from the normal trajectory and may further destabilize the limb.

II. Dysmetria

Patients with lesions of the cerebellum, when moving a limb to a target, sometimes show a marked dysmetria. The movement may first overshoot or undershoot the target before achieving the aimed target (Dow and Moruzzi, 1958; Holmes, 1917, 1939). A similar disorder was observed in the present experiments: during cerebellar dysfunction monkeys made movements that were either tremulous or slightly hypermetric but that finally reached the region of the aimed target (Figs. 2, 13, 14).

Considerable evidence indicates that the execution of fast and accurate normal movements is, at least in part, centrally programmed. These normal movements are associated with the classic triphasic pattern of EMG activity in agonist and antagonist muscles (Wachholder and Altenburger, 1926). Evidence for central programming is indicated by the finding that, in large and small movements of the same peak velocity, the smaller movements have the larger antagonist activity (Flament et al., 1984a; Marsden et al., 1983a). This would not occur if movements were braked solely by simple velocity-dependent stretch reflexes. It has been suggested, however, that braking may be the result of an

acceleration-dependent stretch reflex (Ghez and Martin, 1982). While this mechanism is in accord with the data on small and large movements of the same peak velocity (i.e. small movements have higher peak accelerations and larger antagonist bursts than large movements of the same peak velocity), it is at best a secondary mechanism because the antagonist burst in the triphasic pattern can occur in movements even when peripheral feedback is blocked by ischemia (Jennings and Sanes, 1982; Sanes and Jennings, 1984) or when peripheral feedback is absent as a result of disease (Forget and Lamarre, 1983; Hallett et al., 1975; Rothwell et al., 1982). Furthermore, it must be emphasized that the acceleration-dependent mechanism was postulated from results obtained in a paradigm where the limb is set in motion by the release of a force which opposes isometric muscle contraction. The mechanisms involved in braking such movements would be expected to differ markedly from those in the present control paradigm. The difference is highlighted by the finding that in the release paradigm rhizotomy does cause loss of phasic antagonist activity (Terzuolo et al., 1974).

The fact that cerebellar dysfunction produces disorders in the triphasic pattern (e.g. Figs. 13,15,17) suggests that the cerebellum may, in some way, be involved in the selection, triggering or generation of these fast movements (Hallett et al., 1975b; Lamarre et al., 1978; Lamarre and

Jacks, 1978; Massion and Sasaki, 1979; Meyer-Lohmann et al., 1977; Wiesendanger et al., 1979). A role for the cerebellum in the triggering of motor patterns is consistent with the finding that the time taken to initiate a movement (reaction time) is increased during cerebellar dysfunction (Holmes, 1917, 1922, 1939; Lamarre and Jacks, 1978; Meyer-Lohmann et al., 1977; Trouche and Beaubaton, 1980).

In theory, dysmetria could result from the triggering of an otherwise normal motor program but one which specifies a movement larger or smaller than the required movement. If this occurred the dysmetric movement generated during cerebellar dysfunction would be expected to have the same characteristics as a movement of the same amplitude and velocity made under control conditions, since both would result from the same motor program. The present results show that this does not occur. Movements of all amplitudes made under control conditions had nearly symmetric velocity profiles as previously reported (Flament et al., 1984a). However, during cerebellar nuclear cooling, movements without oscillations were asymmetric, having longer accelerator phases and shorter deceleratory phases (Fig. 15A). Asymmetry during cerebellar cooling has previously been reported for monkey arm movements (Brooks et al., 1973b). Some asymmetry does occur in control movements but the velocity profile could be skewed in either direction: acceleration could be shorter or longer than deceleration

(Flament et al., 1982). The asymmetry seen in normal movements was not as marked as that during cerebellar cooling and the movements were not hypermetric and were terminated without any overshoot of velocity. It thus appears unlikely that dysmetria results from the triggering of a normal motor program that specifies an inappropriate movement amplitude. Instead dysmetria may result from agonist and antagonist muscle activity which is inappropriate in size and timing.

III. Electromyographic Disorder Associated with Dysmetric Movements During Cerebellar Cooling

The EMG disorder associated with the asymmetry in the present experiments was prolongation of agonist activity and delay in onset of antagonist activity. Prolonged agonist activity has been reported for fast elbow flexions (Hallett et al., 1975b) and for thumb movements (Marsden et al., 1977) in cerebellar patients. Monkeys making rapid alternating flexion and extension movements between two fixed stops also showed prolonged agonist activity (Conrad and Brooks, 1974). Thus prolonged agonist and delayed antagonist activity would appear to be a fundamental disorder of cerebellar dysfunction in smooth movements, as previously suggested (Hallett et al., 1975b). In the present experiments there was also a decreased magnitude of the agonist burst.

The nature of the cerebellar contribution to the agonist burst is unclear. One possibility is that the cerebellum contributes to the generation of the phasic component of agonist-related motor cortex discharge. (Meyer-Lohmann et al., 1977). Another possibility is that the cerebellum adjusts the gain of reflex pathways (acceleratory motor loops) that can reinforce motor commands (MacKay and Murphy, 1979b). According to this model a decrease in fusimotor input, as produced by a cerebellar lesion, would reduce the reinforcing influence of spindle feedback on alpha-motoneuron discharge. This could result in a decreased magnitude of muscle activity and a consequent decrease in acceleration magnitude. The present results do not distinguish between these two possibilities, but the previously reported findings that onset of motor cortex neurons was delayed by 50-150 ms during cerebellar lesions (Lamarre et al., 1978; Meyer-Lohmann et al., 1977) appears to favour the former possibility.

Cerebellar dysfunction not only affected the agonist muscle but it also produced a disorder in movement braking. In smooth movements this was the result of a delayed onset of antagonist activity that led to large decelerations that were abnormal because they initiated the terminal tremor (Fig. 13B, 17). With a torque loading the antagonist muscle, movements made during cerebellar cooling were tremulous and antagonist activity was larger and came

earlier in the movement than in control movements (Fig. 13A). These findings are difficult to reconcile with the theory of Holmes (1917, 1922) who proposed that hypermetria was due to decreased antagonist muscle tone. Electromyographic studies of cerebellar patients showed that antagonist activity was prolonged in dysmetric movements (Hallett et al., 1975b). Thus the theory that decreased fusimotor drive to the antagonist is the cause of dysmetria (Gilman, 1969b, 1972; Van Der Meulen and Gilman, 1965) is not supported by human studies nor by those of the present study.

The suggestion that dysmetria results from abnormal antagonist activity of central origin draws support from the finding that deafferented monkeys with cerebellar lesions are strongly ataxic (Liu and Chambers, 1971). Similarly, Gilman et al. (1976) found a worsening of motor performance after cerebellar ablation in deafferented monkeys. However, it is not clear whether ataxia due to cerebellar lesion still had the same characteristics as that following a cerebellar lesion plus deafferentation. Furthermore, although disordered central commands may be generated during cerebellar dysfunction it is hard to explain why this abnormal command would produce shorter latencies of triceps onset than controls when a torque loaded the antagonist (Fig. 21) or why the command would change with added mass such that the early antagonist onset was always attenuated or abolished (Fig. 13).

The results decribed in the present study may be explained by a scheme based on studies of antagonist EMG activity following limb perturbations (Hore and Vilis, 1980, 1985, 1986). In this model the cerebellum receives from motor cortex an efference copy of the agonist command. Together with the prevailing motor set (Hore and Vilis, 1984) this agonist command is used to generate an antagonist command via motor cortex. During cerebellar dysfunction this cortico-cerebello-cortical pathway is blocked and antagonist activity is driven from spinal and transcortical stretch reflexes. Thus when a torque loads the antagonist muscle (i.e. assists the agonist) the agonist command is relatively small and stretch reflexes override agonist activity early in the movement. When mass is added to the manipulandum the agonist command is increased and stretch reflexes are attenuated through reciprocal inhibition. When the agonist command is terminated, delayed antagonist activity results from activity generated by stretch of the antagonist muscle.

No one scheme satisfactorily explains all observations made. In all likelihood dysmetria and the associated asymmetric movement trajectory seen during cerebellar dysfunction are the result of disorders in the size and timing of central commands and of disorders in stretch reflexes.

IV. Conclusions

This study addressed three major disorders associated with cerebellar dysfunction: 1) terminal tremor following a voluntary, goal-directed movement, 2) tremor that occurs during such a movement and 3) dysmetria of smooth, continuous movements.

It was found that tremor following a voluntary movement had the same characteristics as the tremor following a limb perturbation. This suggests that these static tremors could result from the same mechanism. The mechanism does not appear to involve voluntary corrections for a position error based on visual or proprioceptive feedback. Instead, the findings that tremor persists in an isometric task and in deafferented animals points to the involvement of a central oscillator. Proprioceptive feedback does, however, have a strong influence on the characteristics of the tremor. It is suggested that the loss of a mechanism that normally prevents the occurrence of instabilities, and alternating stretch reflexes in the agonist and antagonist muscles, are partly responsible for the tremor. The possibility that the tremor was produced by rhythmic activity in a central oscillator modifiable by peripheral feedback can not be ruled out. The mechanical properties of the limb may also affect the tremor.

The kinetic tremor that occurred during voluntary movements was affected by mechanical loads in the same way

as the static tremor that followed movements, also suggesting a possible common origin. The tremor was initiated by an early burst of activity in the antagonist muscle. This activity may have been produced as a result of inappropriate activity in proprioceptive feedback loops. The deflection produced by this burst was followed by a second agonist burst which had the properties of a servo-like response. This response did not, however, accurately return the limb to the correct trajectory and may, instead, have contributed further instability. It is concluded, therefore, that kinetic tremor, like static tremor, results, at least in part, from disordered activity in reflex loops.

Dysmetria was found to occur mostly in smooth movements. It is unlikely to have resulted from the triggering of an otherwise normal motor program that specified a movement of inappropriate amplitude because whereas normal movements were nearly symmetric, dysmetric movements made during cerebellar nuclear cooling were markedly asymmetric. They had peak accelerations that were of smaller magnitude and longer duration than control movements of the same amplitude and peak velocity, and decelerations that were of larger magnitude and shorter duration. A fundamental disorder of these asymmetric movements was that the agonist burst duration was prolonged and the antagonist burst was delayed, relative to control values.

While this study could not conclusively distinguish between the central or peripheral origin of the cerebellar disorders described, it does provide evidence for a strong peripheral role in producing tremor and other abnormalities of limb trajectory. It also suggests a number of new experiments that might better distinguish between these two possible mechanisms. Clearly, a rigorously controlled study of tremor characteristics in the complete absence of proprioceptive afferent feedback would be invaluable. Equally pertinent would be a direct knowledge of spindle activity, permitting comparison for equivalent movements made during cerebellar cooling and with no cooling. A study of single unit activity in motor cortex could also provide insight into the nature of the cerebellar disorders described in the present study. For example, changes in discharge frequency of stretch-driven units during cerebellar cooling would implicate trans-cortical reflex loops in the disorders whereas oscillatory command neuron activity that phase-leads EMG activity could indicate a central origin for tremor.

APPENDIX 1

The Rank Sum Test

Application

The Rank Sum test is a statistical test which, being non-parametric, can be used on populations that are not necessarily normally distributed. This test can be used to check whether two populations have the same median (Huntsberger and Billingsley, 1977). The null hypothesis is that the populations do not differ.

Calculation

The rank sum is calculated in four steps:

1. The two populations are combined into one but each observation from one population is flagged so as to identify its origin.
2. The observations are ranked in order of increasing size.
3. The rank order of each observation is recorded (along with its flag, if it has one).
4. The average of the rank order of the flagged observations is calculated and subtracted from the average of the rank order of the unflagged samples. The difference is called V.

Before determining whether the two populations are different the standard deviation (s.d.) of V must also be known.

$$s.d._V = ((n_1+n_2)^2(n_1+n_2+1)/12n_1n_2)^{.5}$$

where n_1 = number of observations in population 1

where n_2 = number of observations in population 2

The value of the standardized statistic $V/s.d._V$ is then calculated. If this value is less than 1.645 (the upper 5% point for the normal curve) the data favour the null hypothesis; if greater than 1.645 the null hypothesis is rejected.

Results

The test was applied to the following pairs of populations:

Frequency-Move

No Load vs. Load Antagonist	$V/s.d._V = 14.21$
Load Antagonist vs. Load Antagonist + Increased Mass	$V/s.d._V = 14.74$

Frequency-Hold

No Load vs. Load Antagonist	$V/s.d._V = 21.23$
Load Antagonist vs. Load Antagonist + Increased Mass	$V/s.d._V = 39.38$

Conclusion

Since all values of $V/s.d._V$ exceeded 1.645 the null hypothesis was rejected in all cases, confirming the obvious differences in frequency seen in acceleration records under different mechanical loads (Fig. 20).

REFERENCES

Abend, W., Bizzi, E., Morasso, P. (1982) Human arm trajectory formation. Brain 105:331-348.

Allen, G.I., Tsukahara, N. (1974) Cerebrocerebellar communication systems. Physiol. Rev. 54:957-1006.

Allum, J.H.J. (1975) Responses to load disturbances in human shoulder muscles: the hypothesis that one component is a pulse test information signal. Exp. Brain Res. 22:307-326.

Angel, R.W. (1974) Electromyography during voluntary movement: The two-burst pattern. Electroencephal. Clin. Neurophysiol. 36:493-498.

Angel, R.W., Eppler, W., Iannone, A. (1965) Silent period produced by unloading of muscle during voluntary contraction. J. Physiol. (London) 180:864-870.

Appenteng, K., Prochazka, A., Proske, U., Wand, U. (1982) Fusimotor stimulation can maintain cat soleus Ia firing even during very rapid muscle shortening. J. Physiol. (London) 326:51P-52P.

Atkeson, C.G., Hollerbach, J.M. (1985) Kinematic features of unrestrained vertical arm movements. J. Neurosci. 5:2318-2330.

Baker, J.R. (1970) Principles of Biological Microtechniques. A study of fixation and dyeing. Methuen and Co., Ltd., England.

Basmajian, J.V., Clifford, H.C., McLeod, W.D., Nunnally, H.N. (1975) Computers in Electromyography. Butterworths, London, Boston.

Bava, A., Grimm, R.J. (1978) Activity of fastigial nucleus neurons during wrist movements in primates. Neurosci. Lett. Suppl. 1:141.

Bava, A., Grimm, R.J., Rushmer, D.S. (1983) Fastigial unit activity during voluntary movement in primates. Brain Res. 288:371-374.

Beaubaton, D., Trouche, E., Amato, G. (1980) Dentate and pallidal control of a goal-directed movement in monkeys. In: Tutorial in Motor Behavior; G.E. Stelmach and J. Requin, editors. North-Holland Publishing Co., Amsterdam, pp. 315-327.

Beggs, W.D.A., Howarth, C.I. (1972a) The movement of the hand towards a target. Quart. J. Exp. Psychol. 24:448-453.

Beggs, W.D.A., Howarth, C.I. (1972b) The accuracy of aiming at a target--some further evidence for intermittent control. Acta Psychologica 36:171-177.

Benita, M., Conde, H. (1972) Effects of local cooling upon conduction and synaptic transmission. Brain Res. 36:133-151.

Beppu, H., Suda, M., Tanaka, R. (1984) Analysis of cerebellar motor disorders by visually guided elbow tracking movement. Brain 107:787-809.

Berardelli, A., Rothwell J.C., Day, B.L., Kachi, T., Marsden, C.D. (1984) Duration of the first agonist EMG burst in ballistic arm movements. Brain Res. 304:183-187.

Bizzi, E., Dev., P., Morasso, P., Polit, A. (1978) Effect of load disturbances during centrally initiated movements. J. Neurophysiol. 41:542-556.

Bizzi, E., Kalil, R.E., Tagliasio, V. (1971) Eye-head coordination in monkeys: Evidence for centrally patterned organization. Science 173:452-454.

Bizzi, E., Polit, A., Morasso, P. (1976) Mechanisms underlying achievement of final head position. J. Neurophysiol. 39:435-444.

Bloedel, J.R., Courville, J. (1981) Cerebellar afferent systems. In: Handbook of Physiology--The Nervous System, Vol. II; V.B. Brooks, editor. American Physiological Society, Bethesda, MD., pp. 735-829.

Botterell, E.H., Fulton, J.F. (1938a) Functional localization in the cerebellum of primates. I. Unilateral section of the peduncles. J. Comp. Neurol. 69:31-46.

Botterell, E.H., Fulton, J.F. (1938b) Functional localization in the cerebellum of primates. II. Lesions of the midline structures (vermis) and deep nuclei. J. Comp. Neurol. 69:47-61.

Botterell, E.H., Fulton, J.F. (1938c) Functional localization in the cerebellum of primates. III. Lesions of hemispheres (neocerebellum). J. Comp. Neurol. 69:63-87.

Bremer, F. (1935) Le cervelet. In: Traite de physiologie normale et pathologique, Vol. 10, pt. 1-2; G.H. Roger and L. Binet, editors. Masson, Paris.

Brooks, V.B. (1979a) Control of intended limb movements by the lateral and intermediate cerebellum. In: Integration in the Nervous System; H. Asanuma and V.J. Wilson, editors. Igaku-Shoin, Tokyo-New York.

Brooks, V.B. (1979b) Motor programs revisited. In: Posture and Movement; R.E. Talbot and D.R. Humphrey, editors. Raven Press, New York, pp. 13-49.

Brooks, V.B. (1983a) Motor Control. How posture and movements are governed. J. Am. Phys. Ther. Assn. 63:664-673.

Brooks, V.B (1983b) Study of brain function by local, reversible cooling. Rev. Physiol. Biochem. Pharmacol. 95:1-109.

Brooks, V.B. (1984a) The cerebellum and adaptive tuning of movements. Exp. Brain Res. Suppl. 9:179-183.

Brooks, V.B. (1984b) Cerebellar function in motor control. Human Neurobiol. 2:251-260.

Brooks, V.B., Cooke, J.D., Thomas, J.S. (1973a) The continuity of movements. In: Control of Posture and Locomotion; R.B. Stein, K.G. Pearson, R.S. Smith and J.B. Redford, editors. Plenum Press: New York - London, pp. 257-272.

Brooks, V.B., Kennedy, P.R., Ross, H.-G. (1983) Movement programming depends on understanding of behavioral requirements. Physiol. Behav. 31:561-563.

Brooks, V.B., Kozlovskaya, I.B., Atkin, A., Horvath, F.E., Uno, M. (1973b) Effects of cooling dentate nucleus on tracking-task performance in monkeys. J. Neurophysiol. 36: 974-995.

Brooks, V.B., Thach, W.T. (1981) Cerebellar control of posture and movement. In: Handbook of Physiology -- The Nervous System, Vol. II; V.B. Brooks, editor. Am. Physiol. Soc., Bethesda, MD., pp. 877-946.

Brown, S.H., Cooke, J.D. (1981) Amplitude- and instruction-dependent modulation of movement-related electromyogram activity in humans. J. Physiol. (London) 316:97-107.

Brown, S.H., Cooke, J.D. (1984) Initial agonist burst duration depends on movement amplitude. Exp. Brain Res. 55:523-527.

Burke, D., Eklund, G. (1977) Muscle spindle activity in man during standing. Acta Physiol. Scand. 100:187-199.

Burke, D., Hagbarth, K.-E., Lofstedt, L. (1978a) Muscle spindle responses in man to changes in load during accurate position-maintenance. J. Physiol. (London) 276:159-164.

Burke, D., Hagbarth, K.-E., Lofstedt, L. (1978b) Muscle spindle activity in man during shortening and lengthening contractions. J. Physiol. (London) 277:131-142.

Burke, D., McKeon, B., Skuse, N.F., Westerman, R.A. (1980) Anticipation and fusimotor activity in preparation for a voluntary contraction. J. Physiol. (London) 306:337-348.

Capaday, C., Cooke, J.D. (1981) The effects of muscle vibration on the attainment of intended final position during voluntary human arm movements. Exp. Brain Res. 42: 228-230.

Carrea, R.M.E., Mettler, F.A. (1947) Physiologic consequences following extensive removals of the cerebellar cortex and deep cerebellar nuclei and effect of secondary cerebral ablations in the primate. J. Comp. Neurol. 87:169-288.

Chambers, W.W., Konorski, J., Lui, C.N., Yu, J., Anderson, R. (1972) The effects of cerebellar lesions upon skilled movements and instrumental conditioned reflexes. Acta Neurobiol. Exp. (Warsz) 32:721-732.

Chapman, C.E., Spidaliery, G., Lamarre, Y. (1986) Activity of dentate neurons during arm movements triggered by visual, auditory, and somesthetic stimuli in the monkey. J. Neurophysiol. 55:203-226.

Chase, R.A., Cullen, J.K., Sullivan, S.A., Ommaya, A.K. (1965) Modification of intention tremor in man. Nature (London) 206:485-587.

Cheney, P.D., Fetz, E.E. (1984) Corticomotoneuronal cells contribute to long-latency stretch reflexes in the rhesus monkey. J. Physiol (London) 349:249-272.

Cody, F.W.J., Harrison, L.M., Taylor, A. (1975) Analysis of activity of muscle spindles of the jaw closing muscles during normal movements in the cat. J. Physiol. (London) 253:565-582.

Conrad, B., Benecke, R., Goehmann, M. (1983) Premovement silent period in fast movement initiation. Exp. Brain Res. 51:310-313.

Conrad, B., Brooks, V.B. (1974) Effects of dentate cooling on rapid alternating arm movements. J. Neurophysiol. 37: 792-804.

Conrad, B., Matsunami, K., Meyer-Lohmann, J., Wiesendanger, M., Brooks, V.B. (1974) Cortical load compensation during voluntary elbow movements. Brain Res. 71:507-514.

Conrad, B., Meyer-Lohmann, J., Matsunami, K., Brooks, V.B. (1975) Precentral unit activity following torque pulse injections into elbow movements. Brain Res. 94:219-236.

Cooke, J.D. (1979) Dependence of human arm movements on limb mechanical properties. Brain Res. 165:366-369.

Cooke, J.D. (1980a) The role of stretch reflexes during active movements. Brain Res. 181:493-497.

Cooke, J.D. (1980b) The organization of simple, skilled movements. In: Tutorials in Motor Behavior; A. Stelmach and J. Requin, editors. North-Holland, Amsterdam, pp. 199-212.

Dejong, R.N. (1979) The Neurologic Examination (4th Edition). Harper and Row, New York.

DeMontigny, C., Lamarre, Y. (1973) Rhythmic activity induced by harmaline in the olivo-cerebello-bulbar system of the cat. Brain Res. 53:81-85.

Denny-Brown, D. (1966) The cerebral control of movement. Charles C. Thomas:Springfield.

Desmedt, J.E., Godaux, E. (1978) Ballistic skilled movements: load compensation and patterning of the motor commands. In: Cerebral Motor Control in Man: Long Loop Mechanisms; J.E. Desmedt, editor. (Prog. Clin. Neurophysiol., Vol. 4) Karger, Basel, pp. 21-55.

Desmedt, J.E., Godaux, E. (1979) Voluntary motor commands in human ballistic movements. Annals Neurol. 5:415-421.

Diener, H.C., Dichgans, J., Bacher, M., Guschlbauer, B. (1984) Characteristic alterations of long-loop "reflexes" in patients with Friedreich's disease and late atrophy of the cerebellar anterior lobe. J. Neurol. Neurosurg. Psychiat. 47:679-685.

Dietz, V., Noth, J. (1978) Pre-innervation and stretch responses of triceps brachii in man falling with and without visual control. Brain Res. 142:576-579.

Dietz, V., Schmidtbleicher, D., Noth, J. (1979) Neuronal mechanisms of humans locomotion. J. Neurophysiol. 42:1212-1222.

Dow, R.S., Moruzzi, G. (1958) The Physiology and Patnology of the Cerebellum. Univ. Minnesota Press, Mineappolis.

Dufresne, J.R., Gurfinkel, V.S., Soechting, J.F., Terzuolo, C.A. (1978) Response to transient disturbances during intentional forearm flexion in man. Brain Res. 150:103-115.

Dufresne, J.R., Soechting, J.F., Terzuolo, C.A. (1980) Modulation of the myotatic reflex gain in man during intentional movements. Brain Res. 193:67-84.

Dusser de Barenne, J.G. (1922) Sur l'excitation artificielle du cervelet. Arch. Neerl. Physiol. 7:112-115.

Elble, R.J., Schiever, M.H., Thach, W.T. (1984) Activity of muscle spindles, motor cortex and cerebellar nuclei during action tremor. Brain Res. 323:330-334.

Eldred, E., Granit, R., Merton, P.A. (1953a) Observations on "intact", de-afferented and de-efferented muscle spindles. Acta Physiol. Scand. 29:83-85.

Eldred, E., Granit, R., Merton, P.A. (1953b) Supraspinal control of the muscle spindle and its significance. J. Physiol. (London) 122:498-523.

Emonet-Denand, F., Jami, L., Laporte, Y. (1975) Skeleto-fusimotor axons in hind-limb muscles of the cat. J. Physiol. (London) 249:153-166.

Emonet-Denand, F., Laporte, Y. (1983) Observations on the effects on spindle primary endings of the stimulation at low frequency of dynamic beta-axons. Brain Res. 258:101-104.

Evarts, E.V. (1973) Motor cortex reflexes associated with learned movement. Science 179:501-503.

Evarts, E.V. (1974) Sensorimotor cortex activity associated with movements triggered by visual as compared to somesthetic inputs. In: The Neurosciences. Third Study Program; F.O. Schmitt and F.G. Warden, editors. MIT Press, Cambridge, pp. 327-337.

Evarts, E.V., Tanji, J. (1976) Reflex and intended responses in motor cortex pyramidal tract neurons of monkey. J. Neurophysiol. 39:1069-1080.

Evarts, E.V., Thach, W.T. (1969) Motor mechanisms of the CNS: Cerebro-cerebellar interelations. Ann. Rev. Physiol. 31:451-498.

Ferrier, D., Turner, W.A. (1894) A record of experiments illustrative of the symptomatology and degenerations following lesions of the cerebellum and its peduncles and related structures in monkeys. Phil. Tr. Roy. Soc (B) 185: 719-778.

Flament, D. (1983) Processes responsible for the initiation and termination of fast and accurate goal-directed elbow movements in the monkey. M.Sc. Thesis, University of Western Ontario.

Flament, D., Hore, J. (1986) Movement and electromyographic disorders associated with cerebellar dysmetria. J. Neurophysiol. 55:1221-1233.

Flament, D., Hore, J., Vilis, T. (1982) Variability of fast and accurate arm flexion movements of monkeys. Soc. Neurosci. Abst. 8:731.

Flament, D., Hore, J., Vilis, T. (1983) Braking of fast and accurate elbow flexions of monkeys is programmed to maintain symmetry of acceleration and deceleration. Soc. Neurosci. Abst. 9:1031.

Flament, D., Hore, J., Vilis, T. (1984a) Braking of fast and accurate elbow flexions in the monkey. J. Physiol. (London) 349:195-203.

Flament, D., Vilis, T., Hore, J. (1984b) Dependence of cerebellar tremor on proprioceptive but not visual feedback. Exp. Neurol. 84:314-325.

Flash, T. (1983) Organizing principles underlying the formation of hand trajectories. Ph.D. Thesis, Harvard/MIT Division of Health Sciences and Technology, Massachusetts Institute of Technology, Cambridge, MA.

Flash, T., Hogan, N. (1985) The coordination of arm movements: An experimentally confirmed mathematical model. J. Neurosci. 5:1688-1703.

Forget, R., Lamarre, Y. (1983) Antagonist muscle activity during rapid flexion of the forearm in a functionally deafferented human subject. Soc. Neurosci. Abst. 9:630.

Freund, H.J. (1983) Motor unit and muscle activity in voluntary motor control. Physiol. Rev. 63:387-436.

Freund, H.J., Budingen, H.J. (1978) The relationship between speed and amplitude of the fastest voluntary contractions of human arm muscles. Exp. Brain Res. 31:1-12.

Frysinger, R.C., Bourbonnais, D., Kalaska, J.F., Smith, A.M. (1984) Cerebellar cortical activity during antagonist cocontraction and reciprocal inhibition of forearm muscles. J. Neurophysiol. 51:32-49.

Fulton, J.F., Connor, G. (1939) The physiological basis of three major cerebellar syndromes. Tr. Am. Neurol. Assoc. 65:53-57.

Fulton, J.F., Dow, R.S. (1937) The cerebellum: A summary of functional localization. Yale J. Biol. Med. 10:89-119.

Garland, H., Angel, R.W. (1971) Spinal and supraspinal factors in voluntary movement. Neurol. 33:343-350.

Gemba, H., Sasaki, K. (1978) Tonic vibration reflex and cerebellar disorders. Exptl. Neurol. 60:213-220.

Georgopoulos, A.P., Kalaska, J.F., Massey, J.T. (1981) Spacial trajectories and reaction times of aimed movements: Effects of practice, uncertainty and change in target location. J. Neurophysiol. 46:725-743.

Ghez, C. (1979) Contributions of central programs to rapid movement in the cat. In: Integration in the Nervous System; H. Asanuma and V. Wilson, editors. Igaku-Shoin, Tokyo-New York, pp.305-320.

Ghez, C., Martin, J.H. (1982) The control of rapid limb movement in the cat. III. Agonist-antagonist coupling. Exp. Brain Res. 45:115-125.

Ghez, C., Vicario, D. (1978) The control of rapid limb movement in the cat. II. Scaling of isometric force adjustments. Exp. Brain Res. 33:191-202.

Gilman, S. (1968) A mechanism underlying cerebellar hypotonia. Trans. Am. Neurol. Ass. 93:213-215.

Gilman, S. (1969a) Fusimotor fiber responses in the decerebellate cat. Brain Res. 14:218-221.

Gilman, S. (1969b) The mechanism of cerebellar hypotonia. An experimental study in the monkey. Brain 92:621-638.

Gilman, S. (1972) The nature of cerebellar dyssynergia. In: Modern Trends in Neurology; D. Williams, editor. Butterworths, London, pp. 60-79.

Gilman, S., Carr, D., Hollenberg, J. (1976a) Limb trajectories after cerebellar ablation and deafferentation in the monkey. Trans. Am. Neurol. Assoc. 101:168-170.

Gilman, S., Carr, D., Hollenberg, J. (1976b) Kinematic effects of deafferentation and cerebellar ablation. Brain 99:311-330.

Gilman, S., Ebel, H.C. (1970) Fusimotor neuron responses to natural stimuli as a function of prestimulus fusimotor activity in decerebellate cats. Brain Res. 21:367-384.

Gilman, S., McDonald, W.I. (1967) Cerebellar facilitation of muscle spindle activity. J. Neurophysiol. 30:1494-1512.

Glaser, G.H., Higgins, D.C. (1965) Motor stability, stretch responses and the cerebellum. In: Nobel Symposium I. Muscular afferents and motor control; R. Granit, editor. John Wiley and Sons, New York.

Goldberger, M.E., Growdon, J.H. (1973) Pattern of recovery following cerebellar deep nuclear lesions in monkeys. Exp. Neurol. 39:307-322.

Goodwin, G.M., Hoffman, D., Luschei, E.S. (1978) The strength of the reflex response to sinusoidal stretch of monkey jaw closing muscles during voluntary contraction. J. Physiol. (London) 279:81-111.

Gordon, J., Ghez, C. (1984) EMG patterns in antagonist muscles during isometric contraction in man: Relations to response dynamics. Exp. Brain Res. 55:167-171.

Gottlieb, G.L., Agarwal, G.C. (1973) Postural adaptation. The nature of adaptive mechanisms in the human motor system. In: Control of Posture and Locomotion; R.B. Stein, K.G. Pearson, R.S. Smith and J.B. Redford, editors. Plenum Press, New York, pp. 197-210.

Gottlieb, G.L., Agarwal, G.C. (1979) Response to sudden torques about ankle in man: myotatic reflex. J. Neurophysiol. 42:91-106.

Gottlieb, G.L., Agarwal, G.C. (1980a) Response to sudden torques about ankle in man. II. Postmyotatic reaction. J. Neurophysiol. 43:86-101.

Gottlieb, G.L., Agarwal, G.C. (1980b) Response to sudden torques about ankle in man. III. Suppression of stretch evoked responses during phasic contraction. J. Neurophysiol. 44:233-246.

Gottlieb, G.L., Agarwal, G.C., Jaeger, R.J. (1981) Response to sudden torques about ankle in man. IV. A functional role of alpha-gamma linkage. J. Neurophysiol. 46:179-190.

Gottlieb, G.L., Agarwal, G.C., Jaeger, R.J. (1983) Response to sudden torques about ankle in man. V. Effects of peripheral ischemia. J. Neurophysiol. 50:297-312.

Gottlieb, G.L., Agarwal, G.C., Stark, L. (1970) Interactions between voluntary and postural mechanisms of the human motor system. J. Neurophysiol. 33:365-381.

Granit, R. (1955) Receptors and sensory perception. Yale University Press, New Haven.

Granit, R., Holmgren, B, Merton, P.A. (1955) The two routes for excitation of muscle and their subservience to the cerebellum. J. Physiol. 130:213-224.

Growdon, J.H., Chambers, H.W., Liu, C.N. (1967) An experimental study of cerebellar dyskinesia in the rhesus monkey. Brain 90:603-632.

Hallett, M., Marsden, C.D. (1979) Ballistic flexion movements of the human thumb. J. Physiol. (London) 294:33-50.

Hallett, M., Shahani, B.T., Young, R.R. (1975a) EMG analysis of stereotyped voluntary movements in man. J. Neurol. Neurosurg. Psychiat. 38:1154-1162.

Hallett, M., Shahani, B.T., Young, R.R. (1975b) EMG analysis of patients with cerebellar deficits. J. Neurol. Neurosurg. Psychiat. 38:1163-1169.

Hasan, Z. (1986) Optimized trajectories and joint stiffness in unperturbed, inertially loaded movements. Biol. Cybern. 53:373-382.

Henatsch, H.D. (1967) Instability of the proprioceptive length servo: Its possible role in tremor phenomena. In: Neurophysiological Basis of Normal and Abnormal Motor Activities; M.D. Yahr and D.P. Purpura, editors. Raven Press, New York, pp. 75-89.

Hewer, R.L., Cooper, R., Morgan, M.H. (1972) An investigation into the value of treating intention tremor by weighting the affected arm. Brain 95:579-590.

Higgins, D.C., Glaser, G.H. (1964) Stretch responses during chronic cerebellar ablation. A study of reflex instability. J. Neurophysiol. 27:49-62.

Hoffman, D.S., Strick, P.L. (1981) Trajectories of ballistic movements can be altered by modifying antagonist muscle activity. Soc. Neurosci. Abst. 7:479.

Hoffman, D.S., Strick, P.L. (1982) Evidence that antagonist muscle activity is centrally generated. Soc. Neurosci. Abst. 8:733.

Hogan, N. (1982) Control and coordination of voluntary arm movements. In: Proceedings of the 1982 American Control Conference; M.J. Rabins and Y. Bar-Shalom, editors. American Automatic Control Council, pp. 522-528.

Hogan, N. (1984) An organizing principle for a class of voluntary movements. J. Neurosci. 4:2745-2754.

Holmes, G. (1917) The symptoms of acute cerebellar injuries due to gunshot injuries. Brain 40:461-535.

Holmes, G. (1922) Clinical symptoms of cerebellar disease and their interpretation. The Croonian Lectures I-IV. Lancet 1:1177-1237, 2:59-115.

Holmes, G. (1939) The cerebellum of man. The Hughlings Jackson Memorial Lecture. Brain 62:1-30.

Hopf, H.C., Lowitzsch, K., Schlegel, H.J. (1973) Central versus proprioceptive influences in brisk voluntary movements. In: New Developments in Electromyography and Clinical Neurophysiology, Vol. 3; J.E. Desmedt, editor. Karger:Basel, pp.273-276.

Hore, J., Vilis, T. (1984) Loss of set in muscle responses to limb perturbations during cerebellar dysfunction. J. Neurophysiol. 51:1137-1148.

Hore, J., Vilis, T. (1985) A cerebellar-dependent efference copy mechanism for generating appropriate muscle responses to limb perturbations. In: Cerebellar Function; J.R. Bloedel, J. Dichgans, W. Precht, editors. Springer-Verlag, Berlin, Heidelberg, pp. 24-35.

Houk, J.C. (1976) An assesment of stretch reflex function. In: Understanding the Stretch Reflex; S. Homma, editor. (Prog. Brain Res., Vol. 44) Elsevier/North-Holland Biomedical Press, pp. 303.

Houk, J.C. (1978) Participation of reflex mechanisms and reaction-time processes in the compensatory adjustments to mechanical disturbances. In: Cerebral Motor Control in Man: Long-Loop Mechanisms; J.E. Desmedt, editor. Karger, Basel, pp. 193-215.

Houk, J.C. (1979) Regulation of stiffness by skeletomotor reflexes. Ann. Rev. Physiol. 41:99-114.

Houk, J.C. (1980) Homeostasis and control principles. In: Medical Physiology, Vol.1; V.B. Mountcastle, editor. C.V. Mosby Company, St.Louis, Toronto, London, pp. 246-267.

Houk, J.C., Rymer, W.Z. (1981) Neural control of muscle length and tension. In: Handbook of Physiology. The Nervous System, Vol. II; V.B. Brooks, editor. Am. Physiol. Soc, Bethesda, MD., pp. 257-324.

Howarth, C.I., Beggs, W.D.A., Bowden, J. (1971) The relationship between speed and accuracy of movement aimed at a target. Acta Psychologica 35:207-218.

Hufschmidt, J.J., Hufschmidt, T. (1954) Antagonist inhibition as the earliest sign of a sensory-motor reaction. Nature 174:607.

Hufschmidt, H.J., Linke, D. (1977) Neurophysiologishe Untersuchungen uber den intentionstremor. Arch. Psychiat. Nervenkr. 224:203-212.

Hultborn, H. (1972) Convergence on interneurons in the reciprocal Ia inhibitory pathway to motoneurons. Acta Physiol. Scand. Suppl. 375:1-41.

Hultborn, H. (1976) Transmission in the pathway of IA inhibition to motoneurons and its control during the tonic stretch reflex. In: Understanding the Stretch Reflex; G. Homman, editor. Prog. Brain. Res. Vol. 44. Elsevier/North Holland Biomedical Press.

Huntsberger, D.V., Billingsley, P. (1977) Elements of Statistical Inference, 4th Edition. Allyn & Bacon, Inc., Boston, London, Sydney, Toronto.

Ikai, M. (1955) Inhibition as an accompaniment of rapid voluntary act. Nippon Seirigaku Sasshi (Physiol. Soc. Jpn.) 17:292-298.

Ito, M. (1972) Cerebellar control of the vestibular neurones: physiology and pharmacology. Prog. Brain Res. 37:377-390.

Jennings, V.A., Sanes, J.N. (1982) Effect of ischemic deafferentation on patterns of muscle activity. Soc. Neurosci. Abst. 8:734.

Joyce, G.C., Rack, P.M.H., Ross, H.F. (1974) The forces generated at the human elbow joint in response to imposed sinusoidal movements of the forearm. J. Physiol. (London) 240:351-374.

Kawahats, K., Miyashita, M. (1983) Electromyogram premotion silent period and tension development in human muscle. Exp. Neurol. 82:287-302.

Kornhuber, H.H. (1971) Motor functions of cerebellum and basal ganglia: the cerebellocortical saccadic (ballistic) clock, the cerebellonuclear hold regulator, and the basal ganglia ramp (voluntary speed smooth movement) generator. Kybernetic 8:157-162.

Kozlovskaya, I.B., Uno, M., Atkin, A., Brooks, V.B. (1970) Performance of a step-tracking task by monkeys. Comm. Behav. Biol. 5:153-156.

Kwan, H.C., Murphy, J.T., Repeck, M.W. (1979) Control of stiffness by the medium latency electromyographic response to limb perturbation. Can. J. Physiol. Pharmacol. 57:277-285.

Lamarre, Y., Bioulac, B., Jacks, B. (1978) Activity of precentral neurones in conscious monkeys: Effects of deafferentation and cerebellar ablation. J. Physiol. (Paris) 74:253-264.

Lamarre, Y., Jacks, B. (1978) Involvement of the cerebellum in the initiation of fast ballistic movement in the monkey. EEG Clin. Neurophysiol. Suppl. 34:441-447.

Lamarre, Y., Lund, J.P. (1975) Load compensation in human masseter muscles. J. Physiol. (London) 253:21-35.

Lamarre, Y., Spidaleri, G., Busby, L., Lund, J.P. (1980) Programming of initiation and execution of ballistic arm movements in the monkey. Prog. Brain Res. 54:147-169.

Lance, J.W., DeGail, P., Neilson, P.D. (1966) Tonic and phasic spinal cord mechanisms in man. J. Neurol. Neurosurg. Psychiat. 29:535-544.

Laporte, Y., Emonet-Denand, F., Jami, L. (1981) The skeletofusimotor or beta-innervation of mammalian muscle spindles. Trends Neurosci. 4:97-99.

Lashley, K.S. (1917) The accuracy of movement in the absence of excitation from the moving organ. Am. J. Physiol. 43:169-194.

Lee, R.G., Lucier, G.E., Mustard, B.E., White, D.G. (1986) Modification of motor output to compensate for unanticipated load conditions during rapid voluntary movements. Can. J. Neurol. Sci. 13:97-100.

Leiner, H.C., Leiner, A.L., Dow, R.S. (1986) Does the cerebellum contribute to mental skills? Behav. Neurosci. 4:443-454.

Lestienne, F. (1979) Effects of inertial load and velocity on the braking process of voluntary limb movements. Exp. Brain Res. 35:407-418.

Levine, M.G., Kabat, H. (1952) Cocontraction of reciprocal innervation in voluntary movement in man. Science 116:115-118.

Lippold, O.C.J. (1970) Oscillation in the stretch reflex arc and the origin of the rhythmical 8-12 c/s component of physiological tremor. J. Physiol. (London) 206:359-382.

Lisberger, S.G., Fuchs, A.F. (1978a) Role of primate flocculus during rapid behavioral modification of vestibulo-ocular reflex. I. Purkinje cell activity during visually guided horizontal smooth-pursuit eye movements and passive head rotation. J. Neurophysiol. 41:733-763.

Lisberger, S.G., Fuchs, A.F. (1978b) Role of primate flocculus during rapid behavioral modification of vestibulo-ocular reflex. II. Mossy fiber firing patterns during horizontal head rotation and eye movement. J. Neurophysiol. 41:764-777.

Liu, C.N., Chambers, W.W. (1971) A study of cerebellar dyskinesia in the bilaterally deafferented forelimbs of the monkey (Macaca mulatta and Macaca speciosa). Acta Neurobiol. Exp. 31:263-289.

Loeb, G.E., Duysens, J. (1978) Activity patterns in individual hindlimb primary and secondary muscle spindle afferents during normal movements in unrestrained cats. J. Neurophysiol. 42:420-440.

Luciani, L. (1891) Il Cervelletto: Nuovi Studi di Fisiologia Normale e Patologica. Successori Le Monnier, Firenze.

Luciani, L. (1915) Muscular and Nervous System. Vol. 3 of Human Physiology. London:McMillan & Co.

Lund, J.P., Smith, A.M., Sessle, B.J., Murakami, T. (1979) Activity of trigeminal alpha- and gamma-motoneurons and muscle afferents during performance of a biting task. J. Neurophysiol. 42:710-725.

Lundberg, A. (1971) Function of the ventral spinocerebellar tract: a new hypothesis. Exp. Brain Res. 12:317-330.

MacKay, W.A., Murphy, J.T. (1979a) Cerebellar influence on proprioceptive control loops. In: Cerebro-Cerebellar Interactions; J. Massion and K. Sasaki, editors. Elsevier/North-Holland, New York, pp. 141-162.

MacKay, W.A., Murphy, J.T. (1979b) Cerebellar modulation of reflex gain. Prog. Neurobiol. 13:361-417.

Manocha, S.L., Shantha, T.R., Bourne, G.H. (1968) A stereotaxic atlas of the Cebus monkey (Cebus apella). Clarendon Press, Oxford.

Marsden, C.D., Merton, P.A., Morton, H.B. (1972) Servo action in human voluntary movement. Nature 238:140-143.

Marsden, C.D., Merton, P.A., Morton, H.B. (1976a) Servo action in the human thumb. J. Physiol. (London) 257:1-44.

Marsden, C.D., Merton, P.A., Morton, H.B. (1976b) Stretch reflexes and servo actions in a variety of human muscles. J. Physiol. (London) 259:531-560.

Marsden, C.D., Merton, P.A., Morton, H.B., Hallett, M., Adam, J., Rushton, D.N. (1977) Disorders of movement in cerebellar disease in man. In: Physiological Aspects of Clinical Neurology; F.C. Rose, editor. Blackwell Scientific Publications, pp. 179-199.

Marsden, C.D., Obeso, J.A., Rothwell, J.C. (1981) Action of the antagonist muscle during fast limb movements in man. J. Physiol. (London) 312:47P-48P.

Marsden, C.D., Obeso, J.A., Rothwell, J.C. (1983a) The function of the antagonist muscle during fast limb movements in man. J. Physiol. (London) 335:1-13.

Marsden, C.D., Rothwell, J.C., Day, B.L. (1983b) Long-latency automatic responses to muscle stretch in man: origin and function. In: Motor Control Mechanisms in Health and Disease; J.E. Desmedt, editor. Raven Press, New York, pp. 509-539.

Massion, J., Sasaki, K. (1979) Cerebro-cerebellar interaction: solved and unsolved problems. In: Cerebro-cerebellar Interactions; J. Massion and K. Sasaki, editors. Elsevier/ North-Holland, New York, pp. 261-287.

Matthews, P.B.C. (1964) Muscle spindles and their motor control. Physiol. Rev. 44:219-288.

Matthews, P.B.C. (1981) Muscle spindles: their messages and their fusimotor supply. In: Handbook of Physiology. The Nervous System II; V.B. Brooks, editor. American Physiological Society, Bethesda, MD, pp. 189-228.

Mauritz, K.H., Schmitt, C., Dichgans, J. (1981) Delayed and enhanced long latency reflexes as the possible cause of postural tremor in late cerebellar atrophy. Brain 104:97-116.

McCormick, D.A., Lavond, D.G., Clark, G.A., Kettner, R.E., Rising, C.E., Thompson, R.F. (1981) The engram found? Role of the cerebellum in classical conditioning of nictitating membrane and eyelid response. Bull. Phychon. Soc. 18: 103-105.

McCormick, D.A., Thompson, R.F. (1984) Neuronal responses of the rabbit cerebellum during acquisition and performance of a classically conditioned nictitating membrane-eyelid response. J. Neurosci. 4:2811-2822.

Meinck, H.-M., Benecke, R., Meyer, W., Hohne, J., Conrad, B. (1984) Human ballistic finger flexion: Uncoupling of the three-burst pattern. Exp. Brain Res. 55:127-133.

Melvill Jones, G., Watt, D.G.D. (1971a) Observations on the control of stepping and hopping movements in man. J. Physiol. (London) 219:709-727.

Melvill Jones, G., Watt, D.G.D. (1971b) Muscular control of landing from unexpected falls in man. J. Physiol. (London) 219:729-737.

Merton, P.A. (1953) Speculations on the servo-control of movement in the spinal cord. In: The Spinal Cord; G.E.W. WalstenHolme, editor. Churchill, London, pp. 247-255.

Meyer-Lohmann, J., Conrad, B., Matsunami, K., Brooks, V.B. (1975) Effects of dentate cooling on precentral unit activity following torque pulse injections into elbow movements. Brain Res. 94:237-251.

Meyer-Lohmann, J., Hore, J., Brooks, V.B. (1977) Cerebellar participation in generation of prompt arm movements. J. Neurophysiol. 40:1038-1050.

Miller, A.D., Brooks, V.B. (1982) Parallel pathways for movement initiation in monkeys. Exp. Brain Res. 45:328-332.

Miller, A., Meyer-Lohmann, J., Hore, J., Brooks, V.B. (1974) Relation between cerebellar nuclei and simple reaction time. Proc. Can. Fed. Biol. Soc. 18:148.

Morasso, P. (1981) Spatial control of arm movements. Exp. Brain Res. 42:223-227.

Murphy, J.T., Kwan, H.C., MacKay, W.A., Wong, Y.C. (1975) Physiological basis of cerebellar dysmetria. Can. J. Neurol. Sci. 2:279-284.

Nashner, L.M. (1976) Adapting reflexes controlling the human posture. Exp. Brain Res. 26:59-72.

Nashner, L.M., Grimm, R.J. (1978) Analysis of multiloop dyscontrols in standing cerebellar patients. Prog. Clin. Neurobiol. 4:300-319.

Neilson, P.D., Lance, J.W. (1978) Reflex transmission characteristics during voluntary activity in normal man and patients with movement disorders. Prog. Clin. Neurophysiol. 4:263-299.

Nelson, W.L. (1983) Physical prineiples for economies of skilled movements. Biol. Cybern. 46:135-147.

Oguztoreli, M.N., Stein, R.B. (1975) An analysis of oscillations in neuro-muscular systems. J. Math. Biol. 2: 87-105.

Olszewski, J. (1952) The thalamus of the Macaca Mullata. An atlas for use with the stereotaxic instrument. S. Karger, Basel, New York.

Oscarsson, O. (1971) Note in 'Central Control of Movement'; E.V. Evarts, E. Bizzi, R.E. Burke, M. DeLong, W.T. Thach, editors. Neurosci. Res. Progr. Bull. 9:98-103.

Oscarsson, O. (1973) Functional organization of spinocerebellar paths. In: Somatosensory System. Handbook of Sensory Physiology, Vol. II; A. Iggo, editor. Springer, Berlin, pp. 339-380.

Ostry, D.J., Flanagan, J.R., Cooke, J.D. (1986) The shape of the velocity curve varies with movement duration: evidence from human arm movement, locomotion, mastication and speech. Soc. Neurosci. Abstr. 12:971.

Otero, J.B. (1976) Comparison between red nucleus and precentral neurons during learned movement in the monkey. Brain Res. 101:37-46.

Phillips, C.G. (1969) Motor apparatus of the baboon's hand. Proc. Roy. Soc. Lond. B 173:141-174.

Polit, A., Bizzi, E. (1979) Characteristics of motor programs underlying arm movements in monkeys. J. Neurophysiol. 42:183-194.

Post, E.M., Rymer, W.Z., Hasan, Z. (1980) Relation between intrafusal and extrafusal activity in triceps surae muscles of the decerebrate cat: evidence for beta action. J. Neurophysiol. 44:383-404.

Prochazka, A. (1981) Muscle spindle function during normal movement. Int. Rev. Physiol. 5:47-90.

Prochazka, A., Hulliger, M., Zangger, P., Appenteng, K. (1985) 'Fusimotor set': new evidence for alpha-independent control of gamma-motoneurons during movement in the awake cat. Brain Res. 339:136-140.

Prochazka, A., Stephens, J.A., Wand, P. (1979) Muscle spindle discharge in normal and obstructed movements. J. Physiol. (London) 287:57-66.

Prochazka, A., Wand, P. (1981) Independence of fusimotor and skeletomotor systems during voluntary movement. In: Muscle Receptors and Movement; A. Taylor and A. Prochazka, editors. Macmillan, London, pp. 229-243.

Prochazka, A., Westerman, R.A., Ziccone, S.P. (1976) Discharges of single hindlimb afferents in the freely moving cat. J. Neurophysiol. 39:1090-1104.

Prochazka, A., Westerman, R.A., Ziccone, S.P. (1977) Ia afferent activity during a variety of voluntary movements in the cat. J. Physiol. (London) 268:423-448.

Rack, P.M.H. (1981) Limitations of somatosensory feedback in control of posture and movement. In: Handbook of Physiology. The Nervous System, Vol. II; V.B. Brooks, editor. Am. Physiol. Soc, Bethesda, MD., pp. 229-256.

Rademaker, G.G.J. (1931) Das Stehen: Statische Reaktionen, Gleichgewichtstreaktionen und Muskeltonus unter besonderer Beruchsichtigung ihres Verhaltens bei kleinhirnlosen Tieren. Berlin:J. Springer.

Roberts, T.D.M. (1965) The nature of the controlled variable in the muscle servo. In: Control and Innervation of Skeletal Muscle; B.L. Andrew, editor. E&S Livingstone, Edinburgh, pp. 160-170.

Rolando, L. (1809) Saggio sopra la struttura del cervello dell'uomo e degli animali e sopra le funzioni del sistema nervosa. Sassari:Stampeia da S.S.R.M. Privilegiata.

Rondot, P., Bathien, N., Toma, S. (1979) Physiopathology of cerebellar movement. In: Cerebro-Cerebellar Interactions; J. Massion and K. Sasaki, editors. Elsevier/North-Holland, Amsterdam, pp. 203-230.

Rothwell, J.C., Traub, M.M., Day, B.L., Obeso, J.A., Thomas, P.K., Marsden, C.D. (1982) Manual motor performance in a deafferented man. Brain 105:515-542.

Ruch, T.C. (1951) Motor systems. In: Handbook of Experimental Psychology; S.S. Stevens, editor. Wiley, New York, pp. 154-208.

Rymer, W.Z., Post, E.M., Edwards, F.R. (1981) Functional roles of fusimotor and skeleto-fusimotor neurons studied in the decerebrate cat. In: Muscle Receptors and Movement; A. Taylor and A. Prochazka, editors. MacMillan, London.

Sakai, T., Preston, J.B. (1978) Evidence for a transcortical reflex: primate corticospinal tract neuron responses to ramp stretch of a muscle. Brain Res. 159:463-467.

Sanes, J.N., Jennings, V.A. (1984) Centrally programmed patterns of muscle activity in voluntary motor behavior of humans. Exp. Brain Res. 54:23-32.

Sanes, J.N., Mauritz, K.-H. (1986) Sensory and mechanical control of cerebellar intention tremor in humans. Soc. Neurosci. Abstr. 12:1306.

Schieber, M.H., Thach, W.T. (1980) Alpha-gamma dissociation during slow tracking movements of the monkey's wrist: preliminary evidence from spinal ganglion recording. Brain Res. 202:213-216.

Schieber, M.H., Thach, W.T. (1985) Trained slow tracking. II. Bidirectional discharge patterns of cerebellar nuclear, motor cortex, and spindle afferent neurons. J. Neurophysiol. 54:1228-1270.

Smith, A.M., Bourbonnais, D. (1981) Neuronal activity in cerebellar cortex related to control of prehensile force. J. Neurophysiol. 45:286-303.

Smith, A.M., Frysinger, R.C., Bourbonnais, D. (1983) Discharge patterns of cerebellar cortical neurons during the co-activation and reciprocal inhibition of forearm muscles. Exp. Brain Res. Suppl. 7:298-308.

Snider, R.S. (1940) Functional studies following lesions of the nucleus interpositus in the rabbit. Bull. Johns Hopkins Hosp. 67:139-153.

Snider, R.S., Lee, J.C. (1961) A stereotaxic atlas of the monkey brain (Macaca mulatta). University of Chicago Press, Chicago.

Soechting, J.F., Ranish, N.A., Palminteri, R., Terzuolo, C.A. (1976) Changes in a motor pattern following cerebellar and olivary lesions in the squirrel monkey. Brain Res. 105:21-44.

Sperti, L., Zatti, P. (1953) Osservazioni sul comportamento di cani con lesione cronica di uno o piu nuclei cerebellari. Atti. Soc. Med. Chir., Padova 31:537-541.

Spidalieri, G., Busby, L., Lamarre, Y. (1984) Fast ballistic arm movements triggered by visual, auditory, and somesthetic stimuli in the monkey. II. Effects of unilateral dentate lesion on discharge of precentral cortical neurons and reaction time. J. Neurophysiol. 50:1359-1379.

Stein, R.B., Lee, R.G. (1981) Tremor and Clonus. In: Handbook of Physiology. The Nervous System II; V.B. Brooks, editor. American Physiological Society, Bethesda, MD, pp. 325-344.

Stein, R.B., Lee, R.G., Nichols, T.R. (1978) Modification of ongoing tremors and locomotion by sensory feedback. EEG Clin. Neurophysiol. Suppl. 34:511-519.

Stein, R.B., Oguztoreli, M.N. (1976) Does the velocity sensitivity of muscle spindles stabilize the stretch reflex? Biol. Cybern. 23:219-228.

Stetson, R.H., Bouman, H.D. (1935) The co-ordination of simple skilled movements. Arch. Neerl. Physiol. 20:179-254.

Strick, P.L. (1978) Cerebellar involvement in 'volitional' muscle responses to load changes. In: Prog. Clin. Neurophysiol. Vol. 4; J. Desmedt, editor. pp. 85-93.

Tatton, W.G., Bawa, P. (1979) Input-output properties of motor unit responses in muscles stretched by imposed displacements of the monkey wrist. Exp. Brain Res. 37:439-457.

Taub, E., Goldberg, I.A., Taub, P. (1975) Deafferentation in monkeys: Pointing at a target without visual feedback. Exp. Neurol. 46:178-186.

Terzuolo, C.A., Soechting, J.F., Ranich, N.A. (1974) Studies on the control of some simple motor tasks. V. Changes in motor output following dorsal root section in squirrel monkey. Brain Res. 70:521-526.

Thach, W.T. (1968) Discharge of Purkinje and cerebellar nuclear neurons during rapidly alternating arm movements in the monkey. J. Neurophysiol. 31:785-797.

Thach, W.T. (1970a) Discharge of cerebellar neurons related to two maintained postures and two prompt movements. I. Nuclear cell output. J. Neurophysiol. 33:527-536.

Thach, W.T. (1970b) Discharge of cerebellar neurons related to two maintained postures and two prompt movements. II. Purkinje cell output and input. J. Neurophysiol. 33:537-547.

Thach, W.T. (1975) Timing of activity in cerebellar dentate nucleus and cerebral motor cortex during prompt volitional movements. Brain Res. 88:233-241.

Thach, W.T. (1978) Correlation of neural discharge with pattern and force of muscular activity, joint position, and direction of the intended movement in motor cortex and cerebellum. J. Neurophysiol. 41:654-676.

Thach, W.T., Schieber, M.H., Elble, R.H. (1985) Motor programs: Trajectory nersus stability. In: Cerebellar Functions; J.R. Bloedel, J. Dichgans, W. Precht, editors. Springer-Verlag, Berlin, Heidelberg, N.Y., Tokyo, pp. 36-51.

Thomas, A. (1897) Le Cervelet. Paris:G. Steinheil.

Tilney, F., Pike, F.H. (1925) Muscular coordination experimentally studied in its relation to the cerebellum. Arch. Neurol. Psychiat. 13:289-334.

Trouche, E., Beaubaton, D. (1980) Initiation of a goal-directed movement in the monkey. Role of the cerebellar dentate nucleus. Exp. Brain Res. 40:311-321.

Trouche, E., Beaubaton, D., Amato, G., Grangetto, A. (1979) Impairments and recovery of the spatial and temporal components of a visuomotor pointing movement after unilateral destruction of the dentate nucleus in the baboon. Appl. Neurophysiol. 42:248-254.

Uno, M., Kozlovskaya, I.B., Brooks, V.B. (1973) Effects of cooling interposed nuclei on tracking-task performance in monkeys. J. Neurophysiol. 36:996-1003.

Vallbo, A.B. (1970a) Slowly adapting muscle receptors in man. Acta Physiol. Scand. 78:315-333.

Vallbo, A.B. (1970b) Discharge patterns in human muscle spindle afferents during isometric voluntary contraction. Acta Physiol. Scand. 80:532-566.

Vallbo, A.B. (1971) Muscle spindle response at the onset of isometric voluntary contractions in man. Time difference between fusimotor and skeletomotor effects. J. Physiol. (London) 218:405-431.

Vallbo, A.B. (1973) Impulse activity from human muscle spindles during voluntary contractions. In: Motor Control; A.A. Gydikov, editor. Plenum Press, New York, pp. 33-43.

Vallbo, A.B. (1974) Human muscle spindle discharge during isometric voluntary contractions. Amplitude relations between spindle frequency and torque. Acta Physiol. Scand. 90:319-336.

Vallbo, A.B., Hulliger, M. (1981) Independence of skeletomotor and fusimotor activity in man? Brain Res. 223:176-180.

Van Der Meulen, J.P., Gilman, S. (1965) Recovery of muscle spindle activity in cats after cerebellar ablation. J. Neurophysiol. 28:943-957.

Vilis, T., Hore, J. (1977) Effects of changes in mechanical state of limb on cerebellar intention tremor. J. Neurophysiol. 40:1214-1223.

Vilis, T., Hore, J. (1980) Central neural mechanisms contributing to cerebellar tremor produced by limb perturbations. J. Neurophysiol. 43:279-291.

Vilis, T., Hore, J. (1986) A comparison of disorders in saccades and in fast and accurate elbow flexions during cerebellar dysfunction. In: Oculomotor and Skekelat Motor System Differences and Similarities; H.-J. Freund, U. Buttner, B. Cohen, and J. Noth, editors. Prog. in Brain Res., 64:207-215.

Wachholder, K., Altenburger, H. (1926) Beitruge zur Physiologie der willkurlichen Bewegung. 10. Einzelbewegungen. Pflugers Archiv. fur die gesamte Physiologie des Menschen und der Tiere 214:642-661.

Wadman, W.J., Denier van der Gon, J.J., Geuze, R.H., Mol, C.R. (1979) Control of fast goal directed arm movements. J. Hum. Movement Stud. 5:3-17.

Watt, D.G.D., Stauffer, E.K., Taylor, A., Reinking, R.M., Stuart, D.G. (1976) Analysis of muscle receptor connections of spike-triggered averaging. I. Spindle primary and tendon organ afferents. J. Neurophysiol. 39:1375-1392.

Wetts, R., Kalaska, J.F., Smith, A.M. (1985) Cerebellar nuclear cell activity during antagonist cocontraction and reciprocal inhibition of forearm muscles. J. Neurophysiol. 54:231-244.

Wiegner, A.W., Wierzbicka, M.M. (1986) Acceleration profiles of fast voluntary movements. Soc. Neurosci. Aostr. 12:1303.

Wiesendanger, M., Ruegg, D.G. (1978) Electromyographic assessment of central motor disorders. Muscle & Nerve 1:407-412.

Wiesendanger, M., Ruegg, D.G., Wiesendanger, R. (1979) The corticopontine system in primates: anatomical and functional considerations. In: Cerebro-Cerebellar Interactions; J. Massion and K. Sasaki, editors. Elsevier/North-Holland, pp. 45-65.

Wilkie, D.R. (1950) The relation between force and velocity in human muscle. J. Physiol. (London) 110:249-280.

Yabe, K. (1976) Premotion silent period in rapid voluntary movement. J. Appl. Physiol. 41:470-473.

Yoneda, T., Oishi, K., Ishida, A. (1983) Variation of amount of muscle discharges during ballistic isometric voluntary contraction in man. Brain Res. 275:305-309.