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## MOVEMENT-RELATED GATING OF CLIMBING FIBRE INPUT TO CEREBELLAR CORTICAL ZONES

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**Abstract**—The inferior olive climbing fibre projection and associated spino-olivocerebellar paths (SOCPs) have been studied intensively over the last quarter of a century yet precisely what information they signal to the cerebellar cortex during movements remains unclear. A different approach is to consider the times during a movement when afferent signals are likely to be conveyed via these paths.

Central regulation (gating) of afferent transmission during active movements is well documented in sensory pathways leading to the cerebral cortex and the present review examines the possibility that a similar phenomenon also occurs in SOCPs during movements such as locomotion and reaching. Several lines of evidence are considered which suggest that SOCPs are not always open for transmission. Instead, flow of sensory information to the cerebellum via climbing fibre paths is powerfully modulated during active movements.

The findings are discussed in relation to the parasagittal zonal organization of the cerebellar cortex and, in particular, evidence is presented that different cerebellar zones are subject to similar patterns of gating during reaching but can differ appreciably in the pattern of modulation their SOCPs exhibit during locomotion. Furthermore, differences in gating can occur at different rostrocaudal loci within the same zone, suggesting that in the awake behaving animal, individual cerebellar zones are not functionally homogeneous.

Finally, the data are interpreted in relation to the error detector hypothesis of climbing fibre function and the possibility explored that the gating serves as a task-dependent mechanism that operates to prevent self-generated 'irrelevant' sensory inputs from being relayed via the SOCPs to the cerebellar cortex, while behaviourally 'relevant' signals are selected for transmission. © 1998 Elsevier Science Ltd. All rights reserved

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### ABBREVIATIONS

DAO	Dorsal accessory olive	LF	Lateral funiculus
DF	Dorsal funiculus	SEP	Somatosensory evoked potential
DLF	Dorso-lateral funiculus	SOCP	Spino-olivocerebellar path
MAO	Medial accessory olive	VF	Ventral funiculus

## 1. INTRODUCTION

The central nervous system (CNS) is subject to a continuous barrage of sensory inputs reporting both external events and the internal state of the body and the brain is constantly engaged in processing these signals, selecting at any given time those that merit higher level analysis. This is achieved, it is generally agreed, by selective attenuation or 'gating' of irrelevant inputs. Indeed, a failure to regulate the normal stream of sensory information is thought to be a key feature underlying psychotic disorders such as schizophrenia [for a review of information processing dysfunctions in schizophrenia see Braff (1993)].

The phenomenon of gating has been investigated in most detail in dorsal column-lemniscal pathways, particularly during active movements [for a review see Chapman (1994)]. However, an increasing body of evidence suggests that a similar (most probably related) phenomenon is also present in a major class of afferent connections to the cerebellum. Known collectively as spino-olivocerebellar paths (SOCPs), these pathways terminate as climbing fibres in the cerebellar cortex and the aim of the present review is to consider the evidence that they are also subject to central modulation during movement. Any such regulation will have important implications as to their function, since changes in transmission will set limits to when sensory afferent inputs will be relayed via these paths to the cerebellum.

## 2. BACKGROUND

In mammals the inferior olive is the sole source of climbing fibre afferents to the cerebellum and together with the associated SOCPs forms a vital component of the central neural machinery for motor control. The importance of the climbing fibre system is emphasized by the fact that ablation of the olive results in movement disorders very similar to the motor deficits that follow direct cerebellar damage (Wilson and Magoun, 1945; Llinas *et al.*, 1975; Pompeiano *et al.*, 1981). However, precisely what information the climbing fibres and the SOCPs signal to the cerebellum remains a hotly debated issue [for a recent review see Simpson *et al.* (1996)]; their role in motor control being all the more intriguing in light of a number of unusual features.

### 2.1. Zonal Organization

One notable aspect of the olivocerebellar projection is its highly ordered topography (Fig. 1). Climbing fibre afferents arising from a discrete region of the inferior olivary complex target Purkinje cells aligned into narrow (*ca* 1 mm) rostro-

caudally oriented zones within the cerebellar cortex. The Purkinje cells within each zone project, in turn, to different regions within the deep cerebellar or vestibular nuclei. Each of these nuclei, in turn, sends efferents to a particular group of brainstem nuclei and higher centres. The cerebellum is thus divided into a series of sagittally-orientated olivo-cortico-nuclear compartments which influence different descending motor pathways.

Proceeding from the midline to its lateral aspect the cerebellar cortex can be divided into at least eight longitudinal zones [see Fig. 1(A) for details] and in parallel with this compartmentation are the corresponding origins of climbing fibres to each of the cerebellar cortical zones. While space precludes a comprehensive discussion (see Brodal and Kawamura, 1980; Voogd and Bigaré, 1980; Armstrong, 1990; Buisseret-Delmas and Angaut, 1993; Voogd and Ruigrok, 1997), broadly speaking the three main divisions of the inferior olivary complex send their climbing fibre afferents to the three major longitudinal divisions of the cerebellar cortex: the caudal halves of the two accessory olives project to the midline cerebellar vermis, the rostral halves of the accessory olives project to the paravermal (intermediate) cortex and the principal olive projects to the lateral (hemispherical) cortex. Although an oversimplification [see Fig. 1(B) for further details], this scheme nevertheless serves to illustrate that there is a highly ordered and specific circuit of connectivity between the inferior olive, the cerebellar cortex and the cerebellar output nuclei.

### 2.2. Spino-Olivocerebellar Paths

Electrophysiological investigations have also revealed a complex functional organization. In particular, various ascending spinal pathways have been described that relay in the inferior olive before terminating as climbing fibres in different parasagittal zones of the cerebellar cortex [for a review see Oscarsson (1980)]. Although some details remain to be finalized, experiments that combine electrophysiological mapping with neural tract tracing have shown that the anatomically-defined cortical zones are largely congruent with the physiologically-defined zones (e.g. Trott and Armstrong, 1987a,b; Trott and Apps, 1991, 1993).

In brief, there are four major groups of SOCPs that convey information from skin, muscle and joints to the cerebellum, each with its own route in a particular spinal cord funiculus (ventral funiculus, VF-SOCP; dorsal funiculus, DF-SOCP; dorso-lateral funiculus, DLF-SOCP; lateral funiculus, LF-SOCP). The various SOCPs can be further distinguished by differences in the numbers of spinal and brainstem relays which occur before they terminate

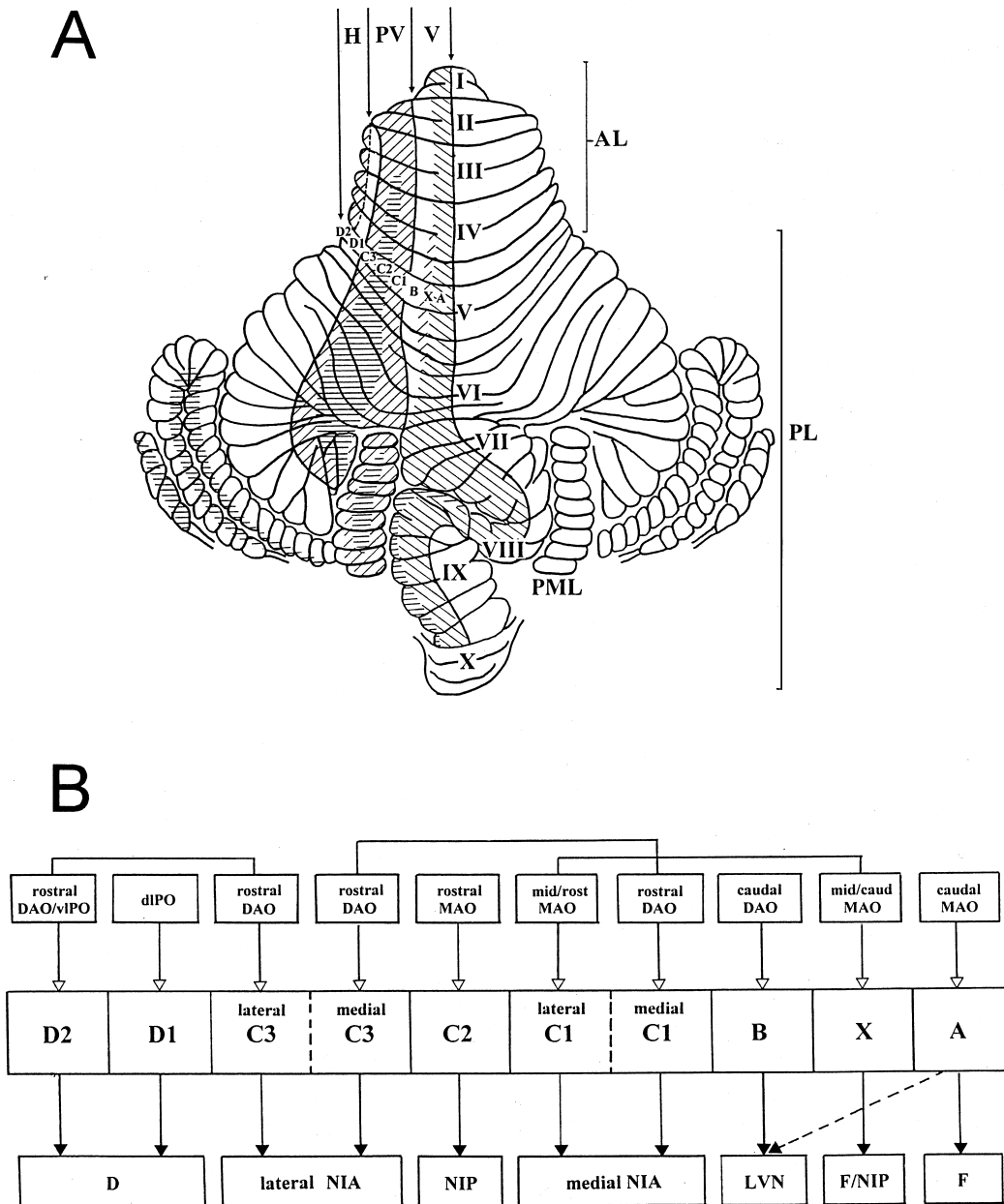


Fig. 1. (A) Dorsal view of the unfolded cat cerebellar cortex to show the approximate location of eight longitudinal zones in the left hemi-cerebellum. (B) Schematic diagram to show the olivary input (top row) and cortico-nuclear output (bottom row) of each cerebellar zone. Note that the C1 and C3 cortical zones can be further subdivided into medial and lateral subzones and that some zones are linked by transverse branching of olivocerebellar axons. H, hemisphere; PV, paravermis; V, vermis; AL, anterior lobe; PL, posterior lobe; PML, paramedian lobule; MAO, medial accessory olive; DAO, dorsal accessory olive; PO, principal olive; dl, dorsal lamella; vl, ventral lamella; F, Fastigius nucleus; NIA, nucleus interpositus anterior; NIP, nucleus interpositus posterior; D, dentate nucleus; LVN, lateral vestibular nucleus. [Part A based on Armstrong *et al.* (1974); Brodal and Kawamura (1980); Ekerot and Larson (1982); Apps *et al.* (1991); Trott and Apps (1991, 1993) part B adapted from Armstrong (1990).].

as climbing fibres in specific longitudinally orientated cerebellar cortical zones [see Fig. 2 for details and for a review see Ito (1984)]. Thus, complementary to the anatomical zonation, the cerebellar cortex can be divided electrophysiologically into at least eight major parasagittal divisions on the basis

of different patterns of peripheral somatosensory convergence and the latency of the SOCPs involved. The electrophysiologically-defined C2 zone, for example, receives peripheral information from all four limbs mainly via a relatively long latency LF-SOCP (Larson *et al.*, 1969b; Armstrong *et al.*, 1973)

while the neighbouring C1 and C3 zones receive peripheral inputs from the ipsilateral limbs, mainly via the shorter latency DF-SOCP (e.g. Oscarsson, 1969; Ekerot and Larson, 1979a, 1982). Anatomical differences such as these presumably reflect differences in function in the awake behaving animal, although the latter have yet to be defined.

Detailed electrophysiological mapping experiments have shown in addition, that the VF- and DF-SOCPs are both compound systems consisting of several paths. Investigations, to date, have focused on the climbing fibre projection via these paths to the cortical B and C3 zones, and have shown that subcomponents within each pathway relay climbing fibre input to narrower subzones or 'microzones' arranged mediolaterally within the broader zones (Andersson and Oscarsson, 1978; Oscarsson, 1979; Ekerot and Larson, 1979b; Ekerot *et al.*, 1991a). Each cerebellar cortical microzone is ca 200  $\mu\text{m}$  in width and is thought to receive climbing fibre afferents that arise from a column of cells in a specific part of the inferior olive (e.g. Apps, 1990; Garwicz *et al.*, 1996; Atkins and Apps, 1997). It is likely that other cortical zones have a microzonal organization as well, although this remains to be established. Nevertheless, it is generally agreed that the microzones and associated olivo-cortico-nuclear 'microcomplexes' or 'modules' represent the basic operational units of the cerebellum in motor control [for a recent review see Garwicz *et al.* (1998)].

### 2.3. Climbing Fibre Action on the Cerebellar Purkinje Cells

Beyond doubt the most striking feature of the inferior olive projection to the cerebellar cortex is that climbing fibre terminals form the most powerful and specific excitatory synapses so far reported in any neurone. Each cortical Purkinje cell receives a single climbing fibre afferent which generates an intense excitation known as a complex spike [Thach (1967); also termed a 'climbing fibre response', see Eccles *et al.* (1966a)]. Furthermore, the density of dendritic lamellar bodies [associated with the presence of neuronal gap junctions, De Zeeuw *et al.* (1995, 1997)] is higher in the inferior olive than in any other area of the brain. As a consequence, neighbouring olive cells can be electrotonically coupled resulting in their synchronous discharge (Llinas *et al.*, 1974; Sotelo *et al.*, 1974), which in turn generates synchronous firing of complex spikes in Purkinje cells arranged preferentially in the rostro-caudal axis [Bell and Kawasaki (1972); Sasaki *et al.* (1989); Llinas and Sasaki (1989); see also Welsh *et al.* (1995)].

Because of the highly secure nature of climbing fibre-Purkinje cell synapses, olive cell activity can be recorded indirectly by monitoring the complex spike discharges of individual Purkinje cells and studies of their activity patterns in the awake animal have revealed an additional, striking feature of the olivo-cerebellar system: complex spikes occur at only a very low, irregular rate, averaging just 1 or 2 per second (e.g. Thach, 1968, 1970; Armstrong and Rawson, 1979; Armstrong and Edgley, 1984; Andersson and Armstrong, 1987; Armstrong *et al.*,

1988; Stone and Lisberger, 1990; Keating and Thach, 1995). By marked contrast, the simple spike discharges of Purkinje cells (generated as a result of activity in the mossy fibre afferents) occur at much higher rates of ca 40–50 impulses  $\text{sec}^{-1}$  (e.g. Thach, 1968, 1970; Hobson and McCarley, 1972; Armstrong and Rawson, 1979; Armstrong and Edgley, 1984; Edgley and Lidieth, 1988; Stone and Lisberger, 1990). Moreover, simple spike activity often increases during locomotion (e.g. Armstrong and Edgley, 1984; Smith and Chapin, 1996a) or during a visually guided task (Bauswein *et al.*, 1983; Mano and Yamamoto, 1980; Marple-Horvat and Stein, 1987; Ebner and Fu, 1997) and typically, the rate of discharge is time-locked to a specific phase of the movement. During walking, for example, Purkinje cells located in the paravermal C1 and C2 zones discharge simple spikes rhythmically in time with stepping movements and as a population are most active during the swing phase of the step cycle (Armstrong and Edgley, 1984).

#### 2.3.1. Complex Spike Activity During Movements

Studies of complex spike discharge patterns in the awake animal (e.g. Armstrong *et al.*, 1982; Andersson and Armstrong, 1987; Armstrong *et al.*, 1988) have found, however, that they do not occur at rigidly fixed times during the step cycle and that any fluctuations in probability that do occur are not statistically different from those which could arise by chance (see Fig. 3). Thus Armstrong *et al.* (1988) conclude that "...there appears to be little or no frequency modulation in the discharge of complex spikes in individual Purkinje cells during the natural course of an unperturbed step."

While some locomotor studies in the decerebrate cat have produced similar negative findings [Boylls (1980); see also Arshavsky *et al.* (1984)], others have succeeded in finding clear, step-related changes in the probability of complex spike discharge by individual Purkinje cells (Udo *et al.*, 1981; Kim *et al.*, 1987) or groups of olive cells in the awake rat (Smith, 1998). With regard to other types of movement the findings are also mixed. For example, Horn *et al.* (1996) recorded directly from the olive in cats trained to perform a reach to grasp movement and found that none of the units studied discharged in relation to specific times during the task. Similarly, Bauswein *et al.* (1983) reported only limited movement-related activity of complex spikes during a lever tracking task in monkeys. By contrast, other investigations have found clear movement-related patterns of complex spike discharge during lever tracking tasks (Harvey *et al.*, 1977; Mano *et al.*, 1986; Wang *et al.*, 1987). More recently, information theory has also been used to show that, as monkeys perform a reaching task, complex spikes encode information about both the intended destination of the reach and the subsequent error at the end of the movement (Kitazawa *et al.*, 1998). While other studies have shown that complex spikes increase in frequency during changes in motor performance associated with learning [e.g. Gilbert and Thach (1977); Ojakangas and Ebner

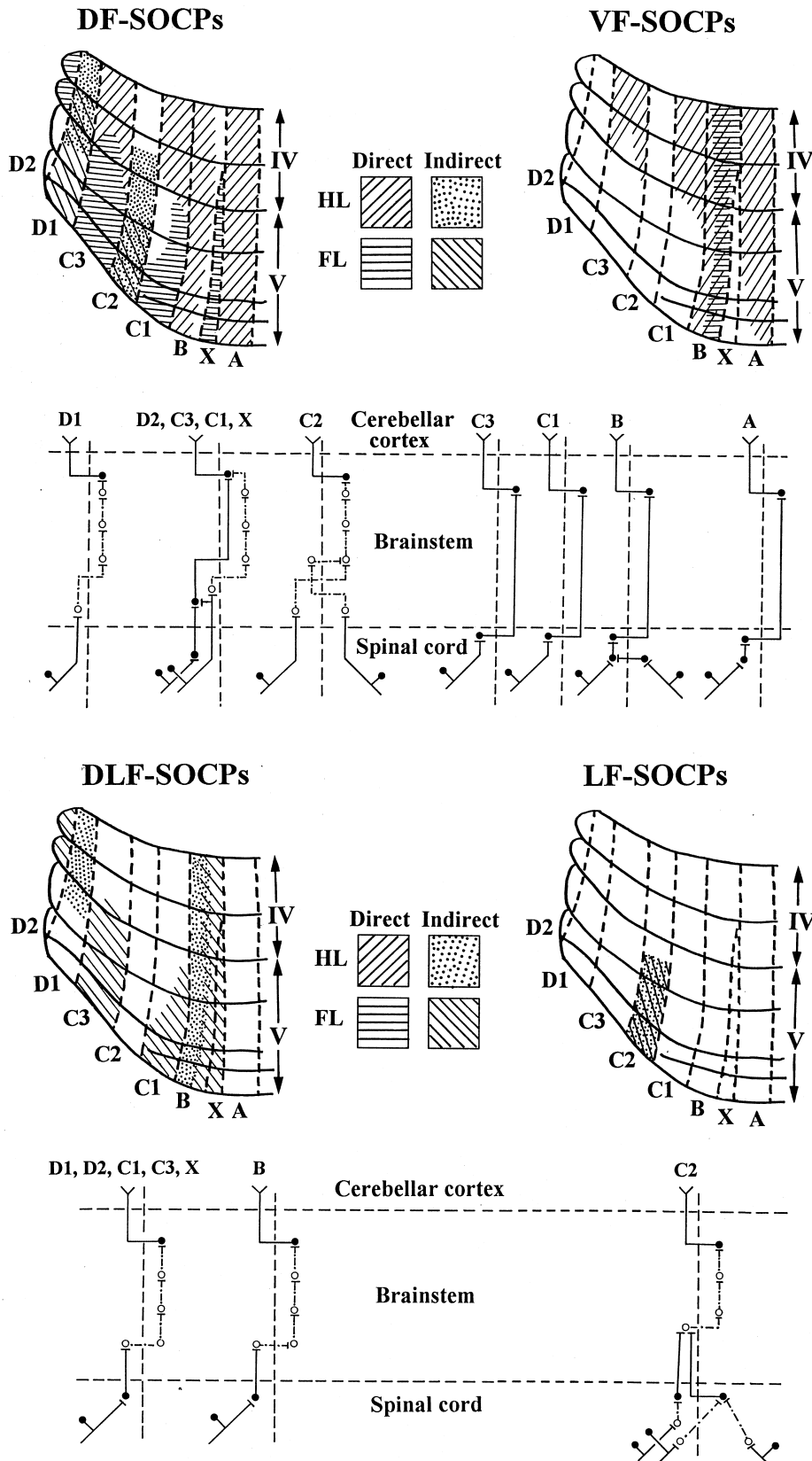


Fig. 2. Simplified diagrams to show the zonal distribution of various SOCPs in the anterior lobe of the cat cerebellum (lobules IV and V). The key indicates the cortical areas activated from fore- and hindlimb nerves via direct and indirect pathways. A breakdown of each main spinal route into a number of component pathways is shown below each cortical map. Filled relays indicate known synapses in a path, open relays indicate hypothetical synapses [modified from Ito (1984) and based on Oscarsson (1969); Larson *et al.* (1969a,b); Oscarsson and Sjölund (1977); Ekerot and Larson (1979a); Andersson and Eriksson (1981); Ekerot *et al.* (1991b)].

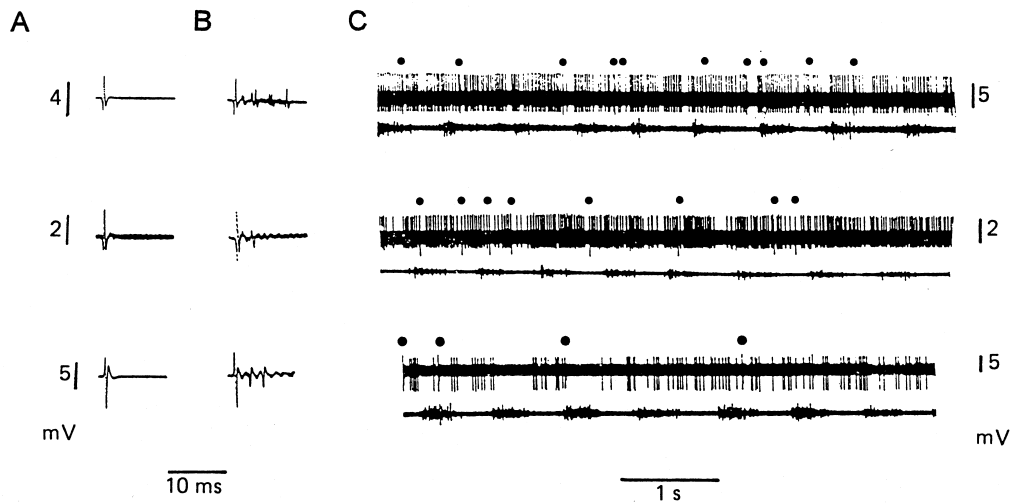


Fig. 3. Examples of the discharges of three Purkinje cells recorded in the paravermal part of lobule V in the awake cat. (A and B) The simple and complex spikes respectively of the three cells. C shows the discharge patterns during treadmill locomotion (upper traces). Complex spikes indicated by dots. Lower traces show electromyographic activity of the ipsilateral triceps brachii muscle. Note the slow, irregular rate of discharge of complex spikes. From Armstrong *et al.* (1988) (reproduced with permission).

(1992, 1994); see also Simpson *et al.* (1996) for further references].

Studies of visually activated climbing fibres in the flocculonodular lobe in intact preparations [for a recent review see Simpson *et al.* (1996)] have also reported complex spike discharge patterns that correlate to the direction and speed of eye movements. Such movements may, however, be a 'special' case as Simpson *et al.* (1996) draw attention to the fact that: "For the low speeds of retinal image motion to which the climbing fibers are best responsive, their low firing rate does not prohibit signaling of speed and direction in the conventional manner of frequency coding...".

#### 2.4. Summary of Climbing Fibre Characteristics

The inferior olive and its climbing fibre projection to the cerebellar cortex display a range of intriguing features, although the most puzzling perhaps, is the rather mixed findings concerning any relation between the complex spike discharges they generate in the cerebellar cortical Purkinje cells and different types of movement. Of course, different discharge characteristics under different experimental conditions may reflect sampling differences of Purkinje cells located at different sites within the cerebellar cortex. However, one consistent finding (at least in the awake cat) is that complex spikes fail to occur at fixed times during more stereotypical movements such as locomotion. This would seem to be a particularly surprising observation given that most olive cells receive a rich supply of ascending peripheral inputs via the SOCPs, including cutaneous afferents that are known to be activated during rhythmic movements such as walking [for example, during the stance phase when the foot is load bearing, e.g. Prochazka *et al.* (1976)]. A possible explanation is offered below.

#### 2.5. Gating of Transmission in the Dorsal Column-Medial Lemniscal System

Movement-related gating of transmission in ascending sensory pathways is a general phenomenon that has been demonstrated to occur at all levels of the neuraxis (from modulation of reflex pathways at the level of the spinal cord to gating of cerebral somatosensory evoked potentials, SEPs). Recently, the subject has been considered in some detail by Chapman (1994) [see also Prochazka (1989)] and therefore only selected data pertinent to the present subject will be considered here.

Among the first reports of such gating were those by Ghez and Lenzi (1971) and Coulter (1974) who demonstrated in the awake cat that transmission in the medial lemniscus (measured as the mass potential discharge evoked by peripheral nerve stimulation) was depressed both prior to and during active voluntary movements. Subsequently, Chapin and Woodward (1982a,b) recorded single units in the forepaw area of the somatosensory cortex of the awake rat and found that almost half of the sample ( $n = 61$ ) did not respond to receptive field stimulation during 'regular' (stereotyped) locomotion, but did respond to passive stimulation and also when the paw was involved in 'irregular' (exploratory) locomotion. A similar observation has been reported in humans in which the N28 component of cerebral SEPs was reduced in size as compared to rest during active, alternating movements of the fingers but increased in size during exploratory finger movements (Knecht *et al.*, 1993).

In the series of studies in rats by Chapin and Woodward (1982a,b) [see also Shin *et al.* (1994)] it was also demonstrated that transmission to the sensorimotor cortex fluctuates relative to the step cycle (see Fig. 4). Cells that responded to electrical stimulation of the distal forelimb during active footfall increased their discharge rate above the level of background activity just before this point in the step

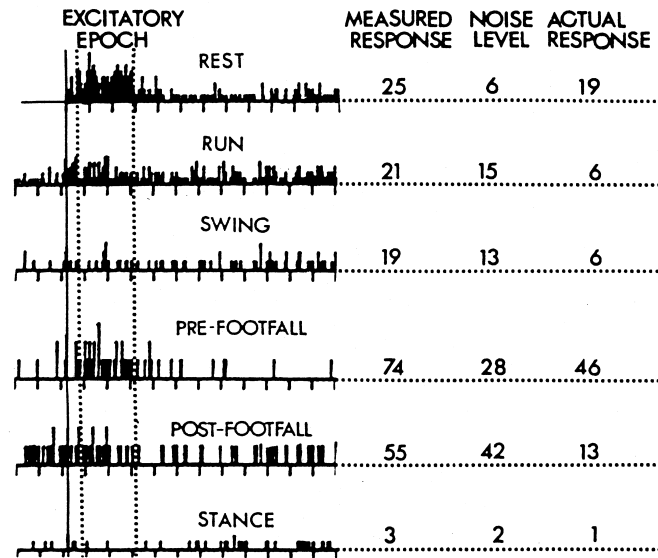


Fig. 4. Peri stimulus histograms to show the discharge frequency (in spikes  $\text{sec}^{-1}$ ) of an individual somatosensory cortical unit in response to electrical stimulation (single 0.1 msec, 0.3 mA pulses delivered at 3 Hz) applied to the contralateral forepaw at rest and during different phases of treadmill locomotion in the awake rat. Vertical line indicates time of stimulus, vertical dotted lines delimit the excitatory epoch (7–45 msec post stimulus) used to calculate the average discharge frequency (measured response). For rest and run, background discharge (noise level) was calculated from longer latency portions of the histograms (200–330 msec post stimulus). Background levels for the remaining histograms were based on average discharge rates during the excitatory epoch in control experiments in which no stimulus was delivered. In each histogram the corresponding 'noise' levels were subtracted from the measured response to produce an estimate of the firing rate due to the stimulus (actual response). By comparison to actual response at rest, note the marked increase in activity in the pre footfall phase of the step cycle and the marked decrease during stance. From Chapin and Woodward (1982b) (reproduced with permission).

cycle (i.e. were phasically 'facilitated') but reduced their discharge rate below background firing levels (i.e. were 'suppressed') during stance. Other cells which did not respond to footfall were either 'suppressed' throughout the step cycle or were 'facilitated' during early swing. Thus sensory transmission to the cerebral cortex undergoes both a tonic reduction during active movement and a time varying modulatory component. Similarly, Palmer *et al.* (1985) recorded the response of motor cortical neurones to electrical stimulation of the forefoot during locomotion in the cat. The responsiveness of the units (also judged by changes in the number of spikes in response to the cutaneous stimulus) was found to fluctuate phasically with the step cycle and in most cases this was not due to step-related fluctuations in the excitability of the cortical neurones. This suggests that the mechanism that gates sensory traffic to the motor cortex operates at a subcortical level and the results of Chapman *et al.* (1988), who recorded modulation of sensory transmission at three levels of the lemniscal system in two monkeys (at the level of the medial lemniscus, sensory thalamus and the somatosensory cortex, see Fig. 5) are consistent with this view.

At least for modulation of transmission that preceded movement, Chapman and colleagues argued that the similarity in timing of changes in amplitude at each level of the dorsal column-medial lemniscal pathway suggests that the modulation has a common origin which most probably operates at the site

of the first relay (i.e. the spinal cord or dorsal column nuclei). The same authors also noted that the depth of movement-related modulation increased at each successive level of the lemniscal system so that the suppression was most marked within the cerebral cortex [see also Shin and Chapin (1990)]. Additional modulatory mechanisms are likely therefore to act at these higher levels. However, the gating-out of responses was not without exceptions. While the recording sites reported by Chapman *et al.* (1988) always exhibited a reduction in response size prior to and/or during movement, at one third of the sites evidence for a transient facilitation prior to the response reduction was also observed, suggesting a degree of functional heterogeneity within the dorsal column-medial lemniscal system [see also Shin *et al.* (1994)].

The fact that gating of responses could occur prior to the onset of EMG activity has been taken as evidence that at least some of the modulation depends on centrifugal (i.e. descending) control mechanisms. However, movement-related activity in peripheral afferents may also play a role. For example, Abbruzzese *et al.* (1981) investigated cerebral SEPs evoked by median nerve stimulation in humans and found that the responses were reduced during both active and passive finger movements of the stimulated hand (cf. Fig. 5). Furthermore, the reductions in size of the SEPs induced by the movements were absent after ischaemic block of large group I afferents from the hand, suggesting the im-

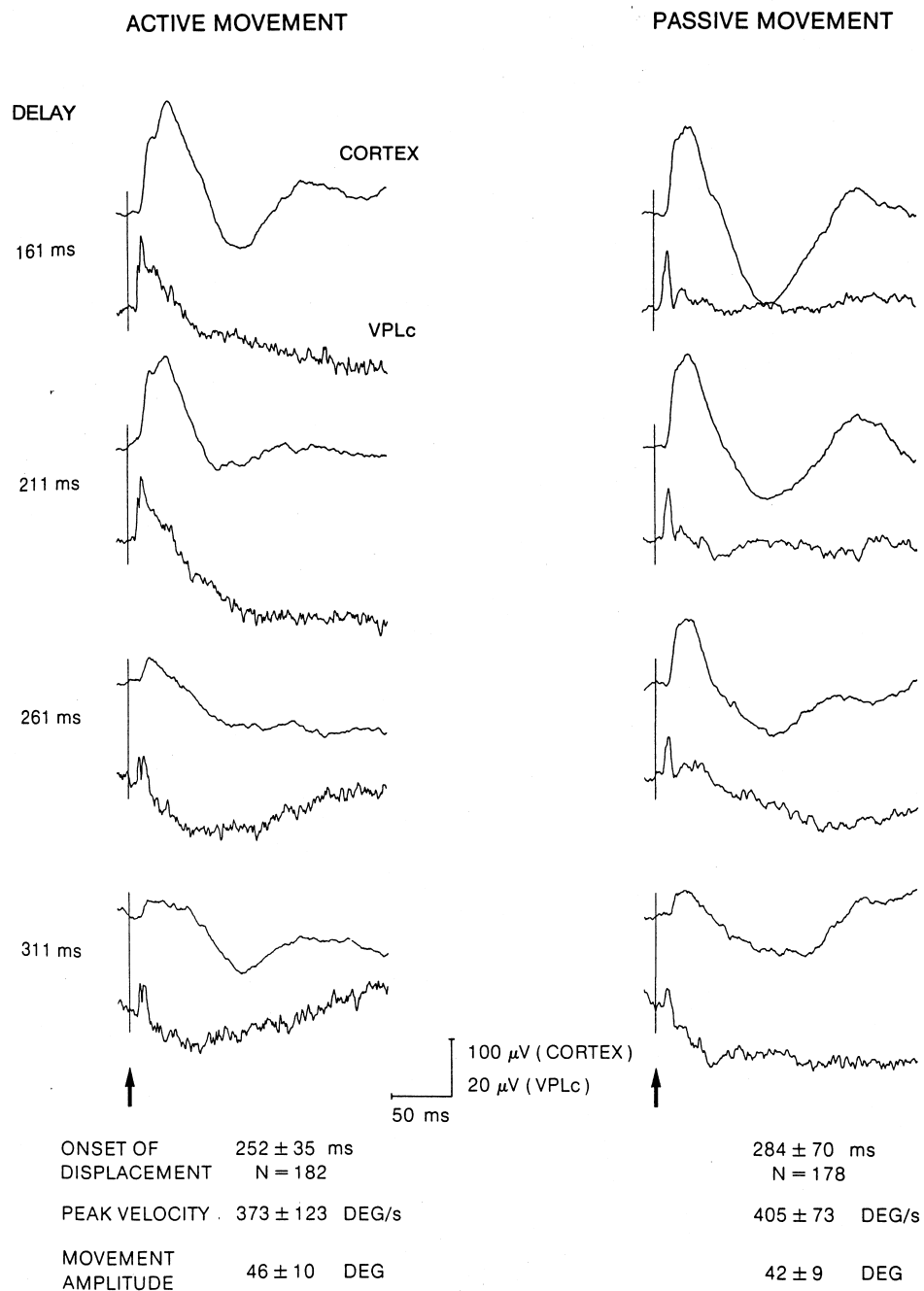


Fig. 5. Evoked field potentials in the somatosensory cerebral cortex and sensory thalamus (ventral posterior lateral nucleus, caudal division, VPLc) recorded simultaneously in the awake monkey during active and passive elbow flexion movements. Average responses ( $n = 20$  trials) evoked by an air puff stimulus (at time of arrow) directed at the receptive field area on the forearm at different time delays after an auditory cue to move. In the left hand column movement onset occurred, on average, 252 msec after the cue (details of average reaction time, peak velocity and movement amplitude are shown below). By comparison to the size of responses evoked at 161 msec delay, active movements produced a marked reduction in response size at both cortical and thalamic sites (e.g. when the stimulus was delivered at 311 msec delay). A modest but statistically significant reduction in cortical response size also occurred at 211 msec delay, that is, on average, 41 msec prior to movement onset. Note that passive movement with similar kinematics to the active movement also produced a marked reduction in response size. From Chapman *et al.* (1988) (reproduced with permission).



portance of proprioceptive inputs in generating the gating effect.

### 2.5.1. Summary of Evidence for Gating in Dorsal Column Medial-Lemniscal Pathways

Evidence for movement-related changes in transmission has been amply confirmed in sensory pathways leading to the cerebral cortex. Most studies have found that transmission is usually reduced prior to and during movement and that the depth of modulation varies in relation to different phases of cyclical movements such as stepping. However, during certain behavioural conditions such as exploratory movements, transmission in dorsal column-lemniscal pathways may be facilitated. Processing of sensory inputs to the cerebral cortex is evidently highly adaptive and the findings have been interpreted as evidence for a task-dependent mechanism by which behaviourally 'irrelevant' signals are suppressed while behaviourally 'relevant' signals are selected for higher order processing [see Prochazka (1989) and Chapman (1994) for a fuller discussion].

## 3. INDIRECT EVIDENCE FOR GATING IN CLIMBING FIBRE PATHWAYS

In studies in awake cats it is now well-established that when an animal is sitting quietly at rest without overt movement, complex spikes in individual Purkinje cells can be readily evoked by light taps or brushes of the receptive field (e.g. Armstrong *et al.*, 1988). Similarly, recordings made directly from the inferior olive in awake cats have found that in the passive animal, olive cells are 'exquisitely sensitive' to natural cutaneous stimuli with receptive fields

often confined to the paw [Gellman *et al.* (1985) see Fig. 6(A)]. Small *passive* movements of the distal joints are also very effective at evoking a response [a feature evident in decerebrate cats as well, see for example Rushmer *et al.* (1976); Kolb and Rubia (1980)]. However, in the study by Gellman *et al.* (1985) the cats were also trained to perform placing of a limb alternately onto two touch-sensitive plates and it was found that none of the olive cells ( $n = 32$ ) responded reliably at times during the active movement when the task would have been expected to elicit sensory traffic from the receptive field area [Fig. 6(D)]. Likewise, Bauswein *et al.* (1983) showed in awake monkeys trained to perform a lever task, that passive hand movements evoked an increase in complex spike discharge while self-generated active movements did not.

The difference in tactile sensitivity between the passive and the moving animal has been taken as evidence for the operation of a gating mechanism that functions during active movements to reduce transmission to the cerebellum of self-generated inputs relayed via the climbing fibre system. The operation of such a mechanism during locomotion in awake cats could account for the lack of step-related complex spike activity at times during the step cycle when there is likely to be considerable sensory traffic from cutaneous afferents. Conversely, the presence of movement-related complex spike discharge patterns in some decerebrate preparations may be explained by the possibility that the same gating mechanism has been lost or modified by decerebration (cf Kim *et al.*, 1987). On the other hand, the presence of movement-related complex spike discharges during certain types of movement in the intact animal (see for example Wang *et al.*, 1987),

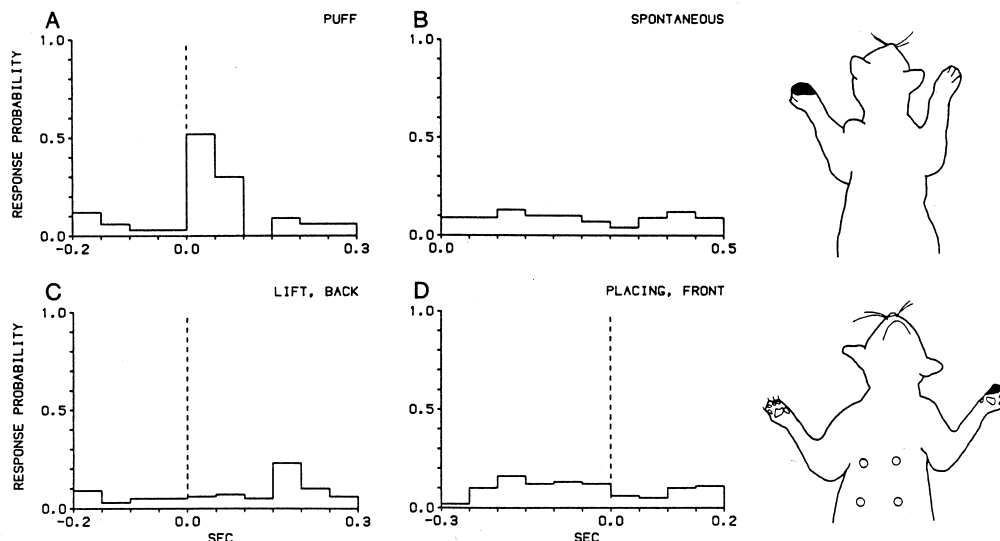


Fig. 6. Peri event histograms to show response probabilities of an individual inferior olive unit recorded in the awake cat (receptive field characteristics shown to the right). (A) In the passive animal an air puff directed at the receptive field (at time zero) produces a high probability of discharge. (B) Low spontaneous probability of discharge in the resting animal. (C) Increased probability of discharge 150–200 msec after paw lift off (time zero) in trials when the limb accidentally bumped into a barrier during a foot placement task. (D) Low probability of discharge during the same active movement despite contact with the receptive field at foot touch down (time zero). From Gellman *et al.* (1985) (reproduced with permission).

may reflect changes in SOCP transmission that are context dependent.

Given that a large number of studies have shown movement-related gating in other sensory pathways (see Section 2.5), the likelihood of a similar modulation of afferent signals in SOCPs is not altogether surprising. Nonetheless, if such a gating mechanism operates on the climbing fibre system it will have important implications regarding access of information to the cerebellar cortex by this afferent route. It is possible therefore, that studies of gating in olivocerebellar pathways will provide useful data about the type of input that is selected in a given behavioural context and, in so doing, shed light on the functional relevance of the climbing fibres in motor control.

#### 4. DIRECT EVIDENCE FOR GATING IN CEREBELLAR CLIMBING FIBRE PATHWAYS

Kennedy *et al.* (1966) were the first to provide direct evidence that sensory transmission to the cerebellum was subject to central control. In the chloralose anaesthetized cat, electrical stimulation of the ipsilateral forepaw evoked cerebellar responses (the earlier components of which were most probably mediated via the DF-SOCP) that were profoundly depressed following decerebration or cerebral cortical ablation that included the somatosensory cortex. Subsequently, Carli *et al.* (1967) provided the first

evidence in the unanaesthetized, behaving animal. A 'late component' evoked in the cerebellar cortex in cats by hindlimb nerve stimulation was suppressed during the orientating reaction produced by an arousal stimulus and during desynchronized REM sleep (see Fig. 7).

These early studies together with more recent, but indirect evidence to suggest that transmission in SOCPs is gated-out during active movements (see Section 3), prompted our research group to undertake a series of experiments to investigate the mechanisms that govern climbing fibre input to the cerebellar cortex (Apps *et al.*, 1990; Lidieth and Apps, 1990; Apps *et al.*, 1995, 1997). In particular, the series of studies aimed to address the following questions:

1. Is transmission in SOCPs reduced during active movements?
2. Do different cerebellar cortical zones differ in terms of patterns of gating their SOCPs exhibit?
3. Are there any differences in the pattern of gating between subcomponents of the SOCPs that target different sites within the same cortical zone? and
4. To what extent is any gating of transmission task dependent?

The approach used in chronically instrumented (intact) cats was similar to that used by Carli *et al.* (1967). Low intensity, single-shock stimuli were delivered to a forelimb cutaneous nerve (the super-

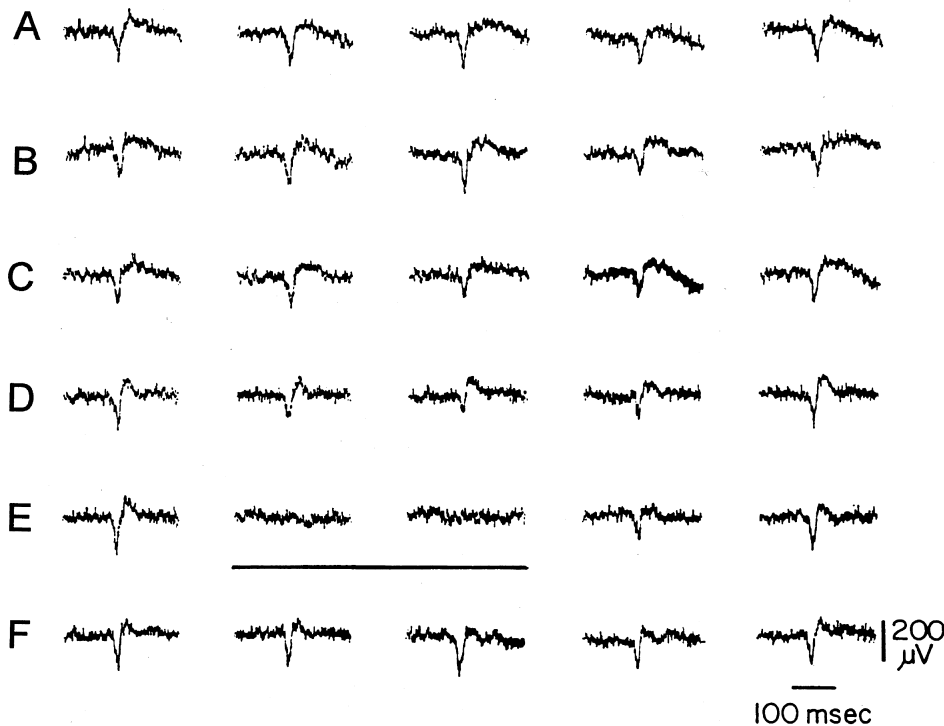


Fig. 7. Evoked cerebellar field potentials recorded from between the vermis and paravermal part of the anterior lobe following electrical stimulation of the ipsilateral tibial nerve in the intact cat. From left to right, consecutive single sweep traces. (A–C) Responses evoked during synchronized sleep and (D–F) responses evoked *ca* 1.5 min later during an episode of desynchronized sleep. Note the complete abolition of the responses in E which coincides with a burst of rapid eye movements (REM, horizontal line). From Carli *et al.* (1967) (reproduced with permission).

ficial radial) as a probe to assess excitability in climbing fibre pathways during rest and active movement. The electrical stimulation of the peripheral nerve set up volleys in the SOCPs that were recorded as evoked climbing fibre field potentials within the cerebellar cortex and changes in the size of these responses [which reflect the synchronous discharge in many climbing fibres, cf Eccles *et al.* (1968)], provided a measure of changes in transmission in the SOCPs to the different cerebellar recording sites under study.

To date, the experiments have focused on climbing fibre input to the paravermal (C1, C2 and C3) cortical zones which are thought to be particularly important in the regulation of on-going voluntary limb movements, such as those involved in stepping and reaching (e.g. Armstrong *et al.*, 1988; Edgley and Lidierth, 1988; Van Kan *et al.*, 1993). Cats were therefore trained to perform one of two types of behavioural task: locomotion on a moving belt or a forelimb reach-to-grasp movement. While the capacity to execute the former type of 'simple' repetitive movement is only transiently impaired by pyramidal tract lesions it is noteworthy that the ability to perform the latter, more demanding task is severely impaired for longer periods [e.g. Liddell and Phillips (1944); Lawrence and Kuypers (1968) see also Chapman and Wiesendanger (1982)]. The two types of movement differ in a number of important ways including their kinematics, degree of stereotypy but also the extent to which they are likely to be subject to descending control.

#### 4.1. Step-Related Gating in Spino-Olivocerebellar Paths

Initial studies investigated the possibility that transmission in SOCPs is modulated during walking and Fig. 8 shows examples of individual cerebellar climbing fibre field potentials typical of the material as a whole. Responses evoked while the animal was sitting quietly at rest are shown in Fig. 8(A) while in Fig. 8(B) the responses at the same cerebellar cortical site are shown during locomotion. It is clear that during rest [Fig. 8(A)] the responses are securely evoked and large in size while, by comparison, during locomotion [Fig. 8(B)] they are much more variable in size and usually smaller (cf Fig. 7). Thus pathway transmission has been reduced during locomotion consistent with the presence of a gating mechanism. However, given that in some cases the onset of response reduction was found to precede the onset of regular stepping, it is likely that such changes are related to the onset of active movement than to locomotion *per se* (cf Apps *et al.*, 1990).

Consistent with these findings are the results of Smith and Chapin (1996b) who studied the gating of responses of single units in the rostral dorsal accessory olive (DAO, the source of climbing fibres to the cerebellar cortical C1 and C3 zones) during rest and locomotion in rats. Snout or forepaw stimulation produced a phasic increase in olivary discharge when the animal was at rest, but produced a transient suppression of activity during treadmill locomotion. Thus, gating of SOCPs during active

movements would seem to be a general phenomenon which is likely to be present in a range of species.

In the locomotor studies by Apps and colleagues the peripheral nerve stimulus was timed to drift relative to different phases of the step cycle [see Fig. 8(B)]. As a consequence, it was also possible to investigate the extent to which SOCP excitability varied in a step-phase dependent manner. For each recording session the step cycle was divided into tenths and responses evoked by stimuli delivered in each tenth were separately pooled and averaged to generate a step histogram showing fluctuations in mean size of response during the course of the step cycle. Figure 9(A), (B) and (C) show representative step histograms constructed from data obtained from recording sites in the paravermal C1, C2 and C3 cortical zones, respectively. In each histogram it is clear that there are substantial fluctuations in the mean size of the evoked climbing fibre potentials that vary in relation to the step cycle. For the C1 and C3 zone recording sites [Fig. 9(A and C)], the responses are largest during the swing phase of the step cycle and smallest during stance, while by marked contrast, the responses at the C2 zone site [Fig. 9(B)] are largest and smallest during mid stance and swing, respectively. Results such as these imply marked differences in function between zones in terms of their SOCP input in the awake, behaving animal. Furthermore, given that the peripheral nerve volley was monitored in each case (see dashed line in each step-histogram) and was found not to vary in parallel with the cerebellar responses, it is safe to conclude that such differences are due to different central mechanisms altering excitability in the relevant SOCPs.

Additional evidence that the modulation occurred centrally rather than due to variations in the peripheral input (for instance, as a result of any possible movement-related variations in the effectiveness of the peripheral nerve stimuli) was also obtained at some C2 recording sites. Because the C2 zone receives bilateral climbing fibre input (mainly via the LF-SOCP) it was possible to record separately the patterns of step-related variations in response size evoked by stimulation of the ipsilateral and contralateral nerves (Apps *et al.*, 1990). At each of six sites the temporal variations in response size during locomotion occurred in phase, despite the fact that the two limbs are 180° out of phase during walking. Furthermore, at a number of C1, C2 and C3 zone recording sites the responses evoked by similar stimuli were monitored during two recording sessions separated by days, sometimes weeks. When in such cases the step histograms from the same recording site were compared, the pattern of step-related modulation in response size was rather similar, suggesting that the pattern of gating remained essentially stable over time (Apps *et al.*, 1995 and unpublished data).

A summary of data obtained from all three paravermal zones in lobule V of the anterior lobe is plotted in Fig. 10 [obtained by pooling results from Apps *et al.* (1990); Lidierth and Apps (1990); Apps *et al.* (1995) and additional unpublished data]. The frequency histogram of Fig. 10(A) emphasizes that the largest responses (i.e. the greatest pathway excit-

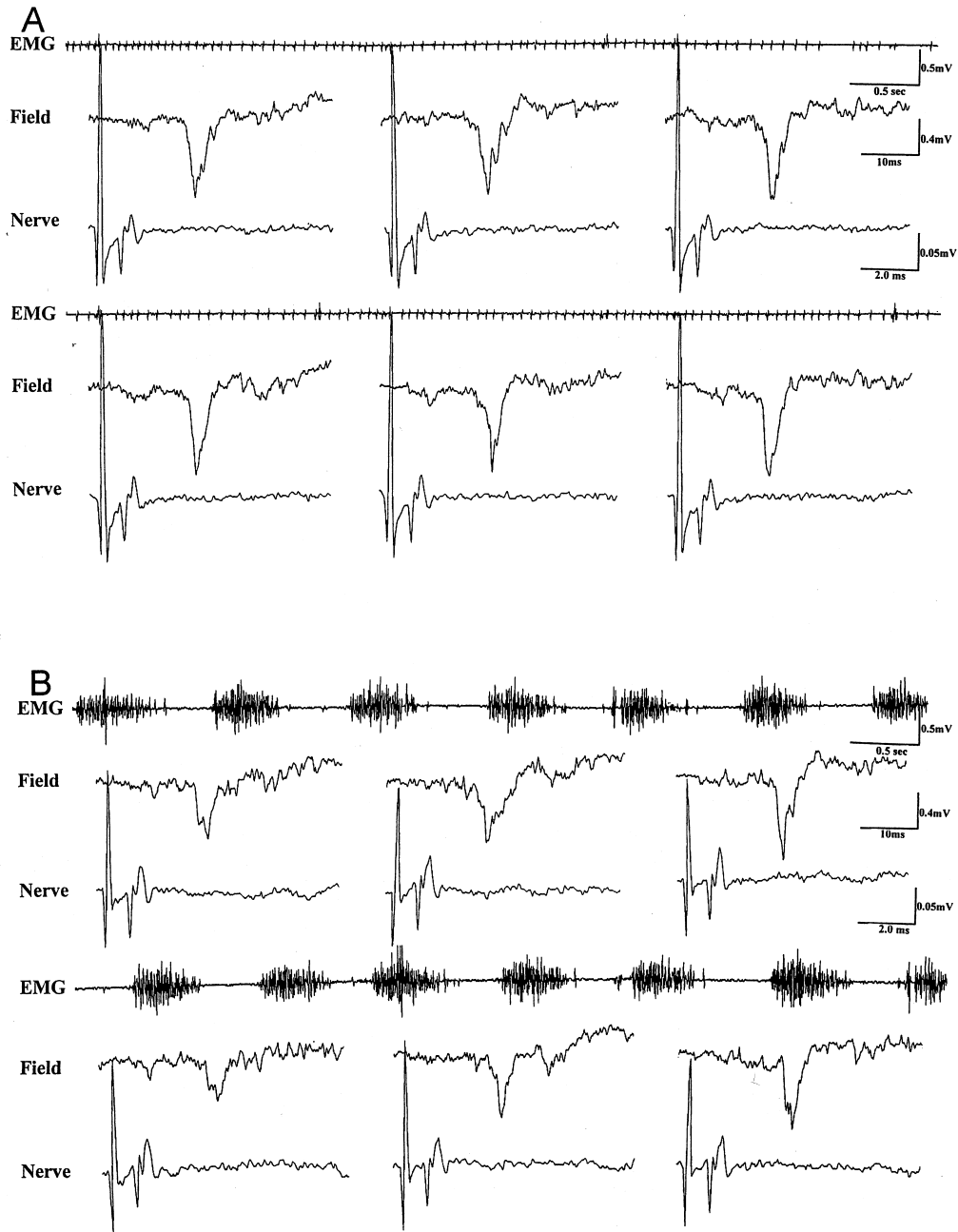


Fig. 8. Evoked cerebellar climbing fibre field potentials recorded at a C2 zone site (lobule V) during rest (A) and at the same site during locomotion on a treadmill (B). In (A) and (B) the electromyographic (EMG) trace is continuous from top left to bottom right and displays activity in the ipsilateral forelimb extensor triceps brachii. Single sweep traces below the emg show the cerebellar response (Field) evoked at 2 sec intervals by ipsilateral superficial radial nerve stimulation (intensity  $\times 2T$ ) together with the corresponding nerve compound action potential (Nerve). Each pair of single sweep traces is triggered at the onset of the stimulus (note different time bases). Note also the more variable and typically reduced size of the cerebellar responses during locomotion as compared to rest, despite relative constancy of the nerve volley.

ability) at C1 zone recording sites occurred overwhelmingly during the later part of the swing phase of the step cycle in the ipsilateral forelimb. In no fewer than 60 of 64 (94%) of the step histograms the largest responses occurred when the limb was extended forwards and down to establish footfall

(bins 9, 10 and 1 which correspond approximately to the E1 phase of the step cycle) and a similar pattern emerges for the more limited data available for the C3 zone [Fig. 10(C)]. By marked contrast, the frequency diagram of Fig. 10(B) shows that the time during the step cycle when C2 responses were

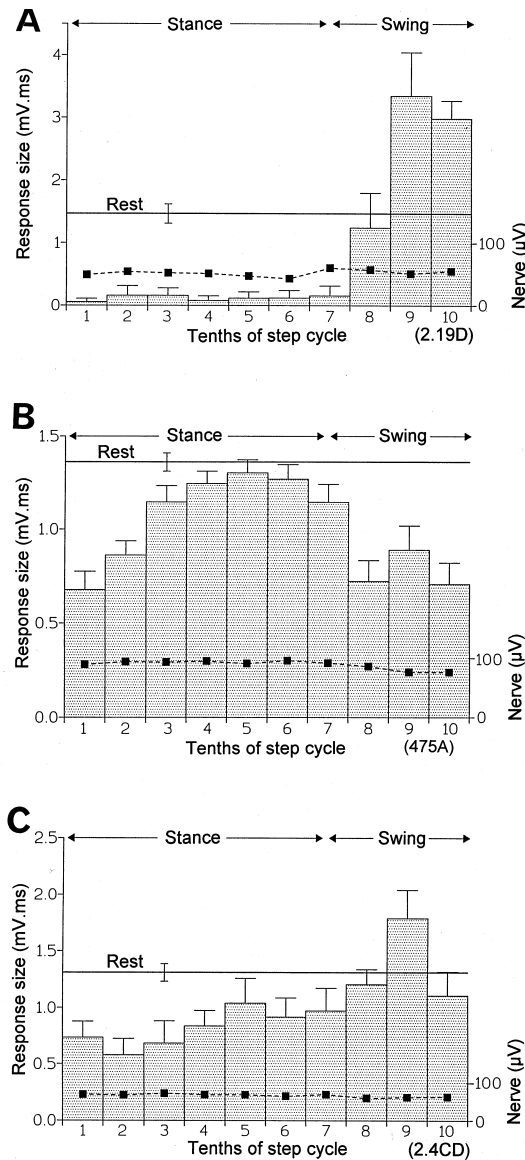


Fig. 9. Step histograms to display for different tenths of the step cycle the mean size of cerebellar climbing fibre response (+SEM) evoked by stimulation of the ipsilateral superficial radial nerve. (A, B and C) example C1, C2 and C3 zone recording sites, respectively (all located in lobule V). In each histogram bin 1 coincides with the onset of activity in the ipsilateral extensor muscle triceps brachii. The horizontal line indicates the mean size of response evoked by similar stimuli delivered in the resting animal and the dashed line indicates the peak-to-peak amplitude of the nerve volley (intensity  $\times 2T$  in each case). The periods of stance and swing are approximate timings for trajectory of the ipsilateral forelimb in this and subsequent figures.

largest, although more variable between sites, nevertheless occurred most frequently during late stance. There are therefore appreciable differences in the pattern of step-related modulation in the SOCPs that target the C1/C3 zones as compared to the C2 zone.

For comparison, the time during the step cycle when responses recorded at sites within the different

zones were smallest is shown in Fig. 10(D, E and F). For C2 zone sites [Fig. 10(E)] minimum response size (i.e. least pathway excitability) occurred throughout swing and the transition from swing to stance, while for C1 and C3 sites [Fig. 10(D and F), respectively], minimum response size occurred throughout stance but most frequently during the early part of this phase of the step cycle. This is a time when the greatest self-generated input from the paw might be expected to occur and it has been argued that the small size of C1/C3 cerebellar responses during this period of the step cycle might therefore reflect the operation of a pathway-gating mechanism designed to reduce transmission of predictable inputs resulting from the animal's own volitional movements (Lidiérth and Apps, 1990; Apps *et al.*, 1995).

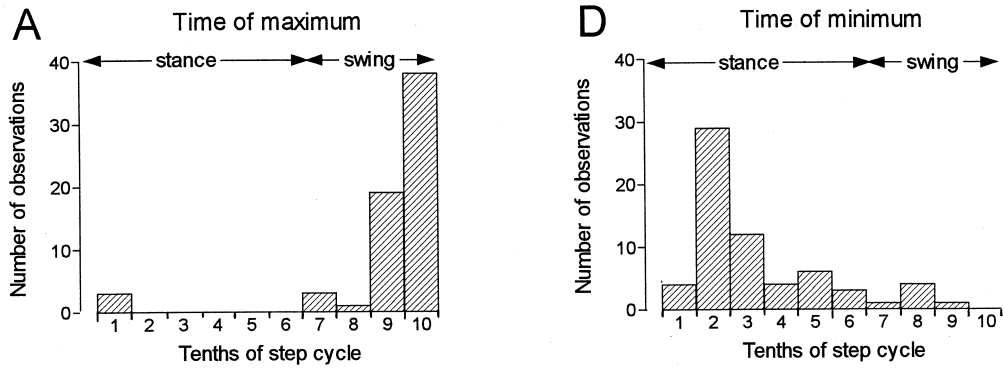
Results consistent with a gating-out of self-generated inputs have also been reported for SOCPs that relay afferent signals from the thorax to the cerebellum (Baker *et al.*, 1993). In the paralysed decerebrate cat, climbing fibre field potentials were evoked in the vermal B zone by electrical stimulation of intercostal nerves at different times during the respiratory cycle. The responses were most probably mediated via the VF-SOCP and in a similar fashion to the findings during locomotion, the phasic activity of the respiratory central pattern generator was found to exert a modulatory influence so that response size was smallest during the inspiratory phase when self-generated afferent traffic is most likely to occur. Thus phase-related modulation of transmission during repetitive movements may be a general feature of SOCPs which may serve to gate-out predictable inputs.

#### 4.1.1. Facilitations and Depressions During the Step Cycle

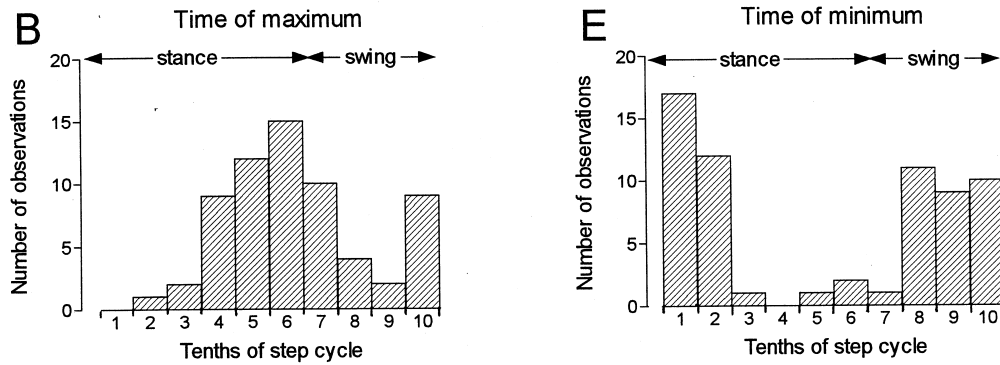
In the study by Apps *et al.* (1995) [see also Apps and Hartell (1995)] an additional difference between the C1/C3 and C2 zone recording sites was revealed when the size of responses evoked during rest was compared with the size of responses evoked by similar stimuli during walking. While the largest responses at C1 and C3 sites during locomotion were often considerably larger than during rest, the smallest responses were usually smaller. In other words, the step-phase dependent modulation involved both depressions and facilitations relative to rest [compare individual bin heights with the horizontal lines in Fig. 9(A and C)]. By contrast, at C2 sites [e.g. Figure 9(B)] the largest responses during locomotion were usually similar in size to rest, while the smallest responses were consistently smaller, that is, both facilitations and depressions were usually present at C1 and C3 sites [Fig. 11(A and C)] while depressions were the more common finding at C2 zone sites [Fig. 11(B)], providing further evidence to suggest differences in function between zones in the awake, behaving animal.

The effect of stimulus intensity was also investigated systematically by Apps *et al.* (1995) [see also Lidiérth and Apps (1990)] and it was found that when stimulus strength was increased, the depth of the step-related modulation in SOCP excitability

## C1 Zone



## C2 Zone



## C3 Zone

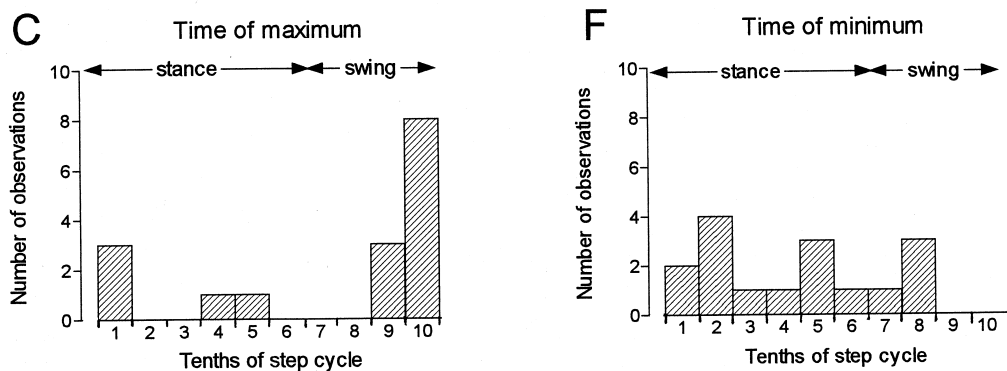


Fig. 10. (A–C) Frequency distributions of the time during the step cycle in the ipsilateral forelimb when the largest SOCP responses were evoked by ipsilateral superficial radial nerve stimulation. (A) C1 zone step histograms ( $n = 64$  histograms from a total of 21 different recording sites); (B) C2 zone step histograms ( $n = 64$  histograms from a total of 25 different sites); and (C) C3 zone step histograms ( $n = 16$  histograms from a total of seven different sites). (D–F) Same as (A–C) but for time of smallest SOCP response [based on Apps *et al.* (1990, 1995); Lidieth and Apps (1990) and unpublished data.].

was usually reduced. At C1 sites for example, the reduction in response size during the stance phase was less pronounced, however, no relationship was found between stimulus strength and the extent to

which the largest responses were facilitated. Furthermore, facilitations were present at some sites when depressions were not and vice versa. Taken together these observations suggest that at least two

different mechanisms might be operating during locomotion: one to increase and one to decrease pathway excitability. In terms of functional significance, the fact that the reduction in pathway excitability was found to be sensitive to the strength of the stimulus implies that larger sensory inputs (such as those that would arise following a substantial perturbation to an ongoing movement) may effectively 'override' or at least partially survive the SOCP gating, irrespective of the phase of the step cycle in which they occur.

#### 4.1.2. Intrazonal Differences in Step-Related Gating

Clear differences in the pattern of step-related gating at different sites within the C2 zone provides good evidence that there may be functionally distinct subpaths within the SOCPs that terminate in different parts of that zone. It remains, however, to be established whether there is a corresponding detailed topography within the olivocerebellar projection from rostral MAO [the source of climbing fibres to the cortical C2 zone, e.g. Trott and Apps (1993)]. By contrast, anatomical studies have shown a clear difference between the medial and lateral halves of the C1 zone which receive their climbing fibre input from rostral DAO and middle parts of MAO, respectively (e.g. Trott and Apps, 1991). These differences in connectivity might be accompanied by differences in function and some evidence in favour of such differences was obtained by Apps *et al.* (1995). Recording sites located medially and laterally within the C1 zone (in lobule V) displayed a small difference in step timing of their largest responses which occurred most frequently in step tenths 9 and 10, respectively.

However, the possibility of more pronounced intrazonal differences in the pattern of step-related gating has been investigated more recently for sites distributed at different rostrocaudal loci within the C1 zone (Apps and Lee, 1997). By comparison with C1 sites in the anterior lobe (lobule V), many C1 sites in the posterior lobe (rostral paramedian lobule) exhibited a very different pattern of step-related modulation because time of largest response occurred most frequently during the stance phase of the step cycle. In other words, significant differences have been found in the pattern of gating observed within the C1 zone, implying functional heterogeneity between its different parts. Given that the gating is likely to occur at a pre-cerebellar level (see Section 5), evidence has therefore been obtained from both the C1 and C2 zones to suggest that some olive cells which are likely to be in close proximity to each other [because they provide climbing fibres to the same cortical zone, see Trott and Apps (1991, 1993)], are not electrotonically coupled during locomotion (cf De Zeeuw *et al.*, 1997).

Different sites within the C1 and C2 zones (at least in lobule V) also differed markedly in their stimulus intensity dependence as determined in the resting animal (Apps *et al.*, 1995 and unpublished observations). At some sites within a zone an increase in intensity from 2 to 3T (where T is threshold for the most excitable fibres in the nerve) produced a substantial increase in response size,

while at other sites within the same zone, a similar change in intensity produced little or no effect on response size. The weight of evidence therefore suggests that different parts of individual paravermal cerebellar cortical zones are likely to be the terminus of different subcomponents of the associated SOCPs (cf Ekerot and Larson, 1979a,b).

#### 4.2. Summary of Step-Related Modulation Studies

Changes in climbing fibre response size during stepping provide clear evidence that SOCP excitability can be modified during active movements. Furthermore, the phasing of the step-related modulations is similar at C1 and C3 zone sites but strikingly different in the intervening C2 zone. The similarity between C1 and C3 sites is not altogether unexpected, given that both zones receive climbing fibre input mainly via the DF-SOCP and that some olive cells in rostral DAO (which act as relays for the DF-SOCP), have been shown to have axons that branch to supply climbing fibres to both zones [Ekerot and Larson (1982) see Fig. 1(B)]. By contrast, the C2 zone receives its climbing fibre input mainly via the LF-SOCP which relays within an entirely separate part of the inferior olive (rostral MAO). Thus, modulation of pathway excitability in the SOCPs supplying different paravermal cortical zones can differ, implying a marked functional difference between zones, as originally hypothesized by Oscarsson (1980). However, since different sites within a single cortical zone can differ not only in their pattern of step-related gating, their stimulus intensity dependence, but also the presence of response facilitations relative to rest, it is evident that the SOCPs projecting to all parts of a given zone cannot be regarded as functionally uniform.

#### 4.3. Reaching-Related Gating in Spino-Olivocerebellar Paths

The paravermal zones are implicated in the control of voluntary reaching movements and the possibility that SOCP excitability changes may also occur during a reaching task has also been investigated. In an approach similar to that employed in the locomotion experiments, low intensity electrical stimuli have been delivered to the reaching limb during different phases of a reach-to-grasp movement while recording multiunit activity from the inferior olive (Horn *et al.*, 1996) or evoked climbing fibre field potentials in the cerebellar paravermal zones (Apps *et al.*, 1997). In both of these studies the most common finding was that the stimulation generated the largest evoked responses while the animal was sitting quietly at rest while stimulation during reaching usually produced smaller responses, suggesting that transmission in the SOCPs was reduced during the task. In Fig. 12 example responses are shown from a C1 zone recording site obtained in the study by Apps *et al.* (1997). A progressive reduction in response size is evident over the course of the reaching movement (despite constancy of the nerve volley) with the smallest climbing fibre responses (marked with a dot) occurring during the grasp phase. Note also the earlier response attributable to activity in

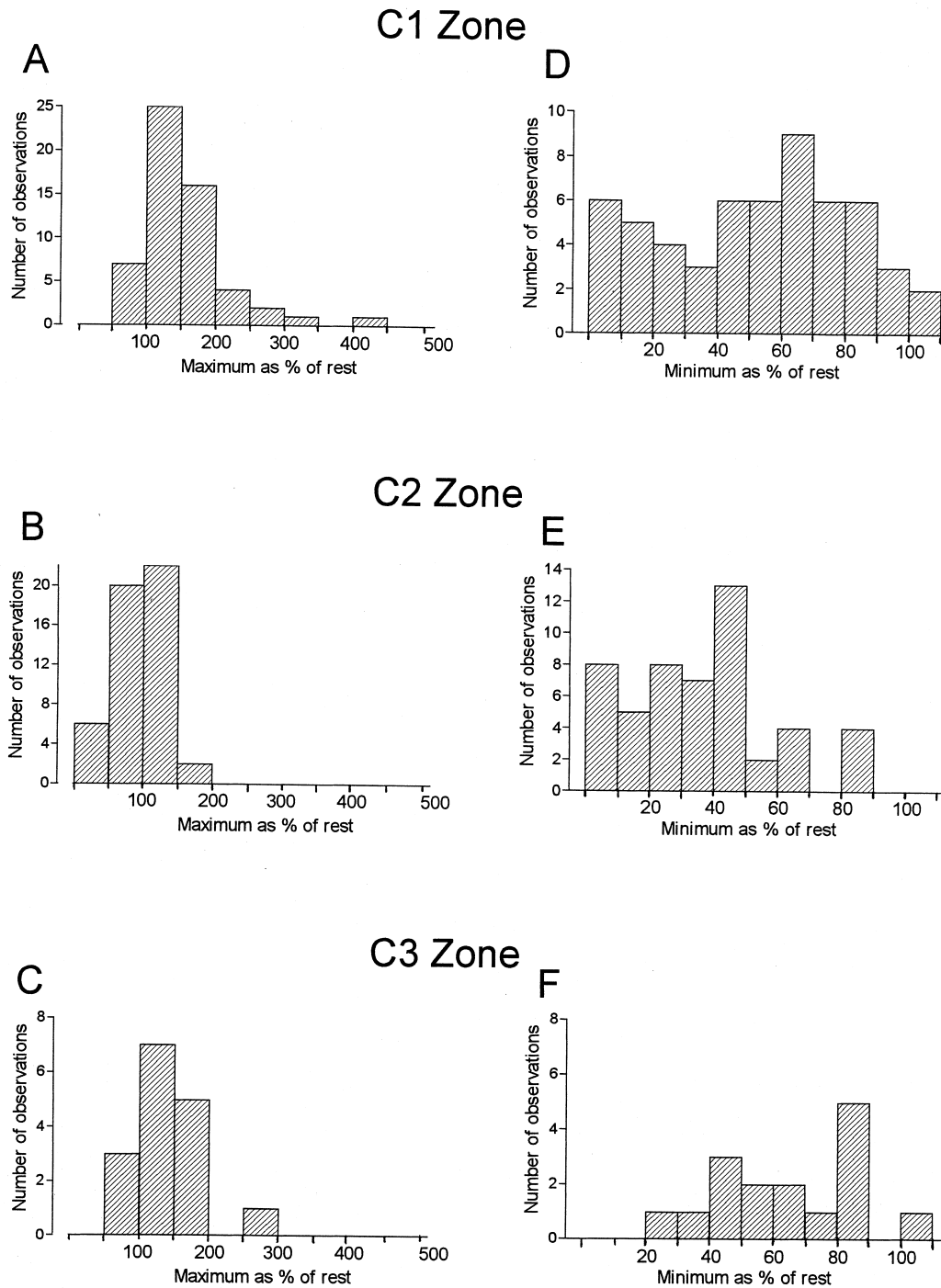


Fig. 11. Frequency distributions of response size during locomotion as compared to rest. (A–C) For each step histogram the step cycle tenth with the largest mean response size is shown expressed as a percentage of mean response size in the resting animal (100%). (D–F) Same as (A–C) but for the step tenth with the smallest mean response size during locomotion. (A and D)  $n = 56$  step histograms from 15 C1 zone recording sites; (B and E)  $n = 51$  step histograms from 14 C2 zone sites; (C and F)  $n = 16$  step histograms from seven C3 zone sites. Based on Apps *et al.* (1995); Apps and Hartell (1995) and unpublished data.

mossy fibre pathways which shows a similar, but much less pronounced reduction in response size over the course of the movement. Similar findings were obtained at other sites, including those located

in the C2 and C3 zones and the findings for the climbing fibre responses are summarized in Fig. 13. For each recording session the mean size of response in the grasp phase of the task has been expressed as



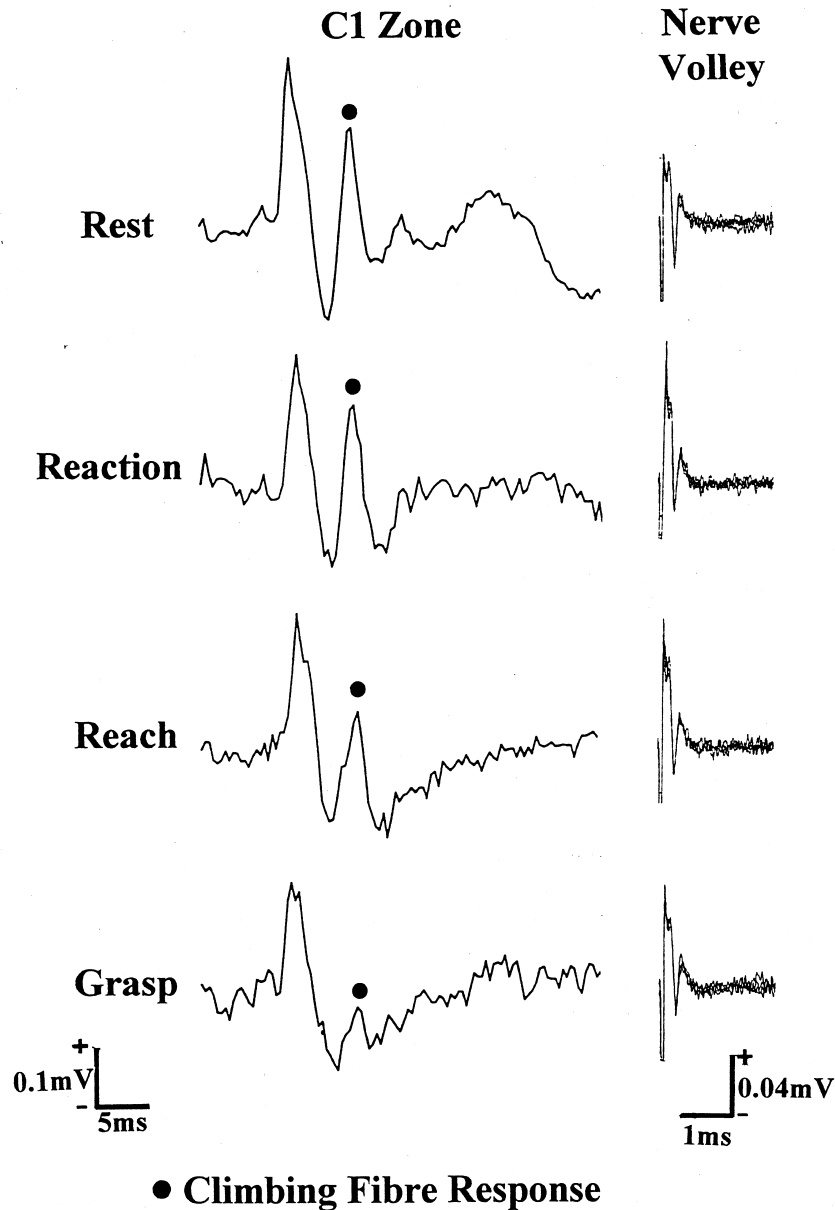


Fig. 12. Evoked cerebellar field potentials recorded from a C1 zone site (lobule V) during rest and three phases of a reaching movement (average responses based from top to bottom on  $n = 49, 7, 14$  and  $6$  sweeps, respectively). Responses evoked by ipsilateral superficial radial nerve stimulation (intensity  $\times 3T$ , delivered at the start of each trace). The right hand column shows the corresponding nerve volley ( $n = 4$  sweeps superimposed). Cerebellar responses marked with a filled circle are attributable to activation via climbing fibres while the responses at shorter latency are the result of activation via mossy fibres. Note the progressive reduction in climbing fibre response size during the task. [Modified from Apps *et al.* (1997).]

a percentage of mean size at rest and it is clear that at most sites the responses are reduced. However, it is also evident that considerable differences occur between sites in the extent to which their responses are reduced relative to rest. Such differences provide additional evidence that there may be subcomponents of the DF- and LF-SOCPs that differ in the extent and manner in which they are modulated during movements.

#### 4.4. Gating of Olivary Transmission During Motor Learning

A number of studies have also investigated the possibility that olive cell activity is gated-out during classical conditioning. In particular, the eyeblink associative learning paradigm has been used in rabbits to show that there is a reduction in unconditioned stimulus-induced multiunit activity in the olive fol-

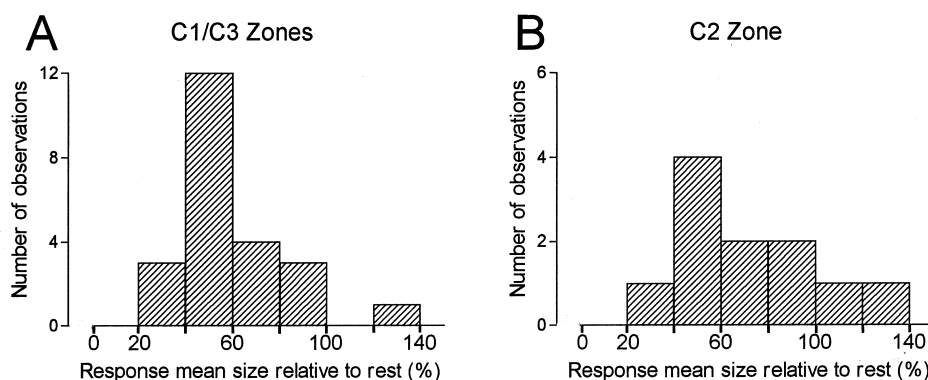


Fig. 13. Frequency distributions of mean response size during the grasp phase of a reaching task as compared to rest (100%). (A) Responses from 23 histograms obtained from a total of 10 C1 and C3 zone sites; (B) responses from 11 histograms obtained from a total of six C2 zone sites. [Modified from Apps *et al.* (1997).].

lowing acquisition of a conditioned response (Sears and Steinmetz, 1991). A similar phenomenon has also been reported for evoked climbing fibre field potentials and complex spikes recorded in the cerebellar cortex (Hesslow and Ivarsson, 1996; Kim *et al.*, 1998). Given that the conditioned response in such experiments is a movement which usually starts just prior to the unconditioned stimulus (US), it is possible that the reduction in US-evoked climbing fibre activity during learning is the result of the conditioned movement. The modulation of transmission in climbing fibre pathways observed during associative learning may be due, therefore, to a movement-related mechanism similar to the gating that occurs during other types of behaviour.

## 5. POSSIBLE SITES FOR MODULATION OF SENSORY TRANSMISSION TO THE CEREBELLUM

Given the potency of the climbing fibre synapses on the cerebellar Purkinje cells it is unlikely that a significant modulatory influence will act at the level of the cerebellar cortex. Purkinje cells discharge complex spikes in response to climbing fibre inputs even when they are subjected to the most intense inhibitory actions of the cerebellar cortical interneurons [Eccles *et al.* (1966b) see also Apps *et al.* (1990) for additional points that argue for excluding the cerebellar cortex as a site for the modulation]. On the other hand, the synaptic complexity of the SOCPs provides ample scope for descending and/or ascending control to be exerted at one or more of the pre-cerebellar relay sites involved. For example, the DF-SOCP which is the most thoroughly studied of the various ascending pathways, could be modulated at the level of the spinal cord, and/or the dorsal column nuclei (Ekerot and Larson, 1979a; Ekerot *et al.*, 1991b) and/or the inferior olive (see Fig. 2).

### 5.1. Descending Control at the Level of the Spinal Cord

Convergence of ascending and descending paths has been demonstrated onto spinal interneurons including cells that give rise to direct spino-olivary fibres associated with the VF-SOCP (e.g. Lundberg and Voorhoeve, 1962; Lundberg *et al.*, 1962; Andersson and Sjölund, 1978; Sjölund, 1978). Indeed, direct evidence for modulation of SOCP transmission at the segmental level was obtained in chloralose anaesthetized cats by Andersson and Sjölund (1978) who altered the excitability of spinal reflex arcs by administration of L-Dopa or Clonidine and found that transmission in subcomponents of the VF-SOCP was profoundly affected. Similar actions have been shown to be produced by electrical stimulation of inhibitory descending tracts, demonstrating that transmission in the pathways under study was subject to supraspinal control (Sjölund, 1978). In a similar fashion, it is well established that descending systems can profoundly modify the activity of postsynaptic dorsal column neurones (e.g. Noble and Riddell, 1989). Thus descending influences also have the potential to regulate transmission at the segmental level of sensory signals relayed via the DF-SOCP.

### 5.2. Descending Control at the Level of the Dorsal Column Nuclei

Physiological studies have demonstrated that convergence of ascending and descending olivary pathways can also occur at the level of the dorsal column nuclei. In the anaesthetized cat, Andersson (1984a) found that climbing fibre responses evoked in the C1 and C3 cerebellar cortical zones, following stimulation of the posterior sigmoid gyrus and following stimulation of ipsilateral forelimb nerves, were both reduced when local anaesthetic was topically applied to the caudal half of the cuneate nucleus. The cuneate nucleus is therefore a relay in a cerebro-olivocerebellar pathway and is also the site of a relay for forelimb-related SOCPs. Moreover, evidence has been obtained to indicate

that these ascending and descending pathways can influence one another. The activity patterns of Purkinje cells located in the medial part of the paravermis (most probably in the C1 zone) were recorded in the anaesthetized cat by Leicht *et al.* (1973), and it was found that a conditioning electrical stimulus applied to the precruciate cortex produced a suppression of complex spikes evoked by a subsequent peripheral mechanical stimulus. Similarly, the somatosensory responses of cells in rostral DAO (the source of climbing fibre afferents to the cerebellar C1 and C3 zones) have been shown in anaesthetized cats to be suppressed following electrical stimulation of the magnocellular red nucleus (Weiss *et al.*, 1990). It is likely, however, that the modulation of climbing fibre transmission reported in both of these studies was mediated by mechanisms acting on the SOCPs at a level (or levels) prior to the olive, because a direct projection to rostral DAO from the magnocellular red nucleus does not seem to be present in cats (e.g. Saint-Cyr and Courville, 1982; Robinson *et al.*, 1987) and the cerebral cortico-olivary projection is rather weak if not absent (e.g. Saint-Cyr, 1983).

In light of the extensive descending inhibitory projections to the dorsal column nuclei they are likely candidates for the site of action of rubro- and cortico-fugal pathways and consistent with this possibility are the anatomical results of McCurdy *et al.* (1992). In a combined anterograde and retrograde tracing study of forelimb motor pathways in cats they showed spatial overlap in the cuneate nucleus between rubro- and cortico-fugal terminations and cuneo-olivary cells that target rostral DAO. Convergence of these descending paths onto cuneate cells projecting to the olive may therefore provide the anatomical substrate for at least some of the modulation of peripheral sensory inputs relayed via the climbing fibre system.

### 5.3. Descending Control at the Level of the Inferior Olive

Concerning possible convergence of ascending and descending pathways at the level of the inferior olive, Miller *et al.* (1969a) [see also Leicht *et al.* (1973)] demonstrated in the anaesthetized cat, that complex spikes could be evoked in individual Purkinje cells by electrical stimulation in the somatosensory cerebral cortex or by stimulation of a number of SOCPs (DF, DLF and VF). Electrical stimulation of midbrain regions (Miller *et al.*, 1969b) revealed a similar convergence of descending and ascending (DLF-SOCP) inputs onto a narrow strip of cortex within the anterior lobe. Likewise, Andersson and Nyquist (1983) reported a parallel distribution pattern of climbing fibre responses evoked in the cerebellar zones following stimulation of the sensorimotor cortex as compared to the zonal distribution following peripheral nerve stimulation [see also Andersson *et al.* (1987)]. It is apparent therefore that cortical Purkinje cells can receive climbing fibre information from the cerebral cortex and from one or several ascending paths. However, the convergence of these inputs may not necessarily occur at the level of the olive. Given that complex

spikes (e.g. Armstrong *et al.*, 1988) or olive cell discharges (Horn *et al.*, 1996) occur spontaneously at similar rates during rest and during movement, olive cell excitability does not seem to be reduced during movements. Instead, any modulation of transmission in the SOCPs seems more likely to occur at a pre-olivary site as detailed above. Nevertheless, powerful inhibitory mechanisms have been demonstrated within the inferior olive (e.g. Armstrong and Harvey, 1966; Andersson, 1984b; Andersson *et al.*, 1988) and inhibitory pathways to the olive have been well documented [in particular, the GABAergic cerebellar nucleo-olivary projection, e.g. Angaut and Sotelo (1989) and De Zeeuw *et al.* (1989)]. Moreover, direct cerebellar inhibition of the olive is thought to provide the mechanism for the reduction of US-evoked climbing fibre responses observed during motor learning (Hesslow and Ivarsson, 1996; Kim *et al.*, 1998). At this juncture it would seem therefore unwise to rule out entirely the possibility that a modulatory influence at the level of the olive is involved in the control SOCP transmission during movement.

### 5.4. Ascending Control Mechanisms

A consideration of the potential sites and mechanisms responsible for modifying transmission in SOCPs would not be complete without considering the evidence for a contribution by peripheral afferents and Leicht *et al.* (1973) were among the first to provide such evidence. In anaesthetized cats they reported that complex spikes evoked in individual Purkinje cells by mechanical vibration applied to receptive fields located on the limb were inhibited following a conditioning cutaneous stimulation (with an air puff) applied to the same limb but outside of the excitatory receptive field. By contrast, the conditioning stimulus had no effect on the simple spike activity of the same Purkinje cells, showing that the afferent inhibition was exerted at a pre-cerebellar level. Also, more recently, Jörntell *et al.* (1996) have shown that complex spikes of single Purkinje cells in the cerebellar cortical C3 zone are driven by inputs from both cutaneous and muscle afferents. Thus raising the possibility that inputs from different modalities may interact during movement to provide an additional form of peripheral afferent control.

The dorsal column nuclei are a potential site of action for sensory afferent inhibition of SOCPs and Lidieth (1991) obtained direct evidence consistent with this possibility. Climbing fibre responses evoked in the cerebellar cortical C1 and C3 zones by forelimb electrical stimulation (mediated via the DF-SOCP) were greatly reduced in size following stimulation of another forelimb nerve at low intensity, while topical application of the GABA antagonist bicuculline to the surface of the dorsal column nuclei reduced the effect of the conditioning stimulus. Thus at least some of the sensory afferent control of transmission was shown to occur at this level of the DF-SOCP.

### 5.5. Summary of Evidence for Sites of Modulation

Modulation of SOCPs is possible at any one or more of the synaptic relays present in each path. Since each level receives substantial descending inputs there is ample scope for supraspinal mechanisms to exert a controlling influence on transmission, particularly at the level of the dorsal column nuclei. However, other peripheral inputs occurring concurrently or slightly earlier may also play a significant role in the regulation of sensory inputs mediated to the cerebellum via the climbing fibre system during active movements.

## 6. THE INFERIOR OLIVE AS AN ERROR DETECTOR

Although the precise function of the inferior olive remains poorly understood [for a review of current points of view see Simpson *et al.* (1996)], one theory that has attracted considerable interest is the 'comparator' or 'error detector' hypothesis (Miller and Oscarsson, 1970). Convergence of ascending and descending inputs at (or before) the level of the inferior olive was used as principal evidence for constructing the hypothesis, which postulates that information forwarded to the cerebellum about motor commands from higher levels can be compared with information ascending from lower motor centres. On the basis of such an integration of inputs related to 'intended' and to 'achieved' motor performance, the cerebellum might be able to apply appropriate compensations to evolving movements so as to prevent or minimize the development of mismatches between intention and achievement. In relation to gating of transmission in SOCPs, the observation that peripheral signals are less well transmitted at certain times during active movements may indicate that these are times when it would be 'undesirable' for any error signal to be relayed to the cerebellum [as it may lead to a behaviourally inappropriate change in cerebellar output, cf Forsberg (1979)]. Conversely, times during a movement when SOCP transmission is facilitated may indicate when it would be behaviourally appropriate for an error signal to be relayed to the cerebellum (see Section 7).

Evidence in favour of the climbing fibres signalling errors in motor performance has been obtained in a range of studies. In particular, an extensive literature has focused on the conditions in which complex spikes are discharged in relation to errors in eye movements. However, such studies have been extensively reviewed [see, for example, Ito (1984) and Simpson *et al.* (1996)] and the present account will focus instead, on evidence relating specifically to SOCPs and the conditions in which they are activated during voluntary movements such as locomotion. Thus, Andersson and Armstrong (1987) recorded the complex spike discharge patterns of Purkinje cells in the cortical B zone in intact cats walking on a horizontal ladder and found that when ladder locomotion was subjected to an intermittent perturbation (an unexpected rung drop), about half of the cells responded with an increase in probability

of complex spike occurrence *ca* 40–120 msec after the onset of rung displacement. On average, the response probability was an increase of *ca* 0.4 per trial (i.e. four complex spikes in ten trials). Similarly, Gellman *et al.* (1985) reported that when a cat accidentally bumped its paw against an obstacle during transfer from one foot plate to another, nine of ten olive cells studied exhibited an increase in probability of discharge, although the increase in probability was again modest [in the one case illustrated the increase in probability was 0.23, see Fig. 6(C)].

Given the usually rather low probability of occurrence of complex spikes in response to such external perturbations it might be argued that the climbing fibre system is not a very reliable pathway for reporting movement 'errors' to the cerebellum. However, according to the comparator hypothesis, SOCPs signal mismatches between intended and achieved movements, rather than peripheral events. Precisely what was 'intended' on each trial when an animal encounters an unexpected obstacle is more difficult to gauge and it is possible that this may alter from trial to trial. Furthermore, if each olive cell reports only a certain type of movement error then it is possible that it will respond on some occasions but not on others. Also, signals may be encoded by groups of olive cells. The combined action of many climbing fibres on arrays of cerebellar cortical Purkinje cells may then result in any fluctuations in response probability being averaged out by the extensive convergence within the cortico-nuclear projection. Such a possibility is open to experimental test by recording from individual deep cerebellar nuclear neurones during a perturbation or, alternatively, recordings could be made simultaneously from a number of cerebellar Purkinje cells.

To date, the latter possibility has been investigated and the complex spike discharge patterns from arrays of up to five sagittally aligned Purkinje cells in the paravermis have been recorded simultaneously during locomotion in the decerebrate ferret (Lou and Bloedel, 1992). Consistent with the error detector hypothesis, intermittent perturbations of the step cycle were found to evoke 'synchronous' climbing fibre activity, that is, a complex spike in one Purkinje cell within 80 msec of the occurrence of a complex spike in another. Interestingly, the combination of Purkinje cells that responded in successive trials varied considerably, although as a population they faithfully signalled the perturbation.

To summarize, in certain behavioural conditions the climbing fibre system may signal the occurrence of unexpected external perturbations of movement, and as much as these can be regarded as producing a mismatch between intended and achieved movement the climbing fibre activity may represent an error signal. Gating of transmission in SOCPs may then reflect that signalling of such errors is 'permitted' only at certain times during a movement (see Section 7). On the other hand, the observation that complex spikes can be activated in relation to some movements in which no external perturbation has been applied (e.g. Wang *et al.*, 1987; Mano *et al.*, 1986), may be due to the gating mechanism(s) being context-dependent so that transmission of self-gen-

erated sensory signals is 'permitted' during certain types of behaviour but not others.

### 7. POSSIBLE FUNCTIONAL SIGNIFICANCE OF GATING IN SPINO-OLIVOCEREBELLAR PATHS

The C1 and C3 zones receive climbing fibre input exclusively from the ipsilateral limb and are presumably concerned with its control alone. In light of the possible role of the climbing fibres in signalling 'errors' to the cerebellum [or more precisely unexpected events as suggested by Gellman *et al.* (1985)] one possible function of increased pathway excitability at C1 and C3 sites during the swing phase of the step cycle is that it reflects: "...the existence of a temporally tuned transcerebellar mechanism, designed to intervene in the execution of the current step when an obstacle is contacted as the limb is manoeuvred towards footfall." (Apps *et al.*, 1995). However, a slight modification of this statement may be required, because the time of best transmission at C1 and C3 sites occurred most frequently during late swing, that is, at a time when the limb is fully extended just prior to footfall. As a result, it seems likely that the limb will be committed to completing that particular step with insufficient time for any modification. The increased transmission may then reflect the operation of a gating mechanism that permits transmission of cutaneous feedback that may be used to modify some part of the next rather than the current step.

At C2 zone sites responses to stimulation of the ipsilateral or contralateral limb evoked fluctuations in response size during locomotion that occurred in phase, despite the fact that the two limbs move out of phase. The modulatory mechanism acting on the SOCPs supplying the zone must therefore occur at or after the level when bilateral convergence occurs in the path. Any possible functional significance of excitability changes at C2 zone sites is therefore more difficult to determine since the changes are likely to relate to a complex integration of inputs from both limbs (perhaps from all four, given that the C2 zone receives convergent input from all four limbs). However, excitability at C2 zone sites was usually greatest during the stance phase of the ipsilateral forelimb. In relation to the error detector hypothesis, one possibility that is open to experimental test is that during locomotion, Purkinje cells within the C2 zone, in a similar fashion to those studied in the B zone (cf Andersson and Armstrong, 1987), will discharge complex spikes when an 'error' signal is generated during the stance phase in the ipsilateral limb.

The gating-out of responses at C1, C2 and C3 sites during a reaching movement and most notably during the grasp phase of the task seems, at first, rather surprising. However, the cerebellar responses were evoked by stimulation of the superficial radial nerve which is purely cutaneous, and in the cat supplies the dorsal surface of the distal limb, including the paw dorsum (Kitchell *et al.*, 1982). One possible explanation is that 'switching' of transmission of inputs occurs during reaching and, in

particular, during the grasp phase of such a movement. While cutaneous inputs arising from the paw dorsum may be gated-out, inputs from other sensory surfaces (such as those located on the ventral surface of the paw involved in taking hold of the food reward) may be gated-in. However, Horn *et al.* (1996) found that during a reaching task, olive cells in rostral DAO typically had a reduced response to peripheral electrical stimulation compared to rest, irrespective of the location of their cutaneous receptive fields.

An alternative possibility therefore, is that a 'switch' occurs during reaching so that proprioceptive inputs are selected for transmission during the later phase of the movement. Such a proposal is compatible with the multimodal climbing fibre response characteristics of individual Purkinje cells (Jörntell *et al.*, 1996), and is broadly consistent with experimental data which suggest that reaching movements in humans are carried out using two processes. While the first process is based on an internal simulation of the reaching movement, the second uses proprioceptive feedback to update the internal model to ensure that the target is achieved. Results that are consistent with the presence of these two processes in humans have been obtained recently in subjects performing a reaching movement in the dark with a computer controlled lever (Wolpert *et al.*, 1995). The subjects were asked to estimate the location of their hand after externally imposed forces were applied to the lever and the results were compatible with the presence of an internal model to simulate the movement and the use of proprioceptive feedback to update the model. Interestingly, the data suggested that the weight attached to the two processes changed during the course of the reaching movement: during the early stages the internal model dominated while in the later stages sensory feedback became more important.

#### 7.1. Forward Models

The comparator or error detector hypothesis proposes that the olive acts to compare descending motor commands (efference copy) with ascending signals that convey information about an evolving movement (reafference) and 'errors' result when there is a mismatch between these two inputs. Such a scheme has a close affinity with the use of internal models in control theory and it has been proposed that forward models may be used by the CNS to internally simulate the behaviour of the motor system [for a recent review see Miall and Wolpert (1996)].

A forward model can be used to estimate what the sensory consequences of a movement will be and thereby cancel reafference generated by the movement. As a result, any externally generated influences (such as an unexpected sensory input due to a movement perturbation) can be distinguished from those arising from self-generated inputs. In relation to the climbing fibre system it is now well established that a modulatory influence is exerted on ascending sensory inputs during active movements and one possibility is that this may reflect the output of an internal model which anticipates and cancels

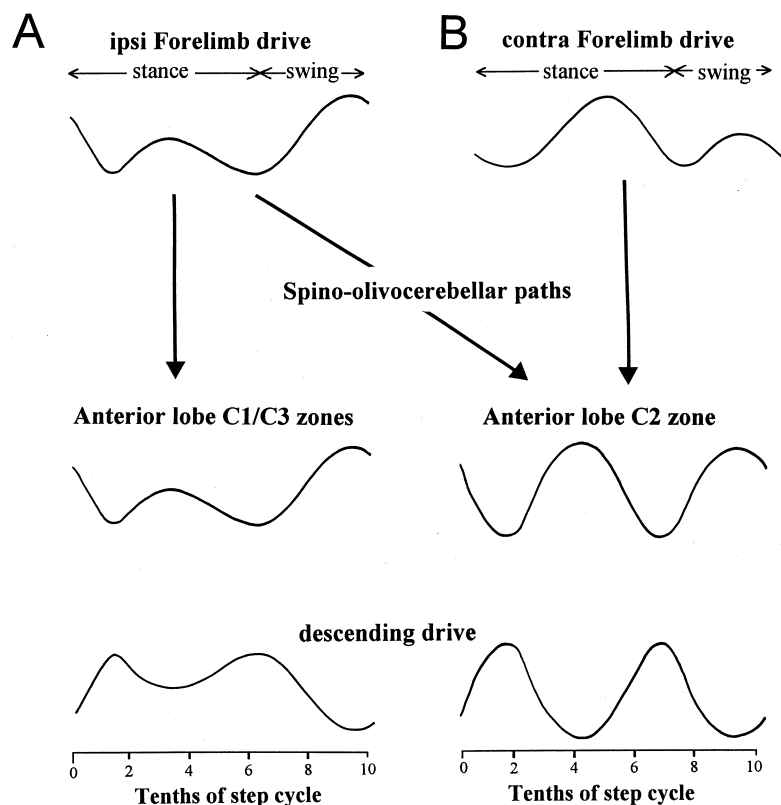


Fig. 14. Hypothetical scheme to show how the variation in size of evoked climbing fibre responses during locomotion at (A) C1/C3 and (B) C2 zone sites (in the anterior lobe, lobule V) might arise from the influence of two ascending modulatory drives each related to the movement cycle in one forelimb. Waveforms in bottom panel show the hypothetical pattern of descending drives which are mirror images of the corresponding ascending modulatory drives. Convergence of the ascending and descending drives results in uniform excitability of climbing fibres during the step cycle. For further details see text. [Based on Lidiirth and Apps (1990).]

the sensory effects of movement. This is not to imply, however, that this is the only function of the gating because external stimuli clearly can also be very effectively gated-out during movement [see for example Horn *et al.* (1996)].

### 7.2. Modulatory Drive

The results of Apps *et al.* (1990, 1995) suggest that separate modulatory drives act on the C1 and C2 cerebellar zones during locomotion (at least for those sites so far studied in the anterior lobe) and Lidiirth and Apps (1990) proposed that the variations in response size at C1 sites might be generated by a modulatory drive related to movements of the ipsilateral limb [Fig. 14(A)], while the C2 zone (which receives climbing fibre input from both forelimbs) may receive two modulatory drives which summate: one from the ipsilateral forelimb but also a similar, but 180° phase-shifted drive related to the movements of the contralateral limb [Fig. 14(B)]. Summation of these two drives would then produce two peaks of activity in each step cycle which resembles the experimentally observed pattern [see Fig. 10(B)]. However, it is noteworthy that the more extensive data obtained by pooling results from several studies shows that, in the large majority of C2

zone sites, the time of maximum response occurred around mid/late stance with a second smaller peak in late swing. The possibility remains that two basic types of step-related gating exist that modify excitability in SOCPs that target the C2 zone. However, there may be two classes of C2 sites, the most common (at least in lobule V) is influenced primarily by the contralateral drive, whereas a second, less common type is influenced mainly by the ipsilateral drive.

Pertinent to this issue are the results obtained during a reaching movement (Apps *et al.*, 1997). The exclusive use of the ipsilateral forelimb in such a task may well result in the absence of a modulatory influence from the contralateral limb to C2 recording sites and consistent with this possibility was the finding that both C1/C3 and C2 sites exhibited rather similar patterns of modulation. The presence at some C1 and C3 recording sites of facilitations during the step cycle presumably reflects the action of an additional task-dependent modulatory influence that does not usually operate during reaching (at least for the cutaneous inputs so far studied). This difference may reflect the fact that stepping is a repetitive, stereotypical movement while reaching is more 'skilled'. However, it might be objected that the influence of one or more modula-

tory drives on spinal inputs to the olive is not consistent with single unit studies in awake cats which have failed to demonstrate any cyclical activity patterns in the discharges of complex spikes by individual Purkinje cells during movements such as stepping. To reconcile this apparent discrepancy it is possible that the olive (or a pre-olivary stage in the SOCPs) receives a mirror image of the spinal modulatory drive from another (descending?) source (Fig. 14) so that, overall, excitability is kept uniform throughout the step cycle.

Consistent with this proposal are preliminary data obtained from a total of four C1/C3 zone recording sites in one cat (Fig. 15). A bipolar stimulating electrode was chronically implanted into the contralateral cerebral peduncle (CP) and used to evoke climbing fibre field potentials in the cerebellar cortex during different phases of the step cycle (cf Section 4). Of considerable interest from the few recording sites so far obtained, is the suggestion that the pattern of gating differs markedly from that described previously for SOCPs studied under the same conditions. While the largest responses evoked by CP stimulation occurred during stance and the transition from stance to swing [Fig. 15(A)], at three of the same sites [and consistent with previous reports, see Lidieth and Apps (1990); Apps *et al.* (1995)], the largest responses to ipsilateral superficial radial stimulation occurred during late swing [Fig. 15(B), and compare with Fig. 10(A)].

## 8. CONCLUDING REMARKS

The present review has highlighted a series of studies that have demonstrated that transmission in SOCPs is powerfully gated during active movements, suggesting that access of sensory signals to the cerebellar cortex via the climbing fibre system is subject to central control. Although the function of such gating remains to be determined, it would seem to be a fundamental characteristic of climbing fibre pathways in general and may, in part, explain the scarcity of positive findings concerning the conditions for activation of complex spikes during volitional movements. Moreover, since the movement-related gating of SOCPs is similar in many respects to the pattern of gating observed in sensory pathways leading to the cerebral cortex, it is possible that some of the gating may have a common origin. Indeed, at this stage the possibility cannot be ruled out that the gating-out of peripheral sensory signals during some types of behaviour may be an epiphenomenon. During active movements the central pathways that relay peripheral afferent signals may be otherwise 'engaged' in generating subsequent elements of a compound movement. The 'gating' can then be thought of more as a limitation of the CNS in processing sensory signals during movement rather than a specific function in its own right. However, given that transmission of climbing fibre inputs to the cerebellum is not only task dependent but also that different cerebellar cortical zones (and even different parts of a given zone) can differ appreciably in the pattern of modulation their SOCPs exhibit during a particular task, it is clear that the

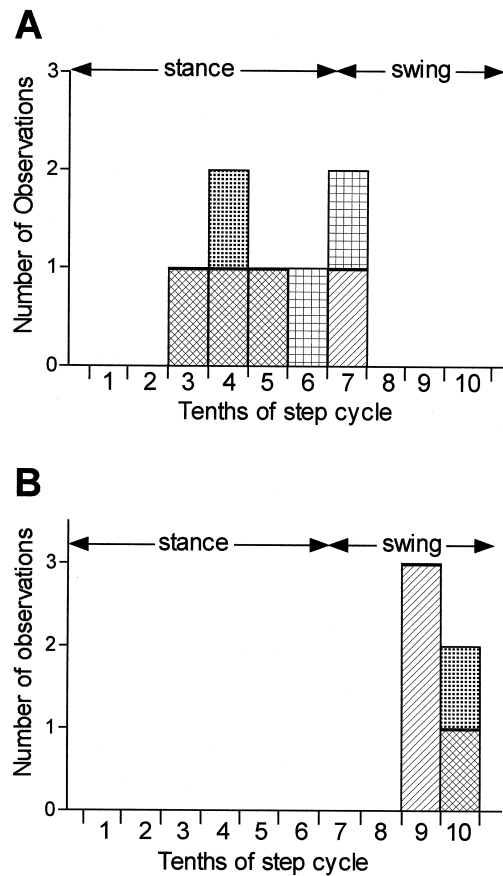


Fig. 15. Frequency histograms to show the time during the step cycle when the largest mean size of climbing fibre response occurred as a result of (A) CP stimulation (three pulses at 1 kHz, 0.2 msec duration, 0.08–0.6 mA intensity in different recording sessions, three C1 and one C3 zone sites,  $n = 7$  step histograms) and (B) same three C1 zone recordings sites ( $n = 5$  step histograms) in response to ipsilateral superficial radial stimulation. Different sites indicated by different hatching.

gating does not affect the various SOCPs and their sub-components in a non-specific fashion. Instead, different SOCPs are subject to different modulatory influences. Furthermore, transmission can be facilitated in selected SOCPs, for example, during the swing phase of the step cycle in DF-SOCPs that target the C1 and C3 zones, suggesting that the gating can also operate to enhance transmission of peripheral signals at specific times during certain types of active movement. Clearly, the regulation of sensory inputs to the cerebellar cortex via the SOCPs is complex and it remains an interesting possibility that this reflects varying functions of the climbing fibre system according to prevailing behavioural conditions. The challenge remains for future studies to establish why different SOCPs are organized to have their greatest and least pathway excitability at different times during some types of active movements but not others.

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