The properties of dorseal spinocerebellar tract neurones and their role in signalling tactile information from the skin to the cerebellum

Author:
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Publication Date:
2004

DOI:
https://doi.org/10.26190/unsworks/13228

PLEASE TYPE

THE UNIVERSITY OF NEW SOUTH WALES
Thesis/Project Report Sheet

Surname or Family name: RAKIC

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Abbreviation for degree as given in the University calendar: M.Sc

School: School of Medical Sciences Faculty: Medicine

Title: The Properties of Dorsal Spinocerebellar Tract Neurones and their Role in Signalling Tactile Information from the Skin to the Cerebellum

Abstract 350 words maximum: (PLEASE TYPE)

The dorsal spinocerebellar tract (DSCT) appears to be the major pathway conveying kinaesthetic and tactile information from the hindlimb to the cerebellum. The aim of the present study was to investigate quantitatively the capacity of dorsal spinocerebellar tract (DSCT) neurones to signal static and dynamic tactile information to the cerebellum.

The analysis, conducted in anaesthetised cats, was based on extracellular recording, in Clarke's column and the adjacent dorsal horn of the lumbar spinal cord, from single DSCT neurones activated by tactile inputs from the hairy skin of the ipsilateral hindlimb. Each neurone studied quantitatively was first identified as a DSCT neurone using an antidromic collision procedure and the receptive field carefully mapped. Static tactile stimuli of graded intensities of skin indentation (up to 1500 μm), and dynamic tactile stimuli in the form of sinusoidal vibration were delivered to the most sensitive point in the individual neurone's receptive field.

A small minority (<15%) of sampled DSCT neurones displayed a slowly adapting or static tactile sensitivity, and had rather coarsely-graded stimulus-response relations as a function of graded increases in the amplitude of skin indentation. The vast majority of the DSCT neurones sampled (>85% of neurones) was sensitive to just the dynamic components of tactile stimuli. However, their capacity for signalling information about the intensive and frequency parameters of controlled vibrotactile stimuli was limited to a low-frequency bandwidth up to ~10Hz. At higher vibration frequencies, responsiveness was confined to the onset of the vibrotactile stimulus train.

The study demonstrates that tactile information conveyed by individual DSCT neurones to the cerebellum, for the purpose of regulating movement and posture, appears to be limited in comparison with the detail and precision of tactile information conveyed by neurones of the dorsal column-medial lemniscal pathway to the cerebral cortex, for the purpose of sensation and perceptual experience.

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The Properties of Dorsal Spinocerebellar Tract Neurones and Their Role in Signalling Tactile Information from the Skin to the Cerebellum

Severin Rakic M.D., Grad. Dip. in Med.

Submitted for the award of Master of Science

School of Medical Sciences
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September, 2004.

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PUBLICATIONS

The following publications are the result of research undertaken during the period of candidature for the award of Master of Science.

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1. ROBINSON, L., MAHNS, D.A., COLEMAN, G.T., RAKIC, S., PERKINS, N. AND ROWE, M.J. (2001). Central processing of vibrotactile information by cuneate neurons. *Proceeding of the Australian Neuroscience Society* **12**, 221p.

2. PERKINS, N., ROBINSON, L., MAHNS, D.A., RAKIC, S., COLEMAN, G. AND ROWE, M.J. (2001). Coding of vibrotactile frequency information from hairy skin by cuneate neurons.
Proceeding of the Australian Neuroscience Society **12**, 221p.

3. MAHNS, D.A., ROBINSON, L., PERKINS, N., RAKIC, S., COLEMAN, G. AND ROWE, M.J. (2001). The capacity of spinocervical tract neurons to signal vibrotactile information.
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4. PERKINS, N.M. MAHNS, D.A., SAHAI, V. RAKIC, S. AND ROWE, M.J. (2001). Human vibrotactile discriminative capacity in hairy skin compared with glabrous skin.
IUPS Satellite Symposium *Organization and Processing in the Cerebral Cortex for Sensation and Perception'* 64p.

5. PERKINS, N.M, MAHNS, D.A., RAKIC, S. SAHAI, V. AND ROWE, M.J. (2001). Differential receptor contributions to vibrotactile discriminative sensibility in human hairy skin.
IUPS Satellite Symposium *'Organization and Processing in the Cerebral Cortex for Sensation and Perception'* 65p.

6. MAHNS, D.A., ROBINSON, L., PERKINS, N.M., RAKIC, S., COLEMAN, G. AND ROWE, M.J.(2001). Limited coding capacity of spinocervical tract neurones to signal vibrotactile information.
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Proceeding of the Australian Neuroscience Society **13**, 212p.

10. PERKINS, N.M., MAHNS, D.A., RAKIC, S., SAHAI, V. AND ROWE, M.J. (2002). Differential receptor contributions to vibrotactile sensibility in human hairy skin.
Proceeding of the Australian Neuroscience Society 13, 211p.

11. MAHNS, D.A., PERKINS, N.M., SAHAI, V., ROBINSON, L., RAKIC, S. AND ROWE, M.J. (2002). Inhibitory processes within the dorsal horn limit the coding capacity of SCT neurones.
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13. RAKIC, S., MAHNS, D.A., SAHAI, V., PERKINS, N.M. AND ROWE, M.J. (2003). The capacity of DSCT neurones to signal static and dynamic tactile information.
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International Brain Research Organization Abst. **4176**, 423p.

ABSTRACT

1. The principal aim of this study was to investigate the capacity of dorsal spinocerebellar tract (DSCT) neurones to signal static and dynamic tactile information. The analysis, conducted in anaesthetised cats, was based on extracellular recordings from single neurones located predominantly in Clarke's column and the adjacent dorsal horn in the lumbar spinal cord.

2. DSCT neurones in the study were activated principally by tactile inputs from the hairy skin and, in part, from the margin of the hairy and glabrous skin on the ipsilateral hindlimb via primary afferent fibres travelling in the sensory nerves that enter the lumbar cord through the dorsal roots. Axons arising from the neurones activated by these afferent fibres form the DSCT pathway which ascends the spinal cord in the lateral funiculus and projects to the ipsilateral cerebellar cortex. Prior to investigation of the tactile responsiveness of the units, each was identified as a DSCT neurone, using an antidromic collision procedure. In addition, the receptive field of individual DSCT neurones was carefully mapped using a *von Frey* hair of different weight.

3. Static tactile stimuli of graded intensities of skin indentation (up to 1500 μm), and dynamic tactile stimuli in the form of sinusoidal vibration (in the range of frequencies between 5 and 300 Hz), superimposed on the indentation step of 400 μm, were delivered by a feed-back controlled mechanical stimulator to the most sensitive point in the individual neurone's receptive field.

4. Of 17 identified DSCT neurones investigated in detail, only a small sample displayed a sensitivity to static skin indentation stimuli. Tested with graded skin indentation in an intensity range up to 1500 μm, these neurones responded vigorously to the onset of the stimulus, and maintained their responsiveness throughout the remainder of the stimulus. However, as these neurones had coarsely-graded stimulus-response relations as a function of graded increases in the indentation amplitude, they displayed, as individual neurones, a rather poor coding capacity for changes in intensity of the indentation delivered to their receptive fields and, presumably, a rather poor detection capacity for the static component of the indentation of the skin within their receptive fields. These slowly adapting tactile neurones also had a limited capacity for signalling *purely* dynamic tactile events when analyzed with controlled forms of vibratory stimuli,

and displayed similar responsiveness to these stimuli as did the purely dynamically-sensitive DSCT neurones (whose properties are summarized below).

5. The vast majority of DSCT neurones in the present study displayed sensitivity to just the dynamic components of the skin indentation, namely, the onset and offset of the indentation step. Application of vibrotactile stimuli in the range of frequencies up to 300 Hz and amplitude up to 100 μm revealed that the capacity of these neurones to signal this dynamic tactile information is limited to low-frequency vibrotactile stimuli of ≤5 Hz. Increases in the vibration amplitude to ~300 μm only slightly widened this narrow bandwidth to frequencies of ≤10 Hz, while responses to vibrotactile stimuli of ≥50 Hz remained confined to the onset of the vibration train. Therefore, stimulus-response relations of DSCT neurones display graded mean spike output as a result of graded increases in vibration amplitude only at frequencies up to ~5-10 Hz, while at higher frequencies (≥50 Hz) mean spike output remained about the same despite increases in vibration amplitude.

6. The present study demonstrated that individual DSCT neurones are limited in their capacity to detect and signal changes in the intensity of the static and dynamic tactile stimuli. They are also limited in their coding capacities for vibrotactile stimuli to the low frequencies (<10 Hz) compared with other tactile pathways, such as the dorsal column medial-lemniscal pathway where individual neurones have the ability to detect and accurately signal changes in both the intensity of the static and dynamic tactile stimuli, and the capacity to signal tactile information over a much broader frequency range of vibrotactile stimuli (between 5 Hz and ~600 Hz). Thus, the information conveyed by the DSCT to the cerebellum for the regulation of movement and posture appears to be limited in comparison with the tactile information conveyed over the dorsal column-medial lemniscal pathway to the cerebral cortex for sensory and perceptual experience.

Chapter 1

INTRODUCTION

1. INTRODUCTION

1.1 Role of the dorsal spinocerebellar tract (DSCT) in cerebellar motor control

Afferent information from cutaneous sources about tactile, thermal and pain stimuli and information from kinaesthetic sources is transferred by several ascending pathways located in the spinal cord and brainstem to the cerebrum as well as to the cerebellum and provides a necessary background for the brain about the ongoing events at the periphery. The information is then processed within the cerebral cortex for the purpose of sensation and perception. However, the afferent information directed to the cerebellum is utilized principally for the control and regulation of movement and posture.

This Introduction provides an overview in the form of a literature review of the structure and the functional organization of one of the principal ascending somatosensory pathways, namely the dorsal spinocerebellar tract (DSCT). This ascending system, together with other spinocerebellar pathways, supplies the cerebellum with a variety of information about proprioceptive and exteroceptive events from muscles, joints and skin of the lower limb. However, the principal emphasis in this review is the DSCT itself. The structural and functional organization of the other spinocerebellar pathways is given in more general form as a comparison to the structural and functional organization of the DSCT. The review also includes some consideration of sensory systems that convey tactile information to thalamo-cortical levels for sensation and perception for comparison with the nature of tactile information conveyed to cerebellum.

1.2 Review of the anatomy of the DSCT and other spinocerebellar pathways

Information conveyed over the spinocerebellar pathways to the cerebellum for the task of motor control provides the cerebellum with a moment-to-moment monitor of peripheral events occurring on the skin and in muscles and joints. These peripherally-derived signals are presumed to contribute to cerebellar-imposed corrections or adjustments to motor outflow from centres that extend from the cerebral cortex to the spinal cord.

Anatomical and electro-physiological studies in cats (Jansen & Brodal, 1958; Larson, Miller & Oscarsson, 1969; Bloedel & Burton, 1970) have identified twelve

spinocerebellar pathways that convey information from upper and lower limbs and trunk to the cerebellum, and have been classified by Oscarsson (1973) into two broad groups (Table 1-1).

The first group, designated by Oscarsson (1973) as *mossy fibre pathways* because of forming moss-like endings within the granular layer of the cerebellar cortex (Eccles et al., 1967; Palkovits, 1971a,b; Ito, 1984), includes pathways such as the DSCT, the cuneocerebellar tract (CCT), the ventral (VSCT) and rostral (RSCT) spinocerebellar tracts and the spino-reticulocerebellar pathway (SRCP), arising from the the lateral reticular nucleus (LRN). All but the last of these are direct spinocerebellar pathways and have been classified as *direct mossy fibre pathways* (Oscarsson & Uddenberg, 1965; Oscarsson, 1973). The LRN-SRCP has been classified as an *indirect mossy fibre pathway* (Oscarsson, 1973), as it is interrupted by an additional brainstem relay in the lateral part of the reticular nuclei (Jansen & Brodal, 1958).

The second broad group of spinocerebellar pathways all relay through the inferior olivary nucleus (Brodal, 1949; Brodal et al., 1950; Szentagothai & Rajkovits, 1959; Eccles et al., 1967) and terminate in elaborate vine-like endings that climb over the dendritic trees of Purkinje cells in the molecular layer of the cerebellar cortex (Jensen & Brodal, 1958; Escobar et al., 1968; Larson et al., 1969a; Mlonyeni, 1973; Ito, 1984). These were designated by Oscarsson (1973) as *climbing fibre pathways*. As a synapse in the inferior olive (Szentagothai & Rajkovits, 1959) interrupts these pathways, they cannot be considered as direct spinocerebellar pathways. Therefore, a more appropriate designation would be spino-olivo-cerebellar pathways. Termination of these afferent pathways in the cerebellar cortex will be discussed in more detail below.

The DSCT conducts tactile and kinaesthetic inputs from the cat's hindlimb, while the cuneocerebellar pathway (CCT) conveys information from the same receptor types in the forelimb of the cat to the cerebellar cortex (Holmqvist, Oscarsson & Rosen, 1963a; Holmqvist, Oscarsson & Uddenberg, 1963b; Oscarsson & Uddenberg, 1964; Cooke et al., 1971a; Mackie et al., 1998 & 1999). However, some anatomical differences between these two tracts exist in terms of their origins and their projections within the cerebellum (Lloyd & McIntyre, 1950; Curtis et al., 1958; Grant, 1962a; Oscarsson, 1965; Eide et al., 1969a; Cooke et al., 1971a; Eccles et al., 1971; Kuno et al., 1973).

Paths and abbreviations	Main peripheral input	Conduction velocity (m/sec)	Latency (msec)	
			Hindlimb	*Forelimb*
Direct mossy fibre paths				
Proprioceptive component of dorsal spinocerebellar tract **DSCT**	Group I afferents Joint afferents	110	5	-
Proprioceptive component of cuneocerebellar tract, **CCT**	Group I afferents (Joint afferents?)	-	-	3
Exteroceptive component of **DSCT**	Cutaneous afferents	110	5	-
Exteroceptive component of **CCT**	Cutaneous afferents	-	-	4
Ventral spinocerebellar tract, **VSCT**	FRA	120	5	-
Rostral spinocerebellar tract, **RSCT**	FRA	95	-	3
Indirect mossy fibre path				
Spinoreticulocerebellar path relayed through lateral reticular nucleus	FRA	120	10	8
Climbing fibre paths				
Dorsal spino-olivocerebellar path, **DF – SOCP**	FRA	-	18	10
Dorsolateral spino-olivocerebellar path, **DLF-SOCP**	Cutaneous afferents	70	21	17
Ventral spino-olivocerebellar path, **VF-SOCP**	FRA	40	22	20
Lateral climbing fibre-spinocerebellar path, **LF – CF – SCP**	FRA	?	25	19
Ventral climbing fibre-spinocerebellar path, **VP-CF – SCP**	FRA	30	25	28

Table 1-1. Spinocerebellar paths: classification, main peripheral input, maximum conduction velocity of spinal tract and cortical latency (arrival time of afferent volley) on nerve stimulation (taken from Oscarsson, 1973, based on the earlier work by Lundberg & Oscarsson, 1960, 1962a; Holmqvist et al., 1963a; Oscarsson & Uddenberg, 1964; Grant et al., 1966; Larson et al., 1969a; and unpublished data). DL, dorsolateral; DLF, dorsolateral funiculus; FRA, flexor reflex afferents; LF, lateral funiculus; VF, ventral funiculus. – denotes an absence of inputs; ? denotes the absence of data or ambiguity.

Whereas the DSCT originates almost entirely from neurones in Clarke's column nucleus in the lumbar spinal cord, the CCT originates from neurones activated by proprioceptors (muscle and possibly joint inputs) located in the external cuneate nucleus and neurones activated by exteroceptors (cutaneous inputs) located in the rostral part of the main cuneate nucleus (Curtis et al., 1958; Eide et al., 1969a; Cooke et al., 1971b Kuno et al., 1973). Although both the DSCT and CCT terminate in the anterior lobe, in the intermediate zone and the vermis of the cerebellum, the DSCT terminates more rostrally than the CCT (Lundberg & Oscarsson, 1960; Grant, 1962b; Voogd et al., 1969). These two tracts are effectively hindlimb and forelimb analogues (Oscarsson, 1965).

1.2.1 Primary afferent fibres that provide input to DSCT neurones of the cat

The DSCT neurones located within Clarke's column nucleus and adjacent regions of the dorsal horn in the lumbar spinal cord receive inputs from muscle and joint proprioceptors and skin exteroceptors of the cat's hindlimb via various sensory nerves. These neurones can be activated selectively by muscle, joint or cutaneous afferents, or by a combination of two of them, or by combinations of all of them (Laporte, Lundberg & Oscarsson, 1956a,b; Curtis et al., 1958; Yamamoto & Miyajima, 1959; Kuno & Miyahara, 1968; Mann, 1971; Lindstrom & Takata, 1972; Kuno et al., 1973).

Afferent fibres providing inputs from muscles to DSCT neurones

Most of the DSCT neurones activated by inputs from muscle receive monosynaptic excitation by group I muscle afferents, arising from both muscle spindle stretch receptors and from tendon organs (Laporte, Lundberg & Oscarsson, 1956a,b). However, each source of muscle inputs projects to different sets of DSCT neurones (Lundberg & Oscarsson, 1956). Some of the neurones receiving group I spindle receptor input receive additional monosynaptic activation from group II muscle afferents, representing a highly specific convergence of primary and secondary muscle spindle afferents from the same muscle sources (Laporte et al., 1956b, Eccles et al., 1961b). However, none of the muscle-related DSCT neurones was found to receive excitatory inputs from more than one muscle nerve (Mann, 1971).

The excitatory inputs to DSCT neurones conveyed by group I afferents are from a single muscle or a group of synergists, while inhibitory actions on DSCT neurones

often arise from several muscles, in particular, the antagonists of those muscles providing excitatory input (Holmqvist et al., 1956).

Projection of afferent fibres from joints to DSCT neurones

The afferent fibres of joint origin supplying DSCT neurones have been shown to arise from the receptors in the capsule of the knee, ankle and the toe joints of the cat (Lindstrom & Takata, 1972; Kuno et al., 1973). These receptors with associated primary afferent fibres are said to be slowly adapting (SA), without exception (Kuno et al., 1973), based on responses observed in DSCT neurones sensitive to stimulation of the receptors (Ruffini endings) in the capsule of the knee joint, electrical stimulation of the knee joint nerve (associated SA type II primary afferent fibres), or stimulation of the receptors by the passive movements of the knee, toe and the ankle joints (Kuno et al., 1973; also see Lindstrom & Takata, 1972). Burgess and Clark (1969) showed that the fibres of rapidly adapting (RA) joint receptors do not provide inputs to DSCT neurones. Instead, they appear to project as uninterrupted primary fibres through the dorsal column funiculus in the spinal cord to the gracile nucleus (Burgess & Clark, 1969).

The DSCT neurones associated with joint afferent inputs receive primary afferent fibres from one joint and some of them even from two joints of the cat's hindlimb (Kuno et al., 1973).

Cutaneous afferent fibres terminating in Clarke's column

The DSCT neurones activated by afferent fibres arising from receptors in the skin of the cat's hindlimb are located principally within Clarke's column nucleus (Kuno et al., 1973). Approximately 30% of these neurones were activated exclusively by hair follicle afferents (HFA) from the hairy skin of the hindlimb, 15% were found to respond only to stimulation of touch domes and their associated slowly adapting type I (SA I) afferent nerve fibres, and ~ 50% of the neurones in Mann's study (1971) responded to stimulation of touch dome (SA I) afferent fibres and the hair follicle afferents (HFA) within their receptive fields. Only few neurones in the sample could not be classified with certainty into one or other of these groups (Mann, 1971).

The relative proportion of DSCT neurones activated by HFA inputs in Mann's study (1971) is in agreement with findings of Kuno et al. (1973). In contrast, the proportion of DSCT neurones activated by touch dome (SA I) afferents in Mann's study

(1971) was 15%, while Kuno et al. (1973) could not isolate more than one unit (~ 2%) sensitive to SA I input.

Several classes of tactile afferent fibres arising in the hindlimb of the cat appear to project via the dorsal columns to the gracile nucleus but fail to provide input to the DSCT neurones (Brown, 1968; Petit & Burgess, 1968; Burgess & Clark, 1969). These include the slowly adapting (SA II) afferent fibres, associated with *Ruffini receptors* in the hairy skin and in the vicinity of the claws, slowly adapting (SA I) afferents with mechanoreceptors in the foot pads, and the dynamically-sensitive afferent fibres associated with *Pacinian corpuscles*, and with *hair follicles* including the G and T type *hair follicle* (Brown & Iggo, 1967; Brown, 1968). However, their role as a part of the dorsal column-lemniscal system in the conduction of tactile information from the cat's hindlimb to the sensory cortex will be considered later in the review for comparison with the role of the DSCT in signaling tactile information to the cerebellar cortex.

Afferent fibres from different peripheral sources that converge to DSCT neurones

Kuno's study (1973) found that 18% of DSCT neurones received convergent inputs from more than one peripheral source. Based on the combination of different input sources this subgroup of DSCT neurones can be classified into four classes:

i. Muscle + joint: 35%
ii. Muscle + cutaneous: 18%
iii. Cutaneous + joint: 18%
iv. Cutaneous + muscle + joint: 29%

} of total DSCT neurones in the convergent subgroup

The high proportion of DSCT neurone excited by pure muscle inputs (~50% of the sample) and the relatively high proportion of the neurones in the convergent group activated by combined inputs from muscles and one or two other sources (Kuno et al., 1973) suggests a role of the DSCT in providing the information to the cerebellar cortex necessary for the regulation of muscle activity, posture and balance of the body.

1.2.2 Location of DSCT neurones within the lumbar spinal cord

It is generally assumed that DSCT neurones originate principally from Clarke's column nucleus located in the intermediate grey matter of the lumbar spinal cord, dorsal

to the central canal and 200-300μm lateral to the midline of the spinal cord (Eccles et al., 1960; Lundberg, 1964; Oscarsson, 1965b; Eide et al., 1969a; Mann, 1971; Kuno et al., 1973). However, some DSCT neurones are located outside Clarke's column in lamina X of the spinal dorsal horn (Kuno et al., 1973; Low, Mantle-St. John & Tracey, 1986). The study undertaken by Kuno et al. (1973) showed that DSCT neurones (total sample of 282 DSCT neurones isolated in the study) that received inputs exclusively from either muscle or skin afferents were all found within Clarke's column, while one out of four DSCT neurones sensitive to joint inputs and two out of six neurones in the group activated by combined inputs were found to be located outside Clarke's column in the adjacent spinal grey matter (Fig.1-1).

The neurones within Clarke's column show some somatotopic distribution related to the level of entry of the sensory afferents into the spinal cord and to the source of their sensory inputs (Szentagothai, 1961). Afferent fibres that entered the spinal cord in the lower segments (e.g., L6-L7) ascend two or more segments of the spinal cord in the dorsal fasciculus, enter Clarke's column nucleus (at level L4-L3) and establish synaptic connections with DSCT neurones. The afferent fibres that enter the spinal cord in these lower segments are gradually shifted medially, first in the dorsal fasciculus in the course of their ascending projection, and then once they enter and ascend in Clarke's column they establish synaptic connections with more and more medially located DSCT neurones (Szentagothai, 1961). Although the borders of the space in which the collaterals arising from the dorsal roots are distributed in Clarke's column are well defined, there is considerable overlap in the collaterals from neighbouring dorsal root segments (Szentagothai, 1961).

DSCT neurones in Clarke's column appear to vary in size. Loewy (1970), reported three size classes of DSCT neurones in Clarke's column of the cat: small cells measuring up to ~15μm in diameter, medium cells from approximately 15μm to 45μm in diameter, and large cells ranging approximately from 45 to 85μm in diameter. The large neurones receive group I muscle afferent input, and when stained with horse radish peroxidase (HRP) in the studies of Houchin et al. (1983) and Tracey and

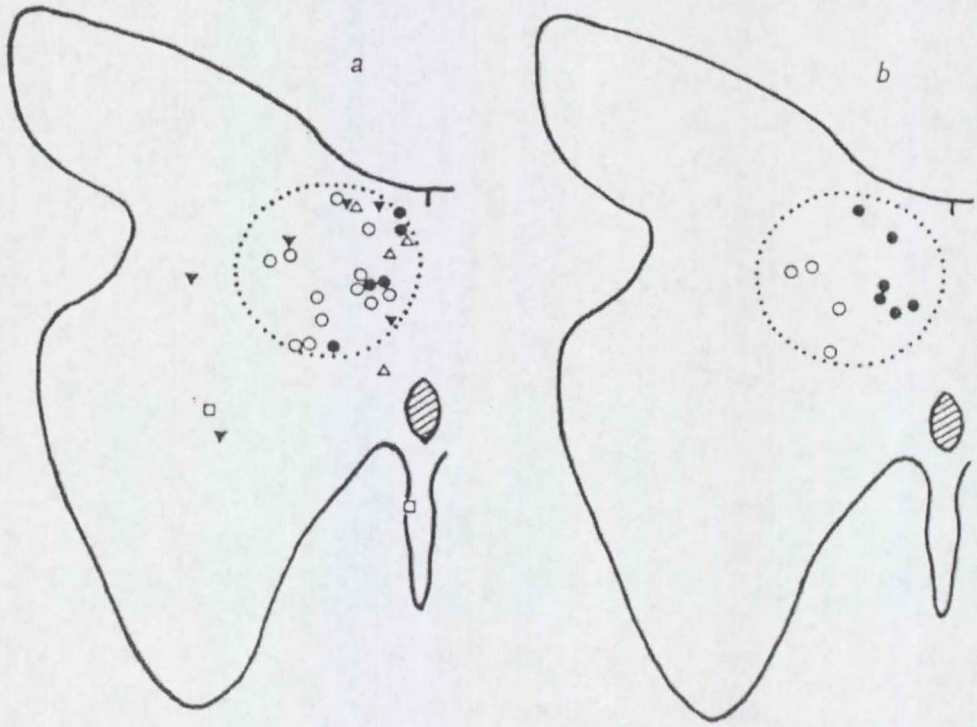

Figure 1-1. Distribution of neurones examined by marking the site of extracellular recording with fast green. Continuous line, the grey-white matter boundary. Dotted circle, Clarke's column. Shaded oval, central canal. a) open circles, muscle group; filled circles, cutaneous group; open triangles, joint group; filled triangles, convergent group; open squares, non-DSCT cells activated synaptically by antidromic stimulation of the dorsolateral funiculus. b) open circles, DSCT neurones activated by the inputs from the posterior biceps-semitendinosus muscle; filled circles, DSCT neurones activated by the input from the triceps surae muscle (from Kuno et al., 1973).

Walmsley (1984), have been shown to have profuse dendritic trees that extend over 3 mm in the rostro-caudal direction with many fine dendritic branches. These long, highly-branched dendrites are the locus of synaptic connections from single afferent fibres (Walmsley et al., 1985).

The Clarke's column nucleus is most developed in the lumbar spinal cord between the L1 and L5 segments (Lundberg & Oscarsson, 1961; Szentagothai, 1961) but appears to extend down to the L7 segment (Holmquist et al., 1956; Curtis, Eccles & Lundberg, 1958; Eccles et al., 1960; Oscarsson, 1965b; Eide et al., 1969a) and all the way up to the first thoracic segment (Th1) of the spinal cord (Low, Mantle-St.John & Tracey, 1986).

Cell bodies of DSCT neurones in Clarke's column nucleus receive information from the periphery through the synaptic connections formed by primary afferent fibres. The axons arising from these DSCT neurones convey the information to the cerebellum (Fig.1-2) (Oscarsson, 1965; Eide et al., 1969b; Eccles et al., 1971; Yaginuma & Matsushita, 1989).

1.2.3 DSCT and the other spinocerebellar pathways in the spinal cord

From twelve ascending spinal pathways identified in previous studies in cats (Jansen & Brodal, 1958; Larson, Miller & Oscarsson, 1969; Bloedel & Burton, 1970) that terminate in the cerebellum only four of them, denoted by Oscarsson (1973) as *direct mossy fibre pathways*, could therefore be considered as direct spinocerebellar pathways regarding their origin, organisation and projection. These pathways (DSCT, VSCT, CCT and RSCT) originate in the spinal cord or its extension into the lower brainstem in the case of, for example, the CCT, and travel uninterrupted to the ipsilateral cerebellar cortex where they terminate (Table1-1). It appears that the VSCT and RSCT terminate in the ipsilateral as well as in the contralateral cerebellar cortex (Grant, 1962b; Lundberg & Oscarsson, 1962a,b; Oscarsson, 1964; Oscarsson & Uddenberg, 1964).

Axons arising from DSCT neurones ascend the spinal cord in a dorsal part of lateral funiculus, enter the cerebellum through the restiform body and terminate as mossy fibres in the cerebellar cortex. This pathway is exclusively or almost exclusively ipsilateral, which means that it conveys inputs from the hindlimb through the same side of the spinal cord, without any crossing of the midline (Oscarsson, 1965).

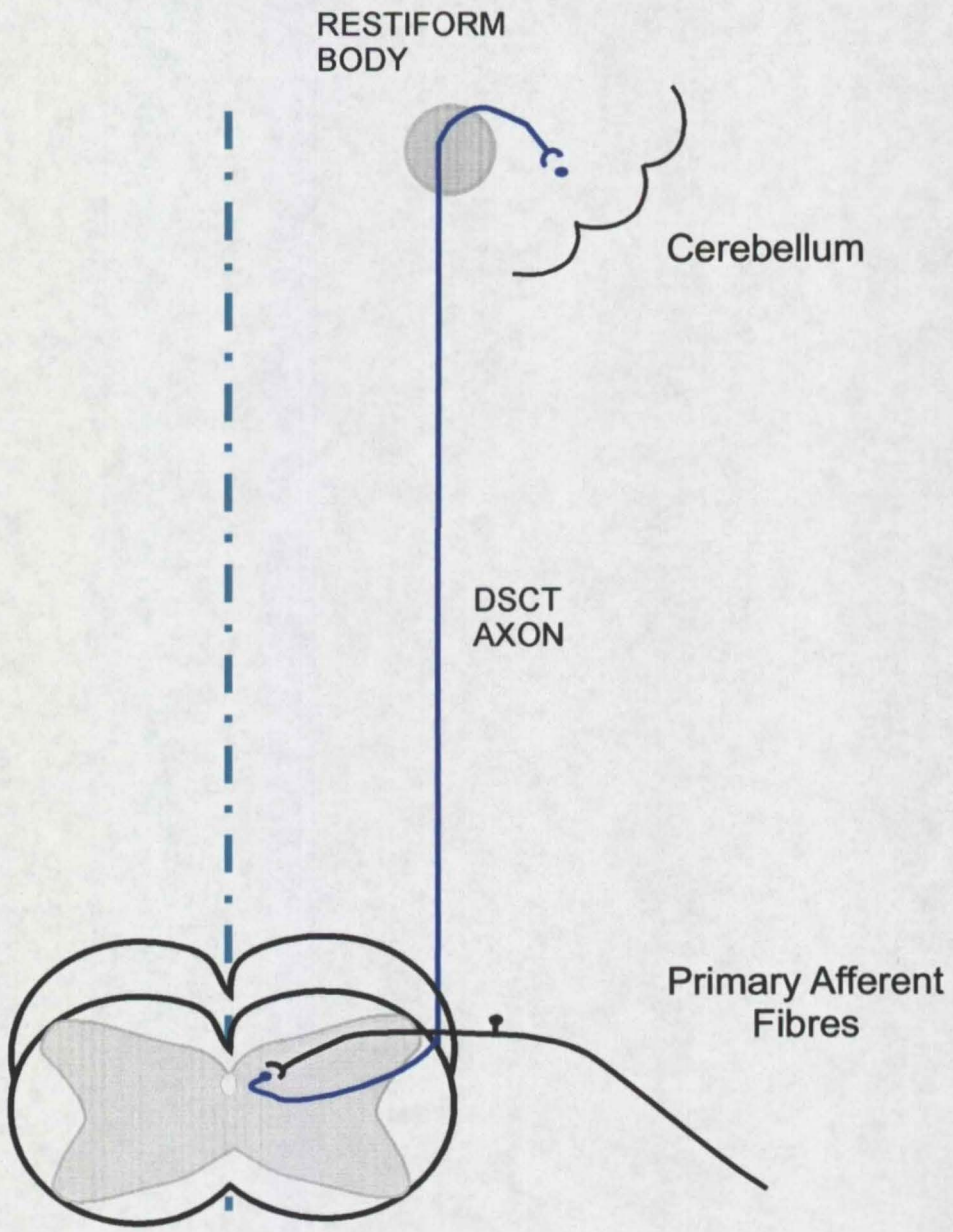

Figure 1-2. Schematic representation of the DSCT pathway with primary afferent fibre, cell of origin located in Clarke's column in the lumbar spinal cord and its termination in the cerebellum.

The ventral spinocerebellar tract (VSCT) originates from the column of the cells in the dorsal horn which extends more caudal than Clarke's column, crosses the spinal cord at the segmental level, ascends the spinal cord located ventral to the DSCT and crosses the spinal cord again before entering the cerebellum exclusively through the brachium conjunctivum (Oscarsson, 1956; Grant, 1962b; Hubbard & Oscarsson, 1962; Lundberg & Oscarsson, 1962a,b; Holmqvist & Oscarsson, 1963).

The rostral spinocerebellar tract (RSCT) is also anatomically distinct from the DSCT, in terms of originating from cell bodies located rostral to Clarke's column, and in having a ventral position to the DSCT in the spinal cord. Furthermore, there are marked differences between the RSCT and VSCT, in particular, the RSCT ascends the spinal cord uncrossed and reaches the cerebellum through the restiform body as well as via the brachium conjunctivum (Oscarsson, 1964; Oscarsson & Uddenberg, 1964, 1965).

Axons of the DSCT do not occupy the most dorsal part of the lateral funiculus in the lumbar region, as this region is occupied by the spinocervical tract (SCT) whose axons terminate in the lateral cervical nucleus (Lundberg & Oscarsson, 1961; Norsell & Voorhoeve, 1962; Holmqvist & Oscarsson, 1963). At the level of the third cervical segment the DSCT has shifted more dorsally and partly overlaps the SCT (Lundberg & Oscarsson, 1961; Grant, 1962b). In the restiform body, through which the axons of DSCT reach the cerebellum, they occupy first a dorsal and then a dorsomedial position (Ferraro & Barrera, 1935b,c; Busch, 1961).

In the Johansson and Silfvenius electro-physiological study (1977) in cats, and HRP retrograde study in rats (Low, Mantle-St.John and Tracey, 1986), it was shown that axons of the proprioceptor-activated DSCT neurones give off an axon collateral to the nucleus Z, a group of neurones located in the brainstem next to the rostral pole of the cuneate nucleus (Johansson & Silfvenius, 1977). As the neurones of this nucleus give rise to axons that might project to the ventrobasal thalamus and in turn to the somatosensory cortex (Landgren & Silfvenius, 1971; Grant et al., 1973), the same class of inputs from the hindlimb perhaps could be conveyed to the cerebellum as well as to the cerebral cortex (Landgren & Silfvenius, 1971). However, this hypothesis is based on electro-physiological studies (Landgren & Silfvenius, 1971; Grant et al., 1973) as there is no anatomical evidence yet in support of this view (Nakatani & Montano, 1980).

The indirect spinocerebellar pathways that involve additional synapses in the brainstem, in particular, in the reticular nucleus or the inferior olive could be classified in two groups (Table1-1; Oscarsson, 1973). In the first group, designated by Oscarsson (1973) as *indirect mossy fibres*, is the spino-reticulocerebellar pathway (LRN-SRCP) which relays in the lateral reticular nuclei (Jansen & Brodal, 1958). Axons arising from the neurones in the lateral reticular nuclei ascend through the restiform body and terminate in the ipsilateral cerebellum. The second group includes fibres that originate from neurones in the inferior olive (Eccles et al., 1966), cross the midline, ascend through the contralateral restiform body and terminate in broader area of the cerebellar cortex (Brodal, 1940; Oscarsson, 1973) as *climbing fibres* (see p. 2) The pathways classified by Oscarsson (1973) in this group are: dorsal spino-olivocerebellar path (DF-SOCP), dorsolateral spino-olivocerebellar path (DLF-SOCP), ventral spino-olivocerebellar path (VF-SOCP), lateral climbing fibre-spinocerebellar path (LF-CF-SCP) and ventral climbing fibre-spinocerebellar path (VF-CF-SCP) (Table 1-1; Oscarsson, 1973).

1.2.4 Termination of the DSCT and the other spinocerebellar pathways in the cerebellar cortex

The cerebellum is the largest part of the hindbrain overlying the fourth ventricle. It originates from dorsal aspect of the brainstem and it is connected with the brainstem (medulla, pons and midbrain) by means of three substantial pairs of fibre bundles, the inferior, middle and superior cerebellar peduncles. The cerebellum consists of *two hemispheres* located laterally and the *vermis* that joins them in the middle. The surface is highly convoluted with folds that are approximately transversely oriented, and are divided by fissures of varying depths. Deep fissures are used as a landmark to divide the cerebellum anatomically into three lobes: anterior, posterior and flocculonodular lobe. The internal structure of the cerebellum of the cat contains an outer mantle of grey matter (cerebellar cortex), covering the white matter in which is embedded the deep cerebellar nuclei. Each side of the cerebellum contains three deep cerebellar nuclei (from outside towards inside): *dentate nucleus, interpositus nuclei and fastigial nucleus* (Gluhbegovic, 1983).

The cerebellar cortex contains three layers: molecular layer, Purkinje cell layer and granular layer. While the Purkinje cells form a single layer between the molecular

(outer) and granular (inner) layer, the granule cells are concentrated in the granular layer while the Golgi, basket and stellate cells are in the more sparsely-cellular molecular layer (Palkovits et al., 1971b; Ito, 1984). Each Purkinje cell has a large soma (50-80 μm) from which the dendritic tree arises and extends up into the molecular layer (Palkovits et al., 1971a).

Mossy fibre terminal projections

The Purkinje cells are excited by two sources of inputs: mossy fibres and climbing fibres (Fig.1-3). Mossy fibre inputs activate Purkinje cells indirectly by forming synapses with granule cells in the inner (granular) layer whose axons then ascend to the molecular layer where an individual granule cell axon bifurcates into two thin parallel branches running about 5mm in opposite directions (Eccles et al., 1966; Palkovits et al., 1971a; Brand et al., 1976). These parallel fibres, branches of the individual granule cell axons, are orientated perpendicular to the plane of the Purkinje cell dendritic tree, and form synaptic contacts with the distal dendrites of Purkinje cells (Palkovits et al., 1971a; Brand et al., 1976). However, it appears that a single parallel fibre with an average length of 2 mm establishes synapses with every fifth Purkinje cell whose dendritic tree it crosses (Palkovits et al., 1972). Therefore, with 225 Purkinje cell dendritic trees, calculated to be accommodated in 2 mm along the longitudinal axis of the folium, each parallel fibre may form synapses with about 45 Purkinje cells (Palkovits, 1972). The parallel fibres projecting to the other 225 Purkinje cells positioned in the same 2 mm longitudinal axis of the folium can establish an equal number of synapses. The individual Purkinje cell could receive an input from as many as 80,000 parallel fibres (Palkovits et al., 1972). There is also substantial divergence at the level of the mossy fibre-granule cell synapse. Synaptic terminals of the mossy fibres form arborized structures called rosettes (Cajal, 1955), with individual mossy fibres estimated to supply from 20-44 different rosettes in one study (Eccles et al., 1967; Fox et al., 1967) and ~16-17 rosettes in another (Palkovits et al., 1972). Since one rosette makes synaptic contacts with ~30 granule cells, Palkovits (1972) calculated that one mossy fibre makes synaptic connections with as many as 400-500 granule cells.

Purkinje cells axons which are the only route out of the cerebellar cortex project to the deep cerebellar nuclei, which then give a rise to the cerebellar output principally through the superior cerebellar peduncle to the thalamus, except for the output to the

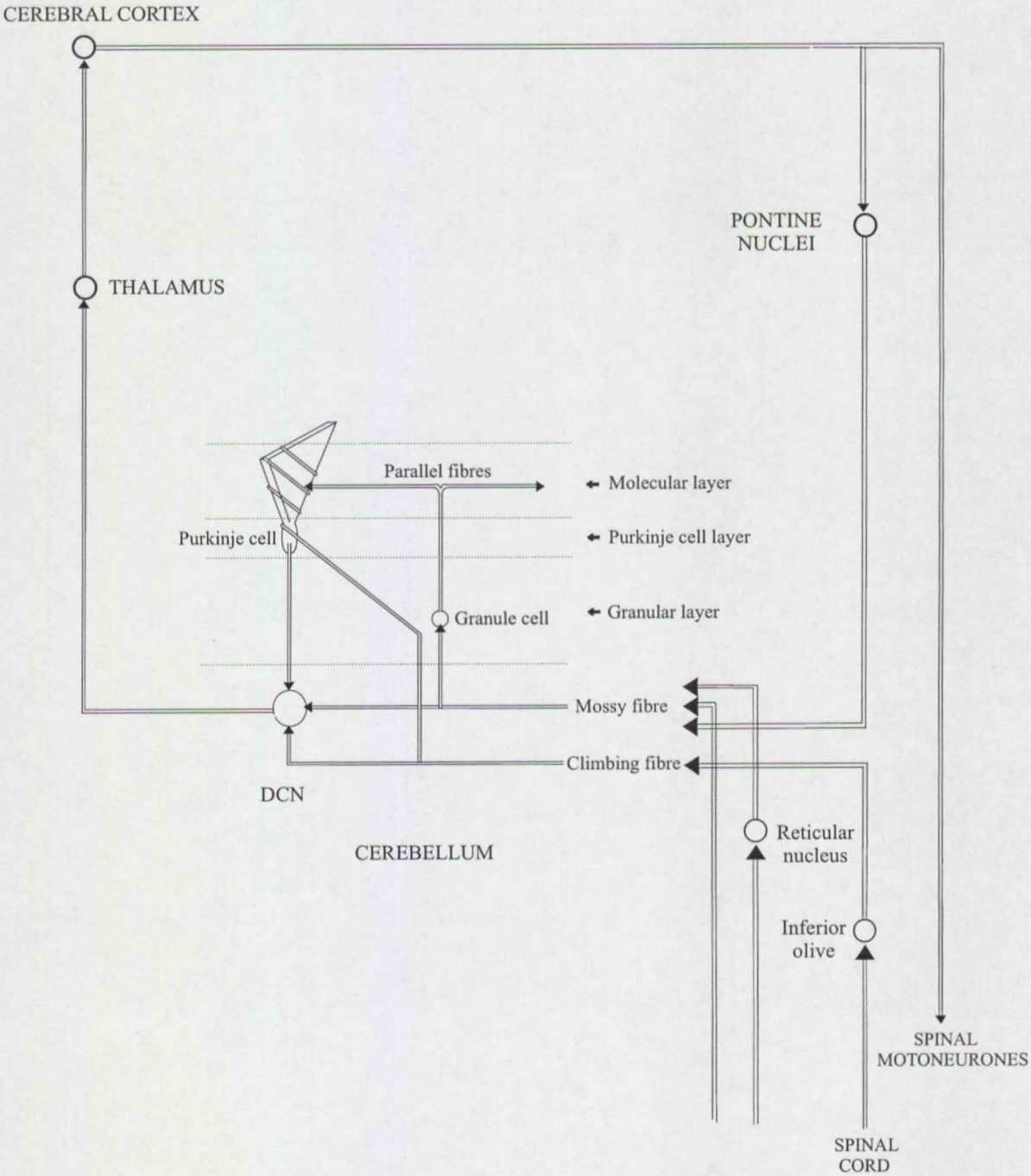

Figure 1-3. Schematic representation of the termination of afferent pathways in the cerebellar cortex (mossy & climbing fibres) and representation of some connections of the cerebellum with other parts of the central nervous system (DCN – Deep cerebellar nuclei). (Based on: Ito, 1984; Palkovits et al., 1971a,b; Mlonyeni, 1973; Oscarsson, 1965).

vestibular nuclei which goes through the inferior cerebellar peduncle (Nolte, 1999). However, it has emerged in the last decade that the deep nuclei are not just simple relay stations for the outputs from the cerebellar cortex (Nolte, 1999). The fact that collaterals arising from climbing fibres and many mossy fibres project to the deep cerebellar nuclei suggests that these inputs may provide a tonic excitation to neurones in the deep nuclei, and that inhibitory inputs from Purkinje cells perhaps modulate the firing rates of these neurones (Blodel & Barton, 1970; Thach, 1972; Nolte, 1999). Apart from giving rise to axons that leave the cerebellum, the deep nuclei project in a recurrent way to the same areas of the cerebellar cortex from which they receive Purkinje axon input (Nolte, 1999). Although the functional significance of these connections is not fully clear, they affirm the existence of complex internal circuity between the cerebellar cortex and the deep cerebellar nuclei.

Perhaps because the cerebellum is involved in such a diverse range of central functions including, the regulation of muscle tone, the control of posture and the equilibrium of the entire body, and the coordination of voluntary movements, it receives inputs from both the cerebral cortex via the pontine nuclei and from the spinal cord and the vestibular nuclei. According to the different projection areas for these inputs in the cerebellar cortex the different regions of the cerebellum are specialised for particular functions. For example, the flocculonodular lobe and part of the uvula receive vestibular inputs and can be called the *vestibulocerebellum*. Most of the vermal and paravermal areas (intermediate zone), except nodulus and uvula, can be labelled as the *spinocerebellum* as they receive spinal somatic afferent inputs. As the inputs from the cerebral cortex project to lateral parts of the cerebellar hemispheres, these regions may be called the *cerebrocerebellum*. There is a certain amount of overlap between these functional portions because of the connections between them. For instance, the *spinocerebellum* also receives inputs from the pontine nuclei and parts of it receive vestibular inputs as well (Nolte, 1999).

Degeneration experiments (Dow and Moruzzi, 1958) and electro-physiological experiments (Grant, 1962b; Brodal et al., 1967) have shown that the DSCT and the CCT terminate as *mossy fibres* in the anterior lobe, paramedian lobules and the pyramis of the cerebellum, while the ventral spinocerebellar tract (VSCT) and the rostral spinocerebellar tract (RSCT) terminate principally in the anterior lobe of the cerebellum (Lundberg & Oscarsson, 1960, 1962a; Grant, 1962b; Oscarsson & Uddenberg, 1964;

Voogd, 1969). The termination of DSCT and CCT fibres is entirely ipsilateral, which is consistent with a role for them in the regulation of movement and posture in the ipsilateral limb, while VSCT and RSCT axons terminate bilaterally in the anterior lobe, which could be associated with a role in the coordination of bilateral limb posture and movement (Grant, 1962a,b; Lundberg & Oscarsson, 1962a; Oscarsson & Uddenberg, 1964). However, the terminations of VSCT and RSCT are most dense on the side ipsilateral to the location of their cells of origin and their receptive fields (Grant, 1962b; Lundberg & Oscarsson, 1962a, Oscarsson & Uddenberg, 1964).

There are also noticeable differences in the termination of the DSCT and CCT in lobules IV and V of the cerebellar anterior lobe. Electrophysiological investigations (Dow & Moruzzi, 1958) suggest that the DSCT terminates in lobule IV and even further rostrally, which is the classical hindlimb representation area, while the CCT terminates in lobule V, which is the classical forelimb representation area (Dow & Moruzzi, 1958).

The axons of the reticulocerebellar pathway (Oscarsson's LRN-SRCP) terminate as *mossy fibres* over a broader area of the ipsilateral cerebellum than do the DSCT and CCT, although, it appears that the vermis is the main termination area of the reticulocerebellar fibres, indicating a possible role of this pathway in the regulation of the equilibrium of entire body (Kitai, Kennedy, Morin & Gardner, 1967; Bruckmoser, Hepp-Reymond & Wiesendanger, 1970b).

Climbing fibre terminal projections

Climbing fibres differ considerably from mossy fibres in terms of their origins and their mode of termination. Mossy fibre inputs to the cerebellar cortex may arise from several different locations in the central nervous system as mentioned above. However, the origin of climbing fibres is confined to the inferior olivary nucleus (Dow, 1942; Szentagothai & Rajkovits, 1959; Desclin, 1976; Desclin & Colin, 1980).

Although there is no marked difference in the estimated ratio of inferior olivary neurones to Purkinje cells in cats from the studies of Escobar et al. (1968) (1:15), and Mlonyeni (1973) (1:10 and 1:11), the reports on the number of Purkinje cells that receive synaptic input from a single climbing fibre are divided. One group (Eccles et al., 1967; Larramendi & Victor, 1967; Chan-Palay & Palay, 1970) supports a theory of a one-to-one relationship between a climbing fibre and the proximal dendrites of only one Purkinje cell, while others (Escobar et al., 1968; Fox, Andrade & Schwyn, 1969;

Mlonyeni, 1973) propose that an individual climbing fibre forms synapses with at least 10 Purkinje cells. However, in either circumstance the relationship between a single climbing fibre and Purkinje cells contrasts sharply with the enormous convergence and divergence in the relationship between mossy fibres and Purkinje cells. Climbing fibres prior to their termination in the cerebellar cortex give off collaterals, as do mossy fibres, to the deep cerebellar nuclei (Scheibel & Scheibel, 1954; Palay & Chan-Palay, 1974; Sugihara et al., 1996).

Anatomical studies (Brodal, 1940; Szentagothai & Rajkovits, 1959) have demonstrated that axons from the inferior olive, after crossing the midline, terminate as climbing fibres in the molecular layer of the cerebellar cortex. Each part of the inferior olivary nucleus seems to project in an orderly way to a particular area of the cerebellar cortex. Therefore, each small olivary area appears to project to a narrow sagittal or parasagittal strip of the cerebellar cortex (Oscarsson, 1969; Voogd, 1969). Furthermore, even though individual climbing fibres may diverge to supply up to ~10 Purkinje cells, each Purkinje cell receives, with few exceptions, input from only one climbing fibre (Eccles et al., 1967).

1.3 Review of the functional organisation of the DSCT

As mentioned above, there are four pathways that originate from the spinal cord (or its extension to the lower brainstem in the case of the CCT) and conduct information from the periphery to the cerebellum via a single synaptic relay: the DSCT, CCT, VSCT and RSCT (Oscarsson, 1973). Efficient synaptic transmission in the spinal relays and fast conduction velocity of the tract fibres enable the information from the hindlimb, in the case of the DSCT and VSCT, and from the forelimb in the case of the CCT and RSCT, to be delivered to the cerebellar cortex with little delay.

The DSCT and CCT are activated by muscle, joint and cutaneous afferents and supply the cerebellum with proprioceptive and exteroceptive information, while the VSCT and RSCT are activated by group I muscle afferents and provide proprioceptive information to the cerebellum (Eccles et al., 1961a; Mann, 1971; Oscarsson, 1973).

The DSCT can be divided in two functional parts according to the source of peripheral inputs to its neurones. The first is a *proprioceptive part* that conveys stretch and tension information from muscle spindle and tendon receptors and other kinaesthetic information from joint receptors. The second is an *exteroceptive part* that

conveys tactile information from receptors in the skin. In terms of the information they signal, these two divisions can be considered as two separate tracts (Oscarsson, 1973). However, many of the DSCT neurones are activated by afferent inputs from two or more different peripheral receptor types. Therefore, any account of the proprioceptive and exteroceptive divisions of the DSCT as quite separate tracts is inadequate, and they will be treated in this review as two components of an overall DSCT system.

1.3.1 Peripheral inputs to DSCT neurones

This section presents a review of the proprioceptive and exteroceptive components of the DSCT. Until now the proprioceptive component has been much more studied than the exteroceptive component, especially in terms of the quantification of the responses evoked in DSCT neurones by stimulation of the particular peripheral receptors (Laporte, Lundberg & Oscarsson, 1956a,b; Lundberg & Oscarsson, 1956; Eccles, Oscarsson & Willis, 1961b).

Proprioceptive component of the peripheral inputs to the DSCT

Afferent inputs to DSCT neurones from muscles

The Group I afferent fibres arising from muscle spindle stretch receptors and from tendon organs of the muscles in the cat's hindlimb, provide monosynaptic activation to DSCT neurones located predominantly in Clarke's column (Lloyd & McIntyre, 1950; Laporte, Lundberg & Oscarsson, 1956a,b). Later studies (Lundberg & Oscarsson, 1956; Lundberg & Winsbury, 1960; Jansen & Rudjord, 1965) showed that inputs from spindle receptors (Group Ia) and tendon organs (Group Ib) activate largely different sets of DSCT neurones. However, some of the neurones were activated from both Group Ia and Group Ib afferent inputs, which might be related to connections via inter-neurones rather than direct monosynaptic input from both sources (Eccles, Oscarsson & Willis, 1961b). Some DSCT neurones receive additional monosynaptic excitation from Group II muscle afferent fibres (Laporte et al., 1956b; Eccles et al., 1961b), which has also been observed in CCT neurones (Rosen, 1969b; Cooke et al., 1971b; Mackie et al., 1999). The contribution of inputs from the secondary spindle endings (Group II muscle afferent inputs) in eliciting monosynaptic excitatory post-synaptic potentials (EPSP) in DSCT neurones was demonstrated in intracellular recording experiments with electrical stimulation of the muscle sensory nerve (Eccles,

Oscarsson & Willis, 1961b). However, in intracellular recording experiments based upon direct receptor stimulation, this Group II contribution could not be distinguished (Oscarsson, 1973).

About fifteen Group I afferent fibres converge onto each DSCT neurone. Electron microscopic studies in Clarke's column have revealed the presence of several types of synaptic contacts, including giant bulbs (Szentagothai & Albert, 1955; Saito, 1974, 1979; Houchin et al., 1983) which contain multiple transmitter release sites. It appears that synaptic transmission between Group I muscle afferent fibres and DSCT neurones occurs in "quantal increments" (Tracey & Walmsley, 1984). These quantal increments, possibly cause fluctuations in the amplitude of the excitatory postsynaptic potentials (EPSPs) and large, unitary EPSPs up to 5mV in amplitude evoked in DSCT neurones could be associated with these multiple transmitter release sites (Tracey & Walmsley, 1984). Two or three unitary EPSPs that are closely spaced, allowing for temporal summation, are sufficient to evoke a discharge (Oscarsson, 1973).

The excitatory actions on DSCT neurones from Group I afferents usually arise from a single muscle or its synergist, but inhibitory actions often come from several muscles, predominantly antagonists of those producing excitation (Holmqvist et al., 1956; Jansen, Nicolaysen & Walloe, 1967).

Two forms of inhibition originating from Group I muscle afferents have been observed on muscle-related DSCT neurones (Curtis, Eccles & Lundberg, 1958; Eccles, Oscarsson & Willis, 1961a). In most DSCT neurones excited by inputs from Group Ia muscle afferent fibres disynaptic *postsynaptic inhibition* is caused by inputs from Group Ib afferent fibres arising from the antagonist muscle (Eccles & Lundberg, 1959b). Presynaptic inhibition has also been observed in DSCT neurones and resembles that observed earlier in lumbosacral motoneurones (Eccles et al., !960a, 1961a). Repetitive volleys in Group I afferent fibres, chiefly Group Ib, give rise to depression of the monosynaptic EPSPs in lumbosacral motoneurones but there is little, if any, effect from the activation of Group II and III afferent fibres (Frank & Fuortes, 1957; Frank, 1959; Eccles et al., 1960a). Inhibition, measured by the reduction in the DSCT mass discharge, was maximal at a conditioning-test interval of about 25 ms and with a conditioning stimulus to the antagonist of at least four stimulus volleys at high frequency (~ 300 Hz) (Eccles et al., 1961a).

Afferent inputs to DSCT neurones from the joints

Afferent fibres from the cat's hindlimb joints (knee, ankle and toe joints) arise from two types of receptors in the joint capsule: slowly adapting and rapidly adapting receptors. The fibres arising from slowly adapting (SA) receptors, believed to be *Ruffini endings* in the joint capsule (Skoglund, 1956), terminate on DSCT neurones located predominantly in Clarke's column nucleus (Lindstrom & Takata, 1972), while those arising from rapidly adapting receptors, believed to be Pacinian corpuscles, project via the spinal dorsal columns to the cervical spinal cord and fail to connect with DSCT neurones (Burgess & Clark, 1969a). These afferent inputs from joint SA receptors to the DSCT might be of particular importance for the ability of both the primate (Merton, 1964) and the cat (Burgess & Clarke's, 1969a) to localise the position of the limb, and may play a role in cerebellar motor regulation (Lindstrom & Takata, 1972). A relatively small proportion of all DSCT neurones sampled in the study of Kuno et al.(1973) was activated by SA joint afferent fibres (~15%). Furthermore, one out of four DSCT neurones activated by inputs from joints in this study was located outside Clarke's column nucleus.

In the sample of DSCT neurones associated with inputs from the joints, 16% of the units were activated by inputs from two joints, in particular, those with the same directions of movements. Therefore, the same DSCT neurone can be activated by inputs from e.g. knee and ankle joint capsules during the flexion or extension movements of these joints (Kuno et al., 1973).

Exteroceptive component of the peripheral inputs to the DSCT

The exteroceptive component of the DSCT is found in the neurones activated by tactile inputs from the skin and carried by cutaneous afferent fibres. In Mann's study (1971), approximately 20% of the sampled DSCT neurones were activated by cutaneous inputs, 8% by combined cutaneous and deep inputs, ~50% by deep inputs (response to light squeezing of muscles, rotation of a joint, or to deep pressure) and about 20% units, antidromically identified as DSCT neurones, could not be activated by any of these inputs and were called mute cells (Mann, 1971).

Cutaneous inputs to DSCT neurones

The cutaneous inputs from the hindlimb are carried by primary afferent fibres which predominantly arise from hair receptors and touch dome receptors in the hairy

skin. However, some DSCT neurones in the study by Mann (1971) responded to stimulation of the toe pads, as well as part or the entire glabrous central foot pad (Mann, 1971).

DSCT neurones activated only by *slowly adapting type I* (SA I, touch dome) afferents (about 15% of DSCT neurones activated by cutaneous inputs), showed large receptive fields (varying between 30 and more than 100 cm^2 in Mann's study, 1971) located on the thigh, calf and the upper part of the foot (Fig. 1-4a; Mann, 1971). It was estimated (Mann, 1971) that these individual DSCT neurones can be activated from more than 100 touch domes. In earlier study (Tapper, 1965) it was reported that there was a modal value of 3 touch domes per SA I afferent fibre. Therefore, it appears that inputs from more than 30 SA I afferent fibres converge onto individual DSCT neurones (Mann, 1971).

The receptive fields of DSCT neurones sensitive just to hair movements (HFA; about 30%) tend to be smaller in size (0.5 to $2cm^2$ in Mann's study, 1971) and were located mostly on the foot and toes of the cat's hindlimb. The receptive field can occupy hairy skin from a region restricted to one toe to the entire surface of the foot, excluding the foot pad and the toe pads. (Fig. 1-4b; Mann, 1971). Most of the DSCT units sensitive only to hair movements (HFA), were activated by small movements of the down, guard and tylotrich hairs or just a guard hair, while for some DSCT neurones in this group the receptor type could not be identified due to loss of these units during the investigation (Mann, 1971).

About one half of the DSCT neurones activated from the skin in Mann's study (1971) were excited by both the touch domes (SA I afferents) and the hair receptors (HFA fibres) within their receptive fields (Fig. 1-4c). The DSCT neurones in this group principally responded to stimulation of down, guard and tylotrich hairs in addition to touch domes, but a small number of them responded to stimulation of down and tylotrich hairs or just the down hairs and touch domes (Mann, 1971).

Small receptive fields of the DSCT neurones activated by hair and touch dome inputs, located mostly on the distal foot and toes, tend to be uniform (e.g., stimulation of hair receptors anywhere within the receptive filed of these DSCT neurones causes discharge) while the large receptive fields, usually located on the upper part of the hindlimb tend to be heterogeneous (e.g., stimulation of touch domes in one part of the

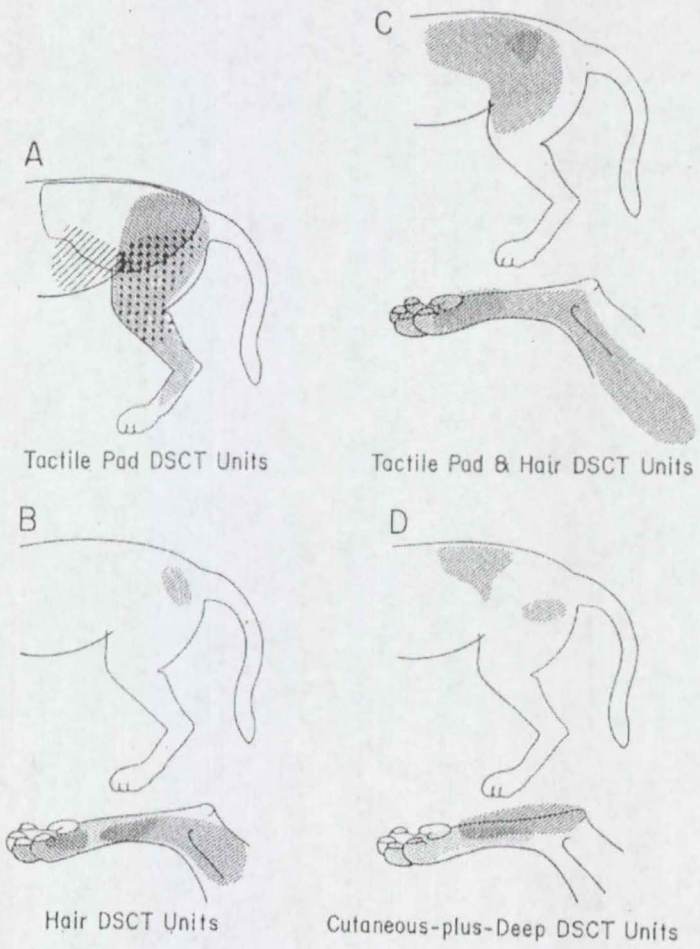

Figure 1-4. Samples of cutaneous receptive fields of the various classes of DSCT cells. Units that responded to tactile pad stimulation (A), hair stimulation (B), tactile pad and hair stimulation (C) and cutaneous plus deep stimulation (D) are illustrated. Four fields are shown in each diagram (from Mann, 1971).

field, usually in the centre, evokes discharge in the DSCT neurone, while elsewhere in the receptive field they are ineffective, but stimulation of the hair receptors elsewhere in the receptive field may elicit discharge in the same unit) (Mann, 1971).

Combined afferent inputs from cutaneous and deep receptors to DSCT neurones

Less than 10% of all DSCT units isolated in Mann's study (1971) belonged to the group that responded to stimulation of both the cutaneous and deep receptors. Although the cutaneous component of the receptive field was examined, no attempt was made to identify the deep structures involved. In general, the receptive fields for the cutaneous component resembled those of purely cutaneous-activated DSCT units, especially in response to hair stimulation (Fig. 1-4d). However, stimuli applied to touch domes did not elicit discharges in DSCT neurones sensitive to combined cutaneous and deep structure inputs, but evoked the discharge in those DSCT neurones selectively activated by cutaneous inputs (Mann, 1971). The discharges were briefer and therefore the response could not be sustained as a slowly adapting response (Mann, 1971). It was demonstrated in the same study that the response was attributable to SA I input from touch domes, as stimulation of the skin surrounding the touch domes produced no response.

It must be emphasised that quantification of the responses of DSCT neurones activated by cutaneous inputs in Mann's study (1971) was not possible as stimulation was carried out with hand-held probes.

1.3.2 Functional organisation of the neurones in Clarke's column nucleus

The proportions of DSCT neurones sensitive to different receptor input and their somatotopic distribution within and around Clarke's column were analyzed in the studies of Kuno et al. (1973) and Szentagothai (1961) (Fig. 1-1). The majority of DSCT neurones (>50%) sampled in the study by Kuno et al. (1973) were activated by inputs from the muscles of the cat's hindlimb, about 20% responded to cutaneous stimulation, while more than 10% of the total number of DSCT units isolated were sensitive to inputs from the joints. Less than 10% of the neurones were activated by combined inputs from different sources.

DSCT neurones activated by inputs from proprioceptors

Properties and coding capacity of DSCT neurones responding to muscle inputs

The majority of DSCT neurones in the muscle-related group showed background discharge in the absence of any stimuli to the muscle. When the muscle receptors were activated by sustained stretch, an increment in mean frequency of discharge could be seen, and that increment was in proportion to the intensity of the stimulus (Kuno et al., 1973). Impulse distributions in the *time interval histograms* of the muscle-related DSCT neurones showed regularity, even during resting conditions, but especially during the activation of muscle receptors (Kuno et al., 1973).

The efficacy of transmission from group I afferents to the neurones in Clarke's column is high, reflected in the fact that DSCT neurones are reported to be capable of following the input generated by electrical stimulation of the presynaptic nerve at rates of 500/s for several seconds (Holmqvist, Lundberg & Oscarsson, 1956; Eccles, Oscarsson & Willis, 1961a; Kuno & Miyahara, 1968). On natural stimulation of muscle receptors by stretching, DSCT neurones respond as if activated either from receptors in muscle spindles or from tendon organs (Lundberg & Oscarsson, 1956; Lundberg & Winsbury, 1960; Eccles, Oscarsson & Willis, 1961a; Jansen & Rudjord, 1965; Eide, Fedina, Jansen, Lundberg & Vyklicky, 1969b). The discharge frequency of the neurones is said to be similar to that in the primary afferent fibres and is linearly related to muscle length (Jansen, Nicolaysen & Rudjord, 1966; Kostyuk, 1969; Jansen & Walloe, 1970).

The factors contributing to efficient transmission from group I afferent fibres to DSCT neurones of the muscle-related group are:

(i) the generation of large excitatory post-synaptic potentials (EPSP), produced by a volley in Group I afferents (Curtis, Eccles & Lundberg, 1958; Eccles et al., 1961a). This EPSP is built up by the summation of a substantial number of unitary EPSPs suggesting extensive convergence of fibres from the same muscle nerve. The EPSP has a long duration, as long as 40 ms (Eccles et al., 1961a), which might be related to the very large synaptic endings of the Group I afferent fibres on the DSCT neurones (Szentagothai & Albert, 1955), and to slow diffusion of the transmitter out of the extensive synaptic clefts (Curtis et al., 1958; Eccles et. al, 1961a; Tracey & Walmsley, 1984).

(ii) the ability of DSCT neurones to follow electric stimulation up to 500/s (Holmqvist et al., 1956) was attributed to the effect of repetitive stimulation in potentiating the sizes of the individual EPSPs produced by the Group Ib (afferent fibres from Golgi tendon organs) volleys, while the frequency-response relationship between DSCT neurones and Group Ia afferent fibres (muscle spindle afferents) resembles that in motoneurones (Eccles et al., 1961a).

(iii) although DSCT neurones have an afterhyperpolarization, in particular that produced by Ia afferents, comparable to that in motoneurones, there is no evidence for recurrent inhibition in DSCT neurones (Eccles et al., 1961a; Oscarsson, 1965; Kuno & Miyahara, 1968; Eide et al., 1969a,b).

Responses of DSCT neurones to inputs from joints

The DSCT neurones in this group, activated exclusively by slowly adapting joint receptors (Lindstrom & Takata, 1972), were found within Clarke's column in ~75% of cases, while the remained 25% were found outside the nucleus (Kuno et al., 1973). The DSCT neurones sensitive to joint inputs showed a substantial level of background activity under resting conditions in the form of random spontaneous activity combined with the occasional, more regular bursts occurring over time periods of >100 ms. Small passive joint movements of flexion or extension lead to an increase in response level and a more regular distribution of the interspike intervals, while the passive joint movements of higher intensity caused a firing of joint-related DSCT neurones at a modal frequency of about 300 impulses/s with a regular discharge distribution in the interval histograms resembling those in muscle-related DSCT neurones during the activation of muscle receptors (Kuno et al., 1973). However, these impulse distributions for DSCT neurones activated by joint inputs varied among the neurones in the study (Kuno et al., 1973). In one extreme case no resting discharge could be seen, but activation of joint receptors produced firing with a unimodal interval histogram (one clear narrow peak) with mean frequency in direct proportion to the intensity of the stimulus, and the interval histogram resembling that of DSCT neurones in the muscle group. In the two other extreme cases, the irregular component was so dominant that the regular component was barely detectable under resting conditions and the interval histograms were very similar to those observed in cutaneous-related DSCT neurones (Kuno et al., 1973).

DSCT neurones activated by inputs from exteroceptors

Responses of DSCT neurones sensitive to cutaneous inputs

The cutaneous-sensitive DSCT units in the study of Kuno et al., (1973) were activated by either electrical stimulation of cutaneous sensory nerves (sural, posterior femoral cutaneous or superficial peroneal nerve) or by natural stimulation of the cat's hindlimb skin (touching dome-like elevated structures on the skin with a glass rod or moving guard and down hairs on the hindlimb). Similar natural stimulation of hair receptors and HFA fibres associated with them as a *rapidly adapting* source and touch domes with their SA type I afferent fibres as a *slowly adapting* source of inputs from the skin was used in the earlier study of Mann (1971) to evoke responses in the skin-related DSCT neurones. A small number of DSCT neurones in the studies of Mann (1971) and Kuno et al. (1973) responded to stimulation of both the cutaneous and deep structures, but neither of these studies attempted to identify the deep structures. Mann (1971) also reported a minimal number of DSCT neurones isolated in his study that responded to natural stimulation of the foot and toe pads.

The discharge patterns of DSCT neurones activated by cutaneous and /or subcutaneous inputs were studied during resting conditions and during receptor activation in the study of Kuno et al. (1973) (Fig. 1-5). Discharge records (Fig. 1-5a,b) of the DSCT neurone activated by HFA inputs and impulse distributions in their time interval histograms (Fig. 1-5c, d) under resting conditions showed occasional bursting and discharge occurred in a temporal sequence that indicated a random process. Activation of the skin receptors (in this case hair receptors) increased the discharge of the DSCT neurones under investigation (Fig. 1-5b), but only in the occurrence of the discharge at long time intervals (10-50 msec), while the discharge pattern at short intervals remained practically unchanged before and during receptor activation (Fig. 1-5a,b). The discharge distribution in the interval histograms of the cutaneous-related DSCT neurones during receptor activation was still in the manner suggesting a random discharge (Fig. 1-5d). This behaviour was observed in all DSCT neurones activated by cutaneous inputs in the study of Kuno et al. (1973), but not in the three DSCT neurones which responded to pressure on glabrous skin of the foot pads (subcutaneous receptors).

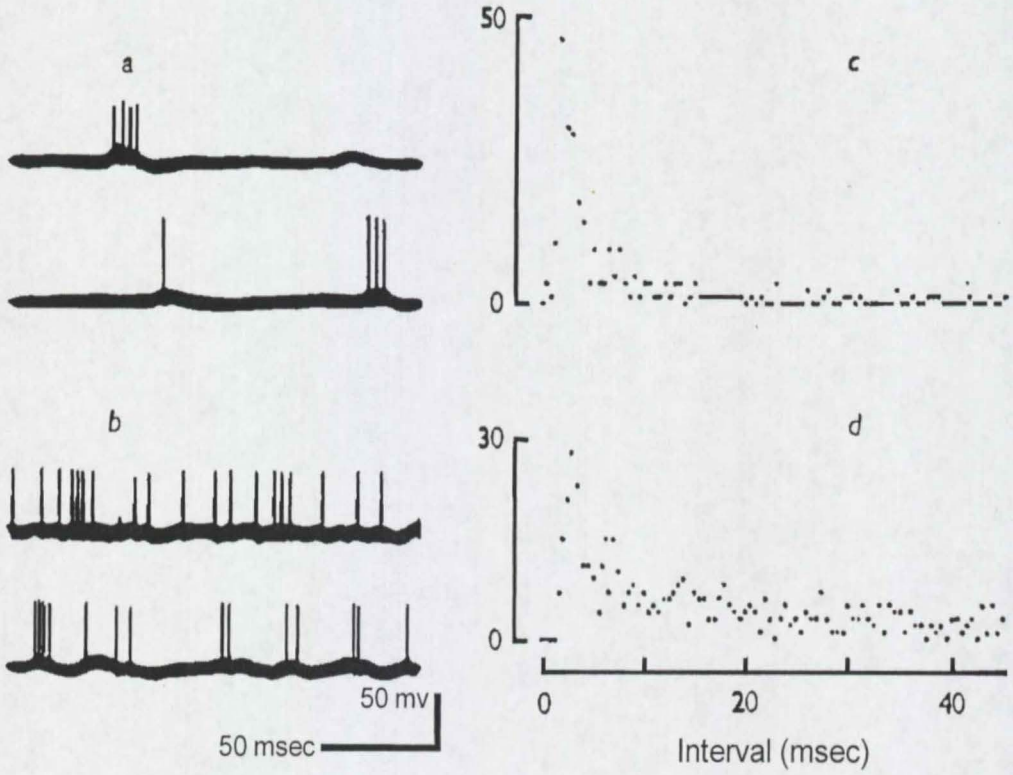

Figure 1-5. **a**, responses of the cutaneous-associated DSCT neurone recorded intracellularly under 'resting' conditions (without added stimuli). **b**, same as a, but during activation of hair receptors. **c**, interval distribution of discharge illustrated in a. **d**, interval distribution of discharge illustrated in b (reproduced from Kuno et al., 1973, with retouching of the vertical aspect of the spikes).

The discharge pattern of these neurones resembled the pattern of joint-related DSCT neurones.

These marked differences in discharge patterns between DSCT neurones activated by inputs from proprioceptors, in particular inputs from muscles, and DSCT neurones activated from cutaneous sources could be attributed to a smaller number of cutaneous afferent fibres that converge onto the individual cutaneous-related DSCT neurones in comparison with the substantial convergence of the muscle afferents onto the individual muscle-related DSCT neurones (Eccles et al., 1961a; Oscarsson, 1973). Thus, the reason an equivalent single volley from cutaneous afferents generates a smaller excitatory postsynaptic potential (EPSP) in DSCT neurones than is the case for muscle afferents (Kuno & Miyahara, 1968; Kuno et al., 1973), is probably because of the more limited convergence from the cutaneous afferents, even though *individual* cutaneous afferents may have more efficient synaptic linkage with DSCT neurones than do individual muscle afferents (Grundfest & Campbell, 1942; Mann, 1971; Kuno et al., 1973).

Response patterns of DSCT neurones activated by combined inputs

This group of DSCT neurones is activated by combined inputs from muscle, joint, cutaneous and subcutaneous sources, with a dominating muscle-joint combination (Kuno et al., 1973). About 10-20% of all DSCT neurones investigated in Kuno's study (1973) were activated by combined inputs and nearly 1/3 of the neurones in this group were located outside Clarke's column nucleus.

The discharge patterns of only three DSCT neurones activated by combined inputs were presented in the paper of Kuno et al. (1973). The interval histograms of these neurones show impulse distributions similar to those observed in the cutaneous-related DSCT neurones described above. An apparent hump on the predominant irregular component in the interval histograms may represent response to activation of muscle, joint or subcutaneous receptors.

1.3.3 Conduction of peripheral inputs through the DSCT

The largely monosynaptic organization of input to DSCT neurones and the high conduction velocity of its input fibres enable this tract to supply the cerebellar cortex with accurate information from the hindlimb necessary for cerebellar regulatory

functions such as the tone in skeletal musculature, posture adjustments and for voluntary movements and equilibrium of the entire body, with little delay (Oscarsson, 1965,1973).

The conduction velocities of some spinocerebellar and olivocerebellar fibres are given in Table 1-1. Those of the DSCT axons are calculated from the latency of the antidromic volley and the conduction distance. Conduction distance is the length between the neurone's soma in Clarke's column and the antidromic stimulating site of DSCT axon terminals in the inferior brachium or restiform body in the cerebellum (Mann, 1971). Antidromic latency is the time difference between the onset of the antidromic stimulus, represented with an artefact on the oscilloscope-monitor, and the occurrence of the associated action potential in the DSCT unit (Mann, 1971). It seems that conduction velocity varies among DSCT axons from between 20 and 110 m/s (Lundberg & Oscarsson, 1960; Lundberg, 1964; Oscarsson, 1973), with a mean value of 78 m/s (Lundberg, 1964).

1.3.4. Distribution of DSCT input information within the cerebellar cortex

As the anatomy of the spinocerebellar pathways, in particular the DSCT, CCT, VSCT and RSCT and their projections over the cerebellar cortex were presented earlier in this review, this section will deal with the functional implications of the anatomical organization of the DSCT input to the cerebellar cortex and its probable regulatory functions.

The termination areas in cerebellar cortex for the four tracts reaching the cerebellum through the inferior peduncle are schematically shown in Fig. 1-6 (Oscarsson, 1965). The horizontal lines in Fig. 1-6 divide lobules IV and V of the anterior lobe, while the vermis and intermediate cortices are separated by vertical lines. The interrupted line in Fig. 1-6 is the border between hindlimb (rostral) and forelimb (caudal) representation areas. As the DSCT and CCT terminate in the ipsilateral anterior lobe, the information conveyed by these two pathways may be utilized in the coordination of movement and posture in the respective ipsilateral limb (Chambers & Sprague, 1955a,b; Lundberg & Oscarsson, 1960; Grant, 1962a,b; Oscarsson, 1965).

The VSCT and RSCT terminate over a broader bilateral area of the cerebellar cortex (Fig. 1-6), partly due to branching of individual fibres which send one collateral

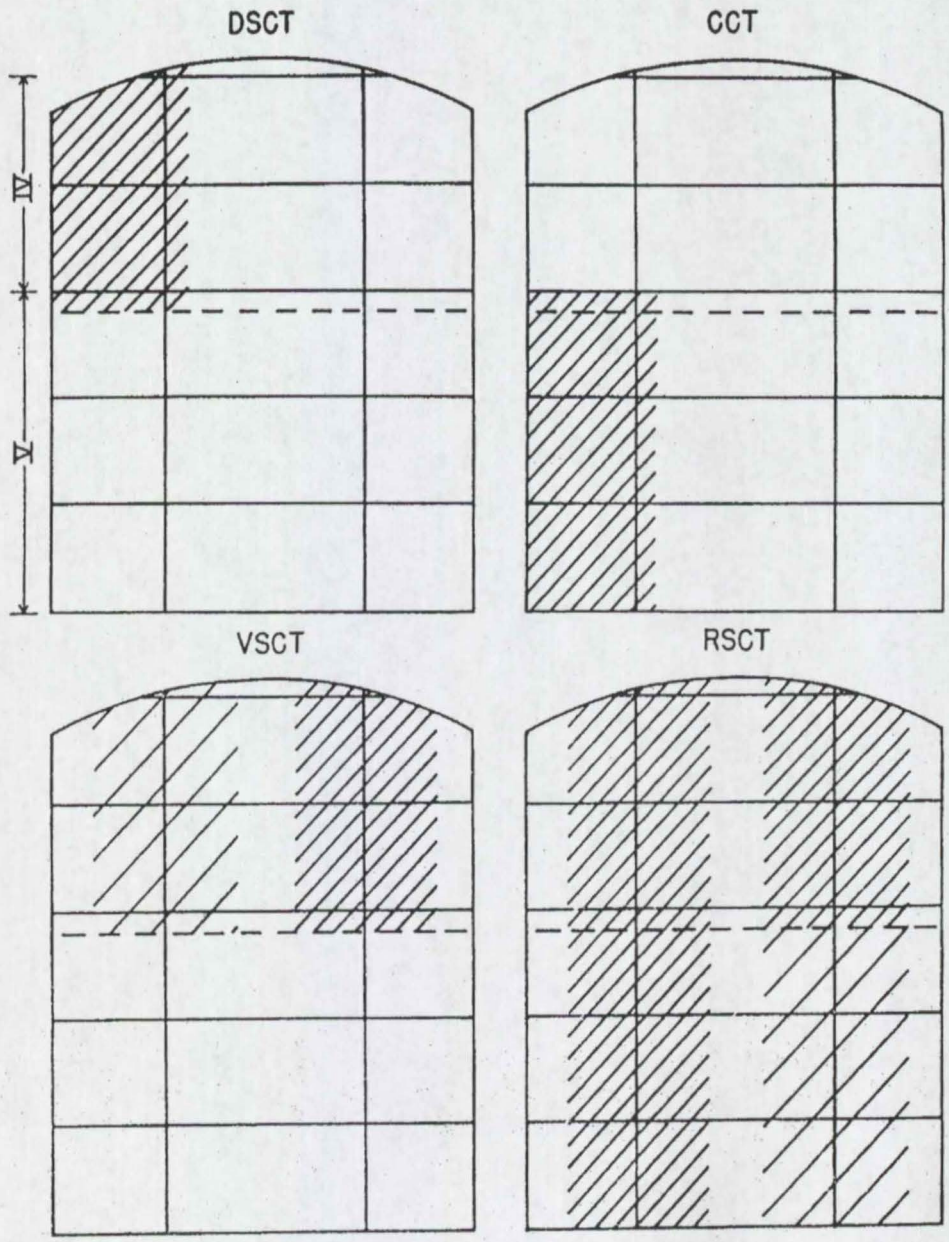

Figure 1-6. Termination of DSCT, CCT, VSCT and RSCT that reach the cerebellum through left peduncles. *Horizontal lines* indicate Larsell's lobules IV and V and commonly occurring sulci. *Interrupted line* represents border between rostral "hind-limb area" and caudal "forelimb area." *Vertical lines* border intermediate cortices (adapted from Oscarsson, 1965).

to the ipsilateral and the other to the contralateral side (Grant, 1962b; Lundberg & Oscarsson, 1962a; Oscarsson & Uddenberg, 1964). However, the termination is denser on the side ipsilateral to the cell of origin in the spinal cord. This bilateral termination of the VSCT and RSCT therefore indicates that peripheral information conveyed by these two pathways may be used in motor coordination of both the ipsilateral and contralateral limb. Furthermore, while the VSCT almost entirely terminates in the somatotopically appropriate area for the hindlimb, the RSCT tends to terminate equally often in both, the forelimb and the hindlimb areas (Fig. 1-6; Lundberg & Oscarsson, 1960; Grant, 1962b; Lundberg & Oscarsson, 1962a; Oscarsson & Uddenberg, 1964) suggesting its (RSCT) possible role in the coordination of both the hindlimb and forelimb movements. As the VSCT and RSCT terminate partly in the vermal cortex it is thought that they have a role in the regulation of tone, posture, locomotion and equilibrium of the entire body (Chambers & Sprague, 1955a,b).

Electrophysiological evidence obtained by weak antidromic stimulation of the cerebellar cortex (Lundberg & Oscarsson, 1960; Lundberg & Oscarsson, 1962a; Oscarsson & Uddenberg, 1964) has shown that there are marked differences in the mode of termination between DSCT fibres and VSCT and RSCT fibres. The DSCT fibres were activated by weak antidromic stimulation from small punctiform areas of the cerebellar cortex, while the VSCT and RSCT fibres could be activated from broader areas of the cerebellar cortex, which indicates that DSCT neurones are linked to a small group of cortical neurones (Purkinje cells), whereas VSCT and RSCT neurones, after preterminal branching, influence cortical cells (Purkinje cells) over a broad area (Lundberg & Oscarsson, 1960; Lundberg & Oscarsson, 1962a; Oscarsson & Uddenberg, 1964). This suggests that information conveyed by the DSCT could be used in the fine coordination of movements and posture of the ipsilateral hindlimb, while the information carried by the VSCT and RSCT may have a role in postural adjustment of the whole body and the limbs bilaterally.

1.4 Parallel ascending pathways that convey tactile information to non-cerebellar destinations such as the somatosensory cortex

This section includes a basic introduction to structural (Fig. 1-7) and functional organization of the sensory pathways arising from the cuneate and gracile nuclei, namely, the dorsal column-medial lemniscal pathway, and those arising from the spinal

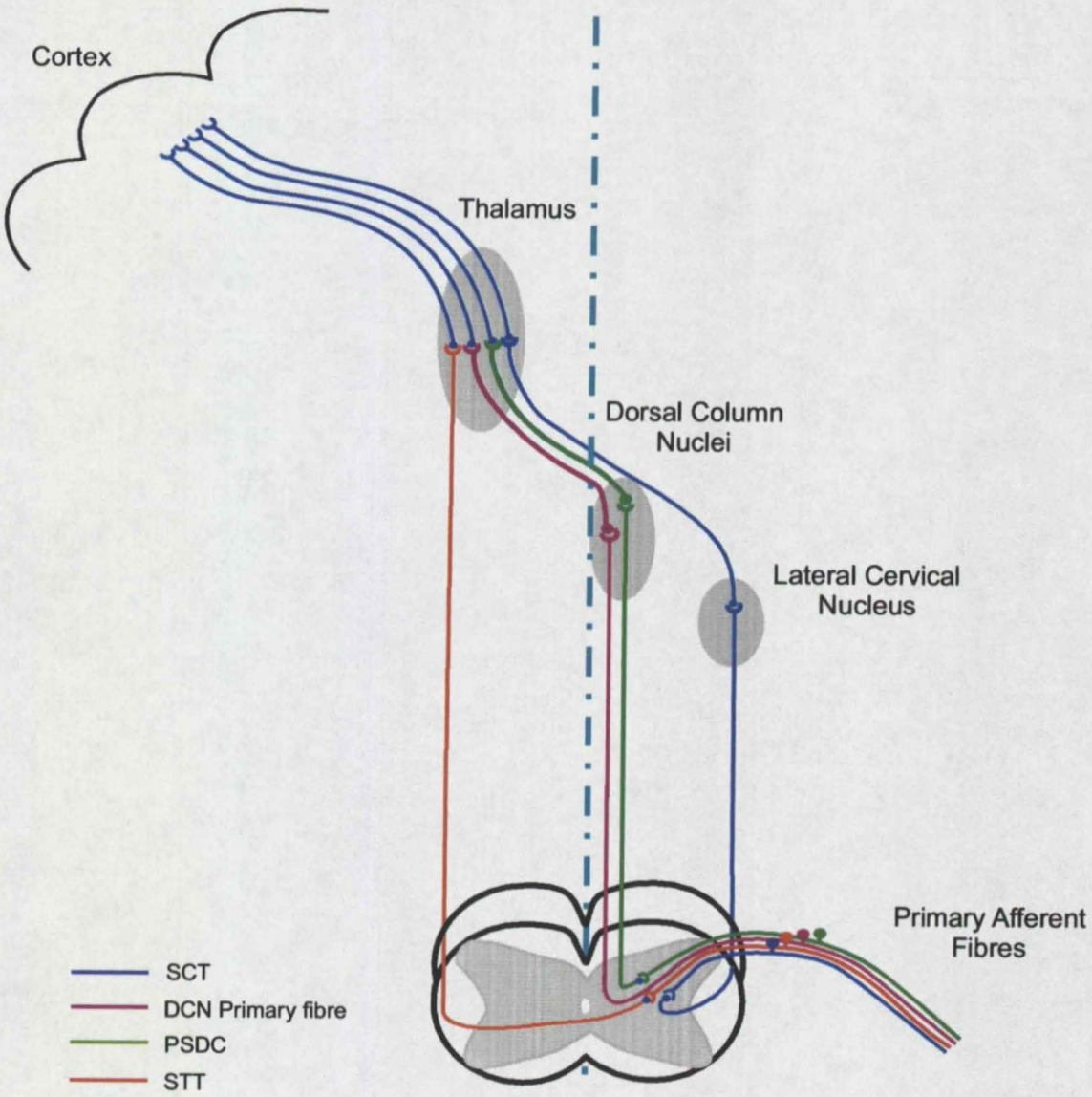

Figure 1-7. Schematic representation of the major tactile pathways arising in the spinal cord, which includes the direct projection pathway formed by primary afferent fibres in the dorsal column, the SCT, the post-synaptic dorsal column system and the STT.

cord such as the spinocervical tract (SCT) and the spinothalamic tract (STT). The capacity of their neurones to signal tactile information, is presented and discussed in order to compare the nature of the tactile information conveyed over these pathways, for the purposes of sensation and perception, with that conveyed over the DSCT to the cerebellum for the regulation of movement and posture.

1.4.1 Structural and functional organization of the dorsal columns (DC)

The dorsal column (DC) is an uncrossed pathway of large diameter myelinated afferent fibres arising from cutaneous and subcutaneous peripheral receptors and ascending the spinal cord in the dorsal funiculus (Fig. 1-7). Afferent fibres from the lower part of the body occupy the more medial part of the dorsal funiculus (fasciculus gracilis) and terminate in the gracile nucleus (lower limb fibres), while the more lateral part of the DC funiculus is occupied by fibres from the upper parts of the body, terminating in the cuneate nucleus. Both nuclei are part of the brainstem structure known as the dorsal column nuclei which includes three nuclei: the main cuneate nucleus, external cuneate nucleus and the gracile nucleus (Norton, 1969; Brown, 1981). The neurones in the main cuneate nucleus receive sensory inputs from mechanoreceptors in the skin via forelimb primary afferent fibres and inputs from neurones located in the dorsal horn (mostly in lamina IV) of the cervical spinal cord via the so-called *postsynaptic dorsal column (PSDC) pathway* (Rustioni & Macchi, 1968; Norton, 1969; Brown, 1973). The neurones excited by equivalent sensory inputs from the hindlimb are located predominantly in the gracile nucleus (Brown, 1968, 1973, 1981; Petit & Burgess, 1968; Petit, Lackner & Burgess, 1969; Lindstrom & Takata, 1972).

The cuneate neurones have the following connections: (*i*) output through the medial lemniscal axons arising from the main cuneate and the gracile nucleus and projecting to the contralateral ventral thalamus which in turn provides output to the somatosensory cortex. This pathway constitutes the dorsal column-medial lemniscal system, which appears to be the major pathway for tactile sensation and perception in mammals. (*ii*) cuneate neurones in the external cuneate nucleus give a rise to the axons which project through the inferior cerebellar peduncle to the cerebellum (Ferraro & Barrera, 1935a).

Previous studies (Douglas et al., 1978; Vickery et al., 1994; Gynther et al., 1995) have revealed the substantial coding capacity of cuneate neurones for static and dynamic tactile information from the forelimb. Potent synaptic linkages between primary afferent fibres and neurones in the cuneate nucleus provide secure transmission of tactile information over this synaptic junction and supply the thalamus and somatosensory cortex with reliable information about changes in the intensity of the static skin indentation (Douglas et al., 1978). The stimulus-response relations obtained in that study (Douglas et al., 1978), for the relation between the step amplitude (graded over a range of 0-2 mm) and the spike output, are almost linear or show a sigmoid pattern (Fig. 1-8A). Furthermore, other studies (Vickery et al., 1994; Gynter et al., 1995) have reported a considerably potential coding capacity of cuneate neurones with slowly adapting (SA) response properties for vibrotactile information over the broad bandwidth of vibration frequencies from 0 to ~400 Hz, and their capacity to respond in a precise temporal pattern over the frequency range from 0 Hz to up to ~300 Hz.

The studies of purely dynamic-sensitive cuneate neurones and their capacity to signal dynamic tactile information from the forelimb *hairy* skin (Robinson et al., 2001; Zachariah et al., 2001) have also revealed a high coding capacity for vibrotactile information over a frequency range at least up to ~100 Hz, with high transmission security between the *individual* hair follicle afferent (HFA) fibres and their target cuneate neurone. In addition, these cuneate neurones display a sensitive detection capacity for vibrotactile stimuli and high coding capacity for changes in vibration amplitude (Robinson et al., 2001). The tightly phase-locked responses reliably reflect the periodicity of vibrotactile stimuli over the frequency range from 5 to ~100 Hz (Robinson et al, 2001; Perkins et al., 2001) and therefore provide accurate, temporally precise tactile information to the somatosensory cortex about the peripheral tactile stimuli applied to the hairy skin (Fig. 1-8B). As these cuneate neurones displayed almost linearly-graded spike output as a function of increases in the intensity of vibrotactile stimuli over a range of frequencies from 5-200 Hz (Fig. 1-8B), they can contribute a sensitive signal of the changing intensity of vibrotactile skin disturbances (Robinson et al., 2001; Perkins et al., 2001).

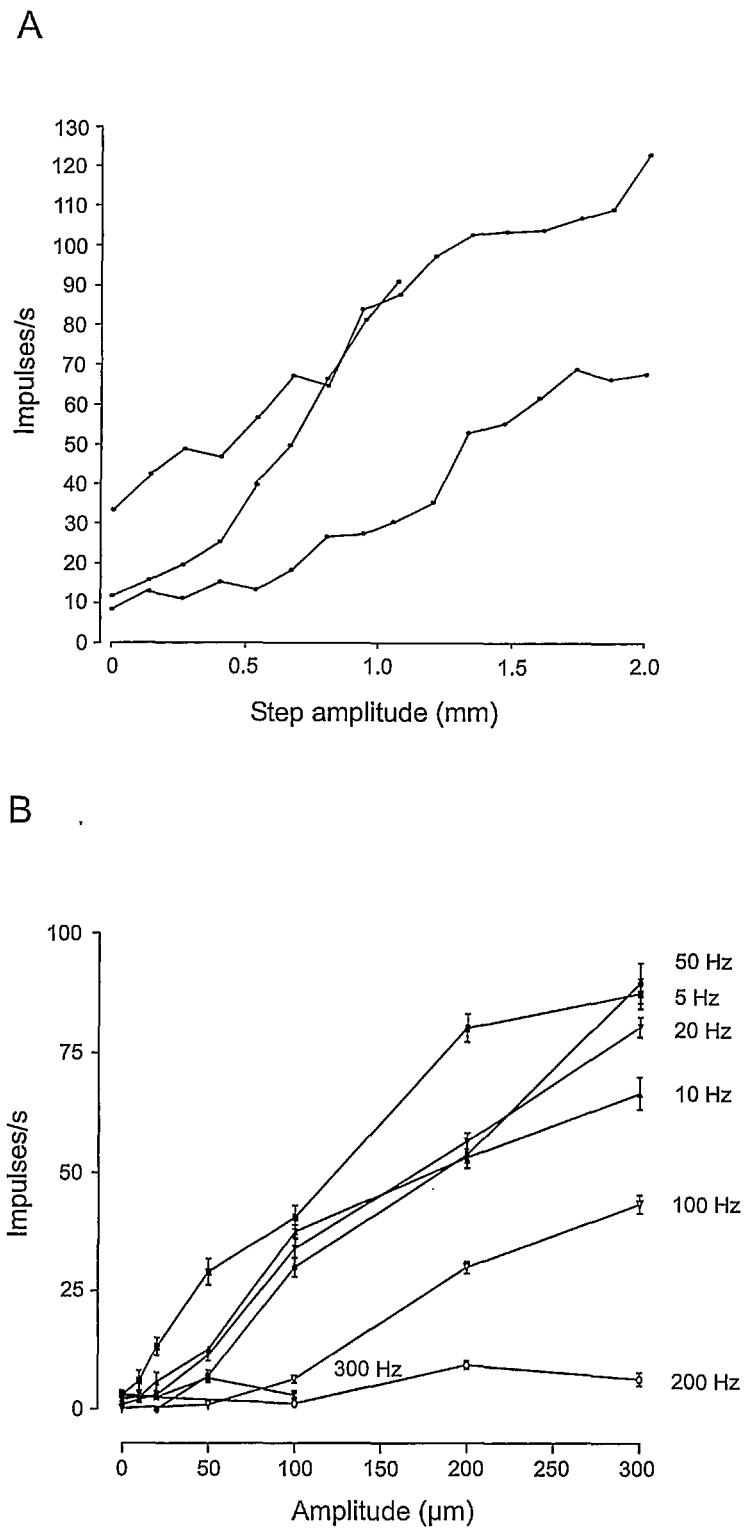

Figure 1-8. Stimulus-response relations for slowly adapting tactile neurones of the cuneate nucleus (A). For two neurones indentation intensity was graded over a range of 2 mm and for the third neurone over approximately 1mm. Each point represents the mean (± S.D.) for ten responses (impulses/s) to the 1 s long step indentation (redrawn from Douglas et al., 1978). Stimulus-response relations for hair follicle associated cuneate neurone (B) at frequencies of 5-300 Hz. The graded relations show that individual cuneate neurones can contribute a sensitive signal of the changing intensity of vibrotactile stimuli in the hairy skin (reproduced from the data of Robinson et al., 2001).

1.4.2 Major anatomical features of the spinocervical tract (SCT) and the processing of tactile information over this sensory pathway

The spinocervical tract (SCT) appears to be, in addition to the dorsal column-medial lemniscal pathway and the spinothalamic tract, a further major tactile sensory pathway that ascends in the spinal cord of mammals (Morin, 1955; Brown, 1973, 1981; Nijensohn & Kerr, 1975; Munoz et al., 1996). The SCT arises from the neurones in Rexed's laminae III, IV and V in the dorsal horn of the lumbar spinal cord (Eccles et al., 1960; Wall, 1960a, 1967; Fetz, 1968), ascends in the dorsolateral funiculus (Lundberg & Oscarsson, 1961; Oscarsson, 1965; Taub & Bishop, 1965) and terminates in the lateral cervical nucleus (Rexed & Strom, 1952; Brodal & Rexed, 1953; Morin, 1955; Lundberg, 1964; Horrobin, 1966). The SCT is an uncrossed pathway in the spinal cord (Fig. 1-7). However, the axons arising from neurones in the lateral cervical nucleus then cross at the junction of the medulla and the spinal cord to the contralateral side and run in the medial lemniscus forming connections within the thalamus (Morin, 1955; Morin & Catalano, 1955; Catalano & Lamarche, 1957; Gordon & Jukes, 1963; Landgren et al., 1965; Horrobin, 1966; Boivie, 1970) and via thalamo-cortical pathways with the somato-sensory cortex (Andersson, 1962; Norrsell & Voorhoeve, 1962; Norrsell & Wolpow, 1966). However, only the spinal part should be considered as the SCT, as the further projections to the contralateral thalamus and somato-sensory cortex constitute the higher segments of this overall pathway between the lateral cervical nucleus and the cerebral cortex (Brown, 1973).

The SCT neurones are principally excited by inputs from cutaneous receptors activated by hair movements and possibly by pressure and pinch (Brown, 1970). There is evidence that some of the SCT neurones could be also excited by heat and intense cold (Brown & Franz, 1969) as well as by high threshold muscle and joint inputs (Lundberg & Oscarsson, 1961; Hongo et al., 1968). An earlier study (Mahns et al., 2001) that investigated the capacity of SCT neurones in cats to signal vibrotactile information showed that SCT neurones, with receptive fields predominantly located on the hindlimb hairy skin, had a coding capacity for dynamic tactile information limited to a narrow, low-frequency bandwidth of vibrotactile stimuli (up to ~10 Hz). When the frequency of the vibrotactile stimuli exceeds 10 Hz the response is typically confined to the onset of the vibration train (Fig. 1-9A). Indeed, these SCT neurones displayed coarsely-graded stimulus-response relations as a function of increases in vibration

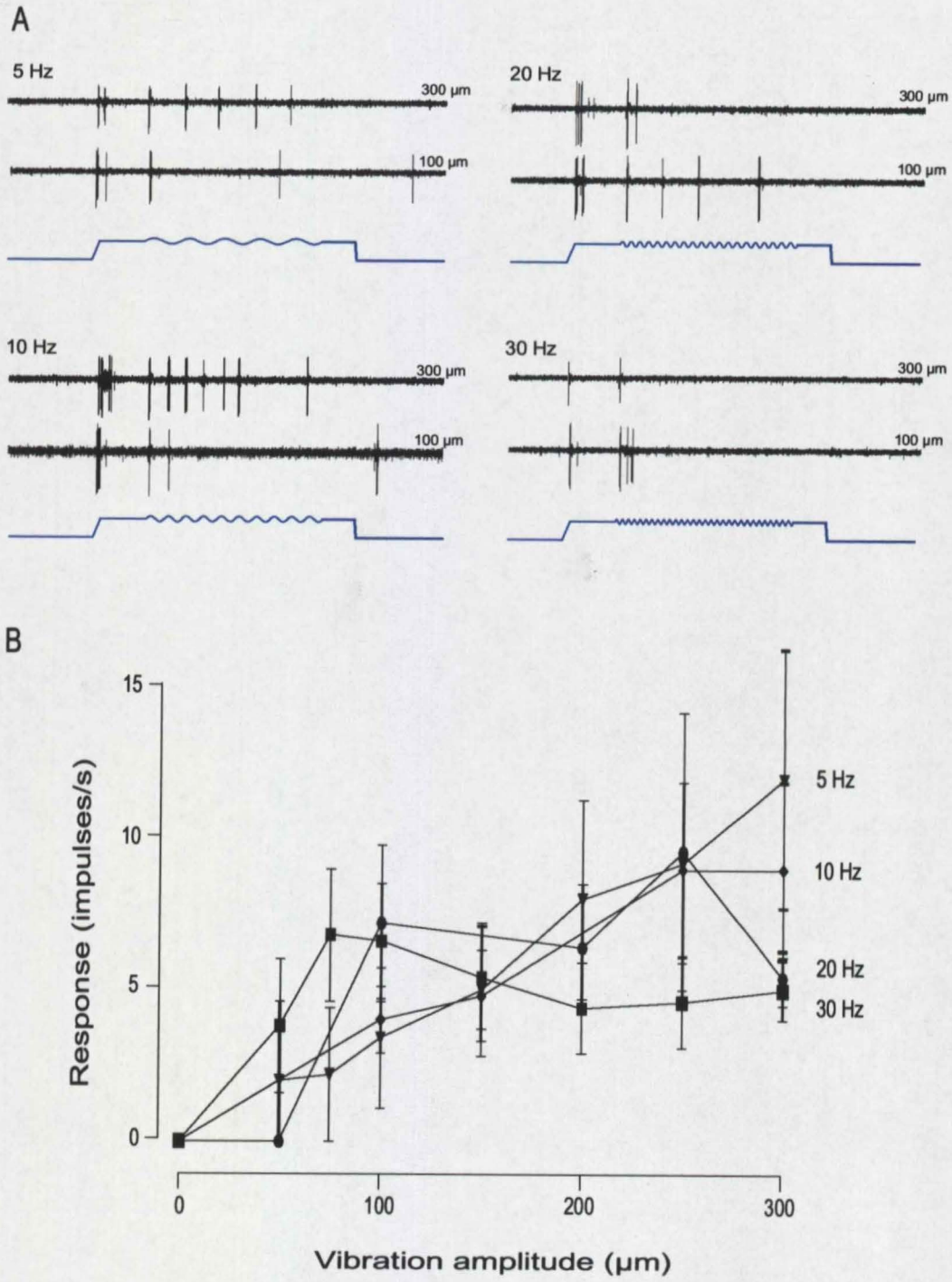

Figure 1-9. Series of recordings from a single SCT neurone (A) showing the limited responsiveness to controlled vibrotactile stimulation at 5-30 Hz. The neurone responds on successive cycles only at 5 Hz, while at 10 Hz can sustain a cycle by cycle response only for the part of the 1 s vibration train and provides poorer signal of the 20 and 30 Hz vibrotactile stimuli. Stimulus-response relations (B) of individual SCT neurone show limited capacity of the neurone to signal changes in intensity of vibrotactile stimuli to the frequencies >10 Hz (reproduced from Mahns et al., 2001).

amplitude, and then only at frequencies up to ~10 Hz (Fig. 1-9B; Mahns et al., 2001). The capacity of SCT neurones to sustain impulse activity on a cycle-by-cycle manner and faithfully code for the periodicity of the vibrotactile stimuli are also limited to the narrow frequency range up to about 10 Hz (Fig. 1-9). Thus, it appears that the capability of the SCT pathway to provide accurate tactile information for the somato-sensory cortex is limited, at least at the single neurone level, to a narrow, low frequency range of vibrotactile stimuli (Mahns et al., 2001).

1.4.3 Organization of the spinothalamic tract (STT) and its contribution in tactile perception and sensation

The spinothalamic tract (STT) is a ventral spinal cord pathway conveying sensory information from the skin to the thalamus (Fig. 1-7). Earlier anatomical studies (Edinger, 1889; Mott, 1895; Collier & Buzzard, 1903; Goldstein, 1910; Walker, 1940; Weaver & Walker, 1941; Bowsher, 1961) reported the existence of two divisions of the STT, the ventral and the lateral spinothalamic tracts. The ventral STT originates from the large cells in the dorsal horn (lamina VII and VIII) of the spinal cord, crosses the cord in the anterior commissure, and ascends in the ventral column (Fig. 1-7). The projection of the tract is to the nucleus ventralis posterolateralis, nucleus parafascicularis and the nucleus centralis lateralis of the thalamus (Bowsher, 1961). There is a general agreement on the presence of a substantial spinothalamic tract in primates, but there is also clear evidence for it in other species, including the cat and rabbit (Wallenberg, 1900; Kohnstamm, 1900; Magni & Oscarsson, 1962), although it seems that in cats the STT is less developed than in primates (Gaze & Gordon, 1955; Morin & Thomas, 1955; Whitlock & Perl, 1959; Perl & Whitlock, 1961; Boivie, 1971).

The STT is assumed to relay touch, itch, pain and temperature information (Kroll, 1930; Foerster & Gagel, 1932; Walker, 1942; Drake & McKenzie, 1953). After the thalamus synaptic relay, the information is conveyed via thalamo-cortical projections to the somato-sensory cortex. The analysis of the response of STT neurones to controlled mechanical stimulation of the hindlimb in earlier studies in cats (Fox et al., 1980; Ferrington et al., 1986) and primates (Willis et al., 1974; Willis et al., 1975; Ferrington et al., 1987) showed a poorer capacity for detection and for the coding of

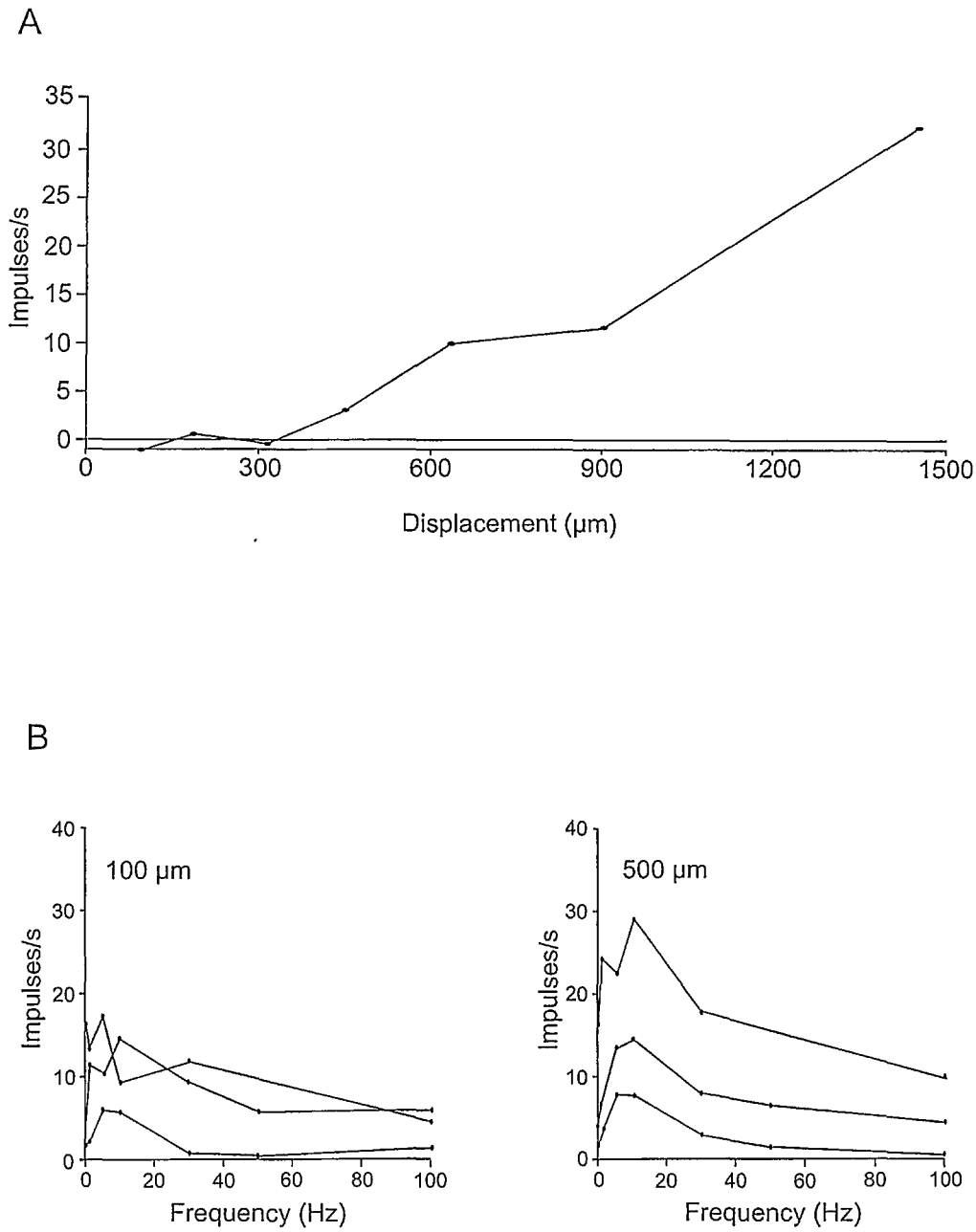

Figure 1-10. Responses of individual STT neurone to graded step displacement of the skin over a range of 1500 μm (A). The line above the horizontal axis represents response threshold. STT neurone shows coarsely graded response to graded increase in skin indentation from 0-1500 μm (reproduced from Willis et al., 1975). Response of three STT neurones to vibrotactile stimulation (B) at range of frequencies (1-100 Hz) and two vibration amplitudes (peak-to-peak 100 μm and 500μm). In both graphs the values indicated at 0 Hz are the responses of the neurones to the study indentation (500 μm) on which the vibratory stimulus was impose. The responsiveness reached its peak at frequencies ≤10 Hz beyond which is falling down. At vibration amplitude of 500 μm this response peak boundary is extended to ~15 Hz (reproduced from Ferrington et al., 1987).

intensity change in tactile stimuli (Fig. 1-10A; Willis et al., 1975) than is the case for cuneate neurones in the dorsal column-lemniscal pathway (Douglas et al., 1978). The response properties of these STT neurones to controlled vibrotactile stimulation of the hindlimb have also shown a limited coding capacity for dynamic tactile information (Ferrington et al., 1987). Although STT neurones whose stimulus-response relations are shown in Fig. 1-10B respond to vibrotactile stimuli over a frequency range up to about 30 Hz, they are capable of accurately coding vibrotactile information over only a narrow frequency bandwidth of about 10 Hz (Fig. 1-10B). Thus, the tactile information that the somato-sensory cortex potentially receives via the STT appears to be limited to low frequency vibrotactile information and rather crude information about the intensity of static skin indentation.

Chapter 2

METHODS

2. METHODS

Experiments were conducted on 20 adult cats of either sex weighing between 2.0 and 6 kg, with most in the range 2.5 to 3.5 kg. Animals were provided by the University of New South Wales Biological Resources Centre, and the experiments conformed with the *Australian Code of Practice for the Care and Use of Animals for Scientific Purposes*. Experiments usually extended over a 12 to 24 hour period, but in some instances the animal was maintained for up to 48 hours. Experiments were terminated by an overdose of sodium pentobarbitone.

2.1 Anaesthesia and preparatory surgery

Animals were fasted for 12 hours prior to the experiment and anaesthetised initially by an intraperitoneal injection of sodium pentobarbitone (*Nembutal*, 40 mg/kg, Abbot) in all but two experiments in which an intramuscular injection of a combination of alfaxalone and alfadolone acetate (*Saffan*, 18 mg/kg, Pitman-Moore) was used to induce anaesthesia. For the pentobarbitone-anaesthetised group, anaesthesia was maintained throughout the experiment by intravenous infusion of sodium pentobarbitone (2-3 mg/kg/hr) and, in the two Saffan cases, by gaseous anaesthesia by means of 1-3% halothane (*Fluothane*, Zeneca) in an 80:20 mix of N_2O:O_2. At the commencement of the experiment, atropine sulfate (*Atropine Injection BP*, 80 μg/kg, Astra) was administered to reduce respiratory secretion, and dexamethason phosphate (*Dexamethasone Sodium Phosphate Injection USP*, 1.2 mg/kg, DBL) administered to reduce the likelihood of oedema of neural tissue.

A tracheostomy was performed and a tracheal cannula inserted. Animals were artificially ventilated at a rate and volume that maintained end-tidal CO_2 in the range of 3.0-4.5 %.

The right jugular vein was cannulated to allow intravenous infusion of the anaesthetic and administration of drugs. The right carotid artery was cannulated and attached to a Statham P23 pressure transducer for the measurement of arterial blood pressure and heart rate.

Rectal temperature was maintained at 38 ± 0.5°C with a feedback-controlled heating blanket and infrared heating lamp. Drainage of the urine and monitoring of diuresis was provided by an urinary catheter inserted into the bladder. Blood pressure,

heart rate and pupillary aperture were monitored constantly throughout the experiment, as autonomic indices of the anaesthetic level. In addition, the animal's hind paw was periodically pinched to test for the presence of a withdrawal reflex. Experiments were terminated with an overdose of sodium pentobarbitone if the blood pressure dropped below 80 mmHg and could not be restored in a short period of time.

In order to accurately position the mechanical stimulator on the skin surface, the hair on the dorsal and ventral aspects of the hind limb was shaved and the paw was fixed in a perspex mould.

2.2 Surgical preparation for electro-physiological recording

2.2.1 Exposure of the recording site in the lumbar spinal cord

To expose lumbar spinal cord segments for recording, a midline incision over the spinous processes L1-L7 was made. After detaching and resecting the paravertebral muscles, a laminaectomy was performed by removing spinous processes and the arches of the L2-L5 vertebrae. The spinal cord was supported by metal clamps attached to the 1st and 7th lumbar spinal processes and fixed to the metal frame. The exposed lumbar cord was protected under warm paraffin oil in the pool made by flaps of skin created by a midline incision, stitched and fixed to the metal frame. In order to prevent occlusion of the local venous circulation, swelling of the cord and dimpling of the surface by the micro-electrode, a large longitudinal incision of the dura was avoided. Prior to recording, the underlying neural tissue was exposed by removing small patches of dura immediately above the recording site.

2.2.2 Exposure of the caudal cerebellum for insertion of antidromic stimulation electrodes in the restiform body

The animal's head was stabilised in a ventro-flexed position by the use of ear bars, inserted into the external auditory canal, and an appropriately angled mouth piece (45^{o} ventro-flexion) in order to expose the brainstem and the cerebellum below the external occipital protuberance.

A midline incision was made in the skin from above the external occipital protuberance to the upper cervical vertebrae. After removing overlying muscle and the atlanto-occipital membrane, the foramen magnum was exposed. The ventroflexed position of the head enabled access to the brainstem and the obex through the gap

between the occiput and the atlas (C1 vertebra). The part of the occiput from the external occipital protuberance to the foramen magnum was removed with rongeurs revealing the vermis and part of the cerebellum overlying the restiform body.

The dura was removed and exposed neural tissue protected with warm liquid paraffin in the shallow pool made by flaps of skin stitched and fixed to the frame.

In circumstances that required additional stability of the spinal cord this was achieved by the administration of a short-lasting muscle relaxant drug, gallamine triethiodide (*Flexedil*, 20 mg in bolus doses that lasted 20-30 min, Sigma). When used in this occasional and intermittent manner, the muscle paralysis did not impede the assessment of anaesthetic efficacy. When necessary, the stability of the lumbar spinal cord was also enhanced by the induction of a pneumothorax and/or by covering the lumbar spinal cord with agar gel (4% in 0.9% saline solution).

2.3 Electrophysiological recording procedures

2.3.1 Recording from DSCT neurones in the lumbar spinal cord

Extracellular recordings were obtained using tungsten micro-electrodes with impedances ranging from 2 to 6 MΩ. The impedance of the micro-electrode was checked in the course of recording sessions and the electrode replaced if the impedance was lower than 2 MΩ.

Recordings were made from DSCT neurones with excitatory receptive fields on either the hairy or glabrous skin of the cat's hindlimb. These neurones were sought principally within Clarke's column nucleus in the lumbar spinal cord (predominantly the L2-L5 segment), located 150-300 μm lateral from the midline at the depth of 2000-3000 μm below the dorsal surface of the cord (Eide et al., 1969a; Curtis, Eccles & Lundberg, 1958; Kuno et al., 1973; Low, Mantle-St.John & Tracey, 1986; Walmsley et al., 1985). All the neurones isolated in the present experiments were at depths between 2 and 3 mm, and were approximately 200 μm lateral to the midline of the spinal cord (Fig. 2.1) and all but two were found in the third lumbar segment. The remaining two neurones were isolated in the second and fifth lumbar segments of the spinal cord.

2.3.2 Antidromic identification of DSCT neurones

In order to determine whether isolated neural units in the lumbar spinal cord activated by tactile inputs were DSCT neurones, we employed electrical stimulation in the ipsilateral restiform body, at the entrance point of DSCT axons into the cerebellum,

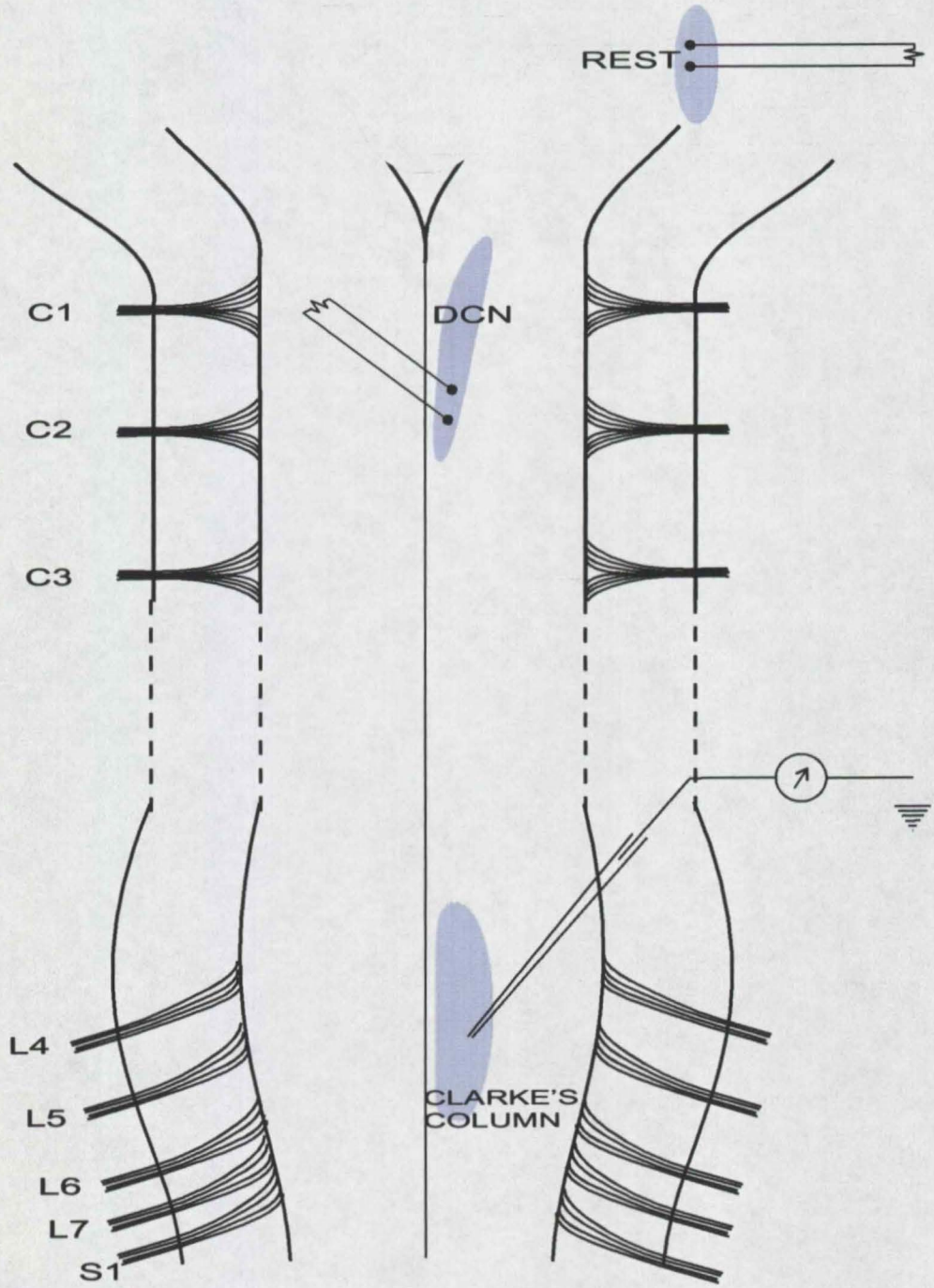

Figure 2-1. A schematic representation of the experimental setup. Antidromic stimulation electrodes in the restiform body (REST) and DCN. Recording electrode in the location of Clarke's column, at approximatelly 200-500 μm lateral from the midline of the lumbar spinal cord.

before they terminate in the cerebellar cortex (Fig. 2.1). A pair of low impedance tungsten electrodes with a 4-5 mm spacing was inserted into the ipsilateral restiform body. Placement of the electrodes is based on the stereotaxic coordinates of Snider & Niemer (1961) and initial recording with these electrodes of responses to hindlimb tapping.

An additional electrical stimulating site at the dorsal surface of the brainstem above the caudal end of the gracile nucleus was set up to clarify whether the unit under investigation could be activated trans-synaptically from the terminals of the dorsal column primary fibres (Fig. 2.1).

The criteria for antidromic identification of the neurones as belonging to the DSCT were: (1) a short (<8 ms) fixed latency of the response at the threshold intensity (Andersen et al., 1964a; Mann, 1971); (2) little or no change in response latency when the stimulus intensity was increased above threshold; (3) ability of the neurone to respond in a 1:1 manner to a brief (1 s) train of electrical stimuli at frequencies at/or in excess of 200 Hz (Mann, 1971); (4) the final and definitive criterion was collision between orthodromic and antidromic spike and extinction of an antidromic spike by the orthodromic one when it fell within the "collision period" (interaction time) (Fig. 2.2). Abolition of the antidromic response was achieved by progressively decreasing the time between the orthodromic spike and the antidromic spike, until the antidromic spike was abolished within the interaction time, a period defined as twice the central conduction latency plus the refractory period (Darian-Smith, Phillips & Ryan, 1963).

Once the single neurone was isolated electrophysiologically in the lumbar cord it was tested for antidromic activation at stimulus intensities up to 10 mA (pulse duration 100μs). When a response to the electrical stimulus was observed the intensity threshold (in mA), the latency, and the capacity of the neurone to respond to a train of electrical stimuli at frequencies from 5 to 333 Hz were assessed.

2.3.3 Mechanical stimulation of the cutaneous receptive field of individual DSCT neurones

Following the isolation of DSCT unit, the receptive field of that unit was carefully mapped using calibrated *von Frey* hairs (~ 50-500mg wt.). Once the receptive field of an individual neurone had been mapped with *von Frey* hairs, precise and reproducible forms of mechanical stimuli were delivered by a feedback-controlled

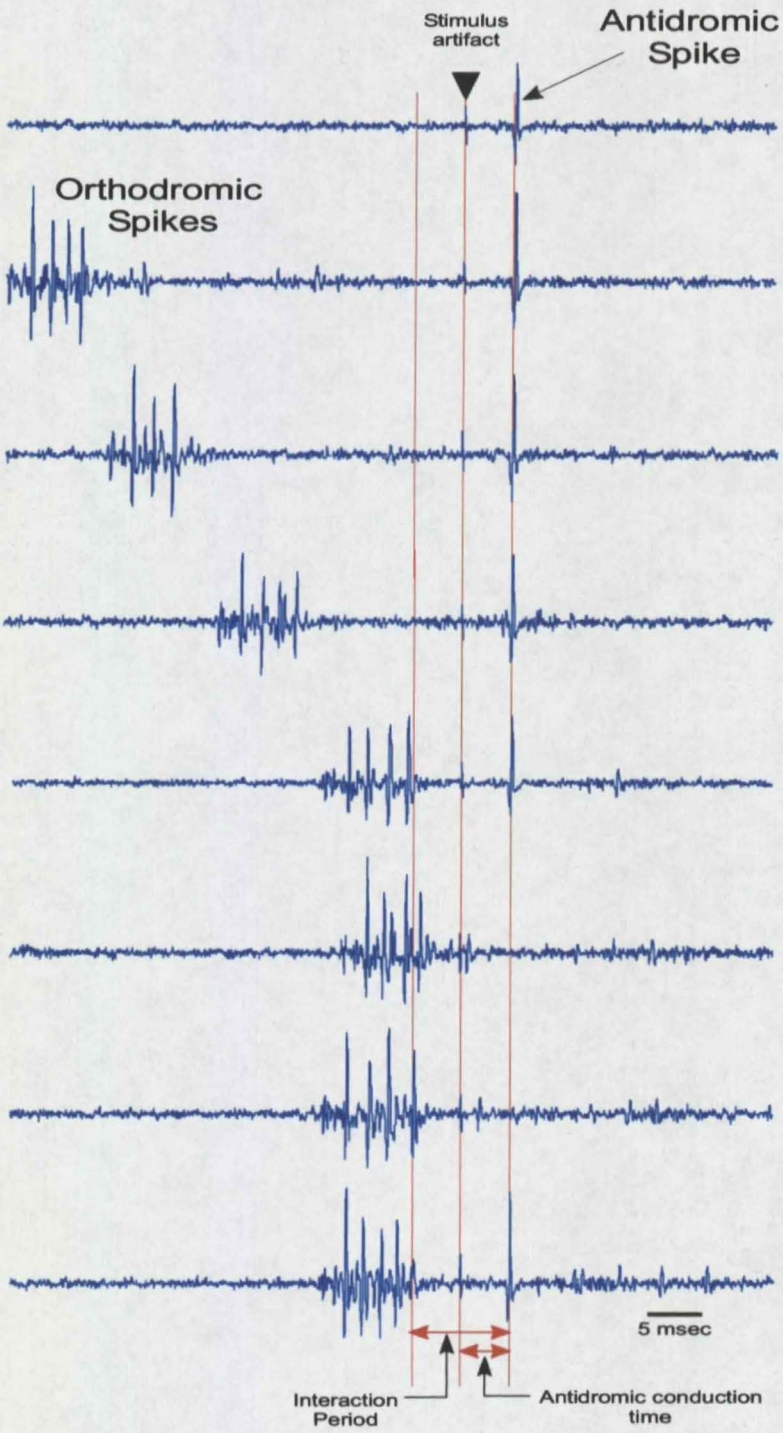

Figure 2-2. An antidromic collision procedure for identification of DSCT neurones located in Clarke's column in the lumbar spinal cord. Red line in the middle: antidromic electrical stimulus. Latency of antidromic spike (antidromic conduction time ~5ms). Interaction period (twice the antidromic conduction time plus the refractory period ~10.5ms). In the top row only antidromic spike present. In the second row from the top: appearance of the orthodromic spike. In the third to fifth row time between anti and orthodromic spike (action potential) was gradually decreased. In the sixth row: antidromic spike abolished by orthodromic within interaction time. Eight (bottom) row: orthodromic spike outside the interaction time and antidromic spike fully recovered.

mechanical stimulator. A stimulating probe with a diameter tip of 1-6 mm was applied to the point of maximum sensitivity within the receptive field of the neuron.

Prior to careful stimulus-response study of antidromically identified DSCT neurones, initial testing for a rapidly adapting or slowly adapting tactile sensitivity of the neurones was undertaken with static displacement of the skin in the centre of each neurone's receptive field. Static indentations of the skin were produced first by displacement of the skin at the point of maximum sensitivity within the neurone's receptive field by means of manual or *von Frey* hair stimulation and then by the application of precisely-controlled step indentation stimuli set by the computer and delivered by a feedback-controlled mechanical stimulator (Ferrington et al., 1987a,b,c; Gynther et al., 1992). If the neurone under investigation responded to these maintained indentations of the skin (usually 1-2 s indentation) with a sustained response throughout the stimulus, the neurone was classified as a *slowly adapting* (SA) tactile-sensitive neurone. When the neurone responded just to the onset and offset of the indentation stimulus, it was classified as a purely dynamically-sensitive, or *rapidly adapting* (RA) neurone.

The stimuli used for studying dynamically-sensitive neurones consisted of 1s long trains of sinusoidal vibration superimposed on a static indentation of the skin, and were delivered normal to the skin surface. The vibration trains varied in frequency, from 5 Hz to 300 Hz, and in amplitude from 0 μm to 300 μm. The vibro-tactile stimuli were usually superimposed upon a background step of 400 μm. However, as the response properties of a given neurone became known adjustments to the timing and amplitude of the step indentation were made (*see Results*). The background step took the form of either a 2s long sustained indentation, in the case of SA neurones, or a step indentation (400 μm) lasting 2 seconds and starting 500 ms prior to the onset of 1s long vibration train superimposed on it in the case of dynamically-sensitive DSCT neurones. The resting or null position of the stimulator was set just at the skin surface. For each set of test parameters, responses were recorded from five successive trials, in which the repetition rate was no faster than one per ten seconds, to allow skin recovery between stimulus deliveries.

Whenever we observed a sustained response of a DSCT neurone to static skin indentation the amplitude of the indentation was systematically varied between 0 and 1500 μm in order to examine the capacity of the neurone for coding this parameter of

skin displacement.

2.3.4 Recording equipment

The neural impulses recorded from Clarke's column nucleus in the lumbar cord were fed through conventional pre-amplifiers (1000x gain) and amplifier/filters (1-10x gain, typical band-pass ~0.01-10 kHz), then displayed on a digital storage oscilloscope, and stored on a 4-channel video recorder (Fig. 2.3). The impulse activity recorded through the electrode was digitized by a Schmitt trigger and sent to a computer for on-line analysis. As analysis of neural activity was based on the time of occurrence of these digitized pulses, it was important that the digitized signal was a reliable reflection of spike activity. This required a good signal-to-noise ratio (generally $\geq$ 5:1). Schmitt trigger levels were carefully adjusted to avoid over-counting or under-counting of spikes.

2.4 Computer analysis of impulse activity in DSCT neurone in response to controlled mechanical stimulation of the hindlimb skin

2.4.1 Computerised data acquisition for analysis

Analysis of the response of DSCT neurones to controlled vibro-tactile stimulation of the hindlimb skin was carried out with the assistance of a laboratory computer (Fig. 2.3) using a program specifically designed for this laboratory. Digital signals were acquired by a 4 channel data acquisition card. The first channel recorded a *time-zero* pulse signalling the commencement of a new analysis period. The second channel recorded pulses from the function generator that were synchronised with the onset of each cycle of the vibration stimulus. The third and fourth channels recorded the occurrence of digitized pulses generated by a Schmitt trigger from the activity of the DCST neurone under study. A computer file usually contained responses to five successive repetitions of a given stimulus.

2.4.2 Response measurement and stimulus-response relations

The responses of DSCT neurones sensitive to dynamic tactile inputs were recorded over a 1 s time period of controlled vibratory stimulation, while the response of the SA-neurones in the study was assessed over the first second of the 2 s static indentation stimuli.

A measure of the response level in the DSCT neurone to a given stimulus was

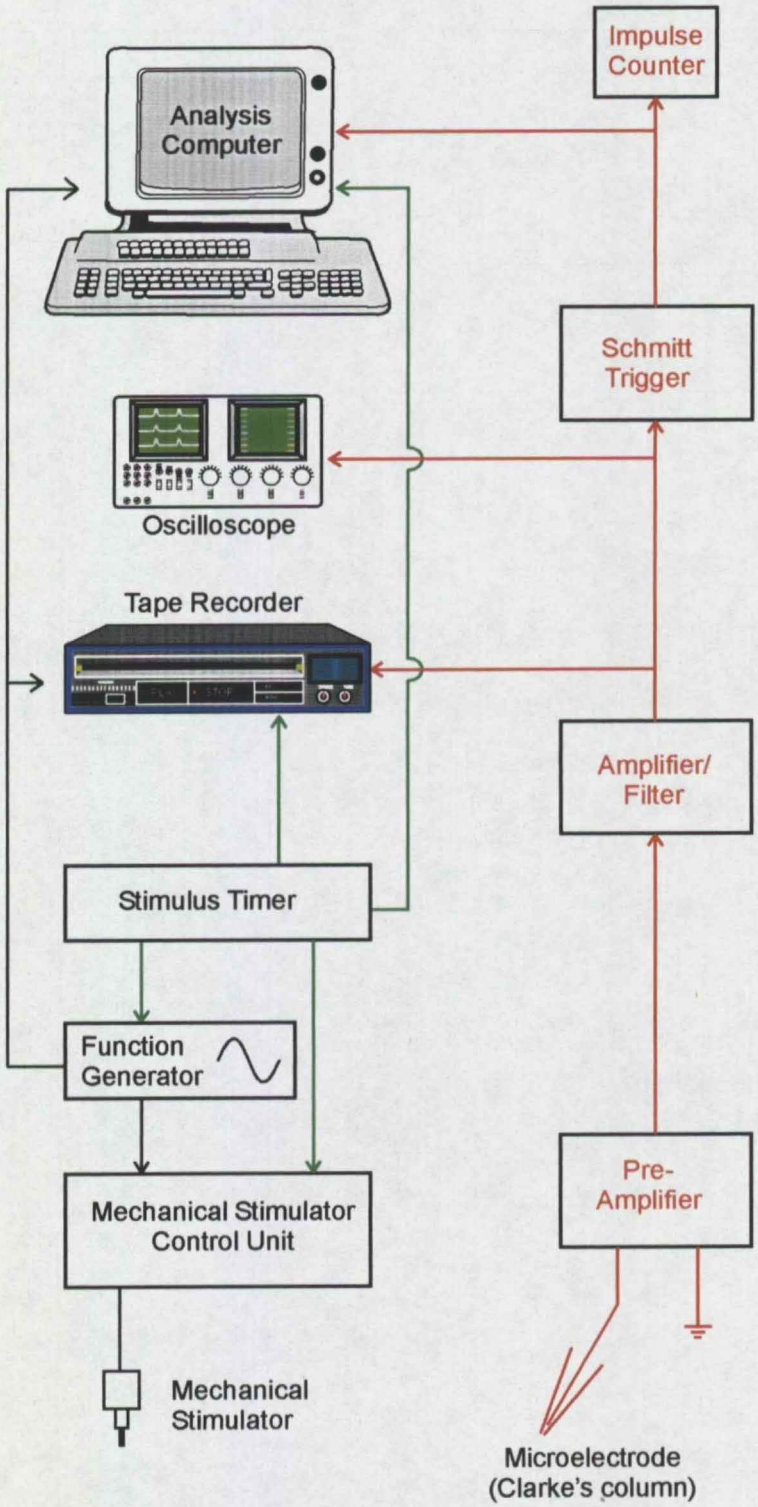

Figure 2-3. Schematic, simplified circuit diagram of the equipment used for tactile stimulation and for extracellular recording from DSCT neurones. Green and black lines indicate the connections in the stimulating apparatus. Red lines indicate recording equipment connections.

provided by computer counting of the number of impulses generated during the 1 s stimulus period. For the five repetitions of the same stimulus, responses were averaged as the mean response ± standard deviation. Responses were quantified in order to measure the capacity of DSCT neurones to signal static or dynamic information about the applied tactile stimuli.

The responsiveness of DSCT neurones to a range of controlled vibro-tactile and static indentation stimulation was analysed by constructing various types of *stimulus-response* graphs. In the *amplitude-response graphs* the response level (impulses/s) was plotted as a function of *stimulus intensity* (amplitude, μm) at the fixed frequency of the stimulus in the case of dynamically-sensitive DSCT neurones. Responsiveness of these neurones was also analysed by plotting the response level against the frequency of the stimulus (in Hz) at the fixed amplitude of the vibro-tactile stimulus (*frequency-response graphs*) in order to reveal the bandwidth of vibrotactile responsiveness for the neurones.

2.4.3 Analysis of temporal patterns in the responses of DSCT neurones

The analysis of temporal response patterns of the DSCT units was undertaken to examine the capacity of the synapse in Clarke's column nucleus to reliably transmit temporal information about the applied skin stimuli. Specialised histograms (see below) were constructed to examine the temporal relations of impulse occurrences relative to the mechanical stimulus features, in particular, to the vibration cycle period in the case of the dynamically-sensitive DSCT neurones.

Peristimulus time histograms (PSTHs)

Peristimulus time histograms (PSTHs) plot the time of impulse occurrences over a defined time period prior to, during, and subsequent to the controlled mechanical stimuli delivered to the receptive field of the DSCT neurone. PSTHs were usually constructed from the responses of the neurone to the five successive trains of static or dynamic stimuli. In the case of the DSCT neurones studied with controlled vibrotactile stimuli, the PSTH normally commenced 0.5-1 s prior to the onset of vibrotactile stimulus and finished 0.5-1 s after the stimulus ended (Fig. 2-4). Thus, it included the response of the unit to the stimulus as well as the segments of background/spontaneous activity.

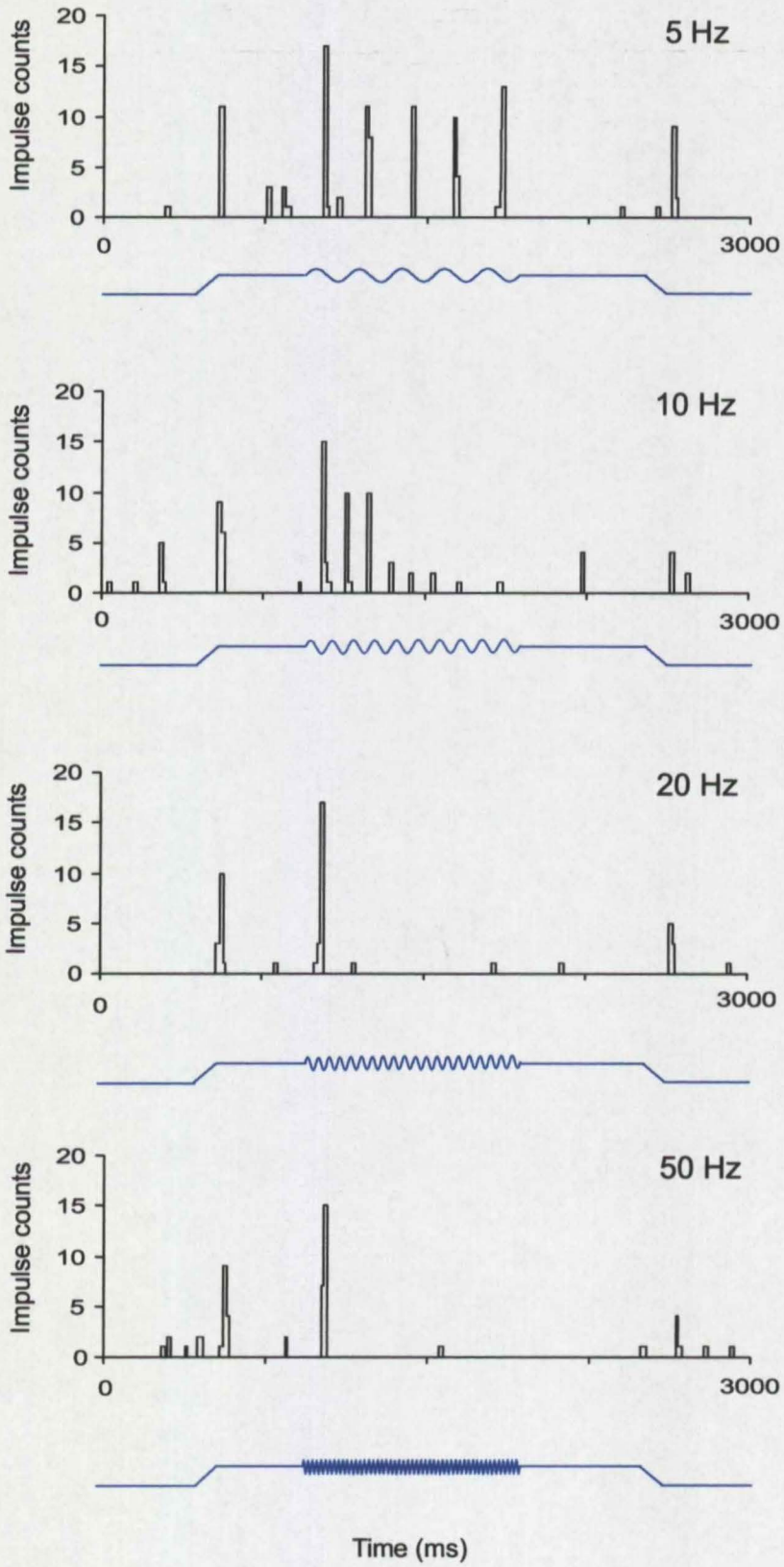

Figure 2-4. Peristimulus time histograms (PSTH) plot the time of response occurrences over a defined time period prior to, during and subsequent to the mechanical stimulus which consisted of a 2 s step indentation on which a 1 s long train of vibration was superimposed.

Cycle histograms

Cycle histograms (CHs) were constructed from responses to vibrotactile stimuli in order to analyse quantitatively the probability of impulse occurrence at different times (or phases) throughout the period of successive vibration cycles (Fig. 2-5). The analysis time, represented by the horizontal axis of the CH, corresponds to the duration of the vibration cycle period (e.g., 20 ms for a 50 Hz stimulus). A marker pulse supplied by the function generator signalled the onset of each successive cycle in the vibration train delivered to the DSCT unit's receptive field. Similar cycle histogram analysis has been used in earlier studies investigating phase relations in the responses of tactile neurones of the somatosensory system (e.g., Talbot et al., 1968; Douglas et al., 1978; Gynther et al., 1992, 1995; Vickery et al., 1992, 1994; Zhang et al., 1995, 1996, 1997a,b; Coleman et al., 2003) and in the responses of neurones of the auditory system to pure tone stimuli (e.g., Rose et al., 1967).

If the responses accumulated in the CH are clustered to form a narrow peak, this indicates a tendency of the unit to respond preferentially during a specific segment or phase of the vibration cycle. A neurone manifesting this response behaviour is said to be tightly *phased-locked.* A rectangular distribution of the response throughout the whole CH indicates that impulse occurrences are not related to a particular phase of the vibratory stimulus and therefore the response does not retain information about the temporal pattern of the stimulus.

Quantification of phase-locking in responses to skin vibration

A quantitative measure for the tightness of *phase-locking* of responses accumulated in the CH was the *vector strength* or *Resultant, R* (Mardia, 1972; Greenstein et al., 1987; Vickery et al., 1994; Coleman et al., 2003). The *resultant* is a quantitative measure of the phase coherence in the pattern of impulse activity elicited by sinusoidal tactile stimulus and was obtained by converting data points stored in the cycle histograms into phase angles (phase angles = time x 2π / cycle period). The start of each cycle represents a phase angle of zero. For n impulses, each occurring at a phase

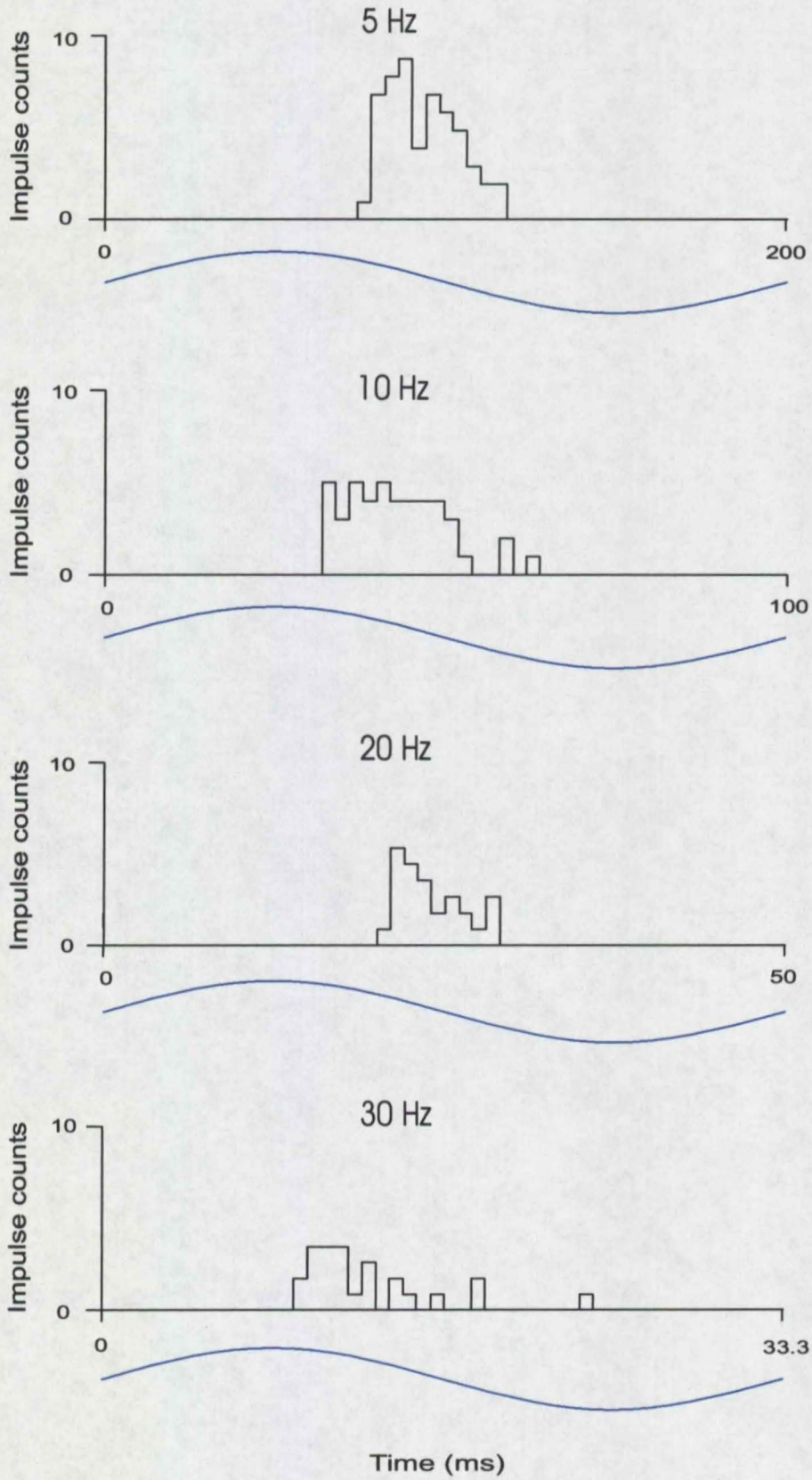

Figure 2-5. Cycle histograms show the time of impulse occurrences relative to the each vibration cycle. The horizontal axis represents the duration of the single vibration cycle for different frequencies of the vibratory stimuli (e.g., 20 ms for a 50 Hz stimulus). The vertical axis displays number of impulse counts accumulated during the five consecutive trains of the vibratory stimuli.

angle x_I, the *resultant* is calculated using the following equation (Goldberg & Brown, 1969; Mardia, 1972):

$$R = \frac{\sqrt{[\sum_{i=1}^{n}\cos(x_i)]^2 + [\sum_{i=1}^{n}\sin(x_i)]^2}}{n}$$

A numeric measure of phase locking, or synchronisation of the discharge to given phase of the sinusoidal vibration, the *resultant (R)*, was obtained from the cycle histogram. Values of R can range from 1, for complete phase synchrony, to 0, for randomly distributed or 'asynchronous' distribution of responses. In previous applications of the cyclic statistic in sensory physiology, values of R below 0.3 were taken to indicate little or no phase-locking, values from 0.3 to 0.7 as moderate phase-locking and 0.7 to 1.0 as a high degree of phase-locking (Durand & Greenwood, 1958; Lavine, 1971; Bledsoe, Rupert and Moushegian, 1982). These analyses permitted evaluation of the extent to which the impulse activity evoked by vibratory stimulation was phase locked or entrained to the stimulus waveform (e.g., Greenstein et al., 1987; Vickery et al., 1994; Mackie et al., 1998; Coleman et al., 2003).

2.5 Histological techniques

A spinal cord block between L1 and L6, together with a tungsten wire electrode inserted in the location of a successful track, was taken at the end of some successful experiments and fixed in 10% formalin in physiological saline. This was used to reconstruct the location of recording sites in histological sections of the spinal cord.

When the spinal cord tissue block had been well fixed, transverse sections of the spinal cord were cut at a 50-75 μm thickness on a freezing microtome. The sections were mounted on pre-coated glass slides and Nissl stained with cresyl violet. This histological reconstruction permitted identification of the location of the neurones recorded during an experiment, and whether they were located within Clarke's column nucleus.

Chapter 3

RESULTS

3. RESULTS

3.1 Identification of DSCT neurones

3.1.1 Antidromic identification of DSCT neurones

The response properties of seventeen identified DSCT neurones were examined in detail. As illustrated in Figure 3-1, the central projection of each DSCT neurone was unequivocally confirmed by the use of the so-called collision technique (Darian-Smith, Phillips and Ryan, 1963). This was based on stimulation of the restiform body in order to generate an antidromic spike in the DSCT axon, which could then be abolished by an ascending orthodromic spike initiated by a tap stimulus (~ 3 ms in duration) applied to the peripheral receptive field of the neurone. In the example shown in Figure 3.1, each tap stimulus evoked a pair of action potentials in the neurone, while stimulation of the restiform body elicited the discharge of a single action potential that occurred at a fixed latency corresponding to the *central conduction time* (*T*; which in this case was 4 ms). The time interval between the orthodromic (mechanical) and the antidromic (electrical) stimulus was progressively reduced in traces B and C of Figure 3.1. When, as shown in panel C, a peripherally-evoked orthodromic spike fell within the *interaction period* (2*T* + a *refractory period* of ~ 0.5 ms) the restiform-induced spike was extinguished, confirming its antidromic character and an axon projection from the neurone to the cerebellum. From the measured central conduction times (3-10 ms) and distances (30-35 cm) a mean conduction velocity in the ascending DSCT axon of ~55 m/s (range 25- up to ~100 m/s, n=17) was calculated that appeared to be consistent with those reported in previous studies (Mann, 1971: Oscarsson, 1965; Lundberg and Oscarsson, 1961) where values also extended from 15 m/s up to very rapid conduction velocities of ~100 m/s.

Subsequent to the antidromic confirmation of the central projection of the neurones, individual DSCT neurones were tested for their capacity to follow repetitive antidromic stimulation from the restiform body. As illustrated in the impulse traces of Figure 3.2, this test was based on the application of one-second long trains of electrical stimuli to the restiform body, with consecutive trains varying in frequency between 5 Hz and 333 Hz. This series of impulse recordings was typical of all DSCT neurones, in that, the responses to antidromic stimulation (spike output) occurred at a fixed latency and were sustained at impulse rates of up to 333 Hz, indicating that either our central

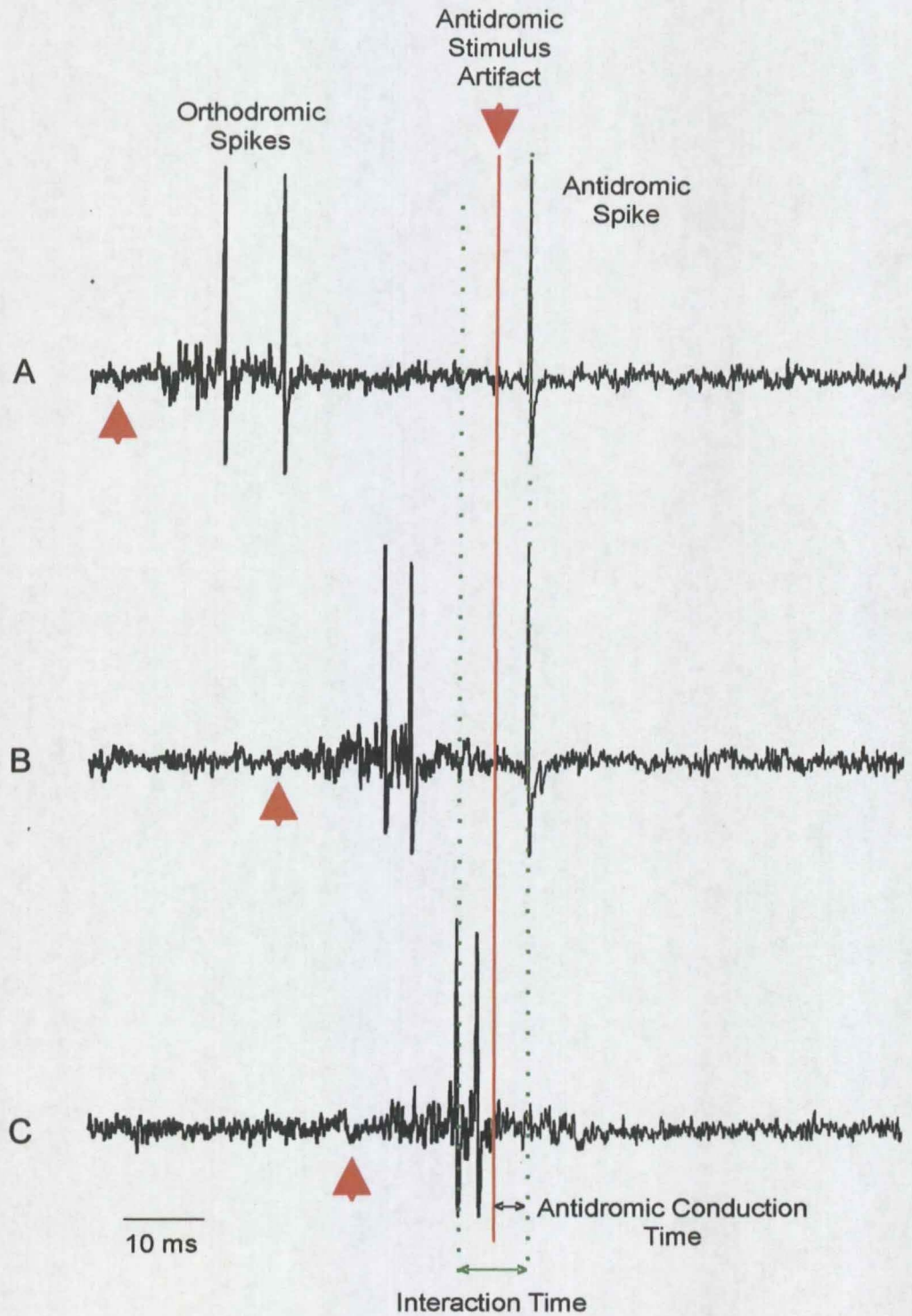

Figure 3-1. Impulse traces illustrating the antidromic identification of a DSCT neurone by the use of the collision technique. In each panel the antidromic spike was initiated by electrical stimulation (red downgoing arrow) of the restiform body and occurred at a *fixed antidromic conduction time* or latency, in this case, of 4 ms. In panels B and C the time between the prior orthodromic spikes, initiated by mechanical stimulation of the peripheral receptive field (red upgoing arrow), and an antidromic spike was reduced until the orthodromic spikes fell within the *interaction period* (Panel C) abolishing the antidromic spike and, therefore confirming the cerebellar projection of the neurone (*see text*).

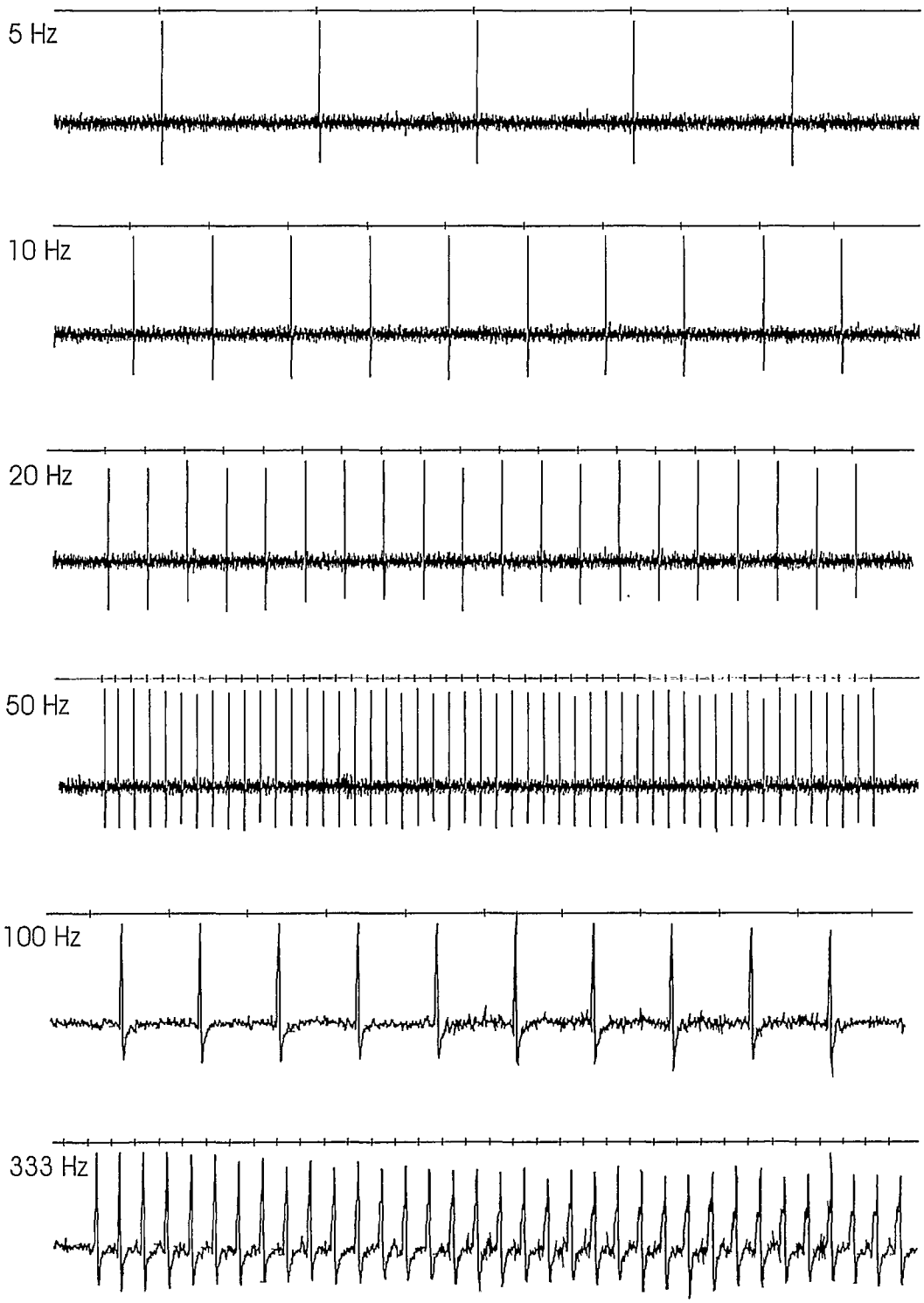

Figure 3-2. A series of impulse traces from a DSCT neurone showing responses to antidromic stimulation from the restiform body at six different frequencies from 5 to 333 Hz. Impulse traces show the response to 1 s trains of the antidromic stimuli, except at 100 and 333 Hz where the time scale is expanded 10 fold (100 ms). The trace with the associated strike marks above each impulse trace represents a stimulus marker for the antidromic stimulus.

recordings were obtained from the ascending axon of DSCT neurones, or that there was little impediment to the antidromic invasion of the soma during repetitive high frequency, antidromic stimulation.

3.1.2 Location of identified DSCT neurones within the spinal cord

All DSCT neurones sampled were isolated in the second to fifth lumbar segments of the spinal cord in a region located 150 to up to ~ 500 μm lateral of the midline and at a depth of 2-3 mm from the cord's dorsal surface. In Figure 3-3 a histological reconstruction of a single electrode penetration made in the fifth lumbar segment of the spinal cord is shown. The antidromically identified DSCT neurone was located within the tract, indicated by the dashed vertical line, ~ 500 μm lateral to the midline and ~ 2.5 mm from the dorsal surface of the spinal cord, in effect located in the neck of the dorsal horn lateral to the *intermediate grey matter* of the spinal cord (100-300 μm lateral to the midline) i.e. a location consistent with the location of Clarke's column nucleus (Curtis et al., 1958; Kuno et al., 1973;Walmsley et al., 1985).

3.1.3 Trans-synaptic activation of DSCT neurones from the spinal dorsal columns

In five experiments, DSCT neurones were tested for the presence of mono-synaptic and/or poly-synaptic linkages arising from those ascending fibres that enter the dorsal columns and which presumably convey tactile information to the gracile nucleus. Whether they also provided input to the DSCT neurones was examined by placing a set of bipolar silver-ball stimulating electrodes over the dorsal column-entry zone of the gracile nucleus. On all five occasions, low-intensity (~150-250 μA, 100 μs duration) electrical stimulation at this point evoked spike-output in DSCT neurones, suggesting that ascending fibres terminating in the gracile nucleus may, in addition, provide synaptic input to the DSCT. However, as shown in Figure 3.4, when the capacity of this synaptic linkage to respond to repetitive trans-synaptic activation from the gracile fasciculus was tested, at frequencies varying from 5 Hz to 333 Hz, it was found that, although the first pulse in a train of stimuli invariably generated a burst of spike output, the capacity of this synaptic linkage to sustain spike output was severely limited when the rate of stimulation exceeded 10 Hz (Fig. 3.4).

While electrical stimulation of the gracile fasciculus can lead to the antidromic activation of ascending primary afferent fibres as well as second order neurones arising

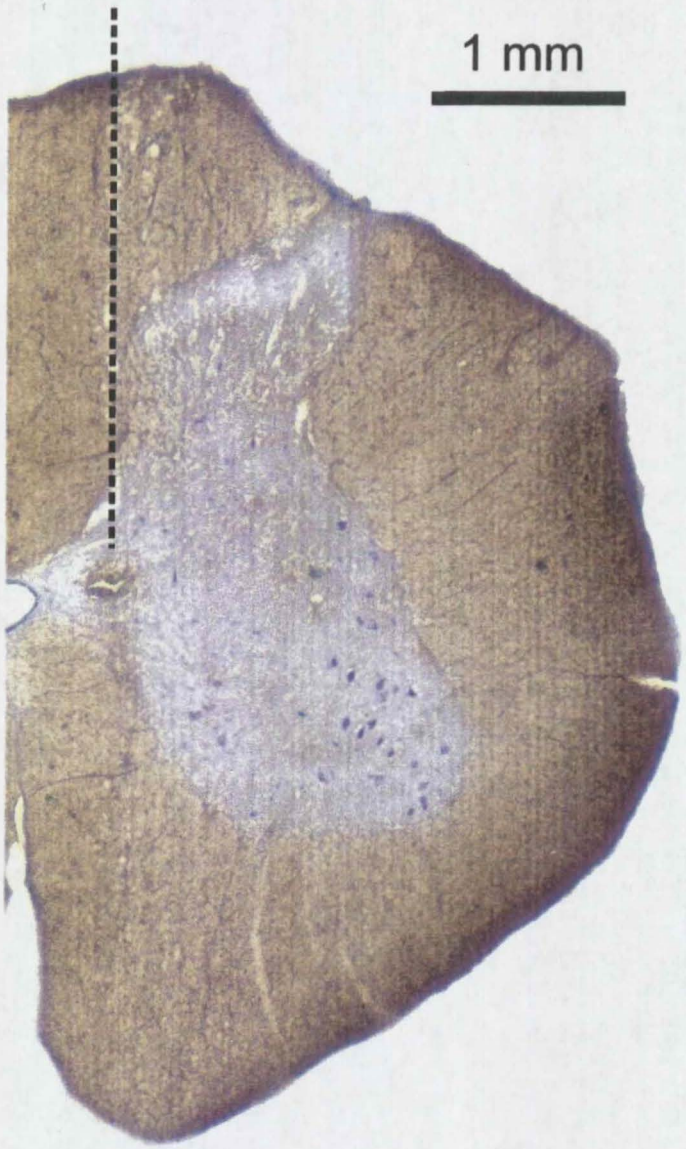

Figure 3-3. Histological hemisection of the lumbar spinal cord ipsilateral to the DSCT neuron's receptive field stained with *Cresyl Violet*. The interrupted line shows the position of the micro-electrode track during the recording, located in the medial region of the spinal *grey matter* ~500 μm lateral to the midline with the tip (lesion lateral to the central canal) at a depth of ~2.5 mm from the dorsal surface of the cord. Purple-stained neurones can be seen scattered in a *grey matter* of the lumbar spinal cord.

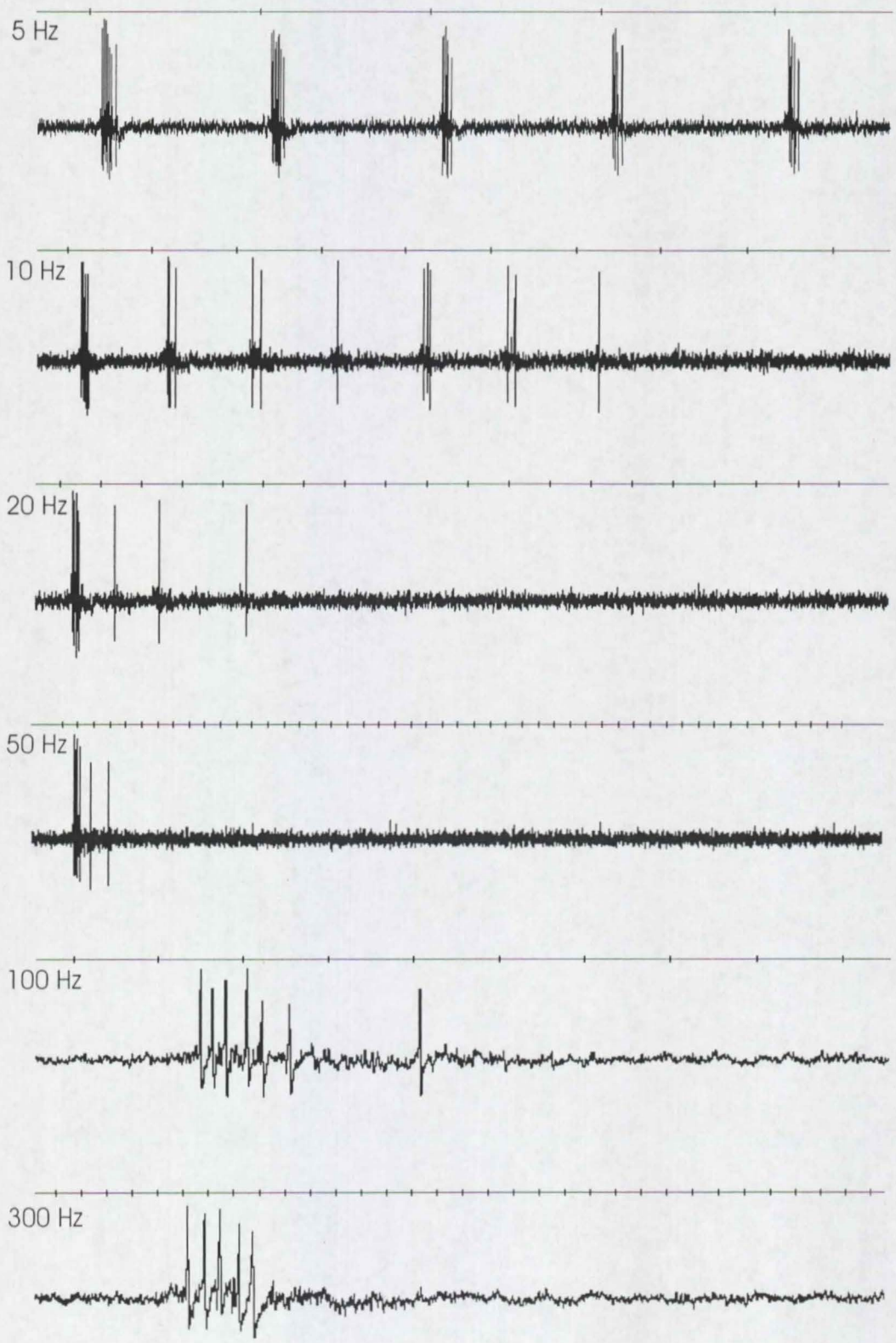

Figure 3-4. A series of impulse traces from a DSCT neurone showing the response of the neurone to repeated stimulation (electrical) of the gracile fasciculus at frequencies 5-300 Hz. The response was recorded to 1 s trains of electrical stimuli, except at frequencies of 100 and 300 Hz where the time scale is expanded 10 fold. Impulses evoked in the neurone are trans-synaptic in nature and of long latency (~ 15 ms). The capacity of this trans-synaptic linkage to follow repeated activation was limited to frequencies of 5-10 Hz.

from the spinal dorsal horn, in particular, postsynaptic dorsal column neurones (Brown 1973), careful inspection of the conduction and interaction times of the gracile-induced antidromic spike can provide some insight into the underlying synaptic arrangements within the spinal cord. It was noted in two DSCT neurones that the trans-synaptic activation from the dorsal columns appeared to be attributable to a linkage arising from primary afferent fibres that, in addition to providing synaptic activation of the DSCT neurone, also had direct projections to the gracile nucleus.

A schematic representation of the synaptic linkage between primary afferent fibres that ascend in the gracile fasciculus, and DSCT neurones, and the representation of the tests used to confirm the presence of such a linkage are shown in Figure 3-5. As with all recordings in this study, the central recording was obtained from a DSCT neurone. However, on two of five occasions, in addition to showing that the DSCT neurones could be activated from their receptive field (*orthodromic path*), we were able to show that the DSCT neurones could be activated *trans-synaptically* following electrical stimulation of ascending fibres in the gracile fasciculus. Collision and extinction of the peripherally-evoked (mechanical) *orthodromic* and electrically-evoked *trans-synaptic* spikes at points above and below the *axonal branch* supplying the DSCT neurone confirmed the direct input of individual tactile afferent fibres to both the dorsal column-gracile pathway on the one hand, and the DSCT system of cerebellar input, on the other. For a collision that occurred above the branch point (Fig. 3-5B), the preceding orthodromic spikes extinguish subsequent descending spikes for a period of time equivalent to that of twice the *central conduction latency* plus a refractory period that typically might be expected to be ~0.5 ms. For a collision that occurred below the branch point (Fig. 3-5C), the preceding antidromic spikes from the dorsal columns, extinguish subsequent orthodromic activity for a period of time equal to twice the *peripheral conduction latency* plus the estimated refractory period of ~0.5 ms. For two DSCT neurones, the presence of a probable mono-synaptic linkage was confirmed by the capacity to collide descending and ascending spikes over a period of time equivalent to twice the combined *central and peripheral conduction latencies* and a *refractory period* of ~0.5 ms, in effect the time taken to traverse the entire length of an ascending primary afferent fibre. When these linkages were tested for their capacity to sustain spike output during repeated trans-synaptic activation (electrically evoked from the gracile fasciculus) a similar attenuation of spike output, to that observed in Figure 3-4,

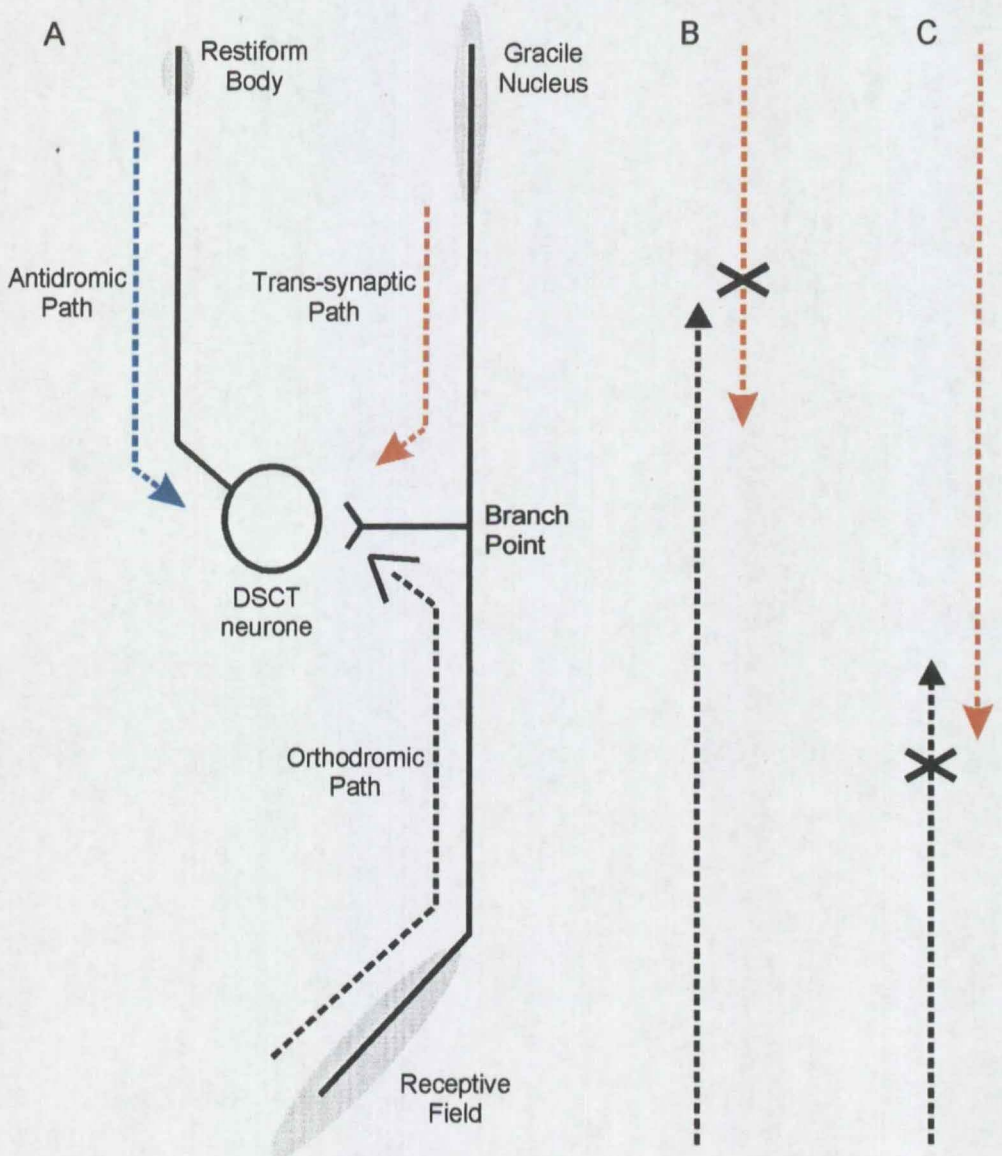

Figure 3-5. A. A schematic representation of the synaptic arrangement within the spinal cord showing the path for *antidromic activation* (indicated by the broken blue line near the ascending DSCT neurone's axon), from the restiform body; *trans-synaptic activation* from the gracile nucleus (indicated by the broken red line next to the dorsal column ascending axon) and the *orthodromic activation* from the peripheral receptive field of the DSCT neurone. Panels B and C depict the collision of a descending antidromic spike (red lines), initiated by electrical stimulation of the gracile fasciculus, with an orthodromic spike (black lines), initiated by stimulation of the receptive field, within the primary afferent fibre above (panel B) and below (panel C) the level of the central branch point supplying the DSCT neurone. A black cross represents the level of collision that occur above (B) and below (C) the branch point respectively.

was seen, consistent with the synaptic activation taking place via the same linkage as that used for the peripheral input to the DSCT neurone.

3.2 Size and distribution of tactile receptive fields of DSCT neurones

After the cerebellar projection of individual DSCT neurones was confirmed, using the *antidromic collision procedure*, their excitatory receptive field on the cat's hindlimb was carefully mapped using calibrated *von-Frey* hairs that varied in force from 10 mg to 1 g. In all seventeen DSCT neurones, the point of maximal sensitivity within their cutaneous receptive field was identified. In the majority of units the broader area of skin from which they could be activated (i.e. their receptive field) was mapped using *von-Frey* hairs of increasing strength. As shown in the six representative receptive fields of Figure 3-6, individual receptive fields varied in their shape and distribution across the skin surface. However, in any given field there was a central region where low intensity stimuli, often < 50 mg *weight von-Frey,* generated spike output, beyond which *von-Frey* hairs of increasing strength were required to evoke a response. Of two DSCT neurones with slowly adapting response properties (*see below*), one had its receptive field on the inter-digital hairy skin (cell 14 in Fig. 3-6) and the other was located at the margin between hairy and glabrous skin (cell 1 in Fig. 3-6). Of fifteen purely dynamically-sensitive DSCT neurones (*see below*), nine had receptive fields confined to the hairy skin of the distal hindlimb (e.g. cell 9 in Fig. 3-6), and inter-digital hairy skin of the paw (e.g. cells 8 and 20 in Fig. 3-6), while one had its receptive field on the hairy skin of the thigh. The remaining five dynamically sensitive DSCT neurones were activated from the margin between hairy and glabrous skin on the footpads (e.g. cell 15 in Fig. 3-6).

3.3 Response of DSCT neurones to controlled mechanical stimulation of the skin

The capacity of individual DSCT neurones to signal both the static and dynamic components of tactile stimuli applied to the skin of the cat's hindlimb was investigated by using controlled forms of mechanical stimulation. In response to a static indentation of the skin, only two cells displayed responses (impulse activity) that were sustained into the static component of the stimulus, and therefore, as shown in the impulse traces of Figure 3-7, displayed responses that outlasted the initial phasic component. These cells were classified as displaying *slowly adapting* (SA) responses. In contrast, the majority of cells (15 out of 17) were purely dynamically sensitive, responding only to

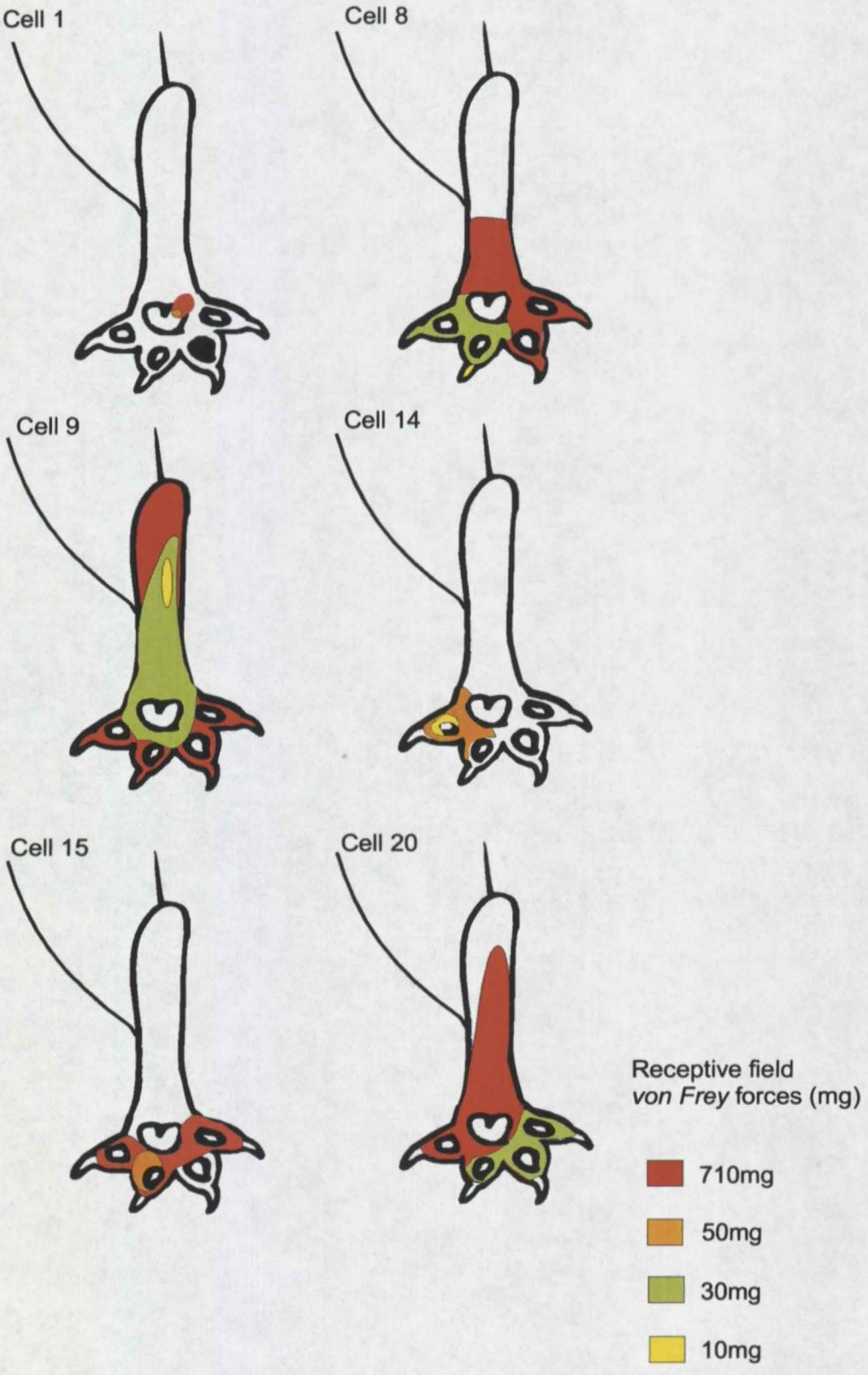

Figure 3-6. Figurines of the cat hindlimb showing examples of receptive fields for six DSCT neurones. For each neurone the receptive field (RF) on the cat's hindlimb was examined using a calibrated *von Frey* hair (VFH) of different weight. In the case of cell 20, for example, there was no detectable RF with a 10 mg VFH but the area shown in green was responsive with a 30 mg VFH. This cell was not tested with a 50 mg VFH, but when tested with a 710 mg VFH the RF expanded beyond the green area to include the red shaded area.

the onset and offset of the step indentation. These cells were than tested more fully for their responsiveness to purely dynamic forms of skin stimulation, in particular, for vibration sensitivity and responsiveness.

3.3.1 Responsiveness of DSCT neurones to static indentation of the skin

The response properties of the two DSCT neurones displaying slowly adapting responses to static indentation were examined quantitatively by the use of controlled mechanical stimuli. These stimuli were applied with circular probes (2 mm in diameter) positioned just in contact with, and normal to the skin surface at the centre of the receptive field. The impulse traces in Figure 3-7 show the responses of the two DSCT neurones that displayed sustained spike-output during static compression of the skin. In both cases, the first one second of recording shows the spontaneous or resting level of activity observed in the absence of mechanical stimulation. Although both cells have a similar resting discharge rate of ~10 impulses/s, the two differed in their discharge pattern. The first cell, shown in panel A, tended to discharge single spikes that occurred in a regular metronome-like manner, while the second cell, shown in panel B, displayed irregular bursts of activity that were followed by periods of quiescence.

In response to static skin indentation both cells displayed responses (spike output) to the dynamic components of the stimulus, i.e. the rise and fall of the step indentation, that occurred at low step amplitudes (200-400 μm), well below those required to elicit sustained spike output. The capacity to generate sustained spike output required a larger step amplitude than that needed to evoke the response at the onset of the indentation (panel A, Fig. 3-7). The presence of a somewhat regular pattern of discharge, both in the absence of, and during skin indentations in the first of these neurones (panel A, Fig. 3-7) provides some indication that the input may have arisen from the activation of SA II afferent fibres i.e. Type II slowly adapting inputs associated with *Ruffini receptor endings* (Iggo, 1968; Iggo & Muir, 1969; Chambers et al., 1972). However, the location of the receptive field at the interface of the glabrous and hairy skin (cell 1, Fig. 3-6), and an absence of responses to skin stretch, makes a more certain classification of the source of input difficult. In contrast, for the other DSCT neurone, the presence of a sporadic discharge pattern, in the absence of stimulation, and the irregularity in the pattern of impulse activity observed during static indentation (panel B, Fig. 3-7) is perhaps more consistent with inputs arising from SA I afferent fibres that

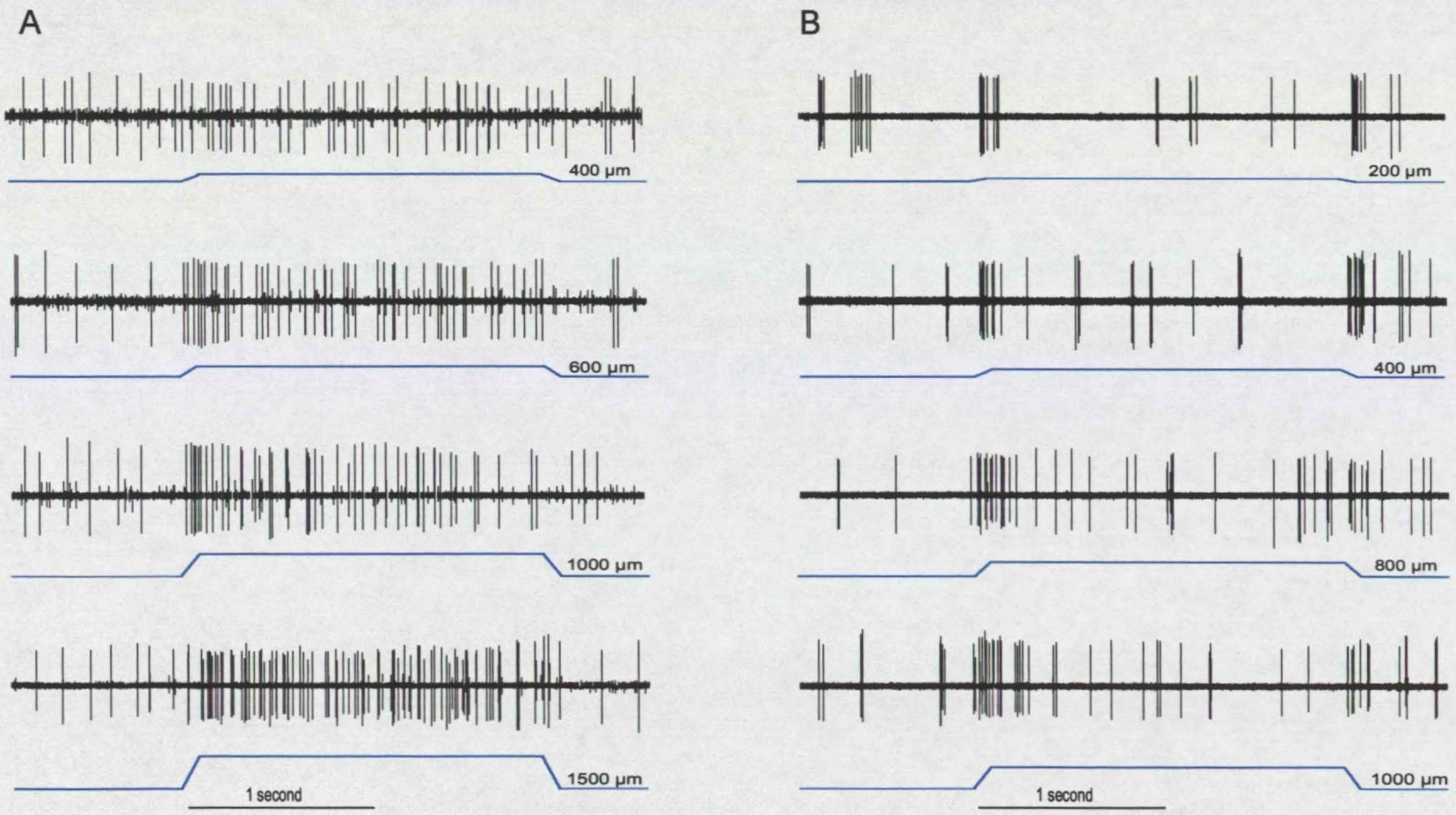

Figure 3-7. Impulse traces recorded from two DSCT neurones in response to graded static indentation of the skin of 400-1500 µm (A) and of 200-1000 µm (B). The indentation stimuli lasted two seconds.

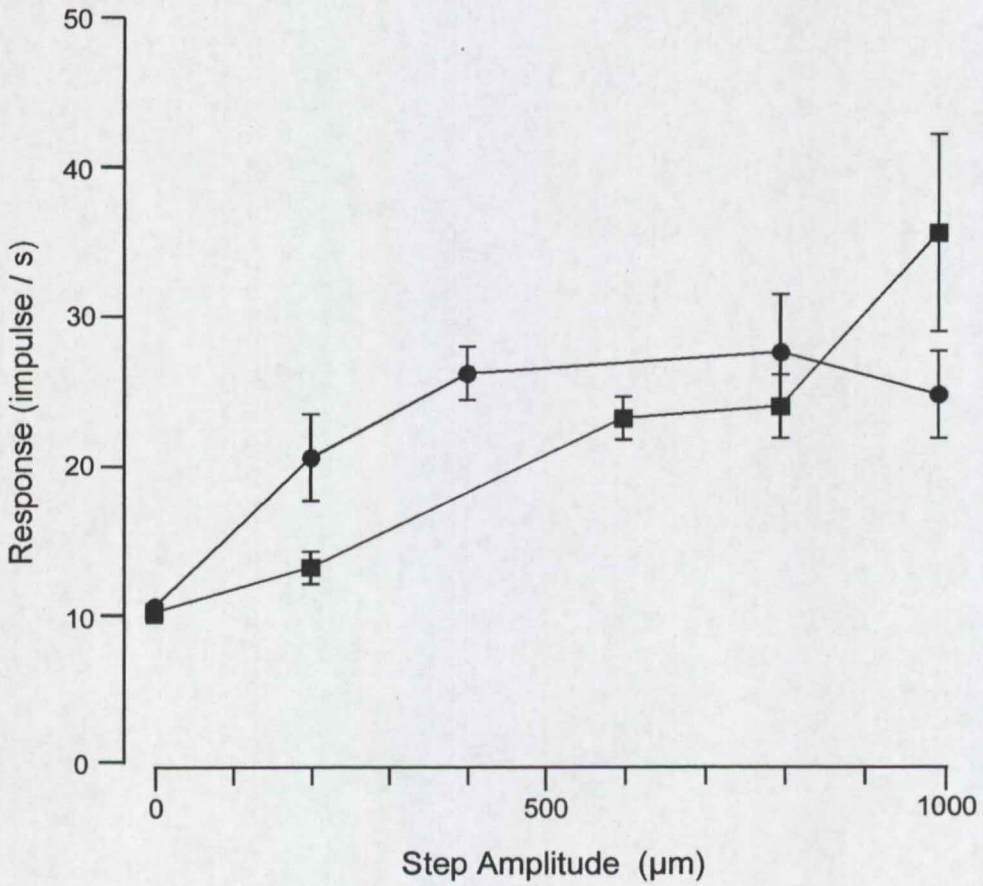

Figure 3-8. Stimulus-response relations showing the mean (± SD; n=5) spike output of two DSCT neurones with slowly adapting response properties to graded static indentation of the skin. The response is expressed as impulse/s evoked over an initial 1s period of static skin indentation and the amplitude of the static indentation is in μm.

are associated with *Merkel receptor complexes* (Chambers & Iggo, 1967; Iggo, 1968; Iggo & Muir, 1969).

When the sensitivity of these neurones to signal changes in the amplitude of skin indentation was examined by constructing *amplitude-response* relations, in which the mean spike output (impulses/s) was expressed as a function of step amplitude, both neurones displayed poorly-graded changes in spike output (Fig. 3-8). Indeed, spike output remained almost constant at amplitudes above ~500 μm. This is in marked contrast to the known capacity of slowly adapting primary afferent fibres and their target neurones in the dorsal column nuclei (Vickery et al., 1994; Gynther et al., 1995) to provide a detailed and finely-graded signal of stimulus intensity over a range of indentation amplitudes up to ~2000 μm.

3.3.2 Responses of DSCT neurones to focal cutaneous vibration

For the majority of the sampled DSCT neurones (15 out of 17), the response to a static step indentation was confined to the dynamic component of the stimulus, i.e., the onset and offset of the step indentation. In order to further examine the capacity of individual DSCT neurones to signal dynamic tactile information, trains of sinusoidal vibratory stimuli were applied to the skin surface superimposed on a static indentation step of 400 μm. These neurones were classified as being purely dynamically-sensitive DSCT neurones and, as shown in the impulse traces of Figure 3-9, displayed a limited capacity to respond to cutaneous vibration. At low frequencies, e.g. 5 and 10 Hz, an increase in vibration amplitude increased the number of cycles over which spike output could be sustained, consequently the average spike output during vibration displayed a somewhat graded increase when the amplitude of the vibratory stimulus was increased. However, any graded increase in spike output became less apparent as the frequency of the stimulus was increased. Indeed, even at 10 Hz increasing the amplitude of the vibratory stimulus failed to elicit a response that could be sustained throughout the whole one-second vibration train (Fig. 3-9). At higher frequencies (≥50 Hz), the attenuation in spike-output beyond the stimulus onset point shown in Figure 3-9 became so marked that all impulse activity was confined to the onset of the vibration train. For this particular cell, the relationship between the intensity of the vibrotactile stimulus and the spike output was quantified by constructing *amplitude-response relations* in which the mean spike output (impulses/s +/- SD, n=5) was plotted as a function of vibration

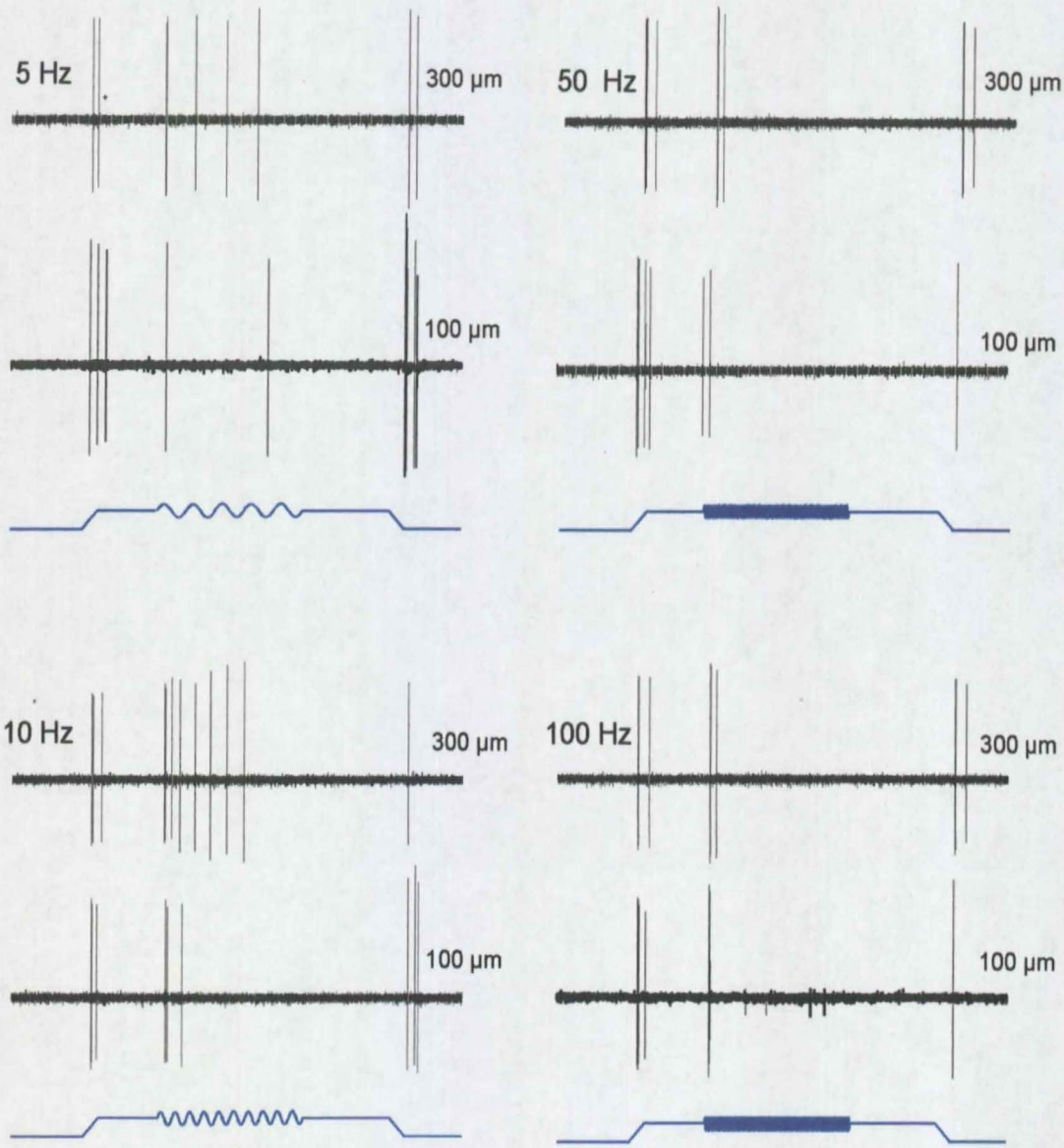

Figure 3-9. Series of impulse recordings evoked in a DSCT neurone by vibrotactile stimuli of different frequencies and amplitudes. The stimulus in each case consisted of a 1 s long vibration train superimposed on 400 µm step indentation lasting 2 s.

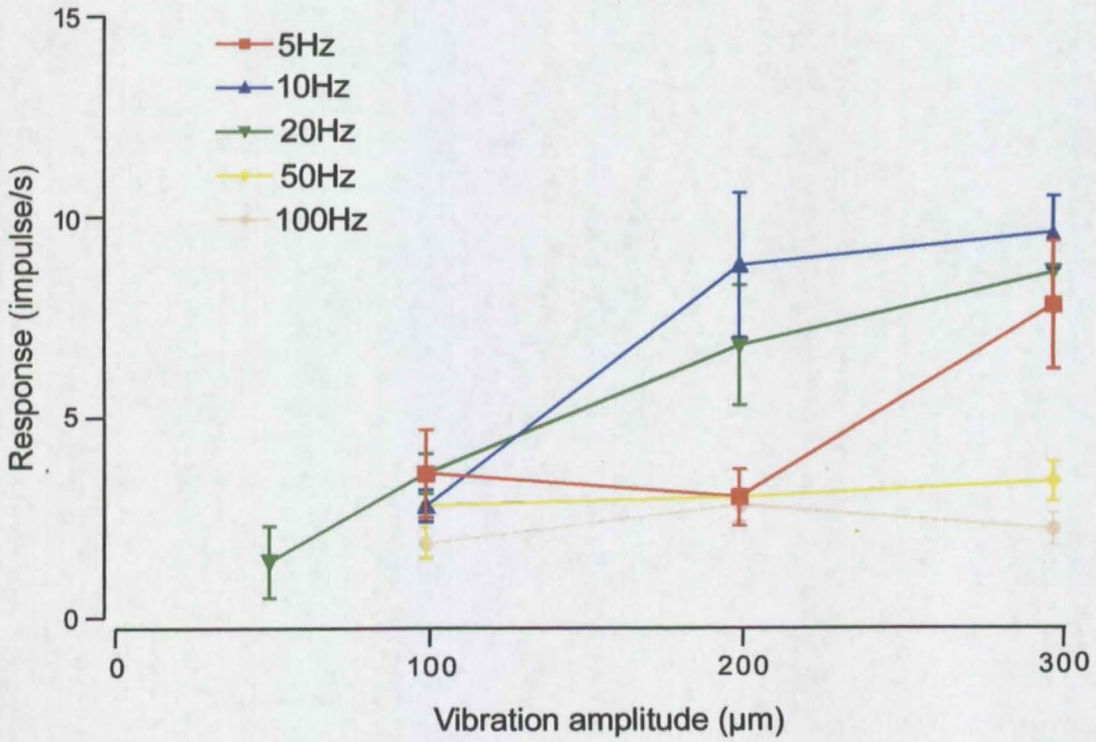

Figure 3-10. *Amplitude-response* relations for a single DSCT neurone quantifying the response to vibration applied to its receptive field focus at frequencies ranging from 5 to 100 Hz. The response of the neurone is expressed in number of impulses/s and is plotted as a function of the amplitude of the vibrotactile stimuli. Each data point represents the mean ± SD of five consecutive (n=5) 1 second trials.

amplitude at frequencies of 5, 10, 50 and 100 Hz (Fig. 3-10). At low frequencies, e.g. 5 and 10 Hz, all the sampled DSCT neurons displayed a response pattern that, given sufficient amplitude, extended beyond the onset of the vibration. Consequently, at low frequencies, impulse activity displayed a coarse grading of spike output as a function of vibration amplitude. In contrast, because the responses to vibrotactile stimulation at frequencies of 50 and 100 Hz were confined to the onset of vibration, there was little or no enhancement of spike output at these frequencies when vibration amplitude was increased. This limited range of frequencies over which these individual DSCT neurones were capable of responding to vibrotactile stimulation, i.e. their bandwidth of dynamic responses, typified the response pattern for all dynamically-sensitive DSCT cells encountered.

The *amplitude-response relations* of Figure 3-11 plot the mean response levels of individual dynamically-sensitive DSCT cells to vibrotactile stimuli at frequencies of 5, 10, 50 and 100 Hz, as a function of vibration amplitude. As with the response of the single DSCT neurone shown in Figures 3-9 and 3-10, the group data displayed coarsely-graded relations at low frequencies (5 and 10 Hz) but virtually no evidence of this when vibration amplitude was increased at frequencies of 50 and 100 Hz (Fig. 3-11). The grading of responsiveness as a function of amplitude at low frequencies occurred because the responses could be sustained beyond the onset of the vibration train, whereas at the higher frequencies (>10 Hz) the responses were essentially confined to the onset of the vibration train, as was seen in Figures 3-9 to 3-11. Thus, although a similar number of amplitude-response relations are shown at 50 and 100 Hz, the majority of these response relations show little or no change in spike output as the amplitude of the vibration increased. Consequently, fewer DSCT cells are capable of coding for the amplitude and/or frequency parameters of vibrotactile stimuli at frequencies in excess of ~10 Hz.

The *amplitude-response curves* shown in Figure 3-12 plot the average spike output, for the pooled group data, as a function of vibration amplitude at frequencies of 5, 10, 20, 50 and 100 Hz. Consistent with the relations displayed by individual DSCT cells, the averaged group data displays a crude grading of responsiveness (spike output) at 5 and 10 Hz. While the pattern of activity may differ markedly at low and high

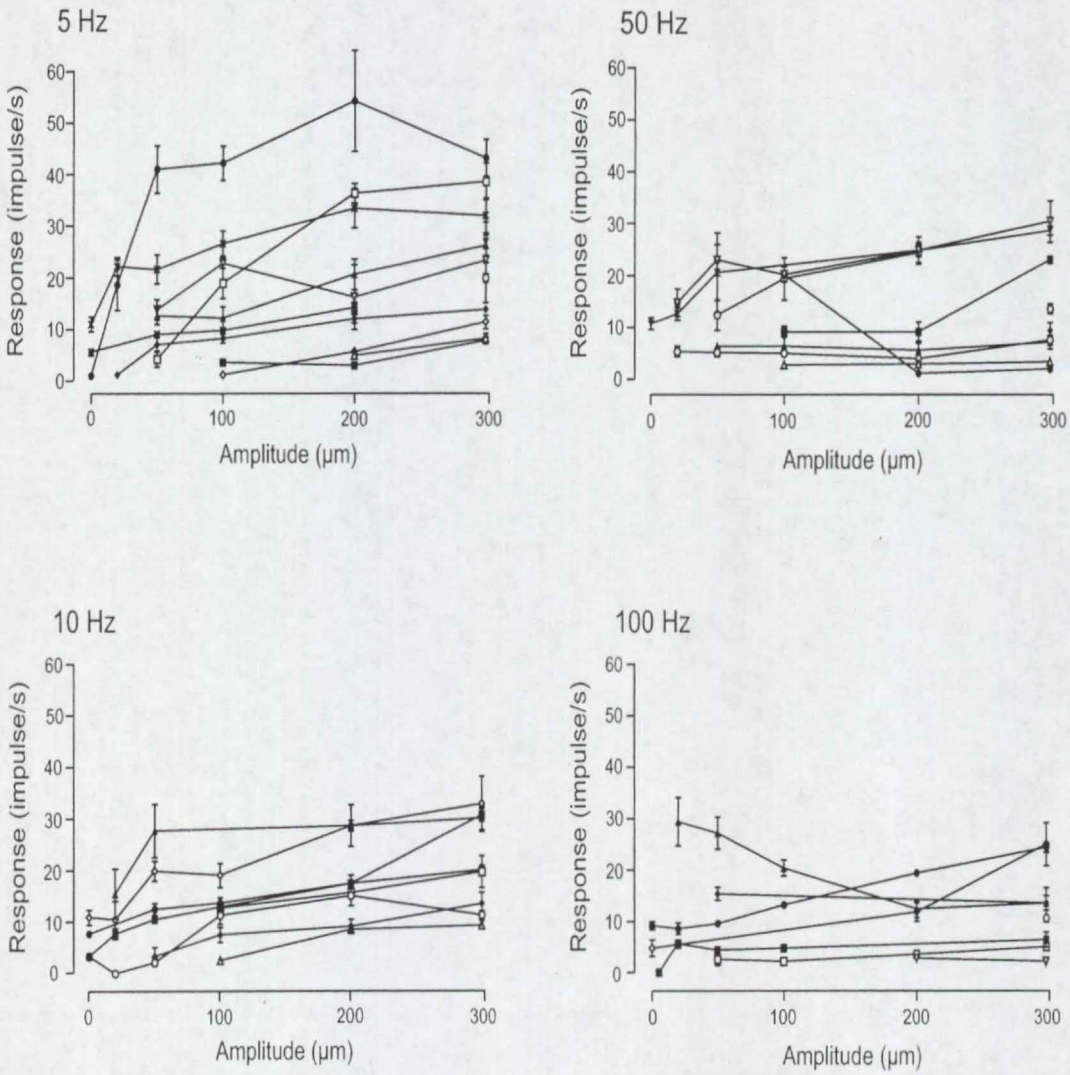

Figure 3-11. Stimulus-response relations showing the mean response (impulses/s ± SD; n=5) for individual dynamically-sensitive DSCT neurones, plotted as a function of vibration amplitude at frequencies of 5, 10, 50 and 100 Hz. Each stimulus consisted on a 1s train of vibration delivered on a fixed background step indentation of 400 µm.

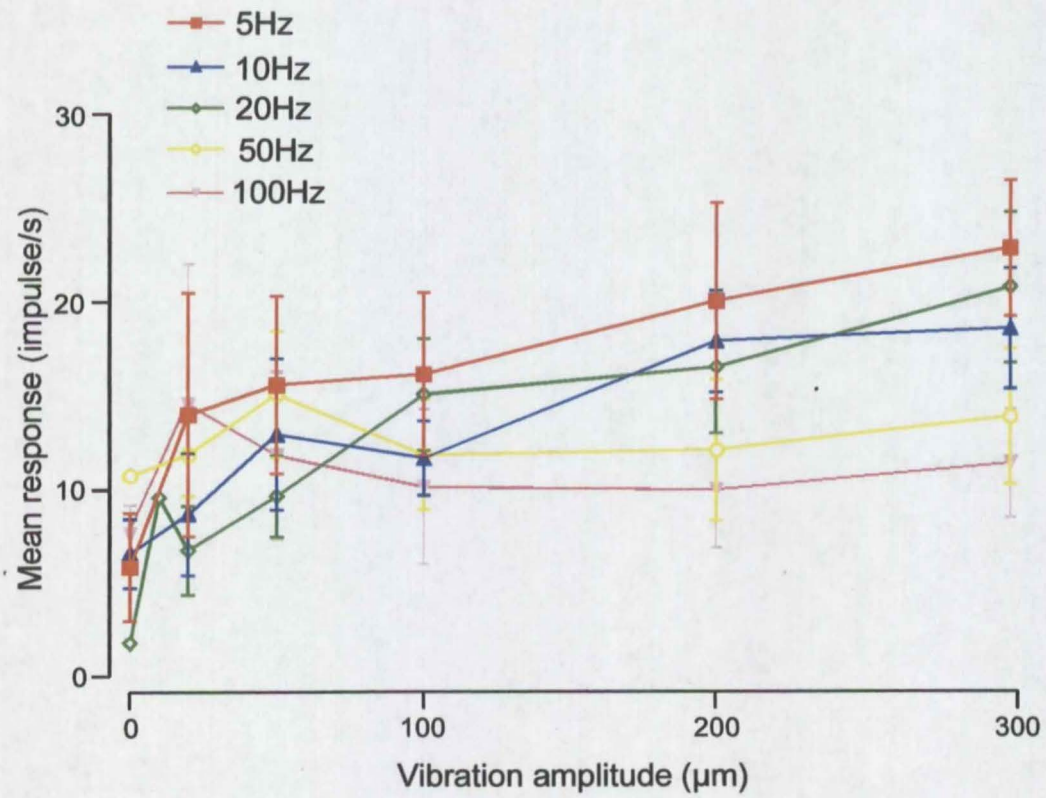

Figure 3-12. Stimulus-response relations showing the mean response level (in impulses/s ± SD; n=5) for all dynamically-sensitive DSCT neurones plotted as a function of vibration amplitude at frequencies of 5, 10, 20, 50 and 100 Hz. Each stimulus consisted of a train of vibration lasting 1s, superimposed on a background step of 400 μm.

frequencies the average spike output differs little (~ 15 – 20 impulses/s) from that observed at frequencies of 50 and 100 Hz (~ 10 – 15 impulses/s), suggesting that the mean spike output from individual DSCT neurones alone cannot provide a reliable signal of vibrotactile stimulus intensity or frequency.

Impulse patterning in the responses of DSCT neurones to vibrotactile stimuli

The limited range of frequencies, or bandwidth of responsiveness, displayed by individual DSCT neurones to vibrotactile stimuli imposes significant constraints on the capacity of the cells to code for the intensive and frequency parameters of vibrotactile stimuli. In Figures 3-13 and 3-14 a range of stimulus histograms were constructed in order to asses the temporal patterning of neural responses to oscillatory (vibration) disturbances taking place on the skin. In Figure 3-13, peri-stimulus time histograms (PSTH) were constructed, in which the impulse activity from five consecutive trials were accumulated in response to cutaneous vibration at frequencies of 5, 10, 50 and 100 Hz with a fixed amplitude of 300 μm. At frequencies of 5 and 10 Hz, the impulse activity was not randomly distributed but displayed a *pattern* of activity that reflected the periodicity of the vibrotactile stimuli. This impulse patterning was most marked at 5 Hz where impulse activity occurred at intervals approximating the cycle period of the stimulus, i.e. ~200 ms. However, the capacity of DSCT neurones to sustain spike output appeared to be subject to temporal constraints, as there was a progressive attenuation in the number of accumulated impulse counts in the PSTH during the 1s train of vibrotactile stimulation. This progressive reduction in spike output, although apparent at 5 and 10 Hz, was most marked at higher frequencies (≥50 Hz) where all the responses were confined to the onset of the vibration train.

In Figure 3-14 the precision of impulse patterning was further quantified by constructing cycle histograms (CH), or folded histograms in order to analyze the phase-locking of the neural responses. In these histograms the timing of individual spikes is plotted relative to the start of the cycle period. The cycle histograms accumulate the responses of DSCT neurones to between 25 (at 25Hz) and 500 (at 100 Hz) cycles of vibration. The CHs shown in Figure 3.14 all share the same scaling of their vertical axis (impulse counts), except at 5 Hz where the axis has been expanded 2.5 fold to accommodate the enhanced response level, and vary in their horizontal scaling (time) according to the cycle period of the vibration. At 5 Hz, impulse activity is confined to a

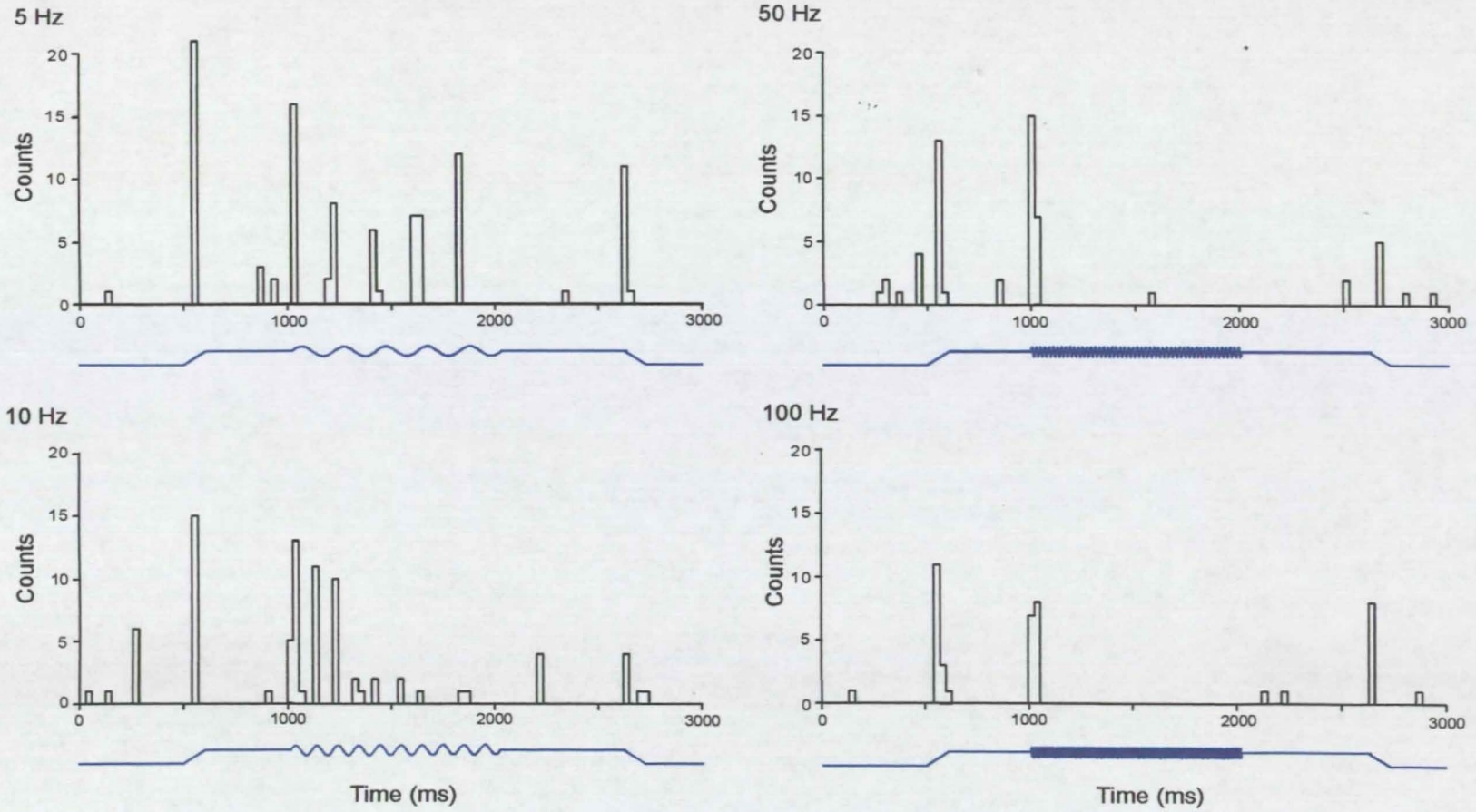

Figure 3-13. Peri-stimulus time histograms showing the accumulated spike output from five repetitions of a 1s duration vibrotactile stimulus at frequencies of 5, 10, 50 and 100 Hz at a fixed amplitude of 300 μm. Each histogram shows the one second period before, during and after the vibration stimulus. Individual addresses or bin widths in the histograms are 10 ms. The horizontal axes represent time (in ms) and the vertical axes represent the accumulated counts.

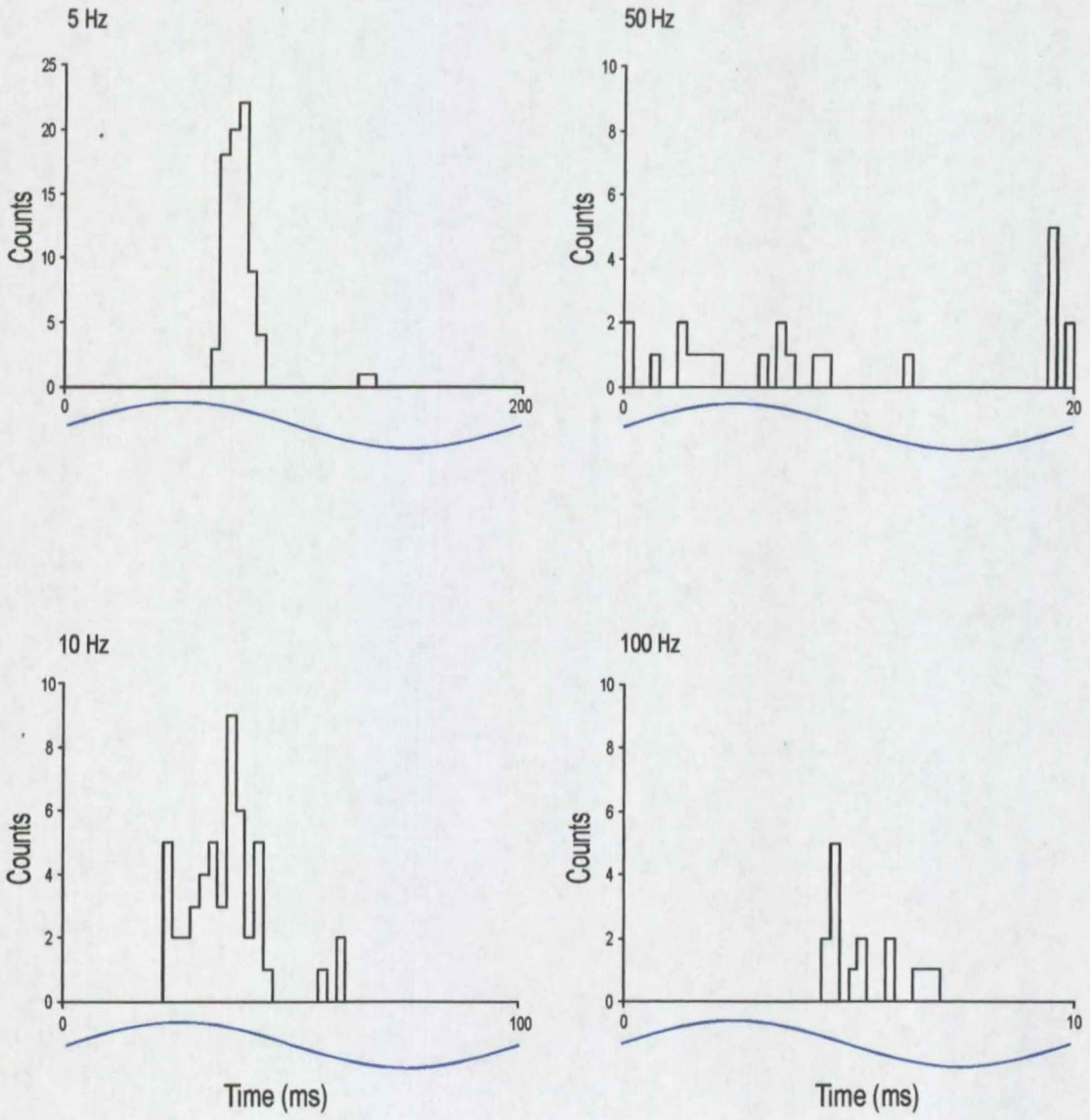

Figure 3-14. Cycle histograms showing the occurrence of DSCT spike output throughout the vibration cycle period at frequencies of 5, 10, 50 and 100 Hz. In each plot the analysis time (horizontal axes) corresponds to the cycle period (in ms) at 5, 10, 50 and 100 Hz. Vertical axes represent the number of impulses evoked in this particular DSCT neurone, in response to five consecutive trains of vibration, each lasting 1 s.

narrow band (~¼) of the cycle period indicating that impulse activity was finely tuned or *phase-locked* to a given phase of the stimulus waveform. At 10 Hz, there appears to be a greater dispersion of impulse activity, with impulse activity dispersing over ~½ of the cycle period. However, some caution is required when comparisons are made across frequencies as a distribution of impulse activity over ~¼ of the cycle period at 5 Hz, is equivalent to a dispersion over an absolute time period (~50 ms) similar to, or even greater than that observed at the higher frequency of 10 Hz. The apparent improvement of phase-locking of impulse activity observed at 100 Hz is entirely misleading as the decreased dispersion reflects the declining response level and the confinement of responses to the very onset of the vibration. Therefore, while these DSCT neurones may act as an effective event marker for the onset of vibration, they provide little if any information on the periodicity of the vibration that follows, especially when the frequency of the stimulus exceeds 10 Hz.

The relation between the amplitude of vibration and the degree of phaselocking was quantified by plotting the numerical value of phase-locking derived from the CH, the *Resultant*, as a function of vibration amplitude at frequencies of 5, 10, 20, 50 and 100 Hz (Fig. 3-15). At 5 and 10 Hz the *Resultant* tended to increase or remain relatively constant (~0.5 – 0.75) as the vibrational amplitude, and consequently, the number of impulse counts contributing to the calculation increased. Although a similar preservation of impulse patterning is indicated when the *Resultant* is plotted as a function of vibration amplitude at frequencies ≥20 Hz, this interpretation needs to be made with considerable caution for the reason indicated above; namely, the vast majority of the impulse counts contributing to the calculation are derived from the onset of vibration. Therefore, at vibration frequencies ≥20 Hz the preservation of *Resultant* values in the range of ~0.5 – 0.75, reflects the consistency of the neurone's response to the onset of the vibration train, rather than any temporally-patterned response, phaselocked to successive cycles of the vibration train.

3.3.3 Responses of DSCT neurones receiving slowly adapting inputs to focal vibration

Although all DSCT cells were initially tested for their response to sustained, static indentation, only two neurones responded in a sustained way to the static stimulus that was consistent with the impulse activity being related to slowly adapting input sources (see above in *section 3.3.1*). However, the dynamic sensitivity of these neurones

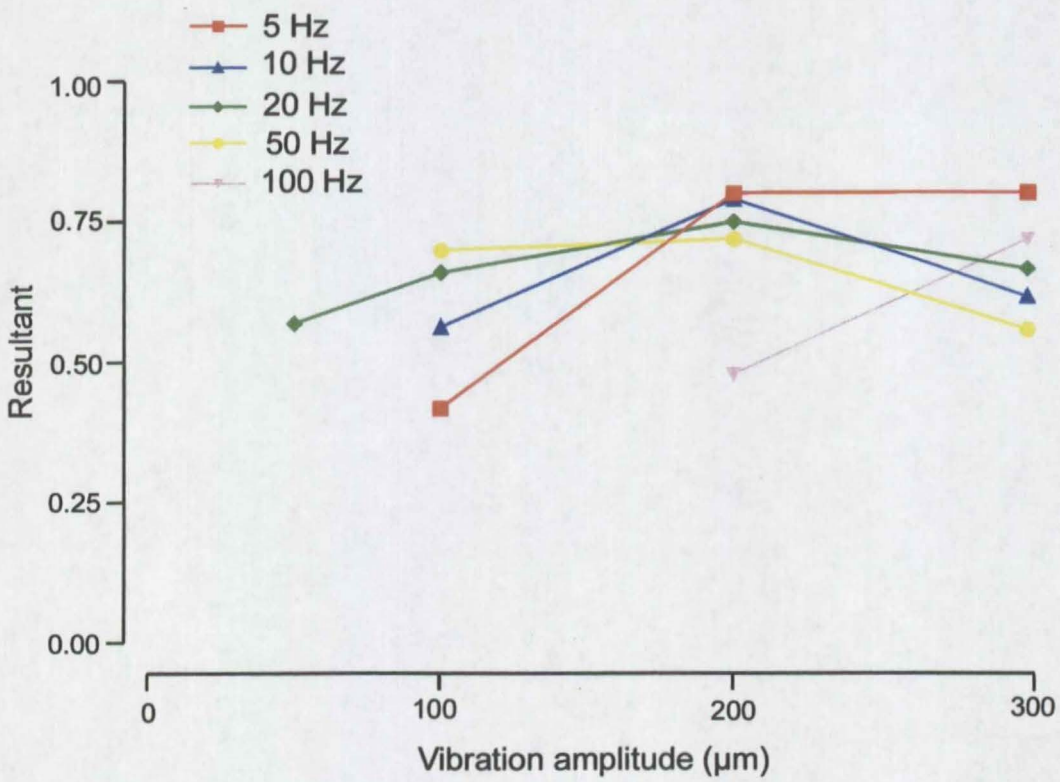

Figure 3-15. Plot of the *Resultant* vector as a function of vibration amplitude of a particular dynamically-sensitive DSCT neurone showing the degree of phase-locking at frequencies of 5, 10, 20, 50 and 100 Hz.

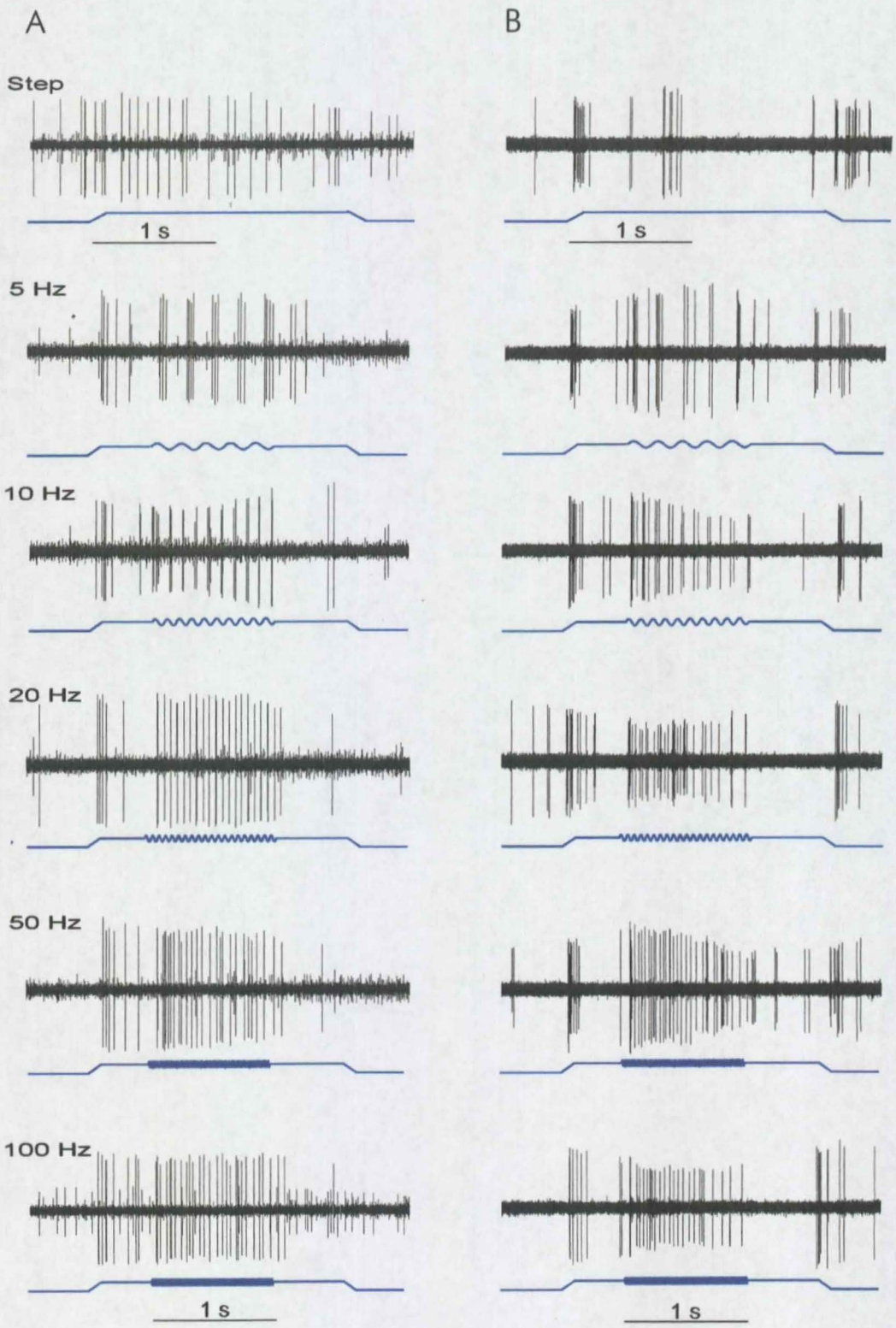

Figure 3-16. Impulse traces of two DSCT neurones (A and B) whose responses to static skin displacements extended beyond the onset transient. In the uppermost traces are examples of response to the static 400 μm step indentation, and in the remaining traces the temporally-modulated responses to vibrotactile stimuli, which were of 1s duration, applied to the skin surface, superimposed upon the background step indentation of 400 μm at frequencies of 5-100 Hz at a fixed vibration amplitude of 300 μm.

was also examined in view of the known capacity of the SA afferent fibres to signal the frequency parameter of vibrotactile stimuli (Gynther et al., 1992; Vickery et al., 1994).

Figure 3.16 illustrates the response of the two slowly adapting DSCT neurones to both static indentation (uppermost traces) and to cutaneous vibration at 5, 10, 20, 50 and 100 Hz at a fixed amplitude of 300 μm. In both cells the presence of a vibrotactile stimulus led to an enhanced discharge rate and a patterning of impulse activity. Although somewhat more evident in the first example (left hand panel A), both cells displayed a clustering of impulse activity that was sustained throughout the one-second vibration train at frequencies of ~5-20 Hz. At frequencies above ~20 Hz, the pattern of activity displayed neither a cycle-by-cycle grouping of impulse activity, nor a consistent capacity to sustain spike output throughout the 1 s vibration train.

The *amplitude-response* relations of Figures 3.17 A and B plot the mean spike output generated in response to vibrotactile stimuli at frequencies of 5-300 Hz, as a function of vibration amplitude. At low frequencies (5-20 Hz) of vibration, both cells displayed a coarsely-graded increase in spike output as vibration amplitude was increased. Over this frequency range (5-20 Hz), the mean response levels (~ 10-30 impulses/s) were comparable with those displayed by the larger population of *purely dynamically-sensitive* neurones. Furthermore, the response levels (~15-30 impulse/s) at higher frequencies (>20 Hz) were no higher than those observed in response to low vibration frequencies, suggesting that mean spike output alone could not provide a signal from which the intensity or frequency parameters of vibrotactile stimuli could be coded by these slowly adapting DSCT neurones.

In the final figure, Figure 3.18, the precision of impulse patterning was quantified by plotting the degree of phase coherence, as measured by the *Resultant*, as function of vibration amplitude at frequencies of 5, 10, 20, 50, 100, 200 and 300 Hz. Consistent with the responses of the purely dynamically-sensitive DSCT neurones the impulse patterning, or phaselocking of spike activity, for the two *SA neurones* tended to be somewhat higher at low vibration frequencies of 5-20 Hz, while at higher vibration frequencies (≥50 Hz), any spike output that did occur beyond the onset of vibration displayed little (R~0.25- 0.50) or no (R <0.25) phaselocking.

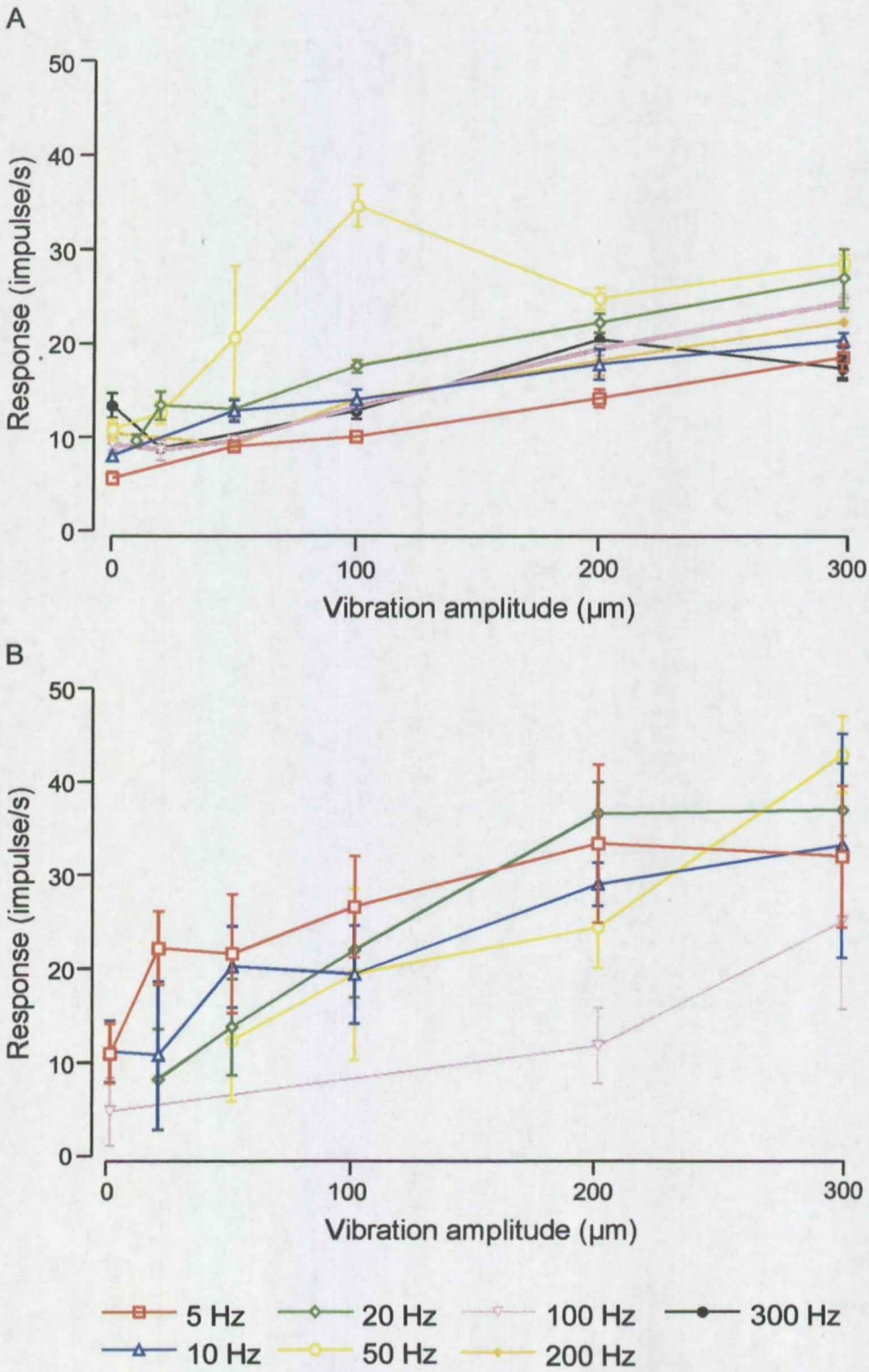

Figure 3-17. Stimulus-response relations quantifying the mean response level (impulse/s) of the two DSCT neurones displaying slowly adapting properties to vibrotactile stimuli at frequencies of 5-300 Hz as a function of vibration amplitude.

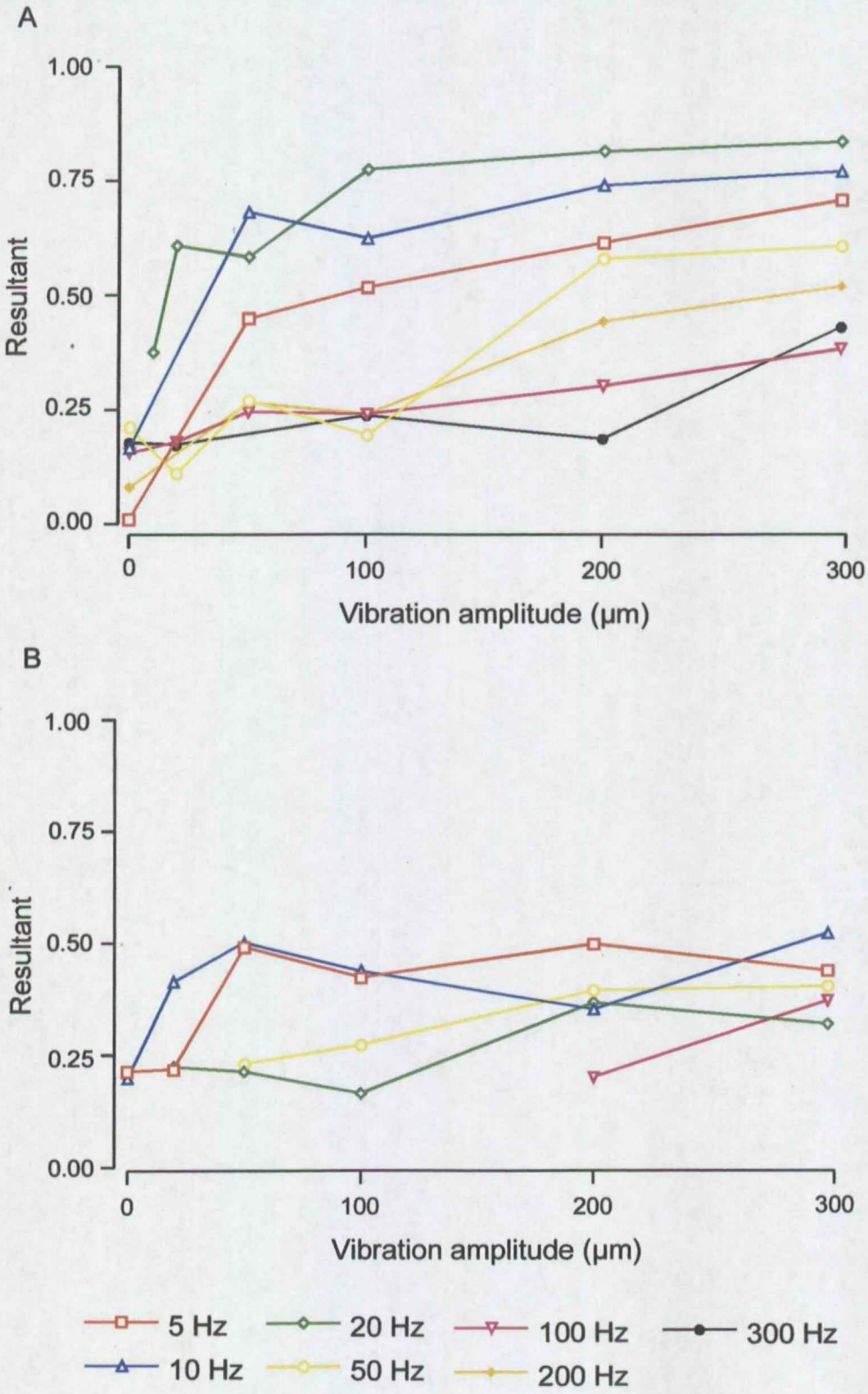

Figure 3-18. Plots of the *Resultant vectors* as a functions of vibration amplitudes for the two DSCT neurones (A and B) with slowly adapting response properties quantifying the degree of phase-locking at vibration frequencies 5-300 Hz.

Chapter 4

Discussion

4. Discussion

The present study has confirmed earlier studies, such as those of Mann (1971), in demonstrating that, in addition to the role in conveying kinaesthetic information from muscles and joints of the hindlimb, the DSCT also has a role in signalling tactile information from the skin to the cerebellum. However, the present study extends earlier observations on tactile signalling over the DSCT by quantifying the transmission characteristics of this system, thereby identifying the capacity of individual DSCT neurones to signal static and dynamic features of tactile stimuli. This quantification provided a base for better understanding the role of tactile information in the cerebellar regulation of movement and posture.

The capacity of tactile-sensitive DSCT neurones to signal information to the cerebellum about mechano-stimulatory events on the skin will be discussed in relation to the capacities of neurones in other ascending spinal pathways, in particular, those that may contribute to tactile sensory and perceptual phenomena through their projections to thalamic and cortical sensory processing areas. These include the dorsal column-medial lemniscal pathway, the spinocervical tract (SCT) and the spinothalamic tract (STT).

4.1 Antidromic identification of DSCT neurones

The criteria used in the present study to confirm a cerebellar projection of the neurones principally located in Clarke's column in the lumbar spinal cord (Curtis et al., 1958; Eide et al; 1969a; Kuno et al; 1973; Low et al., 1986) were more rigorous than those used in earlier studies (Mann, 1971; Kuno et al., 1973), as the *collision technique* was employed in the present study, whereas the earlier studies relied upon suggestive criteria, rather than the more certain *collision technique*. Previously used suggestive criteria were first, that the responses of Clarke's column neurones to electrical stimulation of the ipsilateral *inferior brachium* (Mann, 1971) or dorsolateral funiculus at the level of first thoracic (Th1) segment (Kuno et al. 1973), occurred at a fixed latency, designated the *central conduction time* (*T*), and second, that the response of the neurone could follow repetitive electrical stimulation from the *inferior brachium* at rates up to 200 stimuli/s (Mann, 1971).

Although all the neurones examined in the present study responded with fixed, short latency to electrical stimulation of the ipsilateral *restiform body*, the site close to

the *inferior brachium* used by Mann (1971), and were able to faithfully follow restiform body stimulation in excess of 300/s, the cerebellar projection of each neurone, and therefore its DSCT identity, was unequivocally confirmed only when a descending antidromic spike, elicited by electrical stimulation of the restiform body, was extinguished by an ascending orthodromic spike, initiated by a peripheral tap stimulus delivered to the skin (*antidromic collision procedure* outlined in *Methods* and illustrated in Fig. 2-2).

Because of the application in the present study of this more stringent criterion for verification of the DSCT status of recorded neurones (and, in part, the additional time required to apply the collision test) the sample size of DSCT neurones in the present study was rather small. Other procedures that limited the sample size were those for quantification of tactile responsiveness, and the testing for the responsiveness of DSCT neurones to gracile fasciculus (DC) stimulation, in order to determine whether the DSCT neurones were activated directly by collateral axons of cutaneous afferents that had a direct projection to gracile nucleus neurones. As approximately half the small sample of neurones tested in this way were activated trans-synaptically following gracile fasciculus stimulation it appears that a substantial proportion of tactile afferent fibres convey their inputs to distributed central targets, in this case conveying the same tactile input information to DSCT neurones for cerebellar input, presumably for the purposes of regulating movement and posture, and as well, to the gracile nucleus in the dorsal column-medial lemniscal pathway, and thence to the cerebral cortex for the purposes of sensation and perception.

4.2 Size and distribution of the receptive fields of individual DSCT neurones

Following the identification of DSCT neurones by means of the antidromic collision procedure, the receptive field (RF) for each neurone was carefully mapped using *von-Frey* hairs (see *Methods*). All the neurones in the sample had RFs in the hairy skin or on the margin between hairy and glabrous skin on the cat's hindlimb. The vast majority of DSCT neurones studied displayed a pure dynamic sensitivity and had receptive fields principally confined to the hairy skin. They were presumably activated by hair follicle afferent (HFA) fibres as these are the principal dynamically-sensitive afferent fibre class supplying hairy skin. This proportion of such DSCT neurones is rather similar to that in Mann's study (1971) where ~80 % of the tactile-sensitive DSCT

neurones were activated by movements of the hairs or by combined inputs from the hair follicle sources and from *touch domes*. However, in the earlier study, one cannot be certain that uncontrolled mechanical stimulation of the *touch domes* with hand-held stimulating probes did not activate neighbouring hair follicle receptors due to hand-associated postural tremor. It should be pointed out that the proportion of purely dynamically-sensitive DSCT neurones is somewhat higher than the proportion of purely dynamically-sensitive tactile afferents (~50%) identified in the population of hindlimb, hairy skin-related tactile afferent fibres studied by Burgess et al. (1968). However, whether this reflects a differential projection of dynamically and statically-sensitive afferents into the DSCT system, or other explanations is unclear. Another possible explanation could be that some input from slowly adapting (or statically-sensitive) tactile afferents to DSCT neurones may be transformed at the central synaptic site in Clarke's column leading to an effective 'differentiation of input' in a mathematical sense. This could be part of a central synaptic adaptation process that transforms the static response to a purely dynamic one.

Only a small sample of DSCT neurones in the present study (~5%) with receptive fields on the hairy skin and on the margin between hairy and glabrous skin, displayed slowly adapting (SA) response properties, a lower proportion than among the tactile-sensitive DSCT neurones in Mann's study (1971), possibly because of Mann's assessment of the static versus dynamic-sensitive DSCT neurones being based on activity evoked in the neurones by hand-held, uncontrolled forms of mechanical stimulation.

Although a small proportion (~10%) of neurones sampled in the present study had small, circumscribed RFs on the margin of hairy and glabrous skin around the hindlimb footpads, none of the cells sampled had RFs confined exclusively to the glabrous skin, which is in agreement with Mann's report (1971).

4.2.1. Receptive field characteristics for DSCT neurones and for neurones in the other tactile pathways

The receptive fields (RFs) on the hairy skin for DSCT neurones in the current study were, generally, oval-shaped with the long axis oriented proximal to distal on the limb. However, the individual fields varied in size and distribution on the hindlimb (Fig. 3-6). Those on the upper hindlimb, thigh and the hip tended to be larger in size, with

less distinctive boundaries than those on the distal hindlimb, ankle and foot. The latter were small (on average ~3 cm^2) and had RF borders that were well defined and distinguishable from the neighbouring areas of skin, an observation also reported by Mann (1971), indicating that RFs were smallest in those areas of the body where spatial information would perhaps be most crucial, in particular on the toes, foot and ankle. These observations about shape, size and distribution of the receptive fields in the current study are similar to the observations that have been reported in earlier studies about the receptive fields of tactile-sensitive neurones in relay nuclei of sensory pathways such as the dorsal column-medial lemniscal system (Burgess et al., 1968; Brown, 1968; Petit & Burgess, 1968), the post-synaptic dorsal column system (Brown & Fyffe, 1981), the spinocervical tract (Brown & Franz, 1969) and the spinothalamic tract in primates (Willis et al., 1974). Indeed, receptive fields of these neurones with their shape, size and distribution (small, circumscribed, oval-shaped RFs on the distal part of the limb and the larger RFs on the proximal part of the limb), very much resemble the RFs of DSCT neurones investigated in the present study. The regional differences in size of the RFs on the hindlimb as well as on the forelimb are perhaps related to the higher innervation density observed in the distal part of the limb compared to the upper part of the limb (Burgess et al., 1968).

4.3 Differences between tactile stimuli employed in the present study and those in other studies to investigate the capacity of DSCT neurones to signal tactile information

The controlled mechanical stimuli employed in present study, delivered to the point of maximal sensitivity within the neurones' RFs by a feedback-controlled mechanical stimulator (see *Methods*), permitted quantitative analysis of the tactile-induced responses elicited in the DSCT neurones. In contrast, electrical stimulation of peripheral sensory nerves (Eccles et al., 1961a; Oscarsson, 1965b; Kuno et al., 1973) or mechanical stimulation based upon hand-held stimulating probes (Mann, 1971; Kuno et al., 1973), do not permit any precise quantification of the capacity of DSCT neurones to signal tactile information.

4.4 Differences between DSCT neurones and neurones in other ascending spinal pathways in their capacities to signal tactile information

4.4.1 Signaling of information about static skin displacement

Only a small proportion (2 out of 17) of neurones examined quantitatively displayed a responsiveness to static indentation of the skin, involving a sustained response throughout a 1s-long static indentation stimulus (Fig. 3-7). The input to these two neurones presumably was derived from either Merkel receptors within *touch domes* or Ruffini endings that are also present in the hairy skin (Burgess et al., 1968; Iggo, 1968; Iggo & Muir, 1969; Chambers et al., 1972).

As earlier studies (Gynther et al., 1992; Vickery et al., 1992) showed that small diameter stimulating probes (≤1mm) precisely positioned over the individual *touch dome* (Burgess et al., 1968; Iggo & Muir, 1969) or at the point of maximal sensitivity within the circumscribed RFs associated with SA II afferent fibres arising from *Ruffini endings* were very effective in activating individual slowly adapting tactile sensory nerve fibres. The present study therefore used stimulating probes of small diameter (~1mm). This had the additional value of avoiding, as much as possible, the activation of neighbouring afferent fibres in or near the neurone's RF and led to more selective activation of individual DSCT neurones.

Contribution of tactile receptors in the skin to response properties of DSCT neurones

The two DSCT neurones sensitive to static skin displacements showed some differences in response to static indentation stimuli (Fig. 3-7 A and B). The response properties of each neurone and RF characteristics allow some speculation about the identity of the mechano-receptors providing the inputs to these neurones. One of the neurones (panel A in Fig. 3-7) displayed a sensitivity to tangential skin stretch and had regular spontaneous activity prior to the static indentation stimulus. It also showed an increase in discharge frequency which was in proportion to the amplitude of the indentation stimuli and maintained its almost regular discharge pattern throughout the entire static indentation stimulus, features which resemble the behaviour of SA II afferent fibres arising from *Ruffini endings* (Chambers et al., 1972; Gynther et al., 1992). Furthermore, this neurone displayed an ability to signal dynamic tactile information, for example, about vibrotactile stimuli (Fig. 3-16 A), which is an additional feature of SA II afferent fibres, as was shown in an earlier study (Gynther et

al., 1995).

The response properties of the other DSCT neurone that displayed a sensitivity to static skin indentation (panel B in Fig. 3-7) included, first, an irregular spontaneous activity; second, a marked sensitivity to dynamic components of the indentation stimulus (onset and offset of the stimulus); and third, a response during the indentation that took the form of irregular sporadic bursts. In addition, the neurone displayed an ability to signal vibrotactile information (Fig. 3-16 B). These response features suggest that the input may have come from mechanical receptors within the *touch domes* (*Merkel* receptors).

Comparison between the capacity of individual DSCT neurones and cuneate neurones to signal changes in the intensity of static skin indentation

The impulse traces of the DSCT neurones with slowly adapting response properties were shown in Fig. 3-7. In the absence of stimulation neurone A displayed a regular spontaneous activity of 5-10 impulses/s, while neurone B showed irregular low activity. Application of skin indentations in the range of 400-1500 μm for neurone A and 200-1000 μm for neurone B, elicited graded responses in the case of neurone A with almost regular inter-spike intervals throughout the entire 1 s long stimulus in particular at skin indentations over 600 μm. However, the spike output of neurone B to graded skin indentations remained irregular and occurred sporadically during the stimulus. The stimulus-response relations for these two DSCT neurones, shown in Fig. 3-8, reflect these limitations in the capacity of these neurones to reliably signal static tactile information. The stimulus-response relations were poorly graded in both cases with the response level of neuron A reaching a plateau when indentation amplitude exceeded 500 μm. Further increases in amplitude elicited no further increase in response for this neurone, although increases in the step indentation amplitude beyond 800 μm led to some further increment in the response of neurone B.

In contrast to the poorly graded stimulus-response relations for these DSCT neurones, cuneate neurones display a substantial capacity to signal in a sensitive and graded way static tactile information from both glabrous (Douglas et al., 1978) as well as from the hairy skin (Vickery et al., 1994; Gynther et al., 1995). They appear to have lower response thresholds (~100 μm for glabrous skin, Douglas et al., 1978 and between 100 and 200 μm for hairy skin, Gynther et al., 1995) to static skin indentation

than the two DSCT neurones which displayed response thresholds of ≥250 μm (Fig 3-8), though the small sample of static-sensitive DSCT neurones in the present study provides only tentative support for this contention.

The low response levels generated in DSCT neurones (~20 impulses/s at the plateau level of stimulus-response relations) by static indentation stimuli are in sharp contrast to the published response levels generated in cuneate neurones, even when the input to the cuneate neurones came selectively from single SA I or SA II afferent fibre (Vickery et al., 1994; Gynther et al., 1995). The latter studies of cuneate transmission characteristics were carried out in paired simultaneous recording studies, in which the responses were monitored, firstly, from individual SA I or SA II afferents in fine peripheral nerve fascicles and, secondly, with a microelectrode, from individual cuneate neurones that were the central targets of the selectively activated and monitored SA afferent fibre. This form of analysis has revealed that individual cuneate neurones may be driven at rates of up to ~50 impulses/s (Vickery et al., 1994; Gynther et al., 1995) in response to 1s long *static* skin displacement even when such stimuli activate the minimum possible sensory input, that is, a single tactile afferent fibre. With static stimuli that may recruit multiple SA afferent fibres (Douglas et al., 1978), cuneate neurones have been shown to respond at impulse rates of up to ~100 impulse/s in (see *Introduction*, Fig.1-8a and Douglas et al., 1978). These response levels for cuneate neurones, which are, of course, located in the major tactile sensory pathway to the cerebral cortex, are in marked contrast to the maximum levels of only ~20 impulses/s elicited in the responses of DSCT neurones by comparable static skin stimuli.

As DSCT neurones with slowly adapting response properties in the present study also displayed a sensitivity to the dynamic components (onset and offset) of the indentation stimuli, their capacity to signal information about dynamic skin disturbances, such as vibrotactile stimuli, was compared with the capacity of slowly adapting cuneate neurones to signal vibrotactile information (Vickery et al., 1994; Gynther et al., 1995). Earlier studies have also shown that response properties for SA afferent fibres from the hindlimb, projecting to the gracile nucleus (Vickery et al, 1992) are essentially the same as the properties of the forelimb SA fibres projecting to the cuneate nucleus (Vickery et al., 1994; Gynther et al., 1995), making the comparison between the capacity of cuneate neurones and DSCT neurones to signal vibrotactile information from forelimb and hindlimb possible. In contrast to the statically-sensitive

DSCT neurones that could signal vibrotactile information only over a very narrow frequency bandwidth of 5-10 Hz (Figs. 3-16 and 3-18), the statically-sensitive cuneate neurones showed an ability to accurately code vibrotactile information over a broad range of vibration frequencies from 5 Hz up to perhaps 200-400 Hz from either SA I afferents (Vickery et al., 1994) or SA II afferents (Gynther et al., 1995).

These differences in coding capacities between individual slowly adapting cuneate and DSCT neurones, suggest that the cerebral cortex receives, via the dorsal columns and the medial lemniscal pathway (Brown et al., 1974; Douglas et al., 1978; Vickery et al., 1994; Gynther et al., 1995), detailed and accurate tactile information about the intensity of static displacement or pressure imposed to the skin, for the purposes of perception and sensation, while the information directed to the cerebellum via the DSCT afferent pathway, and utilised principally in the regulation of movement and posture, appears to be less precise and accurate.

Comparison between DSCT and spinothalamic tract (STT) neurones and their capacity to signal static tactile information

The response properties of spinothalamic tract (STT) neurones in cats and monkeys (Dilly et al., 1968; Willis et al., 1974, 1975; Ferrington et al., 1986) indicate that statically-sensitive neurones display a marked sensitivity to the onset of static skin displacement stimuli, but are not able to maintain this responsiveness throughout the 0.5-1 s long, graded (from 0-1500 μm) static indentation stimuli, a response pattern which is very similar to that observed in the statically-sensitive DSCT neurones (Fig. 3-7). As a result of this pattern of behaviour, the stimulus-response curves of STT neurones display rather poorly-graded slopes, resembling those from the slowly adapting DSCT neurones observed in the present study.

Apart from limitations in the capacity of STT neurones to signal changes in the intensity of static skin indentation (Willis et al, 1975), earlier studies of individual STT neurones (Willis et al., 1974; Willis et al., 1975; Fox et al., 1980; Ferrington et al., 1986) have shown that they have limitations in their detection capacities (that is, they had rather high response thresholds to static skin indentation, with values of ~300 μm). Similar limitations in detection capacity (response threshold to static skin indentation ≥200 μm), and in coding capacity for signalling changes in the intensity of skin indentation, were observed for DSCT neurones in the present study. These limitations in

the capacity of STT and DSCT neurones to signal accurate static tactile information in contrast to the substantial capacity of cuneate neurones for signalling this information, tend to confirm the major role that the dorsal column-medial lemniscal pathway has in the transfer of tactile information, while the STT might have only a minor role in conveying innocuous tactile information to higher centres compared with its major role in the transfer of noxious tactile information to the somatosensory cortex.

4.4.2 Comparison of the capacities of dynamically-sensitive DSCT neurones and neurones in other ascending spinal pathways to signal dynamic tactile information

The vast majority of hairy skin-related DSCT neurones sampled displayed a tactile sensitivity that was confined to the dynamic components of skin indentation (e.g. onset and offset of the step indentation) and remained silent during the step indentation. As these neurones displayed a sensitivity to hair movements or light brushing over their receptive fields, it was assumed that their tactile inputs were derived from hair follicle afferent fibres (HFA). Although the DSCT neurones were tested over a broad vibrotactile frequency range (up to 300 Hz), as seen in the series of impulse recordings for one representative neurone in Fig. 3-9, they were limited in their capacity to signal dynamic tactile information to very low frequencies of such vibrotactile stimuli (5-10 Hz). At higher frequencies (≥50 Hz) their responses were typically confined to the onset of the vibration train (details in *Results*). Furthermore, even at the maximum amplitude used for the vibrotactile stimuli (300 μm), DSCT neurones were unable to maintain their responsiveness throughout the entire vibration train at frequencies above 5 Hz. Peristimulus and cycle histograms (Figs. 3-13, 3-14) constructed from responses of these neurones show that the responses were unable to follow vibration frequencies larger than ~5 Hz with any precise temporal pattern that faithfully reflected the periodicity of the vibrotactile stimuli.

Differences between DSCT neurones and cuneate neurones in their capacities to signal vibrotactile information

The response behaviour and capacity of purely dynamically-sensitive DSCT neurones for carrying information about vibrotactile events was dramatically different from that of cuneate neurones within the principal tactile sensory pathway of the

nervous system. An earlier study on the cuneate processing of tactile information from the glabrous skin (Douglas et al., 1978) showed that dynamically-sensitive neurones were capable of signalling many of the features of vibrotactile stimuli over a broad range of frequencies, from <10 Hz to >400 Hz. Over the lower segment of this range (5 up to ~80 Hz) the signalling depended upon cuneate neurones that were activated principally by rapidly adapting (RA) afferent fibres thought to arise from intradermal, encapsulated receptors (*Krauze corpuscles* in cats, but *Meissner corpuscles* in primates) (Burgess & Perl, 1973). Over the higher range of frequencies ~80-400 Hz the cuneate neurones responsible for vibrotactile signalling appeared to be driven principally by *Pacinian corpuscle* inputs (Douglas et al., 1978).

The marked differences in the capacity to accurately signal different features of vibrotactile stimuli between DSCT neurones and cuneate neurones that receive tactile inputs from glabrous skin are apparent in stimulus-response relations constructed at different vibration frequencies, which rose steeply in cuneate neurones at most vibration frequencies, reaching a plateau at vibration amplitudes of 100-200μm. In contrast, DSCT neurones displayed poorly-graded stimulus-response relations as a function of graded increments in vibration amplitude, and were limited in their responsiveness to the low frequencies (<50 Hz). Apart from the poor capacity of DSCT neurones to signal changes in intensity of vibrotactile stimuli in comparison with cuneate neurones, their detection capacity for the vibrotactile stimuli appears also to be poorer (thresholds of ~200 μm) than that of cuneate neurones which displayed high detection capacity for the vibrotactile stimuli applied to the glabrous skin. The latter have threshold values of <10 μm for the neurone class (cuneate RA-neurones; Douglas et al. 1978) sensitive to the lower frequency range of the vibrotactile stimuli, and as low as <1-2 μm for the neurones with inputs derived from the Pacinian-associated afferent fibres (Douglas et al., 1978).

Peristimulus time histograms (PSTH) and cycle histograms (CH) constructed from responses of cuneate neurones displayed their capacity to reliably signal temporal tactile information at vibration frequencies up to 50 Hz for the RA neurones (with inputs from Krause corpuscle-associated afferents), and up to 300 Hz for the Pacinian-associated neurones, in contrast to DSCT neurones and their capacity to signal temporally accurate information which was limited to the narrow frequency range of 5-10 Hz.

The differences between cuneate and DSCT neurones in vibrotactile signalling apply also to cuneate neurones associated with hairy skin inputs. These cuneate neurones are able to signal vibrotactile information over the broad frequency range (in excess of 100 Hz; Robinson et al., 2001), with a remarkably high transmission security between individual hair follicle afferent (HFA) fibres and their target cuneate neurones (Zachariah et al, 2001). In contrast, the capacity of DSCT neurones for signalling vibrotactile information from the hairy skin is limited to a very narrow frequency bandwidth up to 5-10 Hz. Furthermore, cuneate neurones displayed a low response threshold, the lowest (5-25 μm) in the frequency range from 20-50 Hz (Robinson et al., 2001) with slightly higher values at 100 Hz. With sufficient intensity of the vibration (up to 200 μm), the cuneate neurones displayed a responsiveness extending over a broad frequency range of vibrotactile stimuli (up to 300 Hz). This might be due to the recruitment extending (at high frequencies) from HFA fibres to Pacinian afferent inputs from remote sources, such as the interosseous membranes, tendons, joints or the margins of the foot pads (Perkins et al., 2001; Robinson et al., 2001). For cuneate neurones driven by hairy skin vibrotactile inputs the stimulus-response relations were graded so that individual cuneate neurones can contribute a sensitive signal of the changing intensity of vibrotactile disturbances in the hairy skin (see *Introduction* Fig. 1-8b and Robinson et al., 2001).

As the stimulus-response relations of DSCT neurones (Fig. 3-11) were poorly graded even at 5 and 10 Hz, increases in vibration amplitude did not markedly improve the response from that at the threshold level (20-50 μm). Furthermore, at frequencies of ~50 Hz or more, changes in the intensity of the vibrotactile stimuli had even less impact on the response as responsiveness was confined essentially to the onset of the vibration train. The response level at frequencies 50 and 100 Hz (Fig. 3-11), despite increments in vibration amplitude, remained little different from that at the threshold level (20-50 μm) revealing the poor capacity of DSCT neurones to detect and signal changes in the intensity of vibrotactile stimuli, especially at frequencies above 10 Hz.

Peristimulus time histograms and cycle histograms constructed from the responses of hairy-skin related cuneate neurones have revealed a tight grouping and phaselocking of responses over a much broader range of vibrotactile frequencies, from 5 to >100 Hz (recent observations and Perkins et al., 2001), in comparison with DSCT neurones which displayed tight phaselocking of the response only at frequencies of ≤5

Hz, underlining the marked difference from the cuneate neurones with their potent ability to code reliably for the intensity and periodicity parameters of vibrotactile stimuli over a broad range of amplitudes and frequencies. Thus, individual DSCT neurones activated from the hairy skin had very limited capacities to signal information about vibrotactile stimuli, in either the intensity or frequency parameter.

Comparison of the processing and coding of tactile information directed to sensory cortex and to the cerebellum

The quantitative comparison of the response characteristics and coding capacities of DSCT neurones and cuneate neurones indicates that there are very substantial differences. Cuneate neurones that convey tactile information via the thalamus to the somatosensory cortical areas I and II (SI and SII) provide a much more accurate and faithful signal of the intensity as well as the frequency or periodicity features of vibrotactile stimuli than do DSCT neurones in their tactile signalling to the cerebellum. As the tactile information conveyed by DSCT neurones to the cerebellum is presumably utilised for the regulation of movements and posture it might be argued that these tasks may require less accurate information about cutaneous tactile events than is the case for tactile sensory and perceptual experience. Indeed, the dominance of afferent information that the cerebellum receives, via the DSCT, from muscles and joints of the hindlimb (Oscarsson, 1965; Mann, 1971; Kuno et al., 1973) highlights the principal role that these 'deep' sources of information may have in the regulation of movement and posture. However, additional tactile information necessary for cerebellar regulation of movement and posture may, perhaps, be provided by other ascending spinal pathways with terminal projections to the cerebellum, such as the *dorsolateral spino-olivocerebellar pathway* (DLF-SOCP), which contain cutaneous afferent fibres (see *Introduction* Table 1; Oscarsson 1973) or multi-synaptic afferent pathways designated by Oscarsson (1973) as the ascending flexor reflex afferent (FRA) pathways which contain high and low threshold cutaneous afferents, even Oscarsson argued their value as channels for specific and accurate tactile information (Oscarsson, 1973).

Comparison between DSCT and spinocervical tract (SCT) neurones in processing dynamic tactile information

The spinocervical tract (SCT) in cats originates from neurones located in the

dorsal horn in the lumbar cord (Brown et al., 1976; Wilson et al., 1986), ascends the spinal cord occupying the dorsal part of the lateral funiculus and projects to the lateral cervical nucleus (Taub & Bishop, 1965), and then via the medial lemniscus and thalamus to the somatosensory cortex. Earlier studies (Brown & Franz, 1969; Brown, 1973) revealed the types of mechanoreceptors involved in the activation of SCT neurones and the tactile information transferred by this tract from the hindlimb periphery to the lateral cervical nucleus (see *Introduction*). As these studies reported that SCT neurones were almost exclusively activated by dynamically-sensitive afferent fibres from the hairy skin, the study of the SCT conducted in our laboratory (Mahns et al., 2001) investigated the capacity of SCT neurones to signal vibrotactile information from this source. These SCT neurones displayed a rather poor responsiveness to vibrotactile stimulation, limited to a narrow bandwidth at low vibration frequencies, up to ~5-10 Hz. This behaviour is similar to that observed in DSCT neurones in the present study. When the frequency of the vibrotactile stimuli exceeded 10 Hz the response of SCT neurones was typically confined to the onset of the vibration train (see *Introduction* Fig. 1-9a and Mahns et al., 2001), as we have also observed for the DSCT neurones (Fig 3-9). Indeed, in both groups of the neurones, stimulus-response relations were poorly graded at low frequencies (up to 10 Hz) in association with increases in vibration amplitude, while stimulus-response relations above 10 Hz became almost flat (see Fig. 3-10; *Introduction* Fig. 1-9b and Mahns et al., 2001). The increases in vibration amplitude led to only a very limited enhancement of SCT responsiveness above the threshold response levels in the frequency range between 10 and 30 Hz (see Fig. 1-9a and Mahns et al., 2001). At frequencies above 30-50 Hz, response level remained essentially independent of amplitude as the response was confined to the onset of the vibration train, despite the increases in vibration intensity (Mahns et al, 2001). This behaviour was therefore almost identical to that of DSCT neurones.

Further similarity between DSCT and SCT neurones is observed in the limited capacity of both groups of neurones to sustain impulse activity in a cycle-by-cycle manner that reflects the periodicity of the vibratory stimuli throughout periods of vibrotactile stimulation lasting 1s as was used in these studies. Peristimulus time histograms revealed that SCT neurones were able to maintain their cycle-by-cycle responsiveness throughout the whole vibration train only at frequencies up to ~5 Hz. This response severely declined therefore at 10 Hz, while at frequencies above 10 Hz it

was confined to the first cycle of the vibration train, behaviour that was typical of DSCT neurones. The cycle histograms constructed from SCT neurone responses had tight phaselocking of the response at only ≤5 Hz (Mahns et al., 2001), and were therefore very similar to the cycle histograms of DSCT neurones.

This similar, poor capacity of DSCT and SCT neurones to signal reliably changes in intensity as well as the periodicity parameter of dynamic tactile stimuli, is in marked contrast with the considerable capacity of cuneate neurones to sustain high levels of response and precise temporal patterning in their responses to vibrotactile stimuli over a broad frequency bandwidth from 5Hz to > 100 Hz even at low vibration intensities (Douglas et al., 1978; Perkins et al., 2001; Robinson et al., 2001; Zachariah et al., 2001). As both pathways, the DSCT and the SCT, originate from cells located in the dorsal horn in the lumbar spinal cord, the limited response behaviour of both systems may reflect potent inhibitory processes operating rather generally in the dorsal horn (Hongo et al., 1968; Brown & Franz, 1969; Brown, Kirk & Martin, 1973). This hypothesis has been supported first, by the presence of a similar frequency-dependent attenuation of both SCT and DSCT responsiveness to repetitive antidromic and/or trans-synaptic activation from the upper cervical spinal cord or from the terminal region of the gracile fasciculus (Mahns et al., 2002). Second, some earlier studies (Taub, 1964; Wall, 1967; Fetz, 1968; Brown & Franz, 1969) have demonstrated that transmission through the SCT is under descending inhibitory control from several regions of the brain. As other studies (Taub, 1964; Hongo et al., 1968; Brown & Franz, 1969) have shown that natural stimulation of areas of the skin outside the neurones' excitatory receptive fields cause an attenuation in the SCT neurones' responsiveness, this provides further evidence for segmental inhibition operating within the dorsal horn. However, as afferent inhibition exists also within the cuneate and gracile nuclei the inhibitory mechanisms operating within each site, the dorsal horn on the one hand, and dorsal column nuclei, on the other, may well be different. The enhanced responsiveness of SCT neurones to vibrotactile stimulation produced by the intravenous administration of bicuculline (Sahai et al., 2002), a potent gamma aminobutyric acid (GABA) antagonist suggests that GABA may have a mediating role in inhibitory mechanisms within the dorsal horn.

Comparison between capacities of dynamically-sensitive DSCT and STT neurones to signal vibrotactile information

Analysis of the responses of STT neurones in primates (Ferrington et al., 1987) to controlled mechanical stimuli has revealed that the capacity of these neurones to signal vibrotactile information is limited to low vibrotactile frequencies (in the range between 5 and 30 Hz; see *Introduction* Fig. 1-10b and Ferrington et al., 1987). This narrow responsiveness profile very much resembles that of DSCT neurones (Fig. 3-9). Furthermore, peristimulus time histograms and cycle histograms constructed from STT neurone responses have revealed a faithful reflection of features of the periodic vibrotactile stimuli and a high degree of phaselocking *only* at low frequencies (~5-10 Hz), again resembling the DSCT neurones of the present study (Fig. 3-13). These limitations in the capacity of STT neurones to reliably signal the frequency parameters of the vibrotactile stimuli were revealed quantitatively in the *percentage entrainment* values which reached their highest levels at frequencies of only 5-10 Hz (see Ferrington et al., 1987).

The marked differences in coding capacity for tactile information between cuneate and gracile (DCN) neurones, on the one hand, and DSCT, SCT and STT neurones, on the other, confirms the view that the dorsal column-medial lemniscal system is the major ascending spinal pathway conveying tactile sensory information to the somatosensory cortex. In contrast, the tactile information traversing other ascending spinal pathways that are organised in parallel with the dorsal column system, including the SCT and the STT (directed to the somatosensory cortex) and the DSCT (directed to the cerebellum) appears to be much poorer in conveying specific details about the intensity, periodicity or duration of the tactile stimuli. Thus individual neurones of these ascending pathways seem able to act as rather coarse 'tactile event detectors', without any of the refined capacity displayed by DCN neurones, to signal specific details of the various parameters of the tactile events.

4.5 Relation of electro-physiological observations in DSCT neurones to deficits associated with lesions of spinal tracts

Spinal lesion studies in primates (Vierck, 1973,1977; Wall & Noordenbos, 1977; Vierck et al., 1983,1985) have been undertaken in an effort to provide further evidence about the role of tactile information conveyed by different ascending spinal pathways in

both sensory perception and motor regulation. Although selective lesions of the spinal cord have produced different sensory and perceptual deficits, expressed in the inability of trained animals to perform tactile detection and/or discrimination tasks, it is difficult with these methods to be sufficiently selective for lesioning a particular nerve tract to provide unequivocal evidence for the role of that pathway in sensation or motor regulation. Therefore, these approaches are of principal use in providing rather tentative proposals for the role that individual spinal pathways may have in the regulation of movements and posture on the one hand, or in perception and sensation on the other (Vierck, 1973,1977; Wall & Noordenbos, 1977; Vierck et al., 1983,1985).

When lesions are made to both the dorsal columns (DC) and the dorsolateral columns (DLC including the DSCT) in the high cervical segments of the spinal cord in primates they produced marked sensory and motor deficits (Gilman & Denny-Brown, 1966; Vierck, 1977; Vierck et al., 1983, 1985). When the lesion is confined to the DC, leaving intact the dorsolateral columns, the motor disturbances are much less severe in the hindlimb, which may directly implicate the DSCT in motor regulation. However, it must be remembered that dorsolateral column lesions include damage to ascending sensory pathways, in the form of the SCT, in addition to the damage to the DSCT itself. Thus, it is difficult to selectively identify the role of the DSCT in motor regulation based upon such studies.

The limitations and potential ambiguities of interpretation inherent in lesion studies (Gilman & Denny-Brown, 1966; Vierck et al., 1983, 1985) emphasize the importance of careful electro-physiological studies in identifying the functional roles of different spinal pathways such as the DSCT. While earlier studies of this kind on the DSCT (Oscarsson et al., Kuno et al., 1973; Mann, 1971) have provided clear evidence of a contribution of tactile information, in addition to deep inputs, in the peripheral feed-back to the cerebellum for its role in motor regulation, the present study suggest that the nature of tactile information provided is rather cruder and less detailed and precise than that conveyed over the principal ascending tactile pathway (the dorsal column medial-lemniscal pathway) for tactile sensation and perception.

Chapter 5

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ACKNOWLEDGMENTS

At the end I would like to express my deep gratitude and appreciation to all that people whose support and assistance has helped me to complete my postgraduate studies. It was a privilege to work with a group of people who were not only colleagues, but also good friends.

My supervisor, Prof. Mark Rowe with his experience, has been a source of unstinting support and encouragement throughout my research as well as in the interpretation and presentation of the results. His contributions to the experimental design and his thorough approach to critical evaluation of the thesis were especially appreciated.

Dr David Mahns, my co-supervisor, has worked with me on many of the experiments reported in this thesis. The success of the experimental work depended in large part on his willingness to share his experience and expertise in electrophysiological recording techniques and data analysis software used in my research. His help in interpretation of the results and the technical part of the writing was exceptional.

Other present and former members of the laboratory whom I wish to thank for their advice and generous help include Dr Vineet Sahai, Nicholas Perkins, Lisa Robinson, Debbie Sarno and Dr Jason Ivanusic. My gratitude goes to Christine Riordan for her expert technical assistance and patience throughout the time of my M.Sc. studies.

I wish to express my appreciation, also, to the expert staff Rudi Bomba, Ted Crawford, Philip Crawford and Colin Woods in the Mechanical and Electronics Workshops. Without their technical support this or any other project in the School of Medical Sciences could not be completed.

Finally, my deepest gratitude and admiration is reserved for my family, my wife Izetta and daughter Dunya, for their loving support and encouragement throughout this journey. It will be a lifetime's work to repay the debt I owe them.

Severin Rakic

September, 2004

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