Classification, Oscillatory and Alternating Oscillatory Firing of α_1 (FF) and α_2 -Motoneurons (FR) in Patients with Spinal Cord Lesion

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Abstract. Single-nerve fibre action potentials (APs) were recorded extracellularly from sacral nerve roots of people with spinal cord lesion (patients with paraplegia) Single-fibre APs of certain fibres were identified by the conduction velocity and the AP waveform, and simultaneous impulse patterns were extracted from the summed impulse traffic and analysed with respect to spacio-temporal relationships

The velocity values of components of compound APs, induced by electrical nerve root stimulation or electrical intravesical stimulation, were similar to the group conduction velocity values obtained from single-nerve fibre APs of natural impulse traffic

When changing the root temperature in one case from 32°C to 35 5°C, the group conduction velocities changed in the following way secondary muscle spindle afferents (SP2) 40m/s (32°C) to 50 m/s (35 5°C), bladder stretch afferents (S1) 31 3 to 40 m/s, bladder tension afferents (ST) 25 to 33 8 m/s, mucosal afferents (M) 12 5 to 13 8 m/s, α_1 -, α_2-motoneurons 40 to 50 m/s, α_3 33 to 40 m/s The group conduction velocities showed different temperature dependence apart from SP2 fibres and α_2-motoneurons, which were therefore used for calibration

The distance between two Pacinian corpuscle (PC) receptors in a sacral dermatome of one paraplegic patient was calculated to be approximately 20 mm A similar distance between PC receptors was found in a brain-dead individual Receptor densities seem therefore to remain unchanged following spinal cord lesion

Motoneurons fired irregularly repeatedly with impulse trains In paraplegics the oscillation periods and the interspike intervals of the impulse trains varied much more than observed for brain-dead and normal individuals Motoneurons could therefore not always be identified by their pattern of oscillatory firing

Alternating long and short oscillation periods (T) could be measured in an oscillatory firing α_1 (T = 125 ms) and α_2-motoneuron (T = 150 ms) In both cases the average difference between the alternating oscillation periods was 5 ms

Tremor, alternating long and short oscillation periods, cellular oscillator properties, and recurrent excitation and inhibition are discussed with respect to the oscillator theory of the

functioning of the human central nervous system. Mathematical predictions from populations of interacting biological oscillators are compared to measurements on neuronal network data.

The pathologic activation of two-joint muscles following hemiplegia, cerebral palsy and partial spinal cord lesion is discussed with respect to the two coupling phases of the premotor spinal oscillator cycle per somatic nervous system.

Key-words: Paraplegia – Spinal canal anatomy – Nerve fibres – Classification scheme – Single-fibre action potential – Compound action potential – Conduction velocity – Spinal oscillator – Alternating oscillatory firing

Introduction

Currently, research in human neurophysiology and clinical neurophysiology is aimed at developing an effective treatment for paraplegics (= para, patients with spinal cord lesions) [68,69,74-77,94] to improve micturition, defecation [68,69,88-90] and locomotion [90] in particular.

This new development started from scratch by first clarifying the principal aspects of anatomy [68,69,74-77] and developing, in 8 years' time, a new basic electrophysiological recording technique suitable for use in humans, the simultaneous recording of single afferent and efferent nerve fibre extracellular action potentials (APs) with 2 pairs of wire electrodes from undissected nerve roots; this technique can be used for intra-operative diagnosis and research [70,72,77,88].

Further developments in morphometry of nerves (classification of fibre diameters into 4 ranges of myelin sheath thickness (Fig.6)) made it possible to simultaneously characterize nerve fibre groups by group conduction velocities and group nerve fibre diameters (Fig.1) [72,78,88]. In this way, an exact classification scheme could be constructed for the human peripheral nervous system (Fig.2). The scheme represents a solid basis for the classification and identification of nerve fibre groups in the human peripheral nervous system (PNS) and for the analysis of central nervous system (CNS) functions under physiologic and pathophysiologic conditions [88], even though it is incomplete and so far only holds for nerve fibre diameters larger than approximately 3.5 μm.

Another basic electrophysiological method for use in humans, the recording with tungsten electrodes of single-fibre extracellular APs [45,99], made it possible to record impulse patterns of single nerve fibres; the method however rests on the classification schemes of animal peripheral nerve fibres, which do not apply to humans.

The investigation of time-dependent conduction velocity distributions of afferent and efferent fibres allowed an analysis of activity level changes within nerve fibre groups [81,82]. Since it is further possible to distinguish APs between afferent and efferent nerve fibres and to extract from the summed activity of a fibre bunch the discharge patterns of single fibres, it is possible to analyze receptor properties of skin afferents, primary and se-

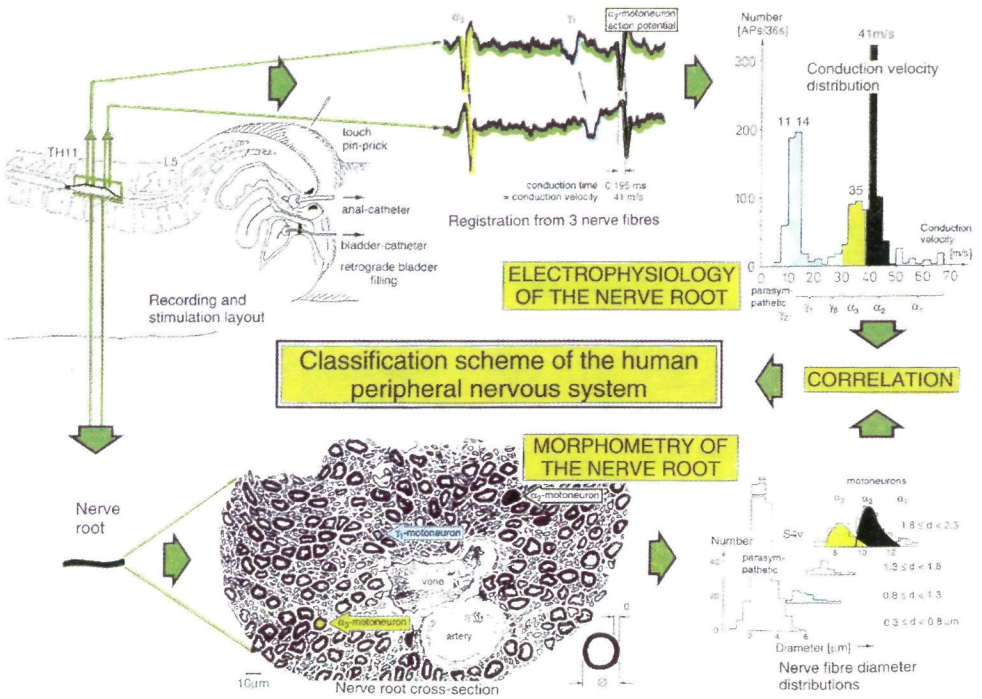

Figure 1. Schematic layout of the classification scheme for the human peripheral nervous system. By recording with two pairs of platinum wire electrodes from a nerve root containing approx. 500 myelinated nerve fibres, a recording is obtained in which 3 action potentials (APs) from 3 motoneurons (main AP phase downwards) can be seen. By measuring the conduction times and with the known electrode pair distance (10 mm) a conduction velocity distribution histogram was constructed in which the nerve fibre groups have been characterized by ranges of conduction velocity values and peaks in asymmetrical distributions. After recording, the root was removed, fixated, embedded and stained, cross-sections were prepared for light microscopy, and used to measure the mean diameter and the myelin sheath thickness (d). Distributions of nerve fibre diameters were constructed for four different ranges of myelin sheath thickness. Nerve fibre groups were characterized by the peak values of asymmetrical distributions. By correlating the peak values of the velocity distributions with those of the diameter distributions obtained from the same root, a classification scheme was constructed of the human peripheral nervous system. Brain-dead human individual HT6.

condary muscle spindle afferents and urinary bladder afferents [77,85,88,91] and to analyze parasympathetic and somatic functions of the human CNS for continence and movements. An insight into the CNS functions can be obtained from studying simultaneous impulse patterns of single afferent and efferent fibres and the phase relations between the impulses of afferents and efferents [83-85,87], following natural stimulation. Since human continence functions are mainly located in S3 and S4 segments, and segmental functions seem to overlap in their representation in the roots, as indicated by dermatome overlap, especially continence functions are ideal for analysis. An extension of the recording method to several roots from different segments will bring further information. With the discovery of the human spi-

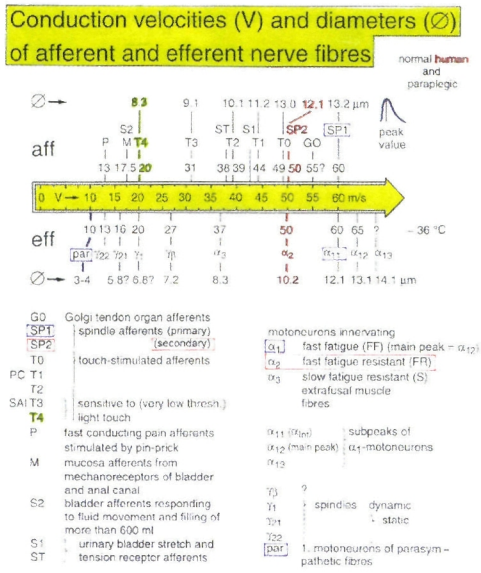

Figure 2. Conduction velocities (V) and nerve fibre diameters (∅) of afferent and efferent nerve fibre groups in normal individuals and in patients with a traumatic spinal cord lesion suffered 0.5 to 6 years ago. The splitting of the α_1-motoneurons into the 3 subgroups, α_{11}, α_{12}, α_{13}, has not yet been confirmed.

nal oscillators [73], CNS functions can be investigated based on the behavior of spinal oscillators. Spinal oscillators can be divided into premotor spinal oscillators, of which the motoneuron is a part, and of propriospinal oscillators [94] of which the motoneuron is not a part. If not specified further, herein we shall speak of premotor spinal oscillators, since rhythmic activity was recorded from motoneuron axons and it seems that the motoneurons are a part of the rhythm generating subnetwork [83]. It has been argued by animal physiologists that it is not surprising that there are spinal and supraspinal loops exhibiting spiking activity. But to improve the quality of life of patients, it is relevant what we can measure and identify in humans. It would mean a big step forward in medicine if neurophysiologists could also cover the field of human neurophysiology by measuring - with the same method - on animals and humans, and prove which animal data also hold for humans, to find out what is fact and what is fiction. The authors have successfully recorded single-nerve fibre action potentials with the same equipment from frog, rat, cat, dog and human nerves and nerve roots. By replacing the wire electrodes by EMG surface electrodes, also electromyographic activity can be recorded with the same equipment and single motor unit activity can be compared with single motoneuron firing patterns [94].

Even though the structure and the function of the neuronal network of the human CNS is far from being even partly understood, progress in the understanding of spinal cord disorder is possible by making use of the premotor spinal oscillators [73,83-85,87,90,94]. The spinal oscillators are functional units which organize themselves in preformated neuronal subnetworks of the CNS by natural adequate impulse patterns of the particular afferents and supraspinal centres (brain stem, motor and sensory cortex, cerebellum, ..). In the isolated

spinal cord, only an afferent input from the periphery induces self-organization of the oscillators. These oscillators are characterized by their rhythm of firing, namely by the frequency of repeated firing with impulse trains and the interspike intervals of the impulse train (Fig.3). If the afferent input to the neuronal network is too low to fire oscillatory or if the neurons in the circuitry are inhibited, the motoneurons are integrated in another organization form of the network. Then, the motoneurons fire in the occasional firing mode [79,81,82] repeatedly every 3 seconds approximately, or they fire transiently oscillatory [73,91].

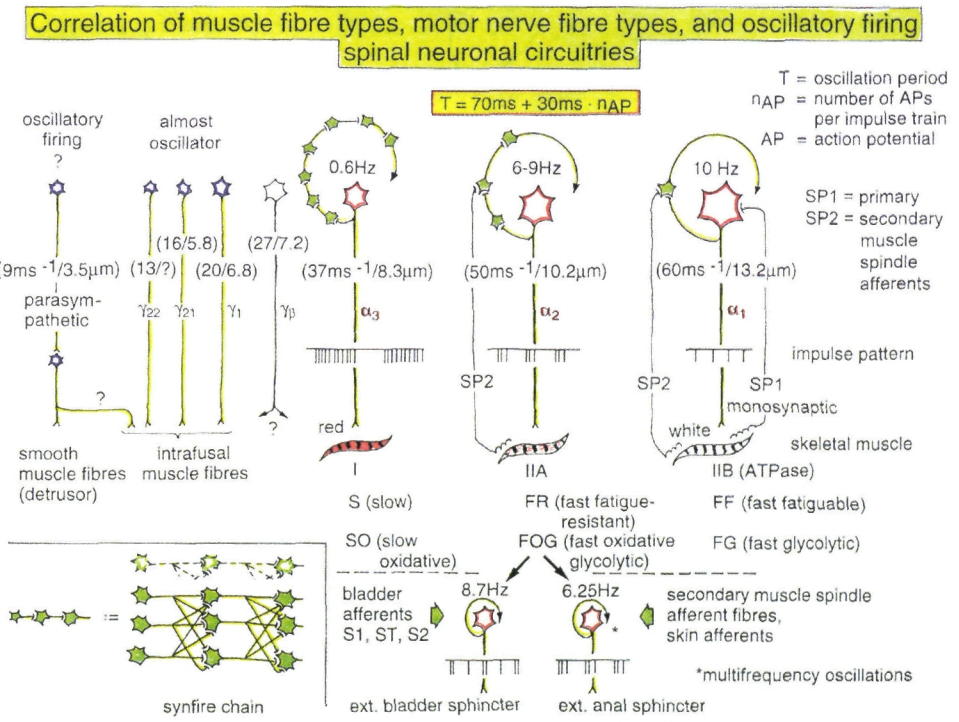

Figure 3. Correlation of muscle fibre types, motor nerve fibre types, and oscillatory firing spinal neuronal networks, based on histochemical, morphological and physiological properties. This Figure provides a simplified correlation between muscle fibre, motoneuron and sacral premotor oscillator types. No additional subtypes have been included. The existence of α_1-motoneuron (FF) oscillators firing at approx. 10 Hz had been predicted [83], and they have been identified in this work [91]. α, motoneuron; γ_1; γ_2, dynamic and static fusimotors; parasympathetic, parasympathetic preganglionic motoneuron; S1, ST, S2, stretch, tension and flow receptor afferents. α_2-oscillators, innervating the striated ext. anal sphincter, show multifrequency oscillations (e.g., f = 5.25, 6.25, 7.7 Hz) [83], as predicted mathematically (page 156 of [60]). The dashed line neurons in the synfire chain (left lower part) indicate the functional fringe of subthreshold excitation of the synfire chain.

Fig. 3 summarizes what has been known so far about these premotor spinal oscillators which, under physiologic conditions, fire rhythmically with impulse trains [73,83-85,87]. α_1 (FF), α_2 (FR) and α_3-motoneurons (S), characterized by group conduction velocity and group nerve fibre diameter, are integrated in their own neuronal network to fire oscillatory for high activation by their respective afferent input, and to innervate their respective muscle fibre type. In man, there mainly are three organization forms of somatic neuronal networks in the lower sacral spinal cord, which drive three kinds of striated muscle fibres (Fig.3). E.g., the α_2-motoneurons which subserve continence functions, are integrated in neuronal network organization forms firing at 6 to 9 Hz; they innervate fast fatigue-resistant muscle fibres (FR) of histochemical type IIA which are fast oxidative glycolytic (FOG) (for Refs. see [90]). The α_2-motoneurons innervating the external (striated) bladder and the anal sphincters are mainly specifically driven by oscillators which fire with 1 to 2 APs every 110 ms (8.7 Hz) and with 3 APs every 160 ms (6.25 Hz) respectively (Fig.3). The neuronal network driving the external anal sphincter is channelled to fire oscillatory upon the activity of secondary muscle spindle afferent fibres (probably innervating the spindles of the anal sphincter) and skin and mucosal afferents innervating the anal canal. The oscillation period (T) of the premotor spinal oscillators is roughly related to the number of APs per impulse train (n_{AP}), and this relationship can be expressed as $T = 70\ ms + 30\ ms \cdot n_{AP}$. Further properties of the spinal oscillators have been discussed elsewhere [73,83]. So far, preganglionic parasympathetic neurons could not be observed to fire oscillatory. Fusimotors seemed not to fire oscillatory under physiologic conditions [85] but seemed to fire oscillatory following spinal cord injury [90,93].

Since premotor spinal oscillators are essential organization forms of the neuronal network of the spinal cord (as their functions can be measured following complete spinal cord lesion), they can be expected to change their properties when the neuronal network of the spinal cord becomes damaged or when there is some pathology in its functioning. Early measurements of the dysfunction of spinal oscillators were used to study principal structures of their neuronal network [83]. In man, intrinsic oscillatory firing properties of individual cells have only been found in the heart so far. The quick switching on and off of oscillatory firing of motoneurons down to one oscillation period cannot be explained by internal bursters.

In this paper functions and dysfunctions of premotor spinal oscillators following spinal cord lesion will be further considered. It seems as if premotor spinal oscillators, subserving continence functions, can consist of two halves in some similarity to the lamprey locomotor system [30,31]. Since however premotor spinal oscillators of leg muscles can change from alternating to symmetrical oscillatory firing [94], which even seems to correlate with phase changes in the synchronization with other spinal oscillators [94], the alternating oscillatory firing has also been attributed to changes in the coupling states of spinal oscillators [94]. More generally therefore, alternating oscillatory firing oscillators may indicate, a.o., coupling of non-equal sub-oscillators, reciprocal inhibition of half-centre oscillators or mutual inhibition of oscillators driving antagonistic muscles.

In previous reports [88-90] of measurements on the same patients, it was shown that the

classification scheme of the human peripheral nervous system does not change 0.5 to 6 years following spinal cord lesion [88]. Data related to dysfunctions of the urinary bladder after spinal cord injury seem to indicate that dyssynergia of the urinary bladder is due to a false organization of the neuronal networks in the sacral micturition centre. The detrusor, driven by the parasympathetic neuronal network, is activated at the same time as is the external bladder sphincter (dyssynergia of the bladder), driven by the somatic neuronal networks. In healthy individuals the external bladder sphincter is inhibited upon the activation of the detrusor. Dyssynergia of the urinary bladder could be explained by a threefold disorganization of the spinal neuronal networks, if one splits in a first approximation spinal networks into interlacing somatic and parasympathetic networks: (1) The somatic neuronal networks organize themselves pathophysiologically, which was judged from the dysfunction of oscillatory firing α-motoneurons. (2) Also, the parasympathetic neuronal networks organize themselves in a false way, as revealed by the detrusor not receiving sustained activation from preganglionic parasympathetic motoneurons. (3) The interaction between the somatic and the parasympathetic neuronal networks changes, as judged from the discoordination of the detrusor and the external bladder sphincter (dyssynergia of the bladder). The idea was put forward that the parasympathetic neuronal network is unable to fire continuously oscillatory any more; the transiently oscillatory firing in paraplegics with a spastic bladder gave only rise to undulating or spot-like activation of the bladder smooth muscle. The continence problem encountered with paraplegic patients with a „spastic" bladder (overactive bladder, nearly no filling volume) seems to be only better understandable if the disorganization of the somatic neuronal network is better understood, since it is easier to record from the thicker α-motoneuron axons (on the average large AP amplitude) than from the thinner parasympathetic preganglionic fibres (on the average small AP amplitude). Disorganization of the somatic neuronal networks causes also dysfunction of premotor spinal oscillators. Since the premotor spinal oscillators are probably organized by the same interneurons which are used for the organization of propriospinal oscillators (rhythmically firing subunits probably recruited for the organization of the spinal pattern generators for rhythmic movement [93]), the disorganization and therefore dysfunction of premotor spinal oscillators reflect the disorganization of somatic neuronal networks. The disorganization of somatic neuronal networks can therefore be detected by the properties of the premotor spinal oscillators as the resonance frequency band width, the regularity of the interspike intervals of the impulse train (with which the oscillator is firing) and the coupling properties between spinal oscillators or systems of coupled oscillators. For systems of coupled oscillators as models of central pattern generators, see [11,51,63]). The disorganization of the somatic neuronal networks in paraplegics may cause spasticity and clonus. In this and the following papers the self-organization of somatic neuronal networks will be considered under physiologic and pathophysiologic conditions.

In 1939 [36] and 1950 [37], E.v. Holst challenged that the CNS was commonly regarded as a reflex apparatus producing motor output. His „relative coordination" of different rhythms [36] of the CNS in different species including man is very similar to recent findings on the correlation of human spinal oscillators [73,83,94]. According to Moshe Abeles [1] the

nervous system is essentially a statistical machine [103]. According to von der Malsburg, information in this statistical machine is encoded not only as the number of active nerve cells and their firing rates („frequency code") but also as interactions between neuronal and neuromuscular elements of cell assemblies expressed in correlation with their firing patterns [100]. This author argues that the synchrony of discharges has a strong influence on nervous dynamics, since neurons essentially are „coincidence detectors" because synchronous inputs excite a postsynaptic cell more effectively than do uncorrelated inputs. Correlations could therefore be processed by neuronal networks. The correlation could be initiated in the network from an external source and then be propagated by „synfire chains"(Fig.3), as suggested by Abeles [1]. The functional organization of the common brainstem system and its dynamic changes is a consequence of afferent inputs and the rhythmic properties of the common brainstem system network. The neuronal network reveals different types of functional organization. In the state of functional organization, in which the neurons discharge rhythmically, the phase relations between the different rhythms are essential for the transfer of information [52,64,97]. It was the opinion of the Sherrington school that all reflectory, excitatory and inhibitory influences onto motor output are due to direct interactions at the motoneuron pool itself (reflex theory) [12]. The opinion of R. Jung was [47] that the bottom-level coordination mechanism, at which all impulses run together, is the „Schaltzellenapparat" (neuronal network apparatus) of the spinal cord; this concept also admits that there are spinal pathways which bypass the „Schaltzellenapparat" and synapse directly onto the motoneurons. This neuronal network apparatus is the common substrate which controls the volitional and unvolitional motor output. The generation of rhythmic activity, as revealed by physiologic tremor, is one function of this „Schaltzellenapparat" (oscillator theory). The current research on spinal oscillators supports the oscillator theory of R. Jung which assumes the neuronal network with its rhythmic properties driving the motoneurons being the bottom-level basic mechanism of coordination; this theory opposes the reflex theory which states that the functions of the human CNS can be explained on the basis of reflexes as mostly assumed by clinical medicine. Sir Matthews could show that the so-called long-latency stretch reflex can be explained by the response of secondary muscle spindle afferents in the spinal cord [54]. In his opinion nevertheless, there is no need for a conceptual revision to be able to understand the function of the spinal cord and its interactions with supraspinal centres.

The brain theory underwent a period of stagnation. At the same time, important conceptual amendments were introduced, mainly characterized by a transition from algorithmic to dynamical description of neuronal systems. In the algorithmic scheme, a process is controlled deterministically by a pre-existing program (or a rigid network): one may speak of hetero-organization. Modern dynamical formulation puts emphasis on probabilistic mechanisms and random search, on the order to implement auto-organization.

Probably, the functioning of the human spinal cord is intermediate, between dynamically preferred connectivity patterns as a basis for self-organization and a rigid network. The monosynaptic reflexes belong to rather rigid network structures, whereas the spinal oscillators are the first step towards self-organization of pre-formatted neuronal network structures.

Materials and Methods

Measurements were collected from 9 patients (mean age 27 years) with spinal cord lesions (Table 1), spastic bladder (hyperactive detrusor (nearly no bladder filling volume)), spastic pelvic floor (including external striated sphincters), dyssynergia of the urinary bladder, and general spasticity Electrophysiologic measurements were performed during surgery, with a new method of recording single-fibre action potentials (APs) extracellularly from undamaged nerve roots or nerve root fascicles The patients underwent surgery to have a sacral anterior root stimulator implanted (according to Brindley [7]) to improve bladder control and to save the kidneys The strategy of the surgery is to deafferentiate the urinary bladder to increase its storage volume and to subsequently stimulate the motor roots (mainly S3 and S4) to empty the bladder To deafferentiate the bladder, afferents and efferents in the nerve roots were identified by electrical stimulation and partly by using the single-fibre AP recording method to recognize afferents in certain roots The surgical procedure involves extirpation of parts of the dorsal roots Cut dorsal roots, from which recording was performed, were fixated and prepared for morphometry (Figs 6,7) Light anesthesia was administered with Propofol

Electrophysiology

Single-fibre APs were recorded extracellularly (Fig 1) from nerve roots with 2 platinum wire electrode pairs (electrode pair distance = 10mm, electrode distance in each pair = 4mm) at 2 sites, preamplified (x1,000), filtered (RC-filter, passing frequency range 100Hz-10kHz), and displayed on a digital storage oscilloscope (Vuko Vks 22-16), and also stored using a PCM-processor (Digital Audio Processor PCM-501ES) and a video recorder The beginning of a touch or a pin-pricking was marked with an upward pulse, and the end with a downward pulse on trace „a" (Fig 9A) These pulses were generated by a marking pulse generator connected to the digital scope, which was switched on and off with a touch sensor working on the basis of resistance changes Also, the pulling and releasing of anal and blad der catheters were mostly marked with the help of a pull-switch connected to the catheters and working in connection with the same marking pulse generator Trace „a" was the recording from the proximal electrode pair and trace „b" from the distal pair Conduction velocities of single-fibres were calculated from the conduction distance (electrode pair distance) and the respective conduction times, the time needed for an AP to cover the conduction distance (time difference between traces „a" and „b" for a particular AP) APs from afferents and efferents could clearly be distinguished since for the used electrode arrangements the main phase (second phase) from afferent fibres is upwards (Figs 3A,9B,C,D) and that of efferents downwards (Figs 1,3A,11) E g , the AP of a skin afferent fibre reaches a pair of electrodes first as negative and then as positive According to the electrode setting used, the main phase is upwards An AP of a motoneuron, coming from the opposite direction, would reach the electrodes in the order positive-negative The potential changes are therefore opposite and

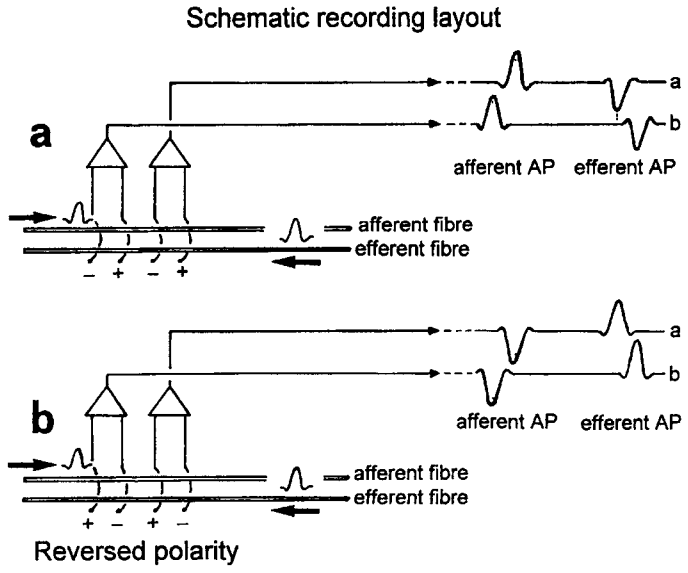

Figure 3A: Schematic layout for recording single-nerve fibre action potentials (APs) The reversing of the inputs to both preamplifiers does not change the ability to differentiate between afferent and efferent APs

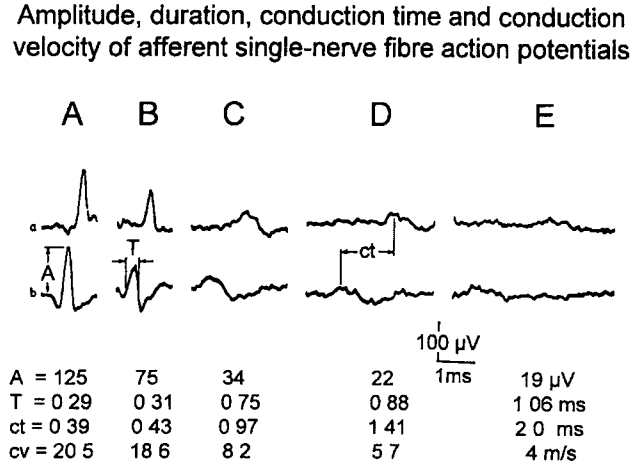

Figure 3B: Extracellular AP waveforms of different amplitude (A), duration (T), conduction time (ct) and conduction velocity (cv) The different nerve fibres in which these APs were conducted were at approx the same distance from the recording electrodes The afferent nerve fibres were stimulated by touch, pain, and bladder and anal canal-catheter pulling and releasing Brain dead individual HT4, 56 years, 32 °C (approximate measuring temperature), recording made from a dorsal S5 root (diameter = 0 17 mm)

the main triphasic AP will point downwards. An AP in an afferent fibre reaches first the caudal electrode pair and then the rostral pair, whereas an AP of the efferent fibre reaches first the rostral electrode pair and then the caudal one. The conduction times are therefore also opposite. For further clarity, a change of the inputs to the preamplifiers does not change the ability to differentiate between afferent and efferent APs, because the amplitudes of both types of APs change their upward or downward direction (Fig.3A). In accordance with animal data [109], the AP amplitude of afferent APs decreases and the AP duration increases with decreasing conduction velocity (increasing conduction time) (Fig.3B), if the different nerve fibres are at the same distance from the recording electrodes. Similar correlations between conduction velocity, AP amplitude and AP duration hold for efferent APs. If APs of two efferent fibres meet at one electrode pair at the same moment, the APs add up algebraically. The adding up of many fibres' impulses, following electrical stimulation will give rise to a compound AP. If the APs of an afferent and an efferent fibre meet at the same point of time at one electrode pair, they partly or fully abolish each other (subtraction of the AP amplitudes). However since these APs will not meet each other at the other electrode pair, the afferent and the efferent APs are clearly distinguishable on the trace of the other electrode pair. The conduction velocities of afferent APs were plotted on an afferent conduction velocity distribution histogram (Figs.7D,8), and those from efferent APs on an efferent velocity histogram (Fig.7D,8). Histogram classes were half closed intervals $\leq$ and $<$; the left border belongs to a particular class, the right one does not. Group conduction velocity and nerve fibre diameter values were the peak values of asymmetrical distributions. Single-fibre APs were always recorded from whole roots or fascicles. We did not try to try single nerve fibres. In nerve roots thinner than 0.6 mm in diameter (radial decline of AP amplitude due to volume conductance is approx. by a factor of 1/10 per 0.3 mm; the root flattens when positioned on the wire electrodes), it is possible to record single-fibre APs from all fibres with a diameter larger than approx. 4 µm. The radial decline of low-amplitude long-lasting extracellular APs (due to volume conductor embedding) of thin fibres, including preganglionic parasympathetic fibres, is less pronounced than it is for high-amplitude short-lasting APs since the low frequency sinusoidal coefficients will have large amplitudes in a Fourier-expansion. Since nerve roots have no epineurium and nearly no perineurium, the nerve fibres in the roots can easily be damaged when recording with wire electrodes. Pressure and stretch will change the AP waveform or even block conduction (most easily at the node of Ranvier) so that one AP can be recorded from one electrode pair only. Double peaked APs can occur, probably when a node of Ranvier is blocked. Mechanical stimulation, nerve fibre compression, resistance artifacts and trigger zones may change impulse shape and activity. For further references, see [88-90].

Doublet firing of secondary muscle spindle afferents: It has been argued that the doublet firing of secondary muscle spindle afferents for slight parasympathetic activation [89] is caused by the injury of nerve fibres. Generally, by measuring functions in a system, one changes more or less the functions of the system. By recording with wire electrodes from a bundle of nerve fibres (nerve root (Figs.1,6)), protected only by a thin sheath of cells, stretch, pressure,

membrane injury or drying up of the fibres can occur. Mechanical alterations of nerve fibres can be judged by the appearance of double-peaked APs caused by blocks at the nodes of Ranvier, which were not observed. Ectopic AP generation due to the drying up of nerve roots can be avoided or eliminated by wetting the root. Further, injury potentials of nerve fibres (long membrane cable) are not long lasting. The injury will depolarize the membrane and therefore, at least partly, inactivate the membrane so that the excitability of the injured membranes will be reduced rather soon. In intracellular recordings from muscle fibre, one therefore additionally injects current to keep the membrane potential or to hyperpolarize it slightly (see Fig.21 of [94]). Actually, the doublet firing lasted long and the firing even increased in that case instead of decreasing. Injury as a cause for the doublet firing is therefore very unlikely. To get more safety concerning the repeatability of natural firing patterns in man, further measurements are needed rather than speculation.

Anatomy

The development of this new technique of recording from man was possible because of the unique anatomical situation present in the human spinal canal. Because of the ascensus of the spinal cord, the lumbosacral nerve roots have become very long and form he cauda equina (Fig.4A,B,C). Since the caudal sacral nerve roots are very thin (Fig.4B,C) and nerve roots are only ensheated by a thin layer of cells (Figs.1,6), they are ideal for recording single-fibre APs from undissected nerve roots. It is also possible to record single-nerve fibre APs from thin peripheral nerves [76], but the epineurium has to be removed and the quality of recording cannot reach that of recordings from roots, because the perineurium is still shunting AP currents, and tissue parts may give rise to resistance artifacts [66].

Since further, humans have no tail mainly continence (mainly S2 to S5) and sexual functions are located in the conus medullaris only. Those functions are therefore represented in the lower sacral nerve roots and they don't mix with tail functions as for example in rat, cat or dog [78-80]. A few nerve fibres to leg muscles run through the lower sacral nerve roots (not mentioned in anatomy books), as can easily be verified by electrical and manual nerve root stimulation and the observation of foot or toe movements.

Values of root thickness of dorsal and ventral roots are shown in Fig.5. Lower sacral nerve roots show quite a lot of variation, including root interconnections (Fig.4C) and ventral root afferents and dorsal root efferents [80]. With respect to electrical nerve root stimulation [7] and nerve anastomoses [74-77] for urinary bladder control, the functions in the roots have to be identified functionally, including electrical nerve root stimulation and recording of afferent APs, to stimulate efferents in ventral roots after the surgery, most efficiently for bladder control or to transpose functions in nerve anastomoses to make relearning of functions possible.

Nerve root diameters, axon densities, root cross-sections and the numbers of nerve fibres per root [69] are given in Fig.5. It can be seen that the dorsal roots are much thicker than the ventral roots in the lower sacral range, and that the root diameters strongly decrease in

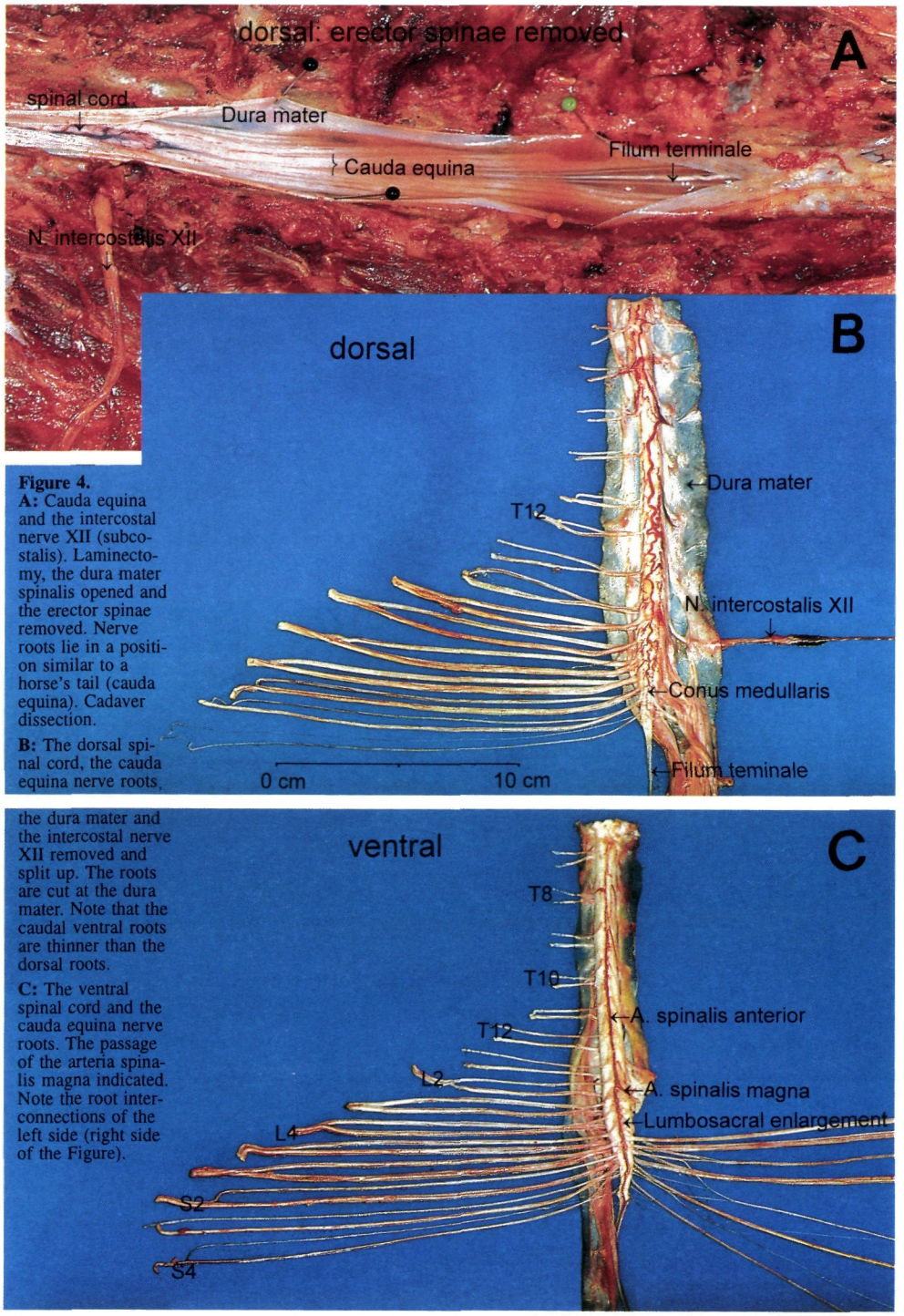

Figure 4.
A: Cauda equina and the intercostal nerve XII (subcostalis). Laminectomy, the dura mater spinalis opened and the erector spinae removed. Nerve roots lie in a position similar to a horse's tail (cauda equina). Cadaver dissection.

B: The dorsal spinal cord, the cauda equina nerve roots, the dura mater and the intercostal nerve XII removed and split up. The roots are cut at the dura mater. Note that the caudal ventral roots are thinner than the dorsal roots.

C: The ventral spinal cord and the cauda equina nerve roots. The passage of the arteria spinalis magna indicated. Note the root interconnections of the left side (right side of the Figure).

the caudal direction (Figs.4B,C,5). It was shown previously that nerve fibre counts of roots obtained from cadavers with the van Gieson method gave similar nerve fibre numbers as those from patients of nerve roots stained with thionin acridine-orange [88] (see below). In one case it was even possible to obtain similar myelinated nerve fibre numbers with the morphometric method as described below and the above mentioned electrophysiologic method [77].

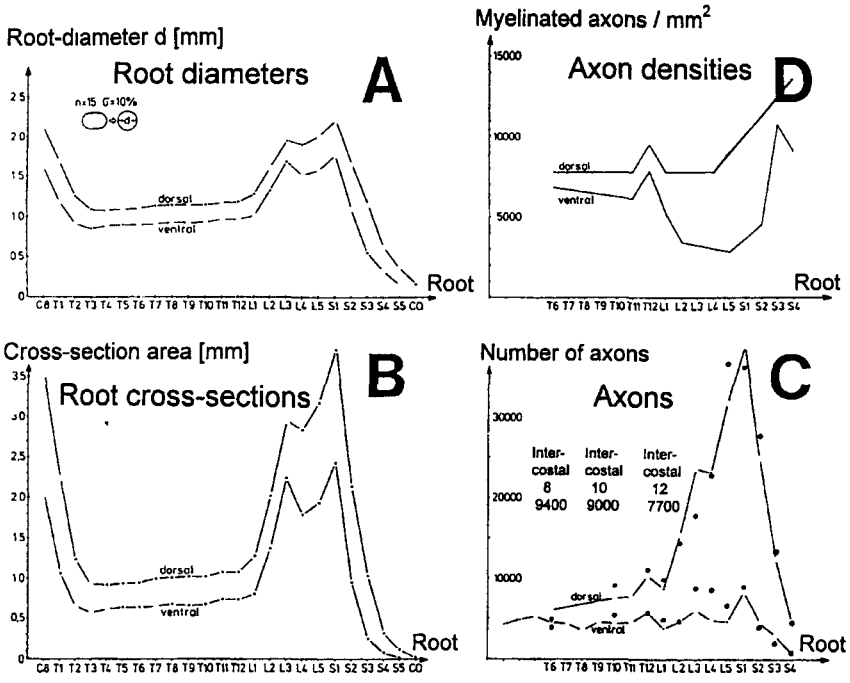

Figure 5. A: Dorsal and ventral mean root diameters measured in 15 cadavers in relation to the root level In the case of elliptic cross sections, the diameter of the circle with the same area was taken The standard deviation was 8-10%, 10% for the smaller roots

B: Mean dorsal and ventral root cross section areas, calculated from A, in relation to the root level

C: Number of myelinated axons of dorsal and ventral roots The line for dorsal roots represents the average of two van Gieson stains and the toluidine stain The line for the ventral roots is the average of 3 ventral root counts taken from [9] The large dots represent counts from the toluidine blue stain, the upper dots stand for the dorsal counts, the lower ones for the ventral counts The deviation shown at the dots indicates the variation of the axon counts The inserted axon counts from intercostal nerves 8, 10 and 12 are from toluidine blue stain counts As viewed under the light microscope, the intercostal nerves 8 and 12 had about the same cross section area, the 10th intercostal was about 10% smaller

D: Approximate densities of myelinated axons in relation to the root level, calculated from B and C (density = number of axons / cross section area) For further details, see [69]

The blood supply to the spinal cord has been quantified by measuring blood vessel diameters and estimating blood supply contributions [71] Since more than 80% of the blood to the thoraco-lumbar arterial territory is supplied by the thickest ventral (A spinalis magna supplies 68% of the blood from the left ventral side mostly at T10 or L1 levels (Fig 4C)), and the thickest dorsal radicular-medullary arteries, these two feeder arteries have to be saved in cauda equina surgery [71]

The number of myelinated nerve fibres supplying the lower human body lies in the range of 0 3x10^6 (Fig 5) Ingbert counted 650,000 myelinated nerve fibres in all the dorsal roots on one side in a human [108] Probably, there are more than 10^6 myelinated fibres contained in the nerve roots emerging from the CNS First measurements indicate that the number of unmyelinated nerve fibres exceeds those of the myelinated fibres in dorsal roots approximately 6 times (depending on the root) (see also page 71 of [107]) This may explain why patients with a clinically complete spinal cord lesion (some tract fibres may still be preserved) often report to still have deep slowly appearing feelings, since the chance for the remaining tract fibres connected to unmyelinated fibres may be much higher than for those connected to myelinated fibres, but also other pathways (sympathetic chain, connection of plexuus), not running through the spinal cord may contribute to the deep slow feeling

Morphometry

Pieces a few cm long were removed from dorsal roots of patients during surgery and used to record from, fixated for 4 hours in 4% glutaraldehyde in cacodylate buffer, afterfixated in 1% OsO_4 for 4 hours, and dehydrated and embedded in Araldite according to standard techniques Pictures of semi-thin sections (approximate depth = 1 µm) stained with thionin acridine-orange, were taken under a light microscope (x1,000) Nerve fibre diameters (= $1/2(\varnothing_1 + \varnothing_2)$ $\varnothing_1$ and $\varnothing_2$ are the larger and the smaller diameter of non-round shaped fibres respectively) and the mean myelin sheath thickness „d" were measured by hand A correction of 8% for shrinkage was allowed The nerve fibre diameters measured were divided into 4 classes of myelin sheath thickness 0 25µm ≤ d < 0 8, 0 8 ≤ d < 1 3, 1 3 ≤ d < 1 8, 1 8 ≤ d < 2 5µm For each range of myelin sheath thickness a diameter distribution histogram was constructed In the case of damaged fibres (split myelin sheath) the myelin sheath thickness was measured at the most preserved part Very strongly damaged fibres were not considered Because of the preference of the authors of even to odd values, neighboring histogram classes show large variations This systematic error can be abolished by increasing the width of the histogram classes from 0 25 µm to 0 5 µm For the diameter distribution 0 25 ≤ d < 0 8µm the higher histogram class was used anyway Computer-assisted morphometry would eliminate such systematic error, but would have less accuracy, since computer programs cannot handle artifacts and altered nerve fibres as if they were normal fibre The reduction of nerve root diameters and axon numbers can be seen in Fig 6

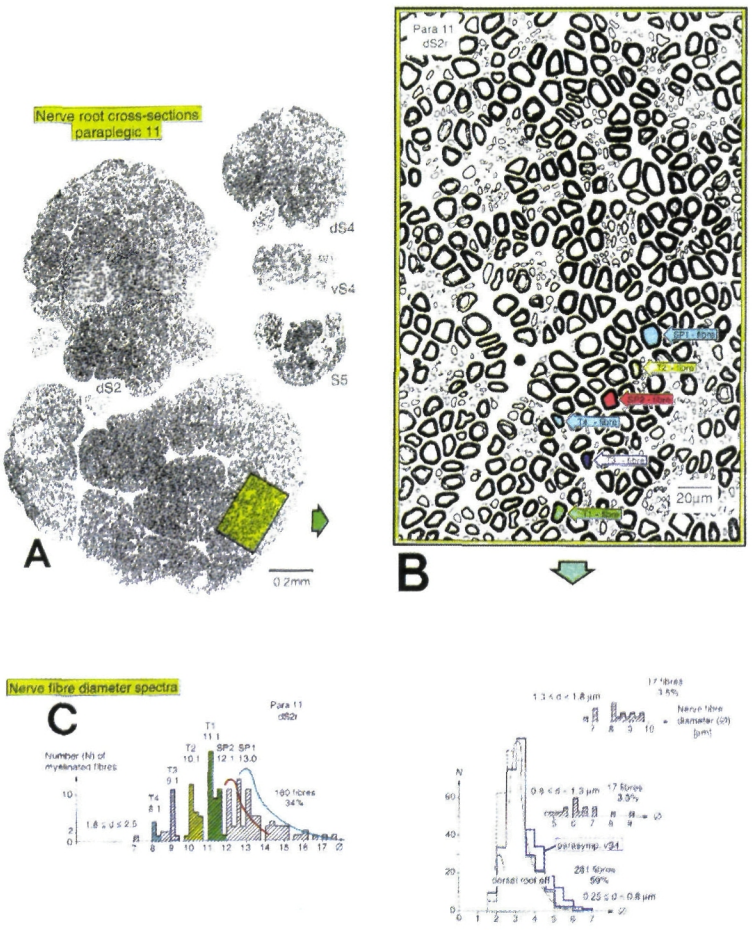

Figure 6. A: Cross-sections of the right nerve roots S5, vS4, dS4, dS2. The dorsal root S2 consists of 2 main fascicles. The square area marked in the lower fascicle of the S2 cross-section is shown in B at a higher magnification.

B: Magnified area of the dS2 cross-section from A. Nerve fibres are marked which according to their diameter and myelin sheath thickness most likely represent primary spindle (SP1), secondary spindle afferent fibres (SP2) and T1 (PC), T2, T3, and T4 skin afferent fibres.

C: Nerve fibre diameter spectra of the dS2 cross-sectional area in B according to 4 ranges of myelin sheath thicknesses (d). Fibre diameter peaks are indicated, which represent primary (SP1) and secondary muscle spindle afferents (SP2), and the myelinated skin afferent fibres T1 (Pacinian corpuscles), T2, T3 (probably SAI) and T4. Distribution curves for SP1 and SP2 fibres are shown. The histogram for parasympathetic fibres (including ventral root afferents) from root vS4 in Fig. 5B of [88] is represented by the dashed line (parasymp. vS4). The histogram for thin fibres ($0.25 \leq d < 0.8$ µm) includes possible afferent fibre distribution curves. Paraplegic 11. For further abbreviations and symbols, see Fig. 2.

Ethics

Informed consent was obtained from the patients prior to the recordings. The method of recording of single-fibre APs was used for intraoperative diagnosis, to identify more safely (e.g. in the case of an anatomical variation) what nerve fibres are contained in what nerve ro-

ot fascicles An improvement of the intraoperative diagnosis may make it possible in the future to deafferentiate the bladder more specifically It would be of great benefit if one could save e g the afferents signalling sexual sensation

Results

Unchanged group conduction velocities and group nerve fibre diameters following cord lesion

Single-nerve fibre action potentials (APs) were recorded extracellularly from sacral nerve roots during surgery in 9 paraplegic patients (para 3 to para 11) with spinal cord lesions of 6 months to 6 years duration Conduction velocities of single fibres were calculated and group conduction velocities were determined from peaks in the velocity distributions It has been shown in an earlier paper for the same patients that the group conduction velocities did not change following spinal cord lesion [88] It was further shown that neither the group nerve fibre diameters did change following spinal cord lesion [88] Thus, the classification scheme of the human peripheral nervous system (Fig 2) can be used even in individuals with spinal cord lesions

Since in this and the following papers emphasis will be laid on differentiation between α_1 (FF) and α_2-motoneurons (FR) and primary (SP1) and secondary muscle spindle afferents (SP2), velocity and diameter distributions of these nerve fibre groups are shown in Fig 7 for the sake of clarity It is shown in Fig 7D that α_1, α_2, SP1 and SP2 fibres conduct slowlier than given in the classification scheme in Fig 2 It was demonstrated earlier (and is shown below (Fig 8)) that the conduction velocity depends on the temperature, and most nerve fibre groups (apart from SP2 and α_2 groups) seemed to have different temperature dependences The differences between the velocities shown in Fig 7D and those in Fig 2 are due to a lower temperature during measurements represented in Fig 7D

The groups of α_1 and α_2-motoneurons and primary (SP1) and secondary spindle afferents (SP2) can be distinguished from each other by their conduction velocities (Fig 7D) Further, the α_2-motoneurons apparently conduct with the same velocity as do the SP2 fibres (calibration relation), and the α_1-motoneurons have a similar conduction velocity as the primary spindle afferents (SP1) The groups of motoneurons and spindle afferents can only partly be distinguished from each other by nerve fibre diameters (Fig 7C) For further details, see [88]

Group conduction velocities related to velocities of components of compound action potentials

In Fig 8A,B the velocity distributions of afferents (A) and efferents (B) are related to the components of compound action potentials evoked by electrical stimulation (pulse length 0 5ms) of the root (CAP comp) and the bladder (vesic stimul) For further details of

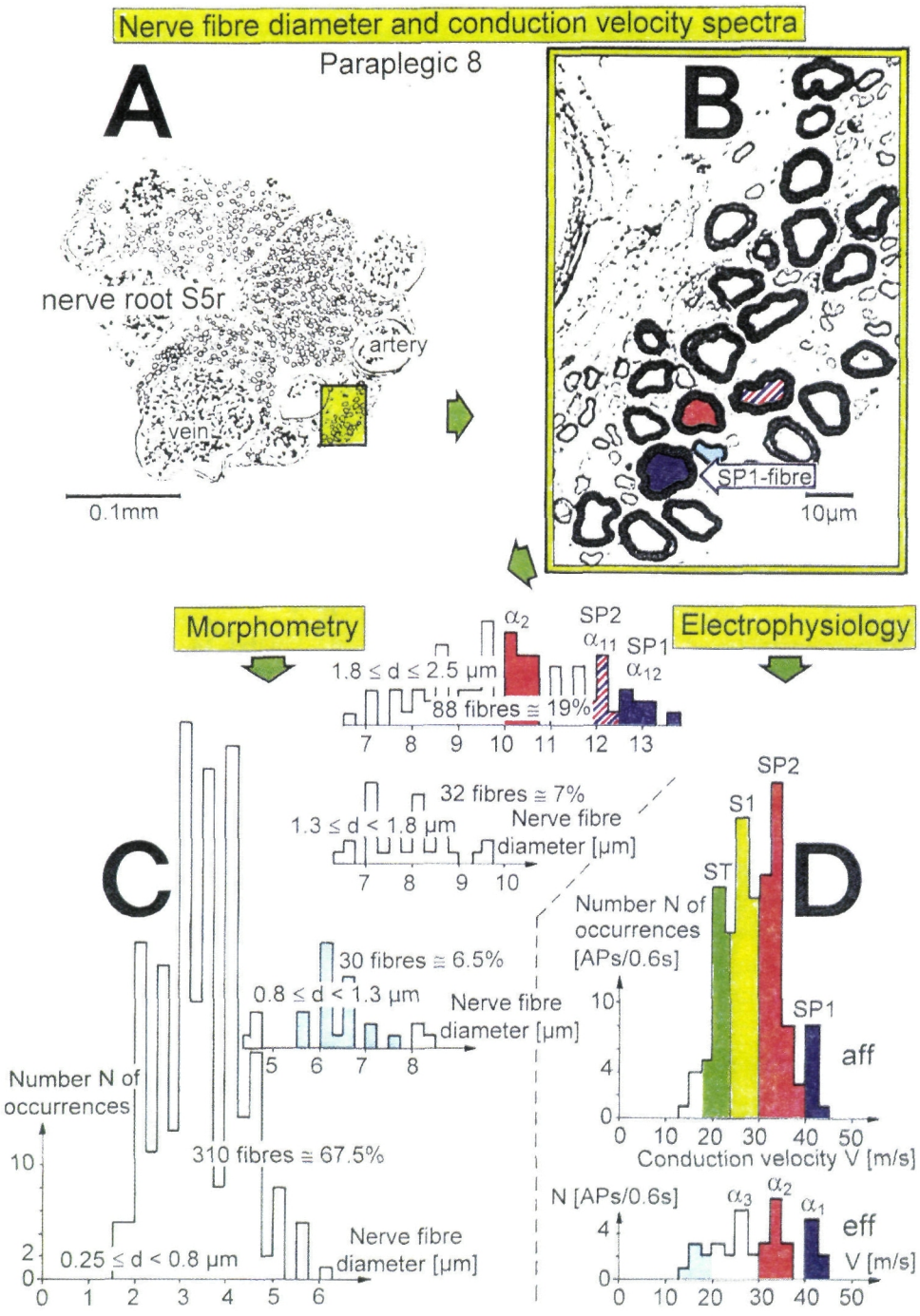

Figure 7. Schematic layout of the classification scheme for the human peripheral nervous system extended for individuals with spinal cord lesions and including primary spindle afferents and α_1-motoneurons (FF). Paraplegic 8, right root S5. For symbols, see legend to Fig.2.

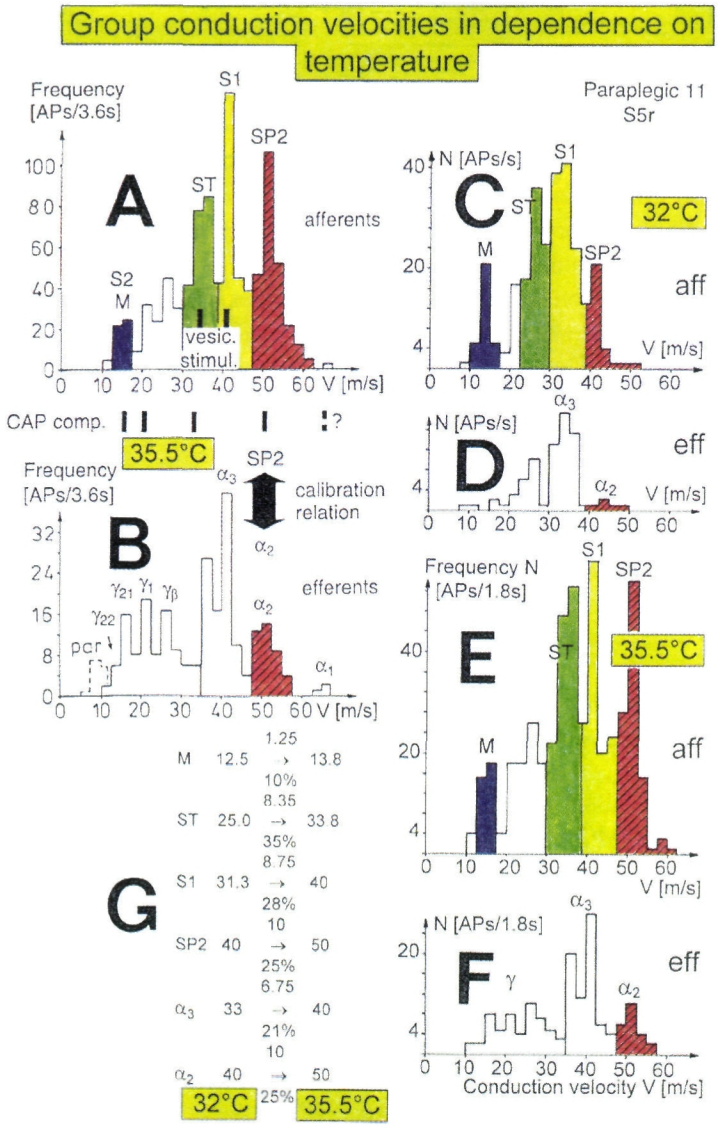

Figure 8. Conduction velocity distribution histograms with marked group distribution peaks in dependence on the nerve root temperature. For symbols of the nerve fibre groups, see legend to Fig.2. In G, the velocity values are given for both temperatures for the different afferent and efferent nerve fibre groups along with the percentages of change. Note that the secondary muscle spindle afferents (SP2) and the α_2-motoneurons (FR) conduct with the same velocity (calibration relation) for both temperatures (temperature-independence of the calibration relation).

electrical nerve root stimulation, see [86], and for electrical intravesical stimulation, see Figs. 9,10 of [88]. The components of the compound action potentials (afferent and efferent fibres are electrically activated) evoked by electrical root stimulation have similar values as the velocity distribution peaks of afferents and efferents (Fig.8A,B) obtained with the single-nerve fibre action potential recording method from natural impulse patterns. The compound action potentials of urinary bladder afferents, evoked by electrical intravesical stimulation, were conducted with the same velocity as the bladder stretch (ST) and tension (S1) receptor afferents, obtained with the single-nerve fibre action potential recording method from natural impulse patterns. The thinner and therefore slowlier conducting bladder afferents (S2,M) (Fig.2) probably had higher stimulation thresholds and were therefore not activated by the used pulse strength (up to 35V) and the used bladder filling volume.

Temperature dependence of group conduction velocities

In all measured cases, the AP durations of the single nerve fibres decreased and the conduction velocities increased with the increasing temperature It seemed further as if the different nerve fibre groups had different temperature dependences, because for lower temperatures, it was much more difficult to identify the different nerve fibre groups by their peaks in the velocity distributions The operational field was therefore often heated with an infra-red lamp to bring the root temperature as close as possible to 36°C

In paraplegic 11, good conduction velocity distribution histograms from the same root under the same recording conditions were obtained for low (32°C) (Fig 8C,D) and for high (35 5°C) (Fig 8E,F) root temperatures The secondary muscle spindle afferents (SP2) and the α_2-motoneurons increased their conduction velocity from 40 to 50 m/s (25% increase), the S1, ST and M afferents from 31 3 to 40 (28%), from 25 to 33 8 (35%) and from 12 5 to 13 8 m/s (10%) respectively with the increasing temperature (Fig 8G) The α_3-motoneurons raised their conduction velocity from 33 to 40 m/s (21% increase) Even though only one set of good quantitative measurements could be obtained so far, the two sets of velocity values clearly show that different nerve fibre groups have different temperature dependences of their group conduction velocity

The SP2 afferents and the α_2-motoneurons showed the same temperature dependence of the group conduction velocity The calibration relation of the velocity distributions of afferent and efferent fibres, namely that the SP2 fibres conduct with the same velocity as the α_2-motoneurons, is therefore temperature independent

Shifts of conduction velocity distribution peaks corresponding to conduction times of approx 0 1ms can safely be measured because of the many measurements contained in the distributions (Fig 8) and owing to the known shape of the conduction velocity distributions (sharp peak and long foot to the right), which are similar to the shape of diameter distributions of nerve fibre groups (Fig 1) On the other hand, repeated evaluation of velocity distributions from different sweep pieces, taken from the tape, showed good reproducibility

Unchanged skin receptor density following spinal cord lesion

In an ealier work it was found on the basis of AP occurrence patterns of certain touch afferents stimulated at different sites that T1 skin receptors (PC) in the skin adjacent to the gluteus maximus of a brain-dead individual were positioned approximately 20 mm apart (Fig 9 and [72,77])

As can be seen in Fig 10, the distance between two T1 (PC) receptors was also approximately 20 mm at similar sites of sacral dermatomes The receptor sites were obtained from the impulse patterns (Fig 10A,B,C,D) recorded upon touching the sites 1, 2 and 3 (Figs 2,3 [92]) It is concluded that neither the receptor density in the skin had changed following spinal cord lesion, provided the skin has not been damaged by trauma or pressure ulcera

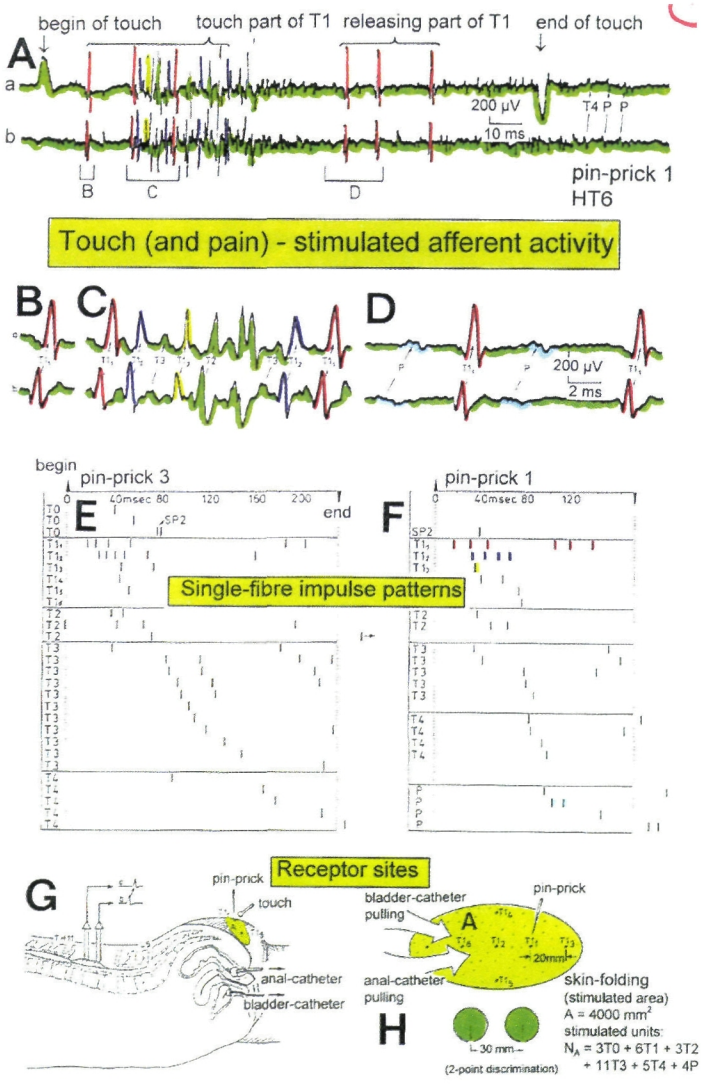

Figure 9. Touch and pain activity stimulated by pricking with a pin S5 or Co dermatomes and recorded extracellularly from a dorsal coccygeal root (brain-dead human individual HT6). T1, T2, T3, T4, P = marked action potentials (APs) from touch and pain fibres. Subscripts 1, 2, 3 mark single fibres.

A: Whole sweep shown at a slow time base. The large upward artifact on trace „a" marks electronically the beginning of the touch. The large downward artifact on trace „a" marks the end of the skin touch. Note that 2 intervals of high activity of large APs occur, one after the beginning of the touch with 1 AP in front, and a second before the end of the touch; potentials with small amplitude follow the potentials of large amplitude. Time intervals B, C and D are shown in a time-expanded form in Figures B, C and D.

B, C, D: Time-expanded sweep pieces from A. Identified APs are indicated. Note that the APs from the $T1_1$ touch unit can be safely identified by the waveforms in B, C, D.

E, F: AP occurrence patterns of single touch and pain fibres following long pin–prick 3 and short pin–prick 1.Upon pin–prick 3, no pain afferents are stimulated. The single–fibre AP activity of the different touch and pain groups are identified by the AP waveforms on traces „a" and „b" and by the conduction times. The single touch afferents of the T1 group are marked with subscripts, and can be seen in all the following stimulations [77]. One active secondary muscle spindle afferent fibre (SP2) could always be identified. Note that the T11 – unit adapts in E following the slow pin–prick (release activity is reduced), but not in F following the short pin–prick (release activity is not reduced).

G: Recording and stimulation arrangement for simultaneous measuring of several single touch and pain units. A = area stimulated by skin folding, drawn in H in more detail. $T1_1$, $T1_6$ = suggested touch points of the $T1_1$ and $T1_6$-units.

H: Drawing of the very approximate skin area stimulated by skin folding. $T1_{1\text{-}6}$ = suggested focal T_1 touch points. Two-point discrimination indicated for comparison. N_A = number of stimulated units in the dorsal coccygeal root. Skin tractions evoked by anal and bladder-catheter pulling are indicated by large open arrows. For further details, see [72,77].

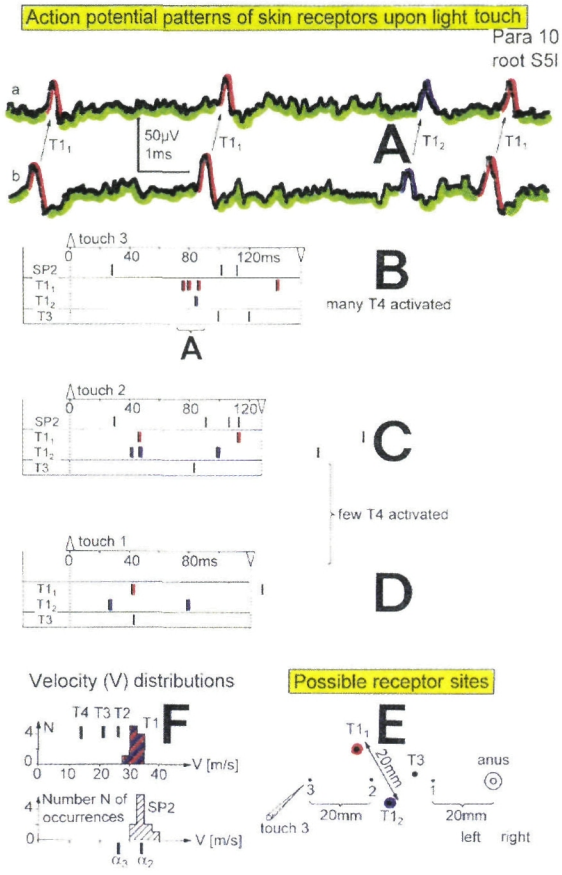

Figure 10. Impulse pattern of single touch afferents of para 10.

A: Original registration of single-touch afferent action potentials (APs), which are identified by conduction velocity distribution histograms to be of T1 (Pacinian corpuscle) type (F). Single-fibre APs are identified by comparisons of waveform and conduction times.

B-D: Natural impulse patterns of T1, SP2 and T3 afferents following touching the sites 1, 2 and 3, which were 20 mm apart (E).

F: Conduction velocity (V) distributions of T1 and secondary spindle afferents (SP2); bars marked by T2, T3, T4, α_2 and α_3 represent skin touch afferent and α-motoneuron groups obtained from peaks of compound APs.

E. Possible receptor sites of single $T1_1$, $T1_2$ and T3 afferent fibres, constructed from the different strengths of activation following touching the sites 1, 2 and 3 (B-D).

Oscillation period, interspike intervals of the impulse train, and afferent drive of oscillatory firing α-motoneurons

The successfully recorded cases of oscillatory firing from different roots of different patients are summarized in Table 1. A majority of oscillatory firing was recorded from α_2-motoneurons (FR), a few recordings were obtained from α_1 (FF) and α_3-motoneurons (S). Since there are normally very few α_1-motoneuron axons in the lower sacral nerve roots [88], it is reasonable that only a single conclusively recognized α_1-recording was found. Since at least some α_3-motoneuron axons run through the lower sacral nerve roots [88], it is unexpected that only one oscillatory firing α_3-motoneuron could be found. This may indicate that α_3-motoneuronal networks are no more able to organize themselves to fire oscillatory in a physiological manner. α_2-Motoneurons fired frequently oscillatory, but their oscillatory firing was much less regular than observed in brain-dead and normal individuals [83,90]. The data in Table 1 indicate that whereas the α_1-neuronal network underwent little changes, the α_2-networks showed much more changes, and the α_3-networks even considerably more

Case	Sex/Age		α_1-Motoneurons					α_2-Motoneurons					α_3-Motoneurons		
Centr temp [°C]	Lesion level/Age	Root	Oscillation period	Number of APs per impulse train	Interspike intervals of impulse train	Firing mode	Afferent drive interspike intervals (ii)	Oscillation period T [ms]	Number of APs per impulse train	Interspike intervals of impulse train [ms]	Firing mode	Afferent drive	Period	Number of APs per impulse train	Firing mode
Para 3 34 6 °C	f 33 C6/3	S5l					SP1 II=95ms	1 130 111 2 134 118 3 142 117	2 1 2 1 2 1	13 10 9 8	O2 O2				
Para 5 34 6°C	f 24 TH12/2	S5r						1 167 2 111	3 (anal) 2 (bladder)	4 3/8 5 7 4	O2 O2	SP2 parasymp activated			
Para 7 35°C	f 37 TH5/2 5	S5r						1 77 72 57	3 2 1	8 15/8 95 8 9	dys irregular				
		S5l	3 (134	2/1	7 4ms	O2)=α_1?		1 107 2 130	2 1 2	4 6 6 2	O2 O2				
		vS4						1 14	2 1		dys very irregular				
Para 8 35 2°C	f 20 TH6/1 5	S5r	1 122	1		O1	SP1 SP2	1 150 172	3 2	6 4/10 4 7 9	O2				
Para 9 34 5°C	f 23 TH1/0 5	vS4r						1 300	1 Synchronization following pin-prick and anal stimulation	-	O1/O3	SP2	1 100 γ_1-fusimotor fired partly oscillatory	1	O1
Para 10 34 3°C	m 30 TH12/0 5	dS4r						1 150	4 3 2	4 2/7 1/9 1, 4 1/7 1 8 6	O2	SP1 or SP2 phase lag ~6 3ms later			
Para 11 35 8°C	f 25 Th5/2	vS3r										SP2 fibres parasymp activated			

Table 1. Oscillatory firing of α_1 (FF), α_2 (FR) and α_3-motoneurons (S) in patients 0 5 to 6 years following spinal lesion (paraplegic = para) Centr temp = central temperature, f = female, m = male, vS4r = right ventral sacral root 4, O1,O2,O3 = firing modes of α_1, α_2 and α_3-motoneurons (see Fig 3) SP1, SP2 = primary, secondary muscle spindle afferents anal, bladder = motoneuron innervated external anal or urinary bladder sphincters

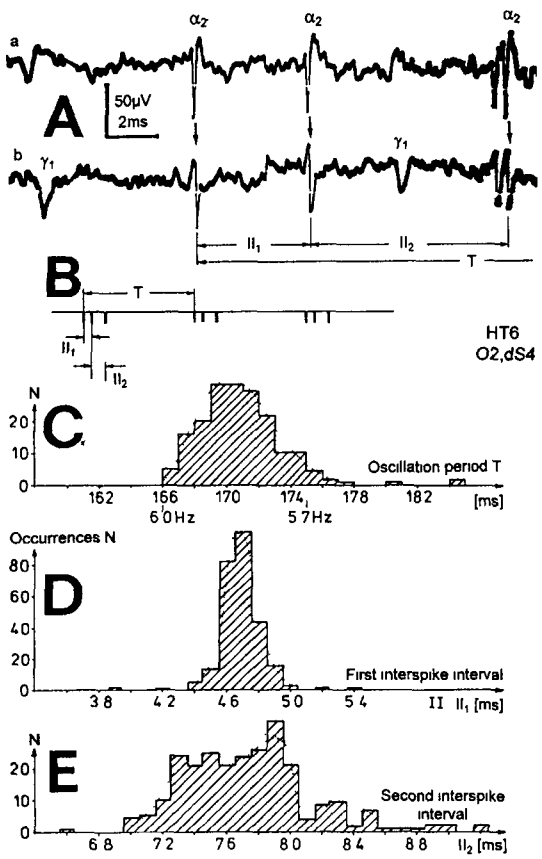

Figure 11. Distribution of oscillation period (T) (C), first (II_1) (D) and second interspike intervals (II_2) (E) of a α_2-motoneuron, firing repeatedly with 3 AP impulse trains

A: Original recording of the 3 AP impulse train, II_1, II_2 and T are indicated γ_1 marks APs from a γ-motoneuron

B: Schematic drawing of the impulse pattern of the α_2-motoneuron

Note that the distribution of II_2 (E) may consist of 3 subpeaks Brain-dead human individual HT6

changes. The α_3-neuronal networks do no more seem able to organize themselves to fire oscillatory. As most interneurons are integrated in the oscillatory firing of α_3-motoneurons and very few in α_1-motoneuron firing (Fig.3), the integrative network functions of the spinal cord seem to have changed or deteriorated following spinal cord lesion.

According to the approximate relation between the oscillation period and the number of APs per impulse train (n_{AP}) ($T = 70$ ms + $n_{AP} \cdot 30$ ms), the α_2-oscillatory firings show some changes associated with spinal cord lesion. Mean interspike intervals (IIs) of impulse trains of oscillatory firing α_2-motoneurons are given in Table 1. They are similar to physiologic values [73]. Differences as compared to normal values will become evident in distributions (see below). Table 1 further shows that the α_1-motoneurons are mainly driven by primary spindle afferents (SP1), and the α_2-motoneurons are driven by secondary spindle afferents (SP2). As will be seen below, the irregularity (pathologic or not) in the oscillatory firing gives further insight into the network structure of premotor spinal oscillators.

Regular oscillatory firing of motoneurons in brain-dead individuals (HTs)

Fig 11 shows an impulse train triplet of an oscillatory firing α_2-motoneuron of the brain-dead individual HT6 [83] The firing pattern is schematically drawn in Fig 11B Distributions of the oscillation period and of the first and the second interspike intervals are plotted in Fig 11C,D,E The distributions of the oscillation period and of the first interspike interval are smooth and show no obvious subpeaks The distribution of the second II shows subpeaks suggesting interactions with other oscillatory firing circuitries

The narrow distribution of the oscillation period and the interspike intervals of the impulse train shows that the oscillatory firing network fired very regularly Other spinal oscillators in brain-dead individuals [83,87] fired not just as regularly as the one shown in Fig 11 It is concluded that in brain-dead and normal individuals the neuronal networks, driving the motoneurons, fired regularly with some variation It will be shown below that this regularity is lost following spinal cord lesion

Irregular oscillatory firing of α motoneurons following spinal cord lesion

Following spinal cord lesion, mean values of oscillation period and interspike intervals for oscillatory firing motoneurons show much more variation (Table 1) than do normal values [73,83] The most regular oscillatory firing α_2-motoneuron, shown in Fig 12, fired nearly as regularly as the α_2-motoneuron of the brain-dead individual HT6 (Fig 11) On the other hand, some oscillatory firing α_2-motoneurons (Table 1) fired extremely irregularly so that it was difficult or even impossible to identify the kind of the motoneuron from the impulse patterns (Fig 3)

The distributions of the oscillation period and of the interspike intervals of the impulse train from an α_2-motoneuron in para 8 (Fig 12) show more scatter than those obtained for HT6 (Fig 11) Further, it can be seen from Fig 12D that the α_2-motoneuron reduced its mean interspike interval from approximately 9 ms to 7 5 ms in the 2 AP firing mode before switching into the 3 AP firing mode with interspike intervals of 7 ms and 11 5 ms (Fig 12F) Firing regularly in the 3 AP mode, the first and the second interspike intervals were approx 6 5 ms and 10 ms (Fig 12B)

Such a change from 2 to 3 AP impulse train firing can be observed if one records from twitch or denervated slow muscle fibres of the frog intracellularly and when the depolarizing pulse amplitude is increased to mimic depolarization by excitatory postsynaptic potentials (for references, see [67]) Upon increasing the repeated transient depolarization, the interspike interval of the 2 AP impulse train reduces before a 3 AP firing occurs (Fig 21 of [94])

Alternating long and short oscillation periods in some oscillatory firing α motoneurons

It was shown in a previous publication that an α_2-motoneuron, innervating the external bladder sphincter in a brain-dead individual, fired oscillatory with long and short oscillation

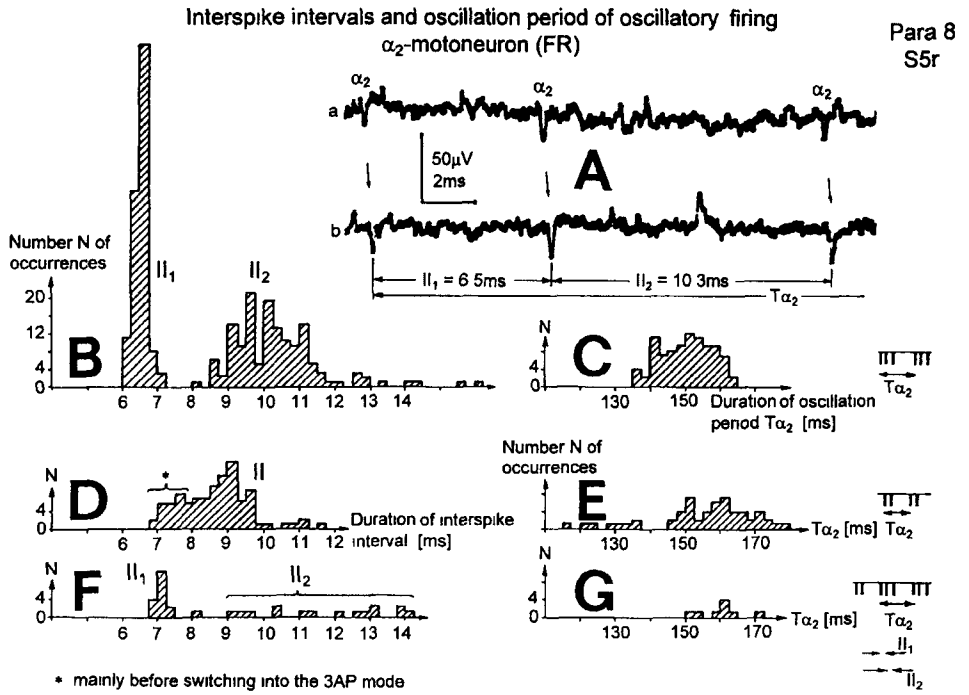

Figure 12. Distribution of oscillation period $T\alpha_2$, First (II, II_1) and second interspike intervals (II_2) of a α_2-motoneuron, innervating the external anal sphincter, firing repeatedly with impulse trains consisting of 2 and 3 APs

A: Original recording of a 3 AP impulse train, oscillation period and interspike intervals are indicated

B: Distributions of the first and second II of the 3 AP impulse train

C: Oscillation period distribution for the 3 AP-firing

D, E: Distributions of interspike intervals and oscillation period $T\alpha_2$, when the α_2-motoneuron fires with impulse trains consisting of 2 APs

F, G: Distribution of first and second interspike intervals and of the oscillation period of the 3 AP impulse train, when the α_2-motoneuron changed from the 2 AP to the 3 AP-firing mode Paraplegic 8, left root S5

periods and long (2 APs) and short (1 AP) impulse trains [73].

In Fig.13 the oscillatory firing of an α_2-motoneuron is shown, which innervated the external bladder sphincter (para 7). No alternating firing with long and short oscillation periods and 1 AP and 2 AP impulse trains was observed. The probably pathologic firing (less regular oscillatory firing than in brain dead individuals) consisted of 2 AP firing (Fig.13A,B), 1 AP firing (Fig.13C), changing from 2 AP to 1 AP firing and vice versa (Fig.13D,F), and irregular oscillatory firing (Fig.13H). The 1 AP firing (C) showed a 4 ms shorter oscillation period than the 2 AP firing (A). The interspike interval was 1 ms shorter when changing from the 2 AP firing to the 1 AP firing (E) in comparison to the change from 1 AP firing to

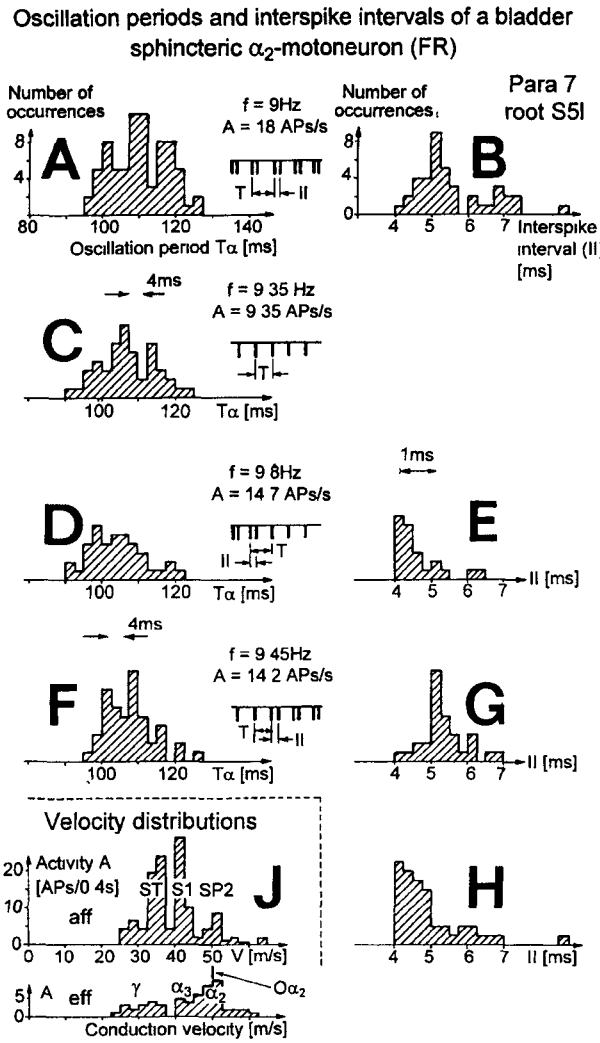

Figure 13. Oscillation period (T) and interspike interval (II) of an α_2-motoneuron innervating the external bladder sphincter, in dependence on the length of the impulse train (impulse train is 1 or 2 AP long)

A, B: T and II for regular firing with 2 APs

C: T for regular firing with 1 AP

D, E: T and II when the pattern changes from regular 2 AP firing to regular 1 AP firing and vice versa (F,G)

H: II for other changes of the firing pattern

J: Conduction velocity distributions of afferents and efferents from which recordings were performed, the velocity of the oscillatory firing motoneuron $O\alpha_2$ is indicated S1, ST = stretch and tension receptor bladder afferents, SP2 = secondary muscle spindle afferent fibre f = frequency, A = activity

Note that in different firing modes, the oscillation period differs by 4 ms and the interspike interval by 1 ms

the 2 AP firing (G). According to Fig.3 ($T = 70\ ms + 30\ ms \cdot n_{AP}$), a change of approx. 30 ms would be expected in the duration of the oscillation period for the change from a longer to a shorter loop (see Figs.10,11 of [83]). The measured oscillation period difference was only 4 ms.

One possible explanation to this large difference is pathologic firing. Another is that spinal oscillators of the trunk, including sphincter muscles for continence, may consist of two more or less coupled oscillators, which partly inhibit each other reciprocally. Also, afferent firing patterns may cause more or less directly alternating oscillation periods.

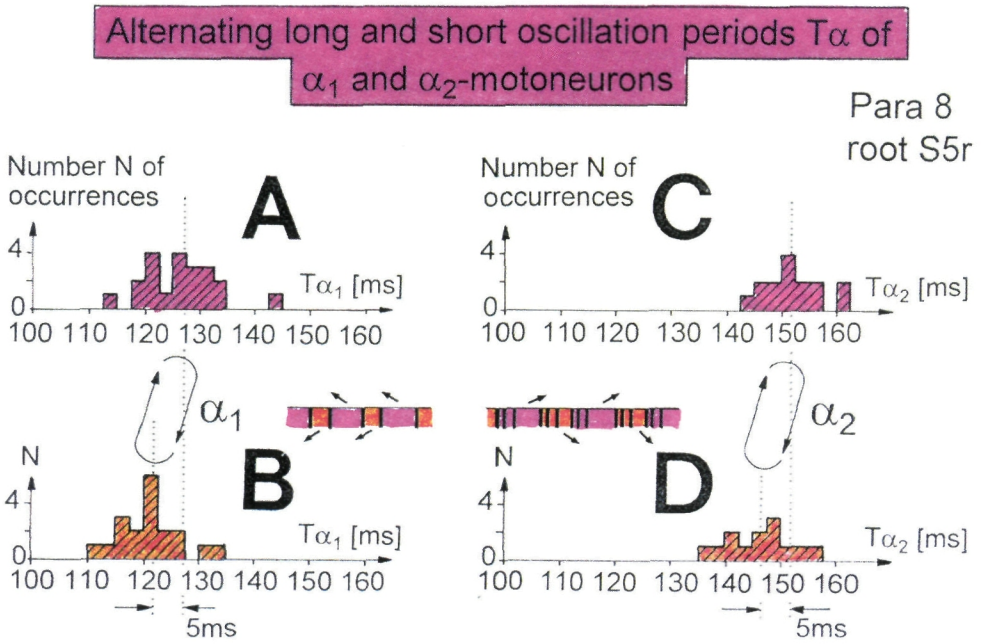

Figure 14. Alternating long and short oscillation periods of oscillatory firing α_1 (A,B) and α_2-motoneurons (C,D). Note that on the average, long and short oscillation periods for both motoneurons differ by 5 ms.

To allow differentiation between alternating oscillatory firing and the change of the oscillation loop, impulse patterns were looked for in which oscillators probably may not have changed their loop as indicated by a constant firing with a certain impulse train length (same number of APs per impulse train). In para 8, an α_1 (FF) and an α_2-motoneuron (FR) could be found which showed alternating long and short durations of the oscillation period (Fig.14). The difference between the long and the short oscillation period was 5 ms for the same impulse train length. It may therefore be that some trunk muscles in humans are driven by spinal oscillators which are coupled in an antagonistic or alternating fashion.

Discussion

Unchanged skin afferent activity following spinal cord lesion

It could be shown in Fig.10 that the T1 (PC) receptor density had not changed as compared to physiologic conditions (Fig.9,[77]). It may therefore be concluded that the receptor densities of other skin receptors had not changed either. Since afferents from normal skin (no trauma-induced scar and no ulcera which may change the anchorage (for references, see [45]) of the receptors) showed impulse patterns (Fig.10) similar to physiological (Fig.9), it is

concluded that the afferent input from the skin had not changed following spinal cord lesion. In regions with trauma-induced scar tissue or where pressure ulcera developed, the afferent pattern may differ, due to e.g. changed anchorage of the receptors.

It was found earlier that neither muscle spindles undergo changes following spinal cord injuries [89]. On the other hand, a changed afferent activity from the urinary bladder was observed [88] because of bladder infections and a hypertrophy of the detrusor (reduced compliance). Activity from joint receptors and Golgi tendon organ afferents could not be measured so far. It seems therefore that if there are no pathologic changes in the periphery and no inflammation or irritation, then the afferent input from the periphery (skin, joint, muscle spindles...) is physiologic. A dysfunction of the distal lesion-isolated spinal cord will then be due to a false or unbalanced input from supraspinal centres including missing inhibition and the pathologic functioning of the spinal cord resulting from the isolation of the cord, and the adaptation to lost tract fibres and the loss of mobility of the patients.

Physiologic firing of motoneurons in man

It has been reported that the firing modes of α-motoneurons for rather constant afferent input are the occasional firing, the transiently oscillatory firing and the continuously oscillatory firing [73,91]. For low level afferent input, the motoneurons are recruited in each of the nerve fibre groups (α_1, α_2, α_3) approx. every 3 s according to the size principle [79,81,82]. With the increasing afferent input the motoneurons switch transiently into the oscillatory firing mode. For a high rather constant afferent input the motoneurons fire continuously oscillatory. If a transient inhibition occurs, the α-motoneurons transiently break their oscillatory firing. The α_1-motoneurons (FF) fire oscillatory with a frequency around 10 Hz (range 8-12 Hz), the α_2-motoneurons (FR) fire oscillatory in the 6-8 Hz range, and the α_3-motoneurons (S) fire with frequencies below 1 Hz (Fig.3) [83,90]. The time-related recruitment of the motoneurons in the oscillatory firing mode is distributed so that the motoneurons do not fire simultaneously. The firing is nicely time-distributed to smoothly activate muscles (Fig.3 of [90]). Individual muscles show different proportions of the three muscle fibre types and are innervated by the corresponding motoneurons (Fig.3). Weight carrying muscles and probably muscles subserving posture are predominantly innervated by α_2 and α_3-motoneurons, and muscles which have to react quickly are prevailingly innervated by α_1-motoneurons. The muscle fibre composition of human muscles is only partly known [44,53,95].

Besides neuronal networks which activate the motoneurons to fire oscillatory there may exist monosynaptic pathways from certain peripheral afferents onto α-motoneurons. Famous and clinically relevant, but overstressed with respect to the function of the CNS, is the so-called monosynaptic stretch reflex discovered by Hoffmann [35], in which the primary spindle afferents directly synapse onto α_1-motoneurons (Fig.3) [91].

Pathophysiologic firing of motoneurons and pathologic coupling of oscillatory firing subnetworks in man following spinal cord lesion

It has been shown in Table 1, and earlier [83], that the oscillatory firing of the different types of motoneurons becomes irregular following spinal cord lesion in comparison to brain-dead and normal individuals [73]

Similarities are found in animals Sensory or descending control systems are responsible for inducing changes in gait The coordinating system, especially in the cat, seems to be somewhat unstable in isolation, exquisitely sensitive to both descending and sensory control, and is easily acted upon to produce a wide variety of other patterns The major phylogenetic trend has been towards increased separation and independence of the limb „oscillators" combined with an increased role to be played by descending and sensory systems which lend a considerably increased flexibility A possible conclusion could be that, during evolution, what is changing in the central pattern generator control of the limbs is the access to, and the need for extrinsic control and the general lability of the coordinating systems [11]

Grillner and Zangger [29] have shown quite clearly in the cat mesencephalic preparation that in the absence of sensory input the flexors and the extensors do not simply alternate They also showed that no single pattern emerges in the simplified preparation There was some evidence for alternation between some pairs of dorsal and ventral muscles, but it was inconsistent Generally, in the mesencephalic as well as the decorticated curarized preparations [62], the removal of sensory feedback destabilizes the coupling between the burst generators, and leads to a deteriorated pattern

The local oscillators of the lampreys, when separated from each other, burst at different frequencies This has not been reported in dogfish On the basis of this difference, Kopell [50] has suggested that dogfish have greater descending control of the coordinating system and perhaps less control intrinsic to the cord than do lampreys It remains uncertain what role is played by sensory input with respect to intersegmental coordination [11]

The motor pattern observed in the intact swimming fish and those recorded from the isolated spinal cord are essentially identical [10,101] In dogfish [26,27] and young chicks [41,42], the intact and the fictive patterns are very similar In cats, the motor pattern is more complex in intact animals It also reflects a more complex modulation by sensory and descending control systems Because of this there is a great deal of variability among individual preparations and there are some differences between the motor patterns of intact, chronic spinal [20], and functionally „isolated" cords [28]

In complete thoraco-lumbar spinal cord lesion in patients, the functionally „isolated" caudal spinal cord has lost the descending control system and may have an impaired sensory control Deteriorated organization of spinal oscillators has to be expected In the chronic case with partial immobility, even more pathologic organization of the isolated cord has to be expected

In the case of an incomplete cervical spinal cord lesion sub C5, the sensory and the supraspinal control systems are impaired, but not completely The pattern generator for leg movements is not expected to be impaired in the lumbosacral enlargement of the cord, since in

animals each unit oscillator spans no more than 1-4 segments [10]. If the lumbosacral enlargement for locomotion starts with L1, then the most rostral oscillators for locomotion will probably not reach the Th9 segments. If we assume that the lesion mainly spans 3 segments, then a lesion sub Th6 should only little affect the spinal locomotor centre. It has however been measured in animals that rhythmogenesis was distributed along the rostrocaudal axis of the spinal cord with a stronger capability of the rostral segments of the lumbosacral cord compared with the more caudal segments (see below). On the other hand, in cats walking seems mainly to be induced by the hip while by the ankle in man (see [94]). Clinically it is found that patients with incomplete spinal cord lesion sub Th6 can relearn walking. In more caudal lesions, it becomes more difficult for patients with incomplete lesions to relearn walking. In the future, it has to be explored with the functional MRI [8] for prognostic reasons where the spinal locomotor centre for different movements is located and what spinal segments and to what degree are impaired. In the above mentioned patient with an incomplete lesion sub C5, the spinal locomotor centre was most likely not impaired. However, the afferent input patterns are impaired because of pathologic movement due to the lesion. With support, the patient moves rather physiologically, but the motor program remains more or less pathologic [94]. Therefore, the lesion-induced unbalanced descending control system (also partly caused by the lesioned ascending afferent input to supraspinal centres (see also [94]) gives rise to false activation times of some muscles. Since tetraparetics (incomplete tetraplegics) can improve their walking when walking on beach sand (deformable ground), it mainly is a stronger afferent input to the spinal cord and the supraspinal control system that improves walking. It will be shown in a following paper [94] that an incomplete tetraplegic could relearn running, besides other movements, by training rhythmic, stereotyped, dynamic, natural movements. Probably, besides training-induced reorganization or changes of spinal cord neuronal networks, supraspinal reorganization of the descending control system took place to compensate for unbalanced lesion of ascending afferent and control fibres. Nearly nothing is known concerning the nature of changes. In a following paper [94] it will be shown on a frog model that localized membrane property changes in combination with synapse migration could be one possibility to achieve changes in the functional organization of neuronal networks.

Partial loss of the coordinating system and the stabilizing sensory feedback may change spinal oscillator coupling and may result in pathologic activation of two-joint muscles

In a patient who relearned running [94], the main cause for the limitation of further improvements of running and other kinds of locomotion was false activation of the left rectus femoris [94]. The rectus femoris muscle extends over two joints, namely hip and knee. Also in cerebral palsy [6] and hemiplegia [5], the two-joint muscles are often activated at the wrong phase of the locomotor cycle or show rather permanent activity. In such cases, orthopedists often transpose tendons to change partially a flexor into an extensor muscle or vice versa [22], to overcome the problem of false recruitment phases of muscles during the motor cycle.

If the phases of activation of muscles during the motor cycle do change following spinal cord lesion [94], cerebral palsy or hemiplegia, and if coupled spinal oscillators have two possible phases for oscillator coupling per oscillation cycle [90,93,94] (per somatic nervous system), and if coupled premotor spinal oscillators can change from alternating to symmetrical oscillatory firing [94] (phase coupling changes), then it is conceivable that with the impairment of the control system supraspinally (cerebral palsy, hemiplegia) or spinally (spinal cord lesion (tract fibres)), the critical two-joint muscles may show most dramatic recruitment changes per motor cycle. If, as discussed above, there is with ongoing phylogenesis more need for extrinsic control because of the increased lability of the coordinating system for motor control (and continence functions [90]), then with the partial loss of the coordinating system and the stabilizing sensory feedback (see above), a loss of specificy and a loss of functional splitting of muscle will follow.

The lost coordination and stability can be explained in the oscillator concept with the deterioration of oscillator properties. Spinal oscillators with broadened frequency band will couple more easily among functionally near oscillators (loss of functional splitting), and may not couple at all with functionally distant oscillators (loss of specificity) [94].

Especially the existence of two coupling phases per oscillation cycle in premotor spinal oscillators [93] gives rise to two possible pathologic muscle activations. First, the premotor spinal oscillators are activated at the wrong coupling phase of the oscillation cycle of two possible coupling phases per somatic nervous system. Motor units of an extensor muscle may now be recruited in the flexor phase. Second, the premotor spinal oscillators are coupling with other spinal oscillators at both phases of its oscillation cycle. Motor units are now recruited in the extensor and the flexor phase. This pathologic double-coupling in combination with broadened coupling phases may result in a rather permanent muscle activity. The loss of specificity and the loss of functional splitting of muscle will most seriously affect the critical two-joint muscles.

There are at least two possible treatments for the false muscle recruitment during the motor cycle. One can think mechanically and improve locomotion in the patient by transposing tendons or one can believe in the plasticity of the human nervous system and try to improve locomotion by a training-induced network plasticity. This research project follows the second line [94], in accordance with W.R. Hess who argued that one should not think too mechanically with respect to the functioning of the human nervous system.

In a subsequent paper [94], the false activation of two-joint muscles will further be analyzed with respect to the false organization of the spinal locomotor program including ontogenetic considerations.

Tremor

It is unlikely that the most important firing mode of the motoneurons, the oscillatory firing, would not be observable macroscopically in certain situations. Indeed, it was already Descartes [16] who wrote about tremor. During the last 100 years, many authors have sug-

gested rhythmic firing of neuronal networks that is responsible for rhythmic movements (trembling, tremor) of the body (trunk) and legs, arms and fingers (for Refs see [47,103]) The conclusions drawn by R Jung from measurements on tremor and clonus in 1941 [47] are nearly identical with the findings concerning the self-organization of spinal oscillators in an earlier [83,84] and this series of papers [91] Only, R Jung did not differentiate between different motoneuron types, and analyzed tremor by using mechanical and electromyographic recordings The similarity between the tremor frequencies and oscillator frequencies of a brain-dead human individual (physiologic case) and two paraplegic patients (pathophysiologic cases) has been described elsewhere [83,93] (see also below) Even though there is little doubt that the cause of tremor (and possibly of clonus) is the oscillatory firing of motoneurons, in detail, it has to be seen how the oscillatory firing turns out to become, or manifests itself in tremor Since in these measurements recordings are performed from sacral nerve roots which innervate the external sphincters of the urinary bladder and the rectum, the pelvic floor and some leg (foot) muscles, direct analyses are only possible with selection to those body parts Since only few α-motoneurons run to the legs through S4 and S5 nerve roots, we are left with muscles on which tremor has not been detected so far (continence muscles) On the other hand, it seems that the α_1, α_2 and α_3-motoneurons are the same all over the body [76], so that the principles will also hold for other body parts If joints are included in the tremor movements, different mechanical factors such as inertia and muscle stiffness come into play Anyhow, in reference to a very important measurement described in a following paper [93] it will be shown that spinal oscillators can build up external loops to muscle spindles and the oscillation frequency of spinal oscillators can be modulated, via these external loops, in a certain frequency range Most problems of the last 100 years concerning the understanding of tremor can be explained by the external loops to muscle spindles and the input from joints, Golgi tendon organs and skin The possibility that the oscillatory firing can be controlled in a certain frequency range by this external loop will give rise to the possibility to formate the pathologically oscillatory firing networks to fire more physiologically again and to reduce spasticity (false activation of muscles with respect to phase and activity level) with the gain of useful locomotion Indeed, it has been possible to enable, by training-induced network plasticity [98], an incomplete tetraplegic to run again [94]

From the changed properties of oscillators (Table 1) it is likely that tremor will change following incomplete spinal cord lesion From electromyographic recordings it can be seen that specific properties of motor unit firing (compound action potential of the muscle fibres innervated by the same motoneuron) are lost [94] The physiologic activation times of the muscles are partly lost [15,94,102]

Coupled half-oscillators for activating human trunk, continence and leg muscles?

Since there is little doubt that spinal oscillators (premotor neuronal network, motoneuron included) and other rhythmically firing neuronal subnetworks (propriospinal oscillators) are the original reason for tremor, the oscillator theory for the understanding of some functi-

ons of the CNS must be able to incorporate or explain the different kinds of tremor
In tremor, it is differentiated between tremor of the extremities and of the trunk Tremor of the limbs may be independent or changing with coordinated bilateral asymmetry In trunk muscles there is absolute coordination in tremor In head and trunk muscles of both sides it shows a symmetric alternating pattern (phase difference 180°) In rostral caudal direction, tremor shows certain constant phase relations [47] Trunk tremor has therefore very similar occurrence patterns as do phylogenetically old movements of the fins of certain fish [36] and the spinal locomotor organization in the lamprey [30,31]

In the lamprey, spinal cord segments produce the motor output underlying locomotion throughout a frequency range of 0 25 - 10 Hz (the frequency range measured in humans is 0 3 -10 Hz (Fig 3, [83])) The motor output can be subdivided into small pieces down to a few segments, each of which can produce rhythmic bursts of activity and a characteristic intersegmental coordination with a constant phase lag between consecutive segments Under intact conditions, this results in an undulatory wave travelling down the body and pushing the animal through the water Each segment contains about 100 motoneurons which supply different parts of the myotome The motoneurons of the left and right side provide alternating burst activity As the motoneurons of one side get excited, the motoneurons on the contralateral side become inhibited in a reciprocal fashion During a swim cycle each motoneuron thus goes through a phase of excitation followed by inhibition [30,31]

It was shown in Fig 14 that an α_1 and an α_2-motoneuron fired continuously oscillatory However, every second cycle the oscillation period was prolonged This kind of firing can possibly be interpreted as every second oscillation cycle being inhibited It is therefore conceivable that an oscillator circuit on one side was inhibited by an oscillator circuit from the other side and vice versa, in some similarity to the lamprey model Whereas motor pools to antagonistic muscle pairs in the lamprey lie on the opposite side of the cord, in quadrupeds motor pools to antagonists within a single limb are on the same side of the cord Further, alternation is the only coordination pattern observed in all intact, reduced, or spinal animals studied (page 159 of [11]) In many quadrupeds, limb muscles at a single cord level can exhibit a range of both alternating or symmetrical (walk and trot) and non-alternating or asymmetrical (canter, gallop etc) phase relations

In the lamprey locomotor system, the motoneurons in each segment show alternating left-right burst activity [30,31] It is therefore conceivable that also in man some oscillatory firing networks consist of two more or less coupled halves which may or may not show alternating long and short oscillation periods Motoneurons innervating antagonistic limb muscles (in man, a few motoneurons, innervating leg muscles, run through the lower sacral roots) run through the same root, whereas motoneurons innervating antagonistic trunk muscles (and possibly also continence muscles) will run through the opposite roots To provide evidence for half centre networks of continence muscles, one would have to record from the two halves of the left and right side of the medulla So far, this has not been possible with the single-nerve fibre AP recording method because this would require recording with four electrode pairs instead of two If coupled antagonistic spinal oscillators fire pathologically it

may be that one part of the oscillator fires more pathologically than the other half In the unbalanced case, it may then be that every second oscillation shows a different oscillation period even for coupled oscillators which normally show no alternating long and short oscillation periods. Anyhow, most likely the mutual inhibition (if existing) was not as strong as in the lamprey model, since the prolongation of the oscillation period was on average only 4

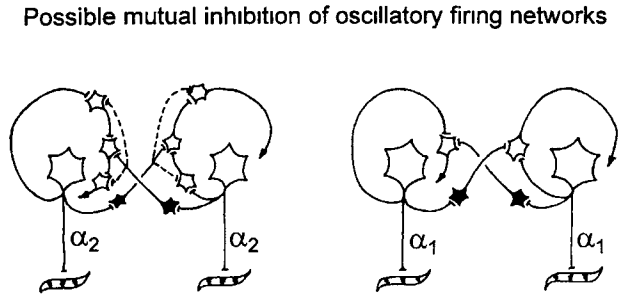

Figure 15. Schematic drawing of possible mutual inhibition of oscillatory firing neuronal networks The muscles indicated are not neccessarily activated antagonistically The filled somas are those of inhibitory cells Dashed axon branches in A indicate projections into the oscillatory firing networks $\alpha_{1,2} = \alpha$ motoneurons

ms (4 and 3 3 %) Nevertheless, these measurements indicate that there may be some mutual inhibition between spinal oscillators Further, this (reciprocal) inhibition may work differently for α_1 and α_2-motoneurons in that the projection onto the (antagonistic) motoneuron network for inhibition is more direct (less interneurons) for the α_1-motoneuron (Fig 15)

It was shown in Fig 3 that primary and secondary muscle spindle afferents project differently onto oscillatory firing α_1-motoneuronal circuits (the primary afferents project monosynaptically, the secondary ones project oligosynaptically) Therefore, also self-organizing projections can be expected from α_1 to α_2 oscillatory firing circuitry and vice versa Further research has to show how directly the reciprocal inhibition acts Simultaneous recordings from right and left nerve roots will provide further information

On the other hand, a change from alternating to symmetrical oscillatory firing has been observed electromyographically in man, which was correlated to a simultaneous phase change in synchronization of two other oscillatory firing motor units [94] This measurement indicates that alternating and symmetrical oscillatory firing are related to coupling changes among populations of interacting spinal oscillators in the human CNS Alternating oscillatory firing may therefore be due to reciprocal inhibition of half-centre oscillators, changes in the couplings of non-equal oscillators or mutual inhibition of oscillators driving antagonistic muscles.

So far, these measurements have provided no information on how each oscillation cycle of each oscillatory firing circuit is terminated Graham Brown who proposed the half-centre model hypothesized that a limiting factor could be fatigue of the inhibiting synapses, which causes the strength of synaptic transmission to decline with time Other possible intrinsic processes, now considered more plausible, are adaptation, in which a neuron responds to constant excitatory input with a declining rate of output, and post-inhibitory rebound, in which the threshold for excitation of a neuron decreases transiently as a result of past inhibition [48]

Intrinsic processes cannot be the only or main cause for the termination of the oscillation cycle. The extreme changes in the duration of consecutive oscillation periods and the reduction of the duration of the oscillation period following spinal cord lesions cannot be explained by changes of membrane properties alone. Large-scale changes of membrane properties are probably negligible after spinal cord lesions since most projections onto motoneurons come from the interneurons, and interneuron cell death following spinal cord lesions has not been observed so far. On the other hand, this reasoning provides no explanation for the spinal shock. Localized changes of membrane properties can however have substantial functional impact as is indicated in a frog model [94]. It is shown below that there are simple neuron wirings that can generate alternating oscillatory firing. But these simple fixed wirings can only explain one but not other network states.

Modelling of human neuronal subnetwork functions

It has been argued that the oscillatory firing with alternating long and short periods can simply be generated by a propriospinal oscillator which drives two interneurons which, in turn, drive with different delays the motoneuron to fire alternating oscillatory (Fig.16). Such simple neuronal wirings are supported by the argument that most important constructions of living organisms (genetic mutation and natural selection) prefer elegant and simple solutions.

Since nearly nothing is known concerning the integrative functions of the human nervous system, many speculations are possible. We therefore have to stik as much as possible to measurements. Indeed, the schematic model of Fig.16 can explain the alternating oscillatory firing of α_1-motoneurons, firing rhythmically with 1 AP. The alternating oscillatory firing of the α_2-motoneurons, firing with impulse trains consisting of several APs (Fig.14),

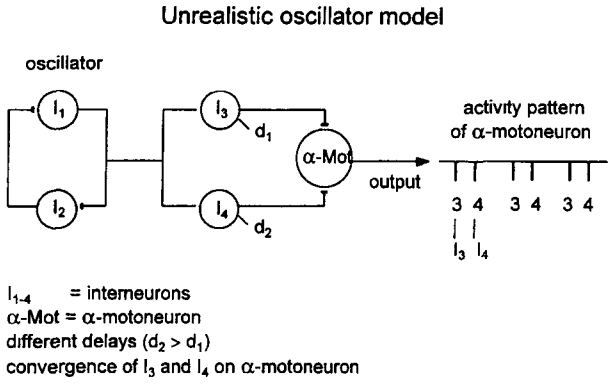

Figure 16. Simple oscillator model which can generate rhythmic firing with every second period prolongated The alternating oscillatory firing is generated by a divergent output from the oscillator, different delays of the interneurons and the convergence of the interneurons onto the motoneuron This oscillator model however, cannot explain the firing patterns of alternating oscillatory firing neuronal subnetworks and additional oscillator data (motoneuron is a part of the premotor spinal oscillator, no change is possible from alternating to symmetrical oscillatory firing, difficult to generate a 100 ms period by 2 interneurons, for further objections see text)

cannot be explained with that model Additional or different interneurons are necessary Further, there is some indication that the motoneuron itself is a part of the premotor spinal oscillator [83] If this is the case, then the model is not valid any more It has been measured further that when the motoneuron is not firing continuously or transiently oscillatory, then the motoneurons are activated approximately every 3s according to the size principle in each motoneuron group [79,81,82] This important different functional state, generating a certain low tonus in the muscles cannot be explained by the model Neither the change from alternating to symmetrical [94] can be explained by the model, similarly as the changing of coupling between different oscillators The model can mimic only one special network function and not all the others For modeling of neuronal functions of animals, see [111]

Modelling of human neuronal subnetworks makes only sense if all the known human data are incorporated Further, the problem for the time being is that nearly no human data are available Animal data, as for example synaptic transmission time (0 5 ms), time for the ascending phase of the exciting postsynaptic potential above threshold for spike generation (~ 2 ms) [111] or membrane properties, have to be measured, especially as there is indication that membrane properties of human neurons are different from those of the animal neurons E g , the conduction velocities of peripheral nerve fibres are much lower than those in the rat and in the cat, and transmission frequencies of up to 5 kHz have been measured in paraplegics [89], whereas textbooks give the highest value of 1 kHz

There are more neurons in the human body than people on earth, which does not point to subnetworks which consist only of a few neurons Maybe, hundreds of interneurons contribute to the oscillatory firing of neuronal subnetworks The quality of the human nervous system lies in its complexity to be able to adapt to the environment, and in its plasticity There may well be simple and elegant strategies for the self-organization of neuronal networks of the spinal cord according to afferent and supraspinal inputs as well

As long as the modelling of human neuronal subnetworks does not incorporate human data, the models may be useful in robotics and computer science, but they have nothing or nearly nothing to do with the human reality In the clinic, we need to understand the functioning of the human nervous system under physiologic and pathophysiologic conditions, and its capacity for reorganization, to adapt treatment to it Actually, the enormous functional possibilities contained in the human nervous system seem to make it possible that only a small part of the system is able to run the basic functions [94]

Origin of oscillatory firing

What is necessary for a neuronal system to produce self-sustaining oscillations, but not requiring phasic external input? The measuring situation, e g , is if in a man with a complete spinal cord lesion an α_2-motoneuron (FR) innervating the external anal sphincter fires oscillatory due to the isometric stretch of the anal sphincter induced by an anal catheter Two features are recognizable First, one action must inevitably be followed by its antagonistic action (sign reversal) Thus, excitation (or firing) of the motoneuron must be followed by inhibi-

tion Likewise, inhibition must lead to excitation (or firing) For example, excitation to initiate the impulse train (burst) must ultimately be followed by inhibition to terminate the burst Inhibition could include (1) activation of an intrinsic membrane current that tends to hyperpolarize the motoneuron, (2) synaptic inhibition, or (3) its functional equivalent, loss of excitation The second major feature of an oscillatory firing motoneuron is that there must be a delay between the initial action and its antagonist [21] A delay is necessary to allow one process (excitation or inhibition) to be expressed before the onset of its inevitable opposite action The delays are relatively long and close in duration to the cycle period

Oscillatory firing can originate in properties intrinsic to single cells (cellular), from the action of single synapses (synaptic) and from the self organization of an assembly of cells due to the input (network) and synapsing into complex circuits [23,96] It is indicated below that the main functional contribution of human spinal oscillators comes from the network properties

Definition of (biological) spinal oscillators

A premotor spinal oscillator is viewed as an assembly of interneurons (changing number of contributing interneurons) and a motoneuron which, by virtue of the intrinsic properties (preformated neuronal network = neuronal connectivity with a selection of synaptic strengths), is capable of self-organizing by pattern messages from supraspinal centres or the periphery in the form of spatio-temporal vectors The premotor spinal oscillator fires rhythmically with impulse trains according to the motoneuron type and is capable of undergoing relative transient coupling with other oscillators of spinal (motoneuronal (premotor) or purely interneuronal (propriospinal)) or supraspinal origin (especially brain stem) to generate systematic macroscopic pattern, e g locomotion or homeostatic regulation In these self-organized circuits, the activation is most probably maintained by circulating synchronized firing (closed „synfire chains") Stabilisation of the reverberatory activity in positive (re-excitatory) loops could be supported by processes similar to synaptic modulation

Since there is indication that motoneurons are a part of the rhythmically firing premotor neuronal network [83], the spinal oscillators are divided here into premotor spinal oscillators and propriospinal oscillators For high activation, the premotor spinal oscillators are the output network of neuronal networks, and the propriospinal oscillators are oscillatory firing subsystems, which generate movement patterns (Fig 20 of [94]) or homeostatic regulation

Transient coupling is generally necessary for relative coordination of the different rhythmic firing systems to generate an integrative function Typical coupling response phenomena have been observed in firing occurrence patterns of spinal oscillators [83] Rhythm coordination seems to be a basic principle of physiological self-organization of many rhythmic subunits There are many kinds of possible transitions between full independence and strict synchronization Complex physiological rhythmicity appears as a general principle of organization, allowing a compromise between stability and flexibility of adaptation If α-motoneuronal spinal oscillators become synchronized over longer time periods, tremor will

be created, which is disadvantageous Prolonged coupling of many premotor and propriospinal oscillators most likely hinders differentiated organization and results in pathologic neuronal network organization like spasticity Similarly, when in the cerebral cortex, the synchronized discharge of large masses of cells becomes excessive, spontaneous movements appear to a pathologic degree as in the epileptic attack, the smaller cell groups losing their individuality of differentiated function [43]

Cellular oscillator properties

Central neurons contain more numerous and complex ionic currents as originally described by Hodgkin and Huxley [34] for the squid axon Different combinations of these currents can impart radically divergent response characteristics to cells (for review, see [2,4,56,58]) Often, the underlying ionic currents are not as important as the nature of the response characteristics to which they give rise The important cellular properties which contribute to pattern generation include (in similarity to statements of Getting [24])

1 Threshold This property determines the level of excitation needed for an oscillator to start firing The threshold for self-organization of the spinal oscillator is given by adequate input (afferent or supraspinal) patterns in the nerve fibre group-spatio-temporal system Adequate input patterns probably trigger as much self-organization among interneurons that excitation just travels from the motoneuron (premotor oscillators) to the interneurons and back to the motoneuron via the afferent input facilitated recurrent excitation pathways, maybe in the form of „synfire chains"

2 Spike-frequency adaptation This property is manifested as a decrease in spike frequency (increase of interspike intervals of successive APs of an impulse train) with time during sustained depolarization of the motoneuron - Spike frequency adaptation is associated with the activation of slow outward potassium currents Adaptation is a self-inhibitory process as it depends upon the recent firing history of the cell, and tends to decrease the responsiveness of the cell for further firing Spike frequency adaptation can serve to shape burst structure (of the impulse train) [40], and it contributes to the regulation of cycle period length [23] approximately following the formula (for the human premotor spinal oscillators) $T = 70$ ms $+ n_{AP} \cdot 30$ ms (T = oscillation period, n_{AP} = number of APs per impulse train) under physiologic conditions

3 Postburst hyperpolarization Following an impulse train, APs were not observed in man Most likely, the motoneurons became hyperpolarized - Following a burst of spikes, many neurons become hyperpolarized for a period of time ranging from milliseconds to seconds (depending on the strength and duration of the preceding burst) The postburst hyperpolarization appears to be a manifestation of a mechanism similar to that responsible for spike-frequency adaptation [40,55] Both characteristics are usually present together Postburst hyperpolarization also is a self-inhibitory process producing an inhibition delayed until after a burst

According to Ekeberg [17] temporal recruitment (spike synchronization) is an important mechanism for determining the transient response of a pool of neurons and it may be related to the afterhypolarization of the neurons.

4 In an α_3-motoneuron (S), firing with impulse trains consisting of approx. 40 APs [73] every 0.7 seconds sometimes a short impulse train was observed ($\approx$ 5 APs) in between the impulse trains It could therefore be that postinhibitory rebound and delayed excitation [24] contributes to the oscillatory firing of the different types of motoneurons in man For endogenous and conditional bursters and synaptic properties, see [24]

Recurrent loop excitation and „inhibition of recurrent inhibition" for the oscillatory firing of motoneurons

Systems which are used infrequently and produce only a few cycles rely heavily upon a balance of synaptic excitation and inhibition for pattern generation [24]

Probably, cellular properties (points 1-4 above) and excitatory and inhibitory connections contribute to the rhythmic firing of spinal oscillators The question is, whether there is a need for recurrent excitation or whether the inhibition of the recurrent inhibition can explain rhythmic firing

Hultborn and Pierrot-Deseilligny [39] maintain that during voluntary tonic soleus contraction of increasing strength or during ramp contraction in man, the Renshaw cell recurrent inhibition is progressively diminished from an initially facilitated level, probably by supraspinal descending influences bypassing the motoneurons. The inhibitory influence on Renshaw cells from supraspinal sources appears to dominate and to offset the excitatory input derived from motoneuron excitation In the vicinity of the inhibited Renshaw cells motoneurons were found that were excited by the supraspinal stimulus with the appropriate discharge pattern to make them candidates for mediating the inhibition on the Renshaw cells Ross and Wittstock [65] reported changes in lumbar Renshaw cell activity correlated with vertical whole-body movements, indicating that macular afferents exert an inhibitory influence on Renshaw cells

Henatsch et al [33], upon conditioning stimulation of the contralateral nucleus ruber, found predominantly facilitation of various monosynaptic reflexes associated with depression of antidromic and orthodromic Renshaw cell discharges, again indicating a flexible coupling of the latter to their input-giving α-motoneurons It is not clear in many cases how the supraspinal effects on Renshaw cells are related to those on the α- (and/or γ-) motoneurons to which the Renshaw cells may be predominantly related

Both the Renshaw cells and Ia inhibitory interneurons exhibit rhythmical modulation of their discharge during fictive scratching and stepping [13,14,19,46] However, they do not belong to the rhythm generator since considerable changes of their activity upon stimulation of ventral roots do not influence the cycle duration [19,46] The Renshaw cells and Ia interneurons exert inhibitory action upon motoneurons, but they are not the neurons responsible for the basic pattern of rhythmic changes of the motoneuron membrane potential

Depolarization appears in motoneurons just at the moment of the maximum drive from Renshaw cells and Ia interneurons [13,19]. Since there probably is similarity between the network organization of premotor spinal oscillators and the rhythmically firing subnetworks, constructing the pattern generators (propriospinal oscillators), Renshaw cells and Ia inhibitory interneurons do not essentially contribute to the rhythm generation.

In connection with the excitatory and inhibitory interneurons of the lamprey it is likely that the alternating long and short durations of oscillation period (Fig.14) can be explained by mutual inhibition. An inhibition of recurrent inhibition in man however, can at best cancel the recurrent inhibition, but cannot explain the oscillatory firing of motoneurons.

If, for example, the recurrent inhibition is completely inhibited by supraspinal activation of spinal neuronal networks, then the oscillatory firing of the α-motoneurons must originate in the motoneuron cell itself. Probably, the α-motoneurons contribute to the oscillatory firing (see above), but cannot explain the oscillatory firing for at least two reasons. First, following spinal cord lesion, the rhythmically firing motoneurons change dramatically their oscillation period duration from one cycle to the next. Such oscillation period changes cannot be explained by an endogenous oscillatory property of individual motoneurons. Membrane properties are known to change following denervation [57]. However, following spinal cord lesion, no interneuron cell death has been observed so far (unpublished information). Since further the motoneurons get the majority of their input from interneurons, the denervation effect by the spinal cord lesion (destroyed spinal tracts) is only weak [110]. It has been shown that following partial denervation, membrane properties change in the denervated areas only ([67],Fig.21 of [94]). Since the synaptic contribution from tract fibres is but small, the overall membrane properties of the α-motoneurons probably change only little. Similar arguments may hold for the interneurons. On the other hand, it will be difficult with the above to explain the spinal shock. The large changes of the oscillation period duration seems to be explainable by membrane property changes allone. An endogenous burster cannot explain the changes in oscillation period. We have to think of a network producing the oscillatory firing. The spinal oscillators, which are under consideration herein, are those networks of which the motoneuron is a part (premotor neuronal network). Probably, oscillatory firing is generated by recurrent loop excitation.

Secondly, in normal human individuals, endogenous bursters cannot explain transient oscillatory firing and resetting of the cycle [92]. Endogenous bursters are thought to generate chronic rather than episodic rhythms.

If, as a working hypothesis, the motoneurons fire rhythmically with impulse trains, via recurrent excitatory loops (because the motoneuron seems to be a part of the premotor spinal oscillators [83]), why no recurrent excitation has been measured? Upon stimulating axon collaterals through electrical stimulation of ventral roots, only inhibitory potentials are recorded in α-motoneurons.

Sophisticated electrical stimulations of CNS neuronal networks are only a good research tool if the neuronal networks are „fixed wired". If the neuronal networks organize themselves according to the natural input patterns of afferent fibres and descending tract fibres,

artificial electrical stimulation represent artificial experimental conditions, and will give rise to artificial network organization.

It would be of importance to have intracellular recordings from oscillatory firing motoneurons. Most likely, one would record excitatory potentials similarly as for respiratory motoneurons [18]. Then, additional electrical stimulation of the ventral or dorsal root efferents may show competition between inhibitory and excitatory synaptic potentials. Anyhow, to explore natural functions and organizations, we have to stimulate naturally to generate natural organizations of the CNS. Probably, recurrent excitatory loops (maybe in the form of synfire chains), are only opened (facilitated) by adequate afferent input patterns if the necessary task groups of interneurons are activated. It is proposed that in the human spinal cord there does exist recurrent loop excitation besides recurrent inhibition, since recurrent inhibition cannot explain oscillatory firing of a neuronal subnetwork of which the motoneuron is a part.

In two sets of animal experiments it has been shown that Ib effects change dramatically during locomotory compared with static conditions. Before locomotion, Ib inputs produced inhibitory postsynaptic potentials, and during locomotion they produced excitatory postsynaptic potentials [25,61].

It has been measured in animals that rhythmogenesis was distributed along the rostrocaudal axis of the spinal cord with a stronger capability of the rostral segments of the lumbosacral cord compared with more caudal segments. The synchronization of motoneuron activity, as well as synaptic drive to caudal motoneurons, was mediated, at least in part, by axons running within the ventrolateral tract. Also, optical imaging showed that each successive rhythmic burst starts in the ventrolateral region (where the motoneurons are located) and then a Ca^{2+} wave invades the lateral part of the intermediate area (Rexed lamina VII and others) of the grey matter (where spinal interneurons are located) [3,38,59].

Synergetics

It is most important to get more data concerning the natural functions of the human CNS. On the other hand, we also need theoretical concepts or approaches which would allow us to understand such a complex system as the human CNS, and give us ideas to be able to develop adequate research strategies. The most advanced theoretical tool currently available is synergetics. The principles of self-organization are the central point of its study [32]. In synergetics, instead of considering an extremely high-dimensional space of all the variables, it is sufficient to consider the low-dimensional space of order parameters and to discuss the kinds of attractors available in such a low-dimensional space. When a system relaxes towards an equilibrium state, one may say that it relaxes to a so-called stable fixed point. When it oscillates coherently, one speaks of a limit cycle attractor, which is described in particular by a specific frequency. One major achievement of synergetics is the insight into the mechanism that produces macroscopic structures, be it temporal, spatial, or functional.

Mathematical predictions from populations of interacting biological oscillators compared to measurements on neuronal network data

Since in certain functional states of organization, at least parts of the neuronal networks of the human CNS do self-organize to oscillators which interact with each other to generate integrative functional structures, a biological oscillator approach to spinal cord functions seems (even though not most basic) of much practical value in explaining rhythmic network data with the properties of populations of interacting oscillators

The premotor spinal oscillators were functioning pathologically, probably because of nonuse and missing supraspinal drive, caused by the complete spinal cord lesion The physiologically functioning α_1-motoneuron oscillators can mathematically be approximated by a single oscillator or better, by a few interacting oscillators with monofrequency oscillation At least a system of several coupled oscillators is required to describe multifrequency oscillations and the occasional firing mode of α_2-oscillators (page 151 of [60]) Since there are easy changes of the oscillation periods from 130 ms to 160 and to 190 ms, a strong coupling has to be assumed between the suboscillators (page 156 of [60]) The premotor α_3-oscillators, consisting of many APs per impulse train and therefore, many units of 30 ms (Fig 3) and rather continuously changing oscillation frequency within a certain range probably consist of a large population of strongly interacting oscillators (page 156 of [60])

To a certain extent, the assumed approximated network structure of oscillators by synfire chains is compatible with the mathematically obtained results on populations of oscillators giving rise to oscillation periods of 130, 160 and 190 ms Several synfire chains with recurrent loop excitation, converging onto one motoneuron, can account for strong coupling of several oscillators with a few frequencies (α_2-oscillators) The repeated firing with impulse trains, probably generated by a transient long depolarization of the motoneuron, can also be generated electronically by a few coupled oscillators The premotor α_3-oscillators can be set up of many synfire chains The generation of numerous APs per impulse train can simply be achieved by coupling of a few oscillators The rather continuous change in oscillation frequency of α_3-oscillators [73] can be simulated mathematically and explained structurally by a number of similar long synfire chains with little length change of neighboring chains The coupling of oscillators is achieved by an overlapping of synfire chains From mathematical point of view, most premotor oscillators are a small population of strongly interacting suboscillators

With the deterioration of the neuronal networks because of nonuse, and missing supraspinal drive or missing synchronization with supraspinal oscillators, most likely the properties of the oscillators and the strength of mutual coupling changed Because of the broadening of the frequency band, masses of oscillators will couple and may give rise to mass contractions of muscles (loss of specificity and loss of functional splitting of muscle functions) Because of a reduced strength of coupling, certain stable functional states of coupled oscillators will not be reached any more (page 156 of [60]) Specific functions are lost and/or altered

How the neuronal networks do self-organize, and the change from one functional state of organization to another (transition of functional states) cannot be solved mathematically or physiologically alone. Network changes by plasticity or deterioration will anyway change the system under consideration. Because of these and other difficulties in mathematical approach it seems important in the long term to establish a mixed strategy involving analysis, computer simulations and measurements with different methods, to understand certain ranges of functioning of the networks, especially for stable or rather stable network states.

However, most important is the need for more data on human spinal oscillators, i.e. data on the physiologic regulation of coupling and recoupling of basic oscillatory firing subsystems; also, it is important to know what kinds of different basic oscillators do exist. At least for premotor oscillators, the assumption that neuronal network structures can be simulated by the interaction of one or two populations of very similar oscillators is not in accordance with the measurements in man. Two groups of oscillators were defined here, the premotor and the propriospinal oscillators. The premotor spinal oscillators split into α_1, α_2 and α_3-oscillators according to the type of the motoneuron integrated. In this work, no measurements were done on propriospinal oscillators. It was suggested earlier that preganglionic parasympathetic motoneurons may also fire oscillatory [90] or almost oscillatory. Thus, premotor parasympathetic oscillators may also exist. Since false interaction between different oscillator populations may occur following spinal cord lesion giving rise to important clinical problems (detrusor (driven by parasympathetic oscillators) - sphincter (driven by α_2-oscillators (Fig.3)) dyssynergia), the interaction between different oscillator populations should be analyzed mathematically (for further details, see [94]). Rhythmic firing and coupling has been observed in many biological systems [49]. Rhythmic coupling in the common brain stem system gives rise to respiratory sinus arrhythmia [52,64,97]. Oscillators are not only a principle network structure of the human CNS since they keep organized at least sometimes during the transition from one functional state of organization to the next [92], but their functioning can comparably easily be measured and may provide for the understanding of the functioning of the human CNS.

Natural impulse patterns and electrostimulation patterns in the treatment of spinal cord lesion

Figs. 9 and 10 show simultaneous impulse patterns secondary to a pin-prick or touch stimulation of sacral dermatomes with a needle. The impulse patterns of the more than 30 myelinated afferents (Fig. 9) were conducted in the fibres of a coccygeal root. Many further afferents in the adjacent S4 root will also have been activated upon that pin-prick since sacral dermatomes strongly overlap. 100 to 200 myelinated afferent fibres will have probably been activated upon touching the skin inside the anal reflex area [91], and will have given rise with their impulse patterns to a contraction of the anal sphincter to secure continence. Such a collection of spatiotemporally related impulse patterns is the input to the sacral neuronal networks to organize them in a way that the premotor spinal α_2 and α_3-oscillators are

activated to fire transiently oscillatory for the contraction time of the external anal sphincter.

One can imagine what an enormous number of specific spatiotemporally related input patterns enter the spinal cord with the movement-induced afferent input from the skin, muscle and joints to organize the neuronal networks of the spinal cord to induce and maintain primary automatic stepping in newborn infants [94]. The nervus suralis contains between 5,000 and 10,000 myelinated afferents (page 69 of [107]) which innervate a skin area of approx. 30 cm^2 of the foot sole.

The message from the receptors in the periphery for the self-organization of the CNS is enormous and specific. It is difficult to see how such a collection of spatio-temporally related afferent input patterns can be simulated by electrostimulation. Even though the natural impulse patterns in the motor system are less complex, one still has to consider that first, the F, FR and S-type muscle fibres get their specific activation patterns (Fig.3); and second, that they are not activated simultaneously but nicely distributed over time (Fig.3 of [90]). The action potentials retrogradely conducted upon the stimulation in the axons will enter the neuronal network via recurrent fibres and will supply at least the premotor spinal oscillators with artificial impulse patterns for pathologic network organization. It further has been shown that the nerve-muscle junctions do sprout and remodel with training [104,105], whereas a direct stimulation of muscle fibres will not increase the area covered by the motor endplate. Similar arguments will hold for stimulation of the CNS, especially the spinal cord. Further, one has to remember that the pattern of electrical stimulation changes the functional properties of muscle fibres [106], as is experienced upon electrical stimulations of the nervous system in very high spinal cord lesions, when the diaphragm changes its speed of contraction with electrical stimulation. It seems therefore that electrostimulation could be a substitute for a missing natural therapy in a very few cases only.

References

1. Abeles M. (1982): Local Cortical Circuits. An Electrophysiological Study. Springer, Berlin
2. Adams D.J., Smith S.J., Thompson S.H. (1980): Ionic currents in molluscan soma. Annu. Rev. Neurosci. 3 : 141-167
3. Bayev K.V., Dekhtyarenko A.M., Zavadskaya T.V., Kostyuk P.G. (1979): Activity of lumbar interneurons during fictitious locomotion of thalamic cats. Neirofiziologiya (Kiev) 11: 329-338
4. Berridge M.J., Rapp P.E. (1979): A comparative survey of the function, mechanism and control of cellular oscillators. J. Exp. Biol. 81: 217-279
5. Bobath B. (1994): Adult Hemiplegia, Evaluation and Treatment. Butterworth Heinemann, Oxford
6. Bobath K. (1980): A Neurophysiological Basis for the Treatment of Cerebral Palsy. William Heinemann Medical Books Ltd., London

7. Brindley G.S., Polkey C.E., Rushton D.N., Cardozzo L. (1986): Sacral anterior root stimulation for bladder control in paraplegia: the first 50 cases. J. Neurol. Neurosurg. Psychiatr. 49: 1104-1114
8. Buonocore M.H., Hecht S.T. (1995): Functional magnetic resonance imaging depict the brain in action. Nature Medicine 1: 379-381
9. Coggeshall R.E., Applebaum M.L., Fazen M., Stubbs T.B., Sykes M.T. (1975): Unmyelinated axons in human ventral roots, a possible explanation for the failure of dorsal rhizotomy to relieve pain. Brain 98: 157-166
10. Cohen A.H., Wallén P. (1980): The neuronal correlate of locomotion in fish: „Fictive swimming" induced in an in vitro preparation of the lamprey spinal cord. Exp. Brain Res. 41: 11-18
11. Cohen A.V. (1988): Evolution of the vertebrate central pattern generator for locomotion. In: Cohen A.H., Rossignol S., Grillner, S. (Eds.), Neural Control of Rhythmic Movements in Vertebrates, pp.129-165, John Wiley & Sons, New York
12. Creed R.S., Denny-Brown J.G., Eccles J.G., Lidell E.G.T., Sherrington C.S. (1932): Reflex Activity of the Spinal Cord. Clarendon Press, Oxford
13. Deliagina T.G., Feldman A.G. (1981): Activity of Renshaw cells during fictive scratch in the cat. Exp. Brain Res. 42: 108-115
14. Deliagina T.G., Orlovsky G.N. (1980).: Activity of Ia inhibitory interneurons during fictitious stretch reflex in the cat. Brain Res. 193: 439-447
15. Dietz D., Colombo G., Jensen L. (1994): Locomotor activity in spinal man. Lancet 344: 1260-1263
16. Descartes R. (1649): Les passion de l'âme. Article XI & CXVIII, Amsterdam
17. Ekeberg Ö. (1993): Response properties of a population of neurons. Int. J. Neur. Syst. 4:1-13
18. Euler C. von (1983): On the central pattern generator for the basic breathing rhythmicity. J. Appl. Physiol. Respirat. Environ. Exercise Physiol. 55: 1647-1659
19. Feldman A.G., Orlovsky G.N. (1975): Activity of interneurons mediating reciprocal Ia inhibition during locomotion. Brain Res. 84: 181-194
20.Forssber H. (1979): On integrative motor functions in the cat's spinal cord. Acta Physiol. Scand., Suppl. 474: 1-56
21. Friesen W.O., Block G.D. (1984): What is a biological oscillator? Amer. J. Physiol. 262: 847-851
22. Gage J.R. (1992): Distal hamstring lengthening / release and rectus femoris transfer. In: Sussman M.D. (Ed.), The Diplegic Child, pp. 317-336, Rosement: AADS
23. Getting P.A. (1983): Mechanism of pattern generation underlying swimming in Tritonia. II Network reconstruction. J. Neurophysiol. 49: 1017-1035
24. Getting P.A. (1988): Comparative analysis of invertebrate central pattern generator. In: Cohen A.H., Rossignol A.H., Grillner, S. (Eds.), Neural Control of Rhythmic Movements in Vertebrates, pp. 101-127, John Wiley & Sons, New York
25. Gossard J.-P., Brownstone R.M., Barajon I., Hultborn H. (1994): Transmission in a loco-

motor-related group Ib pathway from hindlimb extensor muscles in the cat. Exp. Brain Res. 98: 213-228

26. Grillner S., Perret C., Zangger P. (1976).: Central generation of locomotion in spinal dogfish. Brain Res. 109: 255-269
27. Grillner S., Kashin S. (1976): On the generation and performance of swimming in fish. In: Herman R., Grillner S., Stein P., Stuart D. (Eds.), Neural Control of Locomotion, Vol.18, pp. 181-202, Plenum Press, New York
28. Grillner S., Zangger P. (1979): On the central generation of locomotion in the low spinal cat. Exp. Brain Res. 34: 241-261
29. Grillner S , Zangger P. (1984): The effect of dorsal root transection on the efferent motor pattern in the cat's hindlimb during locomotion. Acta Physiol. Scand. 120: 393-405
30. Grillner S., Buchanan J.T., Wallen P., Brodin L. (1988): Neural control of locomotion in lower vertebrates: From behavior to ionic mechanisms. In: Cohen A.H., Rossignol S., Grillner S: (Eds.), Neural Control of Rhythmic Movements in Vertebrates, pp. 1-40, Wiley, New York
31. Grillner S., Wallen P., di Prisco G.V. (1991): The lamprey locomotor system-Basic locomotor synergy. In: Shimamura M., Grillner S., Edgerton V.R. (Eds.), Neurobiological Basis of Human Locomotion, pp. 77-92, Japan Scientific Societies Press, Tokyo
32. Haken H. (1980): Synergetics - Can it help physiology? In: Haken H., Koeppchen H.P. (Eds.), Rhythms in Physiological Systems, pp.155-164, Springer-Verlag, Berlin.
33. Henatsch H.-D., Meyer - Lohmann J., Windhorst U., Schmidt J. (1986): Differential effects of stimulation of the cat"s red nucleus on lumbar alpha motoneurones and their Renshaw cells. Exp. Brain Res. 62: 161-174
34. Hodgkin A.L., Huxley A.F. (1952): A quantitative description of membrane current and its application to conduction and excitation in nerve. J. Physiol. (London) 117: 500-544
35. Hoffmann P. (1934): Die physiologischen Eigenschaften der Eigenreflexe. Erg. Physiol. 36: 15-108
36. Holst E.v. (1939): Die relative Koordination als Phänomen und als Methode zentralnervöser Funktionsanalyse. Erg. Physiol. 42: 228-306
37. Holst E.v., Mittelstedt H. (1950): Das Reafferenzprinzip (Wechselwirkungen zwischen Zentralnervensystem und Peripherie). Naturwissenschaften 20: 464-476
38. Ho S., O'Donovan J. (1993): Regionalization and intersegmental coordination of rhythm-generating networks in the cord of the chick embryo. J. Neurosci. 13: 1354-1371
39. Hultborn H., Pierrot-Deseilligny E. (1979): Changes in recurrent inhibition during voluntary soleus contraction in man studied by an H-reflex technique. J. Physiol. (London) 297: 229-251
40. Hume R.I., Getting P.A. (1982): Motor organization of Tritonia swimming. III. Contribution of intrinsic membrane properties to flexion neuron burst formation. J. Neurophysiol. 47: 91-102

41. Jacobson R.D., Hollyday M. (1982): A behavioral and electromyographic study of walking in the chick. J. Neurophysiol. 48: 238-256
42. Jacobson R.D., Hollyday M. (1982): Electrically evoked walking and fictive locomotion in the chick. J. Neurophysiol. 48: 257-270
43. Jaspers H.H., Andrews H.L. (1983): Brain potentials and voluntary muscle activity in man. J. Neurophysiol. 1: 87-100
44. Jennekens F.G.I., Tomlinson B.E., Walton J.N. (1971): Data on the distribution of fibre types in five human limb muscles. An autopsy study. J. Neurol. Sci. 14: 245-257
45. Johannson R.S. (1978): Tactile sensibility in the human hand: Receptive field characteristics of mechanoreceptive units in the glabrous skin area. J.Physiol. 281: 101-123
46. Jordan L.M., Pratt C.A., Menzies J.E. (1981): Intraspinal mechanisms for the control of locomotion. Adv. Physiol. Sci. 1: 183-185
47. Jung R. (1941): Physiologische Untersuchungen über den Parkinsontremor und andere Zitterformen beim Menschen. Zschr. Ges. Neurol. Psychiat. 173: 263-332
48. Kandel E.R., Schwartz J.H., Jessel T.M. (1991): Principles of Neural Science. Prentice-Hall International Inc., London, pp. 581-584
49. Koepchen H.P. (1990): Physiology of rhythms and control systems: An integrative approach. In: Haken H., Koepchen H.P. (Eds.), Rhythms in Physiological Systems, pp. 3-20, Springer-Verlag, Berlin
50. Kopel N. (1986): Modeling CPGs: A robust approach. In: Grillner S., Stein P.S.G., Stuart D., Forssberg H., Herman R. (Eds.), Neurobiology of Vertebrate Locomotion, pp. 383-385, Macmillian, London
51. Kopell N. (1988): Toward a theory of modelling central pattern generators. In: Cohen A.H., Rossignol S., Grillner S. (1988): Neural Control of Rhythmic Movements in Vertebrates, pp. 369-413, John Wiley & Sons, New York
52. Lambertz M., Rittweger J.E., Kluge W., Langhorst P. (1992): The common brainstem system (CBS): Dynamic properties of the functional organization and their influence on signal processing. Wiss. Z. Humboldt-Univ. Berlin Richtung Med. 41: 83-84
53. Loughlin M. (1993): Muscle Biopsy, A Laboratory Investigation, Butterworth-Heinemann
54. Matthews P.B.C. (1984): Evidence from the use of vibration that the human long-latency stretch reflex depends upon spindle secondary afferents. J. Physiol. (London) 348: 383-415
55. Meech R.W. (1974): Calcium influx induces a post-tetanic hyperpolarization in Aplysia neurons. Comp. Biochem. Physiol. A. 48: 387-395
56. Meech R.W. (1979): Membrane potential oscillations in molluscan „burster" neurons. J. Exp. Biol. 81: 93-112
57. Miledi R., Parker I., Schalow G. (1981): Calcium transients in normal and denervated slow muscle fibres of the frog. J. Physiol. (London) 318: 191-206
58. Noble D. (1983): Ionic mechanisms of rhythmic firing. In: Roberts A., Roberts B.L. (Eds.), Neural Origin of Rhythmic Movements, pp. 1-28, Cambridge University

Press, Cambridge
59 Orlovsky G N , Feldman A G (1972) Classification of lumbosacral neurons according to their discharge patterns during evoked locomotion Neirofiziologiya (Kiev) 4 410-417
60 Pavlidis T (1973) Biological Oscillators Their Mathematical Analysis Academic Press, New York
61 Pearson K G , Collins D F (1993) Reversal of the influence of group Ia afferents from plantaris on activity in medial gastrocnemius muscle during locomotor activity J Neurophysiol 70 1009-1017
62 Perret C , Cabelguen J M (1980) Main characteristics of the hindlimb locomotor cycle in the decorticate cat with special reference to bifunctional muscles Brain Res 187 333-352
63 Rand R H , Cohen A H , Holmes P J (1988) Systems of coupled oscillators as models of central pattern generators In Cohen A H , Rossignol S , Grillner S (Eds), Neural Control of Rhythmic Movements in Vertebrates, pp 333-367, John Wiley & Sons, New York
64 Rittweger J E , Kluge W , Langhorst P , Lambertz M (1992) Rhythmical properties of the common brainstem system (CBS) Wiss Z Humboldt-Univ Berlin Richtung Med 41 91-94
65 Ross H -G , Wittstock C (1987) Renshaw cell activity in falling cats J Physiol (London) 388 83-99
66 Rushton W A H (1945) Resistance artifact in action potential measurements J Physiol (London) 104 19P-20P
67 Schalow G , Schmidt H (1979) Local development of action potentials in slow muscle fibres after complete or partial denervation Proc R Soc , B 203 445-457
68 Schalow G (1985) The problem of cauda equina nerve root identification Zentralblatt Neurochir 46 322-330
69 Schalow G , Aho A , Lang G (1987) Nerve fibre counts for an intercostal nerve to cauda equina nerve root anastomosis Zentralblatt Chir 112 457-461
70 Schalow G , Lang G (1989) Electrodiagnosis of human dorsal sacral nerve roots by recording afferent and efferent extracellular action potentials Neurosurg Rev 12 223-232
71 Schalow G (1990) Feeder arteries, longitudinal trunks and arterial anastomoses of the lower human spinal cord Zentralblatt Neurochir 51 181-184
72 Schalow G (1991) Conduction velocities and nerve fibre diameters of touch, pain, urinary bladder and anal canal afferents and (and (-motoneurons in human dorsal sacral nerve roots Electromyogr Clin Neurophysiol 31 265-296
73 Schalow G (1991) Oscillatory firing of single human sphincteric α_2 and α_3-motoneurons reflexly activated for the continence of urinary bladder and rectum Restoration of bladder function in paraplegia Electromyogr Clin Neurophysiol 31 323-355
74 Schalow G , Aho A , Lang, G (1992) Microanatomy and number of nerve fibres of the

lower intercostal nerves with respect to a nerve anastomosis Donor nerve analysis I (IV), Electromyogr Clin Neurophysiol 32 171-185

75 Schalow G (1992) Number of fibres and fibre diameter distributions of nerves innervating the urinary bladder in humans Acceptor nerve analysis II (IV) Electromyogr Clin Neurophysiol 32 187-196

76 Schalow G , Barth H (1992) Single-fibre action potential recording from the nerve to the musculus obliquus externus abdominis following pin-prick in humans III (IV) Electromyogr Clin Neurophysiol 32 197-205

77 Schalow G (1992) Impulse pattern, innervation density and two point discrimination of skin and mucosal afferents in humans Consideration for a sensory reinnervation of urinary bladder and anal canal in spinal cord lesion IV (IV) Electromyogr Clin Neurophysiol 32 259-285

78 Schalow G , Barth H (1992) Group conduction velocities and nerve fibre diameters of α and γ motoneurons from lower sacral nerve roots of the dog and humans Gen Physiol Biophys 11 85-99

79 Schalow G (1992) Recruitment within the groups of α_1, α_2 and α_3-motoneurons in dogs and humans following bladder and anal catheter pulling Gen Physiol Biophys 11 101-121

80 Schalow G (1992) Ventral root afferent and dorsal root efferent fibres in dog and human lower sacral nerve roots Gen Physiol Biophys 11 123-131

81 Schalow G , Wattig B (1993) Recruitment of α and γ-motoneurons in rats, dogs and humans Electromyogr Clin Neurophysiol 33 387-400

82 Schalow G (1993) Recruitment of motoneurons in the occasional firing mode in paraplegics Electromyogr Clin Neurophysiol 33 401-408

83 Schalow G (1993) Spinal oscillators in man under normal and pathologic conditions Electromyogr Clin Neurophysiol 33 409 426

84 Schalow G (1993) Phase-correlated adequate afferent action potentials as a drive of human spinal oscillators, Electromyogr Clin Neurophysiol 33 465-476

85 Schalow G (1993) Action potential patterns of intrafusal γ and parasympathetic motoneurons, secondary muscle spindle afferents and an oscillatory firing α_2-motoneuron, and the phase relations among them in humans Electromyogr Clin Neurophysiol 33 477 503

86 Schalow G , Zach G A (1994) Nerve compound action potentials analysed with the simultaneously measured single fibre action potentials in humans Electromyogr Clin Neurophysiol 34 451-465

87 Schalow G , Bersch U , Gocking K , Zach G A (1994) Interspike intervals of secondary muscle spindle and urinary bladder afferents in relation to the oscillation periods of sacral spinal oscillators for continence in man Physiol Res 43 7-18

88 Schalow G , Zach G A , Warzok R (1995) Classification of human peripheral nerve fib re groups by conduction velocity and nerve fibre diameter is preserved following spinal cord lesion J Auton Nerv Syst 52 125-150

89 Schalow G , Bersch U , Gocking K , Zach G A (1995) Detrusor-sphincteric dyssynergia in paraplegics compared with the synergia in a brain-dead human by using the single-fibre action potential recording method J Auton Nerv Syst 52 151-180

90 Schalow G , Bersch U , Michel D , Koch H G (1995) Detrusor-sphincteric dyssynergia in humans with spinal cord lesions may be caused by a loss of stable phase relations between and within oscillatory firing neuronal networks J Auton Nerv Syst 52 181-202

91 Schalow G , Zach G A (1996) Mono and polysynaptic drive of oscillatory firing α_1 (FF) and α_2-motoneurons (FR) in a patient with a spinal cord lesion Gen Physiol Biophys 15, Suppl 1, 57-74

92 Schalow G , Zach G A (1996) Reflex stimulation of continuously oscillatory firing α and α-motoneurons in patients with spinal cord lesion Gen Physiol Biophys 15, Suppl 1, 75-93

93 Schalow G , Zach G A (1996) External loops of human premotor spinal oscillators identified by simultaneous measurements of interspike intervals and phase relations Gen Physiol Biophys 15, Suppl 1, 95-119

94 Schalow G , Blanc Y , Jeltsch W , Zach G A (1996) Electromyographic identification of spinal oscillator patterns and recouplings in a patient with icomplete spinal cord lesion Oscillator formation training as a method to improve motor activities Gen Physiol Biophys 15, Suppl 1, 121-220

95 Schroder J M (1982) Pathologie der Muskulatur Springer-Verlag, Berlin

96 Selverston A I , Miller J P , Wahdepuhl M (1983) Cooperative mechanisms for the pro duction of rhythmic movements In Roberts A , Roberts B L (Eds), Neural Origin of Rhythmic Movements, pp 55 88, Cambridge University Press, Cambridge

97 Schulz G , Lambertz M , Schulz B , Langhorst P , Krienke B (1985) Reticular formation of the lower brainstem A common system for cardio-respiratory and somatomotor function discharge pattern of neighboring neurons influenced by somatosensory afferents J Auton Nerv Syst 9 433-449

98 Tsukahara N (1981) Synaptic plasticity in the mammalian central nervous system Annu Rev Neurosci 4 351-379

99 Vallbo A B , Hagbarth K -E , Torebjork H E , Wallin, B G (1979) Somatosensory proprioceptive, and sympathetic activity in human peripheral nerves Physiol Rev 59 919-957

100 von der Malsburg C (1985) Nervous structures with dynamical links Ber Bunsen-Ges Phys Chem 89 703-710

101 Wallen P , William T L (1984) Fictive locomotion in the lamprey spinal cord in vitro compared with swimming in the intact and spinal animal J Physiol (London) 347 225-239

102 Wernig A , Muller S (1992) Laufband locomotion with body weight support improved walking in persons with severe spinal cord injuries Paraplegia 30 229-238

103 Windhorst U (1988) How Brain-like is the Spinal Cord Springer-Verlag, Berlin

104. Wernig A., Herrera A.A. (1986): Sprouting and remodelling at the nerve-muscle junction. Prog. Neurobiol. 27: 251-291
105. Wernig A., Anzil A.P., Bieser A. (1981): Formation and regression of synaptic contacts in the adult muscle. In: Flohr H., Precht W. (Eds.), Lesion-Induced Neuronal Plasticity in Sensorimotor Systems, pp. 38-50, Springer, Berlin
106. Schmidt H., Schalow G. (1983): In-vitro and in-vivo experiments on the incorporation of Na- channels into the membrane of frog slow muscle fibres. In: A.H. Bretaa (Ed.), Membrane Permeability: Experiments and Models, Techsearch Adelaide
107. Dyck P.J., Thomas P.K. (1993): Peripheral Neuropathy, Volume I. Saunders Company, Philadelphia
108. Ingbert C. (1903): An enumeration of the medullated nerve fibres in the dorsal roots of the spinal nerves of man. J.Comp. Neurol. 13: 53
109. Paintal A.S. (1966): The influence of diameter of medullated nerve fibres of cats on the rising and falling phases of the spike and its recovery. J. Physiol. (London) 184: 791-811
110. Bernstein J.J., Wells M.R., Bernstein M.E. (1978): Spinal cord regeneration: synaptic renewal and neurochemistry. In: Cotman C.W. (ed), Neuronal Plasticity. Raven Press, New York, pp. 49-71
111. Janco J., Stavrovskř I., Pavlßsek J. (1994).: Modeling of neuronal functions: a neuron-like element with the graded response. Computer Artif. Intel. 13: 603-620