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External Loops of Human Premotor Spinal Oscillators Identified by Simultaneous Measurements of Interspike Intervals and Phase Relations

G SCHALOW and G A ZACH*

Department of Clinical Research, Swiss Paraplegic Centre Nottwil, CH-6207 Nottwil, Switzerland

Abstract. Single nerve-fibre action potentials (APs) were recorded extracellularly from α and γ-motoneurons and secondary muscle spindle afferents from a ventral S4 nerve root (some afferents are contained in lower sacral motor roots) in an individual with traumatic spinal cord lesion sub TH1 Simultaneous interspike intervals (IIs) of, and phases between, the APs of 5 nerve fibres were measured, and distributions were constructed

The II distributions were of a broad peak type Phase distributions showed 1 to 3 peaks interpreted as phase relations between the firings of the nerve fibres Under certain phase relations, the rhythmic firing of α and γ-motoneurons is further interpreted as an interaction of oscillatory firing neuronal subnetworks driving α and γ-motoneurons

Following repetitive touch and pin-prick stimulation in- and outside the anal reflex area, the II distributions of α and γ-motoneurons and of secondary spindle afferents assimilated partly or fully, while preserving their phase relations This coordinated firing is interpreted as the oscillatory firing of α neuronal networks building up an external loop to the periphery via the γ-loop

Upon touch, pin-prick, and anal reflex stimulation, and anal and bladder catheter pulling, the values and the number of the phase relations changed Mostly two phase relations per oscillation cycle were observed Two phase relations probably represent the physiologic case for the somatic nervous system Only one phase relation was found when full synchronization of all units occurred Three phase relations were found when the parasympathetic nervous system division interacted with the somatic one

Based on data obtained from brain-dead individuals it is discussed that the increased synchronization and instability in the number and the values of phase relations suggested pathologic functioning of the caudal functionally disconnected spinal cord in patients with spinal cord lesions Oscillatory firing neuronal networks, which lost their specific properties, interacted more easily and unspecifically with other oscillatory firing networks

Further, it is discussed that physiologic tremor is caused by chance synchronization of oscillatory firing neuronal networks and therefore originates in the central nervous system (CNS).

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* Clinic Director

Since spinal oscillators build up external loops to the periphery, it is suggested that in patients with incomplete spinal cord lesions it should be possible to re-preformate oscillatory firing neuronal networks by a rhythm training, to reduce spasticity and to re-train useful movements, especially locomotion

Key-words: Human – Spinal cord injury – Single nerve-fibre action potentials – Interspike intervals – Phase relations – Spinal oscillators – External loop – Synchronization

Introduction

Two concepts have been developed to interpret central nervous system (CNS) functions of the human spinal cord One, supported by the Sherrington school [8], rests upon the observation of the monosynaptic stretch reflex and explains human CNS functions through reflexes all reflectory, excitatory and inhibitory actions take place via a direct action onto the motoneuron pool itself (reflex theory) The other concept, supported by v Holst [18] and Jung [19], rests upon the basic observation of rhythmic movements, occurring in physiologic tremor the most basic mechanism for coordinated movements is the „Schaltzellenapparat“ (neuronal network) of the spinal cord, onto which all impulses converge (oscillator theory), this concept also admits that there are spinal pathways which bypass the „Schaltzellenapparat“ and synapse directly onto the motoneurons

Based on the classification scheme of the human peripheral nervous system (Figs 1,11 of [33]), this recent, completely new development [24-39] in human neurophysiology brings further insight into the oscillator theory, and derives new knowledge from analyses of simultaneous natural impulse patterns of single afferent and efferent human nerve fibres (Fig 1) Upon receiving input into the spinal cord, preformatted neuronal networks are getting self-organized and reorganized into spinal oscillators which in turn undergo relative coordination upon inputs from receptors of the skin, joints and muscles and supraspinal centres, this signal processing bears some similarity with what has been a new understanding of how brain functions [42]

Oscillatory firing motoneurons were discovered [25] by splitting multi-unit recordings into simultaneous single-unit impulse patterns of afferent and efferent fibres (Fig 1) The motoneurons are driven by secondary muscle spindle and other afferents [30-32] to serve continence and other functions [32-35] Following spinal cord injury, spinal oscillators were observed to fire less regularly and with impulse trains [28,36] different from normal [25], probably because of both the isolation of the spinal cord from supraspinal centres due to the cord injury, and the isolation from the periphery due to the loss of mobility (nonuse) So, the resonance frequency range for an α_2-motoneuron (FR) grew from approx 1 Hz to 9 Hz [28] The premotor spinal oscillators, probably recruited by central pattern generators (generated by coupling of propriospinal oscillators), lost their specific functions [28,36], were more easily excited (because of the loss of supraspinal inhibition) and got excited at frequencies different from normal

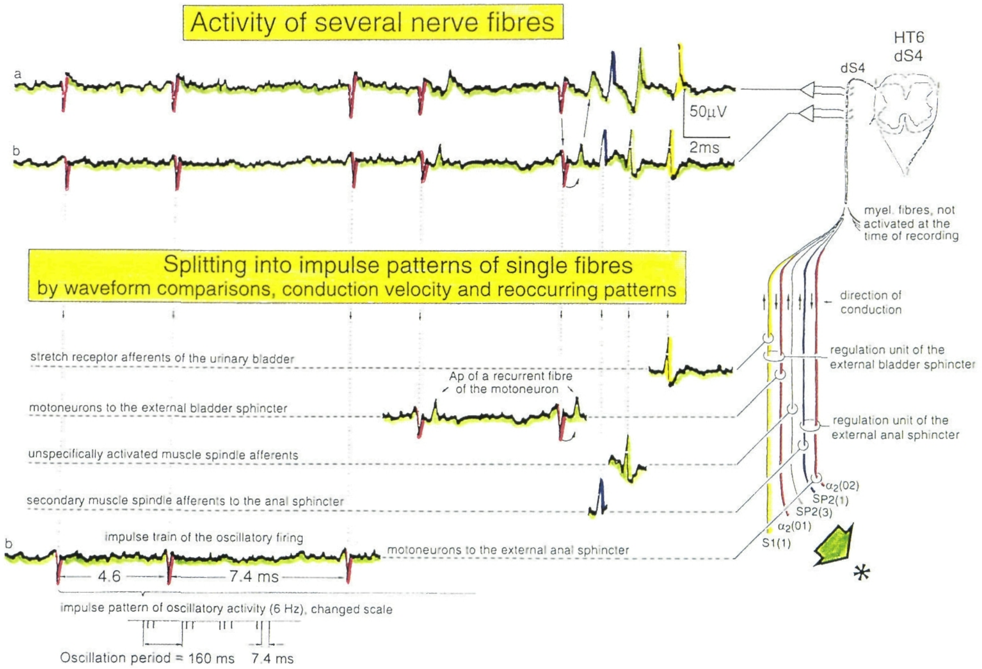

Figure 1. Schematic splitting of the activity of several nerve fibres into simultaneous impulse patterns of single fibres *by comparing waveforms, conduction velocities and reoccurring characteristic impulse patterns (rhythmic firing* of sphincteric motoneurons). The different conduction times and waveforms were recognized on an expanded time scale. „*" see Fig. 9 of [35] for receptor sites and the location of the muscles which are innervated by the sphincteric motoneurons. Stretch receptor and secondary muscle spindle afferents contribute to the drive of sphincteric motoneurons and form, together with other afferents, regulation units.

In this paper we report of simultaneous recordings of impulse patterns from two α-motoneurons, two secondary muscle spindle afferents and one dynamic fusimotor obtained using the single nerve-fibre action potential recording method. By analysing simultaneously interspike interval and phase distributions of the activity of the 5 units, it will be shown that spinal oscillators can synchronize, and that rhythmic firings originate in the neuronal networks of the spinal cord (generally CNS). This single measurement of regulatory functions of the human CNS is a key measurement to understand physiologic tremor and to develop a treatment (oscillator formation training) for patients with incomplete spinal cord injury [39].

Methods

Single-fibre action potentials were recorded extracellularly from undissected nerve roots with two pairs of platinum wire electrode pairs (electrode pair distance 10 mm; electrode distance in each pair 4 mm) at two sites, preamplified (x1000), filtered (RC-filter, passing

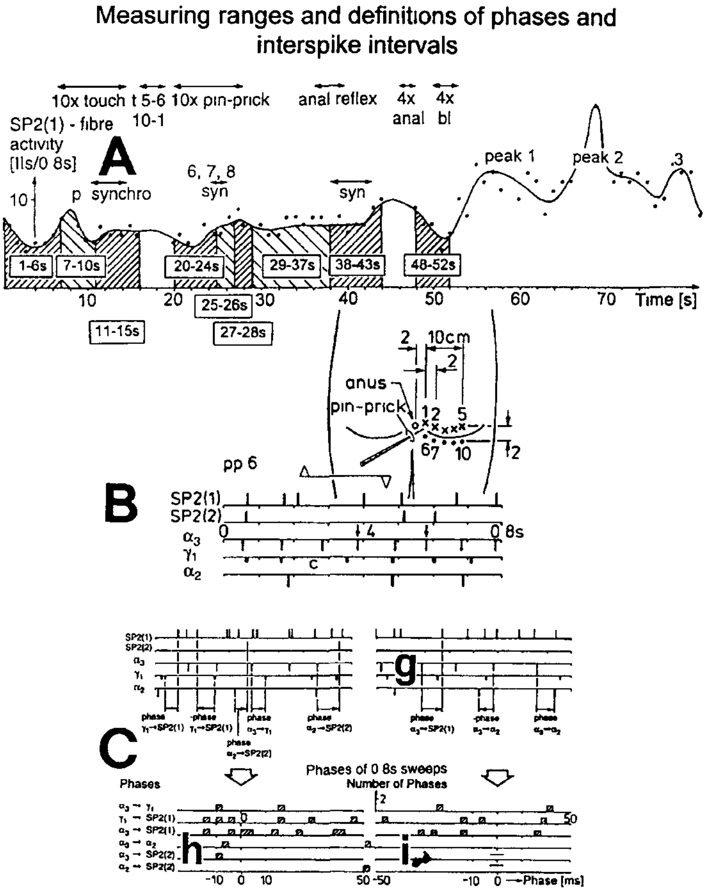

Figure 2. (A) Activity level of secondary muscle spindle afferent fibre SP2(1) in dependence on time (see also Fig 6a of [35]) 10x touch, touching sites 1 to 10 shown in B, t 5-6, touching alongside the skin from site 5 to site 6, 10x pin-prick, pin-pricking sites 1 to 10, anal reflex and reflex stimulation, 4x anal, fourfold anal catheter pulling, 4x bladder, fourfold bladder catheter pulling, peak 1- peak 2 - 3, first, second and third peak of spindle afferent activity due to parasympathetic activation (see [35]), p synchro, partial synchronization, syn, synchronization of α and γ-motoneurons and secondary muscle spindle afferents

(B) Set of single impulse patterns of secondary muscle spindle afferents (SP2(1,2)) and α and γ (intrafusal)-motoneurons and sites of stimulation The small arrows in the impulse pattern of the α_3-motoneuron (S) point to the shortening of the oscillation period following pin-prick 6 (pp6) The triangles indicate the beginning and the end of pin-pricking

(C)(g,h,i) Definitions of the phases between the different motoneurons and spindle afferents in 2 sets of impulse patterns (g) and the corresponding sets of phase relation distributions (h,i)

frequency 100 Hz - 10 kHz), 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. Conduction velocity distributions of afferents and efferents were constructed, calibrated, group conduction velocities were identified [24,33]. From multi-unit impulse patterns, simultaneous patterns of several single afferent and efferent nerve fibres were extracted by shifting a window through the original trace, taken from the tape, and measuring up the action potential (AP) occurrence times from a counter from the scope (Fig.1). APs of a single nerve fibre were identified with the naked eye by picturing first the AP waveforms (templates) with their variations and then identifying the AP occurrence times based on the following criteria: a. AP shape on trace „a“; b. AP shape on trace „b“; c. reoccurrence conduction time; d. AP amplitude. Since the adding up of different AP waveforms or the adding up of artifacts can be distinguished with the naked eye, manual identification is superior to computer analyses unless having a computer programmed for all possible addings up of the different potentials and artifacts. Interspike interval (II) and phase distributions were constructed (Figs.2-4) [35]. The intraoperative recording was performed in a patient with a spinal cord lesion sub TH1, during the implantation of an electrical anterior root stimulator for urinary bladder control. Details of the method are given elsewere [33-36]. Measurements were performed on paraplegic patient 9 (lesion sub TH1 for one year).

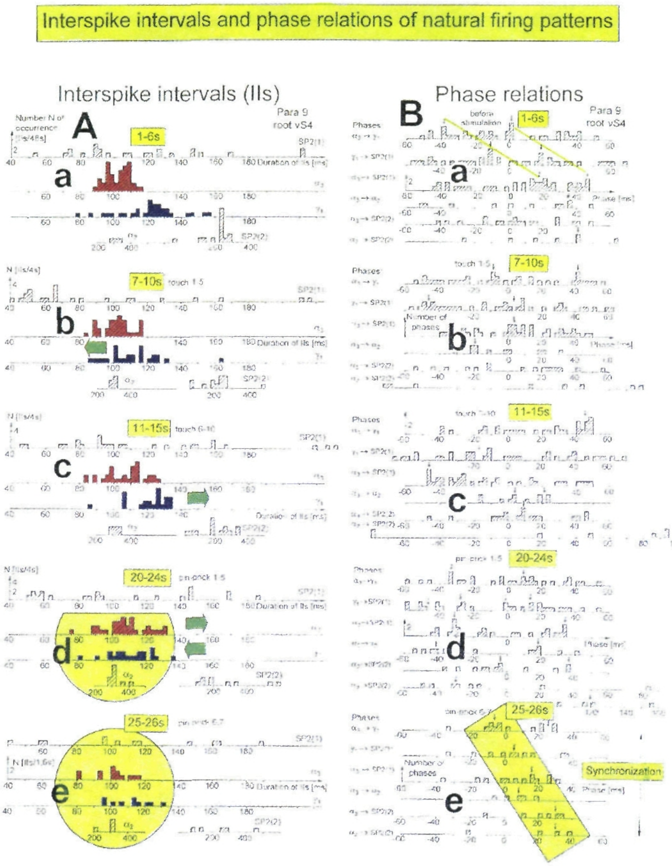

Figure 3. **(A)** Interspike interval distribution of spindle afferents SP2(1) and SP2(2), α_2 (FR) and α_3-motoneurons (S) and the dynamic fusimotor γ_1 for different time intervals upon touch, pinprick and anal catheter pulling (see Fig.2). Interspike intervals (IIs) were collected from several sweeps of 0.8 s duration per second (Fig.2). External loop generation and synchronization of α and γ-motoneurons and secondary muscle spindle afferents are marked by the partial and the full circle. The large arrows point to the increase and decrease of the mean II of the distribution. Unsafe identification of α_2 and α_3-motoneurons (or vice versa) because of loss of specific oscillator properties (see [28,36]). **(B)** Histograms of the phases between afferent and efferent fibres for the time intervals indicated, upon different stimulation (see Fig.2). Phases were collected from several sweeps of 0.8 s duration per second, as shown in Fig. 2C,h,i. The small arrows indicate phase relations. The building up of the external loop of Fig. 3A,B is drawn schematically in Fig. 8A,B,C. For further details of this measurement, see Fig. 3 of [35].

Results

Interspike intervals of, and phases between, the APs of α and γ-motoneurons and secondary muscle spindle afferents in a paraplegic patient, with no additional stimulation.

Impulse patterns of γ (γ_1) and α-motoneurons (α_2, α_3) and secondary muscle spindle afferent fibres (SP2(1), SP2(2)) recorded in paraplegic patient 9 are shown in Fig. 2B,C,g. Original recordings have been published previously (Fig.4 of [34]). To show the activation and the neuronal network organization of mainly the somatic division, the activity level changes of SP2(1) fibre are shown in Fig.2A. Changes in activation and neuronal network organization of the parasympathetic division have been reported elsewere [35]. The times of selected impulse pattern sampling are indicated, and the time intervals are marked for which interspike intervals and phases were pooled.

In this special pathologic case, the α_2 and α_3-motoneurons fired rythmically with impulse trains consisting of one action potential (AP), in contrast to the physiologic firing patterns (Fig.3 of [36]), in which α_2 and α_3-motoneurons fire with impulse trains consisting of more than one AP. The identification of motoneurons by conduction velocity is not absolutely safe since group conduction velocity ranges overlap [33]. It is very unlikely, nevertheless, that one of the motoneurons was an α_1-motoneuron (FF) (missing high conduction velocity

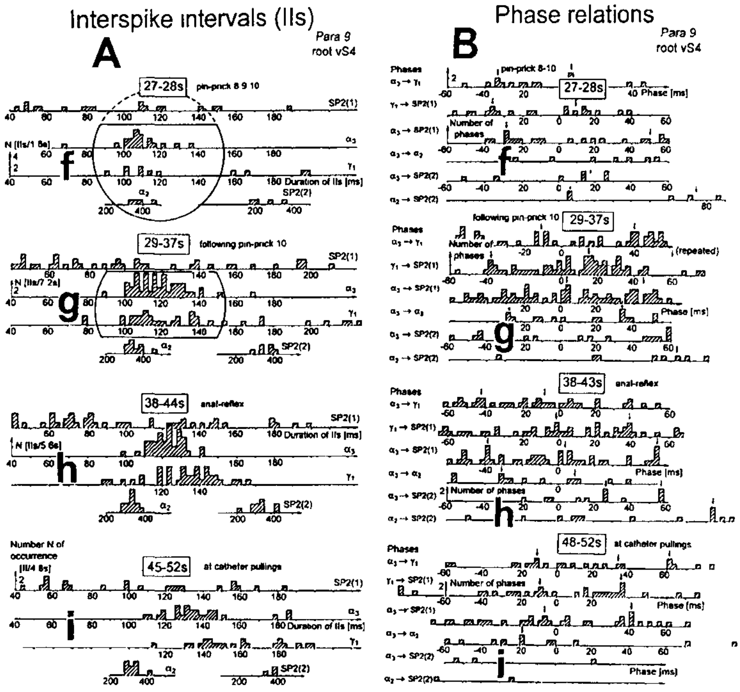

Figure 4. Interspike intervals (IIs) and phase relations for time intervals indicated in Fig 2A For legend, see Fig 3

and high AP amplitude and no correlated primary spindle afferent fibres), even though they fire physiologically with impulse trains consisting of one AP It has been shown that oscillatory firing α_1-motoneurons are mainly driven by time locked primary spindle afferent fibres (Figs 1-3 of [37]) The firing patterns of the α_2 and α_3-motoneurons are strongly pathologic with respect to the length of the oscillation period and the impulse train length so that it has been impossible in this paraplegic to identify the motoneurons by their discharge patterns of oscillatory firing, this would be possible were the neuronal network driving the motoneurons to fire in a physiologic manner

The time correlation of afferent and efferent impulse patterns was easy to detect in the brain-dead individual as the oscillatory firing α_2-motoneuron (O2) fired regularly like an inner clock (Fig 5, Figs 4,5 of [35]) The phases of fusimotors and spindle afferent APs could be defined with respect to the impulses of that inner clock In this paraplegic, the rhythmic firing was rather irregular The motoneuron firing could therefore not be used as a time reference basis More phases between the impulses of the different fibres were necessary to fully describe the correlation between the simultaneous impulse patterns In Fig 2C,g, the mutual phases between the APs of the different fibres are defined Fig 2Ch,i shows the corresponding phase distribution histograms Since too few phases occurred in a sweep of 0 8 s duration, phases occurring in certain time intervals were pooled and plotted in Figs 3,4

In Figs 3 and 4, the interspike intervals (IIs) and the phases are shown for similar time intervals Before stimulation, within the time interval 1-6 s, the α_3-motoneuron fired every 100 ms, the γ_1-motoneuron every 100 to 130 ms, and the SP2(1) fibre every 80 to 150 ms (Fig 3Aa) The α_2-motoneuron mostly fired every 300 ms and the SP2(2) fibre every 250 ms At that particular time interval, similar phases (phase relation of broad peak type) occurred 2 times per α_3-oscillation period between the APs of the α_3 and γ_1 axons, between the γ_1 and the SP2(1) fibres, and between the α_3 and the SP2(1) fibres (Fig 3Ba) One phase relation occurred between the impulses of the α_3 and α_2-motoneurons, and one between the α_3 and the SP2(2) fibres (Fig 7a) The broad phase relations between discharge patterns are interpreted as interactions between populations of neurons

Interspike intervals (IIs) of, and phases between, APs of α and γ-motoneurons and secondary muscle spindle afferents upon touch, pin-prick and anal reflex stimulation

Following different stimulations II distributions and phase relations changed with time Upon touching sites 1 - 5, the IIs of the almost oscillatory firing γ_1-motoneuron reduced in size to become more similar to those of the oscillatory firing α_3-motoneuron (Fig 3Ab) The changing of the different phase relations (see Discussion) indicated changes in the interactions between neuronal subnetworks (Fig 3B) Upon touching sites 6 and 7, the IIs of the almost oscillatory firing γ_1-motoneuron increased again (Fig 3Ac) A transient partial synchronization occurred between the different nerve fibres (see direct impulse pattern in Fig 2 of [38])

Upon pin-pricking sites 1 - 5, the IIs of the almost oscillatory firing γ_1-motoneuron reduced again to have a similar II distribution as the α_3-motoneuron The α_3-motoneuron even slightly increased its IIs (decrease of activity), so that the II distribution of the oscillatory firing α_3-motoneuron and the now oscillatory firing γ_1-motoneuron became very similar (Fig.3Ad).

Upon pin-pricking sites 6 and 7 (inside the anal reflex area [38]), α and γ-motoneurons and secondary muscle spindle afferents showed similar II distributions (Fig 3Ae). In a majority of cases only one phase relation existed per oscillation cycle between the different nerve fibres (Figs.3Be,7e) A synchronization between the APs of the different nerve fibres occurred as can be seen from the direct impulse patterns (Fig.3 of [38]). The occurrence of similar II distributions of, and transient constant phases between the APs of the α_3, γ_1 and SP2(1) fibres is interpreted in the way that, in its oscillatory firing, the oscillatory firing α_3-motoneuron built up an external loop to the muscle spindle innervated by the γ_1 and SP2(1) fibres The γ-loop became integrated into the oscillatory firing of the α_3-motoneuronal network Before pin-pricking, the γ-loop, consisting partly of the γ_1 and SP2(1) fibres, also contributed to the oscillatory firing, since on the average there existed phase relations. With the pin-pricking, also the II distributions assimilated, so that this γ-loop was directly included into the oscillatory firing of the α_3-network rather than only contributing to the drive of it

Upon pin-pricking sites 8, 9 and 10 (outside of the anal-reflex area) and following pin-pricking of site 10, the II distribution of the SP2(1) fibre shifted away from those of the α_3 and γ_1 fibres (Fig.4Af,g). The oscillatory firing α_3-motoneuronal network had abolished its external loop, even though still getting drive from it Upon anal reflex stimulation and catheter pullings, the external loop was not built up again (Fig 4h,i)

Discussion

Overlap of synfire chains as a possible mechanism for the coupling of spinal oscillators

Interspike interval (II) distributions of, and phase distributions between, the action potentials (APs) of the α and γ-motoneurons and the secondary muscle spindle afferents for different stimulations are shown in Figs. 3 and 4 Since the α and γ-motoneurons fired with impulse trains consisting of one AP, the IIs were identical with the oscillation periods of the oscillatory firing α-motoneurons and with most periods of the almost oscillatory firing γ_1 (dynamic)-motoneuron When the distributions of oscillation period durations became very similar, it is very likely that the oscillatory firing networks (premotor or propriospinal) coupled and interacted with each other A working hypothesis has been (Fig 5 of [37]) that such transient coupling of self-organizing oscillators takes place by an overlap of synfire chains. In his classic work, Erich v Holst [18] called the rhythm coordination sliding or „relative" coordination The self-organization of the oscillatory firing networks is initiated in preformated networks by an adequate afferent input (or supraspinal input in the case of an incomplete spinal cord lesion) Such an adequate afferent input is monomodal to polymodal for the α_1 and α_2-motoneuronal networks, and multimodal for α_3-motoneuronal networks In the picture of synfire chains, the self-organization of oscillatory firing preformatted neuronal networks is caused by an afferent input which organizes certain closed synfire chain traces Probably, the synfire chain loop starts from, and ends at the motoneuron

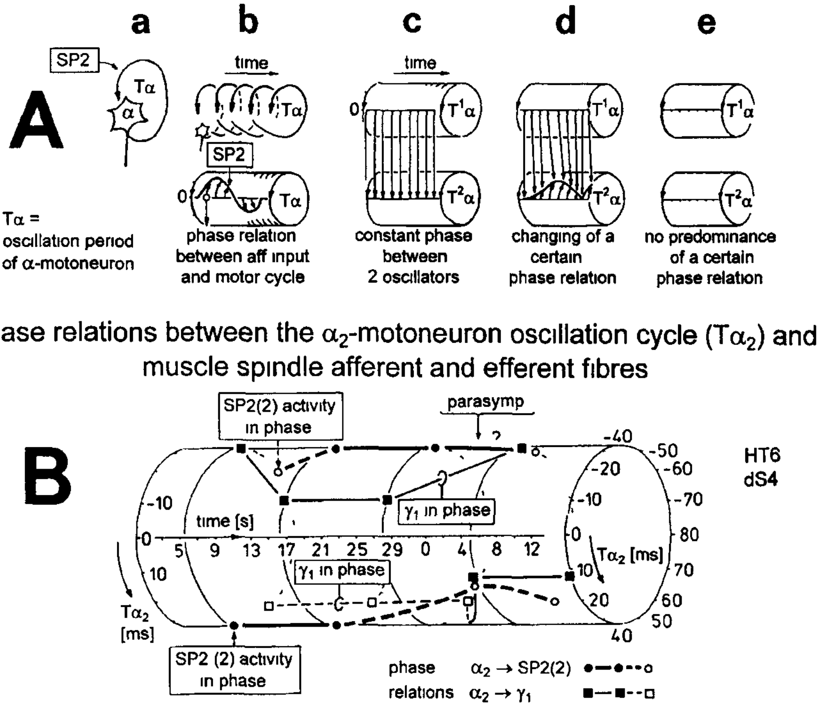

Figure 5. **(A)** Derivation of the simultaneous description of interspike intervals and phase relations (a,b) The oscillation period of an oscillatory firing α motoneuron is schematically characterized by the length of the loop (perimeter) Successive oscillation periods with ongoing time yield a cylinder Flashing with a stroboscope on such a cylinder with the same frequency as that of the rotation of the cylinder would make a black spot on the turning cylinder not move up or down If the frequency of the cylinder or the stroboscope change slowly, the black spot would move up or down If the black spot moves from left to right with ongoing time, a curve is obtained By replacing stroboscope flashing by the occurrence of the APs of the spindle afferent fibre (or another oscillatory firing motoneuron) with respect to the APs of the oscillatory firing motoneuron, phase relation changes are made visible in the lower part of „b“ for a constant oscillation period (cylinder with no diameter changes) (c) A constant phase between two oscillatory firing motoneurons results in a constant line on the cylinder with ongoing time (d) A changing phase gives a curve on the cylinder circumference (e) If there is a loss of predominance of a certain phase between two motoneurons (the black spot gets diffused with ongoing time and is then lost) there is no line or curve

(B) Interspike interval and phase data from a brain-dead individual (root dS4) of [35] have been plotted in the representation of A Filled dots and squares represent average phases (phase relations), thick and thin lines connect the dots to show trends Note that the phase relations change only little, the frequency of the sphincteric α_2-motoneuron ($1/T\alpha_2$) changes only little the cylinder does not change its diameter

Interneurons, having rhythmic activity related to the scratch and step cycle, were found in tetrapods in the lateral part of the intermediate area of the gray matter (Rexed area VII) in the lumbosacral enlargement [2,3]

Representation of phase relations

For a transient coupling of spinal oscillators it is necessary that the oscillation period distributions (frequency distributions) assimilate Additionally, phase relations have to exist between the firings of the oscillators, i e the corresponding phase distributions have to show peaks

Existing relative phase relations are indicated in Figs 3 and 4 by small arrows We shall try to improve the representation of the phase relations shown in Figs 3 and 4, to obtain more information concerning the interactions of oscillatory firing networks and to find reasons for the pathologic organization of neuronal networks in paraplegic patients, and hopefully strategies allowing positive interference

To make the phase relation changes better recognizable, a representation of phase relations is used which comes from the measuring of the speed of rotation

The speed of rotation of a turning cylinder with a spot on its surface can be measured with a stroboscope If the stroboscope flashes light with the same frequency as the cylinder is turning, the spot on the circumference seems to stand still There is a constant phase between the two frequencies (frequencies are same or multiples of each other) If the phase relation changes, the spot will move If no phase relation exists between the turning of the cylinder and the flashing of the light, no spot will be seen In similarity to stroboscopic measurement of frequencies of turning cylinders, the phase relation between two oscillatory firing spinal oscillators is pictured in Fig 5A A time axis is introduced on the horizontal line, to make phase relation changes visible in dependence on time

In Fig 5Aa, the loop excitation is pictured for this oscillator model In Fig 5Ab, the phase relation between the SP2 fibre activity incidence and the oscillatory firing is pictured on the circumference of the oscillation period cylinder of the oscillator Fig 5Ac,d,e shows different phase relations, namely a constant phase relation (c), a changing phase relation (d), and no phase relation (e)

Two phase relations per oscillation cycle

In Fig 5B, phase relation changes are plotted between an α_2-motoneuron and the activity of a secondary muscle spindle afferent fibre and between an α_2 and a γ_1-motoneuron The data were taken from Figs 4,5 of [35] of a brain-dead individual (probably normal with respect to the number of phases per oscillation cycle and with respect to phase changes) It can be seen that there were two phase relations per α_2-oscillation cycle and that the phase relation changed only little with time

In lampreys, which have no paired fins, the phase delays between any two ipsilateral oscillators are very nearly invariant or have two possible phase relations (page 134 of [6]).

Since two phase relations per oscillation cycle were also found among synchronizing oscillatory firing α_1-motor units in electromyographic recordings from leg muscles [39], two phase relations seem to represent the physiologic case.

Phase relation changes in paraplegic patient 9

In Fig. 6A,B different phase relation changes are plotted from Figs. 3 and 4 with respect to the α_3-oscillation cycle (A) and the α_2-oscillation cycle (B). It can be seen that the

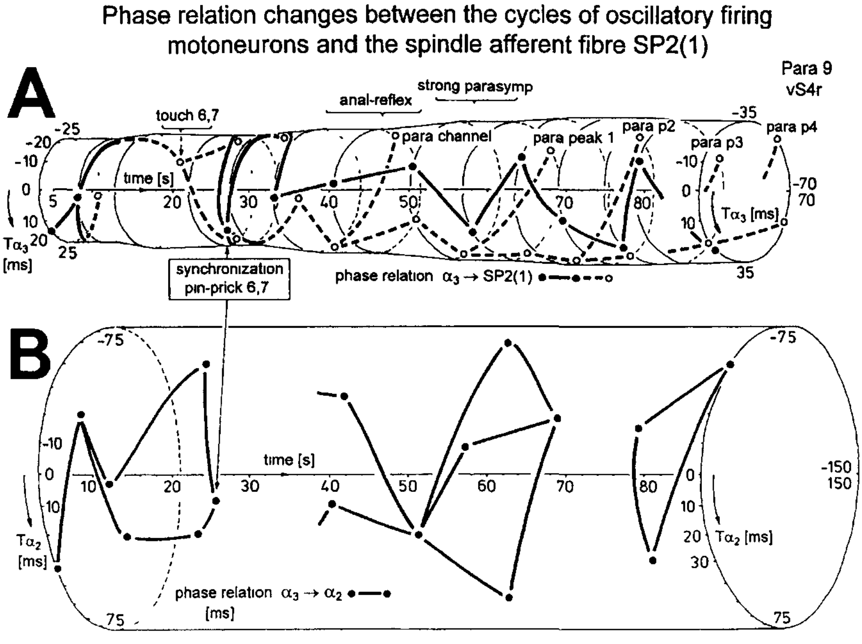

Figure 6. (**A**) Phase relations between the secondary muscle spindle afferent fibre SP2(1) and the oscillatory firing α_3-motoneuron, taken from Fig 3B, plotted on the oscillation period cylinder $T\alpha_3$ (mean oscillation periods are taken from Fig 3A) according to Fig 5A The cylinder changes its diameter (perimeter) because the oscillation period changes Phase changes in ms are scaled on the cylinder circumference The ongoing time (to the right) is scaled on the axis of the cylinder (time intervals are taken from Fig 2C) Existing phase relations are represented by dots (filled and open (back-side)), lines (filled and dashed (back-side)) only connect the phase relations to show trends para peak 1, para p2, para p3, para p4 = activity peaks of the SP2(1) fibre due to parasympathetic activation (see Fig 2A, right)

(**B**) Phase relations between the α_3 and α_2-motoneurons plotted onto the oscillation period cylinder of the α_2-motoneuron Dots represent phase relations, taken from Fig 3B Note that the phase relations in Fig 6 (paraplegic 9) are much more variable than those in Fig 5B (brain-dead human HT6), also, the number of phase relations (Fig 7) changes different phase relations changed strongly in value over time (upon different stimulation), and that also the number of phase relations per oscillation cycle changed

Difference of phase relation changes between a brain-dead individual and a paraplegic patient

The most obvious difference in the phase relation changes between the above mentioned brain-dead human and the paraplegic were that in the paraplegic the phase relations varied very much, whereas they changed only little in the brain-dead individual (phase relations are indicated in Figs 3 and 4 by small arrows) The strong phase relation changes in the paraplegic can be interpreted as instability in the organization of neuronal networks The correlation of neuronal subnetworks was instable in relation to those of the brain-dead individual If we assume that the neuronal network organization and functioning was rather physiologic in the brain-dead with respect to the firing patterns of the premotor spinal oscillators, then the functioning of the networks became instable following spinal cord lesion The more frequent occurrences of changes in phase relations between the different nerve fibres in combination with the changing number of phase relations per oscillation may mean that subnetworks reacted and interacted more quickly and easily with others according to the afferent input Especially because the oscillatory firing networks lost specific properties, their resonance frequencies changed from a narrow to a broad oscillator frequency band, which means that the oscillators were not excited at a certain frequency any more, but they were excited by a broad frequency band They could now be excited at frequencies at which they physiologically would not be excited Overactivation and mass effects could result On the other hand, certain networks could escape from driving afferent influence by changing their phase by phase escape to avoid interaction Functionally distant networks are not reached any more, which also would result in a loss of specific properties Therefore, because of the loss of specific properties, some interactions can occur more easily and other ones not at all For a similar discussion based on mathematical predictions obtained from populations of interacting nonlinear biological oscillators, see [39]

The dysfunction of the neuronal networks could be based on interneuron cell death (not observed so far), false functional organization due to loss of natural afferent input, the spinal cord lesion and loss of mobility or other reasons

W R Hess tried in 1944 to compare biological order and human society [17] In a society the upper behavior of spinal oscillators could be called „putting its flag to the wind“ There could be similarities between the organizations of the human nervous system and the organizations between very many individual nervous systems

Number of phase relation per oscillation cycle in a paraplegic patient

As shown in Figs 3, 4, and 6 the number of phase relations changed between the firings of the different nerve fibres In the brain-dead individual HT6, two phase relations were found between the α_2-motoneuron and the secondary muscle spindle afferent fibre SP2(2) and the α_2 and the γ_1-motoneuron (Fig.5). Also in the paraplegic two phase relations often existed between the firings of the different nerve fibres. It has been discussed earlier that probably a third phase relation occurred when the parasympathetic division channelled an additional input to the oscillatory firing somatic neuronal network (section 4.2 and Fig.10 of [35]; Fig.7j). It may therefore be worthwhile to further analyse the occurring number of phase relations per oscillation cycle upon different, mainly somatic, stimulations.

Since two phase relations occurred per oscillation cycle between the α_3 and the γ_1-motoneurons and the SP2(2) fibre (Figs.3Ba,6a) in paraplegic 9, and also the IIs were rather similar (Fig.2Aa), it is concluded that the neuronal networks of the α_3 and γ_1-motoneurons formed, together with the spindle afferent fibre SP2(1), a functional unit or a part of it. This functional unit is built up by efficacies of synapses and projections between the convergence of several fusimotors on one muscle spindle and by the divergence of muscle spindle projections onto several rhythmically firing populations of neurons driving the α and γ-motoneurons. The α_2-motoneuron and the SP2(2) fibre belonged to a different functional unit (longer IIs and the existence of mostly a single phase relation). The two functional units are charac-

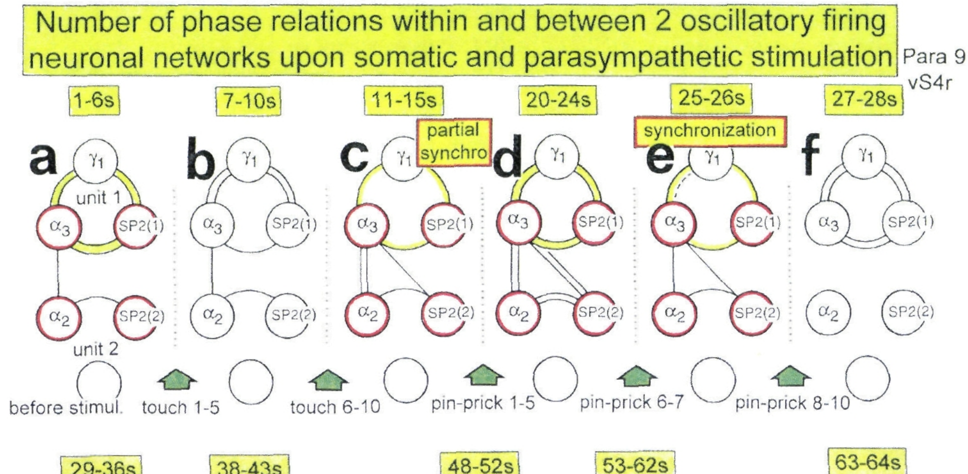

Figure 7. Number of phase relations within and between the two functional units α_3/γ_1/SP2(1) and α_2/-/SP2(2). Time intervals are same as in Fig. 2A. Note that in „a" the functional unit 1 is with two phase relations per oscillation period in a stage similar to those seen in the brain-dead individual; with synchronization, only 1 phase relation occurred (e) and the parasympathetic division channelled an extra phase relation to interact with the somatic division (j).

terized in Fig 7 by two sets of 3 circles each The two functional units interacted with each other, as there were phase relations between the α_2 and α_3-motoneurons (Fig 7)

Before stimulation (but with the anal and bladder catheters positioned), there were two phase relations in unit 1 (Fig 7a) When touching sites 1 to 5 (Fig 2B), only slight changes occurred in the two units with respect to the number of phase relations (Fig 7b) But when touching sites 6 to 10, a partial synchronization occurred (Fig 7c) and functional unit 1 reduced the number of phase relations to one When pin-pricking sites 1 to 5, two phase relations occurred again in unit 1 (Fig 7d) Upon pin-pricking sites 6 and 7 the number of phase relations between all the components of the two units dropped to one (Fig 7e), and synchronization occurred between the firing patterns (Fig 3 of [38])

Since in the brain-dead individual two phase relations per oscillation cycle were observed in the functional units, it is likely that synchronization and the existence of only one phase relation for 2 to 3 seconds reflected a pathologic organization of the networks

Even though upon touching sites 6 to 10 (Fig 7c) or upon pin-pricking sites 6 to 7 (Fig 7e) only one phase relation existed in unit 1, and synchronization occurred with both stimulations, it was shown earlier [38] that the touch afferent input organized a functional state of unit 1 different from that upon pin-pricking The response time till the shortening of the oscillation period was longer than the oscillation period (~ 100 ms) for pin-prick and shorter for touch It has been discussed [38] that repetitive touch stimulation reinforced the sustained stretch reflex of the anal sphincter, and repetitive pin-prick stimulation replaced the sustained stretch reflex by the protection reaction of the anal sphincter The number of phase relations alone therefore only provides limited information on the functional state of the organization of the neuronal networks of the human spinal cord Measurements of a number of parameters are necessary to yield a rather complete description of the functional state of neuronal networks

Following pin-prick 8 and 10 and with no stimulation, two phase relations existed again in functional unit 1 (Fig 7f,g), in some similarity to pre-stimulation status (Fig 7a) Following two times anal reflex stimulation, partial synchronization occurred in the components of the two units (Fig 5 of [38]), and mainly two phase relations existed (Fig 7h) But the organizational state was still not very similar to the pre- (Fig 7a) or post-stimulation state in unit 1 (Fig 7g), since the parasympathetic division was slightly activated following anal reflex stimulation as was measured by the impulse pattern (increase of doublet activity) of the secondary muscle spindle afferent fibre SP2(1) (Figs 5,7 of [34]) Therefore, probably one phase relation was due to the somatic activation in similarity to Fig 7c,e, and the other phase relation was due to the activation by the parasympathetic division During bladder catheter pulling (Fig 7i) and with no stimulation (Fig 7k), the number of phase relations and possibly the functional organization, was again similar to the pre-stimulation state (Fig 7a)

Following bladder catheter pulling (Fig 7j), three phase relations occurred, which again indicates an extra input to the oscillatory firing networks by the parasympathetic division For further details of the activation of the parasympathetic nervous system division, see [33-35]

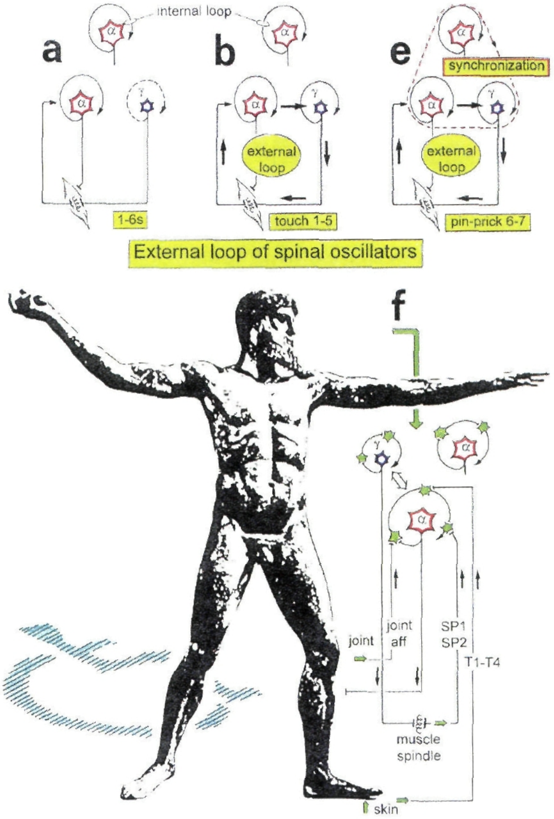

Figure 8. Spreading of oscillatory firing from α-neuronal network to include muscle spindles (periphery) and synchronization of different α and γ-neuronal networks caused by touch and pin-prick stimulation. (a) α-neuronal networks fired oscillatory (solid line loop), γ-neuronal network did not or did only partly (dashed line loop), upon no additional stimulation; taken from Fig. 3Aa,Ba.

(b) Oscillatory firing α and γ-neuronal networks built up a phase relation with muscle spindle afferents and efferents (external loop to the periphery, indicated by thick arrows) upon touch 1-5, taken from Fig. 3Ab, Bb. (c) Oscillatory firing α (internal cicuitry loop) and γ-neuronal networks (external loop) synchronized (broad peak phase relation) upon pin-pricks 6-7, taken from Fig. 3Ae,Be. The dashed line loop represents synchronization. (f) Oscillatory firing α (internal circuitry loop) and γ-neuronal networks (external loop) are extended by analogy from the continence muscles to muscles for locomotion. The open arrows indicate that it may be possible to synchronize spinal oscillators by rhythmic afferent input, generated by rhythmic movements (such as jumping on a springboard or running), and to re-preformate the neuronal circuitry by synapse remodelling to fire more physiologically oscillatory to reduce spasticity and improve locomotion. The Greek god is a bronze statue of Poseidon or Zeus found close to the cape of Artemision (460 BC).

These analyses indicate that the different spatio-temporal afferent input patterns, from the different natural stimulations, caused different neuronal nerwork organizations (or different network reactions, which also means other organizations) to which the α and γ neuronal networks belonged to or were driven by.

Modulation of neuronal network organizations

Transposing the principles of continence functions to those of locomotion, it is likely that sensory mechanisms are important to produce ordinary locomotor synergy during a change of the movement patterns, e.g. when changing the direction of running. The movement-related feedback on the locomotor pattern generators has a potent effect on the spinal neuronal network responsible for the coordination of the locomotor movements (see below, and [40]) Probably, simple rhythmic motor program organization can partly adapt to meet the changing demands of the environment A person can walk or run with a variety of gaits, quickly or slowly While in theory, each variation could be produced by different neuronal circuits, these measurements indicate that neuronal network organizations (in the form of central patterns generators) are continuously modulated by afferent and supraspinal input to produce all the variants on a common theme The question remains, how much modulation of gait is possible with movement-related feedback only and for what changes of movements is supraspinal modulation necessary for the neuronal network organization of the spinal cord There is indication that for stronger changes of rhythmic locomotion in man (such as changing the direction of running) modulation from supraspinal centres is necessary [39] The conclusions are the same as in animal research, for a review see Pavlasek and Petrovicky [43]

Bulding up of an external loop to the periphery by spinal oscillators

Analyses of neuronal network organizations are not only of academic interest It will be shown in a following paper [39] that re-preformation of neuronal networks and the interaction between the somatic and the vegetative nervous system division has direct consequences for the recovery of neuronal network functions of the functionally disconnected spinal cord in incomplete spinal cord lesions With the building up of simultaneous phase relations between α, γ and SP2 fibres and the assimilation of II distributions (coordinations of rhythms), an external loop of spinal oscillators is built up to the periphery, which makes it possible to directly influence the firing of spinal oscillators by a rhythm training

In Fig 3Ba it can be seen that there existed a phase relation between the firings of the α_3, γ_1 and SP2(1) fibres, which means that the γ-loop, including the γ_1 and SP2(1) fibres, contributed to the drive of the α_3-oscillator (probably of α_2-type) However, since the II distributions are different (Fig 3Aa), the γ-loop was not a part of this spinal oscillator, it was only contributing to the drive of it, as pictured in Fig 8a Since the II distribution of the fusimotor γ_1 was often rather broad (see, e g Fig 4Ag), its driving network was not, or only almost oscillatory firing (the dashed line loop in Fig 8a)

Upon touching sites 1 to 5 approximately every 0 8 s, phase relations occurred between the α_3, γ_1 and SP2(1) fibres, even though reaching a different value (Fig 3Bb,c) and the II distributions of the α_3 and γ_1 fibres (Fig 3Ab) and the SP2(1) fibre (Fig 3Ac) became assimilated The γ-loop became directly connected to the oscillatory firing network the premotor spinal oscillator (the network driving the α_3 motoneuron) built up an external loop to the periphery (Fig 8b)

Upon pin-pricking sites 6 and 7, phase relations occurred between the firings of the α_3, γ_1 and SP2(1) fibres (Fig 3Be), and also the II distributions assimilated (Fig 3Ae) The spinal α_3-oscillator had built up a full external loop to include the γ-loop in its oscillatory firing (Fig 8e) Since there was transient synchronous firing of unit 1 with unit 2 (including the α_2 and SP2(2) fibres), probably also the α_2-oscillator built up an external loop to the periphery

Extension of the external loop generation of spinal oscillators to non-continence muscles

If one extends the integration of the γ-loop in the oscillatory firing of spinal oscillators from continence muscles to muscles activated for locomotion (Fig.8f), then for example during running, at least oscillatory firing α_2 or α_3-oscillators build up external loops to the periphery. It seems partly possible during running (rhythmic, stereotype, dynamic locomotion) to synchronize spinal oscillators with the running rhythm. Since spinal oscillators [14,25] fired pathologically following spinal cord lesion [28,35] it may be possible to re-preformate neuronal networks of the spinal cord by a rhythm training, to make spinal oscillators fire more physiologically again, and to reduce spasticity and increase useful locomotion in patients with incomplete spinal cord lesions. It will be shown in a following paper that it is really possible to re-preformate neuronal networks by a rhythm training, so that spinal oscillators fire more rhythmically again [39]. An incomplete tetraplegic (lesion sub C5) relearned running besides other movements. But a certain percentage of sensory fibres and motor fibres, probably of certain tracts, must be retained after the cord lesion, as indicated in Fig. 8f, to make such essential progress in the rehabilitation of spinal cord lesion possible.

Movement-related sensory feedback on the locomotor pattern generator in animals

Although in animals the interneuronal network can operate without sensory information (fictive locomotion), movement-related sensory information is of crucial importance. In both lamprey and dogfish, the central spinal network generating locomotion is strongly affected by sensory signals [4,14,15]. In addition, it is likely that these mechanisms are important to produce ordinary locomotor synergy during rapid changes of the movement pattern such as during turning or when the speed of swimming increases.

The movement-related feedback has a potent effect on the spinal network responsible for the coordination of the locomotor movements. The general nature of the mechanism underlying the control system is suggested by the striking similarities with the system controlling walking in mammals [13].

Phase-dependent modulation of sensory signals in animals

Sensory stimuli applied to the tailfin can elicit swimming or enhance already ongoing swimming. Short-lasting mechanical stimuli applied to the tailfin will enhance the ongoing phase of locomotion. If, for instance, a stimulus is applied during myotomal activity on the left side, the movement to the left will become enhanced and vice versa. This gating of reflex effects is a direct or indirect consequence of the central pattern generator (CPG) activity [12,40]. A response pattern of this type is behaviorally meaningful. It is important that a fish is able to adapt the response pattern to be appropriate to the ongoing phase of locomotion. The effects in fish resemble the phase-dependent gating observed during walking in mammals [10].

Recent evidence suggests that Ib afferents may provide crucial feedback to rhythm-generating circuits as already postulated [9] Experiments during fictive locomotion in cats pre-treated with DOPA have indicated that Ib afferents reset the cycle [7] In spinal cats walking on a treadmill Ib afferents prolonged the stance phase and inhibited the flexion phase [21] Furthermore, two sets of experiments have now shown that Ib effects change dramatically during locomotion compared with static conditions [11,22] Before locomotion, Ib inputs produce inhibitory post synaptic potentials, and during locomotion they produce exciting post synaptic potentials in motoneurons This is a remarkable example of a reflex reversal that rhythmic behavior studies have tought us, and it makes us believe that a great deal of the reflex interactions during motor control have to be re-evaluated during the actual motor behavior [23]

Are spinal motoneurons output elements or part of the pattern-generating network?

Vertebrate motoneurons are, in general, thought to serve as output elements only, and experiments in the lamprey seem to have established that this actually is the case All motoneurons of one segment were activated during fictive locomotion by continuous repetitive antidromic stimulation of the ventral roots (e g , 20 Hz) If motoneurons were a part of the pattern-generating circuitry, the resulting abnormal activity in one segment should have affected the pattern recorded in the adjacent rostral and caudal ventral roots [41] However, no effects were observed It was therefore concluded that interneurons distributed throughout the spinal cord must be able to produce the output pattern and that motoneurons solely or primarily serve as output elements The opposite argument, namely that the motoneurons are not separate from the rhythm generating network, was also put forward [23] Both arguments are not compatible with measurements in humans

At least in man the integration of the spinal motoneurons in the neuronal network organization is changing with respect to the activation and needs For the very low activity mode (occasional firing mode), the motoneurons are integrated in a rhythmic firing network organization, in which the motoneurons are activated approximately every 3 seconds (approx 0 3 Hz) [27] By how many neurons such slow rhythms – or even slower ones (day and night rhythm ~ 25 hours) – could be generated is difficult to speculate, probably by very many For high activations, the motoneurons fire oscillatory according to their motoneuron type between 0 9 and 12 Hz (Fig 3 of [36]) Since this oscillatory firing is observed in continence motoneurons (primarily not recruited by movement pattern generators (CPGs)), between the activations of the CPGs (see the following paper [39]) and for rather isometric contractions of leg muscles [39], the premotor interneurons contributing to the oscillatory firing of the motoneurons are not part of the pattern-generating network for walking or running With running or walking, the CPGs activate these biological premotor spinal oscillators, in which the motoneurons are integrated (Fig 3 of [36])

An essential further step in the understanding of the neuronal network organization of the human spinal cord is that the oscillatory firing motoneurons with their premotor interneurons (premotor spinal oscillators) can be separated from the CPGs (which are most likely composed of propriospinal oscillators [5]), and have been analysed in detail [28]. The output elements in man are therefore primarily the rhythmically firing motoneurons with their premotor interneurons which together build up the premotor spinal oscillators.

Tremor originates in the central nervous system

The single measurement on the regulation of spinal oscillators shown in Figs. 3 and 4 brought about essential pregress in the rehabilitation of incomplete tetraplegics (see above, [39]). However, this measurement has also solved a century-old problem, namely that physiologic tremor originates in the human CNS rather than in the periphery. In the CNS, there could be several reasons for a disorganization of neuronal networks, including drug application.

Fig. 3Aa-e,Ba-e clearly shows that the oscillatory firing starts in the CNS (Fig. 3Aa) and then spreads towards the periphery with repetitive touch every 0.8 s (Fig. 3Ab,c). Actually, the increase of the frequency of the oscillatory firing γ_1-neuronal network and the decrease of the frequency of the oscillatory firing α_3-motoneuronal network (Fig. 3Ad) to completely assimilate their frequencies (oscillation period distributions) under the preservation of certain phase relations (Fig. 3Bd) is an indication of the coupling of the oscillatory firing γ_1 and α_3-neuronal networks. With the assimilation of the firing of the muscle spindle afferent fibre SP2(1) with the firings (same IIs) of the α_3 and γ_1 fibres (and the α_2-motoneuron), under a certain phase relation (Fig. 3Be), the oscillation had spread to the periphery. Muscle stiffness may slightly contribute to the oscillation rhythm. But since there are no joints activated by continence muscles (such as the external anal sphincter), muscle-limb mechanics are not involved. The IIs in Figs. 3Ad,e,4Af of the γ_1, α_3 and SP2(1) fibres were around 110 ms, which resulted in a frequency of 9 Hz ($\alpha_2 \approx 3.3$ Hz). Since these oscillators fired pathologically, this frequency cannot be used to be compared with physiologic tremor frequencies. Two oscillation frequencies of physiologically firing α_2-motoneurons (FR) had values of 6.25 Hz and 8.7 Hz (Fig. 1 of [36]). Agarwal and Gottlieb (1977) [1] found resonance frequencies of the active gastrocnemius-soleus muscles of 6.25 Hz and near 8 Hz. In the red soleus muscle slow (S) and fatigue resistant (FR) muscle fibres are contained, which are innervated by α_3 and α_2-motoneurons respectively. Since the gastrocnemius-soleus muscles are innervated by α_1, α_2 and α_3-motoneurons, one can expect to have corresponding spinal oscillator frequencies of at least 8-12 Hz (α_1), 6.25 and 8.7 Hz (α_2) and $\approx$1 Hz (α_3). If physiologic tremor occurs by chance synchronization of motor units or neuronal networks firing rhythmically at these frequencies, then one can expect from the coupling of spinal oscillators even further frequencies from the addition and subtraction of these frequencies, when oscillators couple. Therefore, tremor frequencies will vary in dependence on which muscle fibre type (and therefore neuronal network type) is activated.

In tremor of hand, arm and leg, muscle-limb mechanics have to be taken into consideration. The frequencies of the spinal oscillators will be modulated by viscoelastic-mass systems Stiffness of the contracting muscles and inertia of the moving parts then may act as a mechanical filter [16], influencing the frequencies of the random synchronization of spinal oscillators

The measurements, yielding Figs 2,3,4, do not explain the cause of tremor, but give evidence for rhythmic firing of transiently coupled motor units originating in the CNS and spreading towards the periphery under certain conditions

Synchronization

Physiologically, oscillatory firing α_2-motoneurons (FR) do not fire synchronically (see Fig 3C of [35]) The random grouping [42] of the impulse trains of the oscillatory firing motoneurons probably gives rise to physiologic tremor The requirements on „synchrony" for rhythmic force generation are not very high due to the long contraction times of motor units The grouping of motor unit action potentials (and subsequent contractions) wax and wane, and this phenomenon readily explains the waxing and waning of tremor amplitudes [42]

It has been shown in Fig 3 that transient synchronization could be achieved by repetitive touch or pin-prick stimulation every 0 8 s inside the anal reflex area in paraplegic 9 For direct impulse patterns of synchronized firing, see Figs 2 and 3 of [38] There is indication that repetitive touch increased the sustained stretch reflex of the anal sphincter (caused by the anal catheter) whereas repetitive pin-prick seemed to replace the sustained stretch reflex of the anal sphincter for continence by the protection reaction of the anal sphincter against pain stimulus application [38] Since conventional anal reflex stimulation also caused partly synchronized firing of oscillatory firing α-motoneurons (Fig 5 of [38]), it seems that different stimulations can cause real transient synchronization (for a few seconds), at least in individuals with clinically complete spinal cord lesion Synchronization between α_1 (FF) and α_2-motoneurons (FR) was also observed (Fig 3 of [37])

Since transient synchronization of oscillatory firing motoneurons was observed in patients with spinal cord lesion (with the single nerve-fibre action potential recording method), it should also be possible to observe synchronization of rhythmically firing motor units electromyographically It will be shown in a following paper that obvious synchronization of α_1-motor units for several seconds was found (probably pathologic) in an incompletely tetraplegic patient [39]

Entrainment of premotor spinal oscillators by movement-induced afferent input or inputs from pattern generators or supraspinal centres

If one approximates for high activation spinal neuronal networks into premotor spinal oscillators (driving the motoneuron) and propriospinal oscillators (generating, by coupling with one another, movement patterns generators) then premotor spinal oscillators can be handled in a first approximation as single linear oscillators The premotor spinal oscillators and the spinal pattern generators are self-organized and driven by afferent and supraspinal inputs When training dynamic, rhythmic, stereotyped movements, the premotor spinal oscillators approximated as linear oscillators are driven by movement-induced afferent input from the periphery (mainly the legs) and the pattern generators, and possibly supraspinal inputs These spinal oscillators, and most likely their neuronal network, can be entrained at least by use of the external loop for a better self-organization re-preformated by plasticity

When a linear oscillatory system is driven by an external periodic input its response contains both frequency components This is also, in general, true for nonlinear oscillators However, in this case, if the external frequency is close to the characteristic frequency of the oscillator itself, then it is possible to have a response at the external frequency only This phenomenon is known as entrainment or synchronization It is of paramount importance with respect to biological oscillators because it allows them to „latch on“ to the environment Thus a rhythm with a free-running period of 24 7 hours may be synchronized to 24 hours when exposed to the natural sequence of day and night (page 71 of [20])

For an oscillator with one degree of freedom which is described by the equation

$$d^2x/dt^2 + f(x, dx/dt) + \omega_0 x = E \cos\omega_1 t$$

(x = variable, t = time, f = nonlinear term, $\omega_0 = 2\pi f_0$ = frequency of the oscillator, ω_1 = entrainment frequency, E = amplitude) there exists a set of paired values of amplitude E and the absolute difference in frequencies $\Delta\omega = |\omega_0 - \omega_1|$ such that the output of the system only contains the frequency ω_1 Fig 9 shows a typical example Entrainment occurs in the shaded part of the plane If E and $\Delta\omega$ are below the curve (outside of the shaded area) usually the frequencies ω_0 and ω_1 are present In the case when $\Delta\omega = 0$ but E is very small the phase of oscillations is not influenced by the input For further details, including van der Pol oscillator, see [20]

For subharmonic and superharmonic entrainment of populations of biological oscillators, see [20,39]

However, oscillator models are still far away from human network properties The movements of the oscillator formation training [39] were very rhythmic and stereotyped (frequ-

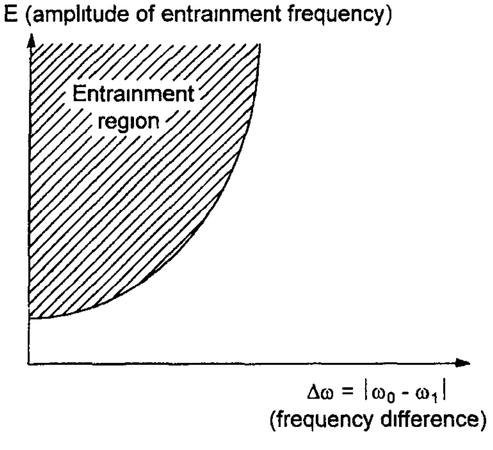

Figure 9 Illustration of the relation between amplitude E of the external input and the difference in frequencies $\Delta\omega$ which produces entrainment of a nonlinear oscillator

ency of jumping = 0 9 Hz) But firstly, the movement-induced afferent input enters the network at different levels (premotor neuronal network, propriospinal oscillatory network, brainstem network and higher centres), second, oscillators can get drive from different sources, and thirdly often the rhythmic input patterns consist of impulse trains with increasing interspike intervals and with delays between the responses from different receptors and receptor types For natural sets of simultaneous impulse patterns of numerous skin receptors induced by touch or pin-prick, see [26,31], and for natural impulse patterns of secondary muscle spindle afferents, see [29] In simulations of networks consisting of populations of interacting oscillators the known natural afferent input patterns have to be used, and oscillator network structures have to be used which give the measured output patterns under both physiologic and pathophysiologic conditions [25,36]

Even though the used oscillator models are quite distant from human self-organization network forms, their results are still very useful for the interpretation, under certain conditions, of measured data and for a better understanding of the new oscillator formation training-based treatment which brings more quality to the life of patients with incomplete spinal cord lesions through a substantial improvement of their mobility [39]

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