Scientific basis for learning transfer from movements to urinary bladder functions for bladder repair in human patients with CNS injury

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Abstract

Coordination Dynamics Therapy (CDT) has been shown to be able to partly repair CNS injury. The repair is based on a movement-based re-learning theory which requires at least three levels of description: the movement or pattern (and anamnesis) level, the collective variable level, and the neuron level. Upon CDT not only the actually performed movement pattern itself is repaired, but the entire dynamics of CNS organization is improved, which is the theoretical basis for (re-)learning transfer. The transfer of learning for repair from jumping on springboard and exercising on a special CDT and recording device to urinary bladder functions is investigated at the neuron level. At the movement or pattern level, the improvement of central nervous system (CNS) functioning in human patients can be seen (or partly measured) by the improvement of the performance of the pattern. At the collective variable level, coordination tendencies can be measured by the so-called 'coordination dynamics' before, during and after treatment. At the neuron level, re-learning can additionally be assessed by surface electromyography (sEMG) as alterations of single motor unit firings and motor programs. But to express the ongoing interaction between the numerous neural, muscular, and metabolic elements involved in perception and action, it is relevant to inquire how the individual afferent and efferent neurons adjust their phase and frequency coordination to other neurons to satisfy learning task requirements. With the single-nerve fibre action potential recording method it was possible to measure that distributed single neurons communicate by phase and frequency coordination. It is shown that this timed firing of neurons is getting impaired upon injury and has to be improved by learning. The stability of phase and frequency coordination among afferent and efferent neuron firings can be related to pattern stability. The stability of phase and frequency coordination at the neuron level can therefore be assessed integratively at the (non-invasive) collective variable level by the arrhythmicity of turning (coordination dynamics) when a patient is exercising on a special CDT device. Upon jumping on springboard and exercising on the special CDT device, the intertwined neuronal networks, subserving movements (somatic) and urinary bladder functions (autonomic and somatic) in the sacral spinal cord, are synchronously activated and entrained to give rise to learning transfer from movements to bladder functions. Jumping on springboard and other movements primarily repair the pattern dynamics, whereas the exactly coordinated performed movements, performed on the special CDT device for turning, primarily improve the preciseness of the timed firing of neurons. The synchronous learning of perceptuomotor and perceptuobladder functioning from a dynamical perspective (giving rise to learning transfer) can be understood at the neuron level. Especially the activated phase and frequency coordination upon natural stimulation under physiologic and pathophysiologic conditions among α and γ-motoneurons, muscle spindle afferents, touch and pain afferents, and urinary bladder stretch and tension receptor afferents in the human sacral spinal cord make understandable that somatic and parasympathetic functions are integrated in their functioning and give rise to learning transfer from movements to bladder functions. The power of this human treatment research project lies in the unit of theory, diagnostic/measurement, and praxis, namely that CNS injury can partly be repaired, including urinary bladder functions, and the repair can partly be understood even at the neuron level of description in human.

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Data Summary

Single-nerve fibre action potentials (APs) were recorded extracellularly from skin and bladder afferents, α and γ-motoneurons, and secondary muscle spindle afferents from thin sacral nerve roots mainly in a patient with traumatic spinal cord injury sub TH1 and a brain-dead human. Simultaneous single-fibre impulse patterns of skin and urinary bladder afferents and α and γ-motoneurons and secondary muscle spindle afferents were analyzed upon natural stimulation. Phase and frequency coordination for CNS self-organization of neuronal network patterns is analyzed in a brain-dead human (rather physiologic) and patients with spinal cord injury (pathologic case) (1) to explore what has changed in the CNS organization following spinal cord injury, (2) to find a scientific basis for learning transfer from movements to urinary bladder functions upon administering a movement and learning therapy called 'coordination dynamics therapy', and (3) to understand why integrative patterns do loose stability following injury.

Pattern change (100 ms) needs more time than pattern enhancement (6 ms)

The time for pattern change was measured in a patient at the neuron level. Identified α and γ-motoneurons fired oscillatory, due to the sustained stretch reflex of the external sphincters (as a part of the continence automatism) induced by an anal catheter (and may be the bladder catheter). The motoneurons and the secondary muscle spindle afferents transiently synchronized their firing upon repetitive touch and pin-prick inside the anal reflex area, by reducing the duration of their oscillation period till to a resetting of the oscillation cycle.

The responses to pin-prick stimulation were different from those to touch stimulation in three aspects. Firstly, the response time till to the shortening of the oscillation period was longer than the oscillation period (≈100 ms) for pin-prick and shorter for touch. Second, the response to pain application was longer (shortening of several oscillation periods) and stronger than for touch stimulation. Pin-prick stimulation reduced the oscillation period to between 5 and 40 ms (mean = 18 ms), and touch stimulation to between 8 and 28 ms (mean = 15 ms). Third, transient synchronization of afferents and efferents was most pronounced for pin-prick stimulation.

The shortest latency, however, following touch was approx. 10 ms when measuring from the afferent volley running in the direction of the spinal cord, and 110 ms following pin-prick. It is discussed that repetitive touch stimulation reinforced the sustained stretch reflex of the anal sphincter which is possible with no network reorganization (variation of the same network state) and therefore fast, whereas repetitive pin-prick stimulation replaced the sustained stretch reflex by the protection reaction of the anal sphincter (switching from one network state to another) which made time consuming network reorganization necessary. Taking the conduction velocities of skin and pain afferents into consideration, the reinforcement of the continence pattern needed approximately 6 ms and the pattern change from the continence to the protection pattern needed approximately 100 ms.

Exact phase and frequency coordination in the brain-dead human

In the brain-dead human, natural simultaneous firing patterns of secondary muscle spindle afferents and α and γ-motoneurons showed relative phase and frequency coordination. The correlation between the firing of a motoneuron and a spindle afferent fibre was in the range of between 3 and 5 ms. The Eigenfrequencies of α_2-oscillators changed only little with time and the phase relations between the α and γ-motoneurons and the secondary muscle spindle afferents were rather stable. The overlap of the interspike interval distributions of the secondary spindle and bladder stretch receptor afferents with the 'Eigenfrequency' ranges (and their halves) of the oscillators showed what afferents were driving what motoneurons with respect to frequency coordination. Relative phase and frequency coordination was rather stable and specific for the physiologic CNS organization.

In a patient with a spinal cord injury this phase and frequency coordination was analyzed to study CNS self-organization. Simultaneous interspike intervals (IIs) of and phases between, the APs of 5 nerve fibres

were recorded, and distributions constructed. The interspike interval (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.

Loop of premotor spinal oscillators to the periphery

Following repetitive touch and pin-prick stimulation (frequency $\gamma \approx 1$ Hz) 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 by the oscillatory firing α neuronal networks building up an external loop to the periphery via the γ-loop.

Change of phase relations

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.

Impairment of phase and frequency coordination following spinal cord injury

According to the exact phase and frequency coordination among neuron firing obtained from the brain-dead individual in comparison with the impaired coordination in spinal cord injury patients, it is likely that the increased synchronization tendency and instability in the number and the values of phase relations suggest pathologic functioning of the caudal functionally disconnected spinal cord in patients with spinal cord injuries: Oscillatory firing neuronal networks, which lost their specific Eigenfrequencies, interact more easily and unspecifically with other oscillatory firing networks.

Building of oscillator loops to the periphery for re-learning patterns and phase and frequency coordination

Since spinal oscillators built up external loops to the periphery, it becomes possible in humans with spinal cord injury to re-preformate oscillatory firing neuronal networks (and the networks they are integrated in) in the sacral micturition centre by coordinated, rhythmic, dynamic, stereotyped movements, to reduce spasticity, repair movements and repair urinary bladder functions by learning transfer from movements to bladder functions. The results of this and the following article (43) support my key tenet that learning not only stabilizes the to-be-learned patterns (like jumping on springboard or walking on treadmill), but causes also specific modifications of the entire coordination dynamics in the direction of the task requirement and gives rise to transfer of learning. Further, the task requirements when exercising on the special CDT device is to re-learn phase and frequency coordination among neuron firings for that specific movement pattern, but causing also long-lasting alterations (improvements) of the phase and frequency coordination of the underlying coordination dynamics of millions of neurons and contributing in this way substantially to a transfer of abstract learning. Learning transfer from movements to urinary bladder functions is also in accordance with functional anatomy, since the somatic and the autonomic nervous systems dovetail with one another in the sacral micturition centre. Even some muscle spindles of the external sphincters are innervated by the somatic and parasympathetic divisions.

Key-words: Human – CNS injury – Repair physiology – Neurotherapy – Single-nerve fibre action potentials – Interspike intervals – Phase and frequency coordination – Spinal oscillators – External loop – Synchronization – Phase and frequency stability – Pattern stability – Motor learning – Continence – Urinary bladder – Learning transfer.

Introduction

General

Schalow Coordination Dynamics Therapy has been shown to be able to improve the central nervous system (CNS) functioning after stroke (25), traumatic brain injury (26, 33), cerebellar injury (35), spinal cord injury (22, 27, 37-39, 43), cerebral palsy (31), in Parkinson's disease (28, 30), and after hypoxic brain injury (32). This movement-based learning therapy could not only improve the trained movements, but other not trained patterns could also be improved by transfer of learning. In cerebral palsy the higher mental functions (31) and in spinal cord injury the autonomic functions (39), including urinary bladder functions (43), could be improved by this movement-based learning therapy. In this article the mechanisms of the transfer of learning will be tried to clarify to further increase learning transfer and to show on what level of human research urinary bladder functions can be cured in motoric complete cervical spinal cord injury (39, 43).

Upon measuring natural communication among single neurons in the human nervous system, insight will be gained into why some trained movements substantially contribute to transfer of (re-)learning (jumping on springboard, exercising on a special device) and others are not or only little (passive movements of arms and legs).

I will concentrate on the learning transfer from movements to urinary bladder functions, because, first, this learning transfer is very important, and second, high-quality natural impulse patterns have been recorded by me involved in single-nerve cell communication related to movement (somatic division) and continence functions (parasympathetic and somatic divisions). A learning transfer from movements to higher mental functions cannot easily be analyzed at the single-neuron level, since it would be difficult to record single cell communication related to thinking. Phase memory has been measured between single motor units upon repeated muscle activation (19). But to measure longer acting memory of integrative functions is a different task. It will be tried in this article therefore to understand the 'learning transfer' from movements (jumping on springboard (Fig. 1C)) to bladder functions (continence and micturition) on the basis of human electrophysiology at the neuron level in the human sacral spinal cord. I will further try to show that the induction of learning transfer in the injured CNS needs more than understanding the re-learning of movements. The impaired phase and frequency coordination for CNS self-organization has also to be improved by phase and frequency re-learning (when exercising on special devices (Fig. 1D)), to have a neuronal network available which has the capability to learn.

Learning transfer

The injured, malformed or degenerating human CNS can partly be repaired by learning (21-33, 35-39, 43). The training of those movements or functions, which are impaired, is a too simple approach and only partly successful to repair the CNS integratively and the functions which cannot be trained, like continence or intelligence (cerebral palsy), cannot be repaired or improved.

A scientific approach to CNS repair is to train and re-learn those organizational functions of the CNS which are impaired. By comparing the physiologic with the pathologic CNS functions, it was discovered what urinary bladder functions became pathologic and have to be repaired or improved (40-42).

Following severe cervical spinal cord injury (Fig. 1A, B), it was shown that motor functions could partly (39) and urinary bladder functions fully repaired (43). By comparing the natural impulse patterns of single neurons between a brain-dead human and patients with spinal cord injury, it was shown that with respect to bladder dysfunction, mainly the

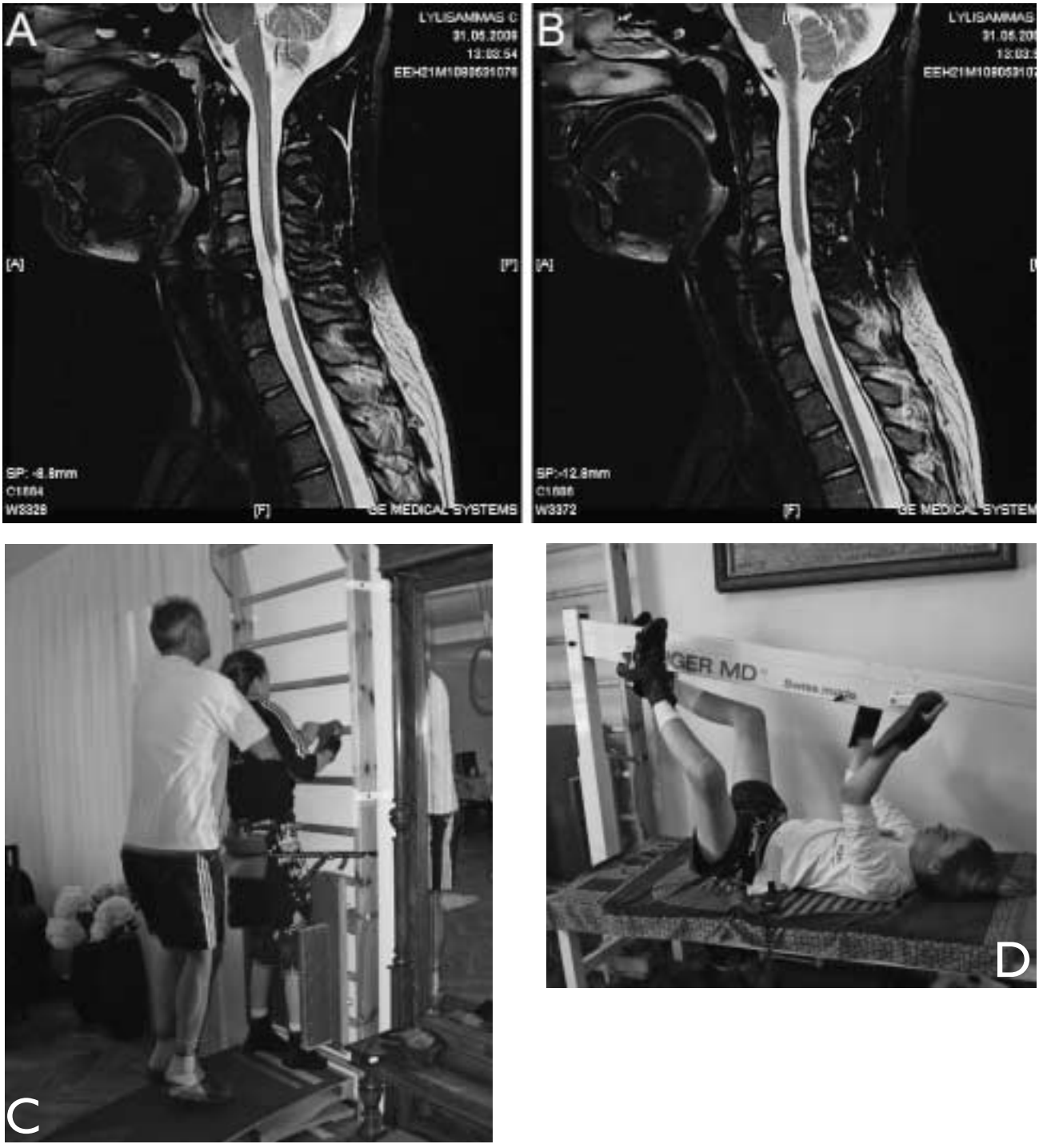

Fig. 1A,B. – Magnetic resonance images of a severe spinal cord injury at C5/6 levels of a 20-year-old female patient after 3 years of optimal coordination dynamics therapy. Both sagittal T2-weighted images show connection between the rostral and caudal spinal cord.
Fig. 1C. – Jumping on springboard of a 20-year-old patient with a severe spinal cord injury at C5/6 levels (Fig. 1A,B) (upon no weight support) after 3 years of optimal coordination dynamics therapy. The father is jumping behind in interpersonal coordination to increase the jumping amplitude.
Fig. 1D. – Same patient as in Fig. 1C upon exercising on a special coordination dynamics therapy device.

self-organization of neuronal networks of the sacral micturition centre went pathologic (40-42, Figs. 20-22) because of the disconnection from supraspinal centres.

This article concentrates on the 'learning transfer' (in severe cervical spinal cord injury) from movements to urinary bladder functions for a repair of bladder functions, consisting of the learning transfer and the improvement of the self-organization of the neuronal networks of the spinal cord and supraspinal centres. In incomplete spinal cord injury, the spared tract fibres can be used for a functional reorganization including a reconnection of the sacral with the pointine micturition centre (38). In almost complete spinal cord injury (39, 43) with nearly no spared tract fibres remained, however, some connections to the pointine micturition have to be (and can be) reconstructed by a limited regeneration of the cord (39, 43). This article is giving the scientific basis for those movements which are most efficient in inducing learning transfer for bladder repair.

Re-learning of phase and frequency coordination and re-learning of bladder functions via learning transfer from movements

Since following CNS injury the phase and frequency coordination of neuron firing for neuronal network organization is impaired (Figs. 20-22), this phase and frequency coordination has efficiently to be improved by learning. This can be achieved when the patient is exercising on the special coordination dynamics therapy device for turning movements (Fig. 1D). From all coordinately performed movements the patient's CNS can relearn the coordinated firing of neurons. However, such relearning of coordinated firing is most efficient if the movement is most integratively and extremely well coordinatedly performed. A re-learned higher precision and specificity of neuronal network organization (a kind of abstract learning) allows higher learning (and information) transfer.

The induction of learning transfer from movements to bladder functions can efficiently be induced when the patient is jumping on springboard, as will be shown in this article, since movement and bladder functions are synchronously activated during the jumping: The networks for generating motor patterns and the networks for generating autonomic and somatic bladder patterns are synchronously activated and entrained in the way that the neurons of the activated networks improve the coordination of their natural impulse traffic. The learning transfer involves two properties to be improved. First, the phase and frequency coordination of neuron firing has to be improvement so that the injured CNS can generate a specific landscape of pattern formation (attractor layout) again with specific stabilities of the attractors and the fluctuation of the pattern states is reduced (Fig. 23). Second, the geographical landscape of attractors has to be changed specifically by learning and learning transfer so that the repaired CNS can generate the physiologic bladder functions with high stability again (43).

Natural impulse patterns of single neurons can explain integrative patterns

The CNS can partly repair itself by the interplay of the body with the external world via the activation of receptors in the different organs and the transmission of the specific information, encoded in natural impulse patterns, in afferents to the neuronal networks and in efferents to the different organs and limbs. Additionally, premotor spinal oscillators (network oscillators) can build up an external loop to the periphery (Fig. 15) (18) to include the periphery more directly in the network organization and reorganize the networks more efficiently by entrainment.

Recording the natural afferent and efferent impulse traffic in nerve roots, leading to neuronal network organizations (Fig. 3), during the organization of urinary bladder and motor patterns upon natural stimulation, changes in the natural impulse traffic (Fig. 8) will reveal changes in the network organizations of continence and motor patterns (Figs. 5-9). The organization of bladder function patterns is stimulated (besides intention) by exciting bladder receptors (Figs. 4E, G, 5G, 15H) and the organization of motor patterns is stimulated by exciting somatic receptors (especially pain receptors of the skin (Figs. 5, 15)).

Since the natural afferent and efferent impulse traffic is part of CNS organization, it should be possible to explain and calculate integrative patterns by using natural impulse patterns of single neurons. It

will be shown that the pattern change between continence and protection can be calculated (Figs. 7-9) based on human neurophysiologic data at the neuron level.

It will therefore be shown that it is possible to measure and understand macroscopic patterns by changes of the natural impulse traffic upon different natural stimulations. Such understanding of integrative functions by impulse pattern at the single-neuron level is a first step in the direction of understanding "I think, therefore I am" (Descartes) by the communication among neurons. The integrative patterns are made visible by an attractor layout, defined in the framework of "System Theory of Pattern Formation for the Injured CNS". Such attractor layouts for continence functions will be used in a following publication to understand urinary bladder repair (43).

Knowing that natural impulse patterns can explain behavioural patterns, it will be tried then to understand the learning transfer between movement and continence patterns. For a deep understanding of CNS self-organization and re-organization upon natural stimulation during pattern change, we have to go into the complexity of CNS self-organization that means we have to go into the complexity of phase and frequency coordination among neuron firings (42) (Figs. 11, 12, 14).

The exploration of phase and frequency coordination in subnetworks shows some similarity to the analysis of electrical circuits by means of the 'rules of Kirchhoff'. In human electrophysiology phase and frequency changes among neurological elements and in electronics currents and voltages among electronic elements are measured. But in both cases a sub-network is analyzed as a part of a larger network.

Instability of phase and frequency coordination at the neuron level causes instability and variability of movement and continence pattern states

A substantial difference between electrical and neuronal networks is the stability of functioning. Instability of macroscopic pattern states is caused by the instability of phase and frequency coordination at the neuron level.

For a repair of the injured CNS by learning and learning transfer, the variability of phase and frequency coordination (Figs. 20-22) has to be improved to generate more specific and exact coordination changes again (Figs. 17-19). In an attractor layout for movements (Fig. 9Ab) or bladder functions (Fig. 9Bb), the stability of an attractor is given by the depth of the potential well. The basin of attraction for jumping in-phase, for example, is deeper than the one for jumping anti-phase (Fig. 9Ab). The jumping in-phase has therefore a higher stability than jumping anti-phase, if the ball (the network state) lies stable in the depth of the basin of attraction that means if the pattern state shows only little fluctuation (Fig. 23A).

If the phase and frequency coordination, however, became impaired (high variability of coordination), the attractor layout will be deformed and the ball (the network state) will move about in the attractor basin (or even jumps out of the basin), which means that the network state became instable and varies very much (or is even lost) (Fig. 23B, C). The performance of jumping on springboard would become poor (changing of stride length, knee flexion, foot positioning, etc.).

There are therefore two kinds of stability of network states. For movement performance with high quality (high quality of CNS organization (healthy CNS)), there are differences in the stability among movement patterns. The jumping in-phase on springboard has a higher stability than jumping anti-phase, probably because the jumping in-phase is easier to generate by the CNS (easier coordinations are only needed). The second kind of stability is related to the precision (fluctuation) of phase and frequency coordination for CNS organization. Following injury, the phase and frequency coordination becomes poor and more or less all movements can be performed by the patients only with poor performance (if at all).

But some movements become more impaired than others. In stroke patients, for example, the performance of arm movements on the injured side is mostly more impaired than the one of the leg movements, because the networks for generating the arm movements have a higher complexity and higher precision of phase and frequency coordination is needed for the organization of the arm movement. The networks for organizing the more stereotyped leg movements are not that complex and are also therefore not that much disturbed by the injury.

To repair the injured CNS by learning, therefore, not only the stability of the physiologic attractors has to be increased (deepening of the attractor basin) and the stability of pathologic attractors, like spasticity, has to be decreased (shallowing of the potential well). Also the fluctuation of phase and frequency coordination has to be reduced so that the CNS can generate specific geographical landscapes of attractors and movement and continence patterns with little variability again.

Without specific phase and frequency changes, there is also no learning transfer possible any more because of missing specific network organization necessary for learning.

Need for a regeneration of the spinal cord

For the repair of a severe spinal cord injury a functional repair is not sufficient; the caudal disconnected spinal cord has to be brought under supraspinal control again and at important network sites, new neurons and new connections have to be built. For directing intention downstream to induce pattern change in complete spinal cord injury, some regeneration of tract fibres is needed.

Specific

System Theory of Pattern Formation (collective variable level of description)

In recent years, several researchers have examined the issue of perceptuomotor learning from a dynamical perspective without, however, providing any operational or formal treatment of individual spontaneous coordination tendencies that exist before, during, and after learning at the collective variable level (the variable is the relative phase between the legs when jumping on springboard, Fig. 9Ab) and partly at the neuron level (phase and frequency coordination dynamics, Figs. 11, 12, 14, 21, 22) to show a self-consistency between the collective and neuron level of description.

By cooperative and competitive interplay the many billions of neurons of the human CNS generate dynamics in self-organization which can, for special patterns, be described by collective variables or order parameters. Specific equations of motion (the dynamics) of these collective variables generate the time course of organizational states. Coordination patterns are not only determined by the task or biological function, but the patterns adjust continuously to the requirements from the environment, memory, intention, and support given by a therapist. All the specific requirements are captured by the concept of behavioural information and are made part of a vector field that attracts toward required patterns. The coordination pattern dynamics, characterized by equations of motion of the collective variables, takes the following form (44):

$$d\mathbf{X}/dt = \mathbf{F}_{intr}(\mathbf{X}) + \sum c_{inf}\mathbf{F}_{inf}(\mathbf{X},t) \quad (2)$$

where $\mathbf{F}_{intr}$ designates the intrinsic dynamics and the sum is over different types of so-called behavioural information, $\mathbf{F}_{inf}$, as environmental, memorized, or intended behavioural information. The relative strength of the different influences is parameterized by c_{inf}. For a mathematical solution to equation (2) for the special movement 'jumping on the springboard' in the Haken-Kelso-Bunz model (5), see Refs. 33, 38. Since it is extremely difficult or not at all possible to find a mathematical solution to the equations of motion of the collective variables (formula 2) (even using many approximations), a substantial progress in evaluating the quality of CNS organization was therefore achieved when it became possible to assess partly the dynamics of CNS organization experimentally (by diagnostic). The dynamics of CNS self-organization at the neuron level by phase and frequency coordination is partly reflected in the temporal stability of coordination patterns, which can be assessed through a process of pattern change. When a subject exercises on the special coordination dynamics therapy and recording device for turning (Fig. 1D), the device is imposing all the continuously changing coordinations of arm and leg movements between pace and trot gait. Pattern stability is assessed by measuring the temporal stability of exercising (df/dt; f = frequency) at an own optimal frequency, e.g. 1 Hz, upon the pattern change of arm and leg movements. There is only one collective parameter describing the coordination tendencies, which is the temporal stability of exercising. Attractor layouts of pattern stability can be recorded (34).

The equations of motion of the collective variables (formula 2) have important clinical implications for treatment. The behavioural requirements $\mathbf{F}_{inf}$ (like intention, support, and instruction) affect the whole coordination dynamics, including stability, rather than certain coordination pattern itself only. If one pattern is trained and improved upon movement-based learning, also the not trained patterns change and improve. There is learning transfer. This learning transfer from movements to urinary bladder functions is tried to understand (and develop further) in this article with data obtained from human electrophysiology.

Magnet effect: Intrinsic coordination tendencies captured by the intrinsic dynamics influence systematically trained patterns because the degree to which intrinsic tendencies conflict or agree with the required patterns determines the variability of the performed coordination pattern. Such attraction to certain sets of phase relations (of hundreds to millions of phases, necessary to generate a pattern by cooperative and competitive stability) among coordinating neurons was called by von Holst 'Magnet effect' (7, 8). The rate of learning transfer is therefore higher if a trained coordination pattern is close to a pattern of the intrinsic coordination tendencies. The trained patterns of nearby phasing's are biased or attracted toward the stable intrinsic patterns. In reverse, if the exercised pattern (with the support of therapists and devices) is functionally close to the former physiologic pattern, the 'Magnet effect' will 'pull' (attract) the deteriorated pattern (due to CNS injury) in the direction of the performed physiologic pattern. With respect to urinary bladder repair, the rate of learning transfer is highest, if the activated pattern is close to the coordination tendencies of the coordinating components of the former micturition and continence patterns. It will be shown in this article that during jumping on springboard, the coordinating components for continence and micturition are activated similarly as during physiologic functioning. The 'Magnet effect' will attract the neuron firings by entrainment of the neuronal networks in the direction of the coordination pattern 'physiologic continence and micturition'.

In conclusion, the equations of motion of the order parameters (collective variables) (formula 2) provide us with treatment principles, but offer no information about the specific behavioural information (F_{inf}) with the use of which the CNS can efficiently be repaired including learning transfer in the given patient. The human neurophysiology data of this paper, on the other hand, lead to a scientific and practical basis to induce learning transfer from movements to urinary bladder functions for bladder repair. In the previous 3 publications it was concentrated on the differences between physiologic and pathologic functioning of the human bladder (40-42), especially on the synergia and the dyssynergia. In this paper the 'repair physiology' for bladder repair is presented. Network organizations and changes will be measured in the parasympathetic and somatic nervous system divisions. The stability of network states will be related to the stability of phase and frequency coordination between single neuron firings. It will be shown that the stability of movement and continence patterns is related to the stability of phase and frequency coordinations of neuron firings involved in movement and continence functions. The improvement of the stability of the phase and frequency coordination among millions of neurons and the change of phase and frequency coordination to generate physiologic patterns is the basis for functional repair including learning transfer. The deterioration of phase and frequency coordination upon neuron damage due to injury or degeneration will affect nearly all the coordination relations related to the cooperative and competitive interplay among neurons for generating a pattern. During functional repair it is tried to establish physiologic stable sets of phase relations again. The jumping on springboard uses mainly the Magnet effect between closely related network states for repair besides the repair of the 'Eigenfrequencies' of premotor spinal oscillators. This article is tackling the communication among single neurons and the entrainment of human neuronal networks for repair.

Electrophysiology (neuron level of description)

I have shown in previous papers that the classification scheme for the human peripheral nervous system (12) is preserved following spinal cord injury (40) and can be used as a basis for a comparison of the natural impulse patterns between patients with spinal cord injury and brain-dead humans to clarify bladder functioning. I have analyzed the detrusor-

sphincteric dyssynergia (pathologic co-contraction of detrusor and external bladder sphincter) of the urinary bladder (41, 42). Parasympathetically evoked impulse patterns of secondary muscle spindle afferents and sphincteric motoneuron activity were compared between paraplegics and a brain-dead human. It was shown that inflammation, hypertrophy and overactivated bladder stretch (S1) and tension receptors (ST) contributed to bladder dysfunction (40). The main reason for the detrusor-sphincteric dyssynergia of the bladder, however, seemed to originate from the CNS organization itself. Following spinal cord injury, with the reorganization of the sacral micturition centre the mutual inhibition of the detrusor and the external bladder sphincter is sometimes lost (41). The mechanism underlying the loss of the mutual inhibition of detrusor and external sphincter may be, besides other reasons, a false sacral reflex reorganization or disconnection from the pontine micturition center, which is believed to coordinate the activation of detrusor and external bladder sphincter. Intermediate stages of the coordination of detrusor and external bladder sphincter are conceivable. Since in a brain-dead human the parasympathetic division inhibited sphincteric motoneurons with detrusor contraction, pathologic reorganization and adaptation of the CNS, caudal to the level of injury, probably takes place already in the spinal shock phase and thereafter. It was further partly shown in previous publications that the phase and frequency coordination among neurons and neural assemblies in the sacral micturition centre of the human CNS got impaired (42). The "Eigenfrequencies" of neuronal assemblies (premotor spinal oscillators) became partly lost (Fig. 20) and the phase coordination between the firings of motoneurons and muscle spindle afferents became unstable in patients with spinal cord injury (Fig. 22) in comparison to the coordination among neurons in the brain-dead human (Fig. 21). The instability of the "Eigenfrequencies" of premotor spinal oscillators and the coordination instabilities among the firings of premotor spinal oscillators and spindle afferents lead to the conclusion that the self-organization of the neuronal networks of the sacral micturition centre becomes unstable following spinal cord injury. The integrative functions of the sacral micturition centre therefore get unstable and the network patterns probably change their stability values according to the actual spinal cord injury. According to the actual injury, some patients have a synergia of the bladder, other ones a dyssynergia and still other ones a mixture of both patterns. Now the step from human neurophysiology (40-42) to the System Theory of Pattern Formation (9, 33, 34, 38, 44, 47) is possible. Since healthy humans have the synergia pattern and the dyssyergia pattern (to stop micturition) and can switch among them by intention, the sacral micturition centre can be repaired by changing the stabilities of these patterns. The problem of synergia and dyssynergia is not any more a problem of fixed pathologic circuitries following injury but is more a question of stability of patterns which can be changed by learning. Since patients with severe spinal cord injury cannot train directly urinary bladder functions (or only little), movements have to be trained with which urinary bladder functions can be improved by transfer of learning.

This paper reports about the measurements in the human CNS which lead to the movements, with which urinary bladder functions can be cured (43) by learning transfer (first fundamental step). To get the urinary bladder under volitional control and to enhance further the stability of micturition and continence functions, some regeneration in patients with spinal cord injury is necessary. The second fundamental step in repair is that this necessary regeneration to cure urinary bladder functions is possible to achieve even in severe cervical spinal cord injury. The following publication will report about it (43). The evolutionary principle of levels of function, which implies that rostral segments of the brain have become dominant over caudal, is restored. The century step is that the urinary bladder functions can be cured and destructive operations are not necessary any more in patients to whom the movement-based learning therapy 'coordination dynamics therapy' can be administered. A drawing back is still that the learning effort is enormous in severe cervical spinal cord injury (36), but the effort is much less in incomplete spinal cord injury (38) and in children with spinal cord injury (27).

Nearly 10% of the society suffers on incontinence, including young women after the birth of the first child (stress incontinence). There are no problems for the young mothers to jump on springboard, to walk or run, or to exercise on the special coordination dynamics therapy device for turning.

Methods

Electrophysiology

Single-nerve fibre action potentials were recorded extracellularly (Fig. 3A) from undissected nerve roots (Fig. 3C) with two pairs of platinum wire electrode pairs (electrode pair distance 10 mm; electrode distance in each pair 4 mm) at two sites (Fig. 3A,B), preamplified (x1000), filtered (RC-filter, passing 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 (12). From multi-unit impulse patterns, simultaneous patterns of several single afferent and efferent nerve fibres were extracted (Fig. 3D) 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. APs of a single nerve fibre were identified with the naked eye by picturing first the AP wave forms (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 of conduction time, d. AP amplitude. Since the adding up of different AP wave forms or the adding up with artifacts can be distinguished with the naked eye, manual identification is superior to computer analyses unless having a computer programmed for all possible adding's up of the different potentials and artifacts. Interspike interval (II) and phase distributions were constructed (Figs. 11, 12). The intraoperative recordings were mainly performed in a brain-dead human and in a patient with a spinal cord lesion sub TH1 (for one year (paraplegic 9)) during the implantation of an electrical anterior root stimulator for urinary bladder control.

Re-learning at the movement, collective variable, and neuron levels:

CNS repair is based on a pattern re-learning theory, the theory of coordination dynamics, which requires at least three levels of description: the movement or pattern level (walking, micturition); the coordinative, collective variable level (relative phase between the legs, when jumping on springboard); and the neuron level (phase and frequency coordination among neuron firings). The nervous system supplies coordination dynamics at these three levels of description rather than particular patterns.

At the movement level, existing coordination tendencies are evaluated by the performance of movements and can partly be quantified for example by the speed of the performed movement (speed of crawling).

At the collective variable level, existing coordination tendencies are treated in terms of dynamics, i.e., as equations of motion (if possible) of a relevant collective variable that changes during the learning process ($d\mathbf{X}/dt = \mathbf{F}_{intr}(\mathbf{X}) + \sum c_{inf}\mathbf{F}_{inf}(\mathbf{X},t)$, see Introduction). By defining a potential function, behavioral changes can be represented by the overdamped movement of a rolling ball (the state of the system) in the potential "landscape". For jumping on springboard and bladder continence, such attractor layouts are shown in Fig. 9. For the bladder function, no collective variable could be given.

At the neuron level, existing coordination tendencies are treated in terms of phase and frequency changes among single neuron firings (α and γ-motoneurons and muscle spindle, skin and bladder afferents). Changes of coordination tendencies are measured, invasively, before injury (physiologic, brain-dead human) and after injury (pathologic, patient with spinal cord injury) and their temporal evolution (non-invasively). Non-invasively, single motoneuron firing can be measured by surface electromyography (sEMG) when recording single motor unit firing for example in spinal cord injury patients (29).

The repair of the human CNS by learning can be assessed by measuring the existing inner coordination tendencies and their evolution before, during, and after (movement-based) learning. The improvement of CNS self-organization is quantified at the movement level by the performance, at the collective variable level by the arrhythmicity of turning (df/dt, f = frequency) upon exercising on the special coordination dynamics therapy device for turning (Fig. 1D), and at the neuron level by improvements of motor programs and single motor unit firings (sEMG).

Informational relevant for repair are the existing CNS organizations in patients following CNS injury, here operationalized in terms of behavioral patterns and conceptualized as an attractor layout or coordination dynamics. Cooperative and competitive mechanisms can be evaluated only in relation to existing coordination tendencies, making the individual learner or patient the significant unit, not the group or the species.

Since re-learning of patterns involves alterations of the entire attractor layout of the coordination dynamics of movements, autonomic, higher mental, and other functions (even though the dynamics cannot be described till now), learning transfer is also occurring between movement and urinary bladder functions. In the Results natural impulse patterns at the neuron level in human are presented, with which insight will be gained into why some excessively trained movements contribute to re-learning and learning transfer (synchronous activation of receptors for movement and continence functions upon jumping on springboard (Fig. 15), frequency coordination between afferents and motoneurons (Figs. 18, 19)) and others are not (passive movement with no or only little activation of the neuronal networks). In the Discussion, the learning process is tried to clarify in terms of movements, dynamics of collective variables, and dynamics of phase and frequency coordination among single neurons.

Definition of the term "coordination dynamics" to clarify unfortunate connotations

By using the movement, performed on the special CDT and recording device (Fig. 1D), as behavioral information in the equation of motion, the collective variable of the corresponding coordination dynamics is the arrhythmicity of turning (temporal stability of this specific coordination pattern range) with pattern change from trot gait (anti-phase) to pace gait (in-phase coordination between arm and legs) and backwards. The arrhythmicity of turning, with ongoing time, was termed "coordination dynamics" in former publications. The mean arrhythmicity of turning per minute was called coordination dynamics value and the measured change of the arrhythmicity of turning for the pattern range from trot to pace gait and back to trot gait was termed attractor layout of the collective variable "df/dt" or "df/dt/f". The coordination dynamics values for different loads, ranging between 20 and 200N, are the backbone of my approach to quantify the quality of CNS organization during repair. Therefore this special coordination dynamics therapy device offers the possibility to measure certain aspects of CNS organization non-invasively to probe CNS organization with ongoing therapy and it can be used to re-learn phase and frequency coordination at the neuron level, at the collective variable level, and at the movement and pattern level.

But the term "coordination dynamics" is also used more generally in this article to describe the self-organization of the neuronal networks of the CNS and its temporal evolution, especially during re-learning.

Results

Clinical urinary bladder function test (Urodynamics)

To understand learning transfer, defined within the framework of System Theory of Pattern Formation for Repair, from movements to urinary bladder functions with human electrophysiology on the single-neuron level, it is started with the clinical diagnostic of the urinary bladder, the urodynamics.

The functioning of the urinary bladder can be evaluated by measuring the pressure in the bladder and in the abdomen (colon) and the electromyographic (EMG) activity of the external sphincters and/or functionally associated pelvic floor muscles (45). Such bladder diagnosis is called urodynamics (Fig. 2). Especially the simultaneous activation of the detrusor (line detrusor pressure in Fig. 2B) and the sphincteric and/or pelvic floor muscles (line pelvic floor EMG in Fig. 2B), the so-called detrusor-sphincter-dyssynergy, can be measured, which may destroy the kidneys on the long term.

Upon retrograde filling of the bladder in a patient with a spinal cord injury, the pressure in the bladder and colon is measured and the electromyographic activity (EMG) of the pelvic floor is recorded with surface electrodes (Fig. 2). The detrusor pressure is obtained by subtracting the abdominal pressure from the bladder pressure. The continence status of the patient is diagnosed by the reports of the first feeling

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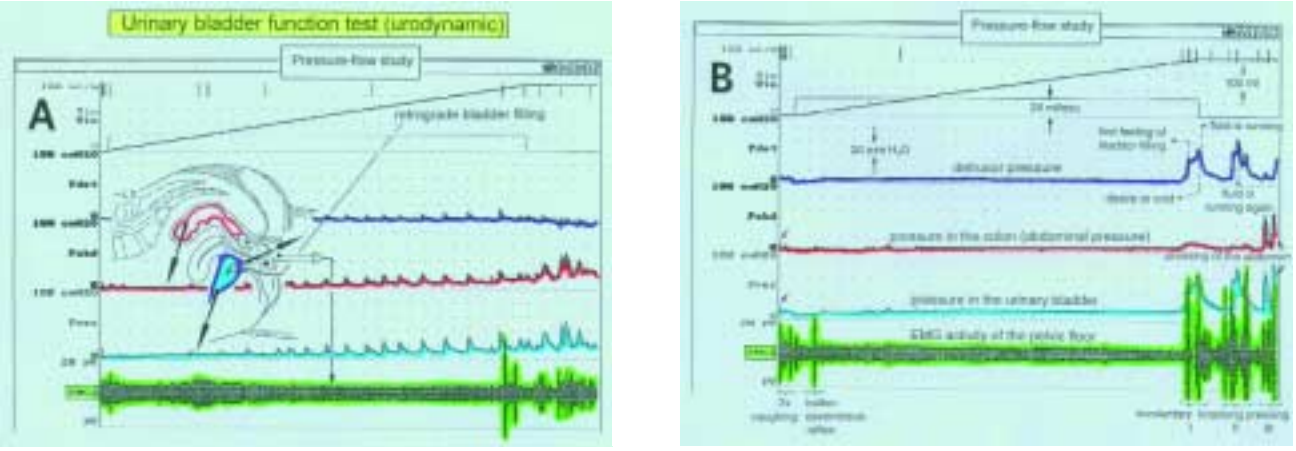

Fig. 2. – Improvement of the urinary bladder functions mainly due to therapy, quantified by urodynamics in a 30-year-old female patient. A. 3 months after the accident in the mountains with resulting paraplegia sub Th12 following spinal cord lesion. B. 12 months after the accident (lesion level lowered to sub L3). In A, the detrusor pressure (P_{det}) is generated by the contracture of the bladder wall, as the pressure difference between abdominal pressure (P_{abd}, measured in the colon) and the bladder pressure (P_{ves}, measured in the bladder). Electromyographic recording obtained with surface electrodes from the sphincters and the pelvic floor (EMG) is shown; the external sphincters and the functionally correlated pelvic floor muscles show similar EMG activity (the rhythmic pressure peaks in A do not originate in the bladder). In A, the detrusor shows nearly no activity with retrograde bladder filling at 25 ml/min; in B, the detrusor shows first activity at 360 ml bladder filling. A detrusor-sphincteric-dyssynergy occurs, because the detrusor pressure peaks occur at the same time as the sphincter EMG activity peaks (B) (bladder and sphincter contract at the same time, so that fluid can only emerge from the bladder at high bladder pressure; there is a danger of reflux through the ureter into the kidneys). The EMG peaks are a bit irregular, probably because the fluid, leaving the bladder, shunts transiently the EMG electrodes. Exact functional description of B: 2x caughing (B below) increases the EMG activity and passively the pressure in the abdomen and in the bladder (marked by the small arrows, physiologic). The bulbocavernosus reflex (induced by pressure applied to the clitoris) increased the EMG activity of the sphincters (physiologic). Conclusion: The reflex arch is in order; sacral nerve roots and nerves have not been damaged in the accident. I (bottom right): The patient feels an increase of unvolitional detrusor pressure (first feeling of bladder pressure at 360 ml). She tries to contract the sphincters to stop the bladder emptying. Shortly after the desire to empty the bladder, as the detrusor pressure decreases, fluid is leaving the bladder. II: Due to tapping onto the bladder, the bladder reflex is activated (detrusor activated, nearly no abdominal pressure); fluid is leaving the bladder. III: Due to the abdominal muscular pressure the pressure in the abdomen increases as does passively the pressure in the bladder (the detrusor is not activated); fluid left the bladder. With a delay, the detrusor was activated by the bladder reflex. - The urinary bladder of the patient is partly functioning. It has to be further improved by therapy induced reorganization of the CNS: (1) An earlier feeling of bladder filling, (2) an increase of the time difference between the feeling of the first bladder filling and the unvolitionally emptying of the bladder (for the time being, approx. 10 min, in dependence on whether the patient is physically active (such as walking) or not, (3) further learning how to activate the detrusor on volition, and (4) the physiologic coordination between the bladder and the external sphincter functioning (to stop the detrusor-sphincter-dyssynergy). In cooperation with U. Bersch, Urology, SPZ Nottwil.

of bladder fullness, the desire to void, and the leaving of fluid out of the bladder. The EMG activity of the pelvic floor informs when the external bladder and anal sphincters are activated. Upon knocking, pressing, coughing, and stimulating bladder reflexes, the bladder status is obtained. This patient of Fig. 2 with a spinal cord injury subTh12 had a detrusor-sphincteric dyssynergy of the bladder, because the EMG activity of the external sphincters increased (the sphincters became activated) with the increase of the detrusor pressure (activation of the detrusor). Improvement of urinary bladder function mainly due to therapy could be quantified by repeated urodynamics measurements (Fig. 2A, B).

Limitation of urodynamics and need for human electrophysiology for causal repair

The evaluation of bladder functioning by means of urodynamics gave the information that the patient had a dyssynergy of the bladder. Repeated testing informed about changes in bladder functioning. But such bladder function tests are giving no information

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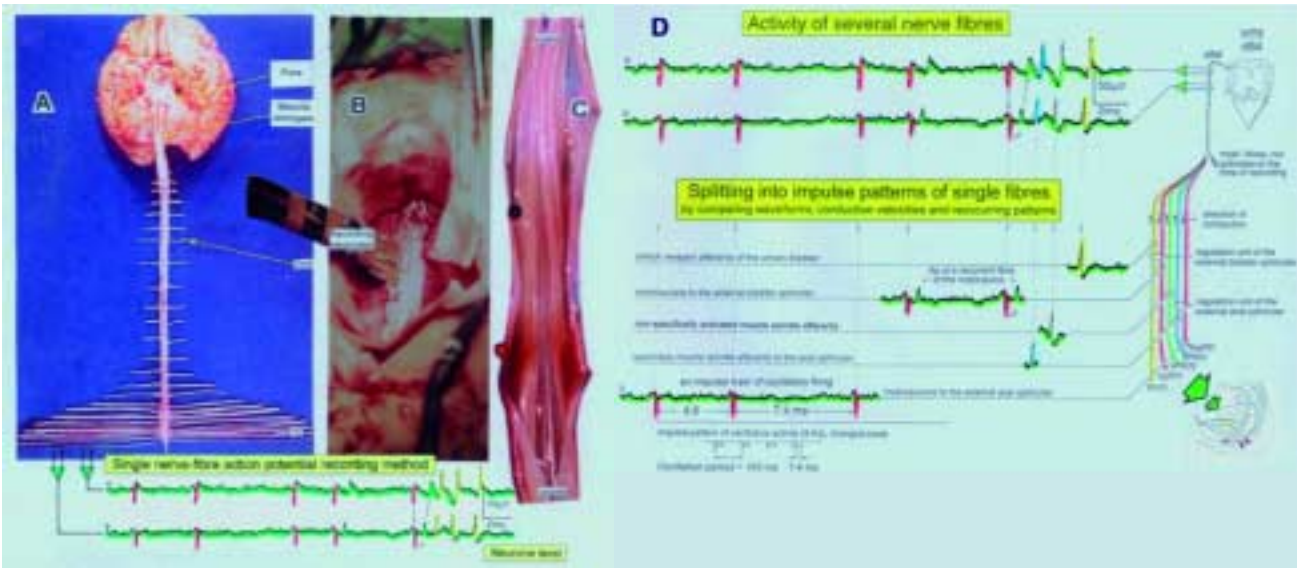

Fig. 3. – Layout of the recording of single-nerve fibre action potentials to analyze the self-organization of neuronal networks of the human CNS under physiologic and pathophysiologic conditions. A,B,C. By recording with two pairs of platinum wire electrodes (B) from sacral nerve roots (cauda equina, C) containing between 200 and 500 myelinated nerve fibres, records were obtained in which single nerve-fibre action potentials (APs) were identified from motoneurons (main AP phase downwards) and afferents (main AP phase upwards). By measuring the conduction times and with the known electrode pair distance (10 mm), conduction velocity distribution histograms were constructed in which the myelinated nerve fibre groups larger than 4μm could be characterized by group conduction velocity values. After the recording, morphometry was performed. Distributions of nerve fibre diameters were constructed and 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 for the same root, a classification scheme was constructed of the human peripheral nervous system. It became thus possible to record natural impulse patterns simultaneously from identified single afferent and efferent nerve fibres and to analyze self-organizing mechanisms of the human CNS under physiologic and pathologic conditions. A. Human CNS with the schematic illustration of the recording layout and original record of single nerve-fibre action potentials. Note the time calibration of 2 ms. B. Intraoperative recording layout (when implanting a bladder stimulator) with two pairs of wire electrodes and one temperature sensor. A thin nerve root is positioned over the platinum wire electrodes. C. Dissection of the human cauda equina; at the caudal end of the filum terminale with thin nerve roots are seen. D. 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. Stretch receptor and secondary muscle spindle afferents contribute to the drive of sphincteric motoneurons and form, together with other afferents, regulation units.

on the pathology of the CNS organization and how to repair urinary bladder functioning causally.

By performing similar bladder tests under operational conditions and recording single-nerve fibre action potentials from sacral nerve roots (Fig. 3), the pathology of CNS organization can be explored in patients with spinal cord injury (40-42) and ideas can be found how to repair the injured CNS causally. Since humans have a high capability for learning it may be possible to repair the injured networks by learning. But we have to 'tell' the CNS what it has to re-learn for repair. By comparing bladder and motor functions at the neuron level, it may be understandable why learning transfer from movements to bladder functions is possible.

Bladder functioning at the neuron level

With the single-nerve fibre action potential recording method (12) it has so far been possible to record single-nerve fibre action potentials from nerve fibres down to a diameter of approximately 3.5 μm in undissected thin long nerve root fascicles. It is therefore possible to record natural impulse patterns from parasympathetic efferents (par), urinary bladder stretch and tension receptor afferents (S1, ST), mucosa afferents from mechanoreceptors of the bladder, the urethra and the anal canal (M), from afferents responding to fluid movement (S2), and from α_2, α_3 and γ-motoneurons and muscle spindle afferents innervating the external striated urinary

bladder and anal sphincters (or functionally associated pelvic floor muscles), and to analyze regulatory and organizational mechanisms of parasympathetic neurons and motoneurons in the human CNS.

In operation (laminectomy) natural impulse traffic to and from the CNS can be recorded from sacral nerve roots (Fig. 3A-C). The summed impulse traffic can be splitted into the natural impulse patterns of single afferent and efferent fibres (Fig. 3D). Upon retrograde bladder filling (as in the clinical diagnostic, Fig. 2) and the identification of the neuron type, with the use of the classification scheme for human nerve fibres (partly shown in Fig. 4G), the natural impulse patterns of identified afferent and efferent fibres can be obtained (Fig. 3D) and analyzed.

The obtained natural impulse patterns answered an old question: Is it the firing rate of a neuron that codes the information transmitted and processed or does the precise timing of cell discharge codes information. Fig. 4B,D shows that the information is coded by specific impulse patterns, including the precise timing and the firing rate.

In response to retrograde bladder filling of a brain-dead human, the self-organization of a premotor spinal α_2-oscillator innervating the external striated urinary bladder sphincter is shown in Fig. 4D. Because the motoneuron axon of O1 had a recurrent fibre (Fig. 4A) at the recording site, each single AP of this motoneuron could be identified safely by the AP of the recurrent fibre. The function of the motoneuron was to secure bladder continence. The activity from urinary bladder receptors, i.e. the activity of bladder stretch (S1), tension (ST) and flow receptor afferents (S2) (Fig. 4E), was an adequate afferent input to the motoneuron. Phase relations between the firing patterns of bladder afferent fibre S1(1) and oscillatory firing urinary bladder sphincteric motoneuron O1 can be seen in the schematized firing patterns in Fig. 4B. They were an indicator that the natural impulse pattern of the S1(1) fibre was an adequate drive of the sphincteric motoneuron O1. For retrograde bladder filling up to 550 ml, motoneuron O1 only fired occasionally (Fig. 4D,F). This was the storage phase of the bladder, during which the intravesical bladder pressure increased only little. For higher bladder filling volumes, the motoneuron switched via the transient oscillatory firing mode to the continuous oscillatory firing mode (Fig. 4D) to generate a higher activity (Fig. 4F) for a stronger drive of the urethral sphincter to more strongly secure continence when the storage phase was nearly passed and the bladder pressure increased more strongly. For bladder filling volumes higher than 800 ml, the activity of the spinal oscillator decreased again; probably, the oscillator became inhibited (Fig. 4D). Pain fibres (not shown in Fig. 4G) may have inhibited the oscillatory firing to protect the bladder from mechanical damage. The overflow mechanism was started. Probably, fluid entered the trigonum vesicae to activate flow receptors, so that the flow receptor activity (S2) increased strongly (Fig. 4E). The premotor spinal oscillator O1, of which motoneuron O1 is probably a part (16), was organized by the adequate afferent input (S1, ST, S2,...) induced by bladder filling. The oscillator to be formed in the premotor neuronal network in the spinal cord, consisting of motoneurons and interneurons, needs a certain preformation of the networks (connectivity, synapse efficacies, membrane properties of neurites,...) and adequate afferent input patterns. In modeling such networks, the organization of the premotor spinal oscillators in the spinal cord neuronal networks cannot be separated from its space-time distributed adequate afferent input patterns, giving rise to self-organization. From Figure 4B it can be seen that the stretch receptor afferent APs (S1(1)) show a relative phase correlation to the impulse trains of the oscillatory firing motoneuron O1. The successive interspike intervals (IIs) of the S1(1) afferents have, on the average, a value similar to that of the oscillation period of oscillator O1 (Fig. 4C).

Other premotor spinal oscillators, activating the external striated bladder sphincter not shown here, will also have self-organized themselves by the same or similar afferent input. However, these oscillators subserving the same function will be correlated in their firing in the way that they do not fire in synchrony but distributed in their phases with respect to one another (probably by relative inhibition with respect to each other) to secure that the sphincter muscle does not show rhythmic movements (tremor). Such non-synchrony correlated oscillatory firing of several oscillators has in a small time window been measured (16).

In the case of a non-injured CNS, this premotor spinal oscillator O1 could also be activated volitionally from supraspinal centres. It would be very

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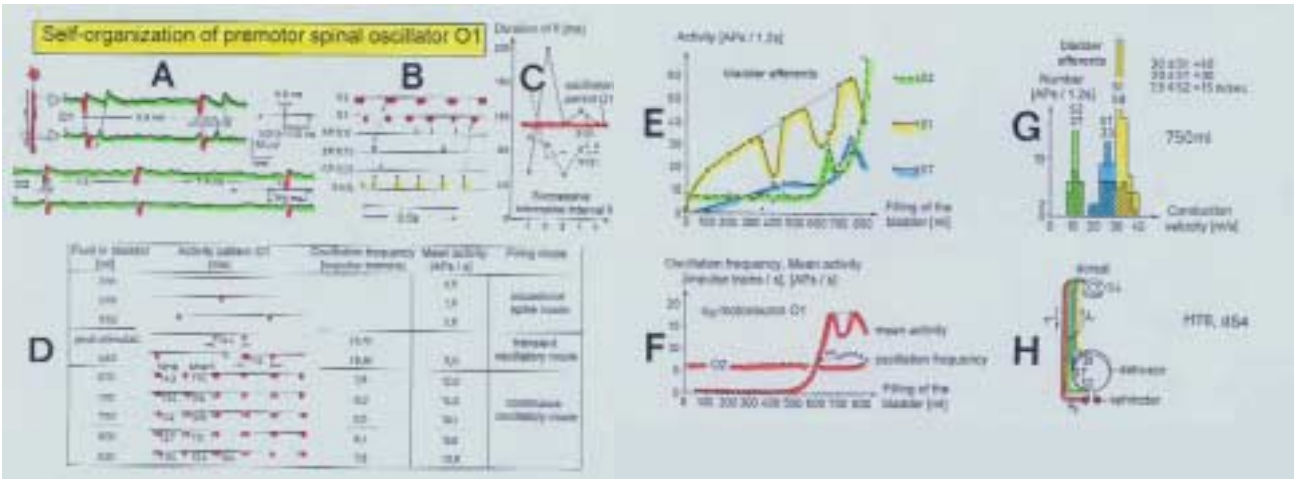

Fig. 4. – Self-organization of premotor spinal α_2-oscillator O1, which innervates the external urinary bladder sphincter (skeletal muscle). Brain-dead human HT6; recording from a dorsal S4 nerve root.

A. Recordings from α_2-motoneurons O_1 and O_2, firing in the oscillatory mode with impulse trains of 2 (uppper recording) and 3 (lower recording) action potentials (APs). The durations of the oscillation periods were 110 (O_1) and 164 ms (O_2). The interspike intervals of the impulse trains were 5.9 ms (O_1) and 4.6 and 7.4 ms (O_2). Motoneuron O_1 conducted at 36 m/s; its recurrent fibre conducted at 21 m/s. The measurment layout is shown schematically. The inserts show the oscillatory firing modes; they have not been drawn to scale.

B. Impulse patterns of oscillatory firing α_2-motoneuron O_2 innervating the external anal sphincter, in relation to the muscle spindle afferent activity SP2(1 to 3), activated by the stretch of the anal sphincter by the anal catheter, and impulse patterns of oscillatory firing α_2-motoneuron O1 innervating the external urethral sphincter, in relation to the stretch receptor afferent activity (S1(1)) of the urinary bladder, activated by 750 ml bladder filling. Phase relations between APs of SP2(2) and O_2 and between APs of S1(1) and O_1 are indicated by the small arrows.

C. Three series of successive interspike intervals of the 2 stretch receptor afferent fibres S1(1) and S1(2) activated by retrograde bladder filling. The oscillation period of oscillatory firing motoneuron O1, activated only by bladder filling is shown.

D. The firing in the occasional spike mode, the transient and the constant oscillatory firing mode of α_2-motoneuron O_1 in response to filling of the bladder. In the 'activity pattern' column changing durations of oscillation periods are given. The oscillation frequencies in the brackets give the frequencies at the moment of oscillation for the transient oscillatory mode. Downward deflections are schematized APs. Interspike intervals of the close APs ≈ 6.0 ms (A).

E. Activity levels of stretch (S1) and tension (ST) and flow receptor afferents (S2) (E) and of sphincteric α_2-motoneuron O_1 (F) in response to retrograde filling of the bladder. The activity values of the S1, ST and S2 afferents are taken from histograms like the one in G. Filling of the bladder was stopped once between 600 and 650 ml.

F. The small dotted lines represent mean activity (APs/s) and oscillation frequency (impulse trains/s) of α_2-motoneuron O_1 if bladder filling were not stopped in between. Note that the mean activity increases continuously with the filling of the bladder from 550 to 650 ml, even though motoneuron O_1 started to fire in the oscillatory mode from 620 ml on (D). Note further that the oscillatory firing motoneuron O_2 (frequency of firing with impulse trains is shown) is nearly not affected by the filling of the bladder and by the start of the oscillatory firing of motoneuron O_1.

G. Conduction velocity frequency distribution histogram of stretch, tension and flow receptor afferent activity at 750 ml. The activities of afferents S1, ST and S2 are quantified by counting the afferent conduction velocities under the peaks (open plus hatched part), with the conduction velocity limits given in the insert. The counts (27, 33, 59) are given below the peak labelled S1, ST and S2 and plotted into E for the afferent activity at 750 ml.

H. Schematic drawing of the anatomical arrangement of the afferents and the motoneuron O_1.

interesting to see how the afferent input patterns from supraspinal centres to the spinal premotor network would look like.

By recording from the dorsal S4 root of the brain-dead human HT6, impulse trains from another oscillatory firing motoneuron and its driving afferents were measured, which served quite a different function (Fig. 4F). The α_2-oscillator O2 (Fig. 4A,B) innervating the striated external anal sphincter was activated by secondary muscle spindle afferent activity, induced by the anal catheter-stretched muscle spindles, probably located in the anal sphincter or functionally associated pelvic floor muscles. Also, mucosal and skin receptors within the anal reflex

area will induce self-organization of premotor oscillators activating the external anal sphincter to secure anal continence. It is evident from the impulse patterns shown schematically in Fig. 4B that the impulse trains of this oscillator O2 show a phase relation and an interspike interval relation to its driving spindle afferent APs. But no synchronized firing can be seen between the sphincteric α_2-motoneurons, innervating the external bladder sphincter (O1) and anal sphincter (O2), probably the CNS networks tried to avoid an increased physiologic tremor (macroscopic rhythmic activation of muscles, due to sub-optimal regulation).

Important for the application of human neurophysiology to neuroretherapy is the duality of the functions of the sphincteric motoneurons and secondary muscle spindle afferents, subserving somatosensory and autonomic (parasympathetic) functions. In animals it was found that also sympathetic fibres innervate muscle spindles (10). It could therefore be (and seems to be so) that also parasympathetic fibres innervate muscle spindles in the parasympathetic innervation area (S2-S5).

Motoneurons innervating the external sphincters of the bladder and the anal canal subserve somatic functions (contraction of the sphincters on volition or for protection reaction) and parasympathetic functions for the coordination of the detrusor function (parasympathetic) and the external sphincter function. This duality of the sphincteric motoneurons (and spindle afferents in the parasympathetic domain) makes the pattern change from continence to protection reaction understandable and makes learning transfer between somatic and parasympathetic patterns likely. The motoneurons build up two phase relations per oscillation cycle with other motoneurons and secondary spindle afferents for somatic activation (Figs. 3,7 of (18)), and build up 3 phase relations per oscillation cycle when also the parasympathetic division is activated (Figs. 4,7 of (18), see also below). The neuronal networks of the somatic and the parasympathetic nervous systems are interlaced and interact with each other. It should therefore be possible to improve parasympathetic functions when improving somatic functions by coordination dynamics therapy, especially as there is indication that also parasympathetic efferents fire rhythmically (41).

The repair of the urinary bladder functioning by reorganization of networks seems to be most difficult because there is false neuronal network organization in the parasympathetic nervous system (overactive (spastic) detrusor) and the somatic division (spastic external (striated) bladder sphincter), and there is false interaction of the interlacing somatic and parasympathetic networks (detrusor-sphincteric dyssynergy: when the detrusor contracts, the external sphincter is also contracting instead of opening (relaxing)) (40-42).

But how can continence pattern organizations are stimulated by movements (jumping on springboard) via bladder afferents.

Movement stimulation from natural afferent impulse patterns from the skin (and bladder)

When stimulating the skin (Fig. 5G, H) under the same recording conditions as for bladder afferences and efferences (Figs. 3, 4), the afferent input from the skin can nicely be recorded (Fig. 5A-E). By wave form comparisons on a stretched time scale (Fig. 5B-D) sets of natural impulse patterns of different skin mechanoreceptors can be recorded (Fig. 5Eb, F). The activity patterns (Fig. 5A) shows a touching and a releasing part of activity as can be seen from the action potential appearance of large amplitude units (T1(Parcinian Corpuscle) and T2) and from the schematic activity pattern of the $T1_1$ unit (Figs. 5Eb, F). All the 4 touch (T1 till T4) and 1 pain groups, recorded here, seem to have their own touching and releasing part, but according to their latencies and conduction velocities, at different times. It can be seen from Figure 5 that the touching activity part of the slower conducting T3 and T4 fibres with their smaller action potential amplitudes (Figs. 5A, C) started about in the middle of the T1 and T2 activity part and lay mainly between the touching and the releasing parts of the T1 and T2 units. The releasing activity of the T3 and T4 fibres appeared after that of the T1 fibres. The activity of the pain fibres (here the slowest conducting fibres) appeared even later at the recording electrodes and stopped appearing after the end of the pin-pricking (recorded at the proximal cauda equine, Fig. 3).

The very late pain after pin-pricking which one normally also feels is probably conducted by very thin myelinated or non-myelinated fibres and cannot be recorded under such conditions.

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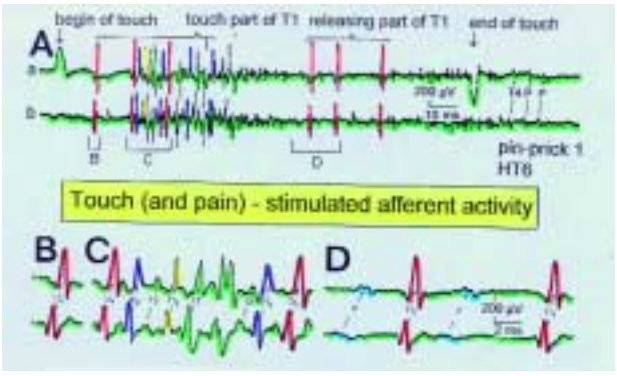

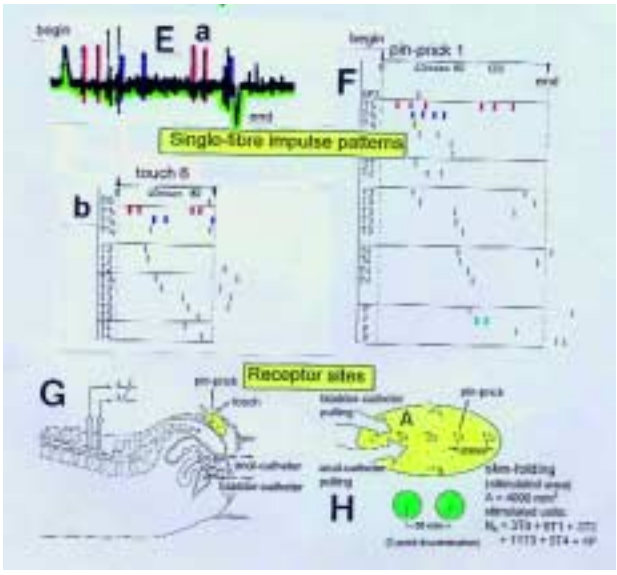

Fig. 5. – Touch (and pain)-stimulated afferent activity. Touch and pain activity stimulated by pin-pricking (A) and touching (Ea) at S5 or Co dermatomes and recorded extracellularly from a dorsal coccygeal root (brain-dead human HT6). T1, T2, T3, T4, P = mark action potentials (APs) from single touch and pain fibres. Subscripts 1, 2, 3 mark single fibres.

A. Whole sweep following pin-prick 1 shown at a slow time base. The large upward artifact on trace 'a' marks electronically the beginning of the pin-prick. The large downward artifact on trace 'a' marks the end of the pin-prick. Note that 2 intervals of high activity of large APs occur, one after the beginning of the pin-prick with 1 AP in front, and a second before the end of the pin-prick; potentials with small amplitude follow 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 of 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.

Eb, F. AP occurrence patterns of single touch and pain fibres following short touch 6 and pin-prick 1. No pain afferents are stimulated upon touch 6. Upon pin-prick 1, the single-fibre AP activity of the different touch and pain groups is 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. One active secondary muscle spindle afferent fibre (SP2) could always be identified in F. Note that for pin-prick 1, touch and pain afferents are stimulated whereas for touch 6 only touch afferents.

G. Recording and stimulation arrangement for simultaneous recording 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 T1 touch points. Two-point discrimination indicated for the sake of comparison. N_A = number of stimulated units in the dorsal coccygeal root. Skin tractions evoked by anal and bladder-catheter pulling are indicated by the large open arrows.

The different delays and impulse train lengths of the T1 units is interpreted with the spatial distribution of the T1 receptors and the skin indentation upon touch and pin-pricking (Fig. 5H). The $T1_1$ unit, for example, had its receptor nearest to the needle and responded fastest and longest since the skin indentation first reached the $T1_1$ receptor, gave rise to the largest skin shift and turned away last. The $T1_2$ receptor, being further away from the centre of skin touch, was reached later by the skin indentation, the skin shift was not so large and the skin turned back to the former position quicker. The action potentials in the $T1_2$ unit therefore appeared later, showed only 2 (extracellular) action potentials in the impulse train and the release activity part also appeared earlier.

Such natural impulse patterns in many skin afferents inform the CNS about changes in the periphery of the body and give rise to certain network organizations. The neuronal networks of the spinal cord (and supraspinal centres) do self-organize by the natural impulse patterns from the receptors in the periphery (in spinal cord injury) and from supraspinal centres (physiologically both contributions). It is difficult to say whether the networks adapted their self-organization to the impulse patterns of the receptors of the periphery or whether, during phylogeny or ontogeny, the receptors adapted their firing to the needs of the neuronal network. Nevertheless, it is obvious that the natural firing patterns of the afferents and their space-time distributions give rise to the self-organization of the neu-

ronal networks, and are therefore of utmost importance for the understanding of the functioning of the CNS. Such parameters are difficult to measure.

To make a conclusion on the organization and reorganization of neuronal networks from the wiring of the neurons (see in (1)) is risky, because one would need to know, for example in human, the efficacies of the excitatory and inhibitory synapses (LTP, LTD), the membrane properties of local critical areas of neurites, and how membrane properties change with learning and reorganization following CNS injury.

Two of the original recordings of simultaneous skin afferent patterns of 14 and 22 receptors are shown in Fig. 5. The summed natural firing patterns upon touch (Fig. 5Ea) are split and are schematically drawn in Fig. 5Eb, and those upon pin-prick (Fig. 5A-D) can be seen in Fig. 5F (12, 62).

Electrostimulation of nerves in patients cannot mimic such spatio-temporal impulse codes elicited by natural stimulation, and will give rise to non-natural neuronal network organization of the CNS. When performing electrostimulation in patients, it should be therefore clear what network states are about to be activated in the CNS and how the artificial patterns differ from the natural pattern states.

In basic research, it also should be borne in mind that artificial electrostimulation patterns give rise to artificial neuronal network organization of the CNS. Electrostimulation is therefore not very suitable to analyze natural integrative functions of the CNS.

Below I shall discuss the fact that the spatio-temporal touch afferent patterns (like touch 6 in Fig. 5Eb) give rise to a self-organized network state subserving anal continence, whereas additional activated pain afferents (like pin-pricking 1 in Fig. 5F) stimulate a network state inducing an escape and protection response.

Due to catheters positioned in the anal canal and the urethra (approximately isometric stretch) (Fig. 5G), α and γ-motoneurons (partly) fired oscillatory (Fig. 3) as a result of the sustained stretch reflex of the external sphincters (not clear for the urethra) as a part of the continence pattern. These impulse patterns were more distributed and only seldom added up with the afferent input from the mechanoreceptors of the skin (schematically pictured in Fig. 6B, SP2(2)-trace), conducted in different fibres but through the same nerve root.

Natural firing patterns of proprioceptive afferents and α and γ-motoneurons measured simultaneously, and the phase (and frequency) relations between them

Original recordings of the firing of α-motoneurons (oscillatory), proprioceptive and bladder afferents are shown in Fig. 3. Due to catheters positioned in the anal canal and urethra, continence pattern states are activated. These continence states of the CNS are secured by the ongoing communication with the bladder and anal canal via the fibres in the S2-S5 nerve roots. Touch, pin-prick, anal and bladder catheter pulling, and filling of the continence organs will change the natural impulse traffic in those fibres.

Fig. 6 shows such schematic natural simultaneous impulse patterns of a static and a dynamic γ-motoneuron, two secondary muscle spindle afferents and an oscillatory firing α_2-motoneuron O2 in a dorsal S4 nerve root (there are afferences and efferences in dorsal or ventral lower sacral roots) during continence pattern changes. The small arrows and the dotted lines indicate existing relative phase coordinations between the static and the dynamic γ-motoneurons and motoneuron O2, and between γ-motoneurons and secondary muscle spindle afferents. The dashed-circle line indicates a phase relation between the APs of the static γ-motoneuron (γ_1) and the cross-correlation between SP2(2)-fibre (single ending 1 of the mother fibre) and SP2(5)-muscle spindle afferent fibre. Including the phase relations between the firings of secondary muscle spindle afferents and the oscillatory firing motoneuron O2 we obtain interlaced loops of coordinations between the firings of γ-motoneurons and secondary muscle spindle afferents, and between secondary spindle afferents and α-motoneurons and between α-motoneurons and γ-motoneurons (co-activity of α and γ-motoneurons) (Fig. 13). It becomes obvious from the correlations between the natural impulse patterns (including those of single encoding sites of spindle afferents) that the γ-loop is not a single loop, but a network of loops, because of the divergent projections of γ-motoneurons onto muscle spindles and the probably divergent and convergent projections of secondary muscle spindle afferents into the neuronal network of the spinal cord, consisting of α and γ-motoneurons and interneurons.

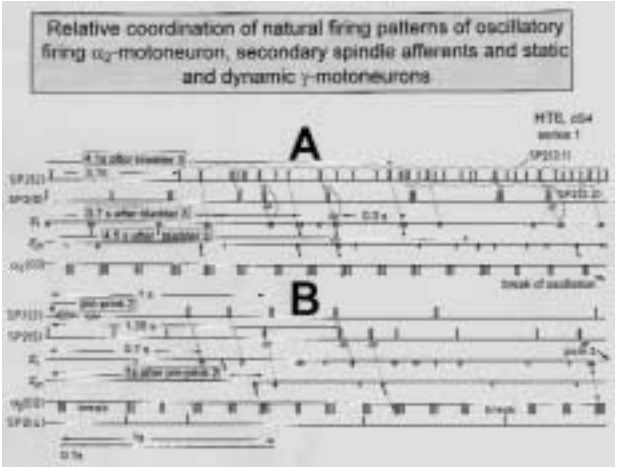

Fig. 6. – Impulse patterns of simultaneously recorded γ-motoneurons (γ_1 and γ_{21}), secondary spindle afferent fibres (SP2(2), SP2(4), SP2(5)) and oscillatory firing α_2-motoneuron O2 following bladder catheter pulling (bladder 3) (A) and pin-prick 2 (B). B was recorded before A. In A the impulse patterns of the 2 encoding sites SP2(2.1) and SP2(2.2) of the single parent fibre SP2(2) are indicated by the dotted curves. Times to the activity increases of γ-motoneurons and secondary spindle afferents following stimulation are indicated. Similar time intervals of the occurrence of γ-motoneuron APs and SP2(5) fibre APs (phase coordination) are indicated by the open arrows, and the similar time intervals of γ-motoneuron APs and α-motoneuron APs are indicated by small arrows. Similar time intervals of the APs of fibres SP2(2) and SP2(5) are indicated by the double dotted lines, those of γ_1-APs and the SP2(2) fibre APs by a dotted line, and those of γ_1-APs and the SP2(2)-SP2(5) correlation by a curved dashed line. HT6; dS4.

More general, phase and frequency coordination can be seen among the natural firing patterns in the afferent and efferent fibres, this means that upstream in the CNS there should also be phase and frequency coordination among neuron firing. More precise measurements will be presented below.

Two phase relations have been observed to occur mostly between the APs of the secondary muscle spindle afferents and the oscillatory firing motoneuron per one oscillation period (Figs. 11, 12, 14) (for somatic activation) in accordance with the 'in phase' and 'antiphase' jumping on springboard and crawling.

With this coordinated natural impulse traffic to and from the periphery also the change of integrative pattern states can partly be understood from bladder to movement states, as will be shown.

Response of an oscillatory firing α-motoneuron to touch and painful pin-prick stimulation (neuronal network pattern change)

I will show now that a small change in the natural impulse patterns traveling into the sacral micturition centre will change there the neuronal network pattern.

Ten schematically drawn sweep pieces of simultaneous impulse patterns of α_2, α_3 and γ_1-motoneurons and the secondary muscle spindle afferent fibres SP2(1) and SP2(2) are shown in Fig. 7. Following a sequence of 10 touch stimulations (Fig. 7, upper right insert), the rhythmically firing motoneurons responded by a change in the duration of the oscillation period. Of interest is here how fast the α_3-motoneuron reduced its oscillation period following the start of the touch stimulation (measured electrically) or following the volley of skin-afferent APs running through the ventral root skin afferent fibres. The delay of the first reduction of the oscillation period is defined in Fig. 7 following touch 7. Begin and end of the stimulations are marked. There is a possibility that the α_3-motoneuron (S) is actually an α_2-motoneuron (FR), and the α_2 is an α_3-motoneuron. Because of the pathologic oscillatory firing, the type of the motoneuron cannot be safely identified from the firing pattern any more, and identification on the basis of conduction velocity is not safe as the distributions of conduction velocities of α_2 and α_3-motoneurons (and of other nerve fibre groups) overlap.

It can be seen in Fig. 7 that the α_3-motoneuron mostly reduced its oscillation period after a delay (measured from the beginning of the afferent volley) shorter than the duration of the oscillation period. The first reduction of the oscillation period is marked by a small arrow. The response times are analyzed quantitatively in Fig. 8. Following touches 6 and 7 a partial transient synchronization of the firings of afferents and efferents occurred, as can be seen by the similar occurrence times of the impulses. Also, a slight partial synchronization followed touches 2 and 3.

Since on the average, the delay in the shortening of the oscillation period occurred after a time interval shorter than the oscillation period, it is of interest to see whether the response times were similar to those for pin-pricking. It has been established in man that the difference between touch and pin-prick

stimulation is that for pin-pricking additionally pain fibres are activated (Fig. 5), and pain fibre activity may facilitate different pathways to the motoneuronal networks.

The touch sites 1, 2, 6 and 7 were inside the anal reflex area and the sites 4, 5, 9 and 10 were outside of it. The anal reflex area extended approx. 6 cm laterally from the anus.

After touching experiments with the touch stimulation at pen-marked sites 1 to 10 close to the anus (Fig. 7), the touching sites were now pin-pricked in a similar fashion approx. every 0.8 s to 1 s. After a delay there again was a reduction in the duration of the oscillation periods.

The responses to pin-pricking differed from those following touch stimulation in three aspects. First, the response delay times were longer than the oscillation periods. Second, the response to pain application had a longer duration and was stronger; mostly, the duration of two oscillation periods was reduced following pin-prick stimulation and the reduction of the duration was larger. Following pin-pricks 3, 7 and 8 there occurred a very short oscillation period which resembled a resetting of the oscillation cycle. Third, the transient synchronizations of afferents and efferents following pin-pricks 6 were more pronounced.

Latency difference in the reduction of the duration of the oscillation period following touch and pin-prick stimulation

It can be seen from Fig. 8 A that in 9 out of 10 cases, the latency of the oscillation period shortening following touch stimulation of the perianal skin (see insert in Fig. 7) was shorter in duration than the oscillation period (≈100 ms), represented by the dotted line. The shortest latency was approx. 10 ms, when measuring from the afferent volley running in direction of the spinal cord. The latency of the first reduction of the oscillation period, measured from the skin touch stimulation artifact, was longer or shorter than the duration of the oscillation period (Fig. 8B). The shortest latency was approx. 30 ms. The difference of the latency, i.e. the time from the stimulation artifact (touching of the skin) to the moment when the skin afferent volley passed the recording electrodes, was approx. 20 ms. According to the group conduction velocities of skin afferents (T1 skin afferents (PC) ≈ 44 m/s at 36°C), most of the time was lost in the touch receptors and the thin nerve fibres connected to them. With a conduction distance of 0.3 m, a conduction time of $t_{cond} = s/v = 300\ mm/\ 44\ mm(ms)^{-1} = 7\ ms$ results.

The latency till the reduction of the first oscillation period duration following pin-pricking the sites 1 to 10 was mostly longer than the oscillation period itself, independent of whether measured from the skin afferent volley (Fig. 8E) or from the stimulation artifact (Fig. 8F). Since not every pin-prick was strong enough to generate pain (stimulation of pain receptors), it is concluded that the latency from the pin-pricking to the first reduction of the oscillation period was longer than the oscillation period.

By comparing the latencies to the first reduction of the oscillation period following repetitive touch and pin-prick stimulation of sites 1 to 10, it turns out that following touch stimulation the delay is shorter than the oscillation period, whereas it is longer following pin-prick stimulation. It seems therefore that touching reinforced the sustained stretch reflex of the anal sphincter while pin-prick did not.

The first shortening of the oscillation period in comparison to two preceding periods is plotted in Fig. 8D, C (touch) and in Fig. 8H, G (pin-prick). The reduction of the oscillation period for touch stimulation was between 8 and 28 ms and between 5 and 40 ms for pin-pricking. The pin-prick stimulation generated a larger transient reduction of the oscillation period.

When correlating the latency of shortening to the extent of shortening for pin-pricking (Fig. 8 H) it seems as if the shorter latency correlated with a slighter reduction of the oscillation period (more touch-like), and the long latencies correlated with the greater reduction of the oscillation period (more pain-like). A similar relation was not found following touch stimulation (Fig. 8D). Probably, the painful pin-prick stimulation transiently replaced the sustained stretch reflex of the anal sphincter by a protective reaction of the anal sphincter against pain application; the time needed for the reorganization of the oscillatory firing neuronal network was at least one oscillation period long.

The relation between the sites of pin-prick (Fig. 8G) or touch stimulation (Fig. 8C) and the oscillation period shortening shows no clear corre-

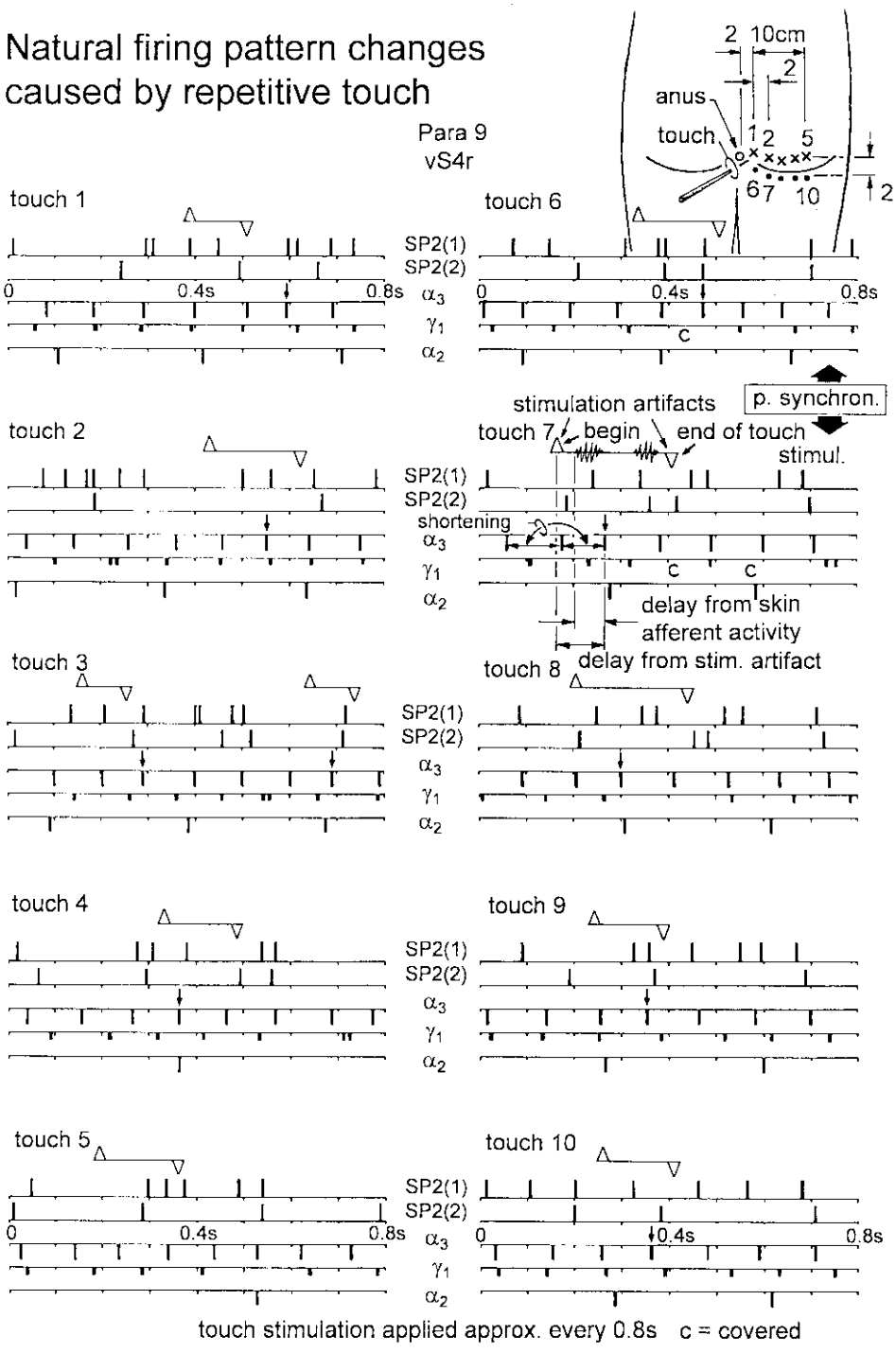

Fig. 7. – Changes of natural impulse patterns of α_2, α_3 and γ-motoneurons and secondary muscle spindle afferents (SP2(1) and SP2(2)) in paraplegic 9 upon touching sites 1 to 5 (x) and 6 to 10 (•) (insert). The small arrows indicate the first shortening of the oscillation period of the α_3-motoneuron following the beginning of the touch stimulation (marked by an artificially generated artifact). Note that partial synchronization (p. synchron.) of the firing of the α_2 and α_3-motoneurons and secondary muscle spindle afferents occurred upon touching sites 6, 7. The α_2 and α_3-motoneurons were only identified by their conduction velocities; it is therefore possible that the α_3-motoneuron was actually an α_2-motoneuron and the α_2-motoneuron an α_3-motoneuron (overlap of velocity distributions); the firing patterns were very pathologic, and could not be used for the motoneuron identification.

lation. The dotted and the dashed lines may show similar latencies. Perhaps the protective reaction against pin-pricking of the anal canal and the pelvic floor is highest at sites 3 and 8 at the border of the anal reflex region.

Time needed for the change from the attractor state 'continence' to the attractor state 'protection'

By comparing the latencies from the moment when the skin afferent volley passed the recording electrodes to the first reduction of the oscillation period following repetitive touch and pin-prick stimulation of the sites 1 to 10, it turns out that the delay following touch stimulation (≈ 10 ms) is much shorter than for pin-prick stimulation (≈ 110 ms). It seems therefore that touching reinforced the sustained stretch reflex of the anal sphincter while pin-prick stimulated the protection reaction against pin-prick (pain). It can be evaluated how much time is needed for the reinforcement of the sustained stretch reflex and for the pattern change from the continence state (sustained stretch reflex) to the protection reaction.

With a conduction distance of 0.1 m (distance between the recording electrodes and spinal cord), a conduction time for the fastest skin afferents (group conduction velocity of T1 skin afferents (Parcinian Corpuscle) ≈ 44 m/s at 36°C) of $t_{cond} = s/v = 100\ mm/ 44\ mm(ms)^{-1} = 2.3$ ms is resulting. The conduction time of the action potentials of the motoneurons to cover the distance from the spinal cord to the recording electrodes is resulting also to approximately 2.3 ms (the group conduction velocities of the α_2 and α_3-motoneurons are 37 and 50 m/s respectively). The processing time to reinforce the continence pattern of the anal sphincter was therefore approximately 5.4 ms (10 ms-4.6 ms = 5.4 ms). If we assume a synaptic transmission time of 2.5 ms, the processing time in the spinal cord is sufficient for the transmission time of two synapses. The reinforcement of the sustained stretch reflex was may be just a disynaptic pathway.

The conduction times to and from the spinal cord of the protection reaction are approximately 10 ms (7.7 + 2.3), because the fastest pain afferent action potentials needed a bit more time than the touch afferent action potentials (group conduction velocity of the fastest pain afferents = 13 m/s; $t_{cond} = s/v = 100\ mm/ 13\ mm(ms)^{-1} = 7.7$ ms). The processing time in the CNS to change from the sustained continence pattern to the protection reaction pattern is therefore approximately 100 ms. This time would be enough to involve 40 synapse transmissions. For a reorganization of the neuronal networks for pattern change, conduction times of intraspinal axons and dendrites would also have to be taken into account. But it is obvious that the pain application induced a completely different CNS response.

That pin-pricking resulted in a longer response time of motoneurons than touching of the perianal skin is not obvious and cannot be explained based on the reflex theory. Being a stronger stimulus, pin pricking (touch plus pain afferent activity, Fig. 5) would be expected to have the same or slightly shorter rather than a much longer response time than touching of the perianal skin (touch afferent activity only, Fig. 5).

It is concluded that the change from one network state to another one, restricted to the spinal cord (measurement in a paraplegic), needed approximately 100 ms.

With respect to movement learning and learning transfer, strong pain has to be avoided during exercising, because a certain pattern (like jumping on springboard) has to be trained (and neuronal networks entrained) and not a mixture of a movement pattern and a protection reaction.

Attractor layouts for jumping on springboard and switching between continence and protection

For jumping on springboard (Fig. 9Aa) the equation of motion of the collective variable φ (angle between the legs) could be solved in the HKB model (5) and a attractor layout constructed for the jumping in in-phase and in anti-phase (Fig. 9Ab). In analogy an attractor layout for bladder continence and protection reaction (Fig. 9Bb) can be drawn, even though the anal continence was measured. The enhancement of the continence safety (deepening of the potential well) needed approximately 6 ms and the change from the pattern continence to protection reaction needed approximately 100 ms.

It is therefore possible to analyze integrative patterns of the human CNS with natural impulse pat-

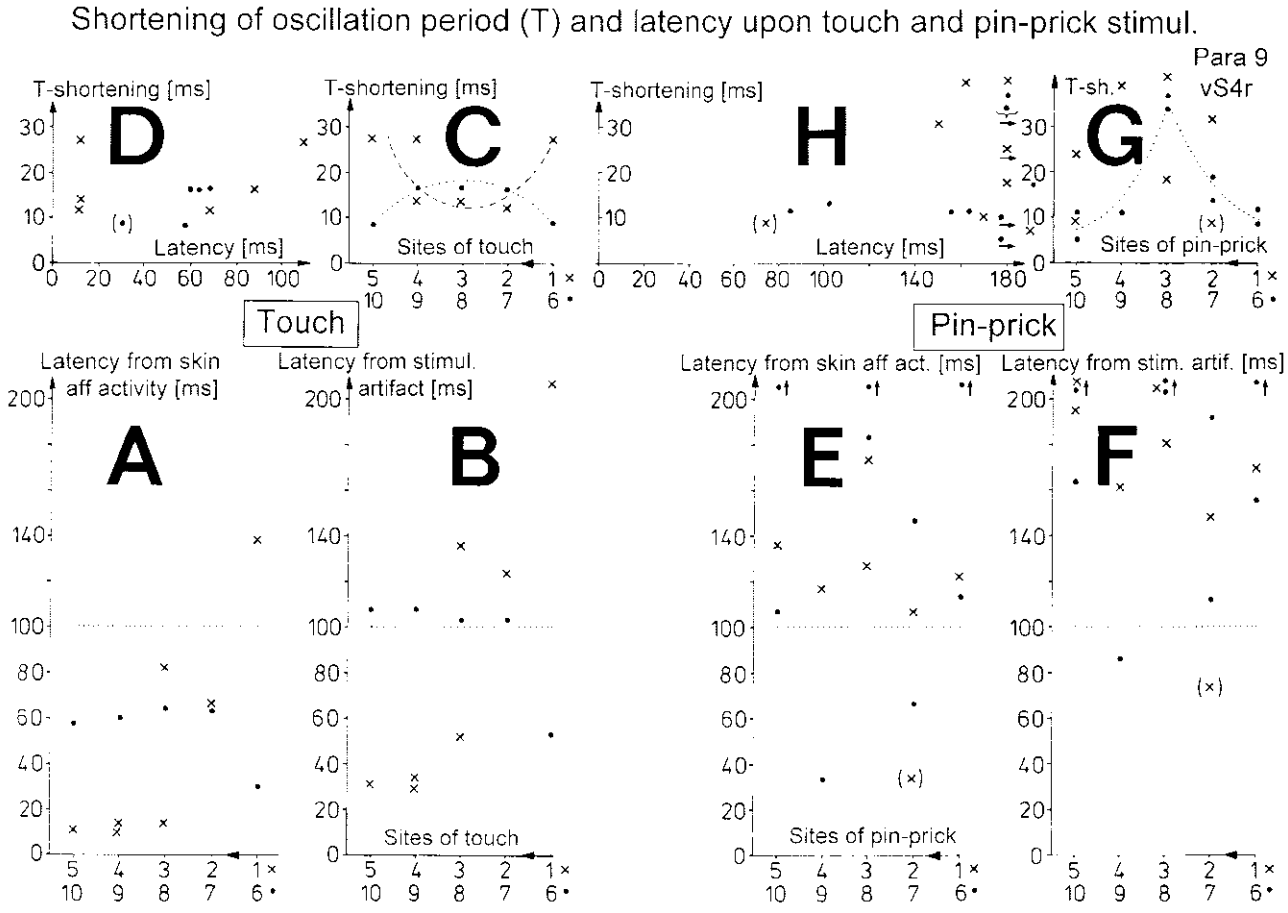

Fig. 8. – Shortening of the oscillation period T of the α_3-motoneuron (perhaps an α_2-motoneuron upon touch and pin-prick stimulation). A, B. Latency of the shortening of the oscillation period (for definition, see Fig. 3) measured from the skin afferent activity (A) and from the stimulation artifact (B) with successive touching of sites 1 to 5 (x) and 6 to 10 (•) as indicated in Fig. 3. Note that the delay is often shorter than the oscillation period. D,C. Shortening of the oscillation period (T-shortening), with respect to two preceding oscillation periods, in relation to the latency of shortening (D) and in relation to successive touching of sites 1 to 10 (C). E.-H. Same description as for A-D, only with respect to pin-pricking. Note that touch stimulation induced a shorter latency for the reduction of the oscillation period than did pin-pricking.

tern of single-nerve fibres recorded from sacral nerve roots. Natural impulse pattern can explain integrative functions of the human CNS.

Relative phase and frequency coordination between the APs of α and γ-motoneurons and secondary muscle spindle afferents with no additional stimulation and upon touch, pin-prick, and bladder catheter pulling

Above it was shown that natural impulse pattern can explain pattern change that means the generation of integrative patterns can partly be understood at the single neuron level. Natural impulse patterns were related to integrative CNS organizations.

Back to the task to understand why jumping on springboard contributes substantially to the repair of bladder functioning. A better understanding can be achieved to go deeper into the complexity of the cooperative and competitive interplay among neurons that means going deeper into the complexity of phase and frequency coordination of CNS self-organization.

Changes of natural firing patterns have roughly been shown in Figure 6. The phase and frequency

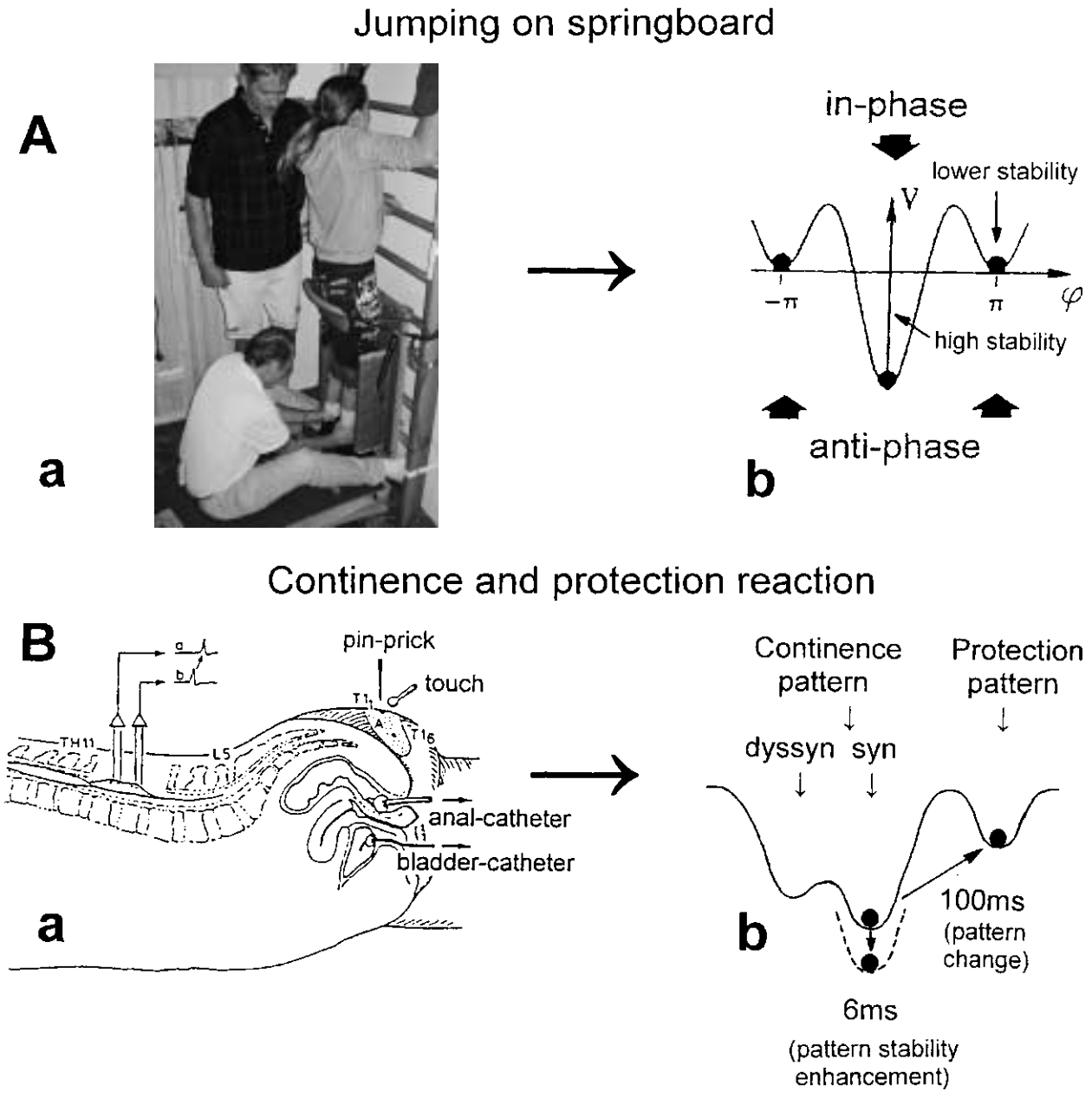

Fig. 9. – Attractor layout for jumping on springboard in comparison to that of continence and protection.

coordination of coordinated firing will now be analyzed more in detail.

Time correlations of afferent and efferent impulse patterns are easy to detect in the brain-dead individual as the oscillatory firing of α_2-motoneuron (O2) was regularly like an inner clock (Figs. 3,4; see below). The phases of fusimotors and spindle afferent APs could be defined with respect to the impulses of that inner clock. In the paraplegic, the rhythmic firing was rather irregular. The motoneuron firing therefore cannot be used any more as a time reference basis. More phases between the extracellular action potentials of the different fibres are necessary to fully describe the correlation between the simultaneous impulse patterns. In Fig. 10 Cg, the mutual phases between the APs of the different

fibres are defined. Fig. 10 Ch,i shows the corresponding phase distribution histograms. Since too few phases occurred in a sweep piece of 0.8 s duration, phases occurring in certain time intervals were pooled and plotted in Figs. 11 and 12.

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 (14), 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. It is very unlikely, nevertheless, that one of the motoneurons was an α_1-motoneuron (FF) (missing high conduction velocity and high AP amplitude and no correlation to 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 (24, 27). The firing patterns of the α_2 and α_3-motoneurons are strongly pathologic with respect to the length of the oscillation period (14, 16) and the impulse train length so that it is impossible in this paraplegic to identify the kind of 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.

In Fig. 11, 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. 11Aa). 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. 11Ba). One phase relation occurred between the impulses of the α_3 and α_2-motoneurons, and two between the α_3 and the SP2(2) fibres. The broad phase relations between discharge patterns are interpreted as interactions between populations of neurons.

Following different stimulations interspike interval (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 be more similar to those of the oscillatory firing α_3-motoneuron (Fig. 11Ab). The changing of the different phase relations indicates changes in the interactions between neuronal subnetworks (Fig. 11Bb). Upon touching sites 6 to10 (especially sites 6, and 7 (inside anal reflex area)), the IIs of the almost oscillatory firing γ_1-motoneuron increased again (Fig. 11Ac). A transient partial synchronization occurred between the different nerve fibres (Figs. 11Bc, 14c).

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. 11Ad).

Upon pin-pricking sites 6 and 7 (inside the anal reflex area), α and γ-motoneurons and secondary muscle spindle afferents showed similar II distributions (Fig. 11Ae). Only one phase relation was organized per oscillation cycle between the different nerve fibres (Figs. 11Be, Fig. 14e). A synchronization between the APs of the different nerve fibres occurred as can be seen from the direct impulse patterns (Fig. 10B). 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, however, 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. The building up of an external loop to the periphery by spinal oscillators is substantially used when a patient with a spinal cord injury is jumping on springboard (see Fig. 15, below).

Upon pin-pricking sites 8, 9 and 10 (outside of the anal reflex area) and following pin-pricking of

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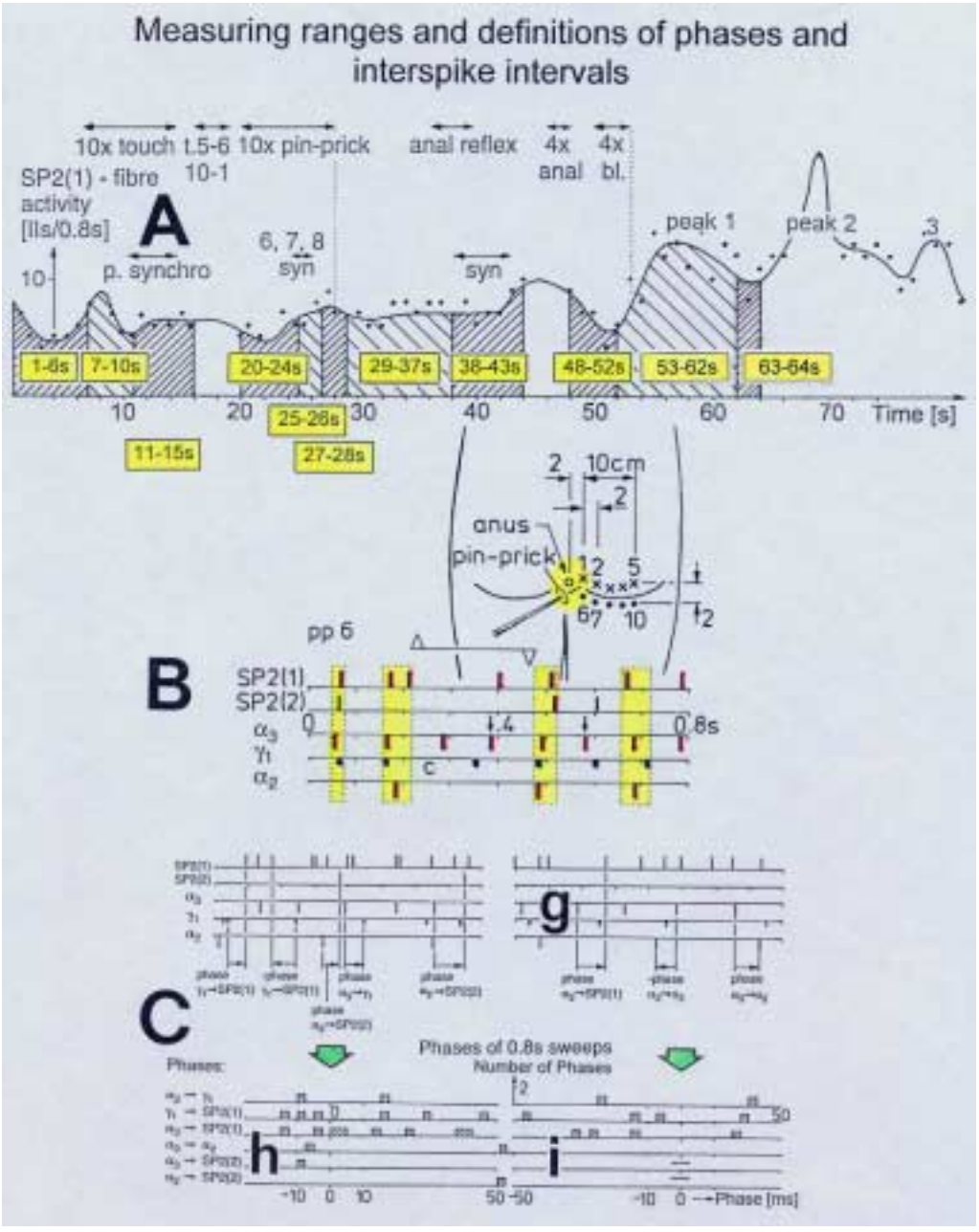

Fig. 10. – Measurement ranges and definitions of phases for the analysis of phase and frequency coordinations between motoneurons and spindle afferents. Coordination (synchronization) between firing patterns can directly be seen in B.

(A) Activity level of secondary muscle spindle afferent fibre SP2(1) in dependence on time. 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 = anal 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; p. synchro = partial synchronization; syn = synchronization of α and γ-motoneurons and secondary muscle spindle afferents. Note the synchronization of the firing patterns following pin-prick 6 inside the anal reflex area.

(B) A 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 α_3-motoneuron (S) point to a 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). Para 9; vS4.

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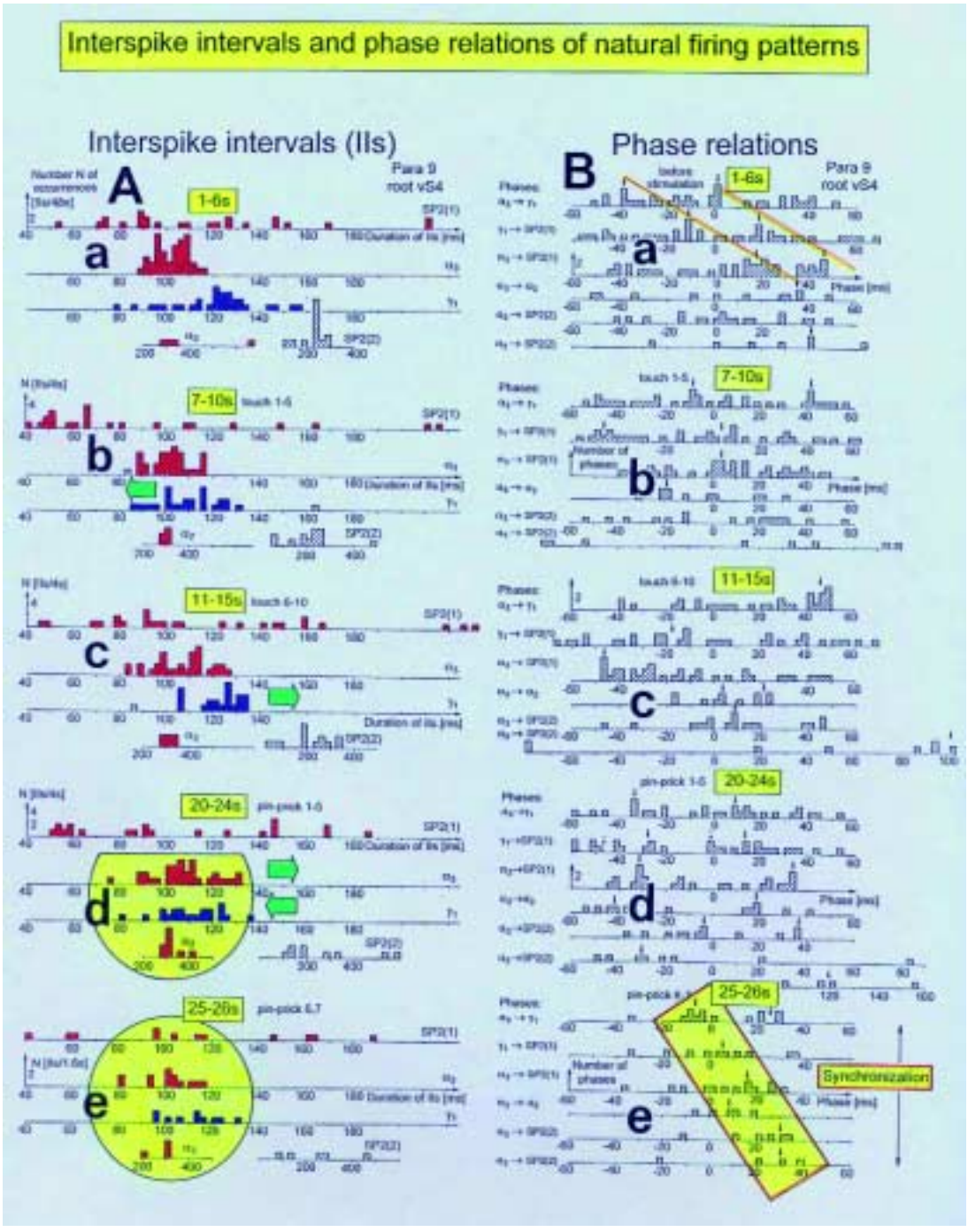

Fig. 11. – Relative phase and frequency coordination between α and γ-motoneurons and secondary muscle spindle afferents due to touching and pin-pricking sacral dermatomes as in Fig. 5G. (A) Interspike interval distribution of spindle afferents SP2(1) and SP2(2), α_2 (FR) and α_3-motoneurons (S) and the dynamic fusimotor γ_1 for different time intervals upon touch, pin-prick and anal catheter pulling. Interspike intervals (IIs) were collected from several sweeps of 0.8 s duration per second. External loop generation and frequency coordination of α and γ-motoneurons and secondary muscle spindle afferents are marked by the semi-circle 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. (B) Histograms of the phases between afferent and efferent fibres for the time intervals indicated, upon different stimulation. Phases were collected from several sweeps of 0.8 s duration per second. The small arrows indicate phase relations. Phase coordination is indicated in a,e. Para 9; vS4.

site 10, the II distribution of the SP2(1) fibre shifted away from those of the α_3 and γ_1 axons. 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 pulling, the external loop was not built up again (Fig. 12).

Following touch, pin-prick and anal reflex stimulation, but not painful catheter pulling, mostly two phase relations existed in paraplegic 9 between the activity of the α_3, γ_1 and SP2(1) fibres per oscillation period (100-140 ms) of the α_3-motoneuron (Figs. 11, 12), but the phase relations changed with ongoing time. With the activation of the parasympathetic division, upon bladder catheter pulling (Fig. 10A), three phase relations occurred per α_3-motoneuron oscillation period (Fig. 12Bc,e). At the peaks of parasympathetic activation, 3 phase relations occurred (Fig. 12Bc,e), and only two phase relations were present with little parasympathetic activation (times between the peaks 1 and 2) (Figs. 10A, 12Bd).

Even though the functional units, consisting of fusimotor and α-motoneuron neuronal networks and spindle afferents fibres, were rather unstable in paraplegic 9, in comparison to the brain dead human (see below), an important difference between skin (somatic) and bladder (parasympathetic) stimulation occurred. Another (third) phase relation per α_3-motoneuron oscillation period occurred with the activation of the parasympathetic division. The activated parasympathetic neuronal network of the sacral micturition and defecation centre seems to have channeled input to the oscillatory firing somatic neuronal network.

Phase relation changes between the action potenials of the α and γ-motoneurons and secondary muscle spindle afferents in paraplegic 9 upon somatic and parasympathetic activation of the sacral micturition centre

As shown in Figs. 11, 12 the number (and the values) of phase relations changed between the firings of the different nerve fibres upon different stimulations. In the brain-dead human 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 of Ref. 42). Also in the paraplegic two phase relations often existed between the firings of the different nerve fibres. It has suggested above that probably a third phase relation occurred when the activated parasympathetic division channeled an additional input to the oscillatory firing somatic neuronal network. It may therefore be worthwhile to further analyse the number of occurring phase relations per oscillation cycle upon different somatic and parasympathetic stimulations.

Since two phase relation occurred per oscillation cycle between the α_3 and γ_1-motoneurons and the SP2(1) fibre (Fig. 11Ba) in paraplegic 9, and also their IIs were rather similar, 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 part of a functional unit. The neural ensemble is built by efficiencies 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 α and γ-motoneurons. Such a functional unit is partly pictured in Fig. 13 and schematized drawn by 3 circles in Fig. 14. The α_2-motoneuron and the SP2(2) fibre belonged to another functional unit (another ensemble) (longer IIs and the existence of only 1 phase relation). The two functional units (ensembles) are characterized in Fig. 14 by two sets of 3 circles each. The two functional units interacted with each other as there existed a phase relation between the α_2 and α_3-motoneurons (Fig. 14).

Before stimulation (but with the anal and bladder catheters positioned), there were two phase relations in unit 1 (Fig. 14a). When touching sites 1 to 5 (Fig. 7), only slight changes occurred in the two units with respect to the number of phase relations (Fig. 14b). But when touching sites 6 to 10, a partial synchronization occurred (Fig. 14c) 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. 14d). Upon pin-pricking sites 6 and 7, the number of phase relations between all the components of the two units dropped to one (Fig. 14e), and synchronization occurred between the firing patterns (Fig. 10B).

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

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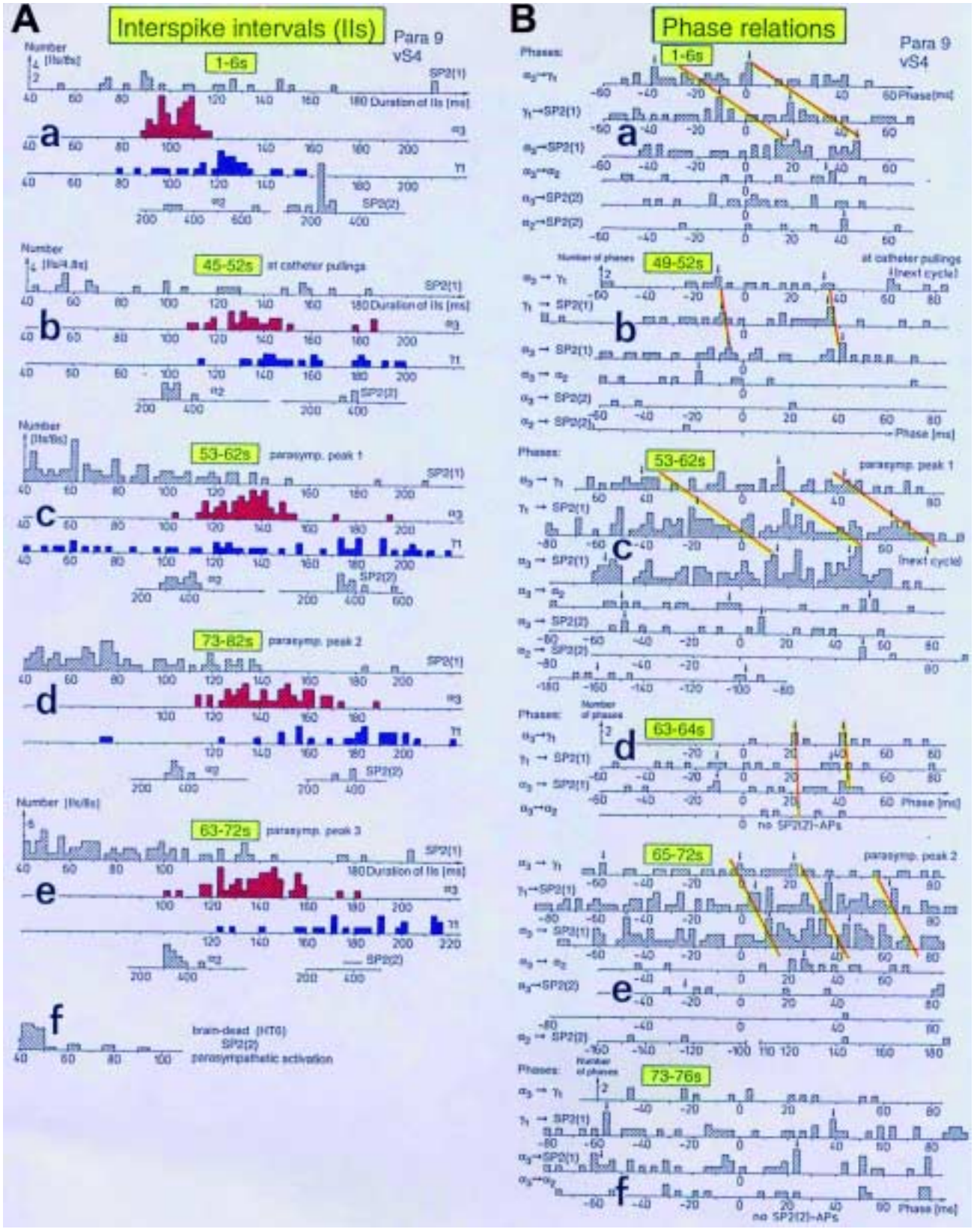

Fig. 12. – Interspike intervals (IIs) and phase relations for time intervals indicated in Fig. 10A. For legend, see Fig. 11.

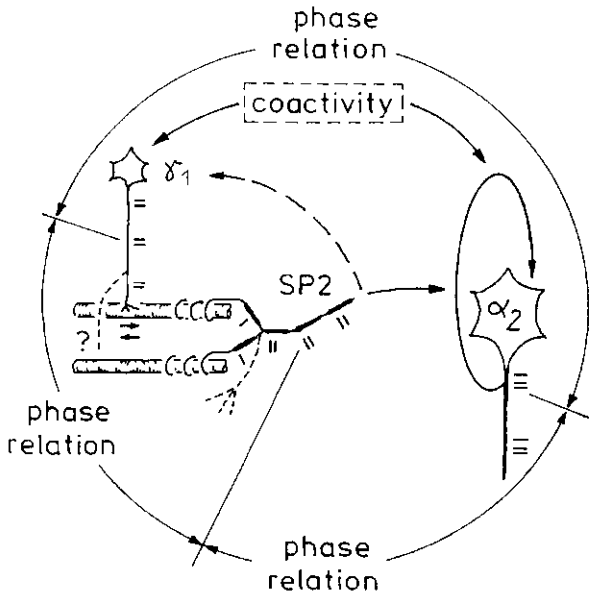

Fig. 13. – Schematized existing phase relation between α_2 and γ_1-motoneurons and a secondary muscle spindle afferent fibre (SP2). Parallel existing phase relations between other parent afferents and the α_2-motoneuron and between parent secondary spindle afferents are not shown. Phase relation means, the increased occurrence of phases in ms in a certain phase range between the action potentials (APs) of the two compared nerve fibres. The complex afferent and efferent muscle spindle innervation was not tried to show. Small arrows at intrafusal muscle fibre indicate local contraction, which is in nuclear chain fibres readily transmitted to the place of afferent innervation. A possible reason of the doublet firing of the SP2 fibre is pictured to occure from single APs (schematized by bars) of two myelinated endings, not necessarily from pacemaker switching. More endings of the parent SP2 fibre and γ_1-motoneurons are indicated by dashed line branches. "Coactivity" indicates a correlation between γ and α-motoneuron spinal cord circuitries for higher activations.

Even though upon touching sites 6 to 10 (Fig. 14c) or upon pin-pricking sites 6 to 7 (Fig. 14e) only one phase relation existed in unit 1, and synchronization occurred with both stimulations, it was shown above (Figs. 8, 9) that the touch afferent input organized a different functional state of unit 1 than 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 was shown above (Fig. 9) that repetitive touch stimulation (most effective inside the anal reflex area) reinforced the sustained stretch reflex of the anal sphincter (continence pattern), and repetitive pin-prick stimulation replaced the continence pattern 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. 14f, g), in some similarity to pre-stimulation status (Fig. 14a). Following two times anal reflex stimulation, partial synchronization occurred in the components of the two units (Fig. 5 of (17)), and mainly two phase relations existed (Fig. 14h). But the organizational state was still not very similar to the pre- (Fig. 14a) or post-stimulation state in unit 1 (Fig. 14 g), 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 (41)). Therefore, probably one phase relation was due to the somatic activation in similarity to Fig. 14c, e and the other phase relation was due to the activation by the parasympathetic division. During bladder catheter pulling (Fig. 14i) and with no stimulation (Fig. 14k), the number of phase relations and possibly the functional organization, was again similar to the pre-stimulation state (Fig. 14a).

Following strong (painful) bladder catheter pulling with a strong activation of the parasympathetic division (time interval 53-62 s (Fig. 14j)), measured by the increased doublet firing (see Fig. 5 of (41)) of the SP2(1) fibre, the functional organization of the sacral micturition center of the disconnected spinal cord changed completely. Functional unit 1 was now correlated by three phase relations per α_3-oscillation cycle. The functional unit 2 also showed 3 phase relations per an α_2-oscillation cycle, and interacted with functional unit 1 by 3 phase relations as well (between the α_3 and α_2-motoneurons; Fig. 14j (53-62 s)).

Between the first and second parasympathetic peak (Fig. 10A) at the time interval 63-64 s (Fig. 14k), the organization form of the two functional units was similar to that before the first parasympathetic activation (49-52 s) (Figs. 14), only the values of the phase relations changed (Fig. 12 Bd).

With the second strong activation of the parasympathetic division (parasymp. peak 2, time interval 65-72 s) the functional unit 1 was bound together again

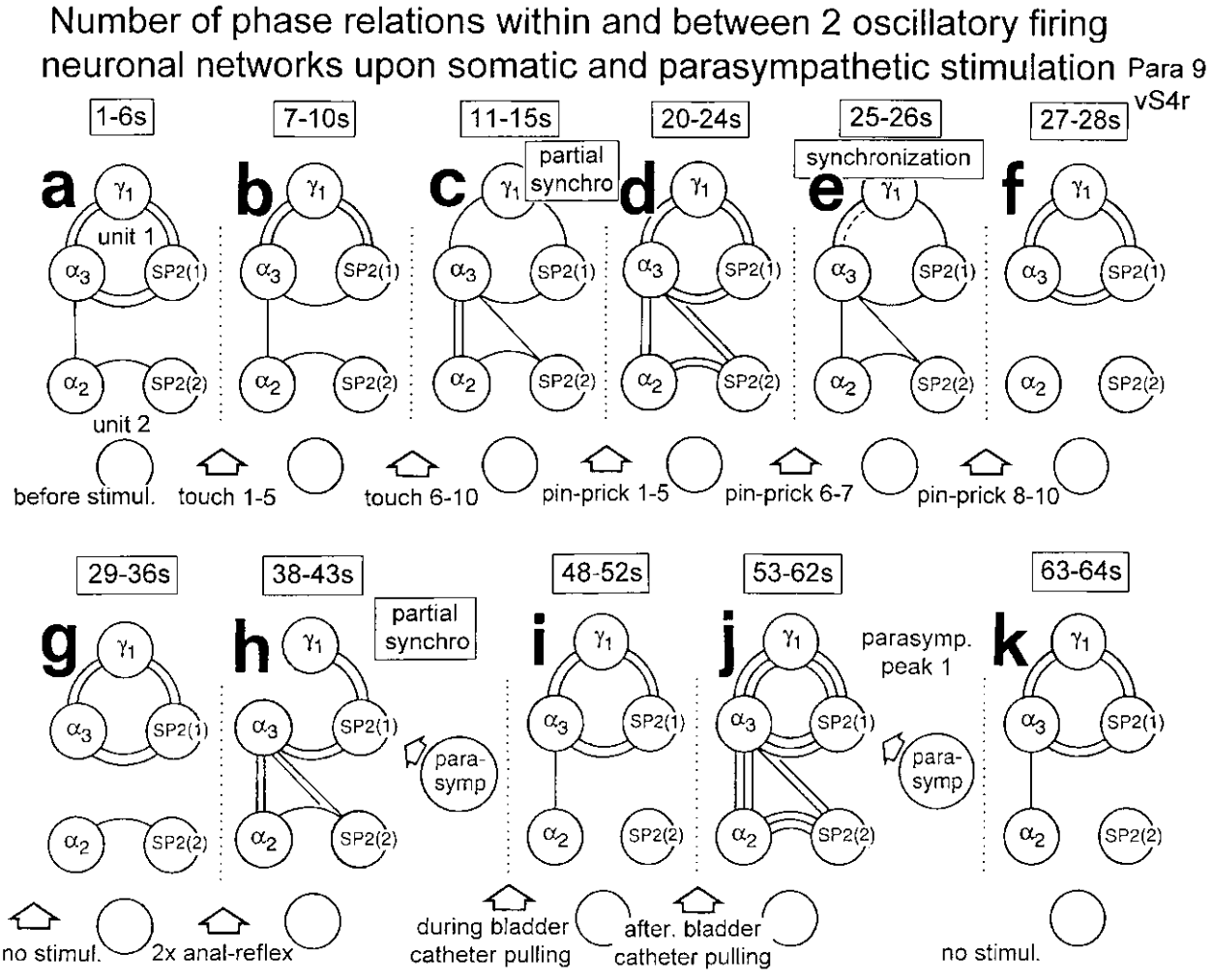

Fig. 14. – Number of phase relations within and between the two functional units α_3/γ_1/SP2(1) and α_2/-/SP2(2). Time intervals are those of Fig. 2A. Note that in 'a' the functional unit 1 is with two phase relations per oscillation period in a stage similar to those seen in the brain-dead individual; with synchronization only 1 phase relation occurred (e) and the parasympathetic division channelled an extra phase relation to interact with the somatic division (j).

by 3 phase relations (Fig. 10A), in similarity to the first strong activation of the parasympathetic division (42), measured by the burst firing of the secondary muscle spindle afferent fibre SP2(1) (Fig. 8 of Ref. 41) and the increased doublet firing of the SP2(1) fibre (Fig. 5 of Ref. 41). The functional unit 2 was disorganized, but phase relations still occurred between the α_3 and the α_2-motoneurons and the SP2(2) fibre (42). The α_2-neuronal network and the fusimotor networks, driving the SP2(2) spindle afferent fibre, were integrated differently.

After the second strong parasympathetic activation, in the time interval 73-76 s (Fig. 10A), the functional organization of the two functional units in the spinal cord was similar to that before the activation of the parasympathetic division. Functional unit 2 was slightly disorganized as the SP2 (2) fibre strongly reduced its firing (42).

Bulding up of external loops to the periphery by premotor spinal oscillators

It will be shown now that with the building up of simultaneous phase relations between α, γ and SP2 fibres and the assimilation of II distributions (coor-

dination's of rhythms), an external loop of premotor spinal oscillators is built up to the periphery, which makes it possible to directly influence the firing of spinal oscillators by a rhythm training. The somatic and parasympathetic pattern organizations in the sacral micturition centre can simultaneously be entrained by jumping on springboard (Fig. 15 g) (including the stimulation of movement (Fig. 15f) and bladder receptors (Fig. 15h)) to allow movement-based learning in the continence and movement patterns and to induce learning transfer from movements to urinary bladder functions. A repair of neuronal network patterns of the functionally disconnected sacral micturition centre in spinal cord injury seems possible.

In Fig. 12Ba it can be seen that there existed two phase relations 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. 11Aa), the γ-loop was not a part of this spinal oscillator; it was only contributing to the drive of it, as pictured in Fig. 15a. Since the II distribution of the fusimotor γ_1 was often rather broad (for example Figs. 11Aa, 12Ac), its driving network was not or only almost oscillatory firing (the dashed line loop in Fig. 15a).

Upon touching sites 1 to 5 approximately every second, phase relations occurred between the α_3, γ_1 and SP2(1) fibres, even though reaching a different value (Fig. 11Bb,c) and the II distributions of the α_3 and γ fibres (Fig. 11Ab) and the SP2(1) fibre (Fig. 11Ac) became assimilated. The γ-loop became directly connected to the oscillatory firing network: the premotor spinal oscillator (the network driving the α_3-motoneuron; the α_3-motoneuron is a part of the network) built up an external loop to the periphery (Fig. 15b).

Upon pin-pricking sites 6 and 7, one phase relations occurred between the firings of the α_3, γ_1 and SP2(1) fibres (Fig. 11Be) and also the II distributions assimilated (Fig. 11Ae). The spinal α_3-oscillator had built up a full external loop to include the γ-loop in its oscillatory firing (Fig. 15e). Since there was transient synchronous firing of unit 1 with unit 2 (including the α_2 and SP2(2) fibres (Figs. 11 Be,14e)), 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 inervating striated continence muscles to muscles activated for locomotion (Fig. 15f), then for example during jumping, running or other coordinated, rhythmic, stereotyped, dynamic movements, at least oscillatory firing α_2 or α_3-oscillators build up external loops to the periphery. It seems partly possible during jumping on springboard to synchronize spinal oscillators with the jumping rhythm, mainly given by the properties (Eigenfrequency) of the springboard. Especially the α_3-motoneuron networks can be entrained efficiently by jumping on springboard, since the 'Eigenfrequency' of the springboard and that of the α_3-oscillator network are both in the range of 1 Hz (for entrainment, see below). The extension of premotor network organizations serving bladder functions to premotor network organizations serving movement functions is most likely justified, since rhythmic firing of single FF and FR-type motor units, which are innervated by α_1 and α_2-motoneurons, has been recorded by surface electromyography (sEMG) during rhythmic, coordinated movements (Eigenfrequency around 1 Hz) in patients with spinal cord injury (Figs. 4, 5 of Ref. (29). Upon exercising on the special coordination dynamics therapy device for turning (Fig. 1D), single FF-type motor units in arm and leg muscles coordinated their rhythmic firing with respect to phase and frequency. These single motor unit recordings performed with sEMG support the recordings from single motoneuron axons.

External loop of premotor spinal oscillators and rhythmic, dynamic stimulation of motor and bladder functions

Upon jumping on springboard (Figs. 1C, 15 g) (and other rhythmic movements like running) premotor spinal oscillators organize themselves to fire transiently oscillatory according to the motor pattern and build up an external loop to the periphery (Fig. 15). If the frequency of the rhythmic

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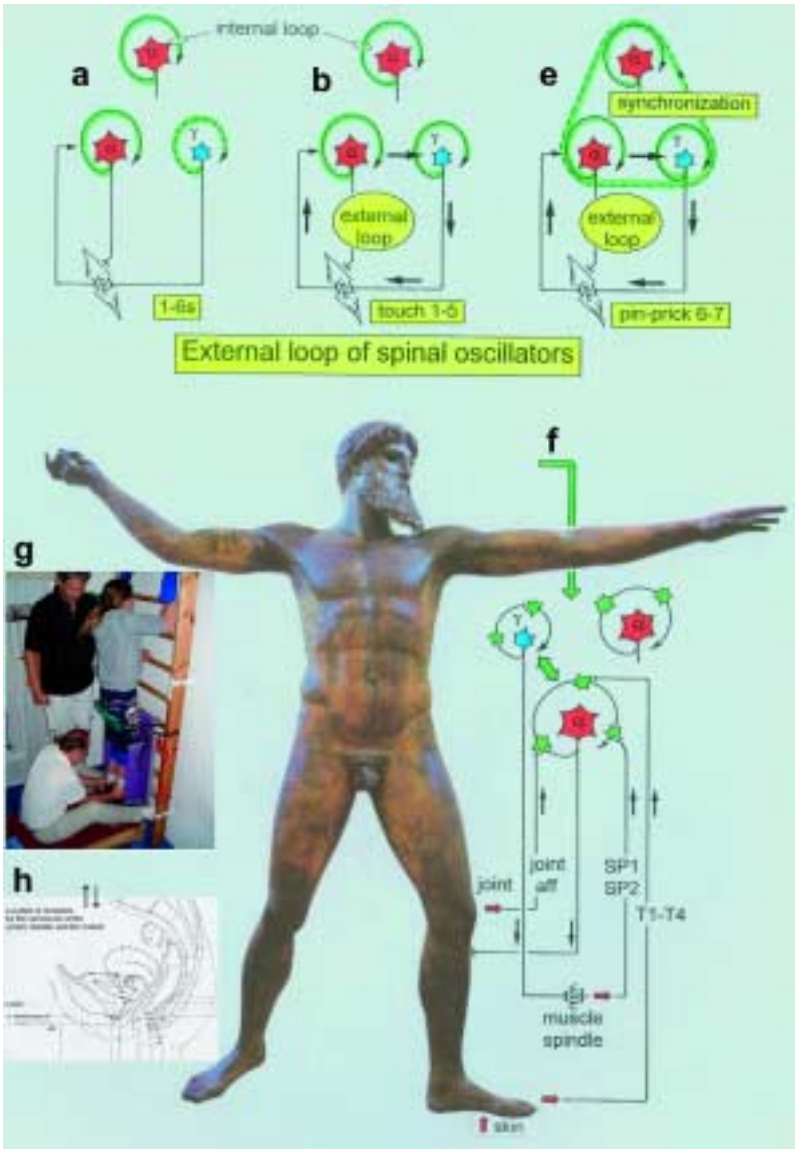

Fig. 15. – Spreading of oscillatory firing from α-motoneuron neuronal network to include muscle spindles (periphery) and synchronization of different α and γ-motoneuron neuronal networks caused by touch and pin-prick stimulation.
(a) α-motoneuron neuronal networks fired oscillatory (solid line loop), γ-motoneuron neuronal network did not or did only partly (dashed line loop), upon no additional stimulation; taken from Fig. 3Aa,Ba of (8).
(b) Oscillatory firing α and γ-motoneuron 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. 1Ab, Bb (8).
(e) Oscillatory firing α (internal circuitry loop) and γ-motoneuron neuronal networks (external loop) synchronized (broad peak phase relation) upon pin-pricks 6-7, taken from Fig. 1Ae,Be of (8). The dashed line loop represents synchronization.
(f) Oscillatory firing α (internal circuitry loop) and γ-motoneuron 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. Extensive pathologic movement like tremor may entrain neuronal circuitry to increase tremor movement. The Greek good is a bronze statue of Zeus found close to the cape of Artemision 460 BC.
(g) Supported jumping on the springboard in anti-phase. The patient with the severe cervical spinal cord injury is supported by the author.
(h) Location of receptors for the continence of urinary bladder and rectum stimulated upon jumping on springboard. For further details see Fig. 10 of Ref.42.

movement has an integer relationship to the 'Eigenfrequencies of the premotor networks and more rostral networks, these premotor networks get entrained for more specific self-organization (see below). When jumping on springboard (Fig. 15 g) not only the motor networks get activated; also the external sphincteric motoneurons, innervating the external bladder and anal sphincter, as a part of the pelvic floor, get rhythmically activated to counteract the rhythmic weight changes of the intestine. Further, the rhythmic, dynamic, stereotyped up and down movements do stimulate stretch, tension, flow, and mechanical receptors of the bladder (detrusor and proximal urethra) (Fig. 15h). This rhythmic movement-related sensory input with ≈1 Hz bears similarity to the sensory input stimulated by bladder and anal catheter pulling during the measurements (Figs. 10, 12). Repetitive phase relation changes in and among neural ensembles will occur in some similarity to the changes following catheter pulling (Fig. 12B). Since the neurons involved in the generation of movement and continence (and micturition) patterns (especially if the neurons serve both functions at the same time) are synchronously, rhythmically activated, the pathologic bladder patterns get entrained from the rather physiologic jumping movement, in some similarity to co-movement. The synchronized activation of the somatic and parasympathetic networks allow efficient learning transfer, since the neurons work as coincidence or more general as coordination detector (30). If there is fluid in the bladder and material in the bowel and rectum, the continence stimulus is stronger. Also walking and running will stimulate and change the intrinsic dynamics of the micturition and defecation centres, but not as strong as the jumping on springboard. The walking and running on a treadmill is performed under weight support, whereas during jumping on springboard no weight support is given and needed (Fig. 15 g). The sympathetic nervous system division, probably innervating the internal urinary bladder sphincter (smooth muscle), will also be activated synchronously. Since the frequency of jumping is with around 1 Hz similar to the 'Eigenfrequency' of the α_3-motoneuron oscillators, these oscillator networks should be entrained most efficiently (see below).

Entrainment of premotor spinal oscillator networks by rhythmic movement-induced afferent input and inputs from 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) then premotor spinal oscillators can be handled in a first approximation as single linear oscillators. The premotor spinal oscillators and the spinal pattern generating networks 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 surrounding pattern generating networks, 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. But the functional repair becomes only physiologic if volitional control (by ascending and descending tracts) is intertwined.

If one assumes that loop circuits do not only exist between the premotor spinal oscillators and the periphery, but are a general structure in the CNS, then motor learning involves the formation of loop circuits (or better loop network circuits) between the cortex and the periphery involving the sensory cortex and the thalamus.

When a linear oscillatory system is driven by an external periodic input its response contains both frequency components. This is also, in general, true with nonlinear oscillators. However, in this case, if the external frequency is close to the Eigenfrequency 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.

An oscillator with one degree of freedom can be 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. 16 shows a typical example. Entrainment occurs in the shaded part of the plane. If E and $\Delta\omega$ are below the curve (outside the shaded area) usually the frequencies ω_0 and ω_1 are present. In the case that $\Delta\omega = 0$ but E is very small the phase of oscillations is not influenced by the input. For further details, including van der Pol oscillator see (11).

Upon jumping on springboard, the entrainment frequency ω_1 (the jumping frequency) is with 0.9 to 1 Hz close to the Eigenfrequency of the premotor spinal α_3-oscillators ($\approx$ 1 Hz). The α_3-oscillators and the networks they are integrated in are entrained directly. For the entrainment of the α_2-oscillators (Eigenfrequency $\approx$ 6 Hz) and α_1-oscillators (Eigenfrequency $\approx$ 10 Hz) subharmonic and superharmonic entrainment has to be considered.

When a nonlinear oscillatory system is driven by an external periodic input z_k, the entrainment can be harmonic (z_k itself has the oscillation period T of the oscillator; case of the α_3-oscillators), subharmonic (z_k has a period which is an integer multiple of T, mT; case of the α_2 and α_1-oscillators) or superharmonic (z_k has a period which is an integer fraction of T, T/m) (11). With the increasing order of subharmonic entrainment, the entrainment strength reduces for the same coupling strength or entrainment amplitude E. For the α_2 and α_1-oscillators the entrainment is subharmonic and the entrainment strength therefore reduced. In α_2-oscillators, two entrainment phases per oscillation period were mostly observed, which correspond to 'in-phase' and 'anti-phase' coordination of arms and legs, which enhances entrainment. Also, the change of the number of phase relations between the neural assemblies in the sacral micturition centre may indicate changing entrainment or coupling communication between the somatic and parasympathetic nervous system divisions.

However, oscillator models are still far away from human network properties. The jumping on springboard is very rhythmic and stereotyped (frequency of jumping $\approx$ 1 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 Figure 5, and for natural impulse patterns of secondary muscle spindle afferents see Figure 6. 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.

Even though the used oscillator models are far away from human self-organization network forms, their results are still very useful for the interpretation, under certain conditions, of measured data and to understand better the jumping on springboard training (as a part of the coordination dynamics therapy) which contributes substantially to the cure of urinary bladder functions (43).

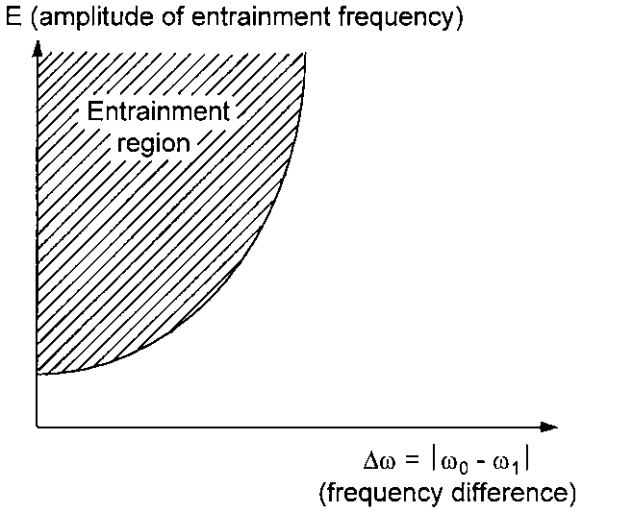

Fig. 16. – Illustration of the relation between the amplitude E of the external input and the difference in frequencies $\Delta\omega$ which produces entrainment of a nonlinear oscillator.

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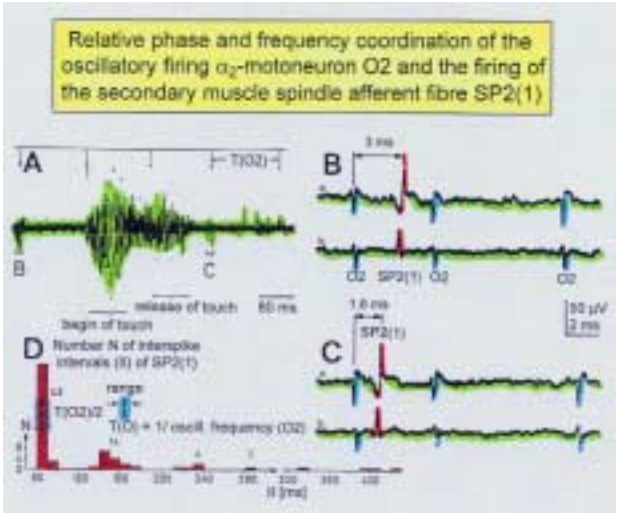

Fig. 17. – Time relation between the occurrence of the action potentials (APs) of oscillatory firing α_2-motoneuron O2 and the firing of the secondary muscle spindle afferent fibre SP2(1). HT6. S4 dorsal root recording.
A. Overall view of the used sweep piece; only trace „a„shown. Four oscillation cycle periods of motoneuron O2 are indicated (T(O2)). The APs of the impulse trains can be recognized only partly, because of the slow time base and poor digitalization. One impulse train (dashed arrow) is lost in the touch stimulated activity, which consists of a touch (large overall activity) and a release part (lower overall amplitude).
B,C. Sweep pieces from A, time stretched. In B, motoneuron impulse train APs is marked O2, spindle afferent APs are marked SP2(1). Note that the APs of the spindle afferent fibre are not time-locked to the first AP of the impulse train of the rhythmically firing motoneuron (relative phase coordination). Digitalization 4 times better than in A, but still rather poor, as can be seen from the low amplitudes of the motoneuron APs on trace „b„in C.
D. Occurrence of interspike intervals of the secondary muscle spindle afferent fibre SP2(1). The numbers give the amount of IIs in each distribution peak. The oscillation period of motoneuron O2 (and the range of variation) and the half period are indicated by short dashed lines. Note that the IIs of fibre SP2(1) are very similar to the oscillation period (or the half of it) of α_2-motoneuron O_2 (relative frequency coordination).

Need for stability of phase and frequency coordination to allow learning transfer

A young mother, with stress incontinence after giving birth to the first child, could well improve her continence status upon jumping on springboard in addition to other training. But her CNS is not injured; just the periphery has to be repaired by means of changing the CNS.

In severe cervical spinal cord injury (Fig. 1A, B), the mainly jumping on springboard (Fig. 1C) is not sufficient for bladder repair. First, of course, the patient has to regain movement functions back (especially the trunk stability) to be able to perform the jumping on springboard. Further, the self-organization of CNS networks by phase and frequency coordination has to be improved to make learning transfer from movements to bladder functions possible, since in every CNS injury the phase and frequency coordination is impaired. Large instabilities in phase and frequency coordination will not allow specific pattern formation as a basis for learning transfer. But the stability of phase and frequency coordination can be improved when the patient is exercising on special coordination dynamics therapy devices, especially the one shown in Figure 1D. In the following, measurements are presented to understand the necessity of improving the stability of phase and frequency coordination for functional repair.

Phase and frequency coordination between oscillatory firing α2-motoneurons and their adequate afferent drive in brain-dead human

The relative phase and frequency coordination between the APs of the oscillatory firing α_2-motoneuron O2 and the secondary muscle spindle afferent fibre SP2(1) has partly been shown in Fig. 6, and can directly be seen in the original recordings in Fig. 17 (brain-dead human). The firing of the oscillator and the sweep pieces which are shown time-expanded are indicated at the summary trace (Fig. 17A). Fig. 17B,C shows the action potential (AP) impulse train of oscillator O2 in connection with one of its driving spindle afferent AP. Because of the duration of the phase relation of around zero milliseconds between the firing of the driving SP2(1)-fibre and the impulse train of the oscillatory firing motoneuron O2, the SP2(1)-fibre AP (every second AP) appeared at a similar time as the impulse train. Because the AP of the spindle afferent fibre had a characteristic waveform, it was easy to extract its impulse pattern from the summed impulse traffic of this S4 dorsal root. During touch-induced skin afferent activity (Fig. 17A), the activities of the motoneuron and the spindle afferent

fibre were covered by the skin afferent activity. After the cessation of the skin afferent activity the afferent and efferent APs were found again at their expected time positions of the regular firings. The phase coordination between the firings of the oscillatory firing motoneuron O2 and the secondary muscle spindle afferent fibre SP2(1) at the time when records B,C were taken, was 1.6 ms (3 ms - 1.4 ms, Fig. 17B,C). In Fig. 17D, the relative frequency coordination between the firings of the SP2(1)-fibre and the impulse train of the oscillator is indicated. For the time period evaluated, the correlation between the firing of the motoneuron and the spindle afferent fibre was in the range of between 3 and 5 ms (Fig. 17D).

Relative frequency coordination

In Fig. 18, considerations concerning the relative frequency coordination are extended to the activity of further afferent fibres and γ-motoneurons of the same root. Fig. 18G shows sweep pieces of the original recordings; A through F show the interspike interval distributions of spindle afferents and γ-motoneurons. It can be seen from the overlapping of the oscillator frequency distribution ranges (and the half of it), and from the interspike interval distributions of the afferents that, from the viewpoint of frequency coordination, fibre SP2(1) contributed strongly to the drive of oscillator O2, whereas there was a weaker contribution from other afferents (less overlapping between the distributions of the afferents and the range of the basic frequency or the first harmonic of the oscillator). Also, γ-motoneurons showed only little frequency correlation at that time period.

Fig. 19 shows the interspike interval distributions of more afferents (including the afferents for bladder filling; stretch receptor afferents S1(1), S1(2)) of another root, together with the oscillation period range (and the half of it) of a second α_2-oscillator (O1). By comparing the oscillation periods (and their halves) and their ranges with the interspike interval distributions of the afferents, it can be suggested which afferents made a (frequency coordination) contribution to the drive of what oscillator at that time interval. For example, the S1(1) urinary bladder stretch afferent fibre activity contributed to the drive of oscillator O1

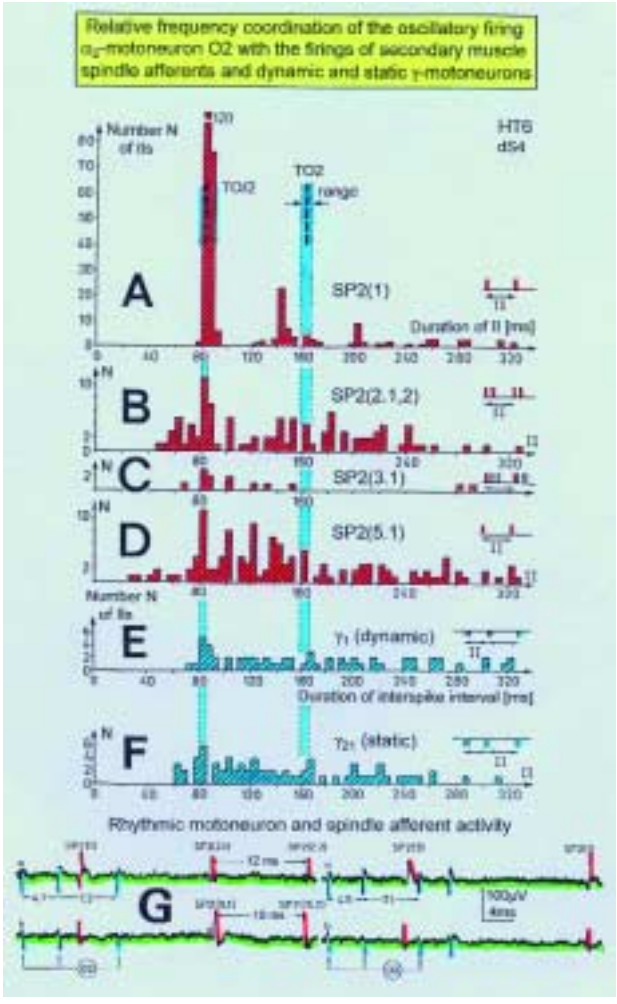

Fig. 18. – Interspike interval distributions of single endings of four secondary muscle spindle afferents (SP2) and two γ-motoneurons, recorded simultaneously. In A, the oscillation period TO2 (impulse train length = 3 APs) with its range of simultaneously recorded oscillatory firing α_2-motoneuron O2 (see G) is drawn for comparison; also, the halves of the oscillation period TO2/2 are indicated. Note that the interspike interval distributions of spindle afferents and γ-motoneurons have shortest interspike interval, nearly identical to the half of the oscillation period (relative frequency coordination). The schematic impulse pattern in A to F shows the procedure for measuring the interspike intervals. Original records of the firing patterns of α_2-motoneuron O2 and the secondary muscle spindle afferents SP2(1), SP2(2), SP2(3) and SP2(5) are shown in G. Brain-dead human HT6, dS4 root.

(activating the external bladder sphincter) because its interspike interval distribution overlaps strongly with the range of the oscillation periods of O1. But the S1(1) distribution does not overlap with the range of the oscillation periods of oscillator O2, or with their

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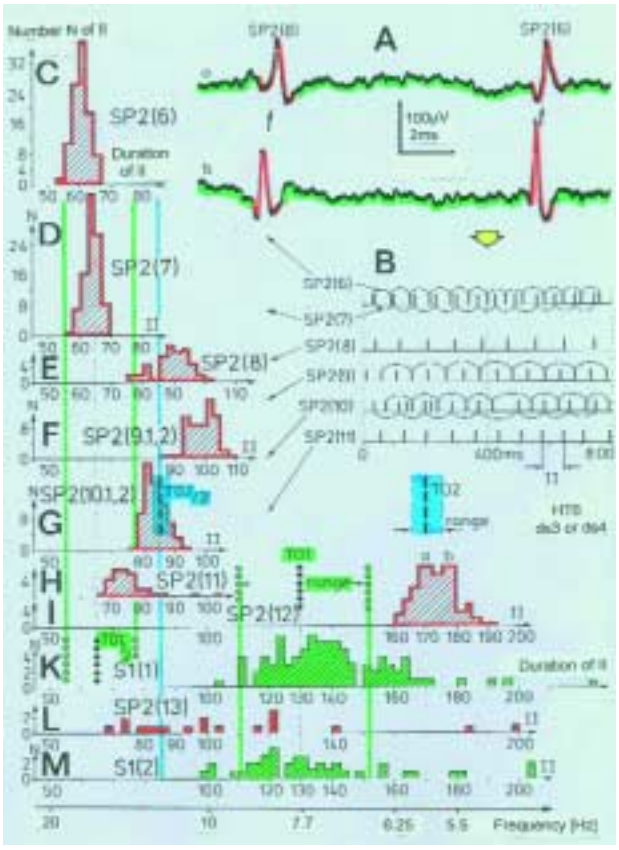

Fig. 19. – Measurements from brain-dead human HT6 from different spinal cord segments after retrograde bladder filling (700 to 800 ml), with the exception of "I", which was obtained before filling. A. Sweep piece of a recording from a dorsal S3 or S2 root filament. It can be seen that the secondary muscle spindle afferent SP2(6) AP can be distinguished by the wave-form on the two traces from the secondary spindle afferent fibre SP2(8) AP (different amplitude of the three phases of the triphasic APs). B. Simultaneously recorded impulse patterns of the six parent secondary spindle afferents SP2(6) through SP2(11) obtained from dS3 or dS2 root recordings. The impulse patterns of SP2(6) and SP2(7) fibres are not separated to show the similarity of the patterns. The impulse patterns of the parent spindle afferents SP2(9) and SP2(10) are split into patterns of the single endings (single ending activity partly connected by circle lines) with the assumption that single endings of parent secondary muscle spindle afferents should have interspike intervals of duration longer than 50 ms. C to H. Interspike interval distributions of six simultaneously recorded single secondary spindle afferent endings. F, G. Interspike interval distributions of parent fibres, which are the sums of the distributions from the two activated endings. I. Interspike interval distributions of a secondary spindle afferent fibre (SP2(12)) of a coccygeal root. K, L, M. Interspike interval distributions of single-fibre afferent activity from a lower sacral dorsal root. In L, most likely the activity from a secondary spindle afferent fibre is shown. In K and M most likely the interspike intervals from afferents (S1(1) and S1(2)), innervating stretch receptors of the urinary bladder wall, are shown. In G, H and K, the durations of the oscillation periods (mean and range) of the oscillatory firing α_2-motoneurons are indicated by thick dashed and dotted lines; the motoneurons innervate the external anal sphincter (TO2) and the external bladder sphincter (TO1). The sites of innervation of the oscillatory firing motoneurons are identified (and distinguished from each other) by anal reflex stimulation, bladder filling and catheter pullings. Note that the TO1 and TO2 ranges and their halves overlap with the interspike interval distributions of the secondary spindle and stretch receptor afferents (relative frequency coordination).

halves or quarters. The S1(1) afferent fibre will therefore not have made a substantial contribution to the drive of oscillator O2. On the other hand, the secondary muscle spindle afferent fibre SP2(12) activated oscillator O2 innervating the external anal sphincter, since its interspike interval distribution overlaps with the range of O2 oscillation periods. But the secondary muscle spindle afferent fibre SP2(12) did not activate oscillator O1, as its interspike interval distribution does not overlap with its oscillation period range or the half of it (Fig. 19).

By comparing interspike interval distributions of afferent fibres with oscillation period distributions it can be estimated what afferents made a (frequency coordination) contribution to the drive of the spinal oscillators. These considerations need no knowledge of the connectivity of the neuronal networks.

In the frequency coordination between the firings of afferents and oscillators and among oscillators, entrainment or coordination may occur sub- or superharmonically (see above). The energy transfer, and therefore the coupling strength will be smaller if the APs coincide in their firing less often. As indicated by my measurements, the coupling and the relative coordination during the self-organization of the neuronal networks of the human spinal cord are of an enormous complexity; this self-organization is induced by sets of mutual impulse patterns from stimulated receptors which are ordered, in time and space (for skin receptors see Fig. 5), so as to reflect, in the spinal cord and higher centres, the interplay of the body with the external world.

Impaired organization of premotor spinal oscillators following spinal cord injury as an indicator for pathologic network organization

Following a spinal cord injury, the oscillatory firing networks lose specific properties. The Eigenfre-

quencies of the premotor spinal oscillators change from a narrow to a broad frequency band (Fig. 20). Self-organized α_2-oscillators fire physiologically at an Eigenfrequency (varying within a small frequency band as probably indicated with the hatched distributions in Fig. 20) with impulse trains consisting of 2 to 3 action potentials. Following brain death, this Eigenfrequency band enlarges (black area in Fig. 20). Following a spinal cord injury, the Eigenfrequency band enlarges strongly and includes in this case the frequencies between 4 and 14 Hz for firing with 2/3 action potentials per impulse train (Fig. 20). The premotor spinal oscillators have lost their specific properties and could now be excited at frequencies at which they physiologically would not be excited (see above).

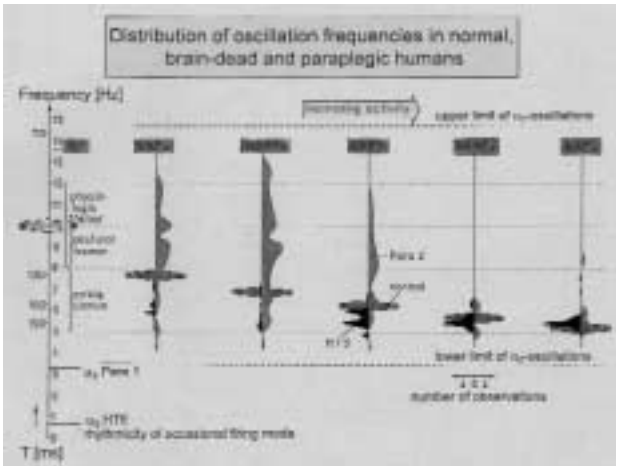

Fig. 20. – Frequency distributions of oscillation frequencies of continuously oscillatory firing α_2-motoneurons with increasing number of APs per impulse train (increased activity) in paraplegic 2 (open), in brain-dead HT5 (filled), and probably normal human (cross-hatched). Frequencies and rhythmic activity changes in the occasional and oscillatory firing mode are indicated. Ranges of physiologic tremor, postural tremor and ankle clonus are also drawn. Note that frequencies for the brain-dead HT5 are too low, and the oscillation frequencies of the spinal cord isolated for a long time (Para 2) are too high and too spread as compared to the theoretically predicted frequency ranges (cross-hatched). T = oscillation frequency.

Explanation for a spastic external bladder sphincter

In the brain-dead human HT6 of Figure 19, the premotor spinal oscillator TO1 could according to the overlap of the narrow frequency band harmonically (for simplicity only this case of activation is considered) only be driven by the activity of the bladder stretch receptor afferents S1(1) and S1(2). This oscillatory firing α_2-motoneuron, innervating the FR-type muscle fibres of the external bladder sphincter, is getting activated with the activity of the stretch receptor afferents, when the urinary bladder is filled to secure continence. All the secondary muscle spindle afferents cannot activate the external bladder sphincter harmonically, because their frequency bands did not overlap (frequency band overlap in the frequency range 6.5 till 9 Hz). Only the stretch receptor bladder afferents can activate the external bladder sphincter to secure continence.

Following a spinal cord injury, the Eigenfrequency band broadens from 6.5/9 Hz to 4/14 Hz. According to Figure 19, also the secondary muscle spindle afferents SP2(8), SP2(9.1,2), SP2(10.1,2), and SP2(12) could activate the motoneuron innervating the external bladder sphincter. The striated external bladder sphincter can be activated by secondary muscle (and probably other) afferents, not involved in continence. This broadening of the frequency band could be one reason for spasticity (continuous contraction) of the external bladder sphincter. Our patient of Figure 1, with a severe cervical spinal cord injury, had at the beginning of coordination dynamics therapy a spastic external bladder sphincter. She was continent, but could not empty the bladder – the emptying of the bladder was achieved by a suprapubic catheter.

Reduction of spasticity of the external bladder sphincter

If one could improve the functioning of the sacral micturition centre and reduce the frequency band of the oscillatory firing premotor spinal oscillators, innervating the external bladder sphincter, then this kind of spasticity of the external bladder sphincter could be reduced. The training was called earlier by me 'oscillator formation training'. It will be shown in this and the following paper (43) that this spasticity reduction could be achieved by learning and learning transfer. But, as will be shown in the following paper (43), the reduction of the spasticity of the external bladder sphincter is only a first step in curing urinary bladder functions.

Following CNS injury (including spinal cord injury) not only the frequency coordination, but also

the phase coordination among neuron firing becomes impaired.

Stable phase coordination in the brain-dead individual

In a paraplegic, existing relative phase relations among α and γ-motoneurons and secondary muscle spindle afferents are indicated in Figs. 11, 12 by small arrows. In Figure 14 the natural impulse patterns were used to show the interaction between the somatic and parasympathetic nervous system divisions in the sacral micturition centre. Now I change the representation of the phase relations (shown in Figs. 11, 12) in order to recognize phase stability, to find reasons for the pathologic organization of neuronal networks in paraplegics. I will start with the physiologic case, namely the brain-dead individual.

To make the phase relation changes with time better recognizable, a representation of phase relations is used which comes from the measuring of the speed (frequency) 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. 21A. A time axis is introduced on the horizontal line, to make phase relation changes visible in dependence on time.

In Fig. 21Aa, the loop excitation is pictured for this oscillator model. In Fig. 21Ab, 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. 21 Ac,d,e shows different phase relations, namely a constant phase relation (c), a changing phase relation (d), and no phase relation (e).

In Fig. 21 B, 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 (42) 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. The phase coordination between the firings of the α_2 and a γ_1-motoneuron and the secondary muscle spindle afferent fibre was stable.

Unstable phase coordination in the patient with a spinal cord injury

In Fig. 22A, B different phase relation changes are plotted from Figs. 11, 12 with respect to the α_3-oscillation cycle (A) and the α_2-oscillation cycle (B). It can be seen that the different phase relations changed strongly in value over time (upon different stimulation), and that also the number of phase relations per oscillation cycle changed. The phase stability of the cooperative and competitive interplay among neurons became impaired. Whether the change of the number of phase relations from 2 to 3 following the activation of the parasympathetic nervous system in the sacral micturition centre (Figs. 12, 14) is physiologic or not is not clear.

Difference of phase stability between a brain-dead human and a paraplegic

The most obvious difference of the phase relation changes between the above mentioned brain-dead human and the paraplegic was that in the paraplegic the phase relations varied very much, whereas they changed only little in the brain-dead human. 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 human. Assuming 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, the functioning of the networks became instable following spinal cord injury. The more frequent occurrences of changes of phase relations between the different nerve fibres in combi-

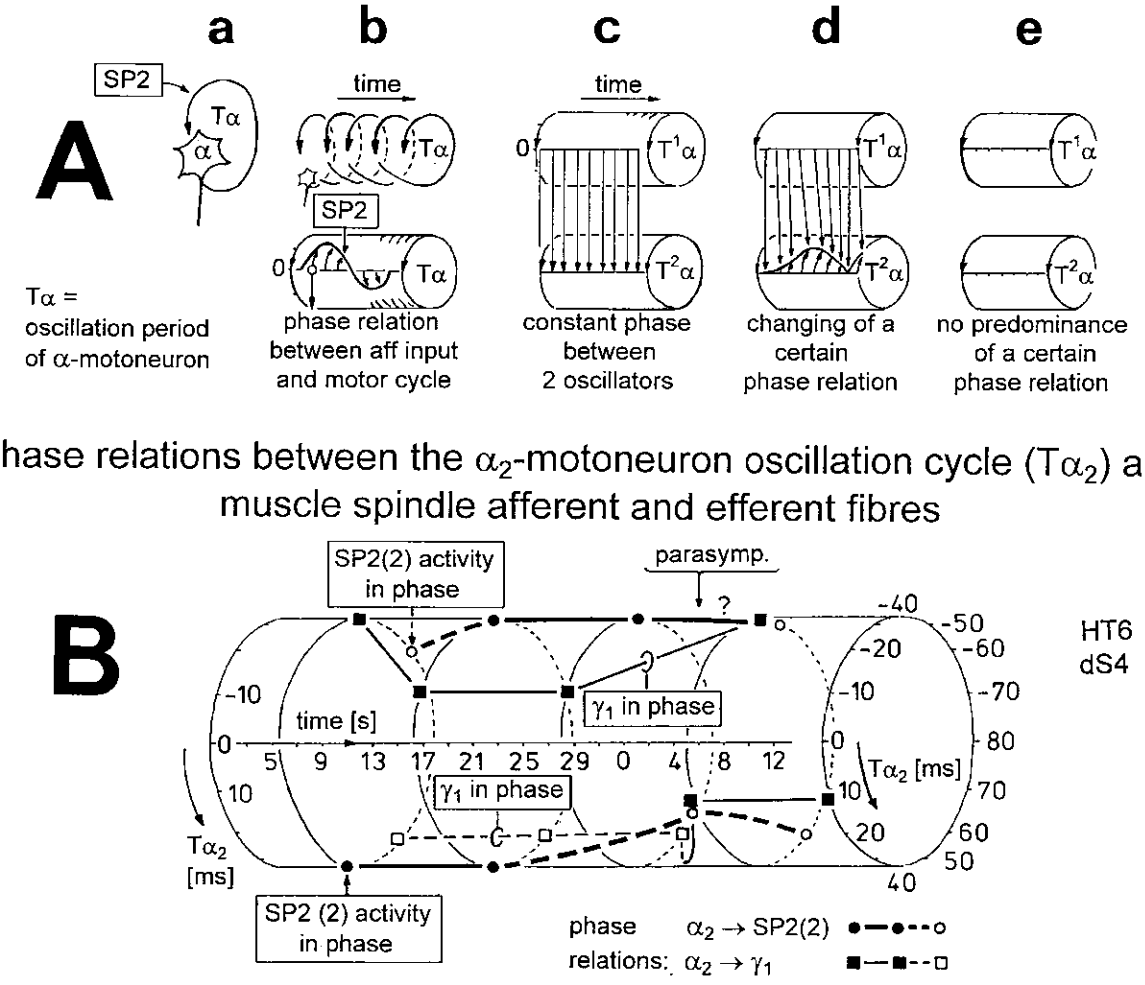

Fig. 21. – (A) Derivation of the simultaneous description of interspike intervals and phase relations.
(a,b) The oscillation period of an oscillatory firing α-motoneuron is schematically characterized by the length of the loop (perimeter). Successive oscillation periods with ongoing time yield a cylinder. 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 changed 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 the flashing of the stroboscope 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 to 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 the brain-dead human HT6 (root dS4) are 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.

nation 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 by a broad frequency band. They could now be excited at frequencies at which they physio-

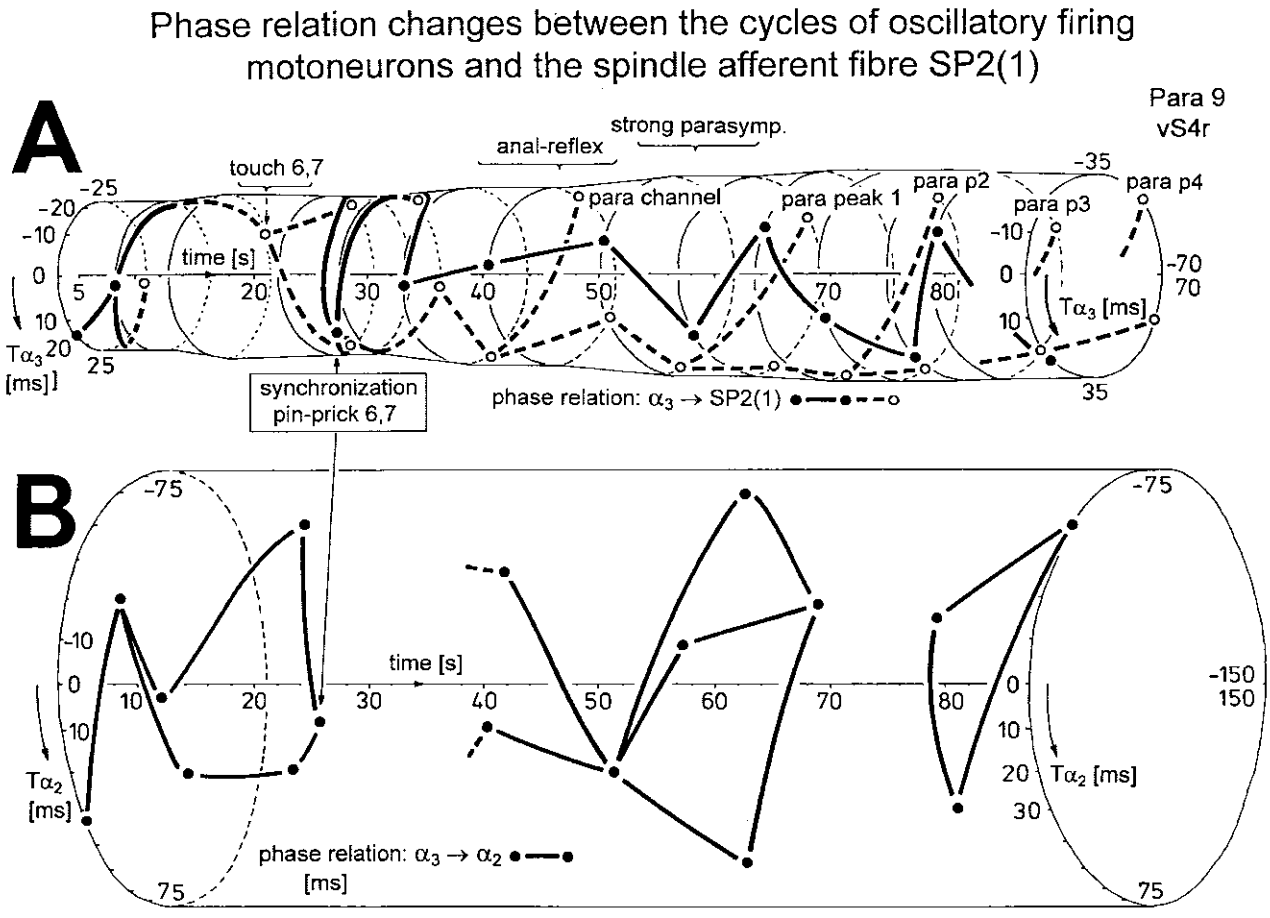

Fig. 22. – (A) Phase relations between the secondary muscle spindle afferent fibre SP2(1) and the oscillatory firing α_3-motoneuron, taken from Figs. 10-12 (and additional data), are plotted on the oscillation period cylinder $T\alpha_3$ (mean oscillation periods are taken from Figs. 11A, 12A) according to Fig. 21A. The cylinder is changing 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. 10A). 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. 10A 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 Figs. 11B,12B. Note that the phase relations of the paraplegic 9 are much more variable than those of the brain-dead human HT6 (Fig. 21B); also, the number of phase relations changes.

logically would not be excited. Overactivation and mass effects could be the result. On the other hand, certain networks could escape from driving afferent influence by changing their phase by phase escape to avoid interaction. Functionally far away 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 could have occurred more easily and other ones not at all.

W.R. Hess tried in 1944 to compare biological order and human society (6). 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.

Change of the neuronal network organization following spinal cord injury - pathologic network organization

Following spinal cord injury the spinal cord neuronal networks have been observed to change their

organization, and this can be quantified by six changes of organization.

1. Following spinal cord injury, the spinal oscillators strongly widen their oscillation frequency band (20), which means that their firing becomes unrhythmical (Fig. 20). An increase of the more irregular oscillator firing can also be seen in the broadened distributions of the interspike intervals of the impulse trains of oscillatory firing α_2 and α_3-motoneurons (16). The loss of specificity of oscillatory properties will at least partly be due to the loss of supraspinal inhibition because muscles below the paretic spinal cord injury are overactivated.
2. Following the injury, the phase relations among the oscillators and between oscillators and their driving afferents (for example, secondary muscle spindle afferents) become very instable (Fig. 22).
3. Because of the widening of the frequency bands (Fig. 20) and the instability in phase coupling (Fig. 22), the oscillators lose partly their rhythmicity and their coordination and cooperation properties. The rhythmicity of movements and their coordination and coupling of arms and legs is reduced. The loss of rhythmicity and the loss of coordination can be observed easily when measuring the coordination dynamics.
4. The spinal oscillators are not under full volitional control by the patient any more (Fig. 48 of Ref. 21). Sometimes, paraparetic or tetraparetic patients can switch on motoneurons to fire oscillatory, but cannot switch them off again.
5. Following natural stimulation, the recruitment of motoneurons in the occasional firing mode (low activity mode of motoneuron firing; see Fig. 4D for bladder filling up to 550 ml) according to the size principle in each nerve fibre group changes (14, 15). The level of motoneuron activation increases following spinal cord injury (probably due to loss of inhibition) and the slowly conducting α_3-motoneurons (S) are recruited before the faster conducting α_2-motoneurons (FR), which is pathologic.
6. The coupling of α and γ-motoneurons changes in strength following natural stimulation (15).

The loss of rhythmic oscillator properties and also the change of motoneuron firing in the occasional firing mode (when the oscillators have not been self-organized because of low activation) indicate deterioration in the self-organization of the spinal cord neuronal networks below the injury and can at least partly explain the pathologic CNS network organization called spasticity and increased clonus.

The impaired phase and frequency coordinations, measured among α and γ-motoneurons and secondary muscle spindle afferents by an increased variability of coordination, can be introduced in a first approximation in the equation of motion at the collective variable level of description for jumping on springboard ($d\varphi/dt = - dV(\varphi)/d\varphi + (Q\varphi\xi_t)^{1/2}$) by an variability increase of strength Q (see Discussion). This increased variability can be pictured by the increased fluctuation of pattern states (pictured by a ball) in an attractor basin (Fig. 23B).

Re-learning of phase and frequency coordination

This partly impaired phase and frequency coordination between the firings of single neurons and neuron assemblies (Figs. 20, 22) can be expected to have consequences in the coordination between arm and leg movements, because motoneurons innervate muscle fibres, and rhythmic coordinated firing of single motor units has been measured electromyographically with surface electrodes (29). Indeed, the coordination between arm and leg movements is partly or fully lost following CNS (brain and spinal cord) injury and is often not taking place in the malfunctioning CNS.

This partly impaired phase and frequency coordination at the single neuron level, the assembly level and the macroscopic level can be measured macroscopically, when the patient is exercising on a special coordination dynamic therapy device (Fig. 1D) on which arms and legs turn with a slightly different frequency (transmission 19 (arms): 18 (legs)). The phase coordination between arms and legs is imposed by the device. The loss of phase and frequency coordination between arm and leg movements becomes visible and measurable by the arrhythmicity of turning when the patient is exercising on the device. During a turning cycle and during the change of coordination between arms and

legs the turning frequency increases and decreases. This frequency variation (df/dt; f = frequency) can be recorded, quantified and displayed on a computer screen.

During the functional reorganization of the injured CNS of patients, the relative phase and frequency coordination of neuron firing has to be entrained as exactly as possible by the movement induced afferent impulse patterns from the receptors (learning through feedback information) to restore coordination in the range between 3 and 5 milliseconds (Fig. 17). The device has therefore to impose the exercising patient a coordination in the millisecond range for the different coordinations of arms and leg movements between pace gait and trot gait. The easy pace and trot gait coordinations, but not the difficult intermediate coordinations, can often be performed by the patient easily. Therefore, the continuous change from the easy to the difficult coordinations and backwards diagnoses the capability of the CNS to organize easy and difficult organizational states. If the movement state can be easily generated by the neuronal networks of the CNS, then the frequency variation of turning is small during the turning cycle, and if the movement state is difficult to organize by the CNS, then the frequency variation is large.

Since in the injured pathologically functioning CNS of patients often coordinations other than pace and trot gait are the easy coordinations, we need a coordination coordinate to judge upon the coordination dynamics. The pace and trot gait coordinations are used for the calibration, since both coordinations between arm and leg movements occur naturally during rhythmic coordinated (automatic) movements like creeping, crawling, walking and running.

The imposed coordination of arm, leg and trunk movements, upon exercising on the special coordination dynamic therapy and measuring device, is in accordance with the coupling possibilities of premotor α_1 (8-12 Hz), α_2 (6-9 Hz) and α_3-oscillators (0.4 (may be down to 0.1) -4 Hz), even though the frequencies are only a relative coordination parameter, whereas phase is an absolute coordination parameter.

When the hand levers are turned at between ≈ 0.4-1.5 Hz, the resulting frequency difference in turning between arms and legs is approx. 8.5 Hz (low α_1-oscillator frequency or high α_2-frequency) for low hand turning frequency of 0.5 Hz (low α_3-frequency). A slowlier turning of the hand levers would train directly more the premotor α_2-oscillators (f < 8.5 Hz). Faster turning of the hand levers (higher α_3-frequency) would train directly the α_1-oscillators in the higher frequency range (f > 8.5 Hz). Therefore, similar frequencies appear with respect to the frequency of turning on the device for measuring CNS organization and reorganization as have been measured for premotor spinal oscillators.

Improvement of the organization of motoneurons in the occasional and oscillatory firing mode

When turning the levers steadily with medium or high strength the premotor spinal oscillators in the patient's CNS are entrained because premotor spinal oscillators self-organize themselves for high activation (Fig. 4D). The turning of the levers is therefore an oscillator (or assembly) formation therapy. The members of premotor oscillator assemblies (most likely the motoneuron and interneurons) are entrained to improve activation and inhibition by adjusting, for example, the efficacies of the corresponding activated synapses. By turning the levers with little strength at approx. 0.4 Hz (releasing the power (load)-setting knob), the motoneurons get only partly organized into premotor spinal oscillators. The motoneurons are firing mainly in the occasional firing mode and are trained for a better recruitment according to the size principle (rhythmicity of repeated recruitment ≈ 0.4 Hz (Fig. 15 of Ref. 21). Between the motoneuron firings in the occasional and oscillatory firing modes, a better coordination of both firing modes is entrained (Figs. 15, 16 of Ref. 21).

Discussion

Correlation between natural impulse patterns of single neurons and integrative patterns

Starting from the clinical evaluation of urinary bladder functioning (Fig. 2, urodynamic), it was shown that bladder functions can be measured at the single-neuron level by recording single-nerve

fibre action potentials from afferent and efferent nerve fibres in sacral nerve roots of the cauda equine during an operation upon stimulating the bladder with bladder filling, anal and bladder catheter pulling, and touching and pin-pricking sacral dermatomes (Figs. 3-5). Natural impulse pattern changes could simultaneously be recorded from α and γ-motoneurons and secondary muscle spindle afferents (Figs. 6-8). Using group conduction velocity values and nerve distances of the human body, conduction times in touch and pain afferents and α-motoneuron axons could be calculated and the times for pattern enhancement and pattern change calculated in the sacral micturition centre. The change from the continence to the protection pattern, measured at the single-neuron level, is pictured in Figure 9, according to the System Theory of Pattern Formation, as a ball (network state) traversing from one basin of attraction into another. The deepness of the potential wells (basins of attraction) indicates the stability of the integrative patterns continence and protection automatism (Fig. 9B). It is shown therefore that from evaluations of changes of natural impulse patterns upon natural stimulation integrative CNS functions can be characterized.

The argument of synergetic that the amount of information necessary to describe individual states of neurons is very large and ways must be found to select relevant variables to compress the amount of information (in equations of motion of order parameters), to describe CNS functions, is only partly right. Also sets of natural impulse patterns of relevant neurons provide deep insight into CNS functioning, because in the process of self-organization of the CNS many neurons are involved which communicate with each other. The measuring of natural impulse pattern is therefore something like a probing of CNS functioning.

From natural impulse patterns to coordination dynamics

To show that learning transfer from movements to bladder functions in the neuronal networks of the sacral micturition centre can be analyzed, phase relations between the firings of different neurons were defined (Fig. 10) and their changes plotted (Figs. 11-14). It is shown that the cooperative and competitive interplay among neurons serving somatic and continence functions, quantified by phase relation and interspike interval changes, was intertwined. The integrative network organizations for continence (and micturition) and movements were generated by the same networks, including time sharing of neuron firing. By training therefore movements, generated in the network of the lower sacral spinal cord, also the bladder functions are influenced. This is just what follows out of the equations of motions of the collective variables ($d\mathbf{X}/dt = \mathbf{F}_{intr}(\mathbf{X}) + \sum c_{inf}\mathbf{F}_{inf}(\mathbf{X},t)$) of the pattern dynamics: Behavioral information $\mathbf{F}_{inf}$ (exercising a movement) affects the whole intrinsic coordination patterns dynamics $\mathbf{F}_{intr}(\mathbf{X})$, including stability, rather than certain coordination patterns itself only.

Coherent activation of bladder and motor functions and entrainment

Upon jumping rhythmically on springboard (Fig. 15 g), in addition to the stimulation of mechanoreceptors for movement control, also mechanoreceptors for bladder and rectum control are synchronously activated with the movement (Fig. 15h). Continence functions are synchronously activated with the jumping (coherent activation of bladder and movement patterns). Since, additionally, for high activation premotor spinal oscillators build up an external to the periphery, neural assemblies are directly entrained to improve their 'Eigenfrequencies' and to coordinate their firing with other oscillators (Fig. 15). The springboard has an Eigenfrequency ($f \approx 1$ Hz; $\omega = 2\pi f$), which makes a training in the entrainment region possible (Fig. 16). A jumping frequency of 1 Hz is especially efficient for the entrainment of α_3-oscillators because they have an 'Eigenfrequency' also around 1 Hz.

Repair of the phase and frequency coordination among neuron firings

A completely different contribution to learning and learning transfer is induced if the patient is exer-

cising on the special the special coordination dynamics therapy device for turning (Fig. 1D). This training of very coordinated arm, leg, and trunk movements, imposed by the device, is improving especially the impaired phase and frequency coordination of neuron firing.

Following spinal cord injury, the phase and frequency coordination becomes impaired, as turns out when comparing the coordinated firing of neurons in a brain-dead human (physiologic) with that of a patient with a spinal cord injury (Fig. 17-22). The network organization becomes deteriorated and escapes entrainment, learning, and learning transfer. The variability of the coordinated firing of neurons becomes too large to enable efficient and specific learning and learning transfer. But when patients exercise very coordinated arm, leg, and trunk movements on the special coordination dynamics therapy device for turning (on which a precise coordination between arm and leg movements is imposed by the device, to which the training individual has to adapt to), the CNS of patients can re-learn specific self-organization, that means, can re-learn more exact phase and frequency coordination among neuron firings from the device. Since the CNS network is an open system, many different very coordinated movements should be trained, not to allow the pathologic organization to escape from the repair.

Including of the measured increased variability of phase and frequency coordination among neuron firings into the coordination dynamics at the collective variable level.

Depending on the relationship between the initial coordination dynamics (so-called intrinsic dynamics, $\mathbf{F}_{intr}(\mathbf{X})$, depending strongly on the severance of the injury) and the patterns to be re-learned (termed behavioral information, $\sum c_{inf}\mathbf{F}_{inf}(\mathbf{X},t)$, which act as attractors of the coordination dynamics toward the required patterns), qualitative changes in the attractor layout occur with learning, accompanied by qualitative evidence for loss of stability. The nature of change due to learning (e.g., abrupt versus gradual) arises from the cooperative and competitive interplay between the behavioral information (supported jumping or walking of the patient) and the intrinsic dynamics.

A completely different, additional nature of necessary learning is needed in the repair of CNS injury. The impaired phase and frequency coordination among neuron firing (Figs. 20-22) has to be repaired by re-learning for proper CNS self-organization. This perturbation of CNS self-organization produces deviations from the attractor states and changes the attractor layout because of altered hard-wiring due to injury. In a first approximation, this tremendously increased variability of phase and frequency coordination can be included into the equations of motion of the collective variables and gives further understanding of pattern change in patients with CNS injury as for example the switch from a movement pattern to a spastic pattern (Fig. 23B).

In the Haken-Kelso-Bunz model, the jumping on springboard (Fig. 1C) can be described in terms of relative phase between the rhythmically moving legs. Without specific behavioral information the dynamical description is defined by a vector field (a differential equation) expressing the rate of change in relative phase, $d\varphi/dt$, as a function of the derivative of its potential, $V(\varphi)$:

$$d\varphi/dt = - dV(\varphi)/d\varphi + (Q\xi_t)^{1/2} \qquad (1)$$

were $V(\varphi) = - a\cos(\varphi) - b\cos(2\varphi)$ and $(Q\xi_t)^{1/2}$ is the phase and frequency variability of strength Q (where ξ_t is Gaussian white noise of unit variance). Zanone and Kelso (49) introduced noise in Equation 1 (from a logic point of view), because all real systems described by low-dimensional dynamics are coupled to many subsystems at a more microscopic level. One may view noise as a continuously applied perturbation that produces deviations from the attractor state. Such fluctuations are conceptionally important in dynamical modeling of phase transition or bifurcation phenomena and are essential in effecting transitions.

I included noise in Equation 1 (from the experimental point of view) because of the measured increased variability of phase and frequency coordination among the coordinated firing of neurons in the human CNS. This at the neuron level measured fluctuation of phase and frequency coordination is giving rise to phase transitions or bifurcation phenomena and is essential in causing transitions among attractor states under physiologic (small fluctuation; Fig. 20 (HT5 or normal Eigenfrequency dis-

tributions); Fig. 21B) and pathologic conditions (large variability of phase and frequency coordination; Fig. 20 (Para 2 distribution); Fig. 22). The relative stability of an attractor states is, therefore, reflected by the depth of each potential well and the strength Q of the variability of phase and frequency coordination, and the attraction of attractor states is reflected by the slope at each point of the potential curve.

The behavioral changes when jumping on springboard (Fig. 1C) are represented by the overdamped movement of a rolling ball in the potential landscape for the physiologic (Fig. 23A, Q small = little fluctuation of phase and frequency coordination) and the pathologic case (Fig. 23B,C, Q large = large variability). The increased fluctuation in the rather stable state, due to increased variability of phase and frequency coordination, will have greater probability of "kicking" the system out of attractor the basin (Fig. 23B,C), especially in the asymmetric case.

In the healthy CNS, the phase and frequency variability is small and the jumping in-phase and anti-phase are stable (Fig. 23A). Following injury, the potential landscape is deformed and the fluctuation of the jumping network states is high (Fig. 23B). The in-phase jumping is still stable in spite of the increased fluctuation, because the basin of attraction is deep. The jumping anti-phase became unstable because the basin of attraction is shallow and the increased fluctuation in the state has a greater probability of "kicking" the system out of the basin. A switch into a spastic state is also possible. In sever CNS injury (Fig. 23C); the patient cannot jump any more anti-phase because of the missing of attractors for anti-phase jumping. The jumping in-phase is still possible but unstable.

Upon performing very exact coordinated movements, imposed by devices (as for example shown in Fig. 1D), the nervous system of the patient learns to reduce the variability of phase and frequency coordination and achieves in this way a small fluctuation of the network states again as shown in Fig. 23A. The treatment (learning) progress is that the in-phase jumping in Fig. 23C and the anti-phase jumping in Fig. 23B become stable (Fig. 23A) again. Also the potential landscape will change due to the reduction of the phase and frequency variability. The important consequence for treatment is that when exercising on special devices and reducing in this way the variability of phase and frequency coordination, the patient can induce the formation of patterns again, without having trained them (learning transfer)! Upon improving the coordinated firing of neurons, a cerebral palsy child my become able to speak or may develop social behaviors.

In conclusion with respect to bladder repair, the impairment of phase and frequency coordination, measured at the neuron level in human, can be included in the coordination dynamics at the collective variable level. The decrease of the variability of phase and frequency coordination is an essential part of urinary bladder repair.

Improvement of phase and frequency coordination in the short-term memory and the urge to void

The effect of improving the phase and frequency coordination in the short-term memory (or short working memory (4)) is significant in the case of the autonomic nervous system. As soon as patients with bladder dysfunction start to exercise on the special device, the urge to void appears, even though often there is only little fluid in the bladder. Following bladder function repair this exaggerated urge to void, upon exercising on that special device, is strongly reduced. Also in healthy, the exercising on that special device improves autonomic functions in the short-tern memory. In patients with spinal cord injury, also the defecation can be improved upon exercising on that device to stop or reduce medication.

Extended equations of motion for learning

It was shown that in the equations of motion of the collective variables (or order parameters) ($d\mathbf{X}/dt = \mathbf{F}_{intr}(\mathbf{X}) + \sum c_{inf}\mathbf{F}_{inf}(\mathbf{X},t)$) that a term can be added to introduce learning in the equation of motion (44, 46). These extended equations were not used by me till now. Emphasis was in this research project to cure CNS injury (including spinal cord injury) and to understand it on the basis of human neurophysiology at the neuron level. Further, the System Theory of Pattern Formation is only a theory and can explain only a certain aspect of human CNS functioning, especially if the CNS is injured. Already the fluctuation of phase and frequency coordination

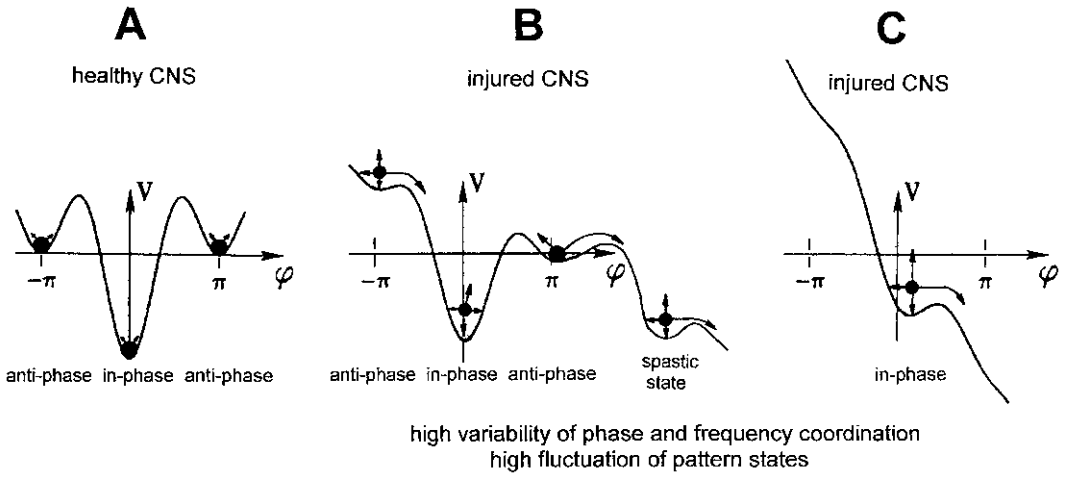

Fig. 23. – The potential, V(φ), of the coordination dynamics for jumping on springboard of a healthy (A) and injured CNS (B,C). The region around each local minimum acts like a well that weakly traps the system into a coordinated state. Behavioral changes are represented by the overdamped movement of a rolling ball in the potential "landscape". High fluctuations in the stable state, due to the high variability of phase and frequency coordination (in the injured case), will have a greater probability of "kicking" the system out of the basins of attraction (B,C) than for low fluctuations, due to small variability of phase and frequency coordination (in the healthy case (A)). In B only the in-phase jumping is stable, even though the fluctuation is high. In C there is only an attractor basin for the in-phase jumping, but the fluctuation is that high that there is high probability that the system is kicked out of the basin of attraction. The patient cannot jump any more in anti-phase and has problems to jump in-phase. The stability of jumping depends on the motor program (deepness of basin of attraction) and the fluctuation of the pattern state caused by the increased variability of phase and frequency coordination due to the injury.

among neuron firing was only formally included in the equations of motion (49).

Correspondence between movement and phase and frequency coordination dynamics

With the presented measurements at the neuron level, I introduce a new, lower level of description to the process of learning and pattern change by considering how changes in coordination dynamics at the collective variable and movement levels correspond to phase and frequency coordination at the neuron level in the human nervous system. Such correspondence between movement and phase and frequency coordination dynamics constitutes a hallmark of the dynamic pattern approach.

Different routes of learning in the healthy CNS: qualitative and quantitative network changes

In the healthy CNS there are two different routes of learning depending on the initial attractor landscape: Learning may lead to qualitative changes or to quantitative changes in the initial coordination dynamics. In the former case, the attractor layout evolves (for example) from a bistable to a multistable structure, whereas in the latter case, the attractor layout is already multistable to begin with, but is transformed to a different multistable structure. Practice stabilizes the to-be-learned pattern, causing specific modifications of the entire coordination dynamics in the direction of the task requirement. Such modifications are essentially nonequilibrium phenomena in which previously stable patterns may destabilize temporarily or permanently. How such alterations actually unfold depends on the individual coordination tendencies existing before learning (46).

Different kinds of re-learning in the injured CNS, depending on the individual coordination tendencies following injury

Pattern change and pattern re-learning involves alterations of the phase and frequency coordination

among the neurons involved in the changes of self-organization. Pattern change may thus provide information on the alterations of the phase and frequency coordination taking place during the re-learning of patterns.

In the injured CNS there are also the two upper routes of re-learning: Pattern re-learning may lead to qualitative changes or to quantitative changes in the coordination dynamics. In the former case, the number of phase relations may change between neuron firings (pattern change; Fig. 12Bc,e) and the attractor layout evolves from a monostable to a bistable or from a bistable to a multistable structure (re-learning; Fig. 3 of Ref. 43), whereas in the latter case, only the values of the phase relations change (Fig. 12Ba,b) and the attractor layout is already multistable to begin with but is transformed to a different multistable structure. The re-learning of the multistable continence and micturition structure with the sub-attractors 'bladder dyssynergia' and 'synergia' needed approximately 18 months upon coordination dynamics therapy, whereas the re-learning of the proper relative stabilities of the synergia and dysynergia for physiologic bladder control needed only 2 months (Fig. 3 of Ref. 43). The difference between qualitative and quantitative network changes cannot only be seen during re-learning, but the difference can also be quantified by the times needed for pattern enhancement and pattern change. The enhancement of the pattern 'continence' (quantitative change) needed approximately 6 ms, whereas the change from the 'continence' to the 'protection pattern' (qualitative change) needed 100 ms (Fig. 9Bb).

In comparison to the learning in the healthy CNS, there are more learning possibilities needed in the injured CNS and they do exist. There is not only learning transfer from one movement to another one (CNS symmetries, co-movement) or learning in the vegetative nervous system, but there is also learning transfer between the somatic and vegetative nervous systems, as is shown in the following article (43).

The qualitative change in re-learning the proper coordination dynamics includes also the attractor layouts of the somatic and vegetative nervous system divisions and their intermingled structure. Such learning brings about one part of the bladder repair. But the other part of bladder repair is the most qualitative re-learning of CNS repair, namely the improvement of the precision of the impaired phase and frequency coordination of neuron firing, which is partly achieved upon exercising very coordinated movements imposed by devices (Fig. 1D), and stimulating very coordinated movement induced afferent input for network entrainment.

Since in every injury, malformation, or degeneration of the CNS this phase and frequency coordination for CNS self-organization is impaired, an improvement of the coordinated firing of neurons will improve CNS functioning including those in Alzheimer and Parkinson's diseases (28). In limited cell death, the CNS can repair itself by learning. But in substantial neuron cell death, therapy for re-learning is needed. Drugs may shift equilibriums in CNS organization for better functioning but cannot repair proper phase and frequency coordination for physiologic functioning.

Learning for functional and structural repair

In psychology, learning has been studied through different windows, such as verbal learning (52), perceptual learning (51), and motor skill learning (50). Theories of learning have similarly taken many different lines of attack. Although, early on, general laws of learning were sought on the behavioral level (54, 55), a shift occurred later to neurophysiological theories of learning (53). I define re-learning in patients as the temporal evolution of the pattern dynamics in the presence of environmental information (therapy) with the intrinsic dynamics mainly depending on the severance of the CNS injury and partly on the repair stage.

Where this re-learning of urinary bladder functions does stand in the spectrum of psychophysiology when I study learning transfer from coordinated movements to autonomic functions at the pattern level, collective variable level, and neuron level? First of all, such learning is, of course, important in its own right, since 10% of the society suffers on incontinence (as on cancer).

I believe that re-learning of motor coordination and the transfer of learning to autonomic and higher mental functions provides the possibility to take the study of learning further, particularly in the old quest for laws of learning.

First, motor coordination is an overt behavior that can be measured as a graded response (rather

than categorically). This is important because graded measures of behavior may provide a natural metric for evaluating the amount of behavioral change during learning. Second, coordinated movement can be measured continuously in time, which opens the analysis of behavior to causality and dynamics. The arrhythmicity of turning, when exercising on a special device (termed coordination dynamics), could be measured (by the coordination dynamics value) during 3 years of learning and causality could be drawn to the improvement of motor coordination and to the step by step repair of hard-wired neural circuitry (Fig. 3 of Ref. 39; most likely due to a limited regeneration of the human spinal cord). Third, healthy and pathologic motor patterns can be generated without specific stimulation from the outside and can be recorded by surface EMG. Support by therapists, during treatment, can shift pathologic movements in the direction of physiologic ones and improve the motor patterns by the improved movement induced afferent input. Therefore, motor patterns are not mere transformation of patterns of stimulation. Together, the three points make it possible to discover intrinsic tendencies of coordination. The interplay of such intrinsic tendencies and learned and re-learned coordination patterns may lead to constraints on learning and, hence, lawful aspects of learning. Fourth, transfer of learning is not only taking place to another not trained movement according to symmetry properties of the CNS (58), but also to autonomic (urinary bladder) and higher mental functions (speech). Fifth, not only can patterns be learned or re-learned, but also an organization principle of the human CNS, namely the phase and frequency coordination among neuron firing can be improved or re-learned. The neuronal networks of the CNS can learn to function more specific in general. Timed firing of neurons and stability of patterns can be altered by learning. With an improved phase and frequency coordination, the patient with CNS injury can reach by intention (supported by movement-related sensory feedback or neural feedback) or spontaneously, patterns organized deeper in the complexity of CNS organization. Sixth, the hard-wired circuitry can be altered by learning to a limited extant. It was shown that learning is that powerful, that the injured (26, 27, 33), malfunctioning (31), or degenerating (28) CNS can partly be repaired. Learning at a time scale of years (not days as in bimanual coordination tasks (9, 46)) may partly repeat development (32, 33). For the repair of urinary bladder functions 2 to 3 years of movement based re-learning were needed (43). The establishment of continence in children during development needs a similar time period.

Seventh, since movement-based learning and structural repair are intertwined, a mechanism for limited structural repair could well be the stimulation of the endogenous stem cell reserves by movement-based learning. At the physical limit (range of over-reaching (36)) performed coordinated movements may stimulate stem cells in the spinal cord to replace lost key neurons for functioning or stimulate the **endogenous stem cells** in the hippocampal dentate gyrus and olfactory bulb. 'Adult born' neurons may migrate to the precise areas vacated by lost neurons (these neuronal networks are most overloaded in activity during the self-organization of physiologic patterns), presumable along processes formed by astrocytes and other structures. They then extend projections toward the denervated targets of original neurons. The migration of the 'adult-born' neurons is guided by target derived grows factors. Their secretion is stimulated by the repeated physiologic activation over months till years. If the pre- and postsynaptic activity of the original neurons and 'adult-born' neurons in the injured area has the most important role in guiding axons (and dendrites) that extend from the different neurons (and this is probably the case), then it is likely that the used endogenous stem cell reserves are located in the human spinal cord, since it would be a long distance for migration from the hippocampal dentate gyrus or olfactory bulb to the injury site in the spinal cord.

It has been reported that neocortical neurogenesis in humans is mainly restricted to development (60). The turning over of the neuron population in the adult human neocortex during the last 5 years was less than 0.07%. Even less neurogenesis we can expect to find in the human spinal cord, because of less plasticity. But plasticity (including learning) is an important aspect of the CNS and is necessary for the integration of new memories and newly learned patterns. It is also easy to see the importance of stability for the maintenance of memories (including pattern and phase and frequency coordination stability). There must be, therefore, a delicate balance between plasticity and stability.

These measurements of very little neurogenesis in the adult human brain are in accordance with the very limited structural repair induced by coordination dynamics therapy. The improvements of motor functions below the spinal cord injury level in motoric complete cervical spinal cord injury (39), however, support the view that new neurons can be built in the adult CNS, but only to a very limited extent. After 1 year of training at physical limits (with more than 30 hours therapy per week) motor functions below the injury level occurred. The consequences for therapy are that the very limited 'adult-born' neurons have to be used optimally by therapy and the self-renewal of the available stem cells has to be stimulated continuously; the patient should not stop the therapy for longer than 2 days! The optimal use of 'adult-born' and functionally integrated neurons means that all newly learned functions should be trained immediately; the therapy has to be updated continuously. The power of this learning therapy is that learning, as a part of the adaptation to the environment, is a very important function for the survival of species including human.

To optimize the structural repair, especially at the injury site, the environment of the repair site has to be conductive for continuous repair. The strategy, to trigger the cells at the injured area to express or re-express endogenous neurtrophins at appropriate levels and locations is what the therapist has to think of. Automatisms like walking or running are inborn and will get most genetic support for repair. The re-learning of fast walking may, therefore, induce the expression of repair-associated genes most efficiently. Upon walking on volition (including intention), the patient is activating the functioning uninjured network parts. The therapist adds the necessary support to bring the patient into a physiologic performance of walking and inducing thus a rather physiologic movement induced afferent input, propagating to the injury site. The natural afferent and efferent impulse patterns in the original and 'adult-born' neurons during walking are the stimulus for generating the geographical landscape of neurotrophins conductive for further structural (and functional) repair, that means self-renewing of multipotent cells, proliferation and integration. An additional application of stem cells may enhance structural repair upon coordination dynamics therapy. – The patients' CNS has to be taught by learning to repair itself.

An application of stem/progenitor cells close to the injured spinal cord (**exogenous stem cell therapy**) is unlikely to work, since the movement-based learning is missing to "tell" the stem/progenitor cells what to do. For the homing of these cells, proper information is needed. An additional application of neurotrophins may not be sufficient for the induction of structural repair, if mechanical aspects are involved in migration, proliferation, and integration and neurotrophins are working physiologically only in the ìm range (37). Grows factors would have to be delivered in sufficient quantities to have an effect but their distribution must be restricted to the site at which they are needed. One of the difficulties in recapitulating the developmental guidance factor milieu will be, therefore, to mimic the floor plate's function in the adult CNS. Further, grows cone attraction and repulsion probably depends on receptor subtypes and intrinsic states of neurons. In the case of learning and re-learning (upon coordination dynamics therapy), the (expression of) repair-associated genes take care of all these problems at the cellular level.

Eights, a repeated expression of the regeneration-associated genes over years at the physical limits of exercising may influence the self-organization of the DNA macromolecule and a window may be opened to view the nature of life from the learning perspective. Movement based learning may not only influence ontogeny (the development of children with cerebral palsy (31)), but also the phylogeny.

The most important issue in the theory of re-learning of motor, vegetative, and higher mental functions following CNS injury is the abstract nature of what has to be re-learned: Patterns have to be re-learned and the precise timed firing of neurons has to be re-learned. The jumping on springboard and other movements are exercised to re-learn movement and continence patterns (and other autonomic functions) including the transfer of learning between them. The turning on the special coordination dynamics therapy and recording device was exercised to improve the impaired timed firing of neurons.

Skill has been defined as a highly organized behavior in both space and time and the central problem of skill learning as how such organization of patterning comes about (50). The understanding that spatiotemporal patterns of behavior of many interacting neurons needs exact timing of neuron

firing and stability of the organizational patterns is foreign to that definition. Also, in the concept that movement is based on a movement plan or score, called motor program, that is established, at least in part, prior to the onset of overt movement (56), the preciseness of timed firing of neurons is missing.

The movements performed during coordination dynamics therapy are designed to repair programs, patterns, and schemata and to improve the timed firing of neurons. But the re-learning of patterns and timed firing of neurons cannot be separated. A 10-year-old boy, who suffered a severe brain injury in a car accident, was exercising daily a year long 2 hours on the special device for turning, without being able to improve the coordination dynamics values, especially for high loads. But when backward crawling, walking and running were included in the training program, the coordination dynamics values improved strongly (33).

What is actually learned upon therapy

The occurrence of transfer of learning poses the question of what is actually learned upon movement-based learning. At the movement level, patterns and pattern stabilities are re-learned. At the collective variable level, phasing patterns and stability are learned. At the neuron level, stability and certain sets (to generate attractors) of phase and frequency coordination are re-learned; the variability of coordinated firing of neurons is reduced. Since new neurons and connections are built by neurogenesis, a specific rearrangement of phase and frequency coordination is additionally performed, to integrate the 'adult-born' neurons functionally. With respect to stability of patterns and the stability of phase and frequency coordination between neuron firings, giving rise to the patterns, there is self-consistency between the collective and neuron levels of description.

Motor learning and transfer of learning in the injured CNS:

1. The amount of motor learning transfer depends on the similarity between the tasks (old standpoint). But when exercising specific movement patterns, dramatic learning transfer can be achieved from movements to bladder functioning patterns (no similar patterns) over 3 years, even though the rate of learning is probably small.
2. Learning and learning transfer are alterations in the layout of underlying coordination dynamics. Learning is a fine-tuning, selective process operating on the existing functional organization. Movement-based learning at the limits induces on the long-term structural repair probably by the activation of endogenous stem cell reserves.
3. The learning situation is entered with a certain degree of preorganization of the CNS due to predisposition and injury that clearly constraints the learning process. The rate of learning will decrease with the increase of the injury which is mainly induced by the increase of the impairment of phase and frequency coordination among neuron firing.
4. Interval training is beneficial, since phase and frequency memory is building up in quality from one series of movements to the next one. This was shown with repeated volitional activation of the same motor units in a patient with spinal cord injury, quantified by sEMG: The phase and frequency coordination did not change from one activation to the next (19). It seems that the neuronal networks remember the phase and frequency coordinations during interval training. The term short-working memory (4) may characterize more specifically this kind of short-term memory.

Theory of transfer of learning

It has long been known that practice of one part of the body in performing a skilled act increases the ability of the bilaterally symmetrical part in the same act (47). In coordination dynamics theory it was found that patterns of coordination between symmetrical parts transfer spontaneously. The spontaneous transfer of learning points to an abstract nature of learning (46).

The present knowledge of transfer of learning so far is the following: (a) The amount of transfer seems to be small and positive unless the tasks are practical identical and (b) the amount of transfer depends on the similarity between the tasks (48).

The relearning of urinary bladder functions upon exercising certain movements (jumping on springboard, exercising on a special device) (43) indicates that the amount of possible transfer of learning has by far been

underestimated. Further, the study of patients with CNS injury reveals more knowledge on CNS functioning, adaptation, and learning than studying only healthy individuals (similarly as in animal research).

Influence of movement induced afferent input on non-equilibrium phase transitions and fluctuation changes of the collective variable upon pattern shift from anti-phase to in-phase movement

Learning a bimanual coordination task was studied as a dynamical process (49). Depending on the relationship between the initial coordination dynamics (so-called intrinsic dynamics) and the pattern to be learned (termed behavioral information, which acts as an attractor of the coordination dynamics toward the required phasing), qualitative changes in the phase diagram occurred with learning, accompanied by qualitative evidence for loss of stability (phase transitions). The nature of change due to learning (e.g. abrupt versus gradual) was shown to arise from the cooperative and competitive interplay between behavioral information and the intrinsic dynamics. Theoretically predicted features of non-equilibrium phase transitions, indicative of loss of stability, accompanied the shift from one pattern (anti-phase) to the other (in-phase), including enhanced fluctuation of relative phase (49).

Upon exercising on the special coordination dynamics therapy and recording device (Fig. 1D), the individual is performing (imposed by the device) continuous coordination changes of arm and leg movements between anti-phase (trot gait) and in-phase (pace gait). Loss of stability is occurring during pattern change from one pattern (anti-phase) to the other (in-phase), quantified by increased arrhythmicity of exercising (df/dt, f = frequency) in accordance with the enhanced fluctuation in the bimanual coordination task (Fig. 1 of Ref.61).

But the coordination dynamics (arrhythmicity of exercising) of a top athlete did not show loss of stability of pattern formation when changing from the anti-phase to the in-phase pattern and healthy individuals can learn to keep the stability during pattern change, if the pattern change is imposed by a device, that means if the movement-related sensory feeedback stabilizes the changing self-organization.

A 10-year-old boy suffered a severe brain injury in a car accident (26), which could partly be repaired by coordination dynamics therapy. First the boy re-learned (beside other movements) the in-phase crawling (pace gait) and then the more difficult anti-phase crawling (trot gait). When the patient was able to perform both crawling patterns, he was asked to crawl in anti-phase and should increase the speed (the frequency) of crawling. With increasing crawling frequency, the patient switched spontaneously from the anti-phase pattern to the easier in-phase pattern, as can be observed in patients during jumping on springboard or during the performance of the bimanual coordination task.

There are two conclusions. First, very coordinately device imposed movements can qualitatively increase the learning capacity. Second, physiologic movement induced afferent input is very beneficial in learning and re-learning and can stabilize unstable patterns. More generally, coordinated bio or neuro-feedback, especially via the visual system, is increasing the rate of learning qualitatively or even quantitatively.

Frequency coordination and motor learning

Since the motoneurons of the spinal cord networks can built up an external loop to the periphery, it seems likely that also loop circuits exist between different brain parts and the periphery or other brain sites (2) for efficient entrainment and functional reorganization of the CNS. The successful brain repair upon coordination dynamics therapy is supporting this assumption. But frequency coordination between different brain parts is more than just synchronization in information processing (3). Synchronization was also observed in my measurements upon rhythmic stimulation (Figs. 10B, 11, 14, 15), but this synchronization was only transiently. The frequency coordination between the motoneurons and their driving muscle spindle and bladder stretch receptor afferents (Figs. 17, 18, 19) indicates that frequency coordination is also exerted via parts or multiples of a driving frequency (subharmonic or superharmonic coordination). Coordinated motor unit firing was recorded in patients with spinal cord injury. The precise timing between the spikes was not a synchrony, but a coordination with different phases and different (Eigen) frequencies (Figs. 4, 5

of Ref. 29). The firing of neurons in the occasional firing mode (14, 15) has not been touched in this discussion.

Further research

The substantial progress in understanding learning and transfer of learning with respect to former research (44, 46) is that the results of this paper are giving functional insights into the process of learning at the neuron level. A better understanding of learning and memory at the neuron and functional anatomy levels may allow the application of movement-based learning to repair other CNS injuries, malformations or degenerations.

The repair of the urinary bladder in severe cervical spinal cord injury is shown in the following paper (43). Since the spinal cord is part of the CNS, the physiological, pathological, and repair physiological mechanisms should also be valid in other parts of the human CNS. The applied movement-based learning therapy 'coordination dynamics therapy' was able to partly repair the injured cerebellum and brain. But since a limited regeneration of the spinal cord could even be achieved in severe cervical spinal cord injury (39) means that other tracts in the human CNS may also have the capability for limited regeneration following injury. If in very severe brain injury, the patient cannot recover from the coma any more, because the ascending reticular activating system (ARAS) is too much damaged (following possibly too late relieve of high brain pressure), a partial regeneration of the ARAS and a functional reorganization may bring some patients out of the permanent coma upon administering efficient treatment for 3 years.

But probably a repair of speech and higher mental functions in cerebral palsy can be achieved easier and should be attacked first. Mainly from the CNS repair in human patients the discipline 'human repair physiology' is getting substantial knowledge.

Ethics of CNS injury and clinical research

In nice review articles in Nature journals on the repair of spinal cord injury in human (57, 59, 63, 64) it has been emphasized that there is as yet no cure (57, page 1; 59, page 639), even though there is (22, 27, 37-39, 43) and the mechanisms that underlie recovery have rarely been definitely established, which is wrong (see this article and Refs. 21, 34, 36-39, 43). Human neurophysiology and clinical research in general and learning in specific are foreign to these articles. Such research politic ruins the progress in human repair physiology and clinical research and steels patients with CNS injury or disease the future. Clinicians have argued that "withholding a potential therapy from a patient with spinal cord injury (in connection with endogenous stem cell therapy) is in itself unethical (cited in 59, page 634). This argument is right (especially if we think of rehabilitation centres which do not want to do the step from care to cure), but proper diagnostic is necessary before, during, and after treatment. On the other hand, performing unqualified human research under the name of therapy trials is also unethical. There must be a balance between progress and safety and also financial interests have to be taken into consideration. Two of the main problems in the cure of CNS injury or disease are that human research is not properly organized world wide and only animal research is getting financial support.

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