Near-total functional recovery achieved in partial spinal cord injury (50% injury) after 3 years of coordination dynamics therapy

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Summary

The present paper explains how an 18 year old boy, who suffered an incomplete spinal cord injury (SCI) at the Cervical 5/6 levels, could achieve a near-complete recovery within 3 years of coordination dynamics therapy (CDT). The anatomically incomplete SCI was evident on MRI (Magnetic Resonance Imaging) which showed that 50% of the cord tissue was destroyed at the injury site. The administered CDT included the training of crawling, walking, running, jumping, and exercising on special CDT devices. Now 21 years old, this chronically injured young man cannot only walk independently, but he can also run and jump. He has attained full bladder control and is off all medications. The underlying mechanism contributing to this excellent recovery will have to be explained in the framework of the System Theory of Pattern Formation. In this framework the clinical improvement can be quantified in terms of coordination dynamics values, behavioural description of movement performance, analysis of motor patterns, and surface electromyography (sEMG) recorded during the movements. The impaired ability of the injured nervous system to self-organize is evidenced by deteriorated motor programs recorded with sEMG, unstable movement performances, and asymmetric attractor layouts in coordination dynamics recordings. On the other hand, the improvement of motor programs after CDT could also be measured by surface EMG, including measurements of antagonistic action of muscles and also by the improvement of the mean stability of motor patterns. These indicators of improving motor programs could be correlated with clinical improvement in certain motor performances like running and jumping. The recovery could mainly be achieved through a functional reorganisation as was indicated by the absence of significant improvement in the power of the quadriceps femoris muscles. The performances of turning on the special CDT device against high loads were diagnostic for the extent of repair of the integrative functions of the CNS. The cure of urinary bladder function is probably attributable to learning transfer from stereotyped, coordinated, integrative movements to the neural networks involved in bladder control. Since the patient received sub-optimal CDT, it took more than 3 years for the recovery. It appears that the repair of the integrative functions of the CNS need longer periods of time. But training such integrative movements is pivotal in inducing learning transfer from motor patterns to autonomic functions that resulted in the cure of urinary bladder function.

Key-words: Spinal cord injury – Coordination dynamics therapy– System theory of pattern formation – Repair – Movement stability – sEMG – Learning transfer – Integrated activity – Antagonistic muscle action – Movement symmetry – Isometric contractions

Introduction

The Coordination Dynamics Therapy (CDT), a movement-based learning therapy, has been shown to be effective in significantly improving the functioning of the injured central nervous system (CNS) in a variety of conditions like stroke (27), traumatic brain injury (28, 38), hypoxic brain injury (37), cerebellar injury (39-41), spinal cord injury (SCI) (29, 30), cerebral palsy (35), and Parkinson's disease (31, 34). To achieve even a partial cure in the above mentioned conditions, functional and structural repair

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of the damaged nervous system is required. Such repair can be brought about only by an intensive long-term therapy with 20 to 30 hours per week for nearly three years. To achieve optimal results, the efficiency of this treatment is very important. In a previous paper the author G.S. reported that the CDT could achieve a partial cure in a group of patients with spinal cord injury (30). In recent publications by the author, evaluating the effect of stem cell therapy and CDT (42, 43), it is indicated that in order to achieve a cure in severe SCI, functional reorganisation alone is inadequate and structural repair is needed for the regeneration of injured tissue to achieve significant behavioural improvement. It is important to differentiate between the structural and the functional repair. To determine what an optimal treatment for achieving structural repair is, objective measurements are essential to correlate the severity of SCI to the extent of the recovery. As far as functional repair is concerned, CDT has been shown to be effective. This functional repair is achieved by recruitment of spared spinal tract fibres and reorganisation of neural networks to generate new physiologic behavioural patterns. The measurement system of CDT is shown to be able to objectively quantify the functional repair, which correlates well with the clinical improvement. Spinal cord MRI, on the other hand, can anatomically quantify the extent of structural damage (that can be clinically correlated to the severity of SCI) and to some degree the extent of structural repair (that may be correlated to clinical recovery). Thus the effectiveness of optimal therapy for structural repair can be assessed in this way.

There are many schemes, clinical scales and scores available for categorizing the degree and severity of SCI. However they are all very gross and highly subjective. From the treatment point of view, to assess its effectiveness and for optimization of the required therapy, (required for complete cure), highly objective measurements of quantifiable parameters are needed with which the severity of the injury, the degree of impairment and also the extent of recovery can be objectively assessed. Generally, the lack of this objectivity in the treatment planning and assessment leads to suboptimal treatment, wastage of crucial time of the therapeutic window, muscle atrophy and other complications of SCI that will further hamper, delay or even block the recovery that would have otherwise been possible. Optimal treatment should be directed at inducing recruitment and functional reorganization of the spared tract fibers and surviving neural circuits.

For optimization of the treatment three steps are necessary. First, an objective quantification of the severity of the injury has to be performed. MR images depicting the extent of anatomical damage of the spinal cord (at a time when macrophages have phagocytosed the destroyed nervous tissue) seem to be a good objective indicator. Second, the severity of the injury should be correlated to the clinical outcome after specific treatment. Third, based on these outcomes, the efficiency of these treatment protocols should be compared, so that they can be suitably modified to achieve better results. All this can be achieved only with objective diagnostics, so that the inefficient treatments (directed towards maintenance therapy), placebo effect, natural recovery, and pseudo-recovery (due to manipulations like drug therapy) can be differentiated from truly efficient treatment protocols that are directed towards complete recovery and not just maintenance.

Method

Coordination Dynamics Therapy - Summary

The treatment method involves the application of different protocols of coordination dynamics therapy (CDT) for the re-learning of movements and autonomic functions. As explained earlier, CDT employs three main strategies:

(1) Training of innate automatisms like creeping, crawling, up-righting, walking, and running (in the forward as well as backward direction), and the re-training of old learned movements, which are deeply ingrained motor patterns with high stability. Training automatisms would recruit spared tract fibres and thereby induce functional reorganisation. It also probably helps in the stimulation, mobilisation, and recruitment of endogenous stem cell reserves at the injury site.

(2) The training of rhythmic, dynamic, stereotyped movements, like jumping on a springboard, should contribute to the reorganisation of spinal neuronal assemblies like premotor spinal oscillators (in some way similar to the so-called central pattern generators) and the coordinated firing between them.

(3) The training of device-imposed movements should improve the impaired time and space-coordinated firing of neurons and neural assemblies. The special CDT device for turning imposes very coordinated movements of not only arms and legs, but of the entire body, which results in a large amount of phase and frequency coordinated afferent inputs entering the spinal cord to entrain the neuronal networks. Such coordinated inputs are also partly generated when the patient trains supported, rhythmic, stereotyped movements with good performance like treadmill walking.

Neurophysiological basis of functional repair across the site of injury by re-learning using CDT

While performing turning movements on a special CDT device, the device enforces movements upon arms and legs which are very precisely coordinated. These active and passive movements result in coordinated afferent and efferent impulse traffic across the length of the spinal cord along various ascending and descending tracts. Such activation also involves segmental and intersegmental neural networks particularly in the lumbar and cervical enlargements, where the segmental centers of the stereotyped arm and leg movements are located. It is known that motoneurons and interneurons also work as coincidence detectors (34). Therefore, the more precisely the coordination of the movement is performed, the more exact the convergence of the coordinated inputs is, and the more likely the chance of motorneuronal activation. For this reason the preciseness of the coordination is extremely important in order to reach the threshold of action potential generation for communication between partly denervated neurons in injured networks. Such coordinated movements of arms and legs force required activation across the injured spinal segments. The communication across the site of injury through the surviving spared tracts is therefore stimulated. Since every injury is unique, different afferent and efferent tracts could be damaged and/or spared to various degrees in every case of SCI. It is nearly impossible to assess exactly which tracts are spared and to what degree. To activate different tracts and neuronal groups that could have been spared, many different kinds of highly coordinated movements need to be trained and over-trained to recruit these spared tract fibers. Only then can a clinically effective functional reorganization be achieved. In other words, even if there is residual anatomical connectivity seen on the MRI, CDT is required for activity dependent re-organization of spared white matter and grey matter to make this spared tissue functionally useful. As expected, the functional repair precedes the structural repair.

Structural repair: recruitment of stem cells, sprouting of axons, change of commitment

In earlier publication by the author G.S. (42, 43), it has been indicated that the functional repair is relatively less difficult to achieve than the structural repair. To induce structural repair, the training and over-training at the limits (42) of highly coordinated, integrative movements is essential. While training at the limits, when all spared white and grey matter at the site of injury is fully recruited, further improvement of performance can only be achieved through a structural repair, including the stimulation, mobilisation, and recruitment of endogenous stem cell reserves (43). The stimulated stem cells assist recovery by replacing the lost neural and glial tissue. Structural repair is further supported by enhanced sprouting and guidance of severed tracts into the distal segment, maximising plasticity in the spared and regenerating neural networks, and possibly changing the neuronal properties and the commitment of partially denervated and differently innervated neurons in response to specific activity dependent stimulation.

Generation of geographical landscape of chemoattractive and repulsive gradients to induce homing of cells and fibres

How does CDT achieve mobilisation and homing of endogenous stem cells and sprouting of fibres? Endogenous and exogenous neurotrophic factors are known to support and promote neuronal regeneration and prevent apoptosis. The secretion of neurotrophins is controlled by the expression of regeneration-associated-genes in the central and peripheral nervous system. The proper signals for expression of

these genes are provided by the appropriate downstream effectors in adult CNS. The denervation of spinal cord neurons after spinal cord injury probably hinders the expression of these genes and in turn does not allow the intrinsic reparative process to fully progress. This lack of signals from denervated downstream neurons and effectors like muscles is substituted by the coordinated proprioceptive and other inputs induced through CDT. Thus, this continuous activation of natural impulse pattern at the injury site helps in generating and maintaining the precise chemo-attractive and repulsive gradients according to the necessary geographical landscape for repair. The appropriateness of the geographical landscape with respect to distance of action (gradients) and composition of neurotrophins is important, as different neurotrophic factors and concentrations may serve different functions in neurogenesis, differentiation, connectivity, and trophism of different types of neurons. Since each spinal cord injury is unique, its geographical landscape for repair and thus the requirement of the reparative process is also unique. CDT creates these natural gradients that are conducive to specific reparative process in each case. This cannot be achieved by exogenous ad-hoc neurotrophin application therapy.

How does CDT help in recreating the proper geographical landscape? What is required during development is also needed during regeneration, namely guidance cues are required to be provided to the regenerating axon at the proper location (17), so that a proper innervation pattern can develop for the functional reorganization. After injury and denervation, these local cues, in the form of re-expression of endogenous neurotrophins across the geographical landscape, would decide the pattern of reorganization. Important automatisms are the most ingrained movements and they probably provide important signals for the landscape formation of neurotrophin expression during the development. Therefore while training and re-learning automatism as in CDT, geographically precise guidance cues for endogenous neuronal network repair are activated. This helps in the reorganization of the spared fiber tracts and neurons in the context of integrative automatisms. Therefore, it is important for the therapists to bring the patient into the pattern of movements in which all the efferent network parts are activated and that the movement induced afferent input is most physiological, so that the geographically precise endogenous signaling cues at the injury site are generated. The therapists have to feel and see the contribution of the patient to the movement and should give the additional support in order to bring the patient's movements into an optimal performance for that particular injury. The interpersonal coordination between therapists and patients has therefore to be optimal. Robot-assisted movements may compensate deficiency in the performance of the patient for that particular movement but will not help much in the repair or recovery, since the geographically landscape of chemo-attractive and repulsive gradients cannot be generated sufficiently well because of missing human-specific behavioral information during support and guidance

Repair support by the cerebellum

The cerebellum with its spinocerebellar system probably serves an important function during the relearning of movements. When the movement is initiated through cortico-spinal pathways, a copy of these efferent inputs is presented to the cerebellum for a comparison with the afferent copy of the proprioceptive, skin, and other inputs generated by that movement. Obviously, after spinal cord injury there is a vast mismatch between the intended movement and the actual movement. Depending on the extent of disruption of motor and sensory tracts and also of the spinocerebellar tracts following spinal cord injury, the cerebellum has, by reorganising efferent pathways, various possibilities to contribute to the functional repair.

A need for System Theory of Pattern Formation to explain learning transfer and pattern stability changes

The above discussion has stressed the importance of re-learning of movement patterns as one of the key therapeutic tools to achieve functional and structural repair. To further optimise the therapy protocols, a system theory of pattern formation is needed. Improvement can then be explained in terms of this theory, e.g. improvement of bladder function by learning transfer from integrative movements to autonomic functions, reduction in spasticity by

decreasing the stability of pathologic motor pattern, and reappearance of the ability to walk and run by increasing the stability of physiological movement patterns. Changes in the stability of movement patterns during the course of therapy can be measured non-invasively by coordination dynamics variables.

To assess the level of physiological organization and thus the functionality of the nervous system, an entirely different system of diagnostics has to be used than in standard neurophysiology, which focuses on measurements of single neurons or mass measurements from a group of neurons or fibre tracts in response to unphysiological stimuli like repetitive stimulation. The CDT diagnostics enable the assessment of functionally coordinated states of the nervous system in terms of the stability of different movement patterns.

System Theory of Pattern Formation for describing CNS functioning in patients

The human CNS contains billions of neurons that are interconnected forming vast, overlapping, converging and integrated neuronal networks. The versatility of human behaviour is only possible due to and can be explained by the immense complexity of these networks. A particular behaviour, either a motor or an emotional pattern, is determined by a certain pattern of activation of different parts of the many interlaced neuronal networks. The possibility of elicitation and consistency of a particular behaviour or motor pattern can be increased by increasing the synaptic (or other connection) strengths in the many pathways concerned. In the case of old learned movements, structural changes in neurons, synapses, and membranes also contribute to this facilitation of pathways. In short, a learning process involves also pattern formation within the system. During learning, the neurons in the network undergo a complex interplay of cooperation and competition that defines the pattern of activation. At the levels of neuronal assemblies and single neurons, this pattern formation is determined by phase and frequency coordination (25, 26, 32) of the participating neurons. Therefore, the learning process cannot be studied by evaluating and analysing single neurons or some synapses in a group of neurons. A radically different methodology is needed to analyse these patterns by using combined variables to describe the coordinated activity of neurons within the network.

Since behaviour is complex, changeable and needs to be modified continuously in response to changes in the internal as well as external environment, this process of pattern formation needs to be dynamic, flexible and adaptive. This dynamism is very important especially for the relearning of movements following CNS injury. CDT involves a dynamic reorganisation of the system by optimising the coordinated interplay of its component neurons and neural ensembles. Since the injury caused loss of neurons and disruption of tract fibres, different movements need to be re-learned by forming different patterns of coordinated activity of spared tract fibres and neurons. Further, since the CNS is an open system, it cannot be repaired by the training of one movement pattern, because of partial pattern escape (28). CDT focuses on the pattern formation of many neuronal circuits within the CNS, rather than the strengthening of individual muscles as contemporary physiotherapy does.

A dynamic system theory of the self-organization, pattern formation, and pattern re-organization of the human CNS was derived (16) from the concepts of synergetics (8, 10) and applied by the author G.S. to the injured, degenerating or malfunctioning human CNS to describe the forming of new different integrative patterns during coordinated activation of patterns of neuronal circuits along the neuroaxis during re-learning of physiologic movements. Collective variables or order parameters capture the collective coordinated activity of the neurons of the CNS for a certain range of movement or other patterns. The specific equations of motion (the dynamics) of these collective variables generate the time course of organizational states. A potential function (see below), derived from the equation of motion, defines the stability of different patterns, which can partly be measured by pattern change via the coordination dynamics for a certain range of movement patterns.

The collective variables can be designated by a vector **X** and the coordination pattern dynamics can abstractly be formulated by the equations of motion (46):

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

where $\mathbf{F}_{intr}$ designates the intrinsic dynamics of nervous system. These intrinsic dynamics capture the anatomical, physiological, and pathological states of the CNS and its musculo-skeletal elements.

$\Sigma c_{inf}\mathbf{F}_{inf}(\mathbf{X},t)$ represents the sum of external influences ($\mathbf{F}_{inf}(\mathbf{X},t)$) with their relative strength (c_{inf}) pertaining to each influence. The so-called behavioural information $\mathbf{F}_{inf}(\mathbf{X},t)$ includes cognitive states, emotional states, intentions, motivations, instructions, inter-personal coordination, movement support etc. While applying therapy to the patient these extrinsic influences become extremely important, because the intrinsic dynamics can be changed with them by altering the equation of motion. By modulating the behavioural information, the intrinsic dynamics of the neuronal networks can be influenced further, if CDT is not efficient any more in repairing the injured CNS (updating of the therapy).

If the behavioural information includes the exercising of extremely coordinated, integrative movements, like exercising on the special CDT device for turning, then the quality of the CNS self-organization can be enhanced by improving the exactness of self-organization, namely the precision of phase and frequency coordination between neuron firing. By improving the precision of organization of the intrinsic dynamics, that is, the specific variability of the injured networks, certain patterns do already then re-appear.

Important clinical implications for treatment of the equations of motion of the collective variables (formula 2)

1. Behavioural requirements $\mathbf{F}_{inf}$ (like intention, support, and instruction) affect the whole coordination dynamics, including stability, rather than only certain coordination patterns (46). The change of the whole coordination dynamics of the CNS by the behavioural information is the scientific basis for learning transfer between different patterns and stability changes of patterns (as for example spasticity reduction).
2. Intrinsic coordination tendencies captured by the intrinsic dynamics influence the performed pattern systematically because the degree to which intrinsic tendencies conflict or agree with the required patterns determines the variability of the performed coordination pattern (46).
3. Reduction in stability (of movement and other patterns) when intrinsic and informational requirements conflict, may lead to loss of stability and abrupt change as behavioural information is changing smoothly (46).
4. The intrinsic dynamics $\mathbf{F}_{intr}$ include vegetative and higher mental functions (these are also patterns of the coordination dynamics), which indicate that via exercising coordinated movements with support and instructions ($\mathbf{F}_{inf}$), urinary bladder function, intelligence and speech may partly be repaired following CNS injury or malformation.
5. When in an injured CNS with a certain set of behavioural information ($\Sigma c_{inf}\mathbf{F}_{inf}$) the intrinsic coordination dynamics ($\mathbf{F}_{intr}$) cannot be changed any more during coordination dynamics therapy, then this set of behavioural information has to be changed (using different $\mathbf{F}_{inf}$) or balanced differently (using different $\mathbf{c}_{inf}$) to further improve CNS organization dynamics.
6. However, the equations of motion of the coordination dynamics (formula 2) provide no information about the specific behavioural information (F_{inf}) and training intensity ($\mathbf{c}_{inf}$) with the use of which the CNS can be efficiently repaired in the given patient. We need to have detailed knowledge of the human CNS on the single neuron and neural assembly level (25), besides the knowledge at the integrative level, to find the specific behavioural information for the repair of the human CNS.

The **first novel step** in coordination dynamics therapy is the inference derived from the formula 2 of the equation of motion. It suggests that the movement training not only improves the performance of that particular movement, but also improves the other non-trainable functions by transfer of learning. These functions include vegetative functions like bladder control, speech, and higher mental functions.

Furthermore, we have an applicable tool at hand with which the stability of physiological network states can be increased (e.g. movements, continence, continuous concentration to certain tasks, speech etc). The same tool can then be used to decrease the stability of pathological network states, like spasticity. The coordination dynamics therapy partly based on the System Theory of Pattern Formation thus offers us an important theoretical basis and a practical tool

to diagnose, quantify and repair the malfunctioning human nervous system at the macroscopic level.

The drawback of the equation of motion of the order parameters (formula 2) is that it is normally not possible to find a mathematical solution to it. But by defining a potential function and by picturing the attractive states and attractors by a ball in a potential well or rather by a ball moving in a geographical landscape of attractors (46) we get a theoretical basis to measure the stability of certain coordinated movement patterns (i.e. the deepness of the potential well of an attractor) in patients with CNS injury who are receiving ongoing therapy. By studying the pattern change of certain highly coordinated arm and leg movements, while a subject is exercising on a special coordination dynamics therapy device, pattern stability can be made visible and the mean stability per one minute can be measured by the arrhythmicity of exercising (see below). Such value, called coordination dynamics value, quantifies CNS functioning objectively and non-invasively. To make the strategy of pattern formation, pattern stability, pattern measuring, and pattern picturing understandable, the procedure is demonstrated for the simple movement 'jumping on springboard', which is used during coordination dynamics therapy, especially for the repair of the urinary bladder.

Equation of motion, potential function and attractor layout for the movement 'jumping on springboard'

For the special movement 'jumping on springboard' with no behavioural information ($\Sigma c_{inf}\mathbf{F}_{inf}(\mathbf{X},t) = 0$) the equations of motion (formula 2) take the form:

$$d\varphi/dt = f_{intr}(\varphi)$$

Where φ is the relative phase between the two moving legs and is the only collective variable of this special movement.

The mathematical solution of $d\varphi/dt = f_{intr}(\varphi)$ in the Haken-Kelso-Bunz model (9) (for the approximations being made, see Ref. 6) gives the equation of motion for jumping on a springboard for the symmetric case (38):

$$d\varphi/dt = - a(t)\sin\varphi - 2b(t)\sin2\varphi$$

The so-called potential function is defined by

$$d\varphi/dt = -\partial V(\varphi,t)/\partial\varphi \quad (16).$$

By integration we obtain the potential function for jumping on a springboard:

$$V(\varphi,t) = - a(t)\cos\varphi - b(t)\cos2\varphi$$

The potential function $V(\varphi,t) = - a(t)\cos\varphi - b(t)\cos2\varphi$ can be plotted for different φ and certain ratios of the parameters a and b and is shown in Fig. 1.

The potential function shows two attractor states, namely the jumping in in-phase ($\varphi = 0$) and the jumping in anti-phase ($\varphi = \pm \pi$. Especially for higher frequencies (smaller b/a) the jumping in-phase has a higher stability (the potential well is deeper) than the jumping in anti-phase. Asymmetry (38, not tackled mathematically here) strongly changes the stabilities of the attractor states (depths of potential wells).

The human CNS, seeking for cooperative stability, slips into the collective states to which it is attracted. For jumping on a springboard these attractive states are the jumping in in-phase and in anti-phase. For crawling the attractive states are the pace (in-phase) and in the trot gait coordinations (anti-phase).

Since such a potential function can no longer be derived from more general movements, especially when the CNS is injured, malformed or degenerating, the temporal stability of different movement patterns for a characterization of CNS functioning has to be measured. This is partly possible by measuring the so-called coordination dynamics.

Geographical landscape of attractors, pattern stability and coordination dynamics values of the patients with CNS injury

The dynamics of CNS organization is partly reflected in the temporal stability of movement patterns, which can be assessed through the process of pattern change. The non-invasive measurement of pattern stability is the **second novel step** in coordination dynamics therapy. When a healthy subject or patient exercises on the special CDT and recording

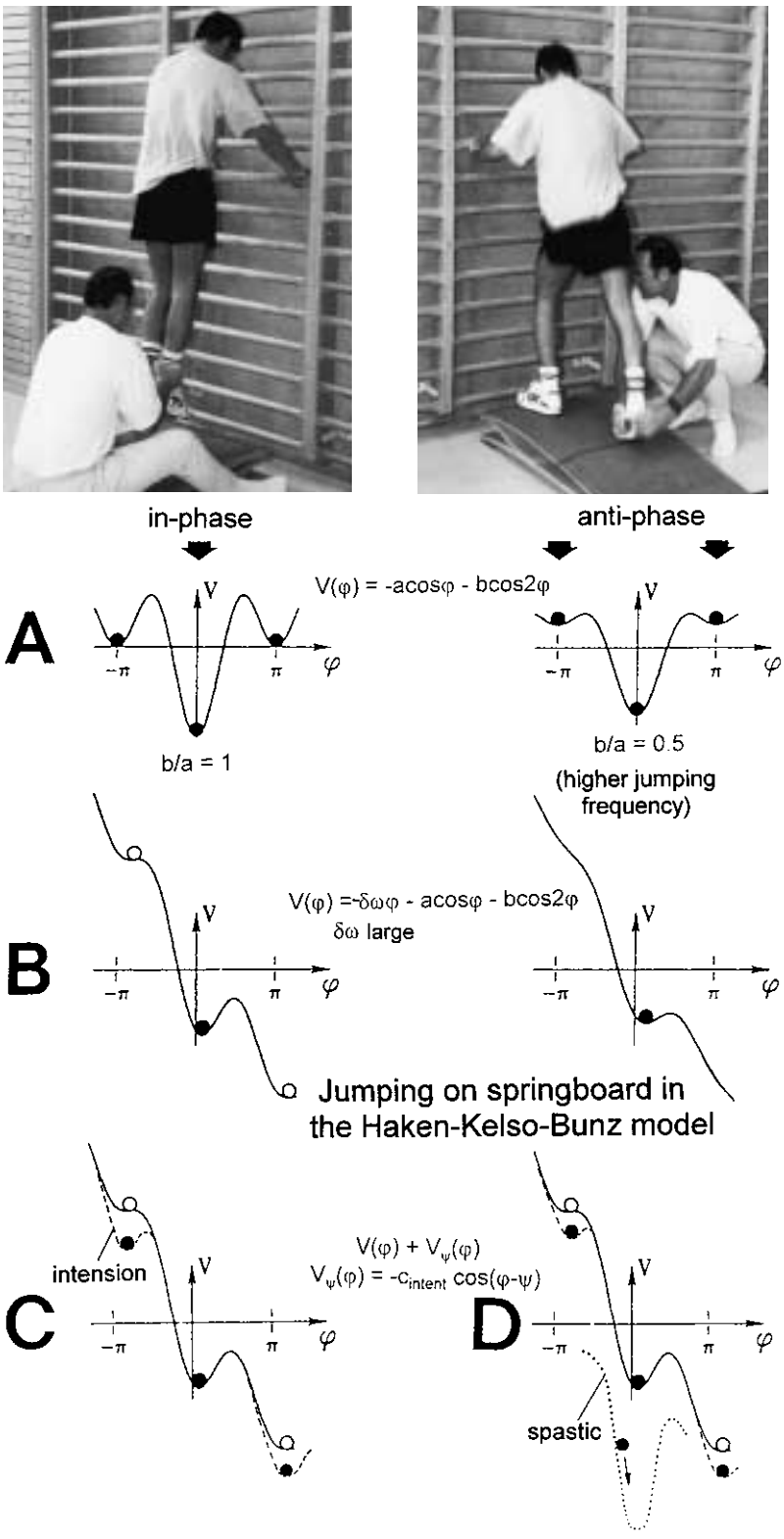

Fig. 1. – The jumping on springboard in in-phase and in anti-phase, analysed by the Haken-Kelso-Bunz model in the framework of coordination dynamics. The stability of jumping patterns is represented by the potential wells (derived from the formulas) and a ball moving in the potential landscape. Dark ball = stable state (attractor state), white ball = unstable state. In 'A', the CNS injury is small; in 'B' and 'C' the injury is more severe with impaired symmetries.

device (36, 37), the device is imposing a spectrum of continuously changing coordinations of arm and leg movements between the two attractor states 'pace gait' and 'trot gait'. On the coordination dynamics trace, the arrhythmicity of turning (df/dt or df/dt/f; f = frequency of turning) is increasing and decreasing and thus forming an attractor layout of states of stability for this range of movement patterns (see Fig. 1 of Ref.40, Fig. 7). It is possible to judge whether the attractor states are positioned at the pace and trot gait patterns or shifted away from them because of pathological or sub-optimal CNS organization. The mean arrhythmicity of turning (the mean stability) over one minute of exercising is referred to as the coordination dynamics value, and is used to quantify the quality of CNS organization with ongoing therapy. Since the quality of CNS functioning can be quantified by a single value, progress in CNS functioning can be evaluated in percentages and can be used to judge improvements in CNS functioning in patients during therapy (Fig. 3) or in children during development (36, 37).

Symmetry impairment and its repair

In addition to stability, symmetries also structure the state space of a multicomponent system with multiple patterns. Furthermore, if the symmetry is impaired (if $\delta\omega$ is large in the potential function $V(\varphi)$ in Fig. 1B) in a patient with CNS injury, a relatively lower level of fluctuation (due to noise or a perturbation) is required to 'kick' the system out of its present state than is required with a symmetric potential well (12, 13, 15, 45). The CNS organization switches more easily from movement state into spastic state or into another movement state. The movement jumping on a springboard in anti-phase becomes more difficult in the asymmetric case of CNS functioning than in the symmetric case because of stability reduction. The patient switches often into the in-phase jumping during jumping in anti-phase or cannot jump any more in anti-phase (Fig. 1).

During therapy, the movements have to be trained with respect to symmetries, in order to repair the different impaired symmetries of CNS functioning to increase the stability of the physiologic network states. Symmetry in forward-backward movement seems to be an important symmetry to be exercised. The impairment of forward-backward symmetry can be measured when the patient is exercising on the special device in the forward and backward direction (Fig. 7E,F).

Finding the behavioural information for the repair of the intrinsic dynamics

The **third novel step** in CDT and the 'System Theory of Pattern Formation for Repair' is that we can find the behavioural information ($\Sigma c_{inf}\mathbf{F}_{inf}(\mathbf{X},t)$) (the therapy) through which it is possible to change and repair the intrinsic dynamics ($\mathbf{F}_{intr}(\mathbf{X})$) of CNS organization from human neurophysiology and pathophysiology.

The most important learning transfer for bladder repair is achieved by the movement 'jumping on a springboard', even though the behavioural information 'exercising on the special device for turning' and 'supported treadmill walking' also contribute substantially to this learning transfer to re-build an attractor for physiological bladder functioning.

Since following CNS injury, movements and other functions are lost or impaired and the phase and frequency coordination of CNS self-organization is impaired, the behavioural information to be used for repair has to (1) include the re-learning of movements and other CNS functions and (2) the improvement of the time and space-coordinated firing of neurons which in turn improves the intrinsic dynamics ($\mathbf{F}_{intr}(\mathbf{X})$) of CNS organisation (see above). The behavioural information required for improving the phase and frequency coordination in the intrinsic dynamics ($\mathbf{F}_{intr}(\mathbf{X})$) is the physiological afferent input coming from the exact coordinated movements of arms, legs, and trunk while the patient is exercising on special devices with highly sophisticated mechanical precision. These types of inputs are also provided when the patient is exercising very coordinated movements like brisk walking or running.

The System Theory of Pattern Formation for Repair is mainly an abstract theory. But by using real neurophysiologic and pathophysiologic data of human CNS functioning, the theory becomes a basis of human CNS organization and reorganization by learning. Every theory, claiming that it can explain or describe human CNS functioning, must be applied to human reality for proof. The proof that

the 'System Theory of Pattern Formation for Repair' is applicable to human is given in the Result section.

Genotype-to-phenotype matching during an individual's lifetime as an integrated mechanism for repair

Development: The nervous system and other phenotypic traits are formed during ontogeny based on the genetic information stored in the cells (genotype). The information specified in the genotype determines those aspects of the nervous system which are expressed as innate behavioural tendencies and predispositions for learning. The inherited genotype can completely specify the phenotypic network; i.e. both the network's architecture and connection weights (in synapses and other connections) are genetically determined. In this case, the behaviour of the network is entirely innate and there is no learning (22). Or the genotype specifies the network's architecture, but the weights are learned (19). In a third case, what have been selected during the evolution are good initial weights for learning or good learning rates and momentums (2).

In humans, the genotype may specify the network's architecture only partly and the connection weights are learned through good weights for learning and good learning rates, apart from the automatisms to guarantee life-saving tactics, which are more or less innate. The price for the higher capacity for learning and the necessary higher specific variability and complexity of the networks is probably the strongly reduced capacity of innate structural repair. During repair, the gene expression changes will only partly specify the network's architecture. Therefore the main emphasis has to be on the movement-based learning. The different learning mechanisms may be the main stimuli for repair in human and not the innate structural repair mechanisms.

A direct genotype-to-phenotype mapping is biologically implausible. In real life, we cannot predict which phenotype will emerge from a given genotype because of the large nonlinearities present in the mapping process. If the genotype is viewed as a set of instructions, it is not the case that each of these instructions will result in a single network property. Rather, the properties of the network emerge as the result of many interactions among the various instructions and their products (20).

Genotypes can directly incorporate innate behaviours that require no learning, or they can incorporate innate predispositions to learn some behaviour. Innate behaviours can be present at birth (congenital) or they can develop during the lifetime under the control of genetically specified information. Already in simple models, neural architectures progressively structure themselves into functional subnetworks or neural modules (20). This is an important feature to model because of the measured spinal oscillators.

The stepping automatism in human is an innate behaviour present at birth, which does not require learning. The walking automatism develops later under genetic control. It is unclear whether the stepping automatism is replaced by the walking pattern or whether supraspinal networks use this stepping automatism, modify it and include it into the walking pattern. After spinal cord injury the stepping and the walking automatism mostly re-appear upon therapy. The patient of this report, who had an incomplete cervical spinal cord injury, could still walk, though with deficits. Only the pre-existent walking pattern had to be improved substantially. In the case of a patient with complete motor paralysis following severe cervical spinal cord injury (the case will be presented in the subsequent publication), the stepping automatism re-appeared upon therapy and was used to repair the walking pattern (44).

Other important processes involved in the genotype-to-phenotype mapping include cell division, cell proliferation from endogenous stem cells, and migration of neurons to reach their terminal position in the CNS. This is of special importance as these processes are now known to occur in the adult human CNS (48, 49). Another crucial property of the genotype/phenotype mapping in an individual is its temporal character. Biological development (or maturation) does not simply yield an "individual"; rather, the phenotypic individual is a succession of different phenotypic forms which are sequentially generated by the genotype in interaction with the environment. Interactions with the environment include early child reflexes such as creeping, crawling, up-righting, walking, running, balance training, visual-motor coordination, and auditory-visual-motor coordination. A model in which the genotype/phenotype mapping (i.e., ontogeny) takes place during the individual's lifetime and is influenced both

by the genotype and by the external environment has been described (21).

The structural repair that is induced in human with CDT tries also to recapitulate the normal process of development as in animal research (11). Therefore, the movement-based learning therapy has to include those movements which are performed during development to facilitate successful succession of different phenotypic forms which are sequentially generated by the genotype (creeping, crawling, up-righting, walking). Movement-based learning is therefore not only needed for functional but also for structural repair and it is of much more importance in humans than in animals.

Repair: Some capacity for neurogenesis exists in the adult CNS, which may be induced pharmacologically or by an intensive and appropriate CDT. This opens up another temporal dimension in the process of adaptation. Migration of neurons into a new position is a widespread phenomenon in the developing brain, and can also be expected to take place in the adapting CNS. So far, it is not understood what initiates, guides and arrests such migration. The positioning of the de novo neurons will be correlated with the generation of novel inputs. It is difficult to explain as to how the dendrites and the cell bodies of the novel neurons are approached by axons from supra-lesion levels, and what guides the axon of the new neuron to grow towards the more caudal neurons. Or is the growing of neurites and the formation of synapses completely random, and the learning network only makes 'sense' of the connections? One possibility for the positioning new neurons and the growing of neurits is the generation of a geographical landscape of chemoattractive and repulsive gradients by CDT to induce homing of cells and fibres (see above).

Principally, after stem cell proliferation some neurons of the identical population could assume a different function by reaching a different target or by segregating their perikarya and dendrites (and thus input) through differential migration or both. How this identity could be achieved is still unclear. Can selector genes be influenced by intensive CDT to achieve different phenotypes of neurons (14)?

Commitment changes of neurons for functional repair: Another possibility for the adaptation of neuronal network functions following CNS injury could be a change of the commitment of neurons. The injury-induced loss of input or target or both, which eliminates the constraints normally acting on the neurons, could allow them to develop a new function (5). If the commitment of neurons could be changed by CDT, then degenerative diseases like Parkinson's disease could also be improved without the building of new nerve cells. Such a commitment property change could be much more powerful with respect to neuronal network reorganization than changing the efficacies of synapses, while leaving out collective effects. In frogs, slow muscle fibres change their membrane properties (ability to generate an action potential) and excitation-contraction coupling (commitment) according to the motoneuron type they are innervated by (18, 24). The neural control of the specialization of synapse formation and membrane properties (and excitation-contraction coupling) seems to be more powerful than the changes of synapses (for example enlargement) achieved by activity changes. This frog model is of special interest because it demonstrates partial commitment changes of cells and similarities in the neural control of membrane properties between ontogenesis and repair. The power of this animal model lies in its safety to identify neural communication between different kinds of motoneurons and target cells during development and repair.

Results

Case report

A 17.5-year-old male patient suffered a cervical spinal cord injury (SCI) at C5-6 levels in a diving accident. The spinal cord injury was incomplete (ASIA grade D). Some sensory-motor functions were preserved below the level of injury. Initially the patient received conventional rehabilitation treatment and then started coordination dynamics therapy (CDT), 5 months after the injury. At the time of initiation of the CDT, this patient needed a stick as support for walking, was wearing an orthosis on the left foot and emptied the bladder with intermittent catheterization. During walking, the left heel was not touching the ground. While jumping on the springboard, his feet had to be supported by the therapist. While turning on the special CDT devise, the left hand had to be fixed.

He received nearly three years of non-optimal CDT. One year after the injury, the metal support, used for spine fixation, was removed. At the end of the 3rd year of CDT, he was able to walk, run, and even jump independently and did not need any internal or external support. He is continent again and off all medications. In that sense it can be safely said that the patient is almost cured of his quadruparesis.

In the following, the clinical aspects and the theoretical concepts behind this recovery will be explained in detail.

Quantification of the anatomical extent of the injury with MRI

Magnetic resonance imaging (MRI) of the cervical spine was performed 3 years after the accident to delineate the anatomical extent of the injury. At the site of injury the extent of loss of tissue would indicate the severity of the injury, and the presence of residual tissue would indicate the extent of spared tissue bridging the injury site that was maintaining the connectivity. The T2-weighted images (Fig. 2A) highlighted the pathology to be more extensive than what was seen on T1-weighted images (Fig. 2D), and axial images delineated a more extensive injury than the sagittal images (Fig 2A-E). By comparing these multiple multi-planar images the author estimated the spared tissue to be 50% of the cross sectional area at the site of injury. The grey matter of the central cord seemed to be more damaged than the circumferential white matter. Since in this case, the injury span was less than one vertebral level (relatively modest distance to bridge the injury site), it is possible that a small part of the visible spared tissue was actually from those tract fibres which regenerated during the course of therapy over the 3 years.

Improvement of coordination dynamics values following therapy

The progressive changes in the coordination dynamics values (mean pattern stability per minute) for loads of between 20N and 150N (and subsequently 200N) over the course of 3 years, while undergoing CDT, reflected gradual improvement in CNS functioning (Fig. 3). As explained earlier, improvement in CNS functioning was indicated by the lowering of coordination dynamics values, i.e. decreased arrhythmicity of exercising and increased pattern stability. At the beginning of CDT, as the therapy progressed, there was strong improvement in (reduction of) coordination dynamics values for loads between 20 and 150N for exercising in the forward and backward (measured intermittently) direction. This improvement was achieved in spite of non-optimal/unsupervised therapy. Subsequently the patient stopped CDT for more than half a year, and then re-started. This break in the therapy resulted in the deterioration in coordination dynamics. Interestingly, when he re-started and continued the therapy, the values improved again especially for exercising at loads of 100 and 150N. Deterioration of CDT values after stopping the therapy and improvement after restarting the therapy indicates that even after a few years of therapy the functional repair of the CNS is incomplete and not persistent. In other words, to maintain an optimal level of improvement of CNS functioning, the continuation of therapy for longer duration is essential.

One year after finishing the therapy, the high load coordination dynamics values worsened again in the patient (Fig. 3), even though the patient felt more power in arms and legs and the low load values (20N) did not increase (get worse) again. The re-increase of the high-load values further show that the CNS repair was still incomplete and not fully persistent. The patient would need a maintenance therapy of about an hour per day.

Learning transfer and integrated functions

It took the patient nearly 8 months to achieve the best performance for low-load exercising (at 20N) on the special CDT device. Similar good performance was achieved for high loads of 100N after only 24 months with ongoing therapy and after 36 months for 150N (Fig. 3).

Exercising at significantly higher loads requires recruitment of more muscle groups of arms and legs and also the trunk. Such recruitment of muscle groups of almost the entire body requires activation of almost the entire central nervous system (CNS). Thus, a widespread activation of downstream and upstream motor neurons and their relevant neuronal networks takes

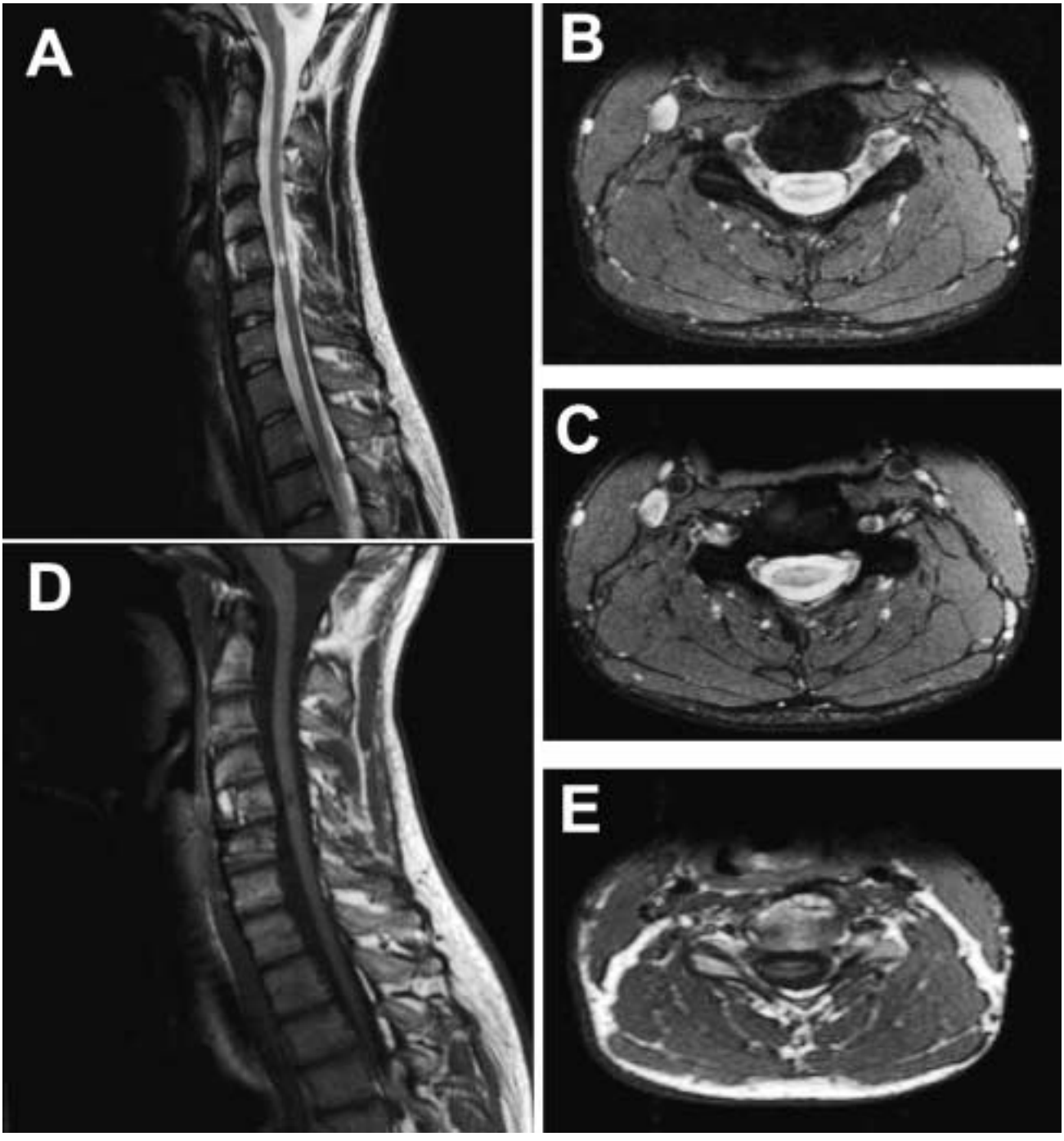

Fig. 2. – Magnetic resonance images show an incomplete spinal cord injury at C5/6 levels, 3 years after the accident, from a 20-year-old patient who jumped into unshallow water. A,D. Sagittal T2 (A) and T1-weighted (D) images. The region of hyperintense signal within the spinal cord of the T2-weighted image (light) indicates nonhemorrhagic spinal cord damage. B,C,E. Axial T2 and T1-weighted images of the spinal cord showing a more severe injury than in the sagittal plane. The authors estimated an anatomical injury of approximately 50%.

place. Such integrated network activation is important because it does not only affect the attractor basin of a particular movement, but also changes the entire attractor layout of the state-space. As the whole attractor layout changes, also the intrinsic dynamics change, which causes learning transfer from the movement to

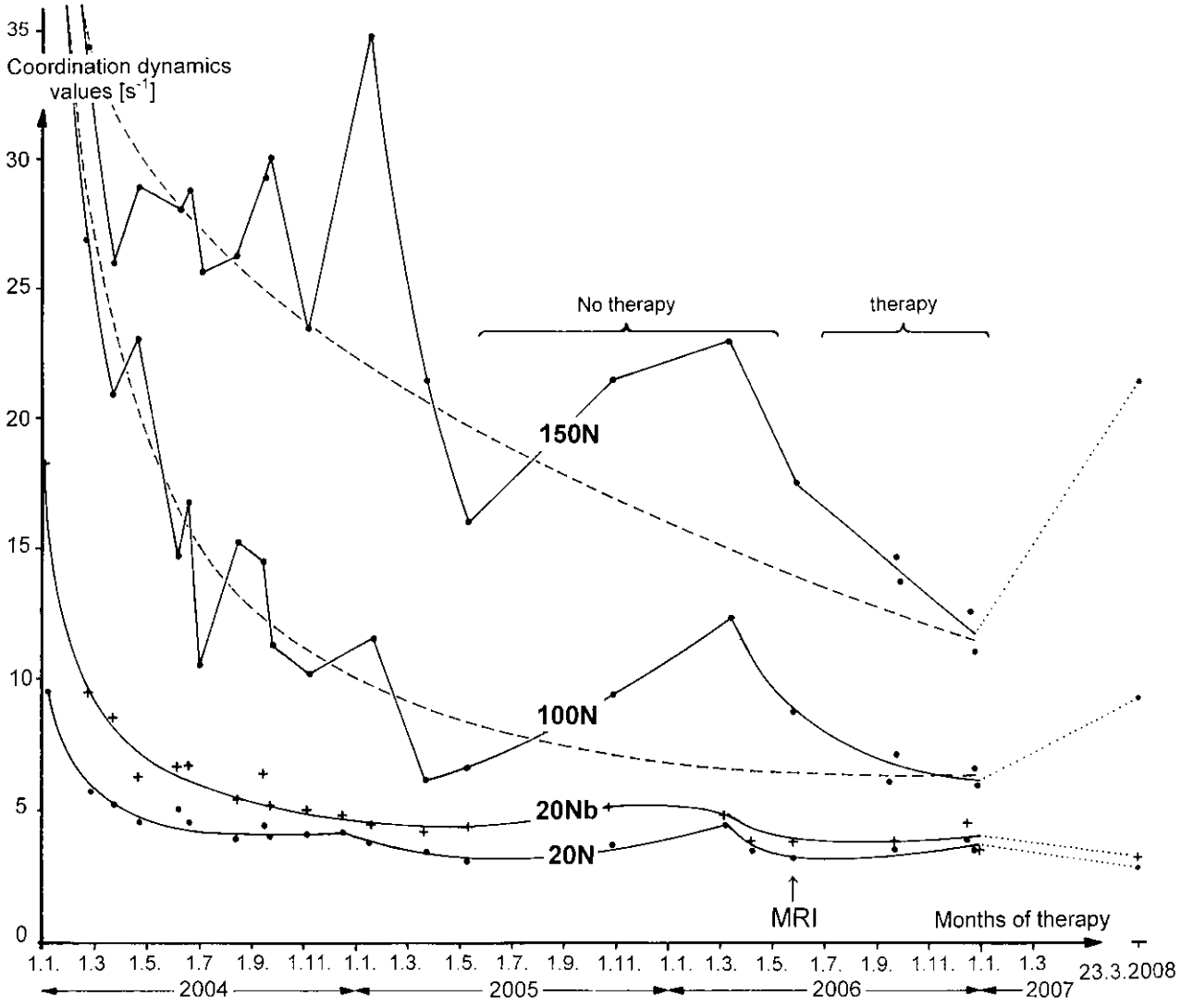

Fig. 3. – Relation of coordination dynamics values to therapy length for increasing load between 20 and 150N. The loads for forward exercising (dots, 20N, 100N, 150N) are marked at the curves (20Nb = backward exercising (crosses) at 20N). Note that with no therapy the coordination dynamics values got worse and upon administering therapy again the values improved again even 2 years after the accident. After stopping therapy, the coordination dynamics values for 100 and 150N increased again (dotted lines).

other CNS functions, like bladder control. The induction of learning transfer by integrated CNS activations is very important, since only those networks can be repaired which can be recruited, substantially activated, and trained or can be reached by learning transfer. Therefore to achieve learning transfer, exercising at higher loads is required for longer duration.

Motor improvement

According to coordination dynamics theory, if coordination dynamics values improve, there should also be visible improvement in motor performance. The motor training of the patient (which included crawling, walking and running on treadmill in the forward and backward direction, jumping on springboard,) was guided by the therapist to correct abnormal movement patterns. At the end of the 3 years of therapy, the significant improvement of coordination dynamics values (Fig 3) was accompanied by a substantial improvement in the performance of movements like running and jumping with the skipping rope (Fig. 4). Quantitatively, the times required for running 60 and 400 meter decreased and the number of jumps per series increased (Fig. 5).

Fig. 4. – Patient with an incomplete cervical spinal cord injury at C5/6 levels (severity 50%) during running in the street and jumping with a skipping-rope.

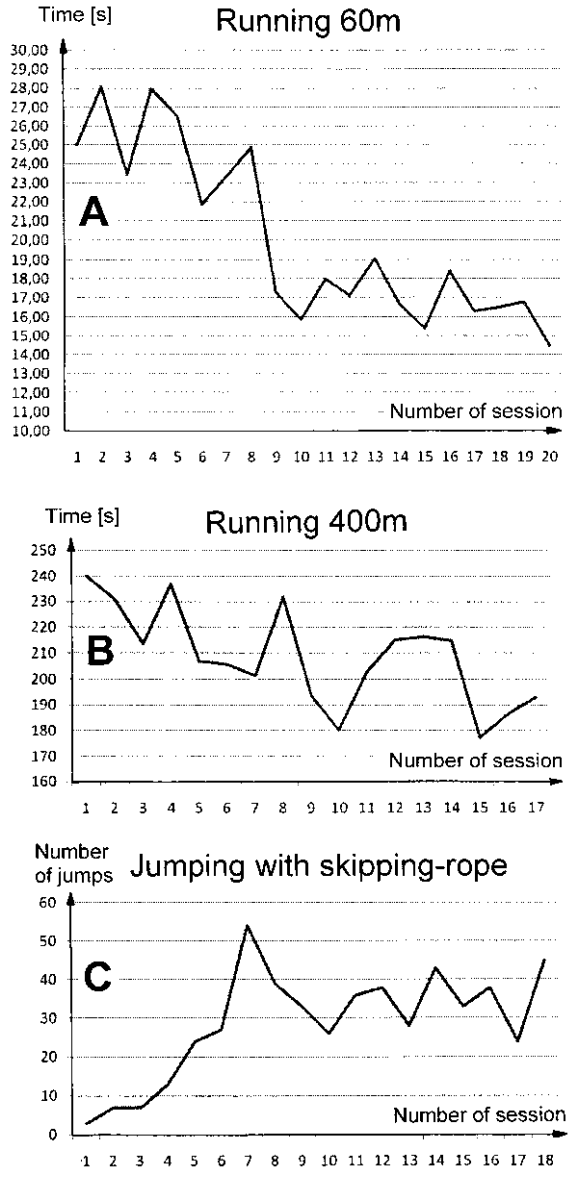

Fig. 5. – Improvement of times for running 60 and 400 m (A,B) and increase of jumps with a skipping-rope per single session (C) in relation to ongoing therapy sessions. Therapy period = second half of 2006 (see Fig. 3).

Electrophysiology (sEMG)

With ongoing therapy, coordination dynamics values can be used to quantify improvement in CNS functioning up to a percent (Fig. 3). Clinically this improvement can be correlated with the corresponding improvement in scores of activities of daily life (Fig 4,5). But for knowing and measuring the physiological and pathophysiological changes occurring at neuronal network level in the CNS with ongoing therapy, surface electromyography (sEMG) is needed. Even single neuron activity can sometimes be measured non-invasively by sEMG. The firing pattern of single neurons (motorneurons) can be studied non-invasively in terms of single motor unit potentials.

[a] Pathologic patterns of motor activation. Surface EMG was performed in this patient while he was undergoing CDT. Figure 6 shows sEMG record-

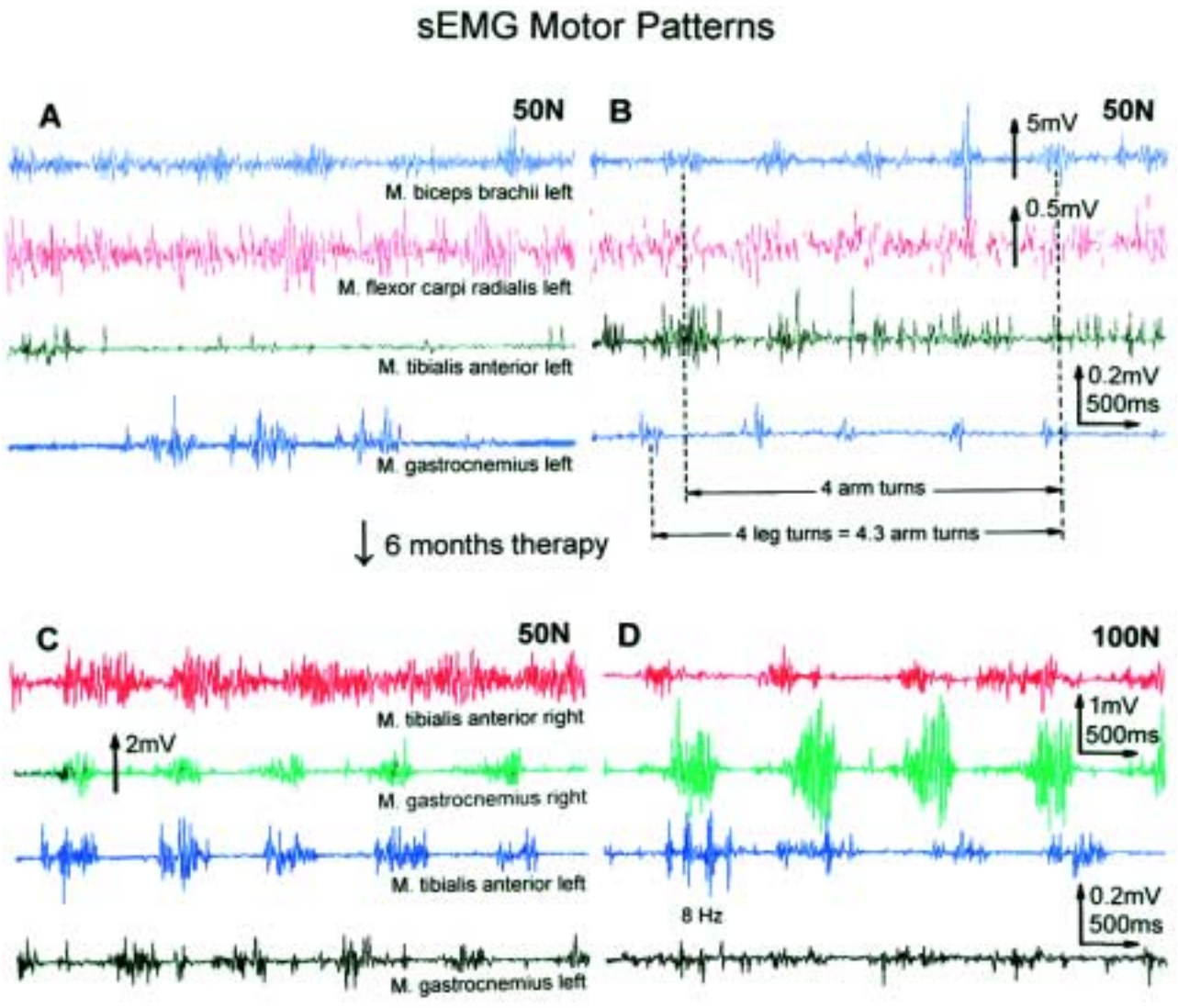

Fig. 6. – Motor patterns of arm and leg muscles recorded by sEMG for the patient with a 50% spinal cord injury at C5/6 levels at the beginning of the coordination dynamics therapy (A,B) and after 6 months of therapy (C,D). Note that the motor patterns of the left tibialis anterior and gastrocnemius muscles improved during these 6 months of therapy (from A,B to C); the patterns varied quite much from recording (A) to recording (B). The sEMG activity has a large amplitude for the biceps brachii muscle and a low amplitude for the tibialis anterior and gastrocnemius muscles (A,B) (note the different calibrations). The patterns were generated when the patient was exercising on the special coordination dynamics therapy device for turning. To measure stability differences of patterns (system theory of pattern formation), the arms turn at a higher frequency than the legs. The revolution relation between arm leavers and leg pedals is 19:18; this relation generates the changing coordination between arms and legs. The different turning frequencies of arms and legs can be seen in the sEMG patterns (B; 4 leg turns = 4.3 arms turns). Upon increasing the load from 50 (C) to 100N (D) during exercising on the special device for turning, the motor patterns of the left tibialis anterior and gastrocnemius muscles deteriorated (D): specific patterns were lost, antagonicity was lost, pathologic synchronization of premotor spinal $\cdot_1$-oscillators at 8 Hz occured; this deterioration of motor patterns stability is in accordance with the increase of the coordination dynamics values (= increase of arrythmicity of exercising) at higher loads (Fig. 3,7).

ings of motor patterns while the patient was exercising on the special CDT device at the beginning of therapy (Fig. 6A,B) and also after 6 months of therapy (Fig. 6C,D). The motor patterns were completely abnormal at the beginning of therapy (Fig. 6A,B). The amplitude of sEMG activity was high in a muscle proximal to the injury (i.e. biceps brachii), while significantly smaller in the muscles

distal to the injury site (i.e. tibialis anterior and gastrocnemius muscles). Note the difference in calibration for displaying the amplitude. The motor patterns in the muscles distal to the injury site C5/6 show obvious improvement after 6 months of CDT (Fig. 6C in comparison to Fig. 6A,B).

[b] Motor pattern stability. At the beginning of therapy, the motor patterns varied significantly while turning on the special CDT device, as can be seen in figure 6A and 6B. This variation persisted for as many as 6 months after starting the therapy. In other words, the stability of the motor pattern of the movement 'exercising on the special devise by turning with arms and legs' was very low at the beginning of therapy. This low pattern stability is also reflected in the high CDT values (high arrythmicity of exercising = low pattern stability) (Fig. 3). Clinically this motor pattern variability correlated with the instability of movement performance, observed during walking and running on treadmill at the beginning of therapy.

[c] Impairment of reciprocal relationship of antagonist muscles. The natural reciprocal relationship of agonist and antagonist muscles of the leg, namely the tibialis anterior (dorsal flexor) and gastrocnemius muscle (planter flexor), was reasonably well preserved on the left side (Fig. 6B,C) but was significantly impaired on the right side. It persisted for as many as 6 months in spite of therapy (Fig. 6D). This impairment of antagonistic muscle action contributed to the difficulty in gait faced by the patient while walking and running.

[d] Measurements of temporal stability of movement patterns by pattern change. As explained above, the sEMG motor patterns were generated and recorded when the patient was exercising on the special CDT and recording device. The mean temporal stability of these motor patterns over one minute (= coordination dynamics value = mean arrhythmicity value) was used to quantify improvements of CNS functioning with therapy (see above, Fig. 3). To measure differences in temporal stability of different movement patterns, such coordinated patterns, involving arm and leg movements, need to be generated with accuracy. This is achieved by the high precision mechanics of the special device for turning movements, when the arms turn at a slightly higher frequency than the legs. The relationship of revolution between arm leavers and legs paddles is 19:18. This difference in revolution produces the changing of coordination patterns of arm and leg movements. Such pattern change must also be seen in the sEMG motor patterns.

The way that the muscle activations changed between the left biceps brachii muscle (arm) and left gastrocnemius muscle (leg) can be seen in Fig. 6B. During 4 gastrocnemius activations (4 turns), the biceps was activated approximately 4.3 times (4.3 turns). This seemingly simple change of arm and leg movements between pace and trot gait is an extremely difficult task for the CNS to generate. All the muscle patterns of arms and legs have to be changed. And if the device is positioned further away from the trunk, then the trunk has to also perform rotating movements in coordination. Since this trunk rotation is changing with the coordination position between arms and legs, all the segmental trunk muscles change their coordination in the rostral and caudal direction. If the CNS is functioning physiologically, then the subject can turn rather easily and smoothly without stress. But if the CNS is injured, then such ongoing change of coordination's among arm, leg, and trunk muscles becomes a very difficult task for the CNS. Patients are often sweating because of the stress the CNS is facing in generating these complicated movements as the pattern keeps changing. As can be seen from Fig. 6B, during the time period of the recording, the patient's CNS could manage quite well the change of the coordination between pace and trot gait. Chaotic activation was not observed on either the biceps brachii or gastrocnemius muscle traces during the movement pattern change.

[e] Impairment of pattern formation is revealed with integrated CNS activation. Upon increasing the load of exercising on the special device from 50 (Fig. 6C) to 100N (Fig. 6D), the motor patterns of the left tibialis anterior and gastrocnemius muscles partly deteriorated (Fig. 6D). The specific patterns and their antagonistic relationship were partly lost. Pathologic synchronization of premotor spinal α_1-oscillators occurred at 8 Hz, as can be seen from the trace of the left tibialis anterior muscle (Fig. 6D). The increasing impairment of CNS self-organization with increasing load of exercising, made visible by the sEMG recordings, is in accordance with the increase of the arrhythmicity of exercising on the special CDT device for increasing load (Fig. 3,

increase of coordination dynamics values at higher loads).

Increase in temporal instability of movement patterns while exercising against high load

From the above discussion it is understandable that the increase of the coordination dynamics values (deterioration of coordination dynamics) while exercising against high load (Fig. 3), is because of the reduction in the temporal stability of movement pattern as shown in sEMG recordings. Kinesiologically, this increased temporal instability of movement pattern formation is apparent when coordination dynamics traces for 1 min are plotted against increasing load (Fig 7). As can be seen from Fig. 7, the arrhythmicity of exercising increased with increasing load. Exercising at 20 (A) and 50N (B), in the recording, the arrhythmicity varied without any specific structure. At 100 (C) and 150N (D), however, structure becomes visible in the coordination dynamics traces. Note in Fig 7, that the coordination dynamics values increased with increasing load. Upon exercising against a load of 200N in the forward direction (E), it can be seen that there is rhythmic increase and decrease of the arrhythmicity of exercising. At times, when the arrhythmicity is small, the arm and leg movement patterns have a high stability. Different patterns of coordinated arm and leg movements (produced while exercising on the special CDT device) have different degrees of stability. Those patterns which are more stable have small amplitude of arrhythmicity; they are the attractor states among different movement patterns. The unstable movement patterns (with a large arrhythmicity of exercising) are no attractor states. Sudden instabilities of movement patterns are perceived by the patient and healthy subjects as sudden increases in the resistance to smooth turning. These are sudden perturbations of CNS organisation and are felt as a stutter during smooth exercising.

Exercising at high loads reveals impairment in the symmetries of CNS organisation

While the patient was exercising against a high load of 200N, rhythmic changes of the arrhythmicity of exercising were observed during forward (Fig. 7E) as well as backward exercising (Fig. 7F). Interestingly, the location of attractor states (patterns of high stability) were seen to be situated at different locations from the calibrated states of 'pace' (P) and 'trot gait' (K), as shown in Fig. 7E,F. For forward turning, the attractor is located on right side, while for backward turning, the attractor is located on left side of the pace and trot gait patterns. This impairment of symmetry for forward-backward movements (different attractor states) became visible only with the very integrated activation of the CNS as in exercising against high load.

Improvement of symmetries of CNS organization increased pattern stability

As the impairment of symmetry is diagnosed with the highly integrated activation of the CNS, in order to improve the symmetry, the high load training of those movements is also required. As the pattern stability with respect to symmetry increases, movement performance improves (Fig 1). In the case of an asymmetric injury (and subsequent asymmetric CNS organisation, large $\delta\omega$ n the potential equation in Fig. 1B), the movement pattern 'jumping-in-antiphase' can be that unstable that the patient is unable to perform this movement. In terms of system theory, the potential well for 'jumping-in-antiphase' in the attractor layout is very shallow or does not exist any more (Fig. 1B). In our patient, initially, only in-phase jumping was possible without support. The anti-phase jumping needed assistance and strong intention (Fig. 1C,D). With training the patient re-learned to jump in anti-phase; the attractor basin for 'jumping-in-anti-phase' became deeper and the movement pattern stable and possible. At the end of therapy, the patient was even able to jump independently with a skipping rope (Fig. 4).

Repair of bladder function

Before World War II, most patients with severe spinal cord injury died because of intercurrent urinary tract infections. Needless to say that one of the most important function to be repaired in patients with spinal cord injury is the control of the urinary bladder.

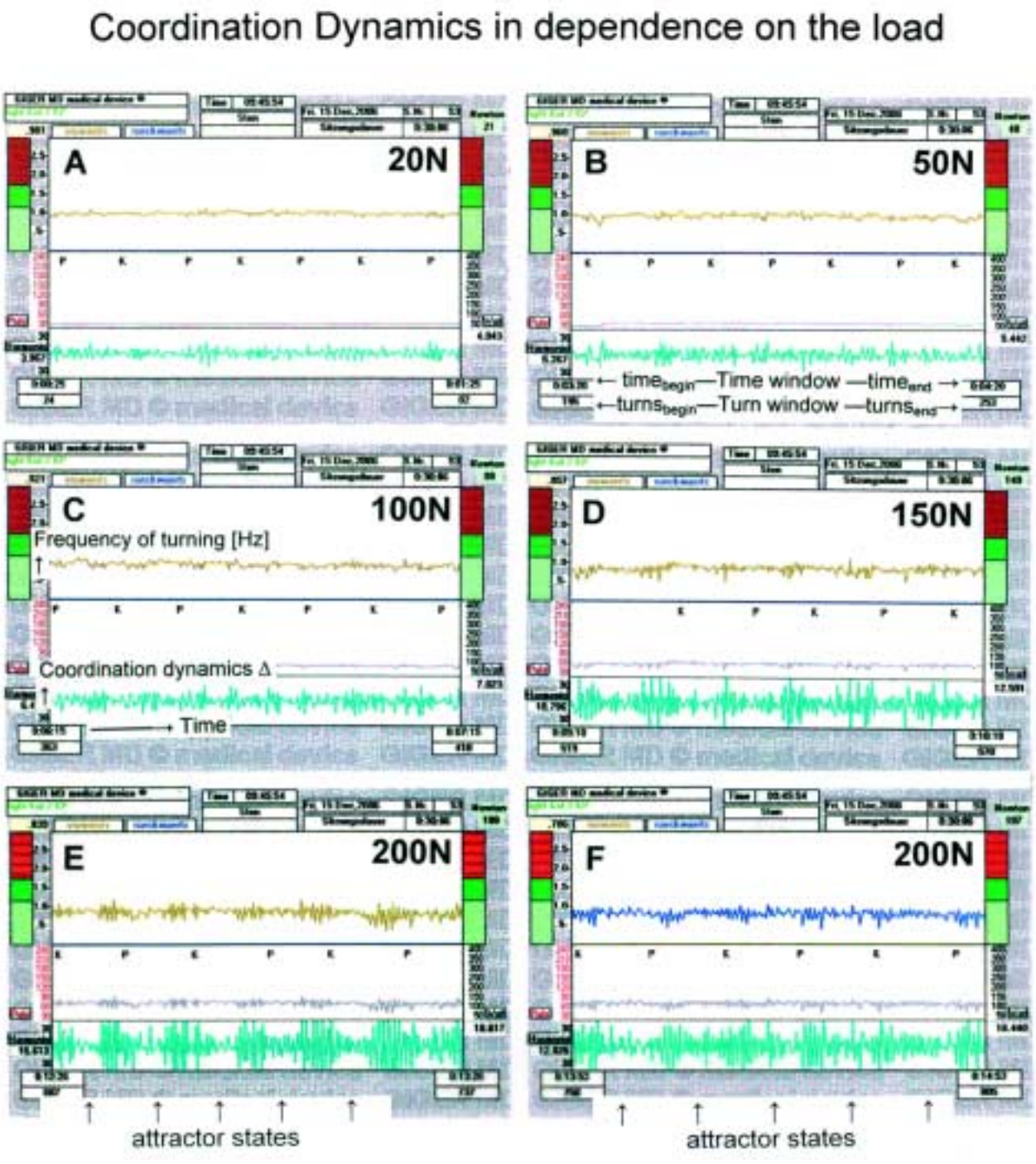

Fig. 7. – Coordination dynamics measurements in a patient with a 50% spinal cord injury upon exercising on the special coordination dynamics therapy and recording device for forward turning at increasing load from 20 to 200N (A-E). The recording sweeps are 1 min long. F. Exercising in the backward direction at 200N. Upper trace = frequency; lower trace = coordination dynamics = arrhythmicity of exercising. P = pace gait coordination, K = trot gait coordination. "P to K" and "K to P" = coordination changes from pace to trot gait and from trot gait to pace gait. Note that for 20N (A) and 50N (B) the coordination dynamics increase is more noise like whereas from 100N (C) to 200N (E) there are rhythmic increases and decreases of the coordination dynamics with the changes of the coordination. Note further that the lowest arrhythmicity of exercising (highest pattern stability = attractor state) lies for forward exercising at 200N (E) to the right side of the pace (P) and trot gait coordination's (K) and for backward exercising (F) to the left side of the pace and trot gait coordination's.

Patients are often reluctant to undergo urodynamic evaluation in a rehabilitation center, because of the fear of contracting urinary tract infection with antibiotic resistant bacteria. Development of urinary tract infection is a major set-back to the therapy, as optimal therapy is not possible in the presence of such infection. If urodynamic assessment is not available, some good practical indicators of improvement in urinary bladder function are the reduction in the incidence of urinary bladder infections and the significant reduction in the volume of post-voidal residual urine in the bladder. Residual urine can be measured by emptying the bladder with a catheter, after the patient has passed urine voluntarily. Residual urine of less than 50 ml indicates good physiological functioning of the bladder.

At the beginning of therapy our patient was using intermittent catheterisation for emptying the bladder. A few months after starting the therapy, he started emptying the bladder manually. Initially he had to compress the lower abdomen to empty the full bladder; but later, more physiological bladder emptying on volition became possible. Over 6 months of therapy the residual urine reduced from 200 ml to 50 ml. Then the patient refused further measurements to avoid unnecessary catheter trauma to the urethral epithelium.

Bowel emptying was not a major problem in our patient. It is usually required to empty the bowel only once a day and there is no risk of infection as in the case of the urinary bladder.

Since the neuronal network for primary sexual functions are located in the same sacral segment S2-S5 as are the centers of bowel and bladder function, improvement in sexual functions is expected to accompany the improvement of urinary bladder functions.

Absence of significant increase in muscle power during isometric contraction, in the face of improvement of motor performance, indicates that repair is achieved mainly through functional reorganization

Conventional concepts of neuro-rehabilitation focus on improvement of the strength of the muscles to achieve motor improvement. We tested whether the improvement of motor performance after CDT was due to the increase of muscle power. The maximal power of isometric contraction of quadriceps femoris muscle was measured.

In the spring of 2004, the maximal isometric contraction power was 411N on the right side and 378N on the left side (normal values are around 700N; the muscles had therefore only 2/3 of their normal power). In November 2006 the values were 404N on the right and 391N on the left side. In December 2006, at the end of therapy and after an intensive therapy for a few months, the maximal isometric contraction power was 416 N on the right and 386 N on the left side. In short, at the end of therapy, after 3 years, when the patient had significantly improved and was walking normally, the muscle power of the quadriceps femoris muscles remained more or less the same. Only the speed of power generation increased (improved).

Improvement in hand grip

The power of hand grip improved considerably during CDT. At the beginning of therapy, after only 4 turns on the special CDT device, the left hand would slip from the handle and was required to be fixed with a bandage. By the end of therapy, the patient could maintain good hand grip even while turning at a high load of 200N. The improvement of hand grip power was also confirmed when measured with a dynamometer. Unfortunately, subsequent readings could not be made due to logistics issues. At the end of therapy some residual deficits did remain. Considering the time profile, the authors feel that the hand grip improvement was mainly achieved through functional re-organization and not by the building of new motoneurons in the gray matter of injured cervical segments C5/7.

Discussion

Repair in the CNS and PNS

From the MR image of the cervical spine in this patient (Fig. 2) it is obvious that it is the grey matter that was mainly damaged. Obviously a part of the white matter was also damaged, considering the clinically apparent long tract deficits in this patient. As the spinal cord is arranged segmentally, the

sensory, motor, and autonomic functions of each segment crucially depend on their connections with the supraspinal centers for all conscious, voluntary or automatic actions. Damage to these supra-spinal connections, as what happens in white matter tract injury, leaves caudal spinal segments partially or totally isolated. Such de-afferentiation of the cord distal to the injury has devastating consequences. This is especially true in the case of the motoneurons of the lumbo-sacral cord. Adequate activation and control of these neurons from supraspinal centers is required to perform walking movements. In the presence of damage to the pre-existent descending pathways, activation of redundant pathways and reorganisation in spared descending tracts is required for functional repair. As described above in our patient, improvement in walking cannot be attributed to the increased strength of the quadriceps femoris muscle, which in fact remained unchanged. Therefore, the repair is unlikely to be achieved by substantial structural changes like the building of new motoneurons and connections (regeneration). It is most likely that the improved performance was due to functional repair strategies, as for example, sprouting of corticospinal axons onto the spared, long descending propriospinal tracts that would have re-established the connectivity of supraspinal segments with lumbar motoneurons. In other words, functional repair would encompass plasticity along various levels and subsystems of the CNS like the cortex, brain stem and spinal cord. For example, cortical sensory-motor areas are known to functionally rearrange (1, 23). At subcortical level, the rubrospinal system can reorganise and compensate for the deficits in the corticospinal system (23).

The functional improvement in the upper limbs is probably attributable to both structural repair and functional re-organization. The improvement in the upper limb function, seen as lowering of the functional level of injury, within 3 years of treatment is more related to recruitment of spared neurons and segmental re-organization of connections. A minor re-organization in the peripheral nervous system could have contributed to this functional recovery.

The grey matter injury at segments C5/6 caused death and loss of neurons, glia and precursor cells. The structural repair in this case would involve mobilization of precursor cells to the injury site, building of new neurons and supporting glia. Even though these neurons may get reinnervated by sprouting or regenerating cortico-spinal axons, for these connections to affect functional recovery, the peripheral axons of these motoneurons would have to grow into the arm up to the hand muscles and innervate them. This would take longer than 2 years, considering the slow speed of axonal growth (1-2 mm/day at its best). The strong improvement observed at the end of the 3rd year of therapy could have been partly due to such structural repair. This also stresses the importance of continuing the therapy beyond 2 years to achieve clinically relevant structural repair.

Importance of integrated CNS activation for learning transfer

In the treatment of patients with spinal cord injury, learning transfer is of prime importance especially for the training of those vital CNS functions like bladder control and sexual functions which cannot be trained directly. The repair of the bladder function is in fact of highest priority as that can ensure longevity of the patient by reducing life-threatening urinary tract infections which are a common cause of mortality in SCI patients.

Neuronal networks of the somatic and autonomic nervous systems are intertwined upstream and downstream and to different degrees. This sharing of networks is of advantage because only then can the autonomic networks be influenced by the training of the somatic networks.

But in order to influence and train the autonomic networks, they need to be recruited and adequately activated during movement therapy. Only an integrated activation of the CNS, upstream, symmetrical, and across many sub-systems, can achieve this effect. In this movement therapy such integrated, highly coordinated activation is achieved while the patient is exercising at high loads (like 200N) on the special CDT device. This exercising is similar to the highly integrative activation during running. It takes longer training time for improving the coordination dynamics of turning against 150 or 200N than is required for turning at 20N (Fig. 3), as large parts of CNS need to be coordinated activated and reorganized.

Within the framework of System Theory of Pattern Formation for Repair (Method), learning trans-

fer can be well understood, going back to the equation of motion. Upon influencing the intrinsic dynamics ($\mathbf{F}_{intr}$) with the behavioural information like running, jumping, and exercising on special devices ($c_{inf}\mathbf{F}_{inf}$), CNS self-organization can be modified as a whole integrated entity.

Unlike as expected in the pattern generator theory (7), while training movements like running or turning on a special device, not merely a circuitry is activated in the neuronal networks. If it would be so, then we would have to train every specific movement separately.

Only the system theory can explain learning transfer. Because of the integrated activation of the entire nervous system, not just a single pattern is formed, but the entire neuronal network is involved, which facilitates learning transfer to other functions; the whole attractor layout is changing.

Importance of symmetries in impairment and training

It is well known that asymmetric movements are less stable than symmetric ones (12, 13, 15, 40; Fig. 1). Symmetries structure the state-space of movement patterns and influence the stability of movement patterns. The impairment of symmetries in CNS functioning, following injury, is uncovered during the integrated activation of the CNS when the patient is exercising at high loads on the special CDT and recording device (Fig. 7E,F). For measuring coordination dynamics, the length of levers and pedals has to be short to reduce kinetic and rotational energies interfering with the true measurement of the arrythmicity of exercising.

Different symmetries can be improved by training symmetric, integrated, and dynamic movements like brisk walking, running, jumping, and exercising on the special device in the forward and backward direction.

The rotational and/or kinetic energies, generated by fast movements, smoothen the movements and make them more symmetrical in the presence of asymmetries. The coordinated and symmetrical afferent inputs generated by these coordinated movements enter the CNS and entrain the neuronal networks, thus correcting the asymmetries. The therapist has to anticipate, observe, support and correct the asymmetries. Such support, given by the therapist with good interpersonal coordination while the patient is jumping on springboard or when he/she is walking on treadmill, increases the symmetry of the movement and in turn the movement induced afferent input.

Pathologic single neuron firing as an important cause of impaired CNS self-organisation

As shown in the sEMG recordings above (Fig. 6D), pathologic synchronization of oscillatory firing motor units occurred intermittently at a frequency of 8 Hz. Such pathological synchronisation of pre-motor spinal oscillators occurs when the physiological mutual inhibition of motoneurons is not sufficiently strong. As analysed and reported earlier in connection with patients with Parkinson's disease (33), such pathological synchronisation starts with the oscillatory firing of α_2-motoneurons. Later, the activated α_1-motoneuron oscillators start to synchronize their firing at the same frequency and thus adding to the pathological synchronisation of the neuronal assemblies. Since α_1-motor units have larger amplitudes than α_2-motor units, the synchronisation is observed in sEMG recordings mostly only when the α_1-oscillators are activated and their firing becomes synchronized.

This synchronized firing of spinal oscillators indicates that after spinal cord injury not just motor patterns are impaired, but the physiological cooperative and competitive interplay of CNS neurons is also impaired, which makes the physiologic self-organisation of neuronal networks impossible.

Repair of bladder function

In this patient the repair of urinary bladder functions could partly be due to spontaneous recovery (autonomic functions are known to sometimes recover spontaneously, even though much later than the motor functions) and partly due to the learning transfer achieved through integrated activation of the CNS described earlier. Transfer of learning occurred from movement patterns to the patterns of urinary bladder storage and emptying. The rhythmic jumping on springboard (Fig. 1) trains the urinary bladder functions most directly. Because of the

rhythmic and dynamic load changes, exerted onto the pelvic floor during jumping, the external bladder and anal sphincters (somatic muscles), as a part of the pelvic floor, are rhythmically and dynamically activated and relaxed, and passively stretched. The inner sphincter (smooth muscle) is probably trained by the pressure changes in the detrusor muscle. This patient had no dyssynergia (co-contraction of the detrusor muscle and the external bladder sphincter) of the urinary bladder, which made it easier to improve bladder functioning.

As explained earlier in the framework of system theory of pattern formation, the behavioural information, in the form of training coordinated, integrated movements, changed the whole attractor layout of pattern formation, thus inducing learning transfer. However a far deeper understanding of the human neurophysiology of bladder functioning is essential to characterise optimal behavioural information (required training) needed for the bladder repair. A detailed analysis and discussion of this problem will be covered in subsequent papers.

Conclusions and need for progress in research and development

It is shown by the above report that a near-total cure could be achieved in the case of a partial spinal cord injury (SCI) mainly by functional reorganisation. Comparing this report with earlier reports, by the author G.S., in similar groups of patients (29,30), the reader will note a definite progress in the treatment of SCI and research in CDT over a period of time. This is reflected in better understanding of the disease, higher efficiency of treatment, and improved diagnostics.

Limitations of basic science research: There are many inadequacies in the current research in SCI. The animal research is mainly concerned with structural repair and the regeneration of the spinal cord in animals. The aspect of functional recovery is rarely understood and never analyzed. Even though structural repair is important in SCI, the researchers rarely discuss the difference in the potential of regeneration between animals and humans (4, 11, 47). In the goldfish, for example, the spinal cord regenerates spontaneously (3). But what inferences can be derived from this regeneration that can be relevant and applicable to humans? For a discussion of the differences in the potential of regeneration in the CNS and PNS between different animals and humans, the reader can see Ref. 43. The presented gross human anatomy may make a casual reader believe that the animal data are indeed applicable to humans. Moreover, the functional recovery is not measured thoroughly. Morphological data at the cellular level, like the degree and extent of growth and regeneration of axons across the injury site, is often not correlated with the functional recovery. The functioning of newly grown axon has to be proven in the context of neuronal network functions and not only by the improved movements of the treated animals, because in animals there also spontaneous recovery and functional reorganization exist, especially if only 50% of the cord is destroyed. Actually, fiber counts in different ascending and descending tracts would be needed to assess what percentage of tract fibers need to be regenerated for meaningful recovery in humans.

A need for scientific and clinical human approach: The diagnostics at the beginning, during, and at the end of therapy is of particular importance to differentiate between spontaneous recovery and the improvement achieved by the treatment. Since spontaneous recovery may occur for up to 1 year after the injury, long-term studies are needed. In case of a partial spinal cord injury, most of the recovery occurs between 2 to 6 months after injury and to a lesser degree up to 1 year. In the present patient, the treatment was started 6 months after the injury and lasted for 3 years; thus the recovery cannot be attributed to spontaneous recovery.

In the case of complete SCI (as assessed by MRI), only very limited spontaneous recovery occurs and the potential for functional reorganisation is very low, since the majority of the distal cord is disconnected from the supraspinal control. In such an injury even the combination treatment of stem cell therapy and coordination dynamics therapy did not bring about significant improvement (42, 43). However, most of the spinal cord injuries are incomplete. Even in the case of a severe injury, a significant part can be salvaged by immediate removal of compression of the spinal cord by surgery and the stabilization of the spine to minimize progressive mechanical injury. A detailed report on the repair in a patient with a severe cervical SCI, where only a

small part of the cross sectional area was preserved, will be given in a subsequent paper (44).

There are many unscientific reports, claiming miraculous recovery in SCI patients, which could very well be attributed to the spontaneous recovery. Most of the rehabilitation centres focus mainly on care and general maintenance of patients and administer prevalent (in the author G.S.'s opinion), inefficient, and arbitrary treatment that does not utilise the full potential of recovery in patients with partial SCI.

Patients want more choices than the 'no hope 'approach of conventional rehabilitation centres and the 'false hope', given by some physicians and researchers working in the field of animal research, and cell and molecular biology.

Over the last 20 years no significant conceptual or real methodical progress has occurred in the field of neuro-rehabilitation. The current science of neuro-rehabiliation is mostly out-dated, as no real review of human neurophysiology has been done for many decades. The lack of any perceived need for development and in turn the absence of any efforts in that direction has perpetuated the inefficient, out-dated and ineffective treatment modalities in the treatment delivery system. This is particularly relevant considering the fact that the young patients who suffered a spinal cord injury have nearly 50 years of their remaining life span that they have to live with a very poor quality of life, while only getting care from the current rehabilitation centres. On the other hand, with optimal and intensive coordination dynamics therapy for a few years after the injury, their quality of life can be enhanced substantially in order to achieve independence in daily activities, and most importantly physiological bladder control.

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