

# Cure of urinary bladder functions in severe (95%) motoric complete cervical spinal cord injury in human

Schalow G.

## Summary

*Severe cervical Spinal Cord Injury (SCI) leads to quadriplegia, and autonomic dysfunctions. Bladder/bowel continence, cardiovascular performance, and breathing are impaired besides movements. Even though there are no fully restorative treatments for SCI, I report about a patient, who suffered a severe cervical, motoric complete SCI, in whom urinary bladder functions were fully repaired by functional and structural repair (limited regeneration of the cord) upon 2.5 years of Coordination Dynamics Therapy (CDT). On the repair of the blood circulation (no occurrence of pressure ulcers any more), breathing and motor functions was reported earlier. The mechanism that underlies this important repair of urinary bladder functions is the learning transfer from movements to bladder functions. The human bladder repair is analyzed at the neuron level, the collective variable level (System Theory of Pattern Formation), the movement, and the clinical diagnostic level.*

*Key-words: Human – Repair physiology – Spinal cord injury – Neurotherapy – Regeneration – Urinary bladder – Learning transfer – Bladder dyssynergia – System theory of pattern formation – Development.*

## Introduction

A movement and learning therapy, called coordination dynamics therapy (CDT), has been developed and shown to be able to improve central nervous system (CNS) functioning after stroke (39), traumatic brain injury (40, 48), hypoxic brain injury (47), cerebellar injury (49-51), spinal cord injury (SCI) (41, 42, 52-54, 59), in cerebral palsy (45), and in Parkinson's disease (43, 44).

The current research in basic clinical neurophysiology and human repair physiology is aimed at developing treatment for CNS injury, especially SCI, to improve movements, autonomic, and higher mental functions.

In a previous publication it was shown that if 50% (according to MRI) of a cervical spinal cord

was spared following injury, the patient could relearn walking, running, and jumping and could become continent within two to three years. The administered CDT could partly cure this incomplete SCI at C5/6 levels mainly by a functional reorganization (53). The question is now, can in a patient with a 10 times more severe SCI the urinary bladder functions still be repaired, if the approximately spared 5% tract fibres of the spinal cord white matter do not lead to the sacral micturition centre (no spared sacral range)? A functional reorganization is most likely not sufficient any more for the bladder repair. A regeneration of the spinal cord would be needed.

It will be shown in this article that in this patient with a severe (motoric complete) cervical SCI the urinary bladder functions could be cured upon 2.5 years of optimal and intensive CDT. In 4 previous publications, the human neurophysiologic and clinical knowledge was built up to understand the dysfunction of the bladder by comparing the orga-

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nization of the neuronal networks of the sacral micturition centre between patients with SCI and a brain-dead human (55-58). The data of the brain-dead human are supposed to be rather physiologic in this respect. It was shown that the natural firing patterns of single somatic and parasympathetic neurons gave rise to the knowledge (55-58) to understand learning transfer from trained movements to urinary bladder functions (58).

It will be shown in this report that the partial solution of the century problem ‘SCI repair in human’, namely the repair of urinary bladder functions, is not a miracle or genius finding, but is the consequence of continuous human neurophysiologic and clinical research. The knowledge to repair urinary bladder functions by CDT cannot only be used in patients with SCI but also in elderly people and young women with stress incontinence.

## Method

### *Coordination Dynamics Therapy*

Schalow Coordination Dynamics Therapy (CDT) is a movement-based learning therapy. Following SCI, the self-organization of the CNS by phase and frequency coordination is impaired and movements, urinary bladder, bowel, and other functions are impaired, pathologic or lost. For the repair of the impaired phase and frequency coordination among the firings of neurons and neural assemblies, the patient is training on special CDT devices. For the repair of the impaired or lost movements, the patient trains the innate automatisms creeping, crawling, walking, and running in the forward and backward direction (for CNS symmetry (50) repair), old-learned movements (because they are deeply built into the CNS and have a high stability) and rhythmic, dynamic, stereotyped movements to repair premotor spinal oscillators. But urinary bladder and bowel functions cannot directly be repaired by training and learning. The repeated retrograde filling of the bladder was not successful in the past (private information). But within the framework of System Theory of Pattern Formation, applied to the injured CNS, urinary bladder functions can be repaired by learning transfer from coordinated movements (58).

### *Collective variable level of description of CNS organization*

The System Theory of Pattern Formation for Repair gives a theory at hand to partly understand the repair of the injured human CNS by learning and learning transfer. Its application to the somatic and autonomic nervous system divisions extends the theory to understand also the repair of urinary bladder functions. By increasing the stabilities of physiologic urinary bladder patterns (bladder synergia) and decreasing the stabilities of pathophysiologic bladder patterns (bladder dyssynergia, spasticity) continence and physiologic micturition can be achieved. The idea to see deterioration of neuronal network organization from the aspect of pattern stability has its origin in the stability changes of phase and frequency coordination following CNS injury, measured with the single-nerve fibre action potential recording method in human (35-38).

By cooperative and competitive interplay the many billions of neurons of the human CNS generate dynamics in self-organization in communication with receptors in the periphery which can explain urinary bladder functions. Schematically, collective variables or order parameters capture the collective coordinated activity of the neurons of the CNS. Specific equations of motion (the dynamics) of these collective variables generate the time course of organizational states. If the collective variables are designated by the vector  $\mathbf{X}$ , the coordination pattern dynamics can abstractly be formulated by the equations of motion (11, 61):

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

where  $\mathbf{F}_{\text{intr}}$  designates the intrinsic dynamics. The sum is over different types of so-called behavioural information,  $\mathbf{F}_{\text{inf}}$ , as environmental, memorized, or intended behavioural information. The relative strength of the different influences is parameterized by  $c_{\text{inf}}$ . With the behavioural information  $\sum c_{\text{inf}}\mathbf{F}_{\text{inf}}(\mathbf{X},t)$  (intention, instruction, treadmill walking, exercising on special devices, crawling, ...) the intrinsic dynamics  $\mathbf{F}_{\text{intr}}(\mathbf{X})$  of neuronal network organization can be changed, including the stability of different patterns, rather than certain coordination patterns itself only (61). Learning a new pattern involves alterations of the entire layout

upon CDT; attractive states are formed anew (Fig. 3, continence and micturition states) or previously attractive states vanish (Fig. 3, spastic state (spasticity of the external bladder sphincter)). The change of the whole coordination dynamics by the behavioural information is the scientific basis for learning transfer between different coordinated movements and urinary bladder functions for urinary bladder repair.

Since I measured an increased variability of phase and frequency coordination among neuron firing following spinal cord injury in the human spinal cord (58), such fluctuation of coordinated firing has to be included in the equations of motion because it alters the attractor layout and reduces pattern stability. In the Haken-Kelso-Bunz model (and it will be used again for explanation), the jumping on springboard 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 expressing the rate of change in relative phase,  $d\phi/dt$ , as a function of the derivative of its potential,  $V(\phi)$ :

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

were  $V(\phi) = -a\cos(\phi) - b\cos(2\phi)$  and  $(Q\xi_t)^{1/2}$  is the term representing the phase and frequency variability of strength  $Q$ . To reduce the fluctuation of phase and frequency among neuron firing to increase pattern stability (reduction of pattern fluctuation (ball moves less about) from Fig. 3C to Fig. 3F), necessary for urinary bladder repair, the patients have to exercise on special instruments to re-learn (improve) the coordinated firing of neurons. The exercising on special devices has to be included as behavioral information in the equations of motion (formula 2).

Since learning and learning transfer during CDT may need a few years, it is of high importance to use such behavioural information which can really repair the urinary bladder. In previous publications (55-58) the proper behavioural information for learning transfer was developed by using the single-nerve fibre action potential recording method. By analyzing natural impulse patterns in sacral nerve roots upon urinary bladder and bowel stimulations, intravesical stimulation, and movements, it was found that jumping on springboard (Fig. 1D) and exercising on

the special CDT device (Fig. 5C, D) are especially efficient to induce learning transfer from movements to urinary bladder functions (58). The jumping on springboard was designed to especially repair patterns, including transfer of learning from somatic to autonomic functions (Fig. 15 of (58)); and the exercising on the special CDT device was primarily used to reduce the variability of phase and frequency coordination and to increase thus the stability of network states by decreasing pattern fluctuation. Movements are exercised to generate a physiologic attractor layout of patterns again (Fig. 3) and the coordinated firing of neurons is trained to reduce fluctuation of pattern states (to increase pattern stability, shown in Fig. 3).

Functional and structural repair are intertwined. To induce and enhance the structural repair in the human CNS (necessary in severe SCI), a different strategy is used than in animals. In rats for example, one is trying to enhance growth of nerve fibres over the injury site. In human I induce structural repair by learning in the long-term memory and learning transfer, for which a high complexity and variability of CNS neuronal networks is needed. To induce structural repair (including network rewiring and neurogenesis) in the spinal cord and supraspinal centres by learning in the long-term memory is in accordance with current thinking about long-term memory in the cortex (75) and a relation between neurogenesis and learning (76).

#### *No indication for spontaneous regeneration in the human spinal cord*

In lower vertebrates the CNS fully regenerate following injury (4). Since ancient times it has been recognized that injury to the spinal cord is a devastating condition and that the human spinal cord does not regenerate spontaneously even after 20 to 30 years, only the complications increase. An evolutionary explanation for the 'loss' of CNS regenerative capacity of human against animals especially lower vertebrates is that this is an unselected by-product of gaining the increasingly complex nervous systems that selection pressures have favoured over time (7). CDT is using this complexity (and variability) of the human nervous system (namely the learning) to partly overcome the 'loss' of CNS regen-

erative capacity and is not going along the line of the nerve fibre growing strategy.

*Structural repair in animals: The nerve fibre growing strategy*

If the spinal cord of a rat is injured, nerve fibres try to grow over the injury site. Since the distance of growing is too short and the number of growing fibres is too small, it is tried to enhance the power of regeneration to get more fibres growing and over longer distances. Nerve growth factors are used. Applied stem cells may proliferate to neurons and their neurites may cover the injured site. If one assumes that the regeneration over the injury site is inhibited, then one tries to inhibit this inhibition. If scar tissue formation inhibits the regeneration, then the scar tissue is removed. This nerve fibre growing strategy is logic with respect to animals, because in less complex nervous systems it is often a question of growing, since nerve fibres partly regenerate to specific sites they innervated before the injury. The learning capacity on the other hand is limited. A rat cannot relearn if the nerves to extensors and flexor are transposed (62). The monkey can relearn (63) and the human can relearn quickly (68). Further, it took more than two years to cure urinary bladder function by learning in severe cervical SCI (see Results). The rat is not living much longer than the time needed for a repair in human. A learning strategy would not be very helpful for the rat CNS. Unless it is assumed that the rate of learning in rat is higher than in human.

*Structural repair in human: The neuronal network learning strategy*

The learning capacity of the human repair (59). The more coordinated the movements are performed, the more the human CNS is outstanding among the different species and there is more time for learning and re-learning than in the rat. To simplify the explanation, I assume an incomplete thoracic SCI and for the repair I concentrate the strategy on the intrinsic spinal cord networks consisting of the intumescentia cervicales, the intumescentia

lumbo-sacralis and the connecting spinal cord parts. For repair the whole subnetwork over the injury site is substantially activated (including the injured networks and the functionally surrounding not injured networks) by exercising rhythmic, dynamic, stereotyped, coordinated arm (mainly located in the networks of the intumescentia cervicalis) and leg movements (mainly located in the intumescentia lumbo-sacralis). To activate many (best all) of the spared fibres over the injury site, different coordinated arm and leg movements have to be exercised (54) as walking (Fig. 1C), running, crawling and exercising on the special CDT device. The crawling, walking, and running are innate automatisms, which may strongly induce genetic support for repair (by changing the expression of regeneration-associated genes) and the exercising on the special device (Fig. 5 C, D) is primarily improving the stability of the impaired phase and frequency coordination (due to the injury). At the beginning of therapy, the repair is mainly a functional one. But when activating the spared fibres at the limits (range of overreaching (52)), a structural repair seems to be induced. The stimulus for improving the network connectivity over the injury site (not necessarily in the spinal cord) is the specific motor learning process. Those connections should be enhanced or newly build (by sprouting, building of new nerve cells from adult-born stem cells, change of efficiencies of synapses) which are needed during that motor learning process. Ongoing pre- and postsynaptic activity in the injured area during the learning induced loop circuit formation has probably an important role in guiding the axons that extend from adult-born neurons. Local target-derived growth factors could attract regenerating fibres, or facilitate growth of regenerating fibres along highly active spared fibres, stimulated upon movement-based learning (range of overreaching (52)). Just placing stem or progenitor cells to the injury site seems not to be helpful to enhance coincidence principle of neurons (44) is used and the more of the relevant fibres and synapses can be activated at their limits at the injury site or those functionally connected to. To enhance specifically the communication over the injury site, the patient has to concentrate (for example) on the automatic walking (Fig. 1C). He/she substitutes partly missing connections in the network activa-

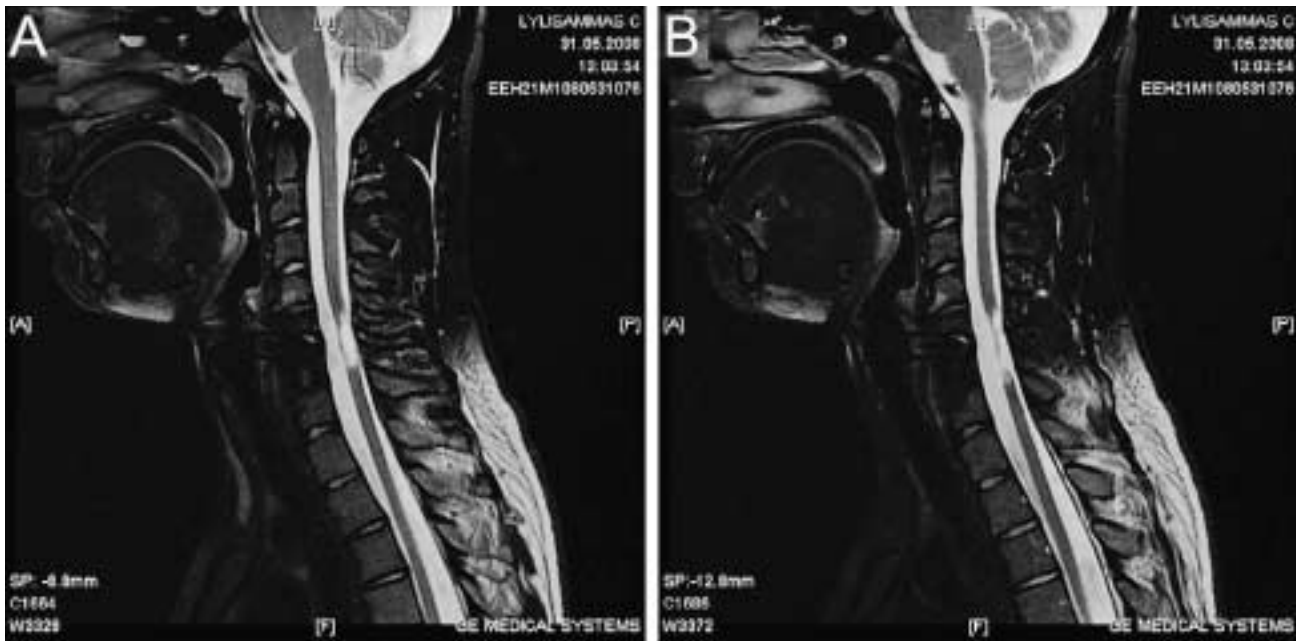


Fig. 1 A, B. – Magnetic resonance images of a severe spinal cord injury at C5/6 levels of a 20-year-old female patient after 3 years of optimal coordination dynamics therapy. Both sagittal T2-weighted images seem to show connection between the rostral and caudal spinal cord. In comparison to the images made approximately 2 years earlier, there seem to be more connections between the disconnected spinal cord parts, because at the beginning of therapy connections could be seen only on one sagittal T2-weighted image.



Fig. 1C. – Fast forward walking on treadmill of a 20-year-old patient with a severe cervical spinal cord injury at C5/6 levels (Fig. 1A,B) after 3 years of optimal coordination dynamics therapy (CDT). Leg support is given by 2 therapists. The patient is inducing the leg movement with the arms; in this moment only with the left arm. Author is on the right side of the patient.



Fig. 1D. – Same patient as in Fig. 1C upon jumping on springboard. The father is jumping behind in interpersonal coordination to increase the jumping amplitude.

tion of the automatic walking by using volitional connections in the learning process (volitional support in the cranial → caudal direction). The therapist, supporting the legs during treadmill walking, brings the patient into the intended automatic walking pattern (Fig. 1C) by adding specifically power at moments when additional power is needed during the walking cycle. In this way massive rather natural afferent impulse patterns (see Figs. 5, 15 of (58)) enter the spinal cord for processing in the caudal → cranial direction to keep the walking pattern activated and to give information to higher centres. In this way it is tried to stimulate the functional and structural repair of the injured circuits without disrupting the consolidation of the spared intact neuronal networks. The functionally recruited spared and overloaded intact fibres (and the synapses activated in (network) loop circuits) are supposed to give the stimulus for specific structural repair. The automatic walking pattern, the patient intends to perform, activates preferentially intrin-

sic spinal neuronal networks. Patients with incomplete SCI, with some sensory functions left, sometimes feel the activation of the intraspinal circuitry: “When I get into the rhythm during fast walking or running, then the moving gets easier as if I am getting wings”.

According to this reasoning, as fewer fibres are spared, according to the injury, as fewer fibres can be activated for functional and structural repair. In other words, as more severe the injury is as more difficult the structural repair will be.

By administering the neuronal network learning strategy, it is tried to ‘teach’ the injured nervous system of the patient to repair itself by learning.

In the process of organization and integration of different parts of the spinal cord during the re-learning of movement and continence patterns, the incoming natural impulse patterns from the receptors of the periphery (bottom-up activity) and supraspinal centres (top-down activity) are integrated with the endogenous activity of the spinal cord by relative phase and frequency coordination. For the integration of newly built circuits, the coordinated firing of neurons has to be continuously re-learned by exercising on special CDT devices (Figs. 2; 5C, D).

Since neurogenesis in the human CNS seems to be extremely limited (71), the movement-based learning therapy (CDT) has to be optimal and continuous to induce the building of new cells from stem cells and to induce the self-renewal of the ‘few’ available stem cells. A break of CDT for a few months will stop the structural repair and a re-start of the neurogenesis may need at least a few months.

#### *Genotype-to-phenotype matching during an individual's lifetime*

The nervous system and other phenotypic traits form during the ontogeny based on the genetic information stored in the cells (genotype). The information specified in the genotype determines aspects of the nervous system which are expressed as innate behavioural tendencies and predispositions to learn. The inherited genotype can completely specify the phenotypic network; i.e. both the network's architecture and connection weights are genetically determined. In this case, the behaviour of the network is

entirely innate and there is no learning (29). Or the genotype specifies the network's architecture, but the weights are learned (28). In still other cases, what has been selected during the evolution are good initial weights for learning or good learning rates and momentums (2). In lamprey and frog the behaviour of the network will be mainly innate. In human the networks will have good initial weights for learning.

A direct genotype-to-phenotype mapping is 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 (18).

Important processes involved in the genotype-to-phenotype mapping include cell division, cell proliferation from stem cells, and migration of neurons to reach their terminal position, especially because these processes may take place in the adult human CNS. A crucial property of the genotype-to-phenotype mapping in individuals is its temporal character. 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. 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 (19).

#### *Activating genotype-to-phenotype mapping for repair*

If there is some similarity between development and repair, the genotype-to-phenotype mapping with its temporal character has to be induced in the patient. The phenotypic repair in the patient is a succession of different phenotypic forms which are sequentially generated by the genotype in interaction with the performed different movements, instructions and concentrations. To repeat in the patient for repair the succession of different phenotypic forms macroscopically and on the cellular level, the movements are tried to administer to the patient

in the sequence creeping, crawling, up-righting, walking and running. Automatisms have to be relearning before volitional movements. In very severe brain injuries or high tetras (C3/5 SCI) the automatisms swallowing and breathing have to be trained from the beginning of therapy.

In animal repair research it is tried to recapitulate the developmental guidance factor milieu (7); in human repair research (CDT) it is tried to induce the expression of regeneration and learning-associated genes to generate different phenotypes of neurons (70) and to repair the networks.

#### *Judging the functional stage of CNS repair for therapy updating*

The stage of repair in patients is quantified by different means to understand how the patient's CNS is functioning and how to adapt the therapy for optimal repair. Objectively the quality of CNS self-organization is measured by recording the coordination dynamics when the patient is exercising on a special device (Fig. 5C, D). The stability of coordinated arm and leg movements is measured by the arrhythmicity of exercising on that device upon the continuously imposed changes of the pattern of coordination between arm and leg movements between pace (in-phase) and trot gait (anti-phase). The performance of other movements, as for example walking, is judged visually for optimal performance. Further, the supervising author is also performing patient's supported treadmill walking to feel the volitional and automatic contributions of the patient's CNS to the walking performance and to give instructions to the therapists how to assist the walking with respect to achieve optimal performance (Fig. 1C). Detailed anamneses of the patient's feelings with respect to the working of new muscles and further re-appearance of sensitivity, gives a clinical understanding of what is changing in the patient's CNS during the therapy-induced repair. By comparing the actual knowledge obtained from the patient with the continuously measured and graphically pictured parameters (as for example shown in Fig. 2) and the research knowledge and practical knowledge of similar patients in mind, the movements, performed during therapy, are updated.

## *Practical aspects*

To get real treatment quickly started in severe cervical spinal cord injury one has to stop as quickly as possible the urinary bladder infections. They make the patient weak and the treatment inefficient. The blood supply of the lower body has to be improved as quickly as possible, to avoid pressure ulcers and make the skin resistant to allow movements, otherwise already strong touching of the patient's skin will lead to bleeding. The special coordination dynamics therapy devices in the sitting and lying position (Fig. 5D; help muscles can be used) are especially useful for starting the treatment and to improve the autonomic functions to improve the blood supply of the lower body (especially the skin) and to get sufficient blood supply to the brain for keeping the patient conscious. The start of the treatment is especially difficult in severe cervical spinal cord injury, since nearly no motor functions are spared for training. As earlier the treatment is started, as less the still innervated and not innervated muscles become atrophied. There even may be a critical period for regeneration in the spinal shock phase (see Discussion). For organizational reasons the treatment is always started to late.

## **Results**

A 17-year-old female patient suffered a severe cervical spinal cord injury in a car accident. No motor functions remained below the injury level of C5/6 and the patient had impaired feelings. From the MR images the author estimated that approximately 5% of the spinal cord matter was spared. When the spinal shock faded away, it became obvious that no motor functions remained below the injury level but spot wise sensitivity remained more or less all over the lower body. Two months after the accident CDT was started. Upon 2.5 years of CDT the sensitivity improved and some motor functions returned below the injury level, indicating that some regeneration of the spinal cord had occurred. The connectivity over the injury site, according to the magnetic resonance imaging (MRI), may have increased to 8% (Fig. 1A, B). In a previous publication I reported about the improvement of the motor functions of this patient (54); the improvement was

compared to a patient in whom 50% of the spinal cord matter was spared (53). This article reports on the cure of the urinary bladder functions.

In three previous publications I reported about the pathologic changes in the sacral micturition centre following a SCI by using the single nerve-fibre action potential recording method (55-57). In a fourth publication the treatment to cure urinary bladder functions was developed by studying the induction of learning transfer from motor to urinary bladder functions (58).

## *Transient increases of the coordination dynamics values fall together with the recovery of motor and urinary bladder functions*

The changes of the coordination dynamics values are shown in Fig. 2 for 2.5 years of therapy. Transient worsening of the coordination dynamics (higher values) fall together with the improvement of motor functions and probably indicate successful regeneration of small amounts of nerve fibres. Following the largest peak of transient increase of the coordination dynamics values (indicating the strongest transient regeneration), the urinary bladder started to function rather physiologically again upon 2.5 years of CDT.

## *Time course of the improvement of urinary bladder functions upon CDT*

I report about the stages of bladder repair upon 2 years of therapy. Changes of functions of the detrusor (bladder) and the external and internal bladder sphincters are extracted from a detailed anamnesis and are pictured by an evolution of the attractor layout with the re-learning of bladder functions (Fig. 3).

1. After the operation (fixation and alignment of the broken cervical spine) a lying catheter was installed in the patient. The patient was suffering continuous infections and fever.

It is understood that the bacteria are 'creeping up' the lying catheter into the bladder (especially in female, because of the anatomy of the urethra) to give rise to ongoing infections in spite of antibiotic therapy. Before World War II (time of no antibi-



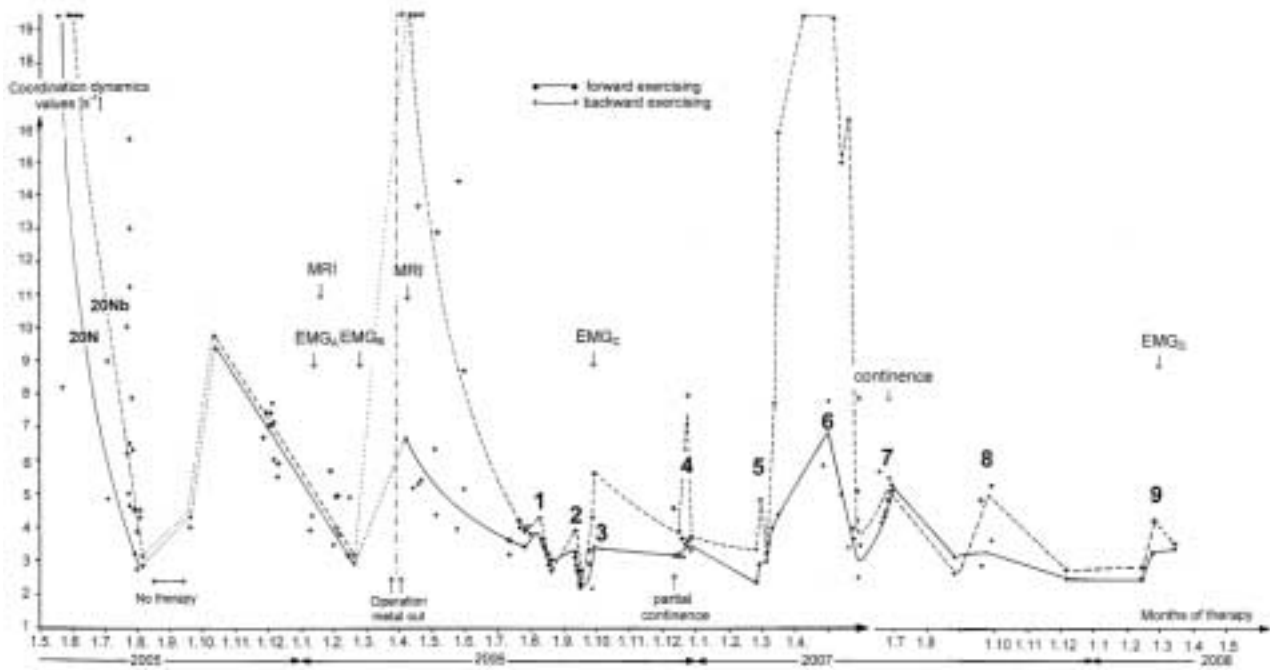


Fig. 2 – Relation of coordination dynamics values to therapy duration for a load of 20N and for exercising in the forward (lines and dots) and backward direction (20Nb; dashed line and crosses). Note that with no therapy the coordination dynamics values got worse (increased) and upon therapy they improved again. Upon metal removal the coordination dynamics values increased strongly. The transient coordination dynamics value increases (peaks ‘1’ through ‘9’ fall together with the re-appearance of certain muscle functions or specific improvements of motor and autonomic functions and indicate therefore most likely small bits of regeneration. After the large peak ‘6’ of transient coordination dynamics value increase urinary bladder functioning was re-learned.

otics), the patients were dying on such infections. It is the benefit of Sir Guttman from Breslau (6) who stopped or reduced these infections by introducing sterile intermittent catheterization. The introduction of antibiotic therapy helped further.

2. One month later (at a time when the spinal shock weaned) a suprapubic catheter was installed and no more infections occurred. But the bladder did not show any physiologic functions. The patient had no feeling of bladder fullness, no desire to void and did not feel when the fluid was leaving the bladder. The catheter was used for emptying (when opened) and storing (when closed) the urine. Since no fluid was leaving the bladder through the sphincters, the external striated sphincter was spastic (continuous contraction) and the internal sphincter (smooth muscle), as a part of the detrusor, was probably not working.

Physiologically, the internal sphincter (smooth muscle, slowly acting, probably a part of the detrusor) is keeping the continence for low and medium bladder pressure. For high bladder pressure and sud-

den bladder pressure increases (as for example during coughing), the fast external sphincter (innervated by  $\alpha_2$ -motoneurons and consisting of fast fatigue resistant muscle fibres (FR)) is contracting to secure continence. If the striated external sphincter is not working properly, patients suffer the so called ‘stress incontinence’.

3. Seven to eight months after the accident (end of 2005), the fluid was leaving the bladder by itself after a small storage phase. This means that therapy had reduced the spasticity of the external sphincter. The patient was now incontinent. So far, the spastic external sphincter had mainly stopped the fluid from leaving the bladder by its spasticity. The internal sphincter started to work a bit to allow a small storage phase. When the fluid was leaving the bladder there was first no feeling of fluid movement. Later on the patient had some feeling of fluid movement. Probably flow receptor afferents (S2) started to work. Three months later the suprapubic catheter was taken out. The patient started to use diapers.

4. 20 months after the accident (beginning of 2007, upon 18 months of therapy) the patient felt bladder fullness and the desire to void. Probably stretch (S1) and tension receptor connections (ST) started to work again. The vegetative symptoms of bladder fullness information (sweating and sudden heart rate increases, probably transmitted by plexus connections) were replaced by bladder fullness feeling and the desire to void.

5. The patient became able to press the fluid out of the bladder. To get all fluid out, the reflex bladder had to be activated a bit, by tapping, touching or massaging the skin above the urinary bladder, which is the reflex skin area for the bladder reflex. Sometimes body positioning was used to influence the bladder reflex. With these manoeuvres the desire to void reappeared and the patient could empty the bladder further.

Often patients (to whom no CDT is administered) are training the bladder reflex for emptying. The reflex is stimulated by tapping the skin above the bladder. But if, for example, the external sphincter is spastic (as in our patient), it may not be possible to generate a good functioning reflex bladder.

6. After the appearance of the desire to void, the patient became able to hold the fluid for 30 s till 1 min. Sometimes she could keep the continence better and sometimes not so good. This means that the external bladder sphincter (which can be controlled volitionally) started slowly to work, but irregularly. The feeling of bladder emptying became similar to those before the spinal cord injury.

7. 24 month after the accident (spring 2007), the bladder started to function rather physiologically again. After a storage phase the fluid came out on volition. The detrusor started to work fully. But if the patient was pressing too much at the end of bladder emptying to get all fluid out, the external sphincter contracted. The external sphincter co-contracted with the detrusor. Detrusor-sphincteric dyssynergia of the urinary bladder occurred. But when she then activated the reflex bladder by tapping or touching the reflex bladder area, the desire to void reappeared and she could empty the bladder fully. The rest urine was not measured.

At this stage of bladder repair two patterns existed: the synergia of the bladder, in which the detrusor and external sphincter contracted antagonistically, and the dyssynergia of the bladder, in

which the detrusor and the external sphincter co-contracted. The synergia pattern was for emptying the bladder and the dyssynergia pattern was the pathologic pattern. The pathologic co-contraction of the external sphincter with the detrusor occurred more easily when there was less fluid in the bladder and the patient had to press more (inducing stress to the CNS).

Physiologically also both bladder emptying patterns do exist. The synergia pattern is for emptying the bladder and the dyssynergia function is for stopping the micturition. But both patterns are under volitional control.

8. Upon 2 years of coordination dynamics therapy (26 months after the accident) the patient was full continent again and could empty the bladder on volition. The time interval from the first feeling of the desire to void to the situation that the fluid was coming out by itself (including 4 times of occurrence of the desire to void) was one hour. The patient did not use diapers any more. The patient had never used drugs which are supposed to improve urinary bladder functions. The repair of urinary bladder functions was achieved by the re-learning of urinary bladder functions including transfer of learning from the movements jumping on springboard, treadmill walking and exercising on the special CDT device for turning (Fig. 5D). The strong improvement of urinary bladder functions occurred, when the coordination dynamics values strongly increased (got worse) (Fig. 2), indicating regeneration.

For patients with incomplete spinal cord injuries, it is very important how long they can hold the urine from the first desire to void till to the moment when the fluid comes spontaneously. Can they safely reach the WC or not? The improvement of bladder functioning can also be judged by how long the patient can hold the fluid following the first desire to void. In this case it was 1 hour after 2 years of CDT.

The feeling of the lower abdomen, which was poor after the accident, improved also strongly at the time of full bladder repair. The patient felt again the lower abdomen very good (inside and outside as the patient reported) and felt also again the working of the abdominal muscles. At that time, also the finger functions got a tiny bit better and her supported treadmill walking improved. During walking on treadmill, and during other movements, the patient got goose-pimples all over the body. It seems that

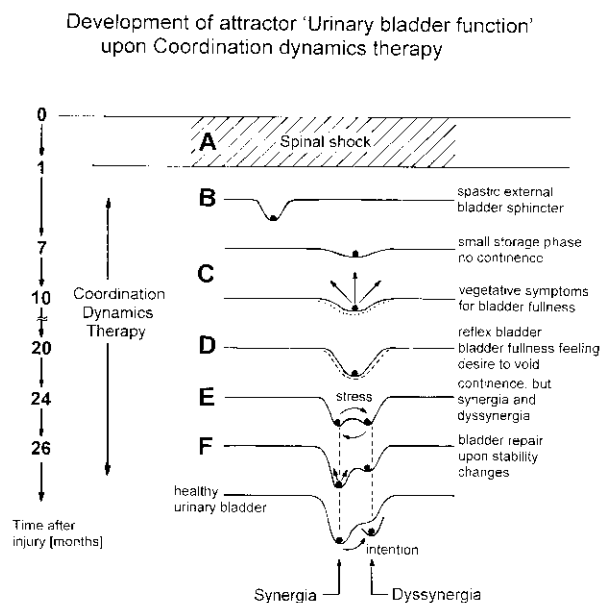


Fig. 3 – Evolution of the attractor layout of bladder functioning induced by learning transfer from movements to bladder functions upon CDT. The region around each local minimum of the potential landscape acts like a well that weekly traps the system into a coordinated state. Black balls correspond to stable minima of the potential. With learning the pattern ‘spasticity of the external bladder sphincter’ vanishes and the patterns for bladder functioning (‘synergia’ and ‘dyssynergia’) appear anew and gain their physiologic stability (physiologic deepness of each basin of attraction). The corresponding attractor layout for physiologic bladder functioning is given. Fluctuation of pattern state (the black ball) (C), and their decrease (F), due to the impairment of phase and frequency coordination of neuron firing, is pictured in ‘C’ and ‘F’ by long and short arrows. Dotted and dashed lines indicate the re-occurrence of bladder sensation. Note that more than two years of optimal CDT were needed for bladder repair.

an overall improvement of vegetative and somatic functions occurred at the time of full bladder repair.

#### *Attractor layout changes during urinary bladder repair*

Within the framework of System Theory of Pattern Formation, the repair of the urinary bladder functions can be understood and pictured by the changes in the attractor layout.

One month after the injury, when the spinal shock faded away (Fig. 3A, only the pathologic bladder pattern ‘spasticity of the external sphincter’ was present (Fig. 3B). Six to 10 months later, the spas-

ticity of the external sphincter reduced and a small storage phase of the bladder re-appeared as a first sign of bladder repair (Fig. 3C). 20 months after the operation, the reflex bladder pattern organized itself with bladder fullness feeling and the desire to void (Fig. 3D). 24 months after the accident, the attractor layout showed two attractors, the bladder synergia (the detrusor action inhibits the external sphincter) and the dyssynergia (co-contraction of detrusor and external sphincter) (Fig. 3E). The state of the system (pictured by the ball) switched easily from the attractor synergia to the attractor dyssynergia. 26 months after the accident, the stability of the attractor synergia had increased and the stability of the attractor dyssynergia had decreased (Fig. 3F). On volition (intention), the micturition could be induced and stopped as in healthy individuals.

### **Conclusion**

Upon 2.5 years of coordination dynamics therapy urinary bladder functions could be cured in severe cervical SCI. Since the injury was motoric complete and the cord was ‘free’ in the spinal canal (Fig. 1A, B), some regeneration in the human spinal cord should have occurred.

### **Discussion**

#### *Integrative functions and central pattern generators for urinary bladder repair*

It was shown in this patient that urinary bladder functions could be cured upon 2.5 years of coordination dynamics therapy (CDT). Three important steps were achieved. First, the patient got the bladder under volitional control again. Second, a physiologic attractor layout for bladder patterns could be generated; and third, the dyssynergia of the urinary bladder could be cured by increasing the stability of the synergia pattern and decreasing the stability of the dyssynergia pattern. The stability changes of the two bladder functioning patterns can be understood within the framework of system theory of pattern formation and human neurophysiology (55-58) but not in the framework of central pattern generators (CPG’s).

*Similarity of development between the ontogenetic landscape for locomotion and the evolution of the attractor layout for urinary bladder functions upon learning*

The development of the potential landscape of urinary bladder functions upon repair (Fig. 3) shows some similarity to the development of the ontogenetic landscape for locomotion (Fig. 4). Also the attractor layout for locomotor functions develops from a monostable to a bistable or multistable structure. With learning not only attractors appear anew but also attractors vanish. During the re-learning of bladder functions, the attractor ‘spasticity of the external bladder sphincter’ vanished. There is some similarity between the repair by re-learning and the development of sensory-motor functions during ontogeny. Following spinal cord injury, the stepping automatism and the urinary bladder reflex re-appear upon learning. During ontogeny and repair, the automatic stepping is changed by supraspinal control into walking and running patterns and the bladder reflex (or automatism) is altered into proper mic-turition and continence functions.

*Vegetative symptoms are no autonomic dysreflexia*

Normally, exercising does not pose special risks to people with SCI, apart from the starting period. Fractures or muscular injuries occur more often in sport than in patients with SCI. It is argued that people with SCI have atypical physiological responses to exercise (for example, abnormal heart rates and sudden strong sweating), which can limit their ability to sustain intensive exercise (31). When a patient cannot feel the fullness of the urinary bladder and has no desire to void, then the bladder can only inform the mind only by vegetative symptoms, namely sudden heart rate increases and sweating.

Most patients know their vegetative symptoms and empty the bladder before stronger exercises. But if patients do not know their vegetative symptoms for body control or ignore them, then even small blood vessels can tear in the brain during sudden blood pressure increases. Patients with SCI have to re-learn their body functions. A big progress for the patient of this report upon 20 month of CDT was, when the vegetative symptoms where replaced by the

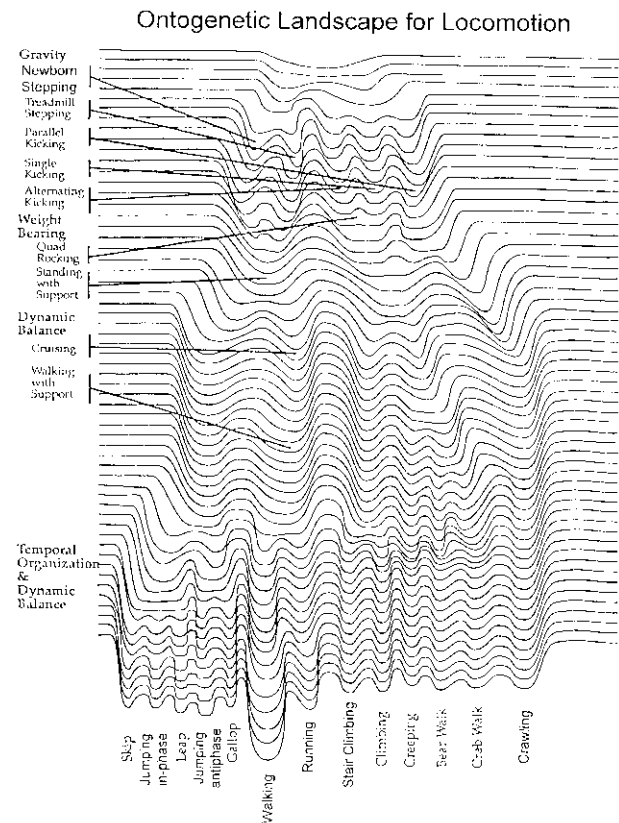


Fig. 4 – Ontogenetic landscape for locomotion. The evolution of the attractor layout for the different movements develops similarly as the re-learning of urinary bladder functioning upon CDT. With permission of Esther Thelen (72).

bladder fullness feeling and the desire to void. To treat a patient with severe cervical SCI, theoretical and practical knowledge is needed for the repair of motor and autonomic functions.

*Urinary bladder repair in children with spinal cord injury*

Nervous system complexity increases not just across phylogeny but also across ontogeny. The loss of regenerative capability with age demonstrates the cost of the complexity (7). In children with spinal cord injury it should therefore be easier to repair urinary bladder functions, since the nervous system is less complex and the rate of learning higher.

A 4-year-old boy suffered a flaccid paralysis due to a SCI sub Th12/L2 in a car accident. At an age of 6 years he underwent CDT for 6 month. The boy came to the therapy centre in a wheelchair and left

it by walking with sticks (42). The functioning of the urinary bladder improved. Before the therapy the bladder was emptied by intermittent catheterization. After 6 months of therapy the patient was continent for at least 3 hours and could empty the bladder on volition with little rest urine.

A more likely explanation that children can re-learn faster lost functions may not be the not fully achieved nervous system complexity, but that the repair during development is partly due to a correction of the development 'en route'. The increase of the nervous system complexity, including neurogenesis and growing of axons and dendrites, can be used by movement-based learning for functional and structural repair. Young cerebral palsy patients have therefore a good prognosis for repair upon CDT (45).

### *Continence in elderly people*

Continence problems in elderly people can have several reasons. But a generally not known reason is that the sacral micturition centre is not getting enough blood supply through the radicular-medullary arteries. The thickest feeder artery to the sacral micturition centre, the A. spinalis magna (Artery of Adamkiewicz), is supplying 68% of the blood (34) and is often very atherosclerotic. A combination of CDT and a reduction of arteriosclerosis may improve continence in elderly people.

### *Therapy induced regeneration*

It has been reported that SCI is a devastating condition for which there is as yet no cure (3, 65), even though it has been published that SCI can partly be cured by CDT (41, 42, 53). Probably, in most of the patients the repair was mainly a functional one. The century step forward is that also in a motoric complete cervical SCI, which is really a devastating condition when there are nearly no motor functions remained, the most important urinary bladder function can be cured and this cure includes some of regeneration of the human spinal cord besides a functional repair.

In experimental (animal) SCI the spinal cord is only partly injured (spinal hemisection; see discussion to the pictures in the Refs. 3,65). But a partial

SCI is not the problem to be solved any more, because it has been shown that a partial SCI can be cured (42, 53). The challenge is the severe and real complete cervical SCI (according to MRI); even though in nearly every injury a few fibres are spared. But researchers in the field of animal research seem to hesitate to handle urinary bladder problems, which they would get if they would transect the whole spinal cord in rat, cat or dog. Emptying the urinary bladder of animals a few times per day seems not to be an attractive part of research work. Also, regeneration will be much more difficult to achieve in complete SCI.

### *Extent of regeneration of the human spinal cord*

An important question is now how many regenerating axons do support the functional improvement obtained in this patient with a motoric complete cervical SCI. When in adult rats as little as 1-2% of the corticospinal tracts was spared following electrolytic lesion, performance of forepaw reaching recovered (20, 21). These observations imply that regeneration of a small percentage of axons and functional reorganization of the CNS, including the intrinsic spinal cord networks, could lead to a significant recovery of function. In adult cats as little as 10% of spinal white matter tracts were sufficient to permit spontaneous walking without external support (69). When in patients large proportions of spinal tracts were transected owing to intractable pain problems, disturbances in motility were small (32).

Since during CDT, those fibres were stimulated to regenerate by coordinated sensory-motor learning in the patient of this report, which were really needed for function, may be 1 till 3% of the white matter regenerated. Since the trunk muscles and also the intercostal muscles started to function again (no paradox breathing any more, repair of respiratory function) beside some upper leg muscles, probably less than 1% of the white matter regenerated for the activation of the neuronal networks for driving the pelvic floor (of which the external bladder and anal sphincters are a part of), the detrusor, and the bowel. It seems that only a very small percentage of fibres needs to be successfully reconnected with their targets to mediate urinary bladder recovery. Since the spinal cord was

strongly injured only over one vertebra length (Fig. 1A, B), axonal growth and elongation will have been shorter than one vertebra length, depending whether atypical synaptic relay circuits were formed at the injury site. This additional small amount of regenerating ascending and descending fibres may not be visible in the MRI's of patients with approximately 5% (sensory) spared white matter.

That these established connections are mainly activated ectopic pathways through root connections, sympathetic chain or plexus connections (misdirected haphazardly during development) is unlikely, since the functions of trunk and leg muscles reappeared from the rostral (below injury level) to caudal direction, indicating a regeneration in general.

#### *Endogenous adult neural stem/precursor cells for spinal cord repair*

The partial structural repair in this patient was probably achieved by activating intrinsic self-repair processes. The efficient and intensive CDT may have generated a local microenvironment in which endogenous adult stem/precursor cells self-renewed, proliferated, differentiated and migrated to contribute to the CNS repair. But what are the explanations why this intrinsic repair mechanism is so slow (more than 2 years) and so limited? First, if the sciatic nerve in human is injured, the repair needs also more than two years. Second, among other reasons (inflammation,..), the therapy should have started already in the spinal shock phase. If the patient would have started already to exercise one week after the accident (or earlier) on the special CDT device in the lying position (safe position for the reconstructed spine for moving arms and legs (Fig. 5D)), the blood supply and the circulation of the cerebrospinal fluid would have re-occurred/improved much faster after the injury. Damage through active secondary processes would have been reduced and adult neural stem/precursor cells could have reached the injury site earlier. Third, if there is similarity between development and repair (see below), may be also a critical window for more efficient repair does exist. A 'plasticity window' could have already been closed before optimal CDT was started. Fourth, the complexity of the human CNS may not allow a faster regeneration to avoid insta-

bility in CNS self-organization (see below). Fives, it has been reported that there is without stimulation only undetectable neurogenesis in the adult neocortex (71).

#### *Combination therapies to enhance regeneration*

It is supposed to be widely accepted that no single approach will prove sufficient for successful regeneration (3, 7). A methodology combining the most effective individual therapies is required. But it is shown in this article that CDT alone could already cure urinary bladder functions. This single human therapy was able to induce successful regeneration. I also believe that a combination of therapies may act synergistically to enhance regeneration. But first, it is not enough to ask for combinational treatments, one also has to support them and second, each single approach must have a solid scientific basis and must be a safe treatment without unacceptable side effects. A combination of stem cell and CDT could enhance regeneration, since the neuronal network repair strategy, used in CDT, can generate a microenvironment at the injury site for the self-renewal, proliferation, differentiation and migration of neural stem/precursor cells, even though a first therapy trial was not successful (59). This movement-based learning therapy (CDT) probably stimulates the endogenous stem cell reserves for structural improvement. Additional administration of embryonic or adult neural stem/precursor cells may then enhance the rate of structural repair.

#### *Scientific basis for therapies to repair the human spinal cord*

Basic scientific research should provide a rational basis for tailoring specific combinations of therapies (65). It has been reported that neuro-rehabilitation should have a scientific basis. But CDT has a theoretical basis (this article and Refs. 38, 50, 52-59). Reviewers cite human work without a scientific basis and argue then, that neuro-rehabilitation methods should have a scientific basis.

It has been measured in human with the single-nerve fibre action potential recording method that the phase and frequency coordination among neu-

ron firings is getting impaired following SCI (58). One important consequence of this impairment is that the variability of phase and frequency coordination increases and CNS organization becomes unstable. A macroscopic consequence of this instability of cell communication for self-organization is that movements and other patterns get changed and unstable. This instability of movement patterns can be measured macroscopically (Fig. 6C, D) and improved when the patient is exercising on the special CDT and recording device (Fig. 5D).

But not only will the injury induce instability of CNS organization. An uncontrolled building of new nerve cells and growing of neurites will also induce instability of phase and frequency coordination of CNS self-organization if the newly formed connections are integrated in the existing injured networks. This instability of CNS functioning will lead to an increase of the instability of physiologic patterns and an increase of the stability of pathologic patterns like the different kinds of spasticity in SCI and epileptic seizures in brain injury. A structural repair of the spinal cord (or CNS) in human must therefore be a strongly controlled specific mechanism to maintain the delicate balance between plasticity and stability. In Fig. 2 it can be seen that with every bit of reoccurrence of muscle function (successful regeneration of a few fibres), the coordination dynamics values got transiently worth (the movement patterns got transiently more instable), till the movement-based learning therapy re-established stability again. These transient instabilities are marked in Fig. 2 with numbers. Following the largest peak 6 of transient instability, the main urinary bladder repair was achieved.

It has been asked for the use of methods that are sensitive enough to detect potentially small increments in function (65). The coordination dynamics measurements can quantify small increments in function and regeneration (Fig. 2). It is not enough to ask for sensitive methods, one also has to use them.

The structural repair has therefore to be highly specific and controlled at the injury site to avoid instability, which means the growing of nerve fibres has to be enhanced and inhibited according to the functional needs of the network repair. If neurobiologists really succeed to induce massive grows of nerve fibre (by enhancing grows or inhibit the inhibition of growth) and if these drugs are applied to

human, than uncontrolled nerve fibre growth may occur and the human CNS probably may get instable in its self-organization; different instabilities may occur as for example epileptic seizures and mass contractions of muscles. Upon administering successfully stem cells and nerve growth factors to patients, there is therefore not only the risk of teratocarcinoma and the toxicity of side effects but also the risk of inducing extensive instabilities in the self-organization of the human CNS. To say it with the poet Goethe: "Die ich rief die Geister (neurogenesis, gliogenesis and neurite growth), werd ich nun nicht los" (uncontrolled growing and generation of CNS instabilities) (Zauberlehrling).

The risk of rising instability of CNS organization is much bigger in the human than in the animal CNS due to the much higher complexity and variability of the human CNS organization, necessary for learning.

Brain imaging research focused on detecting the brain centres involved in various sensorimotor or cognitive tasks, but CNS organization research attempts to understand the self-organization of distributed local networks and their integration and coordination to 'higher' states of processing (66).

Extensive learning potential needs specific variability in the system. For not getting instable in the changing self-organization, there must be stability control. Putting this stability control partly out of order may be dangerous for CNS functioning. In young patients with severe brain injuries strong instabilities can be observed and measured (47).

If in lower animals the circuitry is rather fixed and the nerve cells are rather specifically connected, then the repair needs only the appropriate cells substituted and the connections to be repaired. But if in the human CNS the specific, fixed wiring is rather limited, then the repair has to be controlled by network functions; an uncontrolled neurogenesis and growing of nerve fibres may be dangerous.

### *Similarity between development and CNS repair*

#### *Nerve fibre growing strategy in animals*

It has been shown in frog that there is close similarity between the innervation of muscles during development (33) and reinnervation following den-

ervation (26, 27). Two types of motoneurons with thin and thick axons communicate with slow and twitch muscle fibres to achieve the proper structure, namely that small neurons with thin axons innervate the slow muscle fibres and the large neurons with thick fast conducting axons innervate the twitch muscle fibres. The repair (the reinnervation) is recapitulating the development. Regenerating axons recapitulate developmental guidance during recovery from the denervation injury.

Two approaches have been emphasized to recapitulating development in the injured CNS: re-establishing crucial developmental cues in the correct pattern to guide regenerating axons, and maximizing the sprouting and plasticity of intact fibres through sensory feedback rehabilitation techniques (7). A faithful recapitulation of developmental path finding and circuit-refining mechanism is likely to be beneficial in the repair of SCI in animals, but may only partially hold in humans (see below). By measuring the self-organization of neuronal networks upon pattern change (by using the coordination dynamics assessment) during human development (46) and human CNS repair (47), similarities were found between the attractor layouts. More human research has to be performed to learn, how during development the human CNS is correcting/optimizing its functioning 'en route'.

In this article I report that by learning, learning transfer (58), and strong motivation for training, urinary bladder functions could be repaired including some structural repair. More generalized, I report how the mind is taking part in the functional and structural repair of its neuronal networks by which it is generated.

Almost as soon as the first computers were made, the analogy with the brain was accepted. The model of the brain as a computer, with hard-wired connections that are adaptive and flexible mostly with respect to the software and the information that is distributed over the hardwired network still dominates. The genius property of the human CNS seems to be that by excessive learning in the long-term memory the network circuitry can be changed and is not fixed as in computers. The spirit can rise above the physis.

I believe that the property of improving and repairing the CNS structure by the mind is unique to humans. Therefore, not all repair mechanism of

the human CNS can be explored by animal research. Even monkey experiments cannot substitute for human CNS research. If nerves, tendons or muscles are transposed, the rat cannot relearn (62), the monkey after several trials (63) and the human immediately (68). The relearning capacity in the human CNS with respect to functional reorganization to compensate for changes in the periphery is used in neurosurgery and microsurgery.

Many patients are trying to use their mind to repair their SCI. They concentrate on the movement and performing the movement in mind again and again and the natural impulse patterns, generated in the patients CNS, are running against the injury site in the rostral-caudal direction. But I have not heard of any success with respect to repair in complete SCI by using only the mind. First, at least some fibres probably have to be spared to secrete target-derived growth factors and second, very thoughtful movements have to be performed repeatedly for a long time (in this case 2 years and more) in cooperation with the concentration on the task. Further, to activate substantially the injured neuronal subnetworks for repair, also coordinated movement induced afferent input is needed (see Method). For network repair, the networks have to be intrinsically activated integratively and at physical limits. One kind of input to the injured network is insufficient for repair.

*CNS development and repair in animal and human: Growth, guidance and learning / Why animal research alone cannot cure SCI in human*

Two approaches have been proposed to recapitulating development in the injured CNS: Re-establishing crucial developmental cues in the correct pattern to guide regenerating axons, and maximizing the sprouting and plasticity of intact fibres through sensory feedback rehabilitation techniques (7). Re-establishing at least part of the developmental pattern of guidance molecule expression would contribute to any regenerative approach for treating CNS injury in adult animals (7). Secreted and membrane-bound isoforms of guidance molecules interact with receptor complexes. A recurring theme shared by many of the ligand-receptor combinations directing tract guidance is that interactions can result in growth cone attraction or repulsion, depending



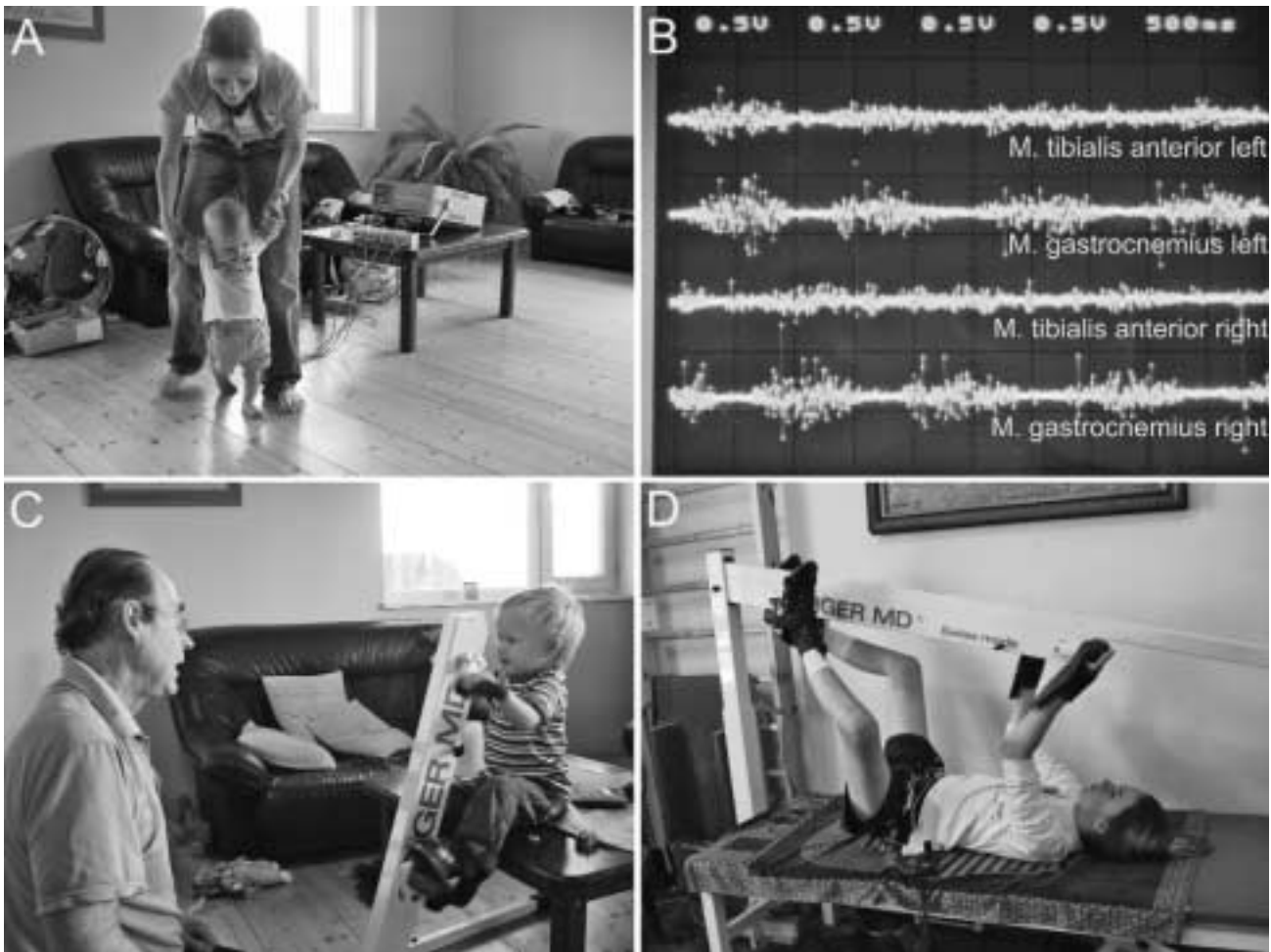


Fig. 5 – A. Recording of surface EMG during walking of 8-months-old “Jürgen”, supported by the mother. B. Surface EMG motor programs of Jürgen show no antagonistic action between the tibialis anterior and gastrocnemius muscles. C. 2-year-old Jürgen becomes able to exercise with difficulties on the special CDT device for babies (the coordination dynamics are given in Fig. 6A). D. Patient with severe cervical spinal cord injury during exercising on the special CDT device in the lying position. Note, in this exercise position, patients with spinal cord injury could train already a few days after the spine fixation, since the back would be nicely supported during exercising.

on the receptor subtype and intrinsic state of the neuron. This intrinsic state differs among not only neuronal subtypes, but also developing neurons, adult neurons and regenerating neurons. Generally, developing neurons possess the intrinsic state most suited for rapid axonal elongation and target finding.

#### Circuit connections and plasticity

In many developing neurons, a surplus of axons initially reaches their targets. Many preliminary synapses form only to retract soon after. Winners of

this game are determined by competition for limiting target-derived growth factors. Eventually, excess neuritic branches are pruned, successful neuritic branches stabilize, and many cell bodies that lack victorious nerve terminals undergo apoptosis.

#### The flexibility of immature circuits

Once axon path-finding and the pruning process have selected for the formation of appropriate synaptic connections, further plasticity occurs in an activity-dependent manner. This results in the potentiation of some connections and inhibition of others.

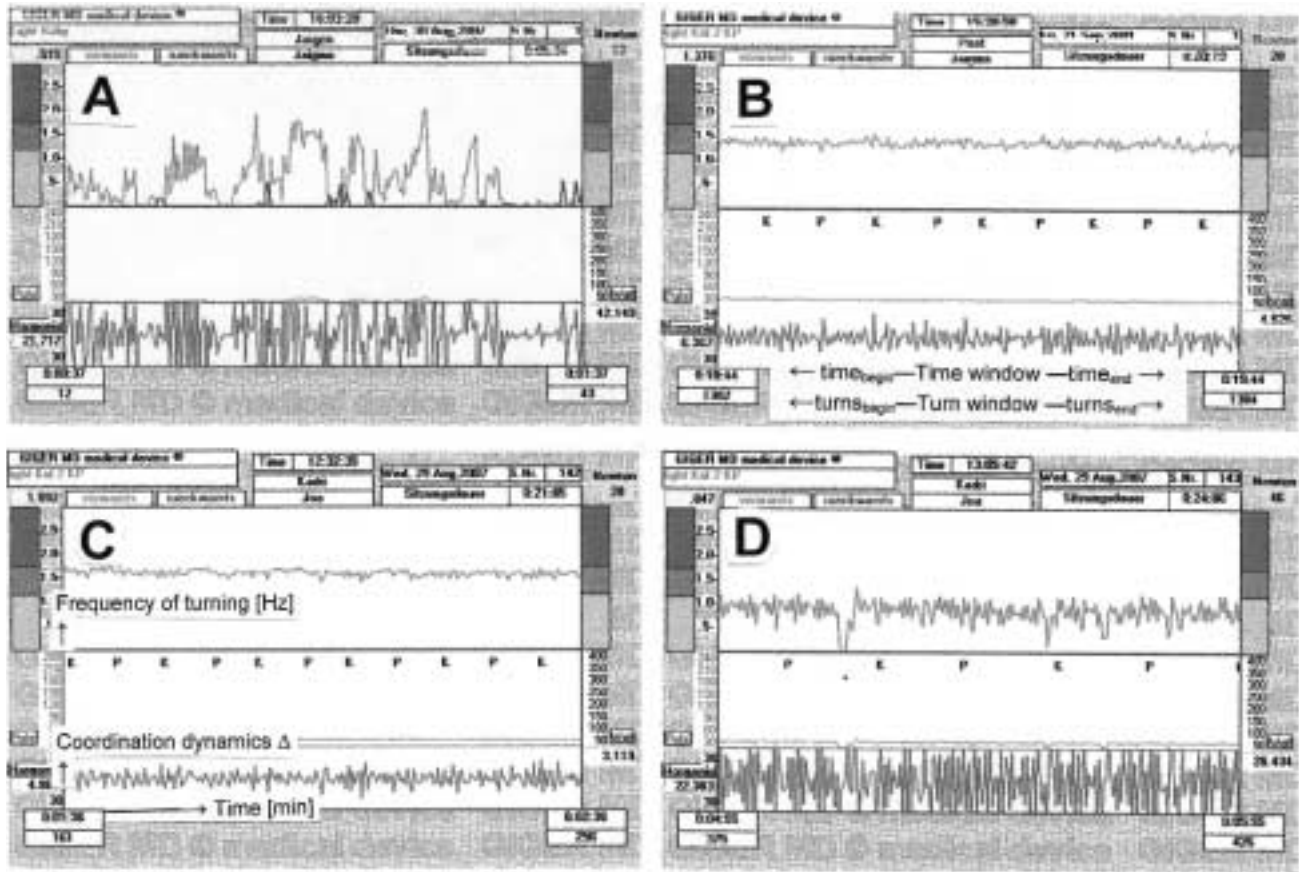


Fig. 6 – Coordination dynamics recordings from a healthy 2-year-old child (Jürgen) (A), his healthy mother (B), and a patient with a formally motoric complete SCI for low (C) and high load (D). Upper trace - frequency; lower trace - arrhythmicity of exercising = coordination dynamics.

Through learning, neuronal networks become progressively more organized.

Disruption of sensory experiences (behavioural information) within certain age windows results in circuit reorganization, allowing the organism to adapt within the new sensory information including the information generated by sensory-motor coordination. In barn owls, over several weeks they adapt not only regaining auditory-visual coordination but also visual-motor coordination (13). The ability to adapt correlates negatively with age – owls over 200 days old are unable to regain auditory-visual coordination (14). Critical periods define the age windows during which various circuits retain the plasticity to sensory deprivation.

### Generating spinal cord plasticity

Plasticity applies also to the intrinsic spinal cord circuits that mediate locomotion. Spinal cord neuronal networks generate coordinated activity between groups of agonist and antagonist limb muscles on opposite sides. The networks allow ambulation to become a nearly automatic neural program. Newborn babies (38 (Fig. 43)) and anencephalic human infants can step automatically. After birth, Jürgen (Fig. 5A, C) could step automatically forward but not backwards. This automatic stepping automatism and walking automatism (including arm and leg movements) in the forward and backward direction is used excessively in CDT. The role of axon guidance molecules

in coordinating proper neuronal network connections in animals has been emphasized (7). But the coordination in human infants is very poor (46). Its improvement depends crucially on the training of coordinated movements. Eight-month-old Jürgen (Fig. 5A) has very poor coordination between the motor programs of tibialis anterior and gastrocnemius muscles (Fig. 5B, missing antagonicity), even though he is healthy and quite early for his age. At an age of 2 years, the coordination between arm and leg movements is still poor (similarly as in other healthy children), as is measured by the coordination dynamics in Fig. 6A. Temporary deprivation of sensory feedback to the rat neuronal networks in the postnatal period results in permanent walking and swimming deficits, defining a critical period for neuronal network plasticity (67). Humans can re-learn walking and other movements throughout life (41, 42) following SCI.

Inhibitory neurotransmitters have a crucial role in plasticity. The transition from synchronous (in-phase, pace gait) to alternating bilateral rhythmic limb movement (anti-phase, trot gait) late in gestation depends on glycinergic signalling (16). Serotonin, acting through 5-hydroxy-tryptamine (5-HT) receptors, delays the maturation of GABA-mediated inputs into lumbar versus brachial spinal circuits (1). Human babies learn first the pace-gait and then the trot-gait crawling. Human infants who left out the crawling period may have coordination problems throughout life unless CDT is administered. The crawling automatism is used in CDT.

#### Closing the plasticity window and learning plasticity

Understanding the mechanism underlying critical period closure will form the basis for approaches to re-establishing plasticity in regenerating adult nervous system. Not only neurotransmitters contribute to the definition of plasticity windows. Extracellular chondroitin sulphate proteoglycans (CSPGs), produced mainly by astrocytes, form perineuronal nets around inhibitory interneurons in the visual cortex, coincident with the closure of the critical period window (17, 25, 30). CSPGs inhibit neurite outgrowth, probably blocking the synaptic structural dynamics that partly underlie plasticity (30). Enzymatic CSPG removal re-opens the critical period (30). Therefore,

maturing astrocytes and oligodendrocytes have a role in consolidating neuronal plasticity.

The mechanisms that evolved to consolidate plastic circuitry directly contribute to the inability to regenerate after CNS injury. Hence, plasticity and regeneration are intertwined. The most effective therapeutic approach in SCI repair in animals will untangle these pathways to allow the regeneration of injured circuits without disrupting the consolidation of existing intact circuits. In humans, the mechanisms that consolidate the plasticity in the circuitry may contribute to the control mechanism to avoid instability of physiologic patterns and to avoid the development of pathologic self-organizations as for example epileptic seizures. But the learning process offers a well balanced mechanism for functional and structural repair without inducing large instabilities in the CNS self-organization. Small instabilities do occur during the regeneration of the human spinal cord, as can be seen from Fig. 2. These re-occurring small instabilities were resolved upon proper CDT.

#### Neural response to injury and differences in mind-structure communication for repair in animals and humans

CNS injury, disease, and malformation wreak havoc on the intricately choreographed neural circuitry. Unlike the many similarities across species in patterns of neural development, responses to injury and repair differ greatly. Responses to injury also vary in individual organisms, depending on time, anatomical location and type of injury. The most effective spontaneous injury responses occur in lower vertebrate species, at younger developmental ages, and in the peripheral nervous system (PNS) rather than the CNS. A detailed understanding of the factors responsible for these differences provides insight into the challenge of improving treatments for adult mammalian and human CNS injury. The main difference for repair between animals and human is that the repair in animals occurs mainly spontaneously and in humans mainly volitionally. The mind-structure communication in animals for inducing non-spontaneous repair is very limited. Also devices for training are missing. Rats, frogs, and lamprays cannot turn on the special CDT device to improve the phase and frequency coordination for

the improvement of CNS self-organization (Fig. 5 CD), cannot jump on springboard for rhythmic natural stimulation of the sacral micturition centre to improve continence (58), cannot perform supported treadmill walking like in Fig. 1C, and cannot be instructed and motivated during therapy. It is impossible to explain a rat that it has to train certain movements for one or two years excessively or should concentrate on certain muscle activations for repairing its injury. If a not functioning limb does hinder too much during locomotion, then the rat is eating it.

#### Translating animal data to human data

To make use of animal research for the improvement of human diseases, a correlation has to be established between animal and human data. For correlating nerve fibre groups for example between rats and humans, there must be a detailed classification schemes for rat nerve fibre groups and human nerve fibre groups (35, 38). By comparison we can see then, what nerve fibre groups in the human PNS can also be found in the rat PNS. Such comparison is not possible till now, because an up-to-date classification scheme for the rat or cat PNS is missing. The existing classification schemes (5, 8, 9, 22) are too inaccurate for a comparison. Animal research needs to improve their basic data. To make use of the regeneration data obtained from animals, also regeneration data of humans are needed for a comparison. Such data do not exist, apart from a few exceptions.

To make thus use of animal data to cure diseases, parallel studies have to be performed in animals and humans and similar treatments and measurements for quantifying progress have to be used. The switch from animal experiments to human trials is a too simple thinking and too dangerous for the patients.

*To repair functions also functions have to be measured (best with basic methods) and they differ strongly between animals and humans*

As emphasized above, in many developing neurons, a surplus of axons initially reach their targets. Winners of this game are determined by competition for limiting target-derived growth factors. Once

axon path-finding and the pruning process have selected for the formation of appropriate synaptic connections, further plasticity occurs in a pattern-activity-dependent manner. This results in the potentiation of some connections and inhibition of others. Through learning, neuronal networks become progressively more organized.

These steps also hold during the development of the frog (tadpole stage), when the faster developing large neurons innervate slow and twitch muscle fibres first. The slow muscle fibres also have fast contracting properties and the membranes are generating action potentials, as the twitch muscle fibres do, even though the morphology is different (no M-line). When the slower developing small motoneurons reach the slow muscle fibres, they 'push' the synapses of the large motoneurons away and change membrane and contracture properties (but not the morphologic properties). The membrane cannot generate an action potential any more and the muscle holds a contracture upon depolarization. The formation of appropriate synaptic connections occurs therefore two times (first with the arrival of the fast and then with the arrival of the slowly conducting axons) and the specificity is only relative in that frog model. In human there are three kinds of muscle fibres, innervated by three kinds of motoneurons (36, 55). The specificity of correlation between muscle fibres and motoneurons is unclear.

The intricate changes during development can only be explored using at least morphology and electrophysiology. The regeneration following a section of the sciatic nerve in the adult frog is following the same scheme, as can be measured with intracellular recording techniques and Ca transient measurements (26, 27). To follow up the morphological changes during reinnervation would be difficult, because the denervated synapses are resolved at different speed, which would make it difficult to distinguish between newly build synapses and old denervated synapses. Only single-cell electrophysiology can follow up the reinnervation processes safely.

In human, the measuring methods are quite different for comparing development and repair of SCI. As non-invasive methods, electromyography and coordination dynamics measurements can be used, beside movement performance measurements. Also the times for development and regeneration in humans are quite different to those of frog, lamprey, and rat.

Fig. 5B shows the EMG motor programs of the right and left tibialis anterior and gastrocnemius muscles in the 8-month-old healthy Jürgen (Fig. 5A). The single muscles can generate motor programs. But the important antagonistic action between the tibialis anterior and gastrocnemius muscles is still missing. There is still much more co-contraction than antagonistic action between the muscle activations. Also in a patient with a severe cerebellum injury, the antagonistic action between the tibialis anterior and gastrocnemius muscle was impaired (49). In the patient of this report (Figs. 1C, 5D), the generation of motor programs was the biggest problem so far (54).

At an age of two years, Jürgen became able to exercise on the special coordination dynamics therapy device (Fig. 5C). Continuously he could perform approximately only 5 turnings. The frequency of turning and the arrhythmicity of exercising changed very much (Fig. 6A). The mother (Fig. 5A) could exercise smoothly (Fig. 6B). The patient with the severe cervical spinal cord injury could turn quite smoothly for a low load of 20N (Fig. 6C). But she managed to turn for higher load (50N) only with high arrhythmicity (Fig. 6D).

The research examples of development and regeneration in animal and human indicate that they nearly belong to different worlds with respect to CNS organization, measurements of the organization, and the repair following injury. The development of the organization of the human CNS needs different movements to be trained for a proper development and is not so much a ‘correction en route’ but an ‘improvement of the direction’, because of higher variability of CNS organization. Two-year-old Jürgen can crawl, walk and climb, but his CNS is unable to generate the complicated coordinated movements between arms and legs, when exercising on the special device upon changing the patterns continuously between pace and trot gait (Fig. 6A). The CNS of the sporty mother can easily generate these intermediate coordinations between pace and trot gait (Fig. 6B). Therefore there is a world of difference between the complexity of CNS organization between Jürgen and his mother with respect to coordinated movements. In the patient with the cervical spinal cord injury (SCI), the supraspinal CNS is working fine; the main problem after some regeneration of the cord is the still missing muscle power.

### *False hope*

Instead of raising false hope that the animal data can be easily used to cure diseases of the human CNS, the universities and research institutions should first do their duty, namely organizing qualified human neurophysiologic research and support also human research.

### *Ethics of spinal cord injury (SCI) research and clinical trials*

‘Transplantation of both embryonic stem cells and embryonic stem cell-derived neural (neuronal or glial) progenitors is able to efficiently promote CNS regeneration in preclinical models of stroke, myelin deficiency, acute spinal cord injury (10, 24) and Parkinson’s disease (23)’. This sentence of an article makes the reader believe that the research made already the step from the animal research to the human research and treatment is already administered to humans. Looking up the references one finds the title: ‘Human embryonic stem cell-derived oligodendrocyte progenitor cell transplants remyelinate and restore locomotion after spinal cord injury’. Patients with SCI or journalists think immediately that the SCI problem is already solved! I have learned that it has to be written in the title on what species the research has been performed. In this case it was the rat. Animal researchers often choose on purpose the words in a way to make the reader believe that this research has already solved the SCI problem in humans. A well known journal in medicine is even redefining medicine. It makes the reader believe that measurements in mouse are a part of medicine (12). I have learned in my medical study that medicine has something to do with the cure of diseases in human.

Speciality journals and general audience media need to set reasonable expectations of the safety and efficacy of potential therapies to avoid raising and then dashing the hopes of those living with SCI or those in government, those carrying out research, or the general public (65).

High ethical standards are required by researchers, clinicians and journalists to ensure that results are communicated to the general public in a manner that reflects honestly the safety and efficacy of a potential therapy (65).

Western scientist and clinicians would argue that controls are necessary to identify unambiguously whether a therapy is safe and effective, some clinicians have claimed that withholding a potential therapy from a patient with SCI is in itself unethical (65). Many SCI units know about CDT. But the patients are not informed that such a therapy exists! A real change from care to cure seems not to be in the interests of the rehabilitation centres, according to my experience.

There is too much false hope generated by animal physiologists, neurobiologists, and researchers working in the field of genetics. Without detailed knowledge of the human physiology and pathophysiology, the animal knowledge is only of limited help to cure diseases in human. False hope also stops the patient to fight for improvements which are needed for everyday life. Why should a patient fight for two years or more with a movement-based learning therapy to get urinary bladder and some motor functions back, if in a few years time the walking can be gained back easily with miracle cells or pills? Such false hope is coming from qualified researchers, when they make believe that the animal data can be easily used to repair the human CNS. Qualified human research is needed and has to be organized. Only if there is overlap between animal and human research, there is the possibility of rather safe transfer of knowledge from animals to humans. As long as human research is not organized properly, the patients have to suffer or even to die.

Authors of recent review articles presented approximately 1000 citations on the repair of the human spinal cord following injury (3, 7, 23, 65). Less than 10% of the citations were from human research. Interesting is that the Author was not cited, even though students, young researchers, some physicians and even many journals find the Author easily in the internet! I learned a lot from these brilliant research articles with respect to animal research. But with respect to human research and applicability to human patients they were out of date by 20 years.

'Miracle' operations are not the only danger for patients and the freedom in research. It is the world wide research, treatment, and teaching system, that does not allow qualified human research, which is urgently needed to cure diseases and make humans living longer with a higher quality of life. And if there are really operations with unbelievable success, then the treatment before those operations was

wrong. Here an example. A paraplegic patient came by wheelchair from a well-known German rehabilitation centre to a neurosurgery department, was operated and walked 2 weeks later out of the neurosurgery department. A second patient was cured in the same way. The reason for this progress was caused by a mistake of the rehabilitation centre. Bones from the spinal canal caused pressure on the spinal cord. The spinal cord stopped working but was damaged only little. A laminectomy freed the spinal cord and the spinal cord started to work again. Follow up MRI's are needed.

### **History of the human research project**

Based on the Author's background of being an engineer in electronics, a theoretical physicist (Dr.rer.nat.), a physician (Dr.med.), and post-doc with Sir Bernard Katz, this research project to cure CNS injuries was started 25 years ago (in 1983) in Finland. It was first supported for 2 years by the 'Deutsche Forschungsgemeinschaft' (DFG). Further funding was refused. Ethical and quality objections were raised. The support of the former Federal President Richard von Weizsäcker could not overthrow the decision of the DFG. The DFG did not want to confirm that the reviewers of the application for funding had a comparable background as the Author. The Author (from West-Berlin) continued the research on personally saved money. He worked together with Departments of Neurosurgery, Neurology, Pathology, and Forensic Medicine of the University of Greifswald in the former German Democratic Republic (GDR), even though this was officially not possible. Since measurements were also performed on brain-dead humans, an ethics committee was established in the former GDR, which decided that the research project was ethically justified. The Author got partially funding from the GDR, even though this was officially not possible for a subject from West-Berlin. Before the re-unification of the GFR and GDR, he could not get funding any more because of shortage of money. The habilitation procedure (Dr.med.habil.) based on the development of the single-nerve fibre action potential recording method in humans was started before the fall of the Berlin wall and was completed thereafter. When working for 6 years in a rehabilitation centre in Switzerland, the Author applied two times for

support by the Swiss National Fund (SNF). Financial support for the research was refused. In recent times, this research project of CNS injury repair has been ignored or there were attempts to destroy it in several ways, including exercising pressure on editors to prevent the publication of papers, exercising pressure on organizers of conferences to prevent presentations, and writing letters to patients and institutions that the method is not working. No real theoretical or clinical scientific discussion could ever be achieved by the Author on the basis of human neurophysiology, even though the results of this research have tremendous clinical consequences. The health care system in middle Europe and North America prefers to let patients with very severe CNS injuries without any qualified treatment instead of inventing and proving new treatments. To find a way to bring qualified movement treatments for CNS repair to patients, the Author has been working for 25 years as a human neurophysiologist and clinical research worker in several countries of Europe, mainly on personally saved money.

Animal physiologists and clinicians have not accepted human neurophysiology and the author has been excluded from the research society (congresses, research funding, academic position, publications).

Max Planck argued that it is not possible to convince other people, one has to wait until they die. Einstein was arguing, that intelligence 'is starved out' (New York Times, 12.6.1953).

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*Address reprint requests to:*

Giselher Schalow  
 Dr .med. habil., Dr.rer.nat., Dipl.Ing.  
 Untere Kirchmatte 6  
 CH-6207 Nottwil  
 Switzerland

[www.cdt.host.sk](http://www.cdt.host.sk), [g\\_schalow@hotmail.com](mailto:g_schalow@hotmail.com)