Partial cure achieved in a patient with near-complete cervical spinal cord injury (95% injury) after 3 years of coordination dynamics therapy

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Summary

This report describes a case of a now 20-year-old young lady with a severe spinal cord injury (SCI) at cervical 5/6 levels (ASIA A), in whom a repair of some spinal cord functions could be achieved within 3 years of optimal coordination dynamics therapy (CDT). Magnetic Resonance Imaging (MRI) showed a destruction of almost 95% of the cross-sectional area at the injury levels. The 5% (if at all) spared cord tissue most likely consisted of only sensory tracts, since no motor functions were preserved below the level of injury. A near-complete recovery of the important vegetative functions urinary bladder control, respiration, and vasomotor tone could be achieved. Her motor and sensory functions also improved to some extent, and she is off all medications. However, her motor recovery was limited and she is still wheel-chair-dependent. ***There is functional and structural (MRI) evidence that the human spinal cord regenerates upon CDT.***

The movement-based learning therapy included the training of supported crawling, up-righting, walking, running, jumping, balance training, and exercising on special CDT devices. The regeneration of the spinal cord started after more than one year of CDT, it was very limited but continuous, and gave rise to substantial functional recovery. The recovery induced by regeneration upon CDT was quantified in terms of transient increases of coordination dynamics values, the improvement of motor programs as assessed by surface electromyography (sEMG), the improvement of movement performances, and the increase of the spinal cord matter at the injury site, quantified by MRI. The similarity between the improvement at cellular and integrative (network) level during this regeneration and development is analyzed with respect to 'walking'. Comparing the effort, required to achieve substantial improvement in this case of severe cervical SCI (with 95% cord destruction; 5% spared tissue) with the effort required in the case of partial cervical SCI (50% destruction; 50% spared tissue), it is noted that the 95% injury is 10 times more intractable. It is inferred that in severe SCI, the repair crucially depends on the percentage of the spared tissue (tracts fibres and neuronal networks) at the injury site. Improper handling of the patient therefore, as false transport or too late relief of spinal cord compression, may give rise to further mechanical damage of the cord tissue for which a later administered intensive CDT cannot compensate for.

Key-words: Spinal cord injury – Coordination dynamics therapy – Repair – Genotype/phenotype mapping – Ontogeny – Stepping automatism – Walking automatism – Urinary bladder – sEMG – Anatogonistic muscle action – Regeneration – Paradoxical breathing – Pressure ulcer – Vasomotor tone – MRI

Introduction

Schalow Coordination Dynamics Therapy (CDT), a movement and learning-based therapy, has been shown to be effective in improving the functioning of the damaged central nervous system (CNS) in varieties of conditions like stroke (15), traumatic brain injury (16, 26), hypoxic brain injury (25), cerebellar injury (27-29), spinal cord injury (SCI) (17, 18, 30-33), cerebral palsy (23) and Parkinson's disease (19, 21, 22). To achieve even a partial cure in the above intractable conditions, functional

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and structural repair of the damaged nervous system is mostly required. Such repair can only be brought about by an intensive long-term therapy that involves working with the patient at least 20 hours per week, for nearly three years. To achieve optimal results, the efficiency of this treatment is very important. To enhance the efficiency of the treatment, clear diagnostic tools are needed to tailor the therapy to the type and severity of the CNS injury and to the ongoing CNS changes accompanying the CNS repair during the treatment.

In two previous publications (17,18) the author has reported that the CDT could achieve a partial cure in a group of patients with SCI (18). A recent publication by the author, evaluating the effect of stem cell therapy and CDT (31), indicates that to achieve a cure of the severe SCI, functional reorganisation alone is inadequate and structural repair is needed for a regeneration of the injured tissue to achieve meaningful behavioural improvement. It is important to differentiate between the structural and the functional repair. To determine what is an optimal treatment to achieve also structural repair, objective measurements are essential to correlate the severity of SCI to the extent of recovery.

In the previous paper it was shown that if 50% (according to MRI) of the cervical spinal cord matter is spared following injury, then the patient can relearn walking, running, and jumping and can become continent within two to three years of even non-optimal CDT. CDT could achieve a near-total cure in this incomplete SCI cord injury probably mainly by functional reorganization (32). The question remains as to how much quality of life a patient can regain if only 5% of the cervical spinal cord matter is spared, that means if the injury is 10 times more severe. If 95% of the spinal cord cross section is destroyed, just functional reorganization is unlikely to be sufficient for even a partial cure. A structural repair, (i.e. a regeneration of the spinal cord) is also needed. In the adult cat it was shown that as little as 10% of spinal white matter tracts were sufficient to permit spontaneous walking without external support (34). Since fibres probably regenerate over longer distances in the cat than in humans, in human we can expect that at least 20% of spinal white matter tracts, including motor fibres, are needed for a repair of walking. Moreover, since the cat (or rat) is walking with 4 limbs, the continence is not a major issue since the body weight is not resting on the pelvic floor. Also, the motor units in the four limbs enlarge far more in rat and cat than in human, to gain sufficient muscle power. For a discussion of regeneration differences between animals and humans, see Ref. 31.

Patients with severe cervical SCI really need repair, since the spinal trauma often leads to devastating medical, psychological, social, and financial consequences. To improve urinary bladder functions, to regain some of hand, finger, and trunk functions, and to become independent in everyday life would be a big progress in the repair of the severe cervical SCI, in which only 5% of the fibres are spared. The animal SCI research usually concentrates on the repair of cases in which approximately 50% of the spinal cord matter is spared (see Figs. 2-4 of Ref. 2), even though the repair for such a severity of injury is solved already in human (18, 32). The challenge for the SCI research is to repair the severe cervical SCI. There is a world of difference in the potential for functional repair if 50% (ASIA D) of a cervical spinal cord matter is spared or only 5% (ASIA between A and B). For a comparison between different treatment methods in SCI, it must therefore be known how much of the spinal cord matter was really destroyed.

In the present and the following papers I will show that in this patient with 5% spared spinal cord matter (probably mainly the white matter) following severe C5/6 SCI (motoric complete), urinary bladder, breathing, and blood circulation functions could be fully repaired and even motor functions could be partly repaired within three years of optimal CDT. The repair of the autonomic functions is most important. Before World War II, most SCI patients died of the recurrent urinary bladder infections. The repair of the breathing significantly reduces the chances of lung infections and with the repair of the blood circulation below the injury level pressure ulcers do not occur any more. It should be emphasized that an optimal CDT for three years is a tremendous effort to organize, since such treatment research seems to be only possible outside the social-medical society so far.

In this first article the focus will be on the repair of the motor functions, breathing, and blood circulation. In the following papers, I will concentrate on the details of the repair of the urinary bladder on the basis of the necessary human anatomy, human neurophysiology, and clinical diagnostics.

Method

Coordination Dynamics Therapy

Summary

Schalow Coordination Dynamics Therapy (CDT) is a movement-based learning therapy that uses different strategies for repair. The strategies are based on correcting the impaired CNS self-organization (impaired phase and frequency coordination of neuron firing following injury (20)), to compensate for the loss of movements, and to repair the impaired autonomic functions. CDT includes:

1. The training of automatisms like creeping, crawling (Fig. 1C), walking (Fig. 1D,E,F,H), and running (Fig. 1L) (i.e. innate movements to recapitulate development) in the forward and backward direction (for symmetry repair).
2. Training at limits (30) to stimulate endogenous stem cell reserves (5) to replace lost tissue.
3. Training old-learned movements (i.e. learned automatisms with high stability as climbing staircases).
4. Training of rhythmic dynamic stereotyped movements such as jumping on the springboard (Fig. 4A,B) (to functionally repair neural assemblies (spinal oscillators)).
5. Training of device imposed movements (to repair the impaired time and space-coordinated firing of neurons and neural assemblies). The special CDT device for turning (Fig. 1A,B,G) is of high importance for repair. It imposes four-limb cyclical rotating movements with changing coordination between arms and legs. Such four-limb movements are the first ones, especially in the lying position (Fig. 1H right), which a patient with a severe cervical SCI can perform by himself/herself, whereby neuronal network activation is achieved across the injury site in the rostral and caudal direction.

To understand the repair of the integrative functions of the human CNS, the System Theory of

Figs. 1A-E. – Movements performed during coordination dynamics therapy (CDT). A. Surface EMG recording layout for measuring motor patterns when exercising on the special CDT and recording device for turning. Skin damage healed at the left knee. The author is performing the sEMG. B. After one year of treatment the trunk stability improved that much that the patient could train the balance while exercising on the special device. C. Patient during crawling with support. The legs of the patient are fixed to the legs of the therapist. The skin is still quite vulnerable; injured fingers are covered. D. Weight-supported neurowalking; device imposed trot gait coordination. The therapist is giving trunk support; at a later therapy stage trunk support was not necessary any more. E. Fast forward walking on treadmill. Leg support is given by one therapist. The patient is inducing the leg movement with the arms to generate very coordinated descending and ascending impulse patterns over the injury site at C5/6 levels.

Figs. 1F-L. – Movements performed during CDT. F. Fast supported backward walking (or running) on treadmill; symmetry counterpart to forward walking. G. Recording layout for measuring coordination dynamics. The patient is sitting actively with trunk stability in the wheelchair and is not slipping out of the wheelchair as during first measurements. H. Supported treadmill walking with 2 therapists and fixed hands (another patient with a severe C5/6 injury, motor bike accident, 5% spared motor tract fibres). I. Supported rhythmic movement from one side to the other; preform of pace gait crawling. An open hand is achieved by support, used in swimming sport. K. Device imposed coordinated arm and leg movements in pace gait coordination. L. Fast forward walking (or running) on treadmill. Leg support is given by 2 therapists. The patient is inducing the leg movement with the arms. Author is on the right side of the patient.

Pattern Formation (4,7) for Repair (28,32) is used. The strategies used for structural repair are discussed below. For further details of the method see Ref. (32). Supported treadmill walking and other movements of patients with severe cervical SCI (Fig. 2) are documented in video films (35).

Recruitment of spared tracts and neuronal networks

Training on special CDT devices (Fig. 1A,B,D, G,K) involves performing integrated movements, in which the arms and legs move exactly coordinated. As the special devices impose these coordinations, the afferent and efferent inputs have to pass to and from across the injury site to establish coordinated communication between the cervical and lumbar cord segments which are supposed to be the respective centers of the stereotyped arm and leg movements (cervical and lumbosacral intumescences). Such exactness of coordinated movements is important for the activation of denervated neurons below and at the injury site. It is known that neurons act as co-incidence and coordination detectors (22). An action potential is only generated in the axon hillock of the neuron if the cell soma of the neuron receives a sufficient number of depolarizations (from afferent inputs), which are synchronised (or more general, coordinated) up to a few milliseconds. Non-exact movements will generate asynchronous depolarisations from the afferent inputs; the threshold potential for the generation of an action potential will not be reached, and the neuron will fail to fire an action potential along the axon; the neuron fails to get activated. Therefore, on a larger scale, to activate all spared tracts, neurons, synapses and networks across the injury site, this exactness of coordinated movements of all four limbs is very important. Since every injury is unique and leaves behind different sets of spared fibres and neurons, different kinds of highly coordinated movements need to be trained to activate all spared fibres and neurones distributed in different network activations. Only those spared tracts and neuronal networks can be reorganised which are recruited and therefore only the highly coordinated activity can generate such a maximum of recruitment and functional connectivity over the injury site through the spared tract fibres.

Structural repair

As explained in earlier papers, when a patient trains at his/her limit (30) on the special CDT device for turning (Fig. 1G) against very high load, this highly coordinated integrated movement activates and recruits many of the neuronal networks across the entire nervous system. Also, it probably stimulates all kinds of repair mechanisms including the recruitment of endogenous stem cells for repair. With ongoing CDT, the stimulated endogenous stem cells may contribute to repair by various mechanisms like replacing lost neurons in the injured grey matter, encouraging and supporting the sprouting of severed axons and guiding them across injury site. The stem cells may also support the plasticity mechanisms at cellular and molecular levels, which are occurring during functional reorganisation in spared neuronal networks with ongoing CDT. The commitment of partially denervated neurons may be changed (3) upon CDT. As explained in an earlier publication, such commitment change could be a powerful mechanism for repair especially in systematic neuron death. A very intensive CDT may also influence selector genes within the stimulated endogenous precursor cells to direct the cells to differentiate along those cell lines (6) which are needed for repair. For example, the formation of inhibitory inter-neurons may be important (as much as the formation of motor neurons) to reduce the co-contraction in spasticity and improve the antagonistic action of neurons and thereby effectively improving the performance of movements. A similar strategy may also help to reduce tremor in patients with Parkinson's disease (21).

Generation of geographical landscape of chemo-attractive and chemorepulsive gradients to induce homing of cells and connections by performing innate and other movements

One of the very important factors in regeneration within the nervous system is the guidance of nerve fibers and nerve cells to rebuild networks. The proponents of stem cell therapy and pharmacological therapy in SCI often play down this important requirement. It is proposed that CDT - the movement-based learning therapy - will support what is called the (natural) activity-guided plasticity during repair. CDT achieves this activity-guided plasticity probably by generating a geographical landscape of chemoattractive and chemorepulsive gradients for the guidance of growing nerve fibres and homing of cells. The generation of the geographical landscape may have the form of selective expression of endogenous neurotrophins at appropriate sites and with appropriate gradients, which will guide the nerve fibers. Or the geographical landscape is generated by selective homing and differentiation of endogenous stem cells through neurogenesis and gliogenesis. Both processes are orchestrated by the specifically activated spared neurons and tract fibres at the injury site over time and space upon performing supported automatic movements like walking on treadmill or performing precisely coordinated movements imposed when exercising on special CDT devices (Figs. 1A,B,D,G,K). This strategy is very similar to what happens during the development of the nervous system. The training of innate, automatic movements, like walking, crawling, and jumping is likely to produce and re-enforce the development-like chemoattactive and chemorepulsive gradients.

The exercising on the special CDT devises primarily entrain the neuronal networks to improve its phase and frequency coordination of neuron firing for improved self-organization by imposing extremely integrative, coordinated movements. Such an improvement of the efficiency of CNS self-organization probably also plays a key role during development for the ‘correction en route’.

The training on the special CDT device for turning (Fig. 1A,B,C,G) is the starting point of CDT, especially for those patients who are bed-ridden or wheelchair bound, since every patient can perform these integrative and precise movements actively mainly by himself and the coordinated firing of neurons must be improved in every patient with an injury of the nervous system. As the geographical landscape of repair processes starts changing and networks are reforming upon CDT, all performable movements should be trained to re-enforce the structural and functional repair.

Geographical landscape of chemoattractive and chemorepulsive gradients, stimulated by pattern dynamics including the improved movement induced afferent input

The geographical precise guidance cues for endogenous neuronal network repair are only then sufficiently well activated if the spared neurons and tract fibres are specifically activated in the context of integrative automatisms (and other movements). Upon performing integrative automatic movement patterns, generated by the networks including the injury site, the support of the therapist has to bring the SCI patient into a pattern, in which all the efferent network parts are activated and the movement induced afferent input is rather physiologic so that the geographical precise endogenous signalling cues, present during development or repair, are stimulated. To achieve this optimal support, the interpersonal coordination between the therapist and the patient is extremely important. The therapist has to feel and instantaneously assess the patient’s efforts and support what is needed to bring about good performance of the movement. This requirement may keep changing from minute to minute and session to session and over the course of therapy as the patient improves. The therapist has to encourage the patient to put in more effort and focus on the quality of performance and support only there where the efforts are falling short. Therefore, for example, the robot-assisted movements for treadmill walking cannot substitute for the therapist-assisted support. The therapist-assisted treadmill training (Fig. 1E,F,H,L) is extremely strenuous for the therapist and therefore not popular. On the other hand, the support required for the exercising on the special CDT device for turning (Fig. 1A,B,G; right side of F,H) is less demanding for the therapist and is another reason to start optimal treatment with such special devices.

Strategy differences for structural repair between animals and humans with respect to genotype-to-phenotype mapping

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 to learn. The inherited genotype can completely specify the phenotypic network; i.e. both the network's architecture and the 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 (12). Or the genotype specifies the network's architecture, but the weights are learned (8). In still other cases, what has been selected during the evolution are good initial weights for learning or good learning rates and momentums (1).

In human, the genotype may specify the network's architecture only partly and the connection weights are learned with good weights for learning and good learning rates, apart from the essential life-saving automatisms, 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, may be the significantly reduced capacity of innate structural repair of the human CNS in relation to that of animals. During repair, the changes in gene expression will only partly specify the network's architecture. The main emphasis has therefore to be laid on the (movement) learning. The different learning mechanisms may be the main stimuli for repair in human and not the innate structural repair mechanisms. For the repair in animals, the network's architecture and connection weights are mainly specified by the genotype. The movement learning is mainly only needed to direct the exogenously applied stem/progenitor cells to the injury site (33). The explicit network's architecture is mainly generated by the genotype-to-phenotype mapping, which includes cell division, cell proliferation from stem cells, and the migration of neurons to reach their terminal position in the CNS.

Stepping and walking automatisms in infants

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 (10).

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 life under the control of genetically specified information.

The stepping automatism in human is an innate behaviour present at birth, which does not require learning. After birth this stepping automatism is induced in babies as a control for a healthy CNS at that stage of ontogenesis, and is stimulated, for example, with the heel strike (Fig. 1M). The stepping automatism exists already before birth.

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 in the walking pattern. The walking of the infant in Fig. 1N,a,c seems to show a more gradual change from the stepping to the walking automatism. At an age of 5 months (Fig. 1N,a), the walking pattern is with more flexion and high lifting of the knees more similar to the stepping automatism (Fig. 1M) than at an age of 8 months (Fig. 1N,c). To learn the walking automatism, the proper motor programs have to be learned by the infant with similar problems as following spinal cord injury. Also, the antagonistic relationship between muscles has to be learned under genetic control. In this case the inhibitory system has not been developed sufficiently so far. The EMG's of the 5 and 8-months-old healthy Jürgen show that the antagonistic action between the tibialis anterior and gastrocnemius muscles has not been developed properly at that developmental stages (Fig. 1N,b,d); the muscles are coactivated quite much. This knowledge of ontogeny will be used in the Discussion for a comparison with repair.

Re-appearance of stepping and walking automatisms during repair

Following severe cervical SCI, parts of the stepping automatism reappear as the first step towards repair of walking. Depending on the composition

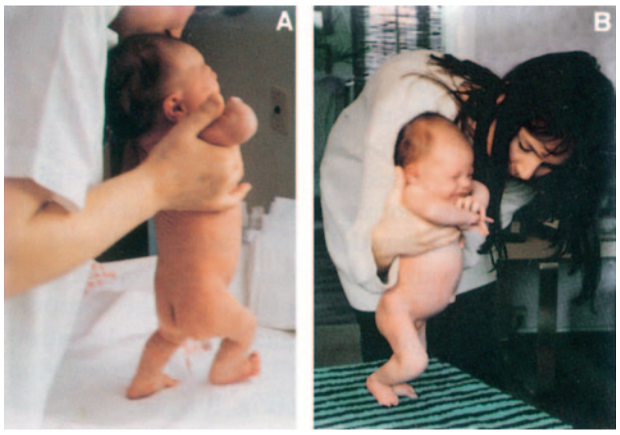


Fig. 1M. – Automatic stepping in a newborn infant. A. The 5-day-old infant, Juliane, performing primary automatic stepping; slight backward posture. The heel of the right foot touched the ground first. B. Infant Juliane, 8-day-old, performing automatic stepping.

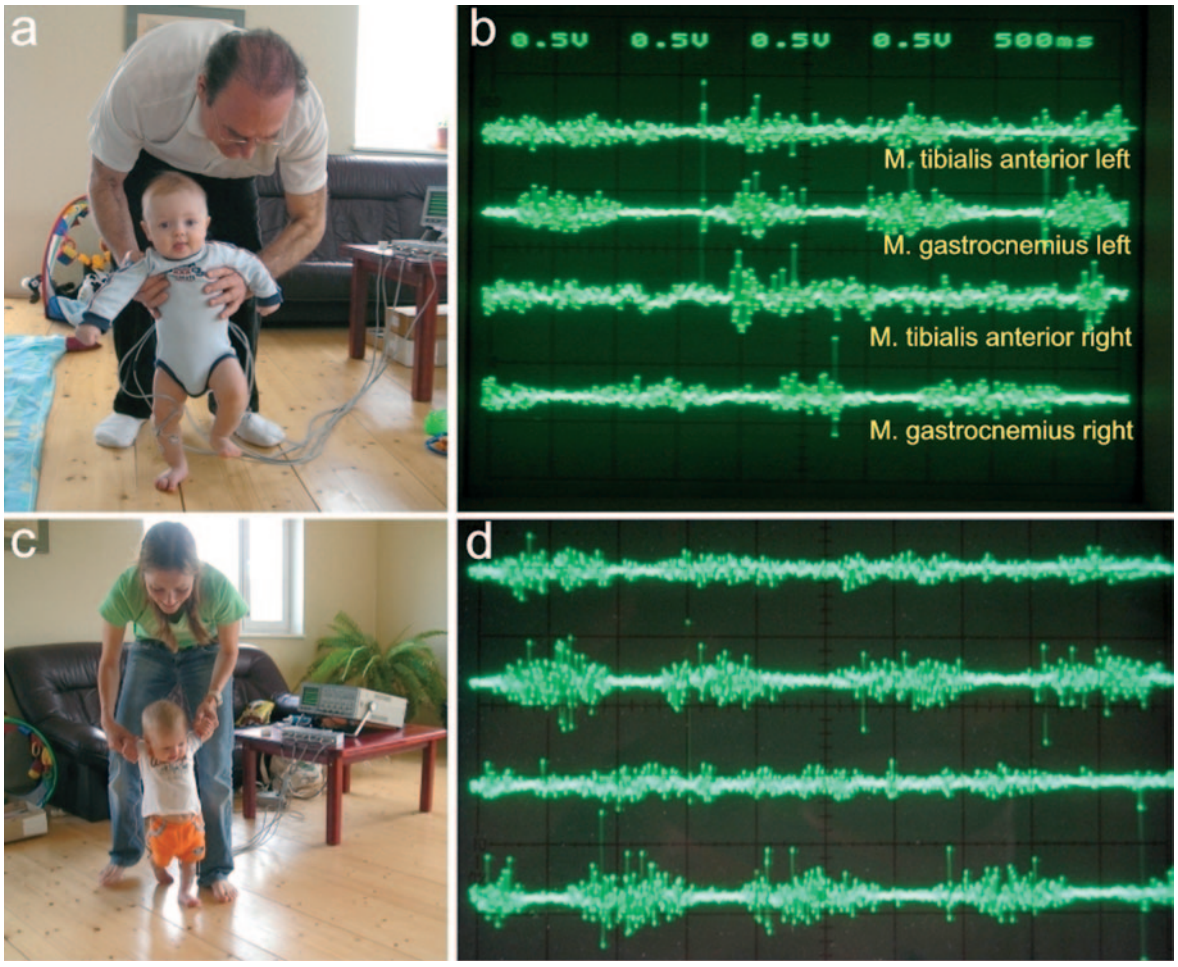


Fig. 1N. – Surface EMG obtained from the healthy 5-months-old (a,b) and 8-months-old old "Jürgen" (c,d) during supported walking. a. Walking resembles automatic stepping, because of the strong lifting of the left knee. The toes of the right foot are plantar flexed, which is not physiologic. b. Surface EMG motor programs of left and right tibialis anterior and gastrocnemius muscles. Note that there is no antagonistic action between the tibislis anterior and gastrocnemius muscles. The right tibialis anterior muscle shows no motor program. c. The walking is more walking like and not so any more much automatic stepping like. d. Better motor programs then 3 months earlier (b). Still there exists no antagonistic action between the tibialis anterior and gastrocnemius muscles. The activation of the right tibialis anterior muscle is a bit better than 3 months ago (b).

of spared fibres, the stepping automatism is induced either automatically (in some similarity to Fig. 1N,a) or volitionally (in some similarity to Fig. 1N,b) by the patient. To enhance the stepping automatism during training of walking and running, the heel has to strike the ground first (Fig. 1M,A). Because of missing dorsal flexion of the feet in patients, the heel strike is achieved by positioning the patient at the very front of the treadmill (Fig. 1L). By doing that, the forefoot reaches over the edge of the treadmill, and the heel strikes the most anterior surface of the treadmill first. The activation and optimisation of the stepping automatism, supported by the volitional emphasis of the patient, is of great importance to activate as many of the spared tract fibres across the injury site as possible. During leg support, the therapists can feel the differences in leg muscle activation, depending on whether the patient's arms are fixed (Fig. 1H, little regained trunk stability) or move in the naturally coordinated pattern (Fig. 1L, trunk stability achieved again). In SCI patients, the stepping automatism can be activated in the forward (Fig. 1E) and backward direction (Fig. 1F) during supported treadmill walking. It seems that in new born babies the stepping automatism can only be stimulated in the forward direction (Fig. 1M)! The induction of the stepping and walking automatisms seem to play a crucial role in the repair of the SCI and the therapists have to feel the contribution from the patient during supported treadmill walking for proper support. If the interpersonal coordination between the therapists and the patient is optimal (Fig. 1E,F,L), the patients will perceive the improvement in his/her performance and will definitely report it. It is difficult to see, how such motor learning situation can be mimicked in animals.

Training of automatisms to recapitulate ontogeny

Another crucial property of the genotype to phenotype mapping 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 in human include the early childhood automatisms creeping, crawling, up-righting, walking, running, balance training, visual-motor coordination, 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 (11).

The structural repair in human patients induced by CDT also tries to recapitulate the development (24, 25) as in animals research (5). Therefore, the movement-based learning therapy has to include those movements which are performed during the development to allow for successful succession of different phenotypic forms which are sequentially generated by the genotype. 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.

Results

Case report

A 17-year-old female patient suffered a severe spinal cord injury (SCI) at cervical 5/6 levels in a car accident. The spine was repositioned and fixed only one day after the day of the accident! When the patient fully woke up two days later, she had no sensations and no motor functions below the level of C4/5. Some function was preserved in certain arm muscles. Four weeks later, as the spinal shock regressed, some sensation reappeared all over the body. Some more muscles started to work in the upper arm. The injury level lowered to C5/6. The spinal shock involved therefore the spinal cord below the injury level and approximately one segment rostral to the injury site. In the following two to three months some more sensations in the body and some muscle functions in the upper arms returned spontaneously. A dorsal flexion of the hand became possible. No finger functions returned. The urinary bladder did not start working again. Her progress was consistent with usual clinical experience, that the spontaneous recovery is very limited in complete or near-complete SCI (Fig. 2). With respect to motor functions, the patient had a typically complete C5/6 injury. The breathing was paradoxical (see below); mainly driven by the diaphragm, innervated by the phrenic nerve. Because of some spared sensations, the patient was able to feel the support given by the therapist during therapy. A few weeks after the accident, the patient heard from friends about coordination dynamics therapy (CDT) and visited the author with her parents for the first measurement of the coordination dynamics. Two months after the accident, CDT was started.

At the beginning, the therapy was not optimal. There were big problems with the blood circulation. The patient often got dizzy and the skin below the injury level was very vulnerable. Also, the patient did not believe very much in the therapy at the beginning and had a big break in treatment after 2.5 months of therapy (Fig. 3). Seven months after the accident, the therapy became optimal and intensive with more than 20 hours of therapy per week. This patient started to fight for her future. The blood circulation improved strongly. Skin wounds occurred only sometimes and healed quickly. There was no risk of pressure ulcers any more. During the second year of treatment the patient trained at her limits with more than 30 hours per week and motor functions below the injury level re-appeared slowly. After 2 years of optimal (and intensive) CDT, the urinary bladder function returned to normal!

The following description explains in detail the re-appearance of motor functions in relation to the continuously performed coordination dynamics measurements for low load (Fig. 3).

In the following papers I will discuss the details of the urinary bladder repair on the basis of the system theory of pattern formation and the neurophysiology of the human bladder.

Anatomy (MRI)

To relate the severity of the anatomical injury of the SCI to the outcome upon optimal CDT, the extent of the anatomical injury was evaluated by using magnetic resonance imaging (MRI). The first MRI was done 10 months after the accident

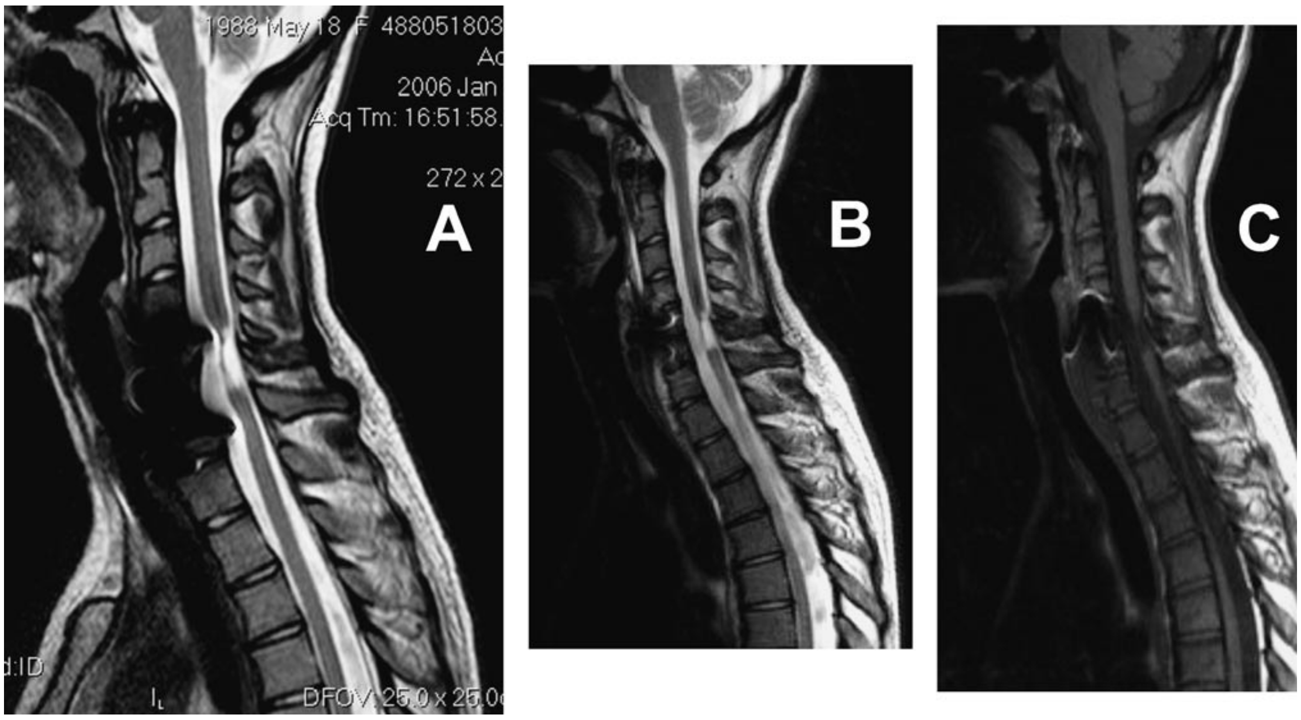


Fig. 2. – Magnetic resonance images of a severe spinal cord injury at C5/6 levels of an 18-year-old female patient who suffered the injury in a car accident. A. Sagittal T2-weighted image before removal of the spine fixation; note the imaging artefact caused by the metal. B, C. Sagittal T2 and T1-weighted images after removal of the titan-fixation. Note that in A and B there seems to exist only one connection between the rostral and caudal spinal cord, whereas in C two bridges may be seen. On all other sagittal images, no connections could be seen between the disconnected spinal cord parts. The author estimated an anatomical injury of 95% (5% spared spinal cord matter).

(Fig. 2A). The MRI seems to show that the screws from the spine fixation touched the spinal cord. After the removal of the fixation screws, the spinal cord seemed to be free, as can be seen in the sagittal T2 and T1-weighted images (from a second MRI), even though the spinal cord was quite close to the dorsal vertebra bone (Fig. 2B,C). But the patient suffered a partial 'Horner syndrome' during the operation, (sympathetic connections were slightly damaged), which was later cured with ongoing therapy. The author could approximately measure on the MRI that only 5% of the spinal cord matter was spared. In all other sagittal MR images related to Fig. 2, no spared spinal cord tissue could be seen at the injury site. Most of the spared tract fibres conducted sensory functions because the patient could not activate any motor functions on volition below the injury level. Since the injury extended over the length of only one vertebra, it seems possible that some fibres could regenerate over that distance with an intensive, long durational CDT.

Experimental evidence in the rat, which has a much higher capacity of regeneration, shows that the longest single regrown axons had a length of up to 14 mm (2).

After 3 years of CDT, a third MRI was done (not marked in Fig. 3). Both sagittal T2-weighted images (Fig. 8) show spinal cord tissue at the injury site, which connects the rostral and caudal spinal cord. In earlier MRI's (Fig. 2), only one sagittal T2-weighted image showed a connection across the injury site. Therefore, the spinal cord matter had increased at the injury site very approximately from 5 to 8%; regeneration had taken place. Since probably not all regenerating fibres are visible in the MRI, more fibres could have regenerated over the injury site. Further, the spinal cord injury site in Fig. 8 looks very healthy; as if a regeneration process is taking place. Such very approximately 3% of regenerated spinal cord matter could give rise to the functional recovery described below in detail.

Start of therapy

Coordination dynamics values were measured (Fig. 1G) continuously during the therapy and are plotted in Fig. 3. Since in severe cervical SCI the arms and hands have very little power (the biceps brachii is usually the strongest muscle left after such injury) and the legs are not helping due to the complete motor paralysis below the injury site, the patient found it very difficult to turn at a load of 20N (low-load exercising) on the special CDT device. However exercising on the special CDT device, at least in the lying position (Fig. 1H, right), is the first coordinated integrative movement which such a patient can perform by herself, since no trunk stability is needed and the patient can use help muscles for exercising. During exercising in the sitting position, the sitting in the wheelchair was a problem. Because of absent trunk stability, the patient was slipping out of the wheelchair. Support for trunk stability had to be given at the beginning.

The absence of trunk control and missing intercostal muscle activation could be seen as the cause of the paradoxical breathing. When the only spared breathing muscle, the diaphragm (innervated by the phrenic nerve from C3/4 segments), contracts during inspiration, the thorax becomes smaller and the abdomen distends. Because of impaired ventilation, there is always a risk of lung infections.

After a few months of therapy, the trunk stability improved to the extent that the patient did not slip out of the wheelchair any more while exercising in the sitting position. The intercostal muscles started to work successively in the rostral-caudal direction. The breathing became rather physiological only after 2 years of therapy. Blood circulation problems (orthostatic hypotension and other dysregulations) during exercising in the sitting position occurred only at the beginning of therapy.

Transient increase in coordination dynamics values for assessing regeneration

At the beginning of therapy the coordination dynamics values for exercising at a load of 20N in the forward and backward direction improved strongly (Fig. 3). When the therapy was stopped for some time in summer 2005, the values worsened. After restarting the treatment, the coordination dynamics values improved (got smaller) again. With the removal of the cervical spine fixation, the values became worse, which may indicate improvement of spinal cord functioning. Because of the relief of the slight cord compression, probably exerted by the fix-

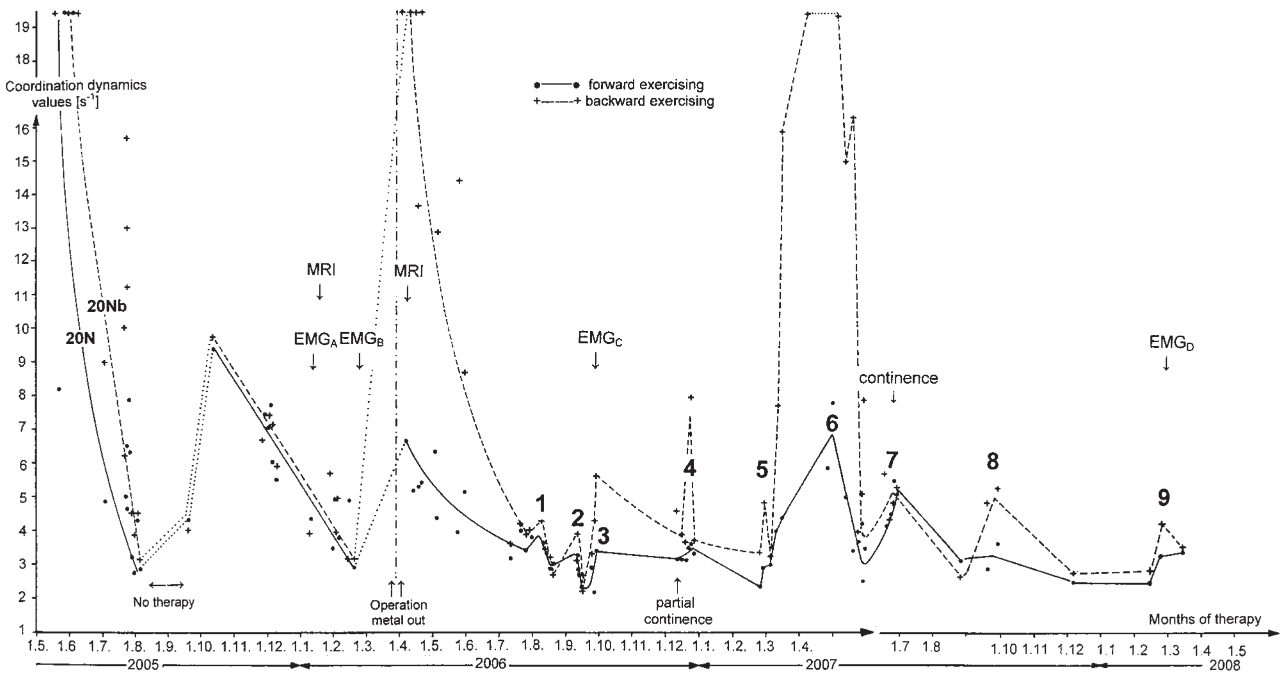


Fig. 3. – Relation of coordination dynamics values to therapy duration for a load of 20N and for exercising in the forward (lines and dots) and backward direction (20Nb; dashed line and crosses). Note that with no therapy the coordination dynamics values got worse (increased) and upon therapy they improved 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.

ation screws (Fig. 2A), the spinal cord functioned more integratively after the operation. The supraspinal centres now had more access to the neuronal networks of the disconnected caudal spinal cord and the enlarged neuronal networks worked initially with poorer coordination. During therapy, the coordinated firing of neurons improved again and also did the coordinated arm and leg movements, quantified by the coordination dynamics value. With ongoing therapy, nine further transient increases in the coordination dynamics value were measured. Each one could be correlated to the onset of a certain new function, indicating that the spinal cord regenerated very slowly in small steps. Each new bit of regeneration increased the access of supraspinal centers to the caudal spinal cord networks and worsened the coordinated firing of neurons transiently. The newly regained functions were trained strongly, to substantially activate the newly formed connections across the injury site.

In Fig. 3, the instances of transient increase in coordination dynamics values are marked with '1' through '9'. At increase '1' the patient felt more muscles working in the right leg. Also, the sensation in the right leg improved. At peak '2', the left gastrocnemius muscle showed spontaneous contraction. At '3' the antigravity muscles seemed to start to work. The patient was able to rhythmically swing a bit on springboard in the standing position. At '4' partial continence was achieved. The first in-phase jumping on springboard (Fig. 4A) became possible at peak '5'. With the large peak '6', the bladder worked better and the lower abdominal muscles started to work. With the transient increase of coordination dynamics values '7', full continence was achieved, even though the feeling of bladder fullness and emptying was still not the same as before the accident. The bladder functioning became more physiological with ongoing therapy. The patient was able to turn in the forward direction for 1.5 min at a load of 50N. The leg muscles seemed to help a bit during turning. This increased turning power is attributable to the beginning of the antagonistic action of the tibialis anterior and gastrocnemius muscles

(Fig. 6C,D). Goose bumps occurred all over the body when walking on treadmill (Fig. 1E,F), indicating a further improvement of functioning of the vegetative nervous system. For the first time during the 2 years of treatment the patient was able to achieve at least 5 turns only with the legs on the special device in the lying position. Definitely, some leg muscles contributed to the coordinated movements. At peak '8', the crawling became better and the arms became stronger. At '9', the patient could activate a bit the right tibialis anterior and gastrocnemius muscles on volition (Fig. 6A,B).

Indication for a regeneration of the human spinal cord achieved by long-term CDT

In conclusion, every instance of transient increase in the coordination dynamics value was associated with the reoccurrence of some somatic and/or autonomic functions. In this case of complete motor SCI, the stepwise improvement of motor functions, associated with increase in coordination dynamics values, indicates ongoing regeneration of the human spinal cord induced by CDT. This regeneration seems to take place by the formation of new functional network connections across the injury site in a step wise manner. The amount of reconstructed functional connections at every step is probably very small since very small increments in muscle power occurred.

Improvement of movements

Even though the patient had no motor functions left below the injury level, the motor functions slowly improved continuously in different groups of muscles with ongoing therapy. The trunk muscles started first to work successively in the rostral-caudal direction.

The exercising on the special device for turning in the lying and sitting position was possible from the beginning. The patient mostly exercised, when sitting in the wheelchair (Fig. 1A,G). When the trunk stability had improved, the patient could also exercise when sitting on a ball (Fig. 1B). In that position, the patient trained simultaneously arm and leg movements, trunk stability, and balance.

Supported treadmill walking (Fig. 1E,F) started first in the sitting and then in the upright position. First no muscles of the patient's legs helped during the supported leg movements; the movements were passive. Later on, the patient could help during treadmill walking. With ongoing therapy, the patient walked also in the backward direction and could move the arms in coordination with the legs (Fig. 1F). The speed was often in the range of 5 km/h. Sometimes even running on treadmill was trained up to a speed of 11 km/h. By moving arms and legs during walking and running, the patient trained automatic coordinated movements, which are generated by neuronal networks including those of the injury site.

The crawling started with the training of the crawling position with support like in Fig. 1I. Then the crawling position could be trained without significant support (Fig. 4C) (35). Slowly the supported crawling became possible (Fig. 1C). At a later stage of treatment, the patient trained the exact anti-phase coordination between arms and legs on a neuro-walker (Fig. 1D). Finger functions were trained, when the patient held the handles as well as possible. At the beginning of 'neuro-walking', the hands had to be fixed. Later on, no fixation was needed any more. For the patient's nervous system to receive also exactly coordinated movement induced afferent inputs, especially from hands and fingers, the patient's hands and fingers were held tightly to the handles of the neuro-walker by the therapist during supported training.

When the jumping on springboard (Fig. 4A,B) became possible (peak '5' of Fig. 3) without weight support (Fig. 4A), motor functions improved faster and full continence was achieved. The patient enjoyed this rather free jumping. The feeling to have full weight on the joints was fascinating for her. In general, the detailed information (anamnesis) of the patient's recurring feelings and movements gave a clinical understanding of the functioning of the patient's nervous system and helped to adapt the therapy to ongoing improvements.

Trunk stability was trained with different movements, including movements on the floor (Fig. 4C-F). Only at the beginning much support was needed, later on no or only little. The turning of the trunk was also exercised on the floor. Thus the patient became able to turn in the bed at night by herself.

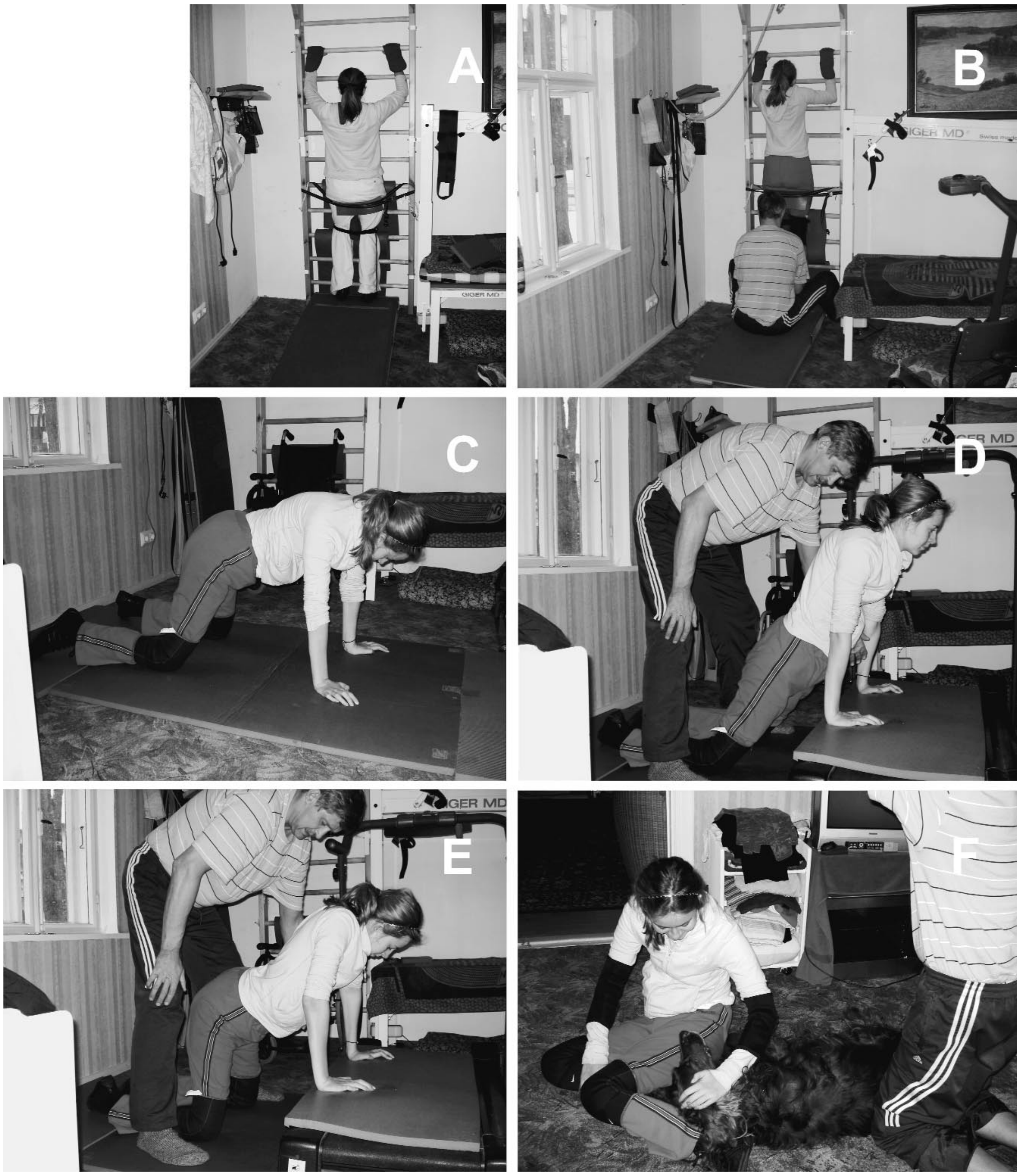


Fig. 4. – Movements mainly performed by the patient; severe cervical spinal cord injury (SCI); for MRI see Fig. 2. A,B. Jumping in-phase on springboard with and without support by a therapist. C. Training of trunk positioning (up-down, right-left, forward-backward). D,E. Up and down movements for training trunk stability; therapist (father) for safety behind. F. Training of trunk stability when playing with the dog; note the natural hand movement and positioning (no functional hand with shortened finger tendons!). Upon 2 years of CDT, the patient had enough arm and hand power for protection, if slipping (not to suffer a second SCI).

Surface EMG demonstrating improvement of motor functions

Surface EMG (sEMG) was performed several times when exercising on the special device (Fig. 1A) to show reinnervation of leg muscles. After 7 months of therapy sEMG was performed the first time (EMG_A, Fig. 3). Upon volitional activation of leg muscles, no EMG activity could be recorded. When exercising on the special CDT device for turning movements (Fig. 1A), however, gastrocnemius muscles could be activated but not the tibilias anterior muscles (Fig. 5A). Upon 9 months of therapy (EMG_B) the tibialis anterior muscles could also be activated, when exercising on the special device (Fig. 5B). But the EMG activity of the gastrocnemius and tibialis anterior muscles occurred at the same time and showed only minimal signs of a motor program. Therefore there was no antagonistic action between these two antagonistic muscles. At that time, the patient could nearly stand without support at the wall bars, but could not turn on the special device with the legs only, for which antagonistic muscle action is needed. It seems that the inhibitory loops or networks were not yet established in the neuronal networks at that stage of regeneration to further differentiate the mass contractions into physiological motor programs including antagonistic muscle action. After 14 months of therapy (EMG_C), the tibialis anterior and gastrocnemius muscles could be activated when exercising on the special device with the hands supporting the knees (pace gait coordination of arm and leg movements). But still no antagonistic EMG activity could be recorded from the gastrocnemius and tibialis anterior muscles (Fig. 5C). These muscles could still not be activated on volition.

After 2.5 years of CDT, however, the patient became able to activate a bit the gastrocnemius muscles on volition. The legs also moved a bit upon plantar flexion and the sEMG (EMG_D in Fig. 3) showed activity of some motor units on the gastrocnemius traces (Fig. 6A,B). In Fig. 6A some FF-type motor units seem to fire transiently oscillatory at a frequency of 20 Hz. As expected, the volitional activity exhausted quickly and was irregular, typical for a re-innervation process. Triphasic motor unit action potentials could be recorded (insets in Fig. 6A,D), indicating that the re-innervation process occurred in the central nervous system (CNS) and not in the peripheral nervous system (PNS) (in the muscle). In the case of regeneration in the PNS, one would expect more complicated wave forms than the classical triphasic muscle action potential. Clear

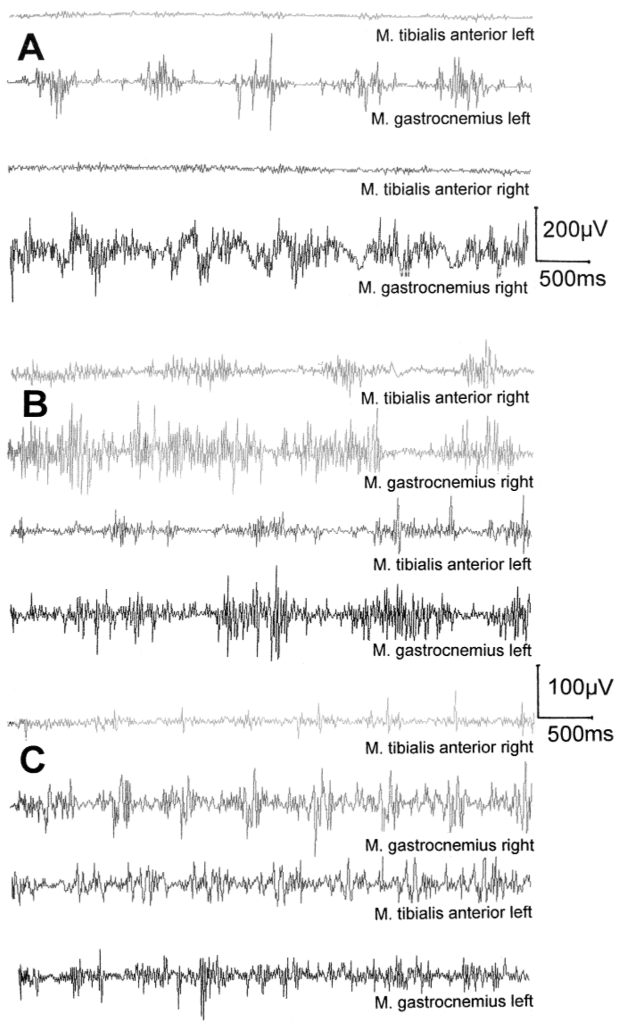


Fig. 5. – Surface EMG motor patterns of the right and left tibialis anterior and gastrocnemius muscles for exercising on the special coordination dynamics therapy and measuring device with ongoing therapy (for measuring layout see Fig. 1A; EMG recording dates are marked in Fig. 3). A (EMG_A). The tibialis anterior muscles are not activated. Movement artefacts on the trace of the right gastrocnemius muscle. B (EMG_B). Tibialis anterior muscles can be activated. Tibilalis anterior and gastrocnemius muscles of each leg are activated simultaneously = no antagonistic action. Patient obtained hand support during exercising. C (EMG_C). Patient exercises by herself with the hands on the knees (pace gait pattern). Still no antagonistic action between the tibialis anterior and gastrocnemius muscles.

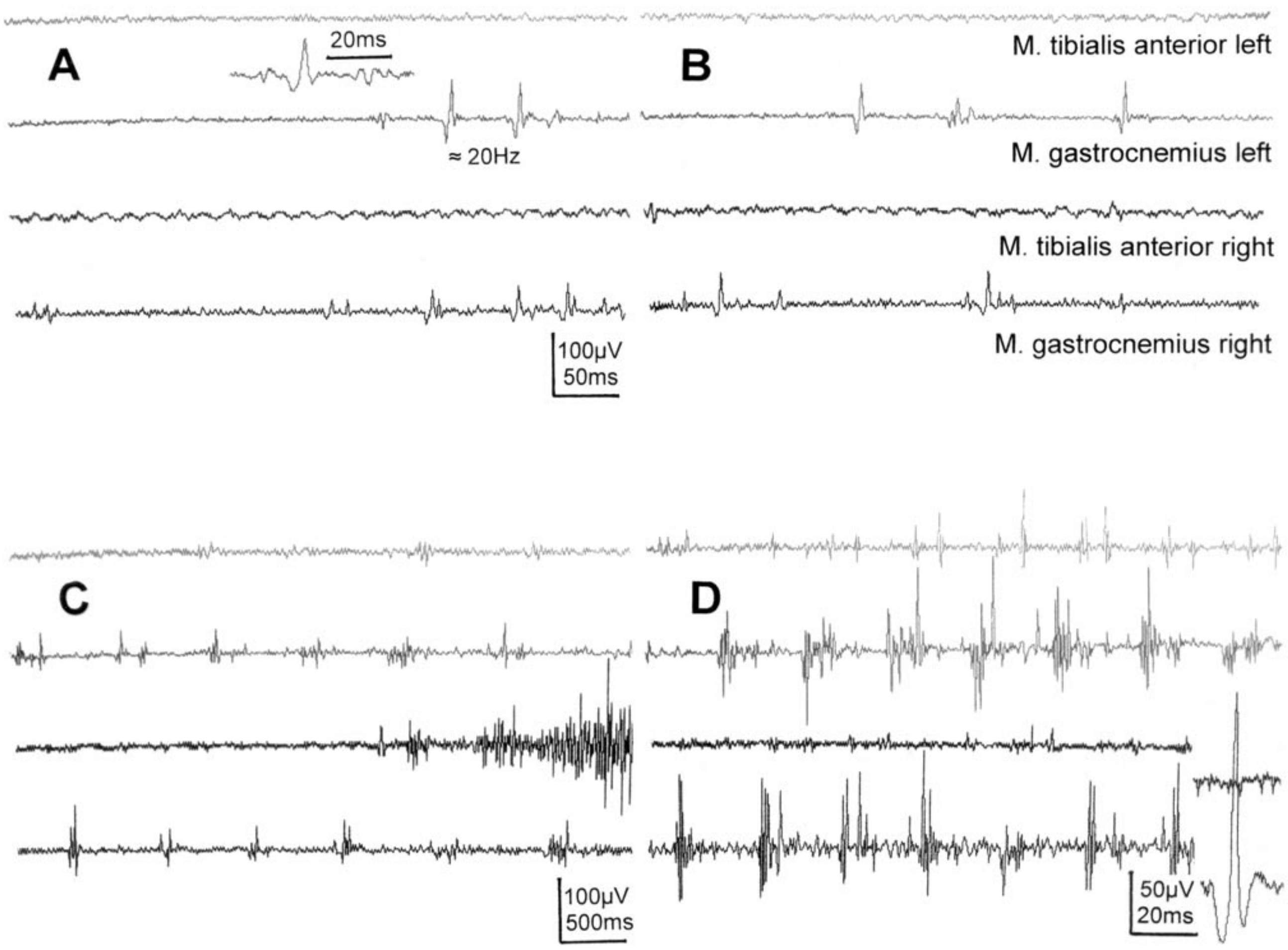


Fig. 6. – Surface EMG motor patterns of the right and left tibialis anterior and gastrocnemius muscles for volitional plantar and dorsal flexion (A,B) and for exercising on the special coordination dynamics therapy and recording device (C,D) after 2.5 years of coordination dynamics therapy (EMG_D). The inserts in A and D show triphasic motor unit potentials at stretched time scale. In "C" the patient is exercising automatically on the device and in "D" with additional volition and concentration; note the beginning of antagonistic action between the tibialis anterior and gastrocnemius muscles. Note further the beginning of continuous activity, due to starting spasticity on the trace of the right tibialis anterior in "C".

signs of an enlargement of motor units by sprouting in the muscle were also not found at this stage of re-innervation. Again, the morphology of motor unit action potentials would have been more complex due to the delayed activation of the by sprouting re-innervated muscle fibres.

Regeneration of the inhibitory system as quantified by sEMG

Varying motor programs could be recorded from the right and left tibialis anterior and gastrocnemius muscles, when the patient exercised somehow automatically (not concentrating on the movements) on the special CDT device for turning (Fig. 6C). The activity in the motor program bursts was comparably low. Upon supporting the automatic exercising volitionally, spasticity occurred first as in Fig. 6C (right side of tibilais anterior trace). When after approximately 10 turns the spasticity had decreased, motor programs occurred with more activity, seemingly similar to those recorded 1.5 years earlier (Fig. 5B,C). The important difference, however, was that some antagonistic action occurred between the tibialis anterior and gastrocnemius muscles. Before the onset of transient spasticity, the right tibialis anterior muscle was also activated antagonistically relative to the right gastocnemius muscle (Fig. 6C). The left tibialis anterior and gastrocnemius muscles also showed some antagonistic activation (Fig. 6D). The tibialis anterior and gastrocnemius muscles did not fully co-contract any more. The inhibition system had started the re-innervate the caudal spinal cord.

With the onset of volitional control in some leg muscles, the patient was able to vary the motor programs and could reduce on volition spastic motor activity more quickly.

Repair of autonomic functions

Even though animal research so far has been paid only little attention to the repair of the autonomic functions, they are very important for the longevity and the quality of everyday life of the patient.

Repair of urinary bladder and sexual functions.

The most important function for everyday life, the urinary bladder function, could be repaired, including the regeneration of the necessary tract fibres for volitional bladder control. Details will be given in the following publications. Since the sexual functions are sited also in the S2 to S5 spinal cord segments, a repair of the bladder function includes at least partly a repair of the sexual function. The jumping on springboard upon no weight reduction (Fig. 4A,B) (which trains the pelvic floor), contributed strongly to the repair of the urinary bladder and sexual functions.

Repair of the blood supply.

A repair of the blood circulation protects the patient from developing pressure ulcers, which can also become life-threatening. Since patients with severe cervical SCI have a very poor blood supply and are sitting often in one position in the wheelchair and/or are always lying in bed in one position, they are very prone to develop pressure ulcers. These ulcers are difficult to heal because of the poor blood supply. The repair of the impaired functioning of the autonomic nervous system in this patient re-established proper blood circulation and heart rate function and decreased the tendency of developing pressure sores. For the repair of the blood supply, a regeneration of the spinal cord may not be necessary, because the autonomic nervous system has different connections outside the spinal cord via different plexuses including the plexus hypogastricus. A network activation (following a network reorganization) of these intermingled plexuses can bypass the damaged spinal cord segments and may contribute to a functional repair.

Repair of breathing.

The repair of proper breathing was also important. Because of the C5/6 SCI, the intercostal nerves could not be activated any more which resulted in paradoxical breathing, whereby the respiration could only be achieved by the diaphragm, innervated by the phrenic nerve (from cord segments C3/4). In paradoxical breathing, the ventilation of the lung is poor and there is always a risk of lunge infections, which are again life-threatening. With the improvement of the trunk function down to the pelvis, the breathing problem was also solved. The muscles of the thoracic cage started to work again in the rostral-caudal direction. The rostral intercostals contribute most to the breathing (13, 14). The repair of breathing indicates some regeneration of the spinal cord since reinnervation of the motoneurons driving the intercostals by supraspinal centers is required for the coordinated functioning of intercostal muscles.

Partial repair of the sensations.

The different modalities of sensations also improved all over the body with ongoing therapy, like feeling of muscles, pain and temperature.

Discussion

Regeneration of the human spinal cord

The patient of this report had suffered a motoric complete cervical spinal cord injury (SCI). No motor functions could be detected below the injury levels C5/6. The approximately 5% spared spinal cord matter was therefore mainly conducting sensations. Within the three years of coordination dynamics therapy (CDT), some motor function of the trunk and legs reappeared. The patient was able to turn only with the legs on the special CDT device. For the in-phase jumping on springboard with slightly flexed knees (not using the legs as crutches) (Fig. 4A), trunk stability and some leg muscle functions are needed. These improvements of motor functions after 1 to 3 years therefore indicates a limited regeneration of the spinal cord.

Further evidence for the regeneration of the spinal cord is given in Fig. 3 with the transient increments in coordination dynamics value "1" through "9". Each peak correlated to the reappearance of a certain muscle or autonomic function. With the establishment of new connections across the injury site, the CNS sites rostral to the injury got more access to the neuronal networks of the caudal spinal cord, which increased the accessible networks and increased the coordination dynamics values. The CNS organization was transiently disturbed. With ongoing therapy, the self-organization of the enlarged networks improved and the coordination dynamics values again reduced quickly. With each small step of regeneration, a further transient increase in the coordination dynamics values occurred.

With the continuous recording of the coordination dynamics every few days, a stepwise regeneration of the spinal cord was detected. These frequent measurements did not result in loss of therapy time since for recording and therapy similar instruments are used. Since the patient always wanted to get good or better coordination dynamics values, she exercised with much concentration during the measurements, which means that the rate of motor learning was high during those measurements.

Upon 2.5 years of CDT it became possible for the first time to record volitional EMG activity on plantar flexion (Fig. 6A,B), which is a further evidence for the regeneration of the spinal cord.

The increased spinal cord matter across the injury site after 3 years of treatment (Fig. 8) supports the functional results that the spinal cord was in the process of regeneration. Actually the estimated 3% of regenerated spinal cord matter could account for this significant functional recovery.

Functional and structural repair is dependent on the severity of the SCI

In previous reports it was shown that CNS functioning could be improved in SCI by coordination dynamics therapy (CDT) up to a partial cure (18, 32). A recent publication on stem cell therapy and CDT, however, indicates that in complete SCI only minor improvement in motor functions below the injury level can be achieved (31). On the other hand, it was shown that if 50% of the spinal cord matter is spared, a near-total cure is possible upon CDT (32). In the present report it is shown that if approximately 5% of the spinal cord cross-sectional area is spared only, still some motor functions below the injury level can be repaired.

Therefore it seems that the extent of possible functional and structural repair is proportional to the amount of spared spinal cord matter. If 50% of the spinal cord matter is spared, a near-total cure is possible if CDT is administered for 3 years. If the injury of the spinal cord is 10 times more severe, that means if only 5% of the spinal cord matter is spared, then only a partial cure is possible even if an optimal CDT is administered for 3 years. If the spinal cord injury is even 10 times more severe, that means if only 0.5% of the spinal cord matter is spared (practical complete injury), then an improvement of motor functions below the injury level is extremely limited (31).

But the extent of the repair probably does not depend only on the percentage of spared spinal cord white and grey matter with respect to the cross-sectional area, but also on the longitudinal extension of the spinal injury. In this case, the longitudinal extension was in the range of one vertebra length. In more extended injury distances, the possible achievable repair will be smaller since less fibres regenerate over longer distances (2).

The repair of the spinal cord injury depends therefore crucially on the amount of spared spinal cord matter. A patient with an injury with 0.5% spared spinal cord cross sectional area has probably 100 times less potential of repair than a patient with an injury of 50% spared spinal cord matter for similar treatment. But this relation does not mean that nothing can be done in complete spinal cord injury (0.5% spared spinal cord matter). If, for example, a repair of the urinary bladder (the biggest problem in spinal cord injury) would need only 0.1% of the spinal cord matter to be reconstructed, then the urinary bladder could also be repaired in the case of a complete spinal cord injury. Also, some caudal autonomic networks have connections to rostral ones outside the spinal cord.

Generation of the geographical landscape of chemoattractive and chemorepulsive gradients for homing of new cells and connections

With respect to functional repair, the relationship between the severity of the injury and the outcome following 3 years of CDT is plausible. If more spinal cord matter is spared, more functional reorganization is possible. If more connections are spared, other CNS networks can take over functions more easily. The geographical landscape of attractors of pattern formation is less pathological for more spared spinal cord matter and probably improves faster in the direction of an attractor layout with physiologic attractors with optimal treatment. The repair of the attractor 'urinary bladder function' upon CDT will be tackled in following publications.

But what does this relationship between outcome and severity of the injury mean for the mechanisms of structural repair? It could mean that the strength of the general stimulus for the regeneration of the human spinal cord depends on the amount of spared tract fibres and neurons available at the injury site and also on their activation while training at the limit (range of overreaching (30)). For the generation of a physiological geographical landscape of chemoattractive and chemorepulsive gradients to encourage sprouting, guidance of regenerating axons, and neurogenesis, many coordinated integrative movements have to be exercised to recruit all the spared tract fibres through the activation of physiologic movement patterns (Figs. 1A-L,4). For the specific repair, the microenvironment of single neurons in the range of 0.1 µm (31) may be of importance to have high enough concentrations of attracting and repulsive neurotrophins available. The microenvironment of neurons, axons, dendrites, and glia willcific homing of these cells and connections to re-establish specific circuitry. This specificity of geographical landscape formation is the basis for the development of a physiologic pattern formation (see Method).

If the regeneration is proportional to the number of successfully activated spared and regenerated fibres, then the structural repair would become more difficult with the increase of the severity of the injury and the extent of the inefficiency of the treatment.

Repair of motor functions

The motor functions did improve, even though the patient was yet far away from walking again. She is still not independent in life. But the independence in everyday life seems possible to achieve, if optimal CDT would be continued. Further motor functions are not only needed for independent locomotion, but also for further structural and functional repair of the spinal cord. A big problem in severe cervical SCI actually is that there are not enough motor functions spared to train and therefore to repair the spinal cord networks.

Lack of muscle power

It was shown that with CDT functional and limited structural repair was possible to achieve. With ongoing therapy more and more muscle functions reappeared. But for everyday life one needs not only muscle function; one also needs adequate muscle power.

If 50% of the spinal cord matter was spared, the patient could generate enough muscle power to walk, run, and jump (32). But if only 5% of the spinal cord matter is spared (Fig. 2), then the carrying of the body weight, as for example during walking, is a big problem.

The difference in functional muscle power generation between the cases of 50% and the 95% injury can be quantified when exercising on the special CDT device for turning. The patient with 50% spared matter relearned exercising at high loads up to 200N within three years but the patient with 5% did not. The patient with 5% spared matter succeeded in exercising just at a load of 50N in 3 years. The difference in functional muscle power can also be seen in Fig. 7. The patient with 50% spared spinal cord matter could easily turn with arms and legs at a load of 50N and the coordination dynamics values continued to improve with therapy. The patient

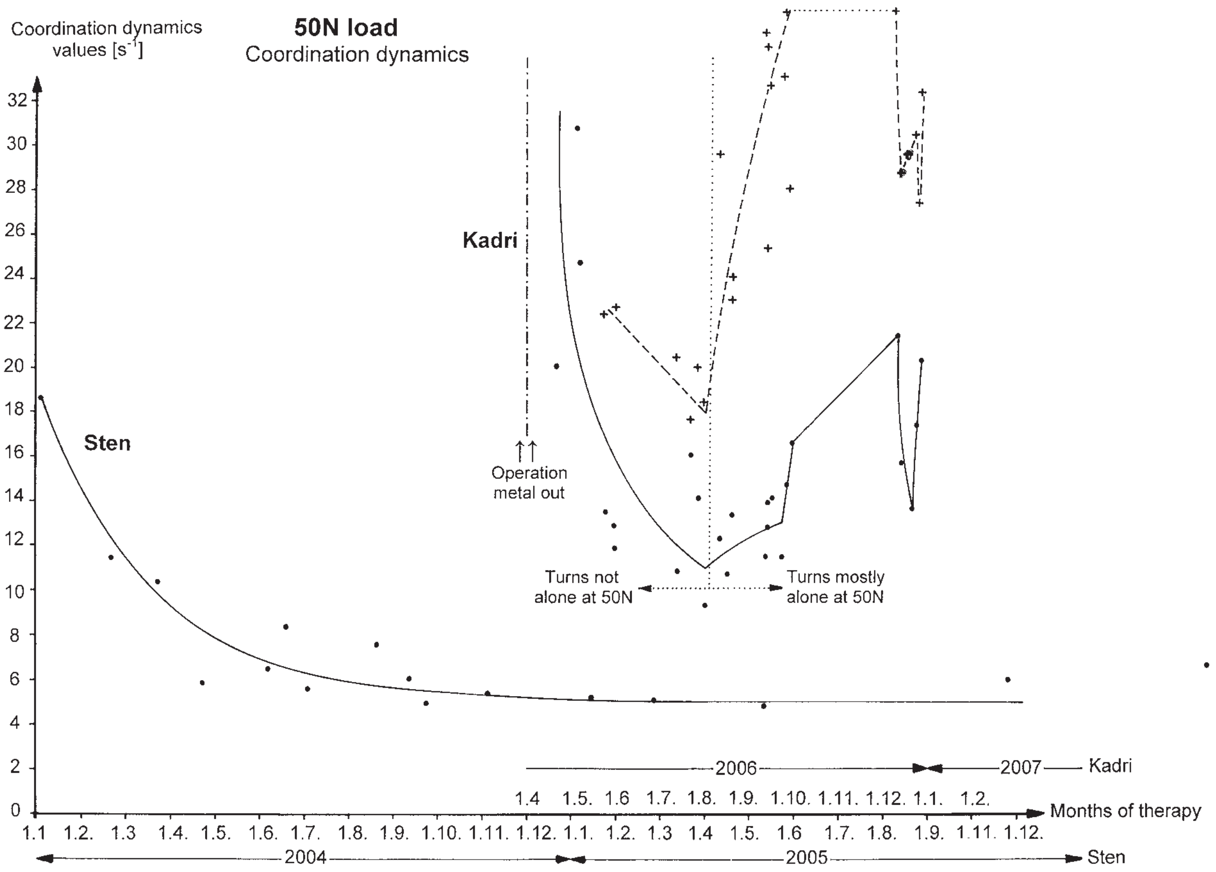


Fig. 7. – Comparison of the relations 'coordination dynamics values to therapy duration' for a load of 50N between a 50% (Sten) and 95% (Kadri) spinal cord C5/6 injury. Note that the coordination dynamics values for the 50% injury improve smoothly upon therapy whereas the ones for the 95% injury do not improve and are unstable (dashed line = backward exercising).

with only 5% spared spinal cord matter however had big problems to manage that load of 50N and the performance was irregular with ongoing therapy and needed help (Fig. 7). The patient always became quickly exhausted (and tired) upon exercising at that load.

Similarity between repair and ontogeny with respect to the stepping and walking automatisms

A new born baby can step automatically on heal strike (Fig. 1M). Later during ontogeny, the automatic walking is learned. It seems that the stepping automatism is integrated and modified by supraspinal centres to generate the walking automatism. In this integration process, at the beginning the walking automatism seems to be more automatic-stepping-like with an emphasized knee lifting (Fig. 1N,a) and becomes more walking-like later on (Fig. 1N,c).

During repair and regeneration following severe SCI, often the stepping automatism did re-appear first and then the volitional walking pattern developed. However, the muscle power was still significantly less than in the less severe injuries. The automatic stepping or automatic walking needed therefore body-weight support in addition to leg support.

Sometimes patients with CNS injury have a pathologic plantar flexion of the toes and have therefore problems to get their feet into the shoes. Such kind of spasticity can be reduced by CDT. During development also an infant may develop such a plantar flexion of the toes transiently as seen in the case of the five-months old infant Jürgen in the right foot (Fig. 1N,a). This is in accordance with the yet-absent proper motor program driving the right tibialis anterior muscle (Fig. 1N,b). Three months later (Fig. 1N,c), the development seemed to have corrected this non-physiologic positioning of the toes 'en route'. At that time the sEMG motor program of the right tibialis anterior muscle also seemed to be better (Fig. 1N,d).

Impairment of antagonistic action between tibialis anterior and gastrocnemius muscles during ontogeny and repair

With the change from the stepping automatism to the walking automatism during ontogeny, strong impairment of the antagonistic action of the tibialis anterior and gastrocnemius muscles could be measured in a healthy 5 and 8-months-old infant (Fig. 1N,b,d).

When the patient with the severe cervical SCI became able to perform supported automatic walking on the treadmill (Fig. 1E,F), a synchronized activation of the right and the left tibialis anterior and gastrocnemius muscles was recorded (Fig. 5) when the patient exercised on the special CDT device for turning (Fig. 1A). But after 2.5 years of CDT, the antagonistic action slowly established in the patient's leg muscles (Fig. 6C,D). Therefore there seems to be similar problems in the establishment of proper motor patterns during ontogeny and repair.

Reinnervation pattern of trunk and leg muscles following SCI may be an example how supraspinal centres establish control over caudal neuronal networks during ontogeny

By measuring continuously the low-load coordination dynamics values with ongoing CDT, it was found that transient increments in the low-load coordination dynamics value occurred continuously (Fig. 3), which corresponded to the re-occurrence of motor and autonomic functions.

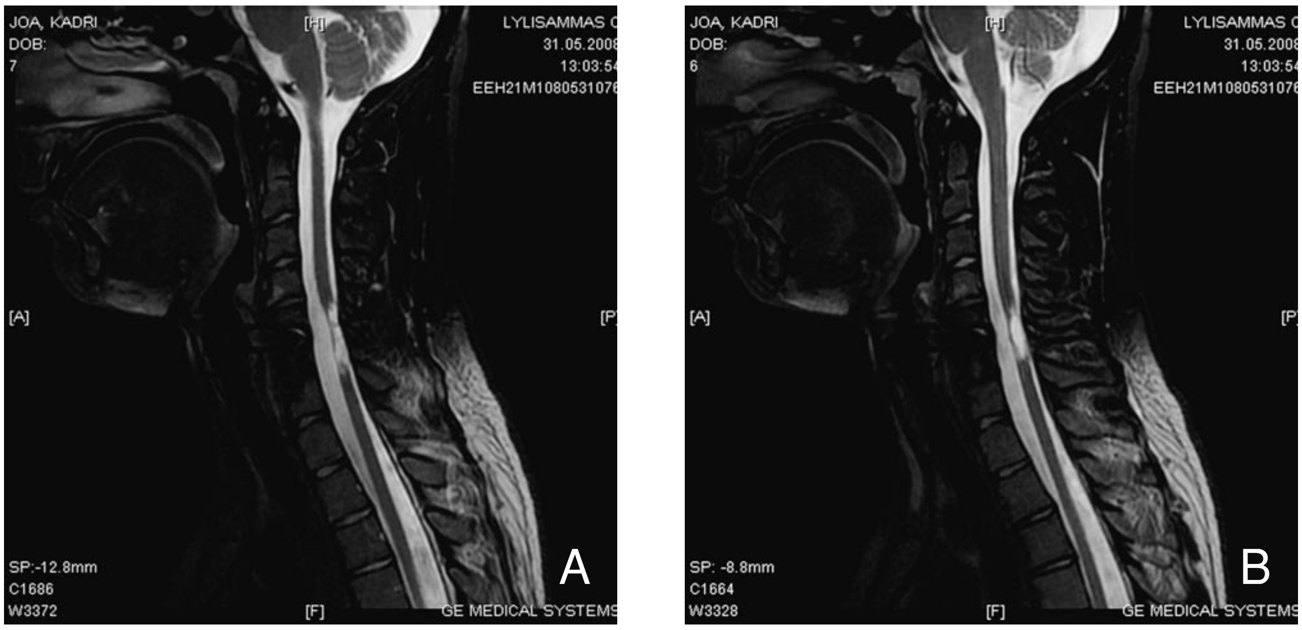
It is conceivable that when supraspinal centres take over control of the neuronal networks of the spinal cord during ontogeny, as for example during the learning of walking, also transient disturbances of the coordinated firing of CNS neuronal network are caused. The disturbances of the coordination dynamics of CNS organization during development are also continuously corrected by learning in the way that the CNS is communicating with the environment. A deprivation of such communication, as too little walking, running, jumping, and training balance during childhood, may lead to deficiencies in the development. In this case, there are not enough possibilities for the CNS to communicate with the environment for a 'correction en route'.

The movement-based learning during ontogeny is especially efficient if it includes highly coordinated movements like fast running and exercising on the special CDT device for turning. The ongoing increases in the coordination dynamics value and the subsequent improvements in Fig. 3 may therefore give an example how in principle the 'correction en route' during ontogeny takes place.

Endogenous versus exogenous stem cell therapy: distance of action of neurotrophins

It has been shown that administered CDT can bring about near-complete cure in SCI if 50% of the spinal cord matter is spared (32). As shown in this article, a partial cure is also achievable, even if only 5% of the cord was spared. But in a complete SCI, CDT has not been very successful so far, and also not the hematopoetic stem cell therapy (31). The movement-based learning therapy (CDT) is therefore especially successful if a sufficient number of tract fibres are spared to allow substantial learning. In this paper it is shown that, even in a near-complete spinal cord injury, some regeneration of the spinal cord could be achieved, though to a very limited degree. In the future it needs to be estimated how much regeneration is possible and necessary to achieve sufficient cure. This very limited structural repair that could be achieved in the above case also means that the endogenous stem cell recruitment, as a part of the structural repair of CDT, was also very limited. Even the combination of exogenous and endogenous (as a part of CDT) stem cell therapy, as was reported earlier (31), was unsuccessful in human, if it worked at all.

In a frog model for studying development and repair, it was partly analyzed that the distance of action of attracting and repulsive neurotrophins were probably in the range of 0.1 μm (31). Such a short distance of action is probably difficult to achieve in exogenous stem cell therapy in human. Further qualified research in animal and human needs to be



Kadri MRI12.3. 2008 Kadri MRI212.3. 2008

Fig. 8. – 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 of Figure 2, there seem to be more connections between the disconnected spinal cord parts, because at the beginning of therapy (Fig. 2) connections could be seen only on one sagittal T2-weighted image.

performed,trophins, till then, the author believes that one is not justified to perform exogenous stem cell therapy in human. It is unethical to perform unqualified experiments on human under the name of therapy trials.

In this research project, the distance of action of geographical landscapes like distributions of attracting and repulsive neurotrophins will be addressed again. But in the following publications I shall first show in detail how the urinary bladder functions in this patient could be cured. I will try to show that only with deep knowledge in human neurophysiology a substantial progress in the cure of diseases can be achieved.

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