Contents

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Giselher Schalow
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Genetic Disease Repair (5p-) Through Coordination Dynamics Therapy I

Giselher Schalow*

Untere Kirchmatte 6, 6207 Nottwil, Switzerland.

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ABSTRACT

The 9.5-year-old patient Anna with severe cri-du-chat syndrome learned creeping, crawling, up righting, walking, running, jumping and climbing staircases through 4.1 months of rather optimal coordination dynamics therapy (CDT). The emotional pattern crying and laughing became operational. It is the first time that a real progress through therapy is published in this genetic disease. The lost piece of chromosome 5 included 5p15.1 through 5p15.33. Vojta, Bobath, and exercising on the "Locomat" did not improve Anna. Only low-intensity CDT at an age between 5.5 to 9.5 years made her walking a few steps. It cannot be excluded that with this optimal 4.1-months CDT at an age of 9.5 years, genetic plasticity started to take place and not only a repair of the malformed central nervous system (CNS) caused by pathologic development due to the genetic disease. This coordinated-movement-based learning therapy seemed to be capable of targeting the epigenome and altering gene expression and hence to repair the CNS in Anna, especially in the phase of super-coordination. The possibility of repair through gene expression changes is supported by CNS repair through CDT in traumatic brain injury, spinal cord injury, stroke, Parkinson, spina bifida, cerebral palsy, coma patients, bladder incontinence, basal ganglia injury, spinal muscular atrophy and cancer growth inhibition. Even though cognitive functions improved, Anna did not learn so far to speak, apart from the three words mama, tata and baba, and to read, write and calculate.

CDT was developed within 36 years on the basis of human repair-neurophysiology, including human anatomy, human neurophysiology and CNS repair data of human patients. The anatomy of the cauda equina nerve roots, down to teased nerve fiber dissections, were clarified to develop the single-nerve-fiber action potential recording method to measure simultaneously the natural impulse pattern of single-nerve fibers running in and out of the CNS and analyze human CNS functioning. With the discovered phase and frequency coordination among neurons for neural network organization, which becomes impaired following injury, malformation and degeneration, CDT was developed to repair the impaired phase and frequency coordination and induce plasticity by using coordinated movements from phylogeneses and ontogenesis. By combining human repair-neurophysiology with the System Theory of Pattern Formation and using a special CDT device for coordination treatment and measurements of arm and leg movements, the progress in CNS repair could objectively be quantified by a single-coordination dynamics value, which could be compared with existing values of healthy children.

Keywords: Human repair-neurophysiology, Single-nerve fiber action potentials, Neural network organization, Phase and frequency coordination, System theory of pattern formation, Coordination dynamics therapy, Continence, Genetic disease repair, Super-coordination phase

INTRODUCTION TO HUMAN REPAIR-NEUROPHYSIOLOGY

Disease repair through Coordination Dynamics Therapy

Human repair-neurophysiology is a new discipline with which the human nervous system can be repaired. Since the nervous system is involved in nearly all body functions, the general health can be improved. By combining Human Neurophysiology with the System Theory of Pattern Formation, there is a theoretical basis that through movement-based learning vegetative and cognitive functions can also be repaired by learning transfer.

Corresponding author: Giselher Schalow, Untere Kirchmatte 6, 6207 Nottwil, Switzerland, Tel: 0041419371641; E-mail: g_schalow@hotmail.com

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Based on human repair-neurophysiology [1,2], a movement-based learning therapy was developed though neural network learning [3], called Coordination Dynamics Therapy (CDT), with which it is possible to improve or repair central nervous system (CNS) functioning after stroke [4], traumatic brain injury [5,6], spinal cord injury [7-13] **(Figure 1A-D)**, cerebellar injury/atrophy [14,15] **(Figure 1E-H)**, cerebral palsy [16], hypoxic brain injury [17], in Parkinson's disease [18], spina bifida (myelomeningocele) [19] and scoliosis [20]. Speech had been induced and improved in a patient with severe cerebral palsy [1]. A permanent coma patient could be brought out-of-coma and relearned to speak and move [21,26] and cancer grows could be inhibited through CDT [22,23] by improving cardio-vascular performance [1,21] and building of natural killer cells [24]. Urinary bladder functions [1] could be cured in cerebral palsy [1] and spinal cord injury [7,12,13]. There is indication that general health can be improved via CDT to live longer with a better quality of life [25] and euthanasia can be avoided in organ donation [26]. Basal ganglia injury was also repaired [27], spinal muscular atrophy stopped [28] and incontinence repaired [29,30].

It was shown that incontinence was firstly due to bladder wall function impairments so that stretch, tension and flow receptors in the bladder wall fired already in the empty bladder and mimicked a rather full bladder, even though being empty, and secondly due to pathologic neural network organization of the sacral and pontine micturition centers. Since in 8 out of 10 patients' continence was repaired [29,30] means that not only the neural networks were repaired, but also the bladder wall was repaired in these patients. Therefore, CDT is repairing more than just the neural networks of the CNS.

Figure 1. The spinal cord injury patient Nefeli relearned to walk and became continent again (A-D) [7,13]. The cerebral palsy girl Sophie with atrophied cerebellum and pons could not stand, walk, run (E, F) or jump and was incontinent. She learned to walk, run (G, H) and jump, became continent and her higher mental functions improved [15].

But why is the training of the very exactly coordinated movements much more successful than the not coordinated or only little coordinated movements? One reason could be that the excitation-neurogenesis coupling [31] is more efficient with coordinated excitation. To get more information on functional gene repair, the 9.5 years old Anna with a genetic disease (5p- syndrome (cru du chat)) is treated in this article for functional improvement of motor, mental and cognitive functions.

Medicine is the discipline to cure or improve diseases in human patients. Often it starts with anatomy, followed by physiology and then the clinic. In this article more details are given of the scientific basis of the treatment CDT to cure or improve many diseases [4-30]. The human repair neurophysiology starts from the scratch, that means with the anatomy. Since primarily the CNS should be repaired, the specific anatomy of the spinal cord and it nerve roots are presented in detail. With the newly developed single-nerve fiber action potential recording method, the functioning of the human CNS is partly analyzed at the single-neuron level and the important phase and frequency coordination among neurons of neural network organizations found. Its impairment is repaired and measured on the basis of human repair-neurophysiology. The repair of CNS and body functioning is demonstrated on continence repair by repairing the sacral and pontine micturition centers and the urinary bladder wall.

In the Method, CDT is explained and, in the Results, the improvements of motor and cognitive functions through CDT of the patient Anna presented.

Anatomy

Anatomy of spinal cord and cauda equina nerve roots

For exploring the spinal canal with the spinal cord and the nerve roots, the dissection of approximately 50 cadavers was started from the back side **(Figure 2)**. The anatomical situation was explored and then the cord with the roots removed.

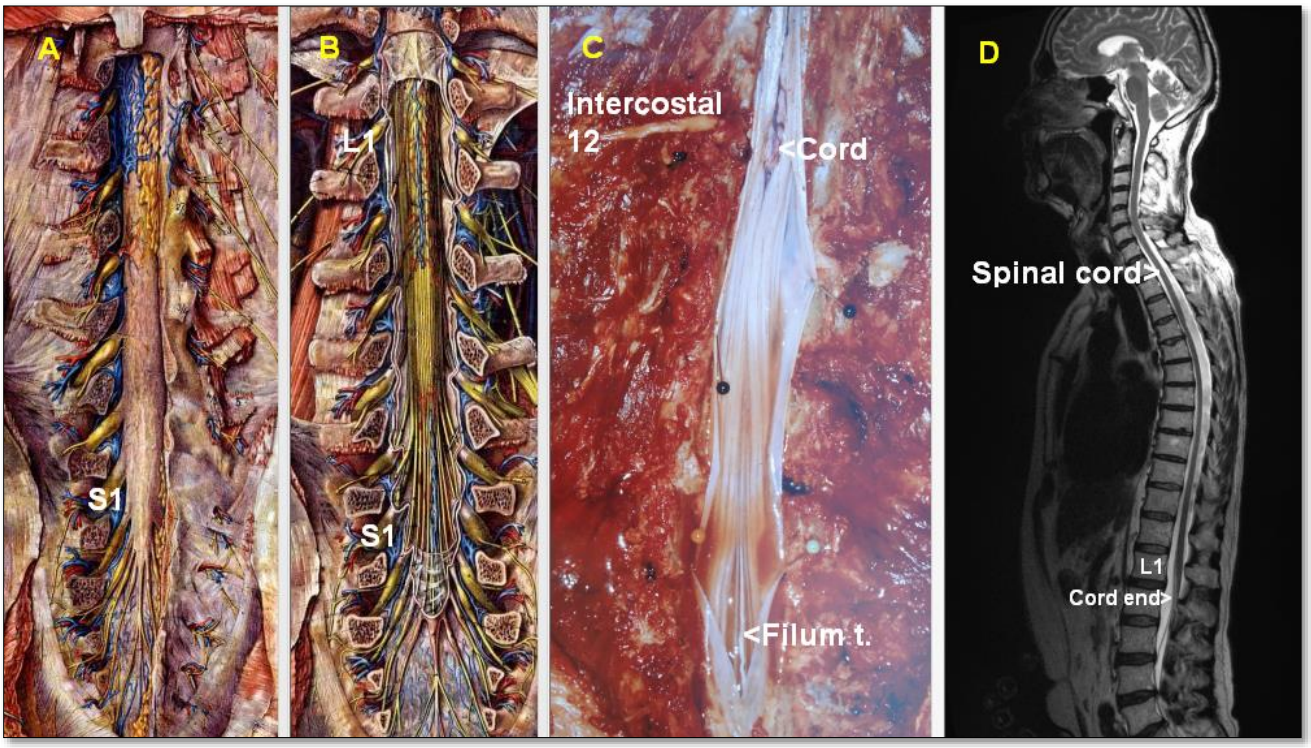

Figure 2. Caudal spinal cord with cauda equina nerve roots and ganglions. A, B. Paintings with dura in place (A) and removed dura (B) (from Pernkopf). C. Original dissection by the Author. Filum t.=filum terminale. D. MRI of the spinal canal with the spinal cord and cauda equina from the Author. Probable spinal cord end is indicated.

Figure 2 shows the lower spinal cord with its nerve roots and nerves. In A the dura is shown with its ganglions. Note the epidural excessive vascularization. During a lumbar puncture, bleeding may occur and for a few hours the patient has to be under control to be sure that the bleeding is not too excessive to produce pressure onto the cord. Bleeding in and outside the brain and spinal cord damages nervous tissue because of pressure due to limited space. In B the dura is removed; the nerve roots, nerves and ganglions can be seen. In the patient Nefeli **(Figure 1)** the cancer (neuroblastoma) grew from the ganglion Th10. The caudal spinal cord with the cauda equina nerve roots can be seen in C. The 12th intercostal nerve and the filum terminale are indicated. In D an MRI shows the whole spinal cord and parts of the cauda equina. The probable caudal end of the cord is indicated. The spinal cord is fixed in the spinal canal by the denticulate ligament so that the vertebra of the spine cannot touch and press. Under physiologic conditions no bone pressure is exerted onto the cord.

Figure 3 shows the human CNS with the nerve roots. Since the single-nerve fiber action potential recording method will be developed below for analyzing CNS

functioning, the anatomy of the nerve roots is of special interest and will be analyzed now.

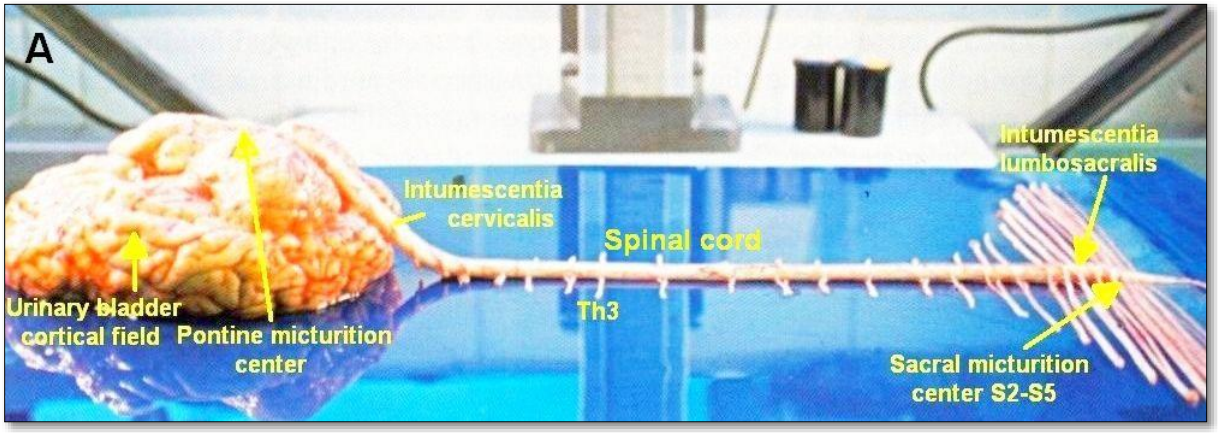

Figure 3. The human CNS with the sacral and pontine micturition centers. A difficult dissection (by the Author) to have the brain and the spinal cord together. To make the length and thickness of the roots visible, the roots are turned away from the cord.

Figure 4 shows the dorsal (A) and ventral (B) view of the lower spinal cord with its nerve roots. The calibrations show that the nerve roots are up to 20cm long. The whole spinal cord is shown in **Figure 4C** the ventral roots are often thinner than the dorsal ones. Especially the lower ventral sacral nerve roots are very thin.

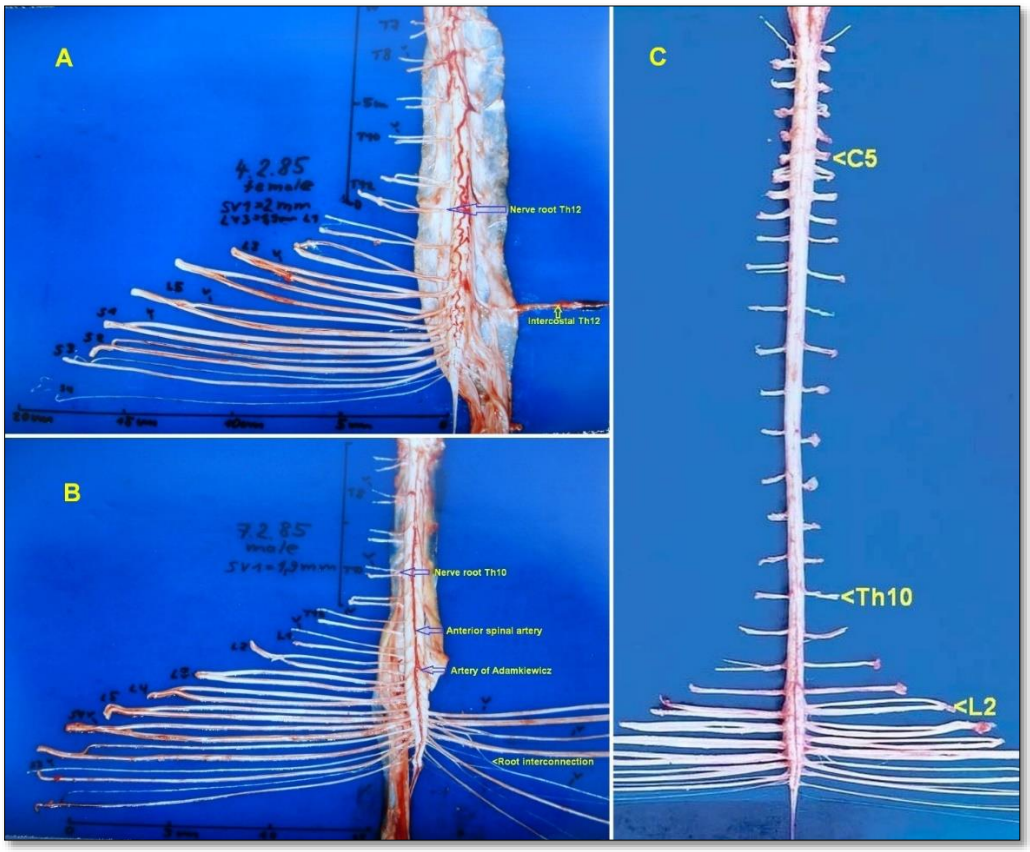

Figure 4. Human spinal cord from dorsal (A) and ventral (B, C). Intumescentia cervicalis and lumbosacralis are visible in C. The caudal ventral roots are thinner than the dorsal roots. The passage of the artery spinalis magna (Artery of Adamkiewicz) and the anterior spinal artery are indicated. The C5, Th10 and L2 roots and the intercostal nerve Th12 are indicated. The S1 root can easily be identified, because its ventral part is the last thick one in the caudal direction. Dissections by the Author.

For recording from identified nerve fibers and their connection to organs, the roots have to be identified with their nerve fiber populations [32].

Diameter, cross-sections and axon densities of nerve roots

The diameters, cross-sections and axon densities of the nerve roots are given in **Figure 5** [33].

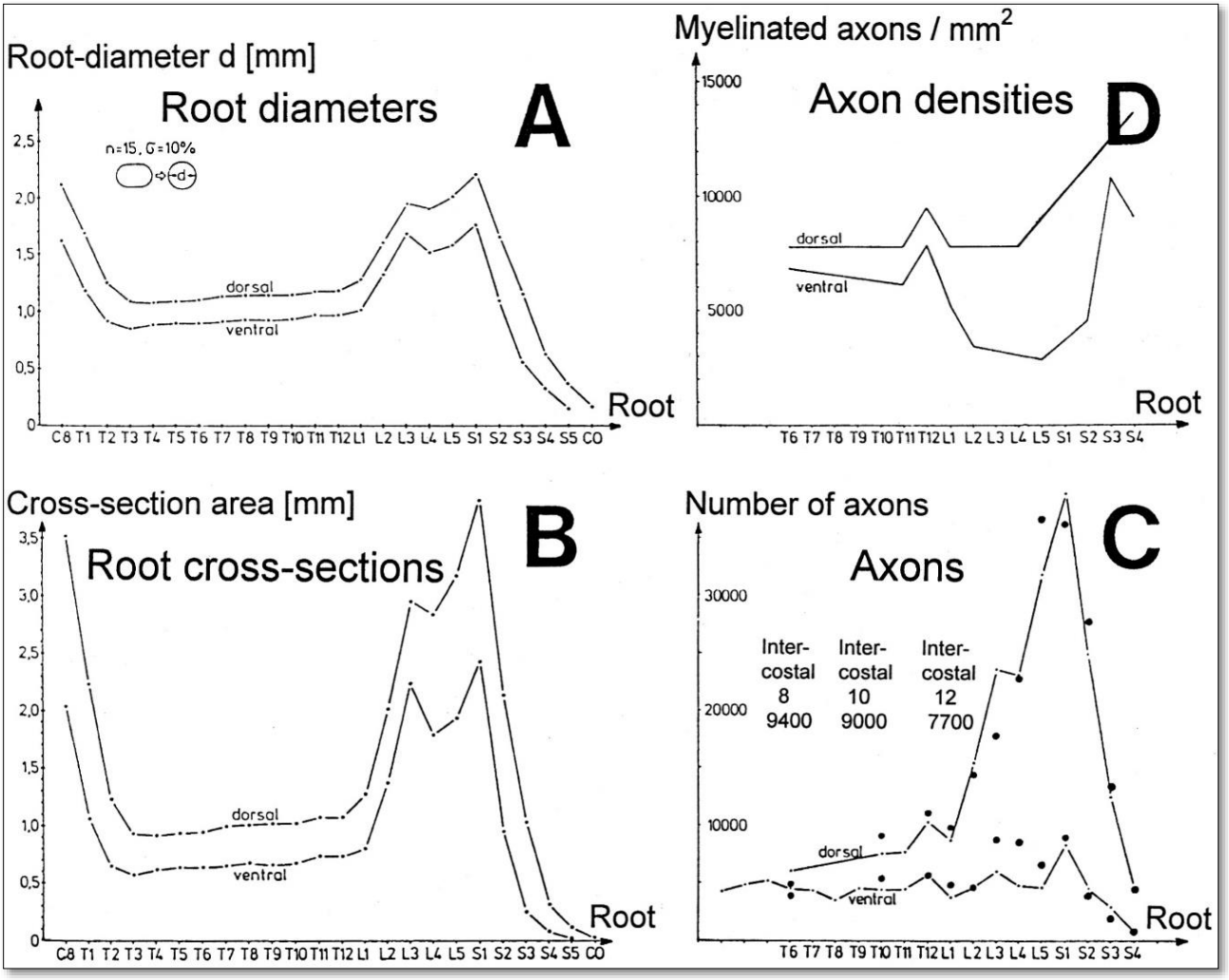

Figure 5. A. Dorsal and ventral mean root diameters of 15 cadavers in relation to the root level. In the case of elliptic shaped cross sections, the diameters of the circle with the same area were taken. The standard deviation was 8 - 10%; 10% for the smaller roots. B. Dorsal and ventral mean root cross section areas, calculated from A, in relation to the root level. C. Number of myelinated axons of dorsal and ventral roots. The line for dorsal roots is the average of 2 van Gieson stains and the tuloidin blue stain. The line for the ventral roots is the average of 3 ventral root counts. The large dots are counts from the tuloidin blue stain; upper dots are the dorsal counts; lower dots are the ventral counts. The deviation of the dots indicates the variation of the axon counts. The inserted axon counts from the intercostal nerves 8, 10, and 12 are from the tuloidin blue stain count. As viewed under the light microscope, the intercostal nerves 8 and 12 had about the same cross section area; the 10th intercostal about a 10% smaller one. D. Approximate densities of myelinated axons in relation to the root level, calculated from B and C (density = number of axons / cross section area).

For recording single-nerve fiber action potentials, we need to know what nerve roots are most suitable for recording extracellular action potentials. Such ideal root is the ventral S4 root, because it is thin, long and does not contain too many afferent and efferent nerve fibers. Such a nerve root is shown in **Figure 6**. For clarity, the sacral lower ventral roots (motor roots) contain besides efferent (motor) fibers also some afferent fibers from receptors of the periphery [34].

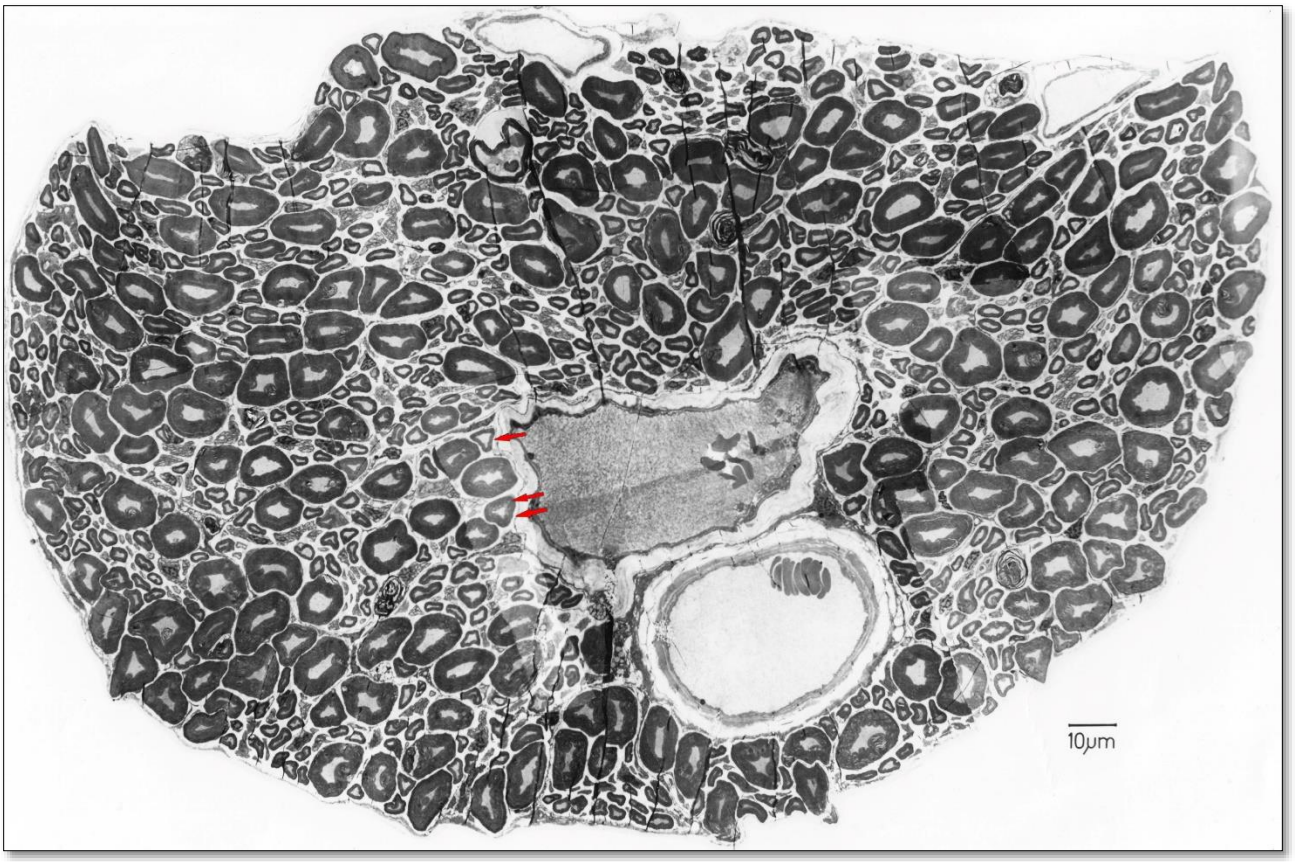

Figure 6. Montage of several electron microscope photographs of the S4 ventral root from HT1. Single arrow marks a nerve fibre with a comparably thin myelin sheath; double arrow marks a nerve fibre of same size with a comparable thick myelin sheath. Note that the nerve roots have no epineurium. Scale not corrected for shrinkage.

Nerve fiber diameter distribution histograms split into 4 classes of myelin sheath thicknesses

Since the diameters and the myelin sheath thickness of myelinated nerve fibers did not increase continuously, nerve fiber diameter spectra for different myelin sheath ranges of different roots were constructed [34]. It can be seen from **Figure 7** that different peaks occurred in the histograms, indicating different nerve fiber diameter populations.

In **Figure 7B** three peaks can be seen in the ventral lumbar 4 root spectrum, which were later identified as α_1, α_2 and α_3-motoneurons. The thick and thickly myelinated α_1-motoneurons were most prominent. Nearly no α_1-motoneurons were present in the ventral S4 root **(Figure 7C)**. In the dorsal L4 root no clear peaks can be seen because of too many present nerve fiber populations **(Figure 7A)**.

Based on morphometry alone it would not be possible to safely characterize nerve fiber groups, because the groups overlap and there are also afferents in the ventral roots. The morphology has to be correlated with the electrophysiology, that means with conduction velocities. The development of the single-nerve fiber action potential recording, which with it was possible to measure simultaneously at the single-neuron level conduction velocities and action potential patterns running in (in afferents) and out (in efferents) of the human spinal cord (CNS), was an essential step forward to repair human CNS functions.

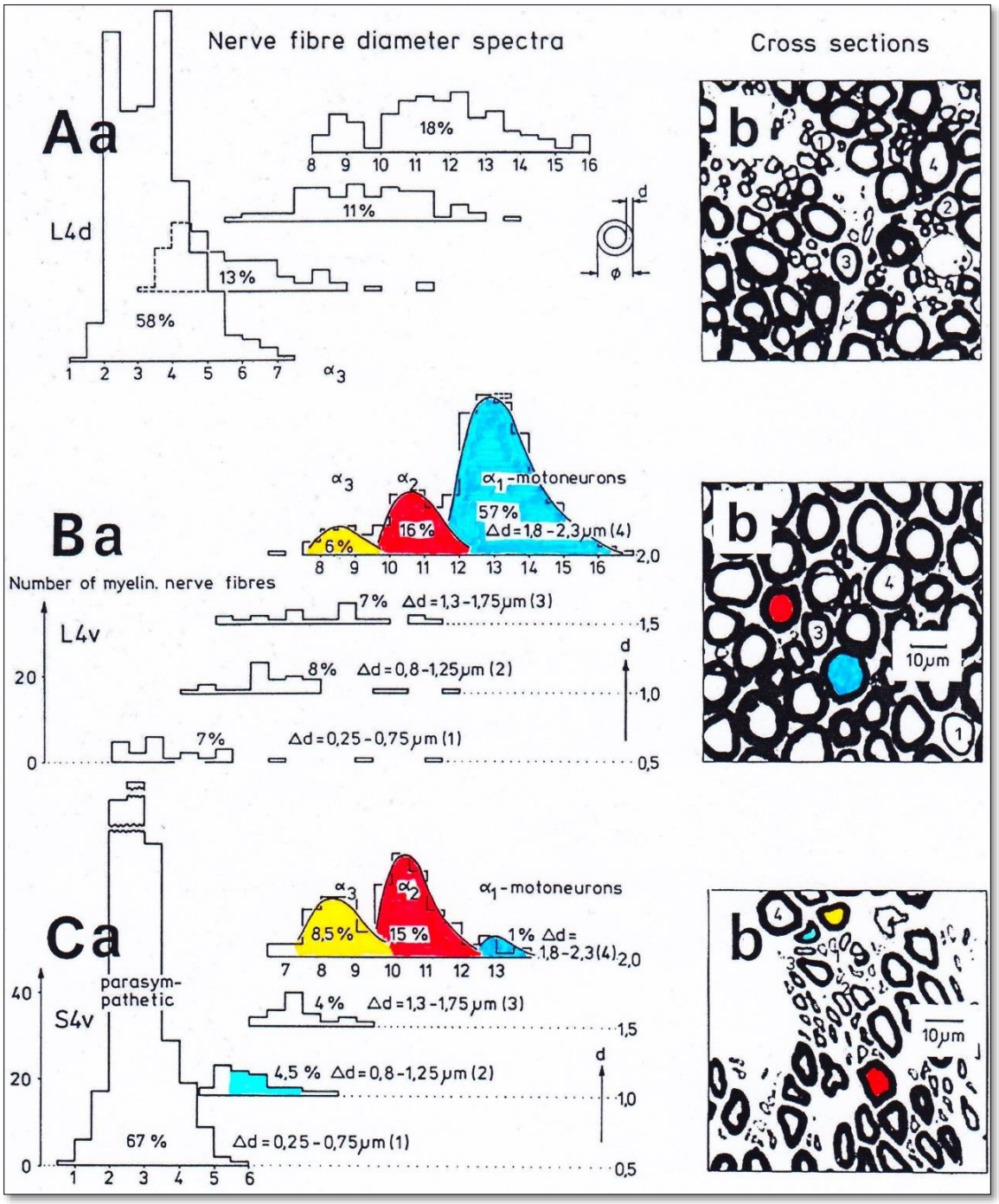

Figure 7. a. Nerve fiber diameter distribution histograms classified by 4 classes of myelin sheath thicknesses as indicated in Ba. % Indicates percentage of fibers in classes or subgroups. b. Corresponding characteristic cross sections (light microscope). A few fibers are numbered by their myelin sheath thickness range they belong to. Dimension scale for A, B, and C is drawn in Bb. 8% shrinkage correction. For the definition of fiber diameter Ø and myelin sheath thickness d see insertion in Aa. A. Nerve fiber diameter spectrum of a 4th dorsal lumbar root of a 47-year-old female human cadaver removed 2 to 5 h after death, 660 fibers were measured. B. Spectra of a 4th ventral lumbar root (same case as in A). 320 fibers were measured. In the myelin sheath thickness range $1.8 \leq d < 2.3\mu m$ the distribution curves of the 3 α-motoneuron classes are drawn into the histogram. C. Diameter distribution from the ventral S4 root of HT1. All 570 myelinated fibers were measured. The approximate drawn distribution curves (not Gaussian) indicate more clearly indicate more clearly the peaks in the diameter spectrum for d = 1.8-2.3 µm.

Human neurophysiology

Single-nerve fiber action potentials and saltatory conduction

To see whether it is possible to record extracellular single-nerve fiber action potentials, the Author recorded from frog peripheral nerves **(Figure 8)**. It turned out that it was quite easily possible because frog peripheral nerves have no epineurium, shunting the extracellular potentials [35]. The successful recording from the frog does not mean that the recording of extracellular action potentials is possible also in human.

It has been recorded with needles from human single-nerve fibers [36,37], but not extracellularly and not simultaneously from afferent and efferent nerve fibers to analyze CNS functioning. From human peripheral nerves one cannot record because the epineurium is short-circuiting extracellular nerve fiber potentials. But nerve roots have no epineurium. It could therefore be possible to measure potentials. If it is possible to measure single extracellular action potentials from human nerve roots, one has to record with experience because membrane properties (resistances, capacitance) may be different and artefacts may occur. As turned out, the membrane properties are really different for example in comparison to those of the rat. Human peripheral nerves conduct more slowly, but the transmission frequency is higher.

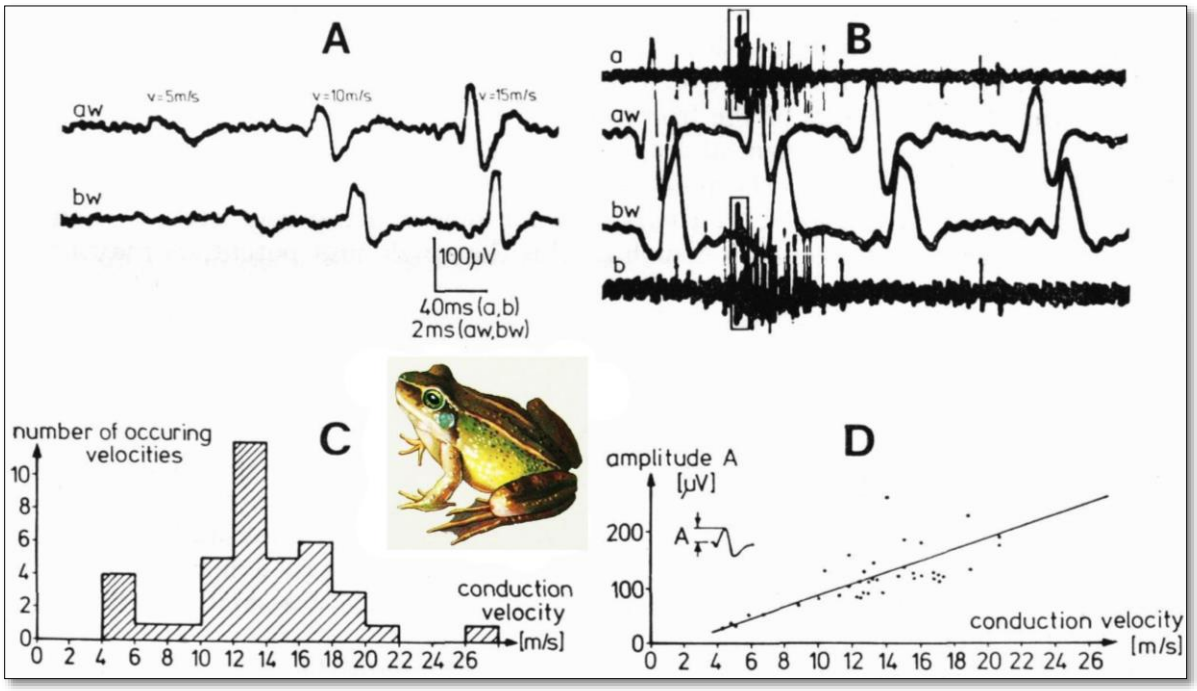

Figure 8. Recording of single-nerve fiber action potentials (APs) from the frog (rana temporaria). A. Recording of three single APs of different conduction velocities and different amplitudes. Note, the AP with the highest conduction velocity (shortest conduction time from one electrode pair (trace a) to the other one (trace b)) has the largest amplitude. B. Overall view of the activity increase on the traces a and b upon touching the skin of the frog. On the window traces, aw and bw (stretched traces) the waveform of the APs of the touch afferents can nicely be seen. C. Conduction velocity frequency distribution histogram at room temperature of spontaneous and stimulated activity. D. AP amplitude in relation to conduction velocity in human. The polarity in the frog recording is different to that in the human recordings.

Single-nerve fiber APs were recorded extracellularly **(Figure 9)** from nerve roots with 2 platinum wire electrode pairs (electrode pair distance (mostly) = 10mm; electrode distance in each pair = 4mm) at 2 sites, pre-amplified (x1000), filtered (RC-filter, passing frequency range 100Hz-10kHz) and displayed on a digital storage oscilloscope (Vuko Vks 22-16), and also stored using a PCM-processor (Digital Audio Processor PCM-501ES) and a video recorder. The beginning of a touch or pin-prick was marked with an upward pulse; and the end with a downward pulse on trace "a". These pulses were generated by a markation pulse generator connected to the digital scope, which was switched on and off with a touch sensor working on the basis of resistance changes. Also, the pulling and releasing of anal and bladder catheters were mostly marked with the help of a pull-switch connected to the catheters and working in connection with the same markation pulse generator. Trace "a" was the

recording from the proximal electrode pair and trace "b" from the distal pair. Conduction velocities of single-nerve fibers were calculated from the conduction distance (electrode pair distance) and the respective conduction times, the time needed for an AP to cover the conduction distance (time difference between traces "a" and "b" for a particular AP) of 10mm. APs from afferents and efferents could clearly be distinguished from each other since for the used electrode arrangements the main phase (second phase) from afferent fibers is upwards and that of efferents downwards **(Figure 9)**. E.g., the AP of a skin afferent fiber reaches a pair of electrodes first as negative and then as positive. According to the electrode setting used, the main phase is upwards. An AP of a motoneuron, coming from the opposite direction, would reach the electrodes in the order positive-negative. The potential changes are therefore opposite and the main triphasic AP will point downwards. An AP in an afferent fiber reaches first the caudal electrode pair and then the rostral pair, whereas an AP of the efferent fiber reaches first the rostral electrode pair and then the caudal one. The conduction times are therefore also opposite. For further clarity, a change of the inputs to the preamplifiers does not change the ability to differentiate between afferent and efferent APs, because the amplitudes of both types of APs change their upward or downward direction **(Figure 9)**.

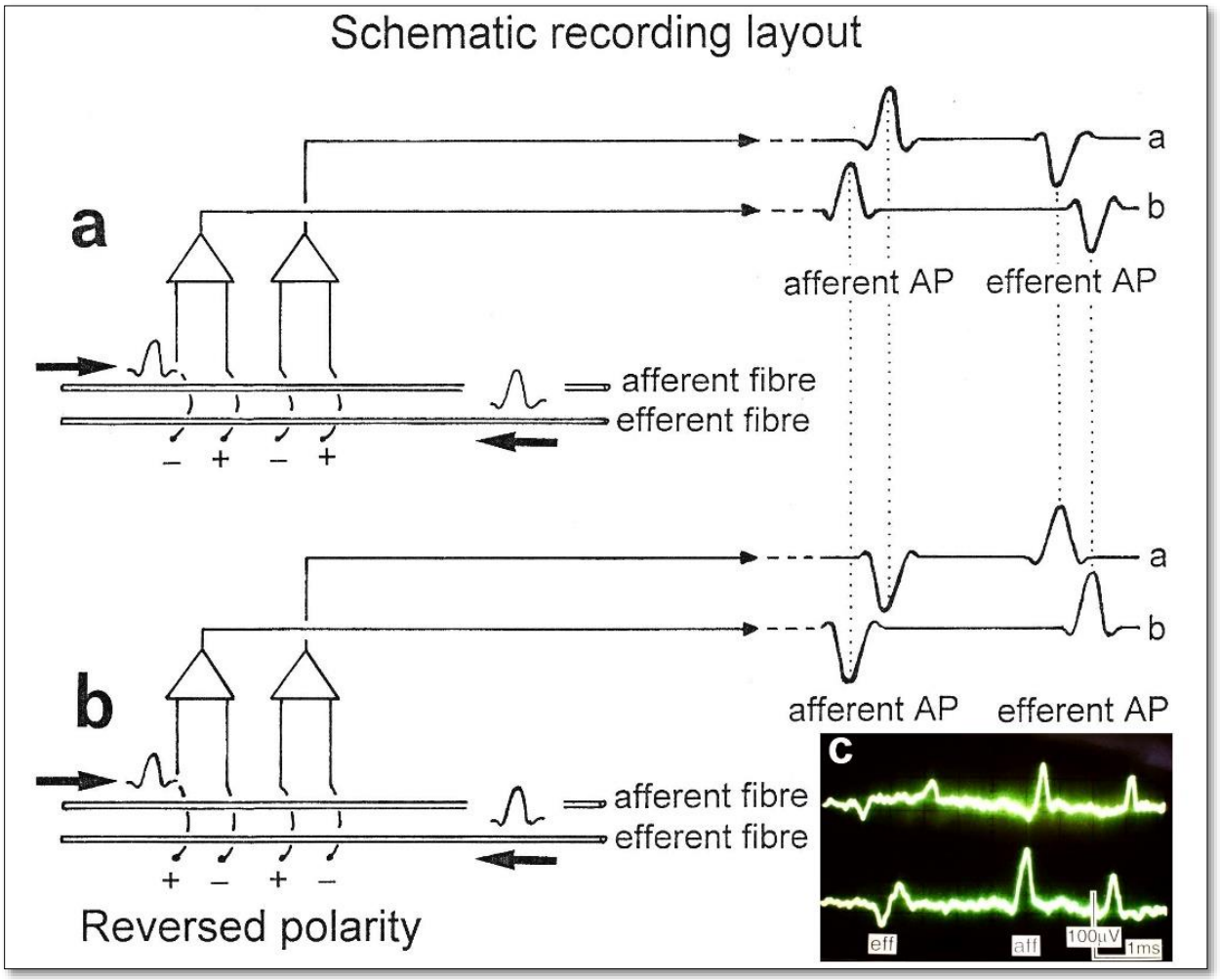

Figure 9. a. Schematic layout for recording single-nerve fiber action potentials (APs). b. The reversing of the inputs to both preamplifiers does not change the ability to differentiate between afferent and efferent APs. c. Original scope recording.

Figure 10 shows the successful recording of extracellular human single afferent and efferent nerve fiber action potentials from cauda equina nerve roots [38,39]. Basic human neurophysiology is only possible in cooperation with clinicians to have measuring possibilities and when measuring from patients one has to offer them treatment. It often happened that new measuring technique had consequences for progress in research and treatment of patients. It will be shown that this is also the case with the single-nerve fiber action potential recording method.

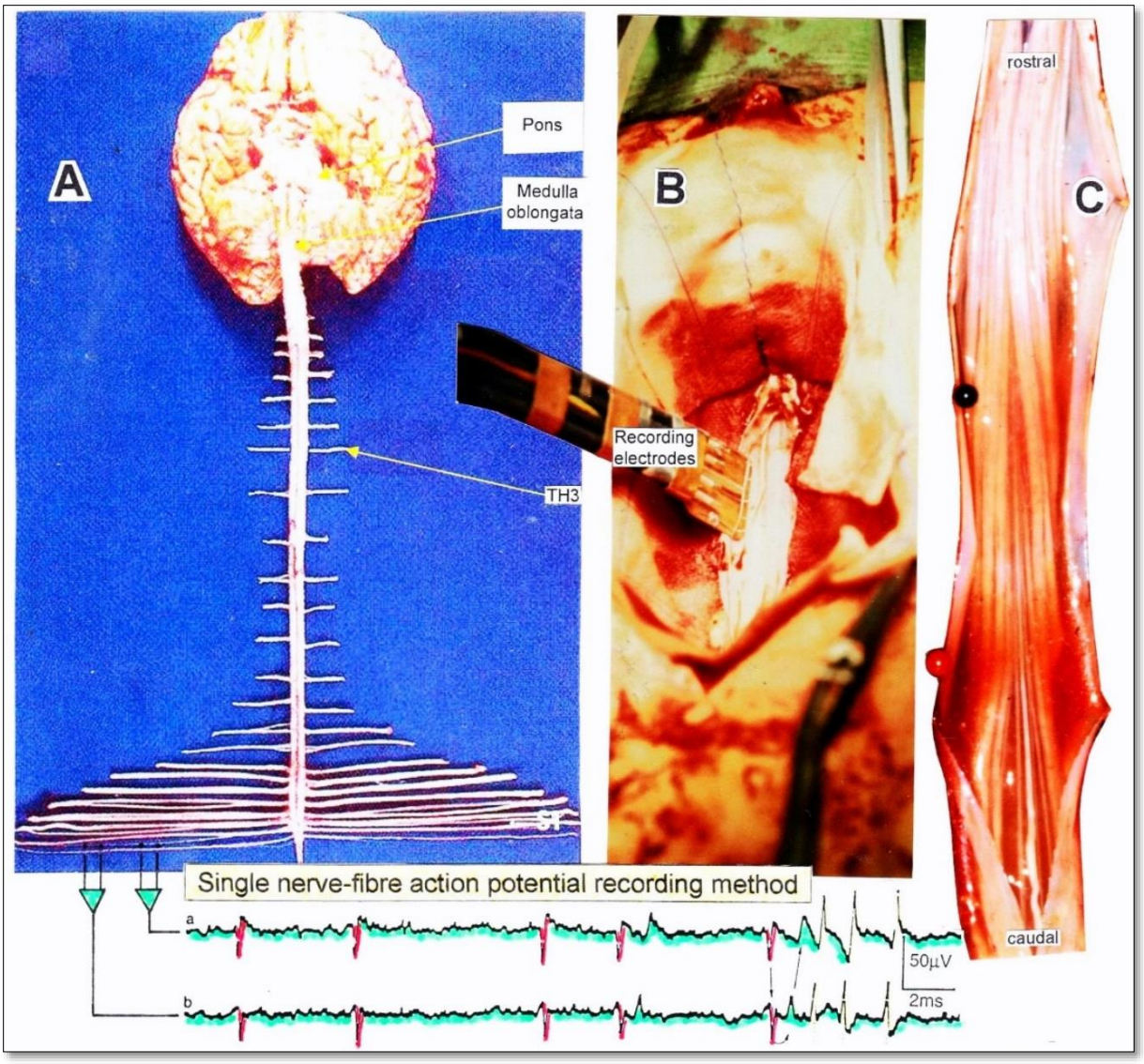

Figure 10. Anatomical layout for the recording of single-nerve fiber action potentials to analyze the self-organization of neuronal networks of the human CNS under physiologic and pathophysiologic conditions. A, B, C. By recording with two pairs of platinum wire electrodes (B) from sacral nerve roots (cauda equina, C) containing between 200 and 500 myelinated nerve fibers, records were obtained in which single nerve-fiber action potentials (APs) were identified from motoneurons (main AP phase downwards) and afferents (main AP phase upwards). Note, in B there is in between the electrode pairs a sensor for the temperature measurement.

In accordance with animal data [40], the AP amplitude of single afferent APs decreases and the AP duration increases with decreasing conduction velocity (increasing conduction time) **(Figure 11)**, if the different nerve fibers have the same distance to the recording electrodes [38].

Similar relationship between conduction velocity, AP amplitude and AP duration hold for efferent APs. With increasing conduction velocity (and increasing diameter) the AP amplitude increases and the AP duration decreases. The scatter in these relations is large because the different fibers in a root are at different distance from the recording electrodes. Also, nerve fibers change their diameter slightly from internode to internode (see below). And as a matter of fact, damaged nerve fibers have strongly reduced conduction velocity and increased AP duration. Poor digitalization and too strong filtering will reduce large AP amplitudes. Nevertheless, good recordings clearly demonstrate that average AP amplitude decreases and AP duration increases with the reduction of the conduction velocity when changing from one nerve fiber group to another.

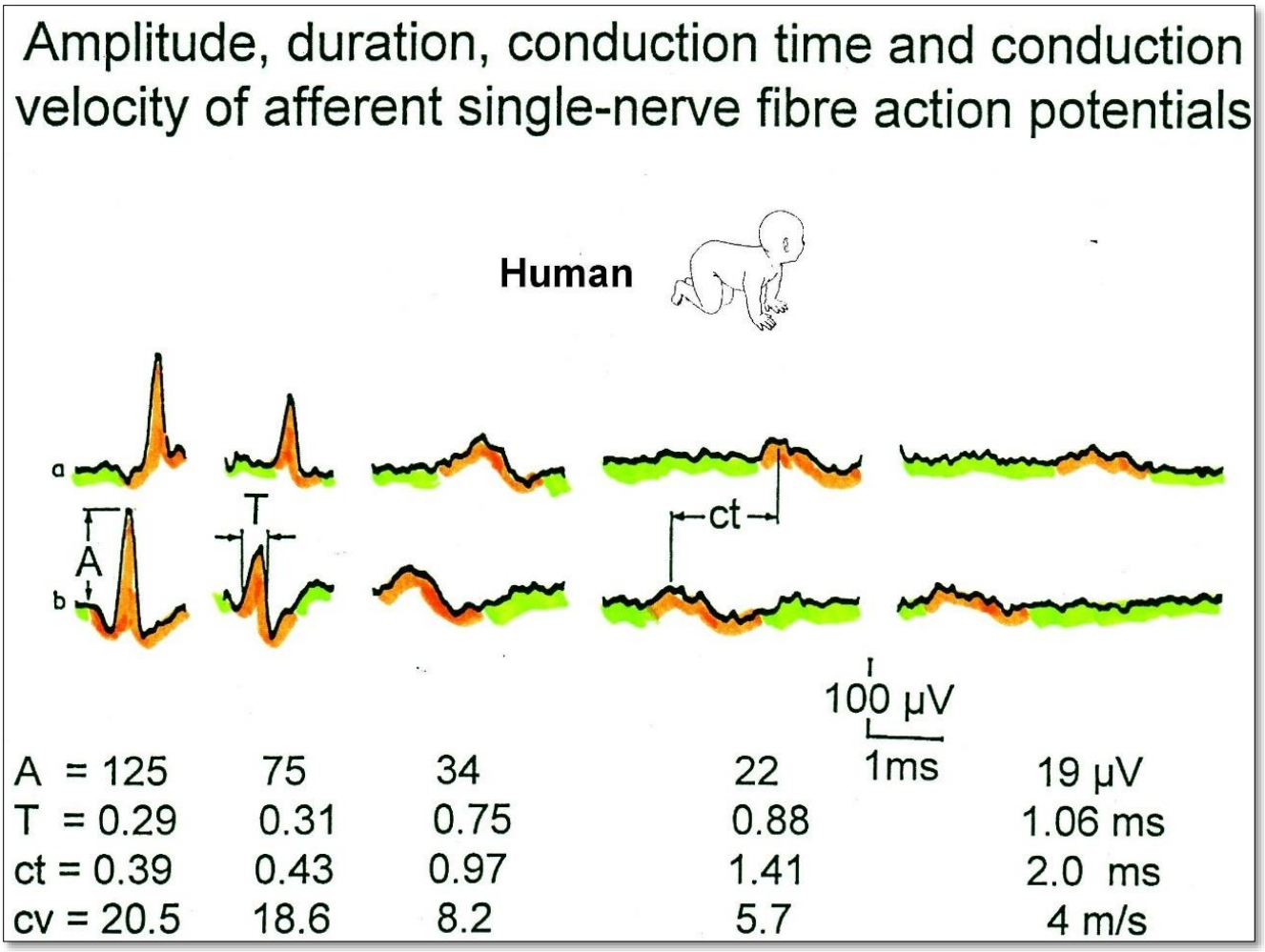

Figure 11. Extracellular AP waveforms of different amplitude (A), duration (T), conduction time (ct) and conduction velocity (cv). The different nerve fibres, in which these APs were conducted, had approx. the same distance to the recording electrodes. The afferent nerve fibres were stimulated by touch, pain, and bladder and anal canal-catheter pulling and releasing. Brain dead human HT4, 56 years, 32 °C (approximate measuring temperature), recording made from a dorsal S5 root (diameter = 0.17 mm).

Because it is recorded from myelinated peripheral nerve fibers, it has to be controlled that the saltatory conduction is not causing problems with the recording and especially how long the internode lengths are. The Author learned from R Stämpfli, an expert with respect to research on the node of Ranvier [41], and applied the technique to the teasing of human peripheral nerve fibers.

Saltatory Conduction

Saltatory conduction of myelinated nerve fibers and diameters for different internode lengths - teased fiber dissection of human nerve fibers.

Measurements of nerve fiber diameters in general and tapering especially depend on the assumption that the nerve fiber diameters are very similar along different internodes. Internodal lengths and their nerve fiber diameters have to be measured for clarification [34] **(Figure 12)**.

With normal effort, 130 **(Figure 12B)** of the 570 myelinated fibers of a S4 ventral root **(Figure 6)** were teased and, additionally, the diameters of 95 of these were measured **(Figure 12D)**. As the similar shape of the diameter histogram of the teased fiber dissection **(Figure 12D**) in comparison to that of **Figure 7Ca** indicates, a somewhat representative selection was teased. In order that several internodal lengths could be determined, as much of a length of a fiber as possible was teased. **Figure 12A** shows a montage of three photographed teased single fibers of different thicknesses. It can be seen that the internodal lengths are not always similar. It seemed that every third to fifth was markedly different from the other ones. At three thick fibers, it was found that the longer

internode corresponded with a thicker nerve fiber as is shown in **Figure 12A**, fiber 1, so that the ratio of internodal length to nerve fiber diameter **(Figure 12C)** was not changed. **Figure 12B** shows the frequency distribution histogram of the internodal length. This distribution also shows four characteristic peaks, as the frequency distribution of the nerve fiber diameters does (**Figure 7Ca**, motoneurons). This similarity can be understood since the nerve fiber selection of the teased fiber dissection of **Figure 12D** was somewhat representative, and the relation between internode length L and fiber diameter d was proportional **(Figure 12C)**. By dividing the internodal length in **Figure 12B** by L/d = 100, one gets a somewhat similar histogram as in **Figure 7Ca**, if the four histograms are added. By teased fiber dissections therefore it is shown [34] **(Figure 12C)** that in human sacral nerve roots the internodal length L is related to the nerve fiber diameter d, including myelin sheath, by L/d = 100. Therefore, in frequency distribution histograms of internodal lengths, grouping of nerve fibers can also be observed **(Figure 12B)**.

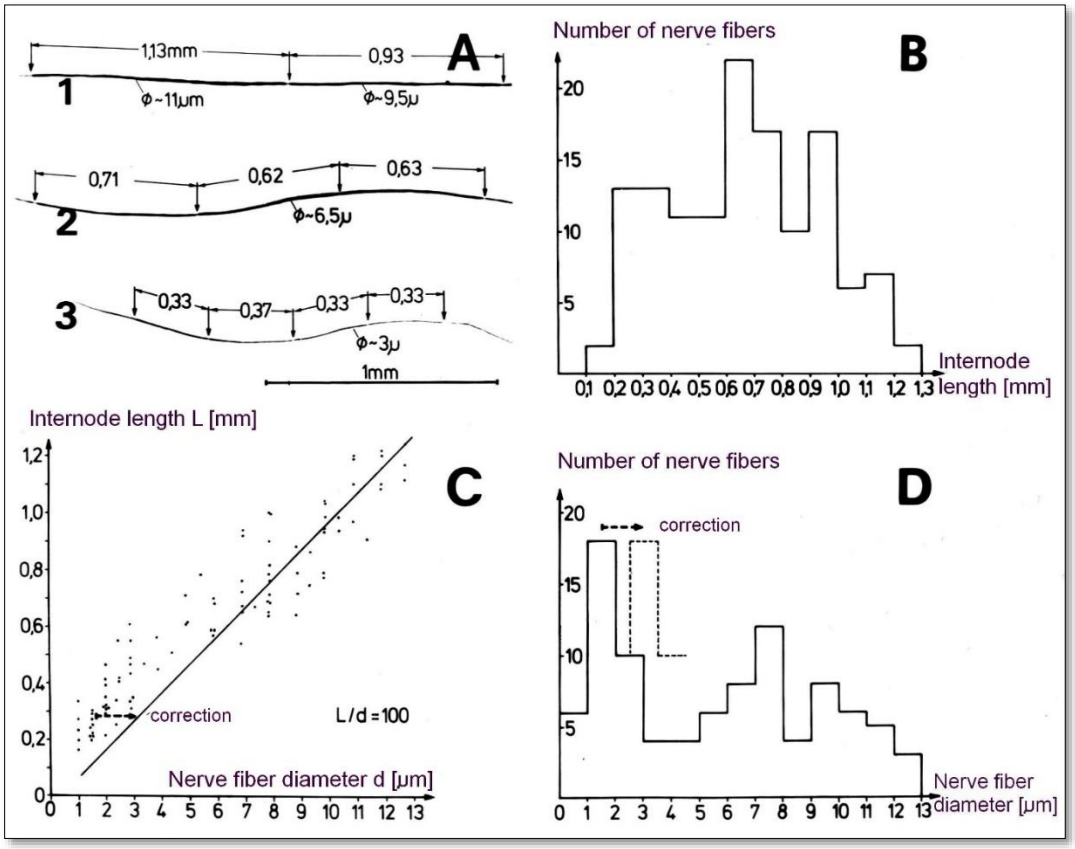

Figure 12. Quantified results of a teased fiber dissection of a whole S4 ventral root from HT1. No shrinkage correction. A. Three original nerve fiber dissections, several internodes are measured and marked. Approximate fiber diameters (Ø) are indicated. B. Frequency distribution histogram of internode lengths. Numbers indicate peaks. Class borders are < and ≤. If more than one internode length of a nerve fiber was measured (30% of the cases), then the mean value was used. C. Internode length in relation to its nerve fiber diameter. A small correction for small nerve fibers was performed (see D). D. Very approximate nerve fiber diameter frequency distribution. Since the diameter of the nerve fibers were measured under the stereo-microscope with a 100 times magnification, the thin nerve fibers were estimated rather than measured. Comparing this diameter frequency distribution of the S4 ventral root (D) with that of a S4 ventral root measured with a light microscope **(Figure 7Ca)**, a correction for small nerve fiber diameters was performed and indicated in the Figure.

Action potential waveform changes due to saltatory conduction

The action potential waveform may vary a bit along the nerve fiber, according to the different localization of the node of Ranvier with respect to the recording electrodes [41,42]. Only three internodes lie between the electrodes of a pair of electrodes for the nerve fibers contained in peak 1 of **Figure 7C** (mean internodal length = 1.2mm **(Figure 12B)**; electrode distance in a pair = 4mm). Furthermore, the measurement of several internode lengths from one fiber indicated that every third to fifth internode length was quite different from the other ones

(Figure 12A) and, also, the nerve fiber diameter was then different from the other ones. Therefore, one cannot exclude some changes in the action potential wave form from differences of the internodes, even though the nerve fiber could have partly compensated for such differences by a different internodal cleft or a different sodium and/or potassium channel density.

Space distribution of single-nerve fiber action potentials

Even though the electrophysiology is presented only in the next section, a recording is needed to show that in a first approximation, one can disregard the saltatory conduction, because the APs are distributed over several until many internodes.

Figure 13 shows the action potential (AP) durations of an α_2-motoneuron, a γ_1 (dynamic), a γ_{21}-motoneuron (static), and a parasympathetic efferent fiber at a measuring temperature of 33°C. The main peaks of the triphasic waveform are approximately 0.15, 0.4, 0.5, and 0.6ms long, respectively. The space distribution (length) (v = s/t; s = v times t) of the single-fiber APs along the fibers were approximately six (40m/s times 0.15ms = 6mm; α_2), 5.3, 5, and 3.2 (par) mm, respectively. With the approximate nerve-fiber diameters of 10.2, 6.8, 5.8, 3.5µm (see classification scheme), we obtain internode lengths of (L/d = 100) 1.02, 0.68, 0.58, and 0.35mm, respectively. The main peak of the triphasic AP was approximately distributed over five (6mm:1.2mm = 5; α_2), 7.8, 8.6, and 9.1(3.2:0.35 = 9.1; par) internodes, respectively.

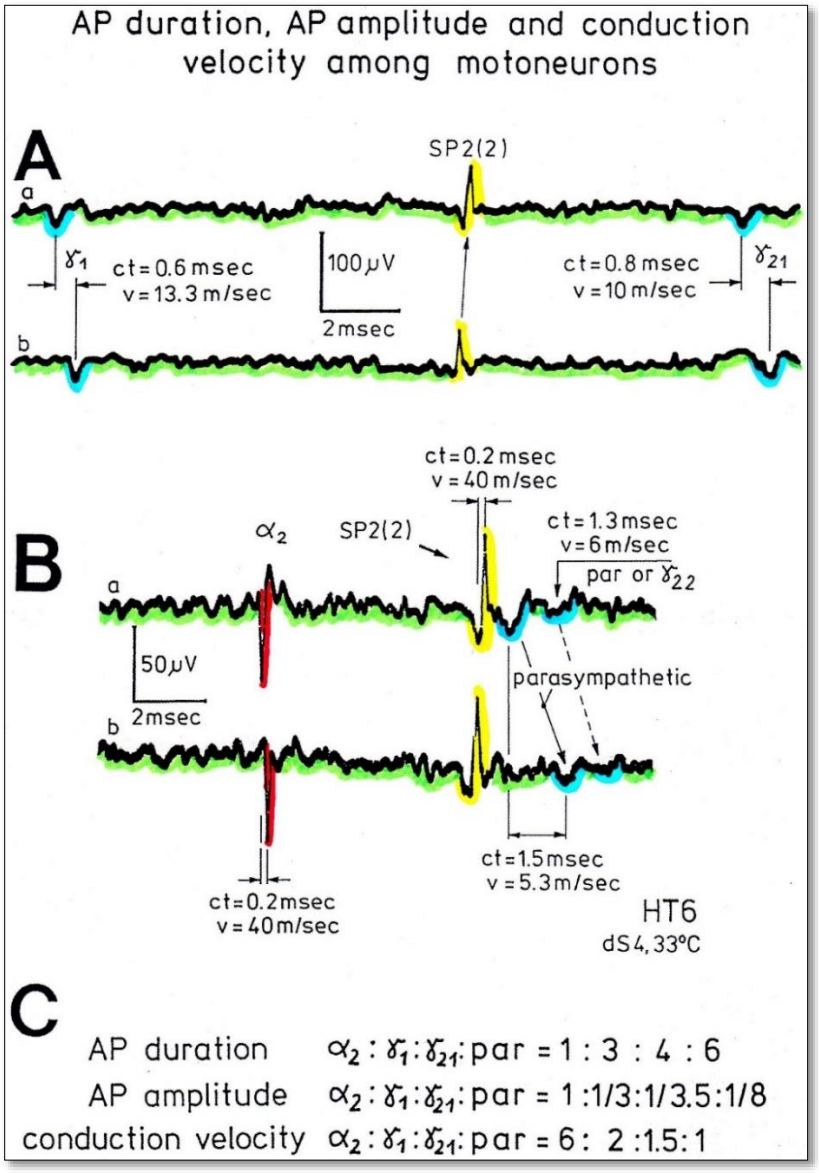

Figure 13. A, B. Recordings of single-nerve fiber action potentials (APs). C. Relation between the AP durations, AP amplitudes and conduction velocities of single α_2, γ_1, γ_{21} and parasympathetic motoneurons. HT6, dS4-root, 33°C.

With this result we can disregard in a first approximation the saltatory conduction, because the action potentials are space-distributed over several internodes. It is changed now to the electrophysiology to establish a qualified classification scheme of human peripheral nerve fibers to explore on its basis the functioning of the human CNS and in turn its repair.

Conduction velocities and classification scheme of human peripheral nerve fibers by group conduction velocity and group nerve fiber diameter

A real recording arrangement during an operation is shown in **Figure 10**. To obtain natural impulse patterns simultaneously from several single afferent and efferent nerve fibers to analyze CNS functioning, the summed impulse traffic of several afferent and efferent fibers in a nerve root has to be split into the impulse patterns of single fibers **(Figure 14)**. The splitting is achieved by recognizing the APs from certain single fibers on the basis of wave form comparisons on the two recording traces and the conduction time which an AP needs to travel from one electrode pair to the other one (10mm) and selecting these APs out. The summed impulse traffic of the recording of **Figure 10** is split into the impulse patterns of 5 single afferent and efferent nerve fibers.

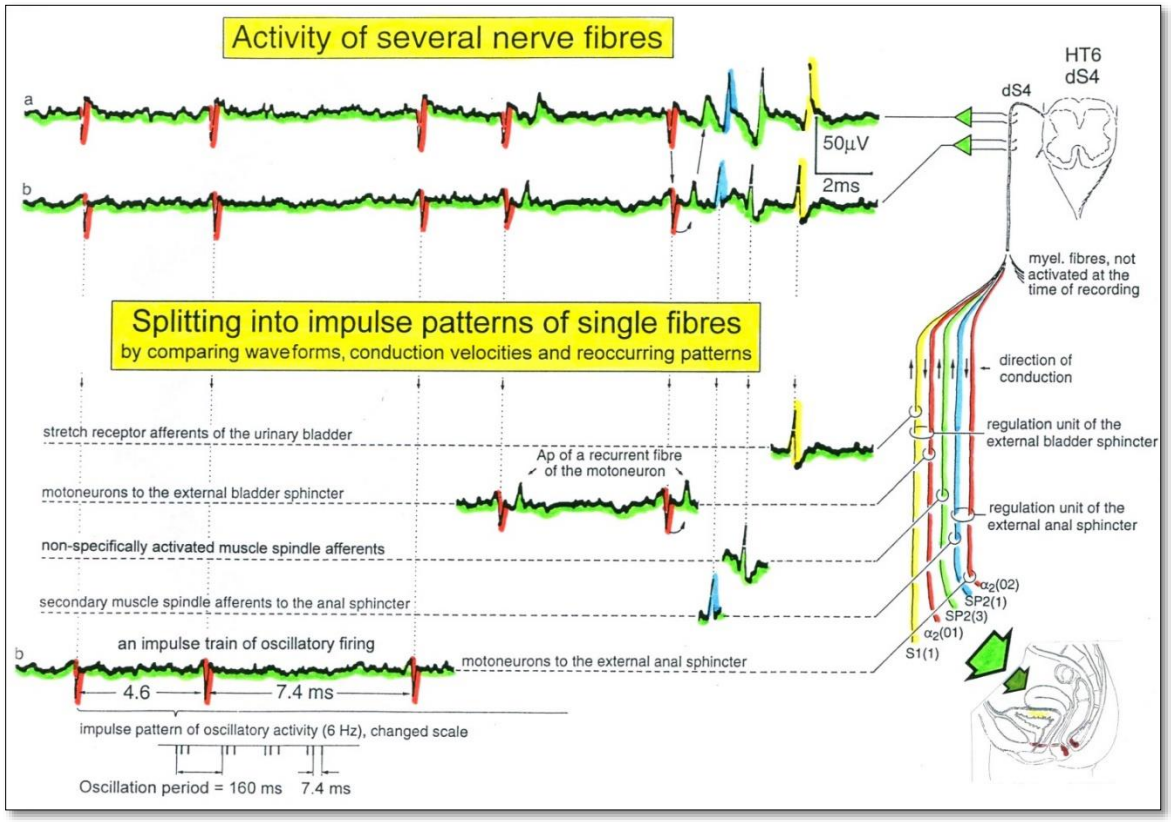

Figure 14. Schematic splitting of the activity of several nerve fibres into simultaneous impulse patterns of single fibres by comparing wave forms, conduction velocities and reoccurring characteristic impulse patterns (rhythmic firing of sphincter motoneurons). The different conduction times and wave forms were recognized on an expanded time scale. Stretch receptor and secondary muscle spindle afferents contribute to the drive of sphincter motoneurons and form, together with other afferents, regulation units.

To know in what kind of nerve fibers the natural impulse patterns are conducted, a precise classification of human peripheral nerve fibers is needed and was constructed by correlating conduction velocity spectra with nerve fiber diameter spectra [43-45].

Figure 15B shows a conduction velocity distribution histogram for motor fibers. Such conduction velocity spectra were correlated with the corresponding diameter spectra **(Figure 7C)** in **Figure 16**.

A comparable conduction velocity spectrum from a dog is shown in **Figure 15A** for comparison with the human one [46]. It can be seen that all measured dog nerve fiber populations conducted faster than those of humans.

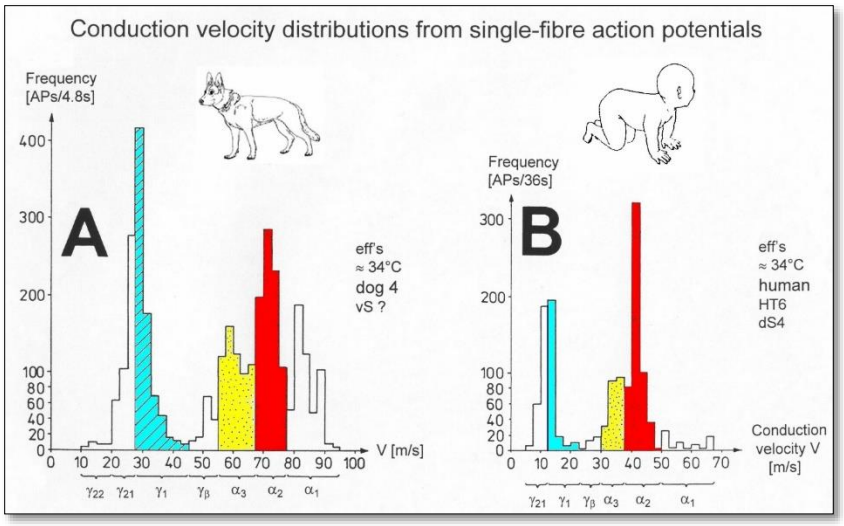

Figure 15. Conduction velocity distribution histograms of efferent action potentials from a dog (A) and a human (HT6; dS4) (B) of lower sacral nerve roots. The distribution peaks are labelled according to the respective groups they represent. Motoneuron velocity ranges are indicated. In A, 24 sweeps of 0.2s, and in B, 30 sweeps (stimulated and non-stimulated) of 1.2s duration were used. Note that dog α and γ-motoneurons conducted faster than the ones of humans, recorded with the same equipment at the same temperature by the Author.

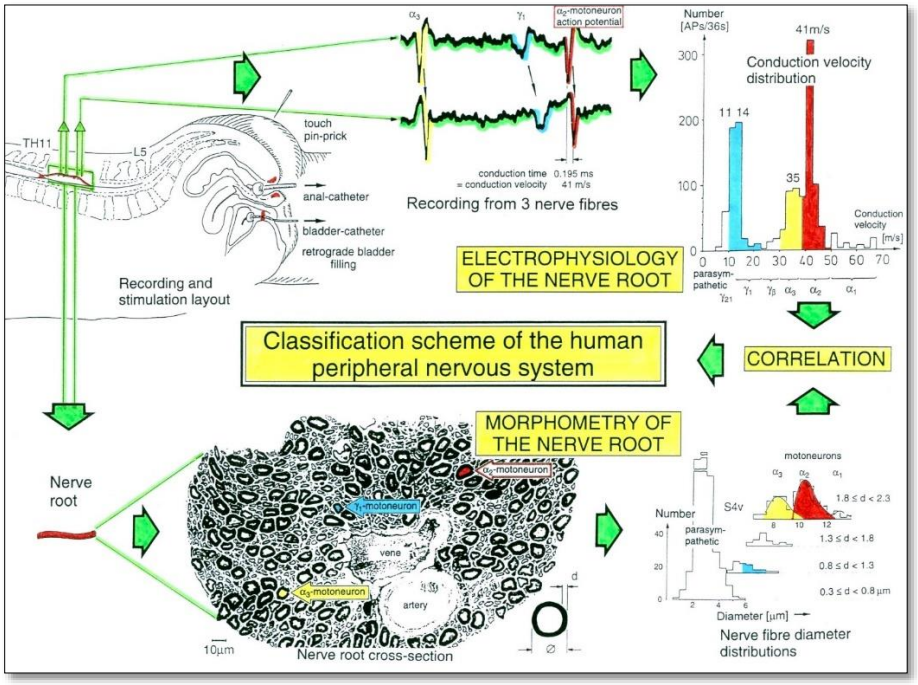

Figure 16. Schematic layout of the classification scheme for the human peripheral nervous system. By recording with two pairs of platinum wire electrodes from a nerve root containing approx. 500 myelinated nerve fibers, a recording is obtained in which three action potentials (APs) from three motoneurons (main AP phase downwards) can be seen. By measuring the conduction times and with the known electrode pair distance (10 mm), a conduction velocity distribution histogram is constructed in which the nerve fiber groups are characterized by ranges of conduction velocity values and peaks in asymmetrical distributions. After recording, the root was removed, fixated, embedded and stained, light microscope cross sections were prepared and used to measure the mean diameter and the myelin sheath thickness (d). Distributions of nerve fiber diameters were constructed for four different ranges of myelin sheath thickness. Nerve fiber groups were characterized by the peak values of asymmetrical distributions. By correlating the peak values of the velocity distributions with those of the diameter distributions obtained from the same root, a classification scheme was constructed of the human peripheral nervous system. Brain-dead human HT6.

This new development of human repair-neurophysiology started thus from scratch by clarifying first the principal aspects of anatomy **(Figures 2-5)** and developing then a new basic electrophysiological recording technique suitable for use in humans, the simultaneous recording of single afferent and efferent nerve fiber extracellular action potentials (APs) with two pairs of wire electrodes from undissected sacral nerve roots. This technique can be used for intra-operative diagnosis and research. Further developments in morphometry of nerve roots (classification of fiber diameters into four ranges of myelin sheath thickness **(Figure 7)**) made it possible to simultaneously characterize nerve fiber groups by group conduction velocities and group nerve fiber diameters **(Figure 17)**.

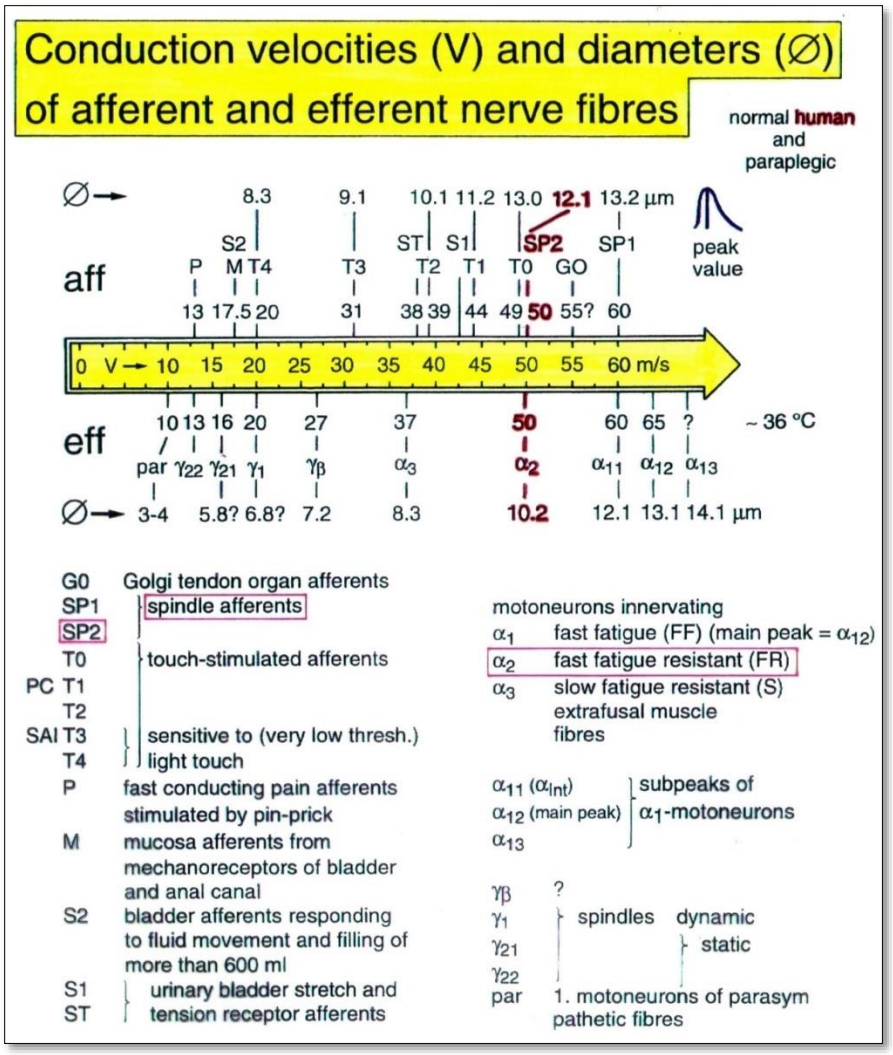

Figure 17. Conduction velocities (V) and nerve fiber diameters (∅) of afferent and efferent nerve fiber groups in normal humans and in patients with a traumatic spinal cord injury for 0.5 to 6 years. The splitting of the α_1-motoneurons into the three subgroups, α_{11}, α_{12}, α_{13}, has not yet been confirmed.

The group conduction velocities and group nerve fiber diameters of the classification scheme had the following pair-values at 35.5°C:

Spindle afferents: SP1(65ms^{-1}/13.1µm), SP2(51/12.1); touch afferents: T1(47/11.1), T2(39/10.1), T3(27/9.1), T4(19/8.1); urinary bladder afferents: S1(41ms^{-1}/-), ST(35/-); α-motoneurons: α_{13}(-/14.4), α_{12}(65ms^{-1}/13.1µm), α_{11}(60?/12.1)[FF], α_2(51/10.3)[FR], α_3(41/8.2)[S]; γ-motoneurons: γ_β(27/7.1), γ_1(21/6.6), γ_{21}(16/5.8), γ_{22}(14/5.1); preganglionic parasympathetic motoneurons: (10ms^{-1}/3.7µm).

With respect to electrical stimulation, it was found that the primary spindle afferents likely have the lowest threshold upon electrical nerve root stimulation, followed

by α_1-motoneurons (FF), secondary muscle spindle afferents, α_2-motoneurons (FR), α_3-motoneurons (S), γ_β, γ_1 (dynamic), γ_{21} (static), γ_{22} (static), and parasympathetic motoneurons.

This classification and identification scheme represents a solid basis for classifying and identifying nerve fiber groups in the human peripheral nervous system (PNS) and analyzing central nervous system (CNS) functions under physiologic and pathophysiologic conditions at the single-neuron level (see below), even though it is incomplete and holds so far only for nerve fiber diameters larger than approximately 3.5µm.

Since it is possible to distinguish APs from afferent and efferent nerve fibers and to extract from the summed activity of a fiber bunch the discharge patterns of single fibers, it is possible to analyze receptor properties of skin afferents (Figure 18), primary and secondary muscle spindle afferents and urinary bladder afferents and analyze parasympathetic and somatic functions of the human CNS for continence and movements. An insight into CNS functions can be obtained from studying simultaneous impulse patterns of single afferent and efferent fibers and the phase relations between the impulses, following natural stimulation. Since human continence functions are mainly located in S3 and S4 segments and segmental functions seem to overlap in their representation in the roots, especially continence functions can ideally be analyzed and repaired [29,30,47,48].

A good example of getting natural patterns of a set of identified nerve fibers is the splitting of the skin afferent activity recorded from a coccygeal root. Upon touch or pin-prick, the impulse patterns of the different single touch and pain receptors are shown in **Figure 18** [49]. Such messages inform the CNS about changes in the periphery. Similar natural impulse patterns inform the CNS about muscle spindles activity [50] and changes in the urinary bladder or anal canal, stimulated by bladder filling or bladder or anal canal catheter pulling.

The upper classification scheme of peripheral nerve fibers would not be very helpful if the nerve fiber diameter would sufficiently change along its way. It was measured therefore that the tapering of nerve fibers is very little. The reduction of the group diameter in the different α-motoneuron groups was 0.2 % per 13 cm [51]. Consequently, a nerve fiber with a diameter of 10μm (α_2-motoneuron) would be reduced to approximately 9.8µm at 1m from the cell soma, if no branching is occurring along its way.

To get more safety concerning nerve fiber groups, nerve compound action potentials were analyzed with the simultaneously recorded single-fiber action potentials [52].

Conduction velocity distribution histogram to classify nerve fiber groups electrically and identify single-nerve fiber action potentials (APs)

Through morphometry, nerve fiber groups could be identified in nerve fiber diameter distribution histograms. By measuring conduction velocities of recorded single-nerve fiber action potentials during a certain time period and plotted conduction velocity distribution histograms, one can recognize different nerve fiber groups in the distributions **(Figure 19)**. With the identified group conduction velocities, one knows for the actual recording in what kind of nerve fiber the action potential was generated. For a safe identification, calibrations are necessary. One calibration relation is that the secondary muscle spindle afferents (SP2) conduct at the same velocity as the α_2-motoneurons **(Figure 19)**. Since in caudal sacral nerve roots only few primary spindle afferents (SP1) and α_1-motoneurons, this identification is easy. But if in more rostral roots are more primary spindle afferents and α_1-motoneurons, then the additional calibration relation holds that the primary spindle afferents conduct with the same velocity as the α_1-motoneurons.

These calibration relations are easily to apply because the spindle afferents and the motoneurons are thick fibers and conduct fast with large action potentials **(Figure 11)**. But the thinner fibers, conducting more slowly and having a small action potential amplitude, are the problem in identification. **Figure 20** shows that parasympathetic APs are just recognizable. The group conduction velocity peaks of the parasympathetic fibers can be distinguished from those of the different γ-motoneurons. But if, when especially the temperature is low the different peaks do not separate (they are fused), then a logarithmic plotting will help.

Identification of peaks of γ-motoneurons and parasympathetic fibers in conduction velocity distributions on a log scale

On a linear scale the conduction velocity peaks may fuse and can only partly be separated by their different functions **(Figure 21Da,Ea)**. By constructing first histogram classes for conduction times however and plotting them then on a log scale from the column values, the velocity peaks separate. **Figure 21D,E** shows that the fused γ-peaks of the linear plots (Da,Ea) split up into different peaks on the log scale (Db,Eabc). Since first histogram classes of conduction times were constructed, using a linear scale, it was also possible to study the dynamics of peaks or peak values upon stimulation. This sophisticated group identification of single-nerve fiber action potentials is necessary to explore human CNS self-organization and learning.

Figures 21Db & 21Eb show several distribution peaks in which the γ_1 and γ_{21}-peaks could be identified from earlier functional considerations. By comparing the velocity distributions obtained upon stimulation with those without stimulation **(Figure 21E)**, and reasonably assuming that the dynamic intrafusal motoneuron peaks are higher upon stimulation **(Figure 21Ed)** and the static ones are higher with no stimulation **(Figure 21Ec)**, a second static γ_2-peak (γ_{22}) could be identified and at least one further rather dynamic motoneuron peak (para) can be seen. This peak distribution observed in the paraplegic patient could also be found in the measurements in HT6 (Figure 21Db). That the "Para" peak contains really activity from parasympathetic fibres was shown in other publications [1,2]. The identification of parasympathetic efferents contributes substantially to the understanding of urinary bladder functions under physiologic and pathophysiologic conditions and its repair by coordination dynamics therapy (see below). The nerve fibre groups obtained from conduction velocity distributions for single fibres are in accordance with the sub-compound action potentials.

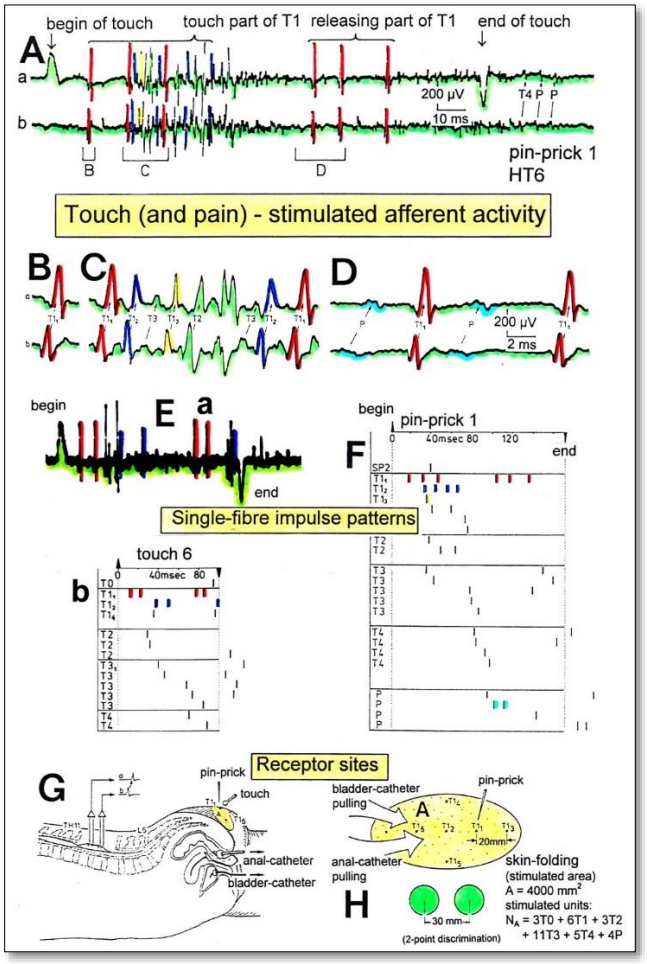

Figure 18. Touch and pain activity stimulated by pin-pricking (A) and touching (Ea) S5 or Co dermatomes and recording extracellularly from a dorsal coccygeal root (brain-dead human HT6). T1, T2, T3, T4, P = mark action potentials (APs) from single touch and pain fibers. Subscripts 1, 2, 3-mark single fibers. A. Whole sweep following pin-prick 1 at a slow time base. The large upward artifact on trace 'a' mark electronically the beginning of the pin-prick/touch. The large downward artifact on trace 'a' marks the end of the pin-prick. Note that 2 intervals of high activity of large APs occurred, one after the beginning of the pin-prick with 1 AP in front, and a second before the end of the pin-prick; potentials with small amplitude follow potentials of large amplitude. Time intervals B, C and D are time-expanded. B, C, D. Time expanded sweep pieces of 'A'. Identified APs are indicated. Note that the APs from the $T1_1$ touch unit can be safely identified by the waveforms in B, C, D. Eb, F. AP occurrence patterns of single touch and pain fibers following short touch 6 and pin-prick 1. No pain afferents are stimulated upon touch 6. Upon pin-prick 1, the single-fiber AP activity of the different touch and pain groups is identified by the AP waveforms on traces 'a' and 'b', and by the conduction times. The single touch afferents of the T1 group are marked with subscripts. One active secondary muscle spindle afferent fiber (SP2) could always be identified in F. Note that for pin-prick 1, touch and pain afferents are stimulated whereas for touch 6 only touch afferents. G. Recording and

stimulation arrangement for simultaneous recording of several single touch and pain units. A = area stimulated by skin folding, drawn in H in more detail. $T1_1$, $T1_6$ = suggested touch points of the $T1_1$ and $T1_6$-units. H. Drawing of the very approximate skin area stimulated by skin folding. $T1_{1\text{-}6}$ = suggested focal T1 touch points. Two-point discrimination indicated for the sake of comparison. N_A = number of stimulated units in the dorsal coccygeal root. Skin tractions evoked by anal and bladder-catheter pulling are indicated by the large open arrows.

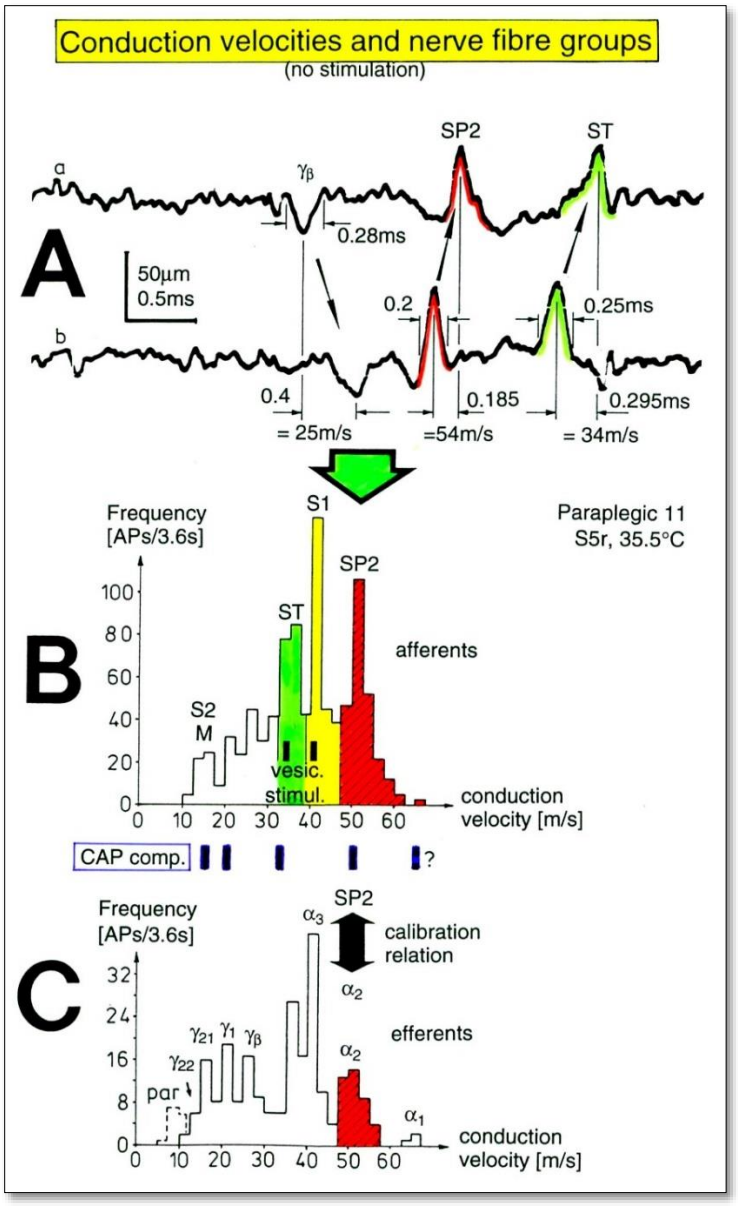

Figure 19. A. Sweep piece of action potential recording. Conduction times and corresponding conduction velocities are indicated. Root temperature at recording electrodes is 35.5°C. --- B, C. Conduction velocity distributions of afferents (B) and efferents (C) obtained for a time interval of 3.6s with no additional stimulation. SP2 = secondary muscle spindle afferents, S1 = stretch receptor afferents of bladder, ST = tension receptor afferents, M = mucosal afferents, S2 = afferents responding to fluid movement; α_1 = α_1-motoneurons (FF), α_2 = α_2-motoneurons (FR), α_3 = α_3-motoneurons (S), $\gamma_{ß}$ = $\gamma_{ß}$-motoneurons, γ_1 = γ_1-fusimotors (dynamic), γ_{21} = γ_{21}-fusimotors (static), γ_{22} = γ_{22}-fusimotors (static), par = preganglionic parasympathetic motoneurons. CAP comp. = group conduction velocities obtained from the components of compound action potentials (CAPs). Vesic. stimul. = group conduction velocities of bladder afferents obtained upon electrical intravesical stimulation (see **Figures 39 & 40**). Calibration relation indicates the same peak group conduction velocity of secondary spindle afferents and α_2-motoneurons (cross-hatched). Velocity histogram classes ≤ and < (half closed (left) interval).

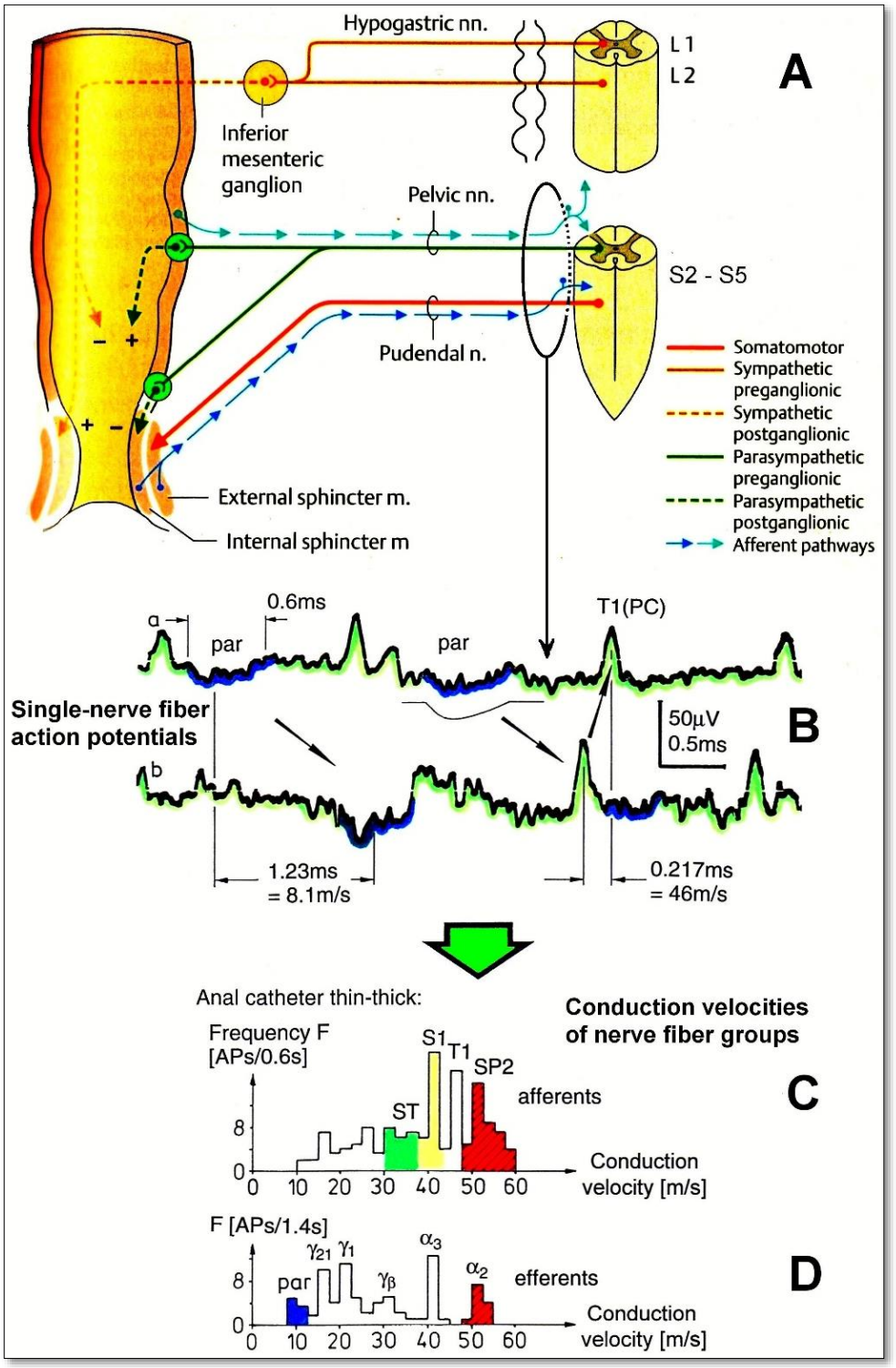

Figure 20. A. Innervation of the rectum [73]. B-D. Sweep piece of recording (B) and conduction velocity distributions (C, D) taken from time intervals following a change of a thin anal catheter (∅ = 12 mm) for a thick one (∅ = 20 mm). Note, the parasympathetic APs are just recognizable in B and also the parasympathetic peak (par) manifests itself in the corresponding conduction velocity distribution (D). For symbols, see legend of **Figure 17.**

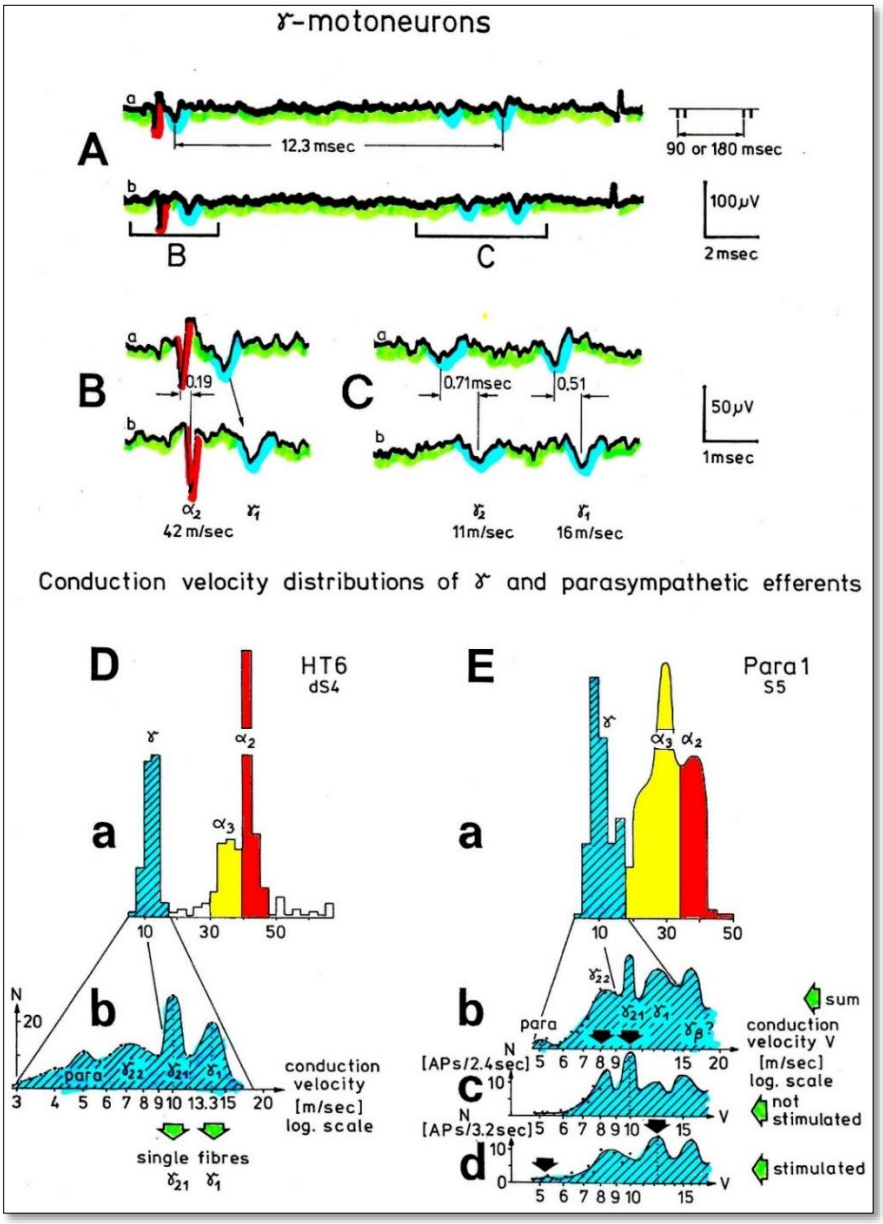

Figure 21. A. Activity from two γ-motoneurons and one α_2-motoneuron. The γ_1-motoneuron may have fired in the oscillatory mode for a few cycles with a period duration of 90ms or 180ms. Interspike intervals of the possible impulse train, consisting of two APs, are indicated (12.3ms). The insert shows the possible oscillation cycle period. HT6; dS4. B, C. Time and amplitude expansions of A. Conduction velocities are indicated. Note that with the increasing conduction velocity, the AP amplitude increases and the duration decreases. D, E. Conduction velocity distributions of motoneurons for the brain-dead human HT6 (D) and paraplegic 1 (E). To make intrafusal motoneuron and parasympathetic peaks visible, the main γ-peak of Da and Ea was plotted on a log scale in Db and Eb. The distribution peaks are labeled with the groups, they most likely represent. In E, the distribution Eb is split into the distribution upon no additional stimulation (Ec) and upon additional stimulation (Ed). Note that in the non-stimulated distribution (Ec) the static γ-motoneuron peaks (γ_{22}, γ_{21}) are highest, whereas for no stimulation (Ed) the parasympathetic (para) and the dynamic γ-motoneuron peaks (γ_1) are highest. When plotting the velocities in Db and Eb logarithmically, the conduction times were first grouped by a conduction time histogram and the column values were then used to construct conduction velocity distribution curves.

Simultaneous recording of afferent and efferent action potentials to analyze integrative properties of the human CNS in brain-dead humans and paraplegics

As we can measure the natural impulse patterns, generated by certain single receptors in the periphery, which run into the spinal cord (CNS) (afferents) and those patterns which leave the CNS via the spinal cord (efferents) in ensembles of single fibers simultaneously **(Figure 22)**, it becomes possible to analyze the integrative properties of the largely unchanged CNS in brain-dead humans (HTs) at the cellular level and the changes in function, caused by CNS injury, degeneration or malformation.

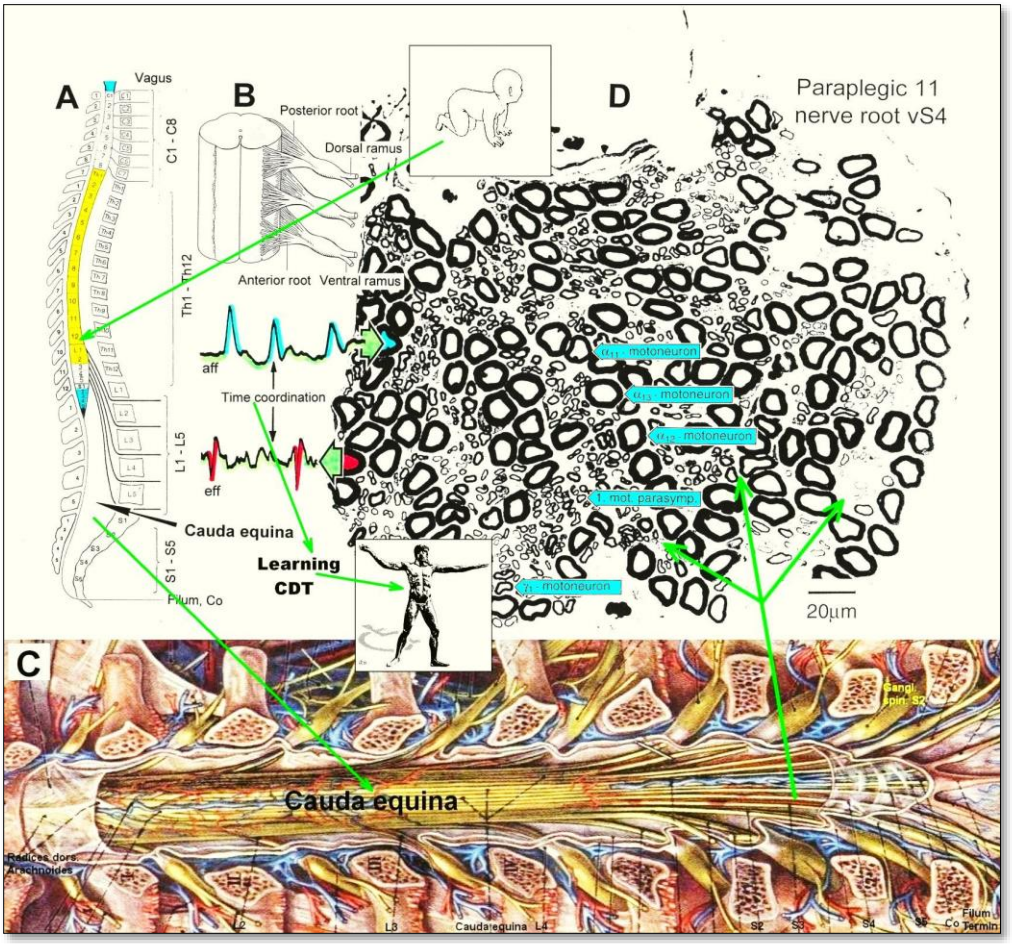

Figure 22. Anatomy to record single-nerve fiber action potentials. A. Ascensus of the human spinal cord gives rise to long nerve roots in the lumbar and sacral range. B. But the nerve roots in the cervical range are short. C. Picture of the opened spinal canal with the cauda equina nerve roots, ganglions and spinal nerves. D. Real ventral S4 nerve root cross section with single-nerve fiber action potentials of afferent (aff) and efferent (eff) fibers and their time coordination. Principle sizes of different nerve fiber cross sections are indicated.

Self-organization of neuronal networks of the human CNS (Electrophysiology), demonstrated by the organization of premotor spinal oscillators

Typical firing patterns of motoneurons can be observed when motoneurons are activated with increasing strength of adequate afferent input. With low afferent input, the motoneurons fire occasionally [53]. With increasing input, they fire intermittently in an oscillatory manner and then continuously in an oscillatory manner **(Figure 23)** [54,55]. The demonstration that neurons of the CNS, in this case motoneurons, can fire with both in an oscillatory manner and non-oscillatory manner is very important for the understanding of the functioning of the human CNS. To describe the functioning of the CNS merely by reflex pathways and loops or coupling of rigid oscillators (of cellular or network origin) is in contradiction to empirical human data, namely that premotor spinal oscillators self-organize as was concluded from measurements of simultaneous natural impulse patterns of afferent and efferent fibers **(Figure 23)**.

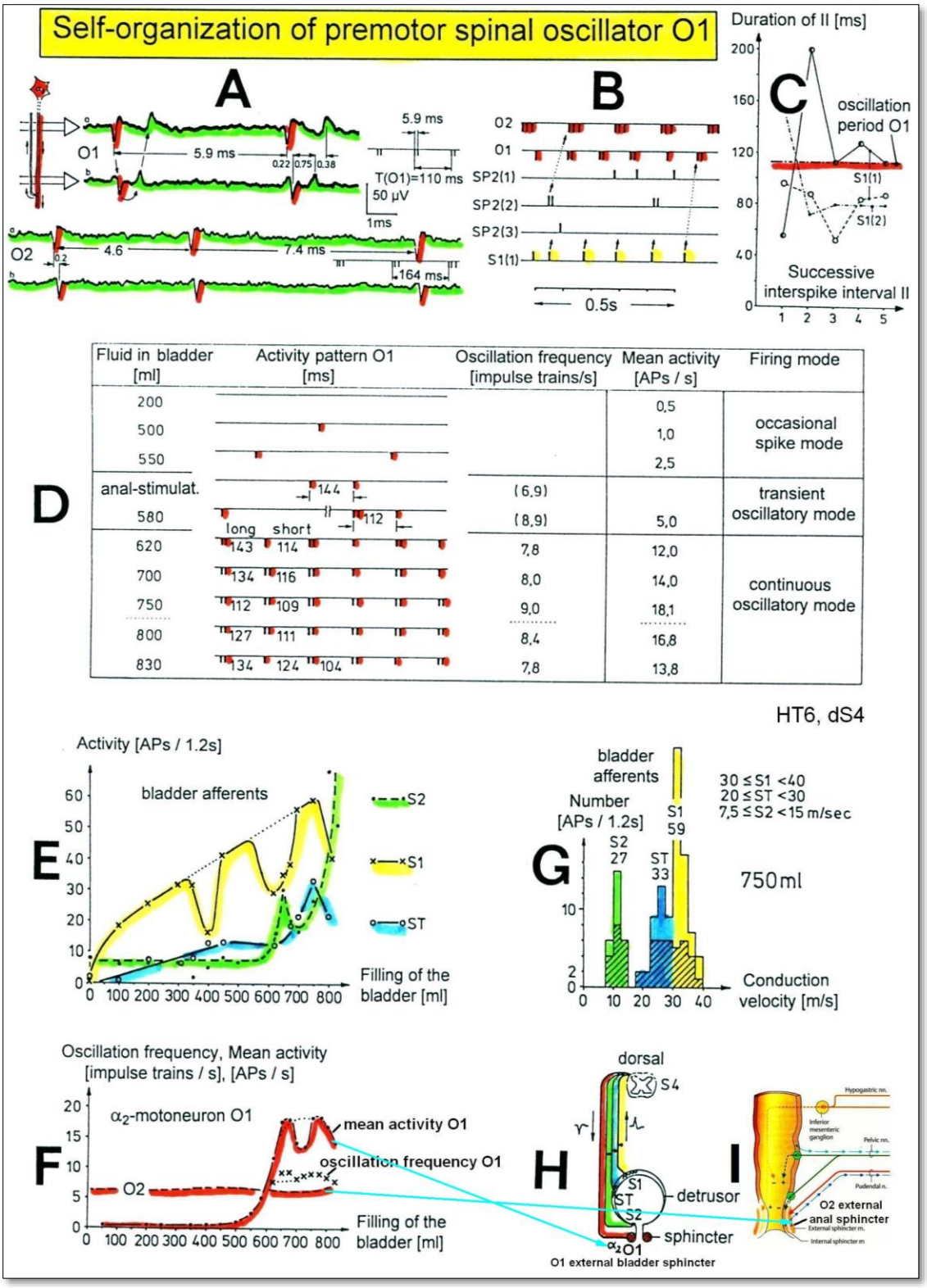

Figure 23. Self-organization of premotor spinal α_2-oscillator O1, which innervates the external urinary bladder sphincter (skeletal muscle). Brain-dead human HT6; recording from a dorsal S4 nerve root. A. Recordings from α_2-motoneurons O_1 and O_2, firing in the oscillatory mode with impulse trains of 2 (upper recording) and 3 (lower recording) action potentials (APs). The durations of the oscillation periods were 110 (O_1) and 164ms (O_2). The interspike intervals of the impulse trains

were 5.9ms (O_1) and 4.6 and 7.4ms (O_2). Motoneuron O_1 conducted at 36 m/s; its recurrent fiber conducted at 21 m/s. The measurement layout is shown schematically. The inserts show the oscillatory firing modes; they have not been drawn to scale. B. Impulse patterns of oscillatory firing α_2-motoneuron O_2 innervating the external anal sphincter, in relation to the muscle spindle afferent activity SP2(1 to 3), activated by the stretch of the anal sphincter by the anal catheter, and impulse patterns of oscillatory firing α_2-motoneuron O1 innervating the external urethral sphincter, in relation to the stretch receptor afferent activity (S1(1)) of the urinary bladder, activated by 750 ml bladder filling. Phase relations between APs of SP2(2) and O_2 and between APs of S1(1) and O_1 are indicated by the small arrows. C. Three series of successive interspike intervals of the stretch receptor afferent fibers S1(1) and S1(2) activated by retrograde bladder filling. The oscillation period of oscillatory firing motoneuron O1, activated only by bladder filling is shown. D. The firing in the occasional spike mode, the transient and the constant oscillatory firing mode of α_2-motoneuron O_1 in response to filling of the bladder. In the 'activity pattern' column changing durations of oscillation periods are given. The oscillation frequencies in the brackets give the frequencies at the moment of oscillation for the transient oscillatory mode. Downward deflections are schematized APs. Interspike intervals of the close APs ≈ 6.0ms (A). E. Activity levels of stretch (S1) and tension (ST) and flow receptor afferents (S2) (E) and of sphincter α_2-motoneuron O_1 (F) in response to retrograde filling of the bladder. The activity values of the S1, ST and S2 afferents are taken from histograms like the one in G. Filling of the bladder was stopped once between 600- and 650-ml. F. The small dotted lines represent mean activity (APs/s) and oscillation frequency (impulse trains/s) of α_2-motoneuron O_1 if bladder filling were not stopped in between. Note that the mean activity increases continuously with the filling of the bladder from 550 to 650 ml, even though motoneuron O_1 started to fire in the oscillatory mode from 620 ml on (D). Note further that the oscillatory firing motoneuron O_2 (frequency of firing with impulse trains is shown) is nearly not affected by the filling of the bladder and by the start of the oscillatory firing of motoneuron O_1. G. Conduction velocity frequency distribution histogram of stretch, tension and flow receptor afferent activity at 750 ml. The activities of afferents S1, ST and S2 are quantified by counting the afferent conduction velocities under the peaks (open plus hatched part), with the conduction velocity limits given in the insert. The counts (27, 33, 59) are given below the peak labeled S1, ST and S2 and plotted into E for the afferent activity at 750 ml. H. Schematic drawing of the anatomical arrangement of the afferents and the motoneuron O_1. I. Arrangements of external anal sphincter, innervated by the α_2-motoneuron O_2.

For high and rather constant afferent input it was found that α-motoneurons fire repeatedly with impulse trains according to their type **(Figure 24)**. The α_1-motoneurons (FF) fire rhythmically at around 10 Hz (range 8 to 20) with an impulse train consisting of 1 AP; α_2-motoneurons (FR) fire at approx. 6 to 9 Hz with 2 to 5 APs per impulse train, and α_3-motoneurons (S) fire with a frequency in the range of 1 Hz and with long impulse trains consisting of up to 40 APs (and more). The rhythmic firing patterns of α-motoneurons are probably generated by local neuronal networks of the spinal cord since oscillatory firing can be recorded from motoneurons of the disconnected spinal cord in spinal cord injury. Probably the motoneuron is a part of the spinal network oscillator. The oscillation period (T) of α_2-motoneurons is roughly related to the number of action potentials (APs) per impulse train (n_{AP}), and this can be expressed by the formula: T = 70ms + 30ms • n_{AP}. A typical premotor α_2-oscillator fires with 3 APs every 160ms (T = 70ms + 30ms • 3 = 160ms), and can change its firing pattern to 2 APs every 130ms for less activation or to 4 APs every 190ms for higher activation.

The α_1-oscillators respond very dynamically, but have little oscillator network properties. Their firing is absolutely correlated to the firing of primary spindle afferent fibers. The α_2-oscillators respond less dynamically, have strong oscillatory properties and self-organize by the adequate afferent input patterns from several kinds of receptors including secondary muscle spindle and urinary bladder afferents. The behavior of α_3-motoneurons is more static and their input is polymodal. The dynamics of responding to inputs increases from α_3 to α_2 to α_1-oscillator in accordance with the dynamics of the 3 muscle fiber types the α-motoneurons innervate. The slow (S), medium fast (FR) (fast fatigue-resistant) and fast contracting muscle fibers (FF) (fast fatigable) have their own corresponding premotor networks in the spinal cord, namely that in which the α_1, α_2 and α_3-networks are integrated in **Figure 24**.

The deterioration of the intrinsic apparatus of the spinal cord, following spinal cord injury, can most easily be seen when plotting frequency distributions of premotor spinal oscillators from a brain-dead human, a paraplegic and a predicted healthy human **(Figure 25)**. The premotor network oscillator lost nearly the specific eigenfrequency **(Figure 25)** and could be activated by all kinds of input with the consequence of the generation of pathologic patterns called spasticity.

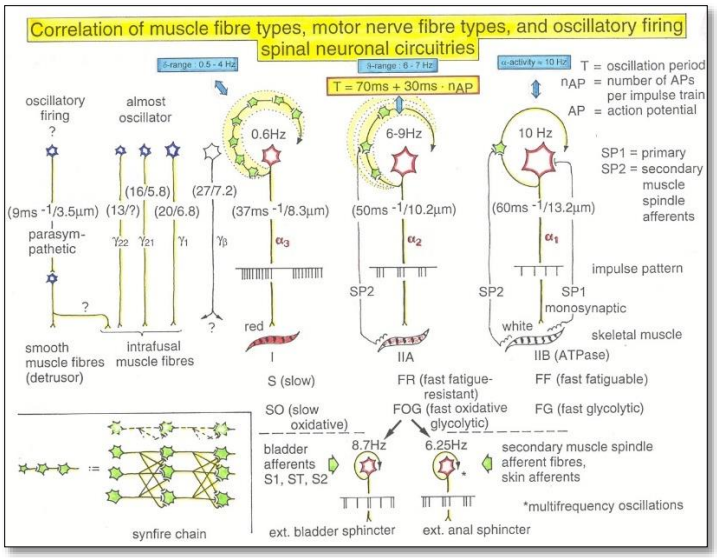

Figure 24. Correlation of muscle fiber types, motor nerve fiber types, and oscillatory firing spinal neuronal networks, based on histochemical, morphological and physiological properties. This figure provides a simplified correlation between muscle fiber, motoneuron and sacral oscillator types. No additional subtypes have been included. The existence of α_1-motoneuron (FF) oscillators firing at 10 Hz has been predicted and they have been identified in paraplegics (unpublished observation). α = motoneuron, γ_1, γ_2 = dynamic and static fusimotors, parasympathetic = parasympathetic preganglionic motoneuron. S1, ST, S2 = stretch, tension and flow receptor afferents.

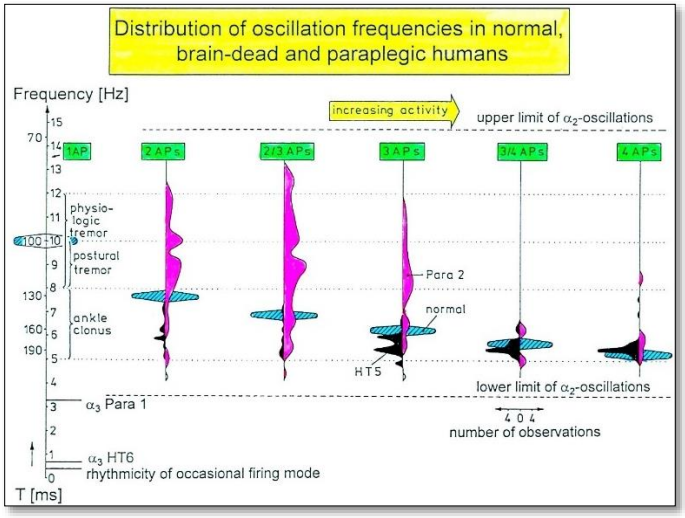

Figure 25. Distributions of oscillation frequencies of continuously oscillatory firing α_2-motoneurons with increasing number of APs per impulse train (increased activity) in paraplegic 2 (open), in the brain-dead HT5 (filled), and in probably normal humans (cross-hatched). Frequencies and rhythmic activity changes in the occasional and oscillatory firing mode are indicated. Ranges of physiologic tremor, postural tremor and ankle clonus are also drawn. Note that frequencies for the brain-dead HT5 are too low, and the oscillation frequencies of the spinal cord isolated for a long time (Para 2) are too high and too spread as compared to the theoretically predicted frequency ranges of healthy humans (cross-hatched). T = oscillation frequency.

Entrainment of network oscillators through jumping on springboard

Spinal oscillators can be improved in its functioning through rhythmic dynamic stereotyped movements, like fast walking and running. Especially jumping rhythmically on springboard **(Figure 26g)** with or without support entrains spinal oscillators. In addition to the stimulation of mechanoreceptors for movement control, also mechanoreceptors for bladder and rectum control are

synchronously activated with the movement. Continence functions are synchronously activated with the jumping (coherent activation of bladder and movement patterns). Since for high activation premotor spinal oscillators build up an external loop to the periphery, neural assemblies are directly entrained to improve their "Eigenfrequencies" and to coordinate their firing with other oscillators **(Figure 26)**. The springboard has an Eigenfrequency ($f \approx 1Hz$; $\omega=2\pi f$), which makes a training in the entrainment region possible. A jumping frequency of 1 Hz is especially efficient for the entrainment of α_3-oscillators because they have an "Eigenfrequency" also around 1 Hz.

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

The efficiency of jumping can be understood when including into consideration afferent inputs to the oscillators. With the building up of simultaneous phase relations between α, γ and SP2 fibers, premotor spinal oscillators built up an external loop to the periphery, which makes it possible to directly influence the firing of spinal oscillators by a rhythm training **(Figure 26)**.

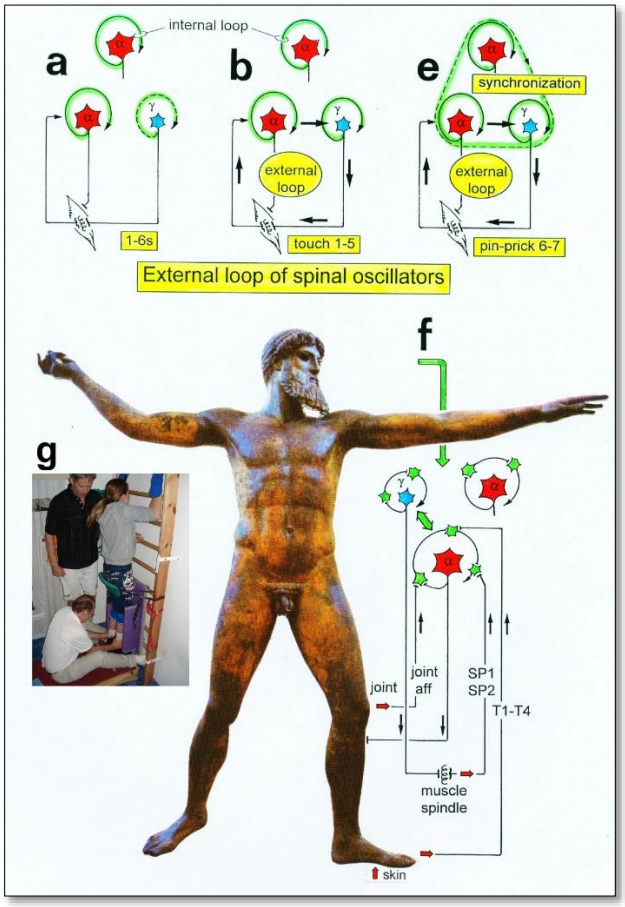

Figure 26. Spreading of oscillatory firing from α-motoneuron neuronal network to include muscle spindles (periphery) and synchronization of different α and γ-motoneuron neuronal networks caused by touch and pinprick stimulation. (a) α-motoneuron neuronal networks fired oscillatory (solid line loop), γ-motoneuron neuronal network did not or did only partly (dashed line loop), upon no additional stimulation. (b) Oscillatory firing α and γ-motoneuron neuronal networks built up a phase relation with muscle spindle afferents and efferents (external loop to the periphery, indicated by thick arrows) upon touch. (e) Oscillatory firing α (internal circuitry loop) and γ-motoneuron neuronal networks (external loop) synchronized (broad peak phase relation) upon pinpricks. The dashed line loop represents synchronization. (f) Oscillatory firing α (internal circuitry loop) and γ-motoneuron neuronal networks (external loop). The open arrows indicate that it may be possible to synchronize spinal oscillators by rhythmic afferent input, generated by rhythmic movements (such as jumping on a springboard (g) or running), and to re-preformat the neuronal circuitry by synapse remodeling to fire more physiologically oscillatory to reduce spasticity and improve locomotion. Extensive pathologic movement like tremor may entrain neuronal circuitry to increase tremor movement. The Greek good is a bronze statue of Zeus found close to the cape of Artemision 460 BC.

Importance of spinal oscillators

Spinal oscillators in the human CNS are of interest for at least 4 reasons. 1) They are important neural networks of the CNS, which generate the high activity mode of motoneurons for muscle activation. 2) They consist, of many interneurons in addition to the motoneuron, the spinal oscillators allow therefore the study of interneuron connectivity under physiologic and pathophysiologic conditions. 3) The oscillation, namely the rhythmic repeated firing with impulse trains, is easy to measure invasively from lower human sacral nerve roots. And tremor (for example in Parkinson), a result of synchronization of oscillatory firing motoneurons, is nearly as easily measurable non-invasively via surface EMG, as reflexes. The oscillators are somehow the CNS interneuron counterpart to the monosynaptic reflexes, which include only the motoneurons. 4) The regular firing of premotor spinal α_2-oscillators can be used as a reference basis to measure phase and frequency coordination during the changes of CNS self-organization, which will be done below.

Coordinated firing of premotor spinal oscillators

The rhythmic firing of the premotor spinal network oscillators was measured to be mainly coordinated **(Figure 27)**. Probably there are hierarchies of different network oscillators to achieve coordinated CNS organization, which is generated by the organization tendencies of the network, descending impulse patterns and spatiotemporal afferent impulse patterns. If premotor spinal oscillators and other oscillators would not coordinate their firing and partly synchronize their firing, tremor would occur. Pathologic synchronization can be observed in Parkinson patients [56,57].

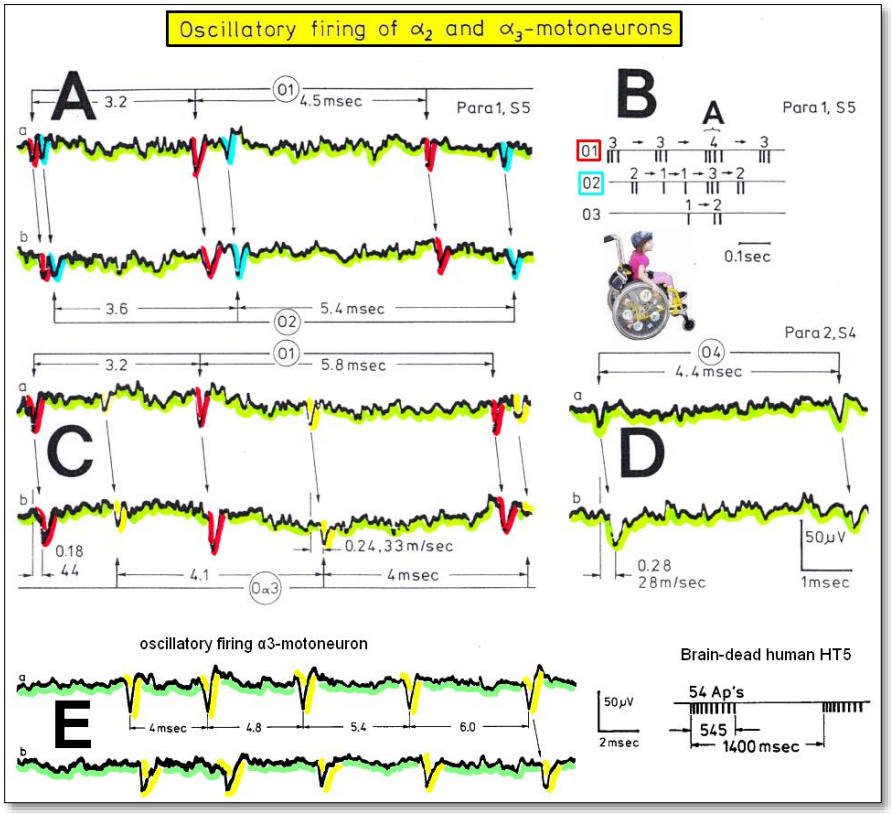

Figure 27. Recordings of impulse trains of oscillatory firing motoneurons in paraplegic 1 and 2. A. Impulse train of the continuously oscillatory firing α_2-motoneuron O1 (3 of the 4 APs are shown) together with the impulse train of the transiently oscillatory firing α_2-motoneuron O2. Interspike intervals of the impulse train are indicated. B. Schematic drawing of the impulse patterns of the 3 oscillatory firing α_2-motoneurons O1, O2 and O3: O1 continuously oscillatory firing, O2 and O3 transiently oscillatory firing. "A" marks the sweep piece shown in A. Paraplegic 1. C. Impulse train of the α_2-motoneuron O1 together with a part of the impulse train of the oscillatory firing α_3-motoneuron Oα3. Interspike intervals, conduction times and conduction velocities are indicated. Paraplegic 1, S5 root recording. D. Impulse train (consisting of 2 APs) with the corresponding interspike interval, conduction time and conduction velocity of the continuously oscillatory firing α_2-motoneuron O4. Paraplegic 2, S4 root recording. E. Start of the impulse train of an oscillatory firing α_3-motoneuron of the brain-dead human HT5 [54].

If spinal cord networks get injured as in spinal cord injury, the network oscillators partly lose their specific oscillator properties, namely the eigenfrequency. The oscillators do not fire anymore by one or several specific eigenfrequencies, but fire unregularly at many frequencies (**Figure 25**, para 2). These damaged oscillators can now synchronize with many other network oscillators and a rather chaotic neural network organization may occur. Pathologic patterns like spasticity can occur in spinal cord injury. Continuous jumping on springboard trains especially the premotor spinal oscillators to fire more rhythmically again **(Figure 26g)** and was called therefore 'oscillator formation training' [58]; it is a part of coordination dynamics therapy. Rhythmic dynamic stereotyped movements train generally the rhythmic and coordinated firing of the oscillators of the CNS.

The recording of the coordinated firing of premotor spinal oscillators at the single neuron level in human **(Figure 27A-C)** was a fundamental measurement of CNS organization. The recording of oscillatory and coordinated firing of α_1-motor units (FF-type) by surface electromyography in suitable patients is comparable easy.

In spinal muscular atrophy [28], also pathologic pattern organization can be expected, and was observed, because of the death of motoneurons and may be other neurons, and in consequence an impaired phase ad frequency coordination.

Similar efferent impulse patterns obtained with the electrophysiological methods single-nerve fiber action potential recording method and single-motor unit surface EMG.

In **Figure 28**, the different frequency patterns of oscillatory firing of motoneurons are shown. Original records were taken with the single-nerve fiber action potential recording method from motoneuron axons and surface electromyography (sEMG) from single-motor units. α_1-Motoneurons innervate FF-type muscle fibers and fire rhythmically with impulse trains consisting of 1 action potential in the order of 10Hz **(Figure 24)**. α_2-Motoneurons innervate FR-type muscle fibers and fire rhythmically with impulse trains consisting of 2 to 5 action potentials in the range of 4 to 7 Hz. The amplitude of the extracellular action potential of the α_2-motoneurons (axon group diameter = 10.2µm, axon group conduction velocity = 50m/s) is on average smaller than that of the α_1-motoneurons (axon group diameter = 13.1µm, axon group conduction velocity = 65m/s) **(Figure 17)**, depending on the position of the axon in the nerve root with respect to the recording electrodes. FR-type motor unit potentials have much smaller amplitudes than the motor unit potentials of FF-type muscle fibers. The α_3-motoneurons (axon group diameter = 8.3µm, axon group conduction velocity = 37m/s) innervate S-type muscle fibers and fire oscillatory at a frequency of around 1 Hz with long impulse trains (up to 50 action potentials per impulse train). The motor unit firing of single S-type muscle fiber motor units could not be safely identified by sEMG because their amplitudes are still smaller than those of FR-type motor units and are thus difficult to identify. The impulse patterns of oscillatory firing motoneurons obtained with sEMG are similar or the same as those obtained with the single-nerve fiber action potential recording method **(Figure 28)**. This confirms the accuracy of the single-nerve fiber action potential recording method. Since sEMG is a non-invasive recording method, oscillatory firing can be recorded easily when using appropriate patients.

Through oscillator formation training mainly the oscillators and their coordination were repaired, but not so much upstream networks. But in brain injury and malformation, the CNS has to be repaired further upstream in the deep complexity of CNS organization. A more general repair has to be achieved. Therefore, for repair one needs to know more generally what got impaired in the organization of human neural networks.

Now it is tried to measure organization principles of the human CNS. It will be shown that neurons and sub-neuronal networks coordinate their firing up to a few milliseconds. If this phase and frequency [35,36] coordination becomes impaired, organization patterns of the CNS become impaired, instable or are even lost. Every functional or structural modulation of the neuronal networks changes this phase and frequency coordination among neuron firing. Learning is related to the exactness and complexity of the many coordination's among single neuron firings or sub-neuronal networks. One strategy for repair is to improve the by injury impaired phase and frequency coordination among neuron firing by movement-based learning. The coordinated movements have to activate the CNS integrative, so that as many phase and frequency coordination's as possible are trained simultaneously to improve the exactness and complexity of CNS self-organization. By exercising very coordinated movements on the special coordination dynamics therapy (CDT) device, the CNS learns from the device via the movement induced afferent input to improve its coordinated firing of neurons and sub-neural networks.

Characterization of γ (and α) -motoneurons in human and animal

Since group conduction velocity distributions overlap, γ (and α) -motoneurons have to be identified additionally by their functions (by their natural impulse patterns).

In measurements in man, the groups of α and γ-motoneurons were identified by the speed and the

dynamics to respond to natural stimulations such as touch, pinprick and catheter pulling, and by the conduction velocity [59]. The characteristics of the static (γ_2) and the dynamic (γ_1) γ-motoneurons are not the same as in animal research. In humans, the γ-motoneurons were therefore characterized by CNS properties, namely by the cell soma and in what neuronal networks the motoneuron cells are integrated, whereas in animal research, they were characterized by the periphery, namely how do primary muscle spindle afferents respond to repetitive 75 Hz stimulation (not always 75 Hz) of the static and dynamic γ-motoneurons in parallel with a ramp stretch [60].

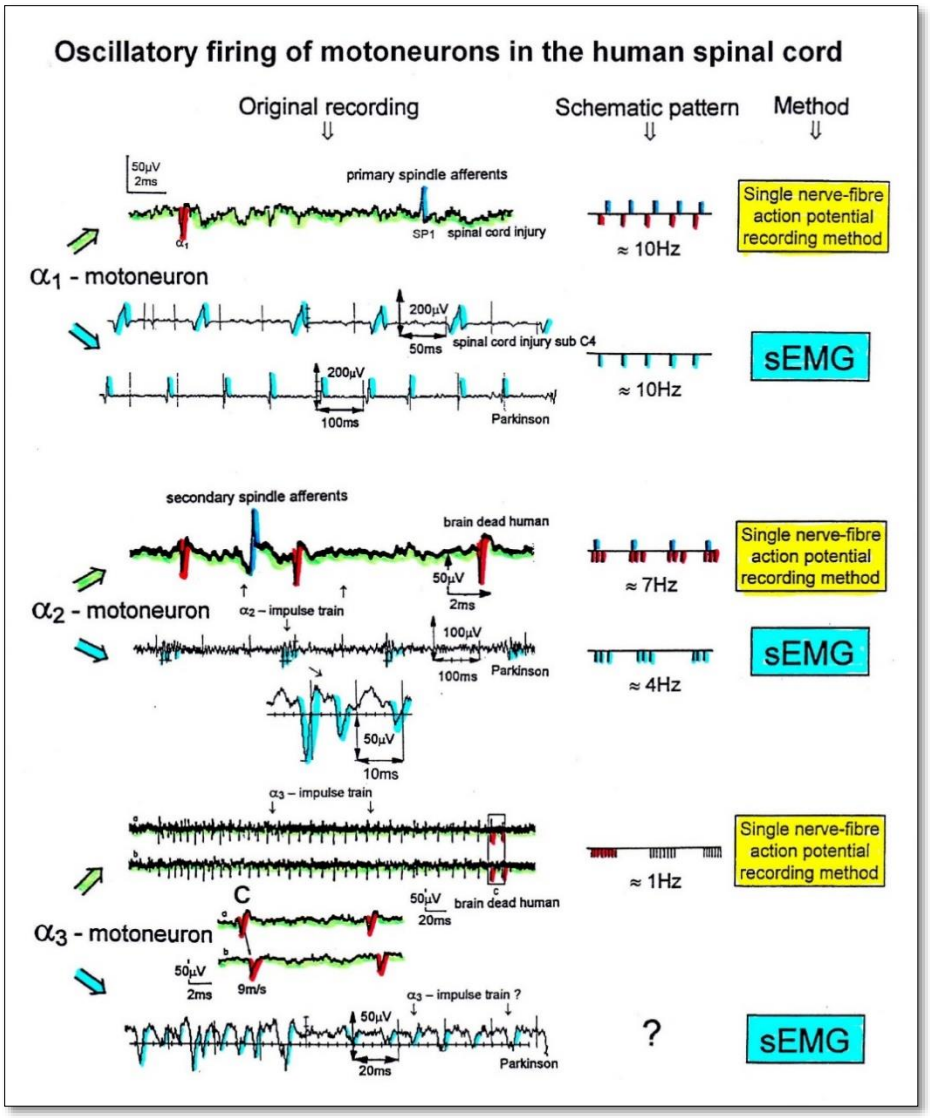

Figure 28. Oscillatory firing patterns of α_1, α_2, and α_3-motoneurons recorded from motoneuron axons with the single-nerve fiber action potential recording method and by surface electromyography (sEMG) from FF, FR, and S-type motor units. The left panel shows original recordings, the middle panel the schematic patterns; the recording methods are indicated on the right side. The recordings were taken from patients with spinal cord injury and Parkinson's disease and from brain-dead humans.

To fulfil the needs of the human research and the clinical demands, we need a multiple group characterization of γ-motoneurons, which can be used in animal research and in the clinical setting. For α-motoneurons, this has partly been achieved. α_2-Motoneurons, for example, fire for continuous high activation at a frequency of about 6.7 Hz, have a group conduction velocity of 50 m/s, a group nerve fiber diameter of 10.2 µm and innervate FR-type muscle fibers, which are fast oxidative glycolytic fibers **(Figure 24)**. For dynamic and static γ-motoneurons, such a multiple characterization is not known in humans. In human measurements, three conduction velocity peaks of γ-motoneurons (γ_1, γ_{21}, γ_{22}) seem to exist. The γ_1-motoneurons respond faster to stimulation than the γ_2-

motoneurons [59]. It has to be shown whether the human γ_1-motoneurons (identified centrally) actually correspond to the dynamic γ-motoneurons as identified in animal research (identified in the periphery) and whether the γ_2-motoneurons correspond to the static γ-motoneurons. The notion will be helpful that there is no tapering of nerve fibers. First electrophysiologic measurements from single human muscle spindles in the periphery indicate that the human muscle spindles may function similarly as do cat spindles, even though the human muscle spindles seem to be more complex [61], and human muscles may be quite different in different parts of the body.

Phase and frequency coordination among oscillatory firing motoneurons and its impairment following injury, malformation and degeneration

Phase and frequency coordination among α_2-motoneurons and their adequate afferent drive in brain-dead human

The coordination among neuron firings will be analyzed now in detail. It includes most likely all neurons of the CNS. It is an organization principle of CNS organization. With the single-nerve fiber action potential recording method the coordination is measured among the firings conducted in afferent and efferent nerve fibers. It was found that the coordination is given by the phases and frequencies among the action potentials (APs).

The relative phase and frequency coordination between the APs of the oscillatory firing α_2-motoneuron O2 and the secondary muscle spindle afferent fiber SP2(1) can directly be seen in the original recordings of **Figure 29** (brain-dead human).

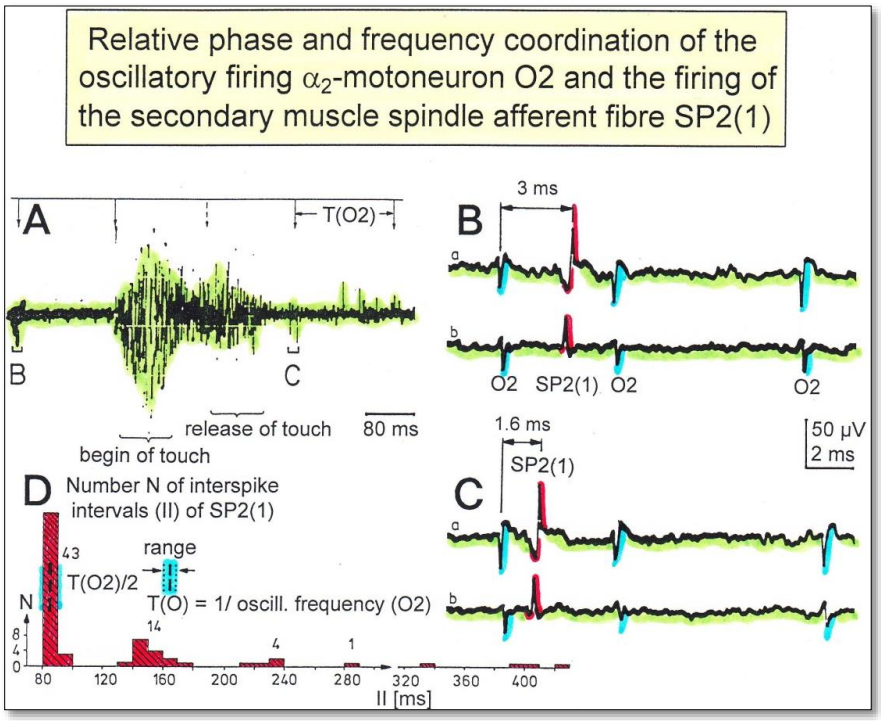

Figure 29. Time relation between the occurrence of the action potentials (APs) of oscillatory firing α_2-motoneuron O2 and the firing of the secondary muscle spindle afferent fiber SP2(1). HT6. S4 dorsal root recording. A. Overall view of the used sweep piece; only trace "a" shown. Four oscillation cycle periods of motoneuron O2 are indicated (T(O2)). The APs of the impulse trains can be recognized only partly, because of the slow time base and poor digitalization. One impulse train (dashed arrow) is lost in the touch stimulated activity, which consists of a touch (large overall activity) and a release part (lower overall amplitude). B, C. Sweep pieces from A, time stretched. In B, motoneuron impulse train APs is marked O2, spindle afferent APs are marked SP2(1). Note that the APs of the spindle afferent fiber are not time-locked to the first AP of the impulse train of the rhythmically firing motoneuron (relative phase coordination). Digitalization four times better than in A, but still rather poor, as can be seen from the low amplitudes of the motoneuron APs on trace "b" in C. D. Occurrence of interspike intervals of the secondary muscle spindle afferent fiber SP2(1). The numbers give the amount of IIs in each distribution peak. The oscillation period of motoneuron O2 (and the range of variation) and the half period are indicated by short dashed lines. Note that the IIs of fiber SP2(1) are very similar to the oscillation period (or the half of it) of α_2-motoneuron O_2 (relative frequency coordination).

The firing of the oscillator and the sweep pieces that are shown time-expanded are indicated at the summary trace **(Figure 29A)**. **Figure 29B, C** shows the AP impulse train of oscillator O2 in connection with an AP of its driving spindle afferent fiber. Because of the duration of the phase relation of around zero milliseconds between the firing of the driving SP2(1)-fiber and the impulse train of the oscillatory firing motoneuron O2, the SP2(1)-fiber AP (every second AP of the SP2(1)-fiber) appeared at a similar time as the impulse train. Because the AP of the spindle afferent fiber had a characteristic waveform, it was easy to extract its impulse pattern from the summed impulse traffic of this S4 dorsal (!) root. During touch-induced skin afferent activity **(Figure 29A)**, the activities of the motoneuron and the spindle afferent fiber were covered by the skin afferent activity. After the cessation of the skin afferent activity, the afferent and efferent APs were found again at their expected time positions of the regular firings. The phase coordination between the firings of the oscillatory firing motoneuron O2 and the secondary muscle spindle afferent fiber SP2(1) at the time when records B and C were taken, was 1.6 ms (3 ms - 1.4 ms, 17B, C). In **Figure 29D**, the relative frequency coordination between the firings of the SP2(1)-fiber and the impulse train of the oscillator is indicated. For the time period evaluated, the correlation between the firing of the motoneuron and the spindle afferent fiber was in the range of between 3 and 5ms.

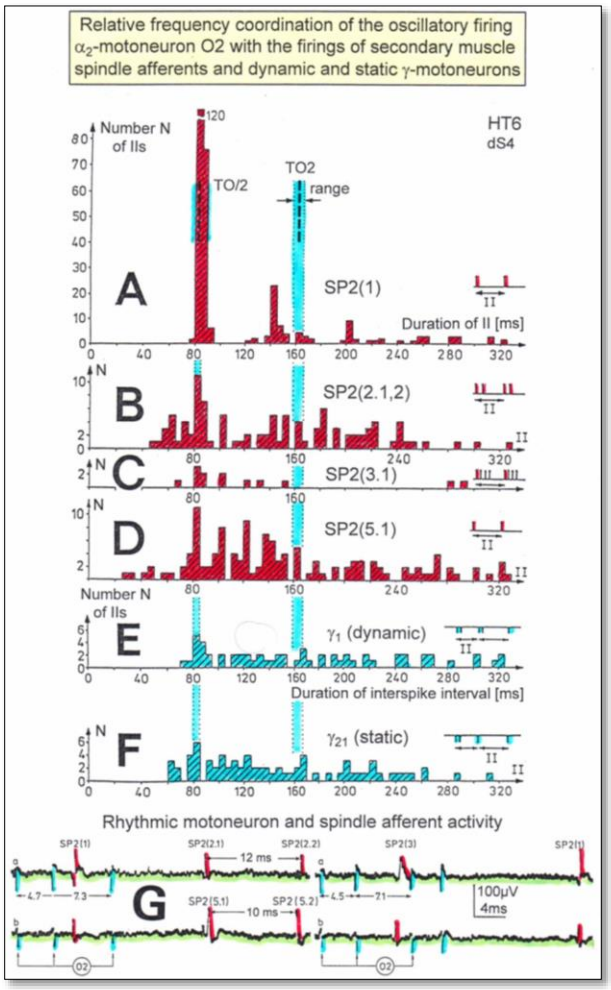

Figure 30. Interspike interval distributions of single endings of four secondary muscle spindle afferents (SP2) and two γ-motoneurons, recorded simultaneously. In A, the oscillation period TO2 (impulse train length = 3 APs) with its range of simultaneously recorded oscillatory firing α_2-motoneuron O2 (see G) is drawn for comparison; also, the halves of the oscillation period TO2/2 are indicated. Note that the interspike interval distributions of spindle afferents and γ-motoneurons have shortest interspike interval, nearly identical to the half of the oscillation period (relative frequency coordination). The schematic impulse pattern in A to F shows the procedure for measuring the interspike intervals. Original records of the firing patterns of α_2-motoneuron O2 and the secondary muscle spindle afferents SP2(1), SP2(2), SP2(3) and SP2(5) are shown in G. Brain-dead human HT6, dS4 root.

Relative frequency coordination

In **Figure 30**, considerations concerning the relative frequency coordination are extended to the activity of further afferent fibers and γ-motoneurons of the same root. **Figure 30G** shows sweep pieces of the original recordings; A through F show the interspike interval distributions of spindle afferents and γ-motoneurons. It can be seen from the overlapping of the oscillator frequency distribution ranges (and the half of it) and from the interspike interval distributions of the afferents that from the viewpoint of frequency coordination, fiber SP2(1) contributed strongly to the drive of oscillator O2, whereas there was a weaker contribution from other afferents (less overlapping between the distributions of the afferents and the range of the basic frequency or the first harmonic of the oscillator). Also, γ-motoneurons showed only little frequency correlation at that time period.

Figure 31 shows the interspike interval distributions of more afferents (including the afferents for bladder filling; stretch receptor afferents S1(1), S1(2)) of another root, together with the oscillation period range (and the half of it) of a second α_2-oscillator (O1). By comparing the oscillation periods (and their halves) and their ranges with the interspike interval distributions of the afferents, it can be suggested which afferents made a (frequency coordination) contribution to the drive of what oscillator at that time interval. For example, the S1(1) urinary bladder stretch afferent fiber activity contributed to the drive of oscillator O1 (activating the external bladder sphincter) because its interspike interval distribution overlaps strongly with the range of the oscillation periods of O1. But the S1(1) distribution does not overlap with the range of the oscillation periods of oscillator O2 or with their halves or quarters. The S1(1) afferent fiber will therefore not have made a substantial contribution to the drive of oscillator O2. On the other hand, the secondary muscle spindle afferent fiber SP2(12) activated oscillator O2 innervating the external anal sphincter, since its interspike interval distribution overlaps with the range of O2 oscillation periods. But the secondary muscle spindle afferent fiber SP2(12) did not activate oscillator O1, as its interspike interval distribution does not overlap with its oscillation period range or the half of it **(Figure 31)**.

By comparing interspike interval distributions of afferent fibers with oscillation period distributions, it can be estimated what afferents made a (frequency coordination) contribution to the drive of the spinal oscillators. These considerations need no knowledge of the connectivity of the neuronal networks. In the frequency coordination between the firings of afferents and oscillators and among oscillators, entrainment or coordination may occur sub- or super-harmonically. The energy transfer, and therefore the coupling strength, will be smaller if the APs coincide in their firing less often.

As indicated by the measurements, the coupling and the relative coordination during the self-organization of the neuronal networks of the human spinal cord are of an enormous complexity; this self-organization is induced by sets of mutual impulse patterns from stimulated receptors, which are ordered, in time and space, so as to reflect, in the spinal cord and higher centers, the interplay of the body with the external world.

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

Following spinal cord injury, the oscillatory firing networks lose specific properties. The Eigenfrequencies of the premotor spinal oscillators change from a narrow to a broad frequency band **(Figure 25)**.

Self-organized α_2-oscillators fire physiologically at an Eigenfrequency (varying within a small frequency band as probably indicated with the hatched distributions in **Figure 25**) with impulse trains consisting of two to three action potentials. Following brain death, this Eigenfrequency band enlarges (black area in **Figure 25**). Following a spinal cord injury, the Eigenfrequency band enlarges strongly and includes in this case the frequencies between 4 and 14Hz for firing with two or three action potentials per impulse train **(Figure 25)**. The premotor spinal oscillators have lost their specific properties and could now be excited at frequencies at which they physiologically would not be excited. This is one reason for spasticity.

Stable phase coordination in the brain-dead individual

To make the phase relation changes better recognizable with time, a representation of phase relations is used, which comes from the measuring of the speed (frequency) of rotation.

The speed of rotation of a turning cylinder with a spot on its surface can be measured with a stroboscope.

If the stroboscope flashes light with the same frequency as the cylinder is turning, the spot on the circumference seems to stand still. There is a constant phase between the two frequencies (frequencies are same or multiples of each other). If the phase relation changes, the spot will move.

If no phase relation exists between the turning of the cylinder and the flashing of the light, no spot will be seen. In similarity to stroboscopic measurement of frequencies of turning cylinders, the phase relation between two oscillatory firing spinal oscillators is pictured in **Figure 32A**. A time axis is introduced on the horizontal line to

make phase relation changes visible in dependence on time.

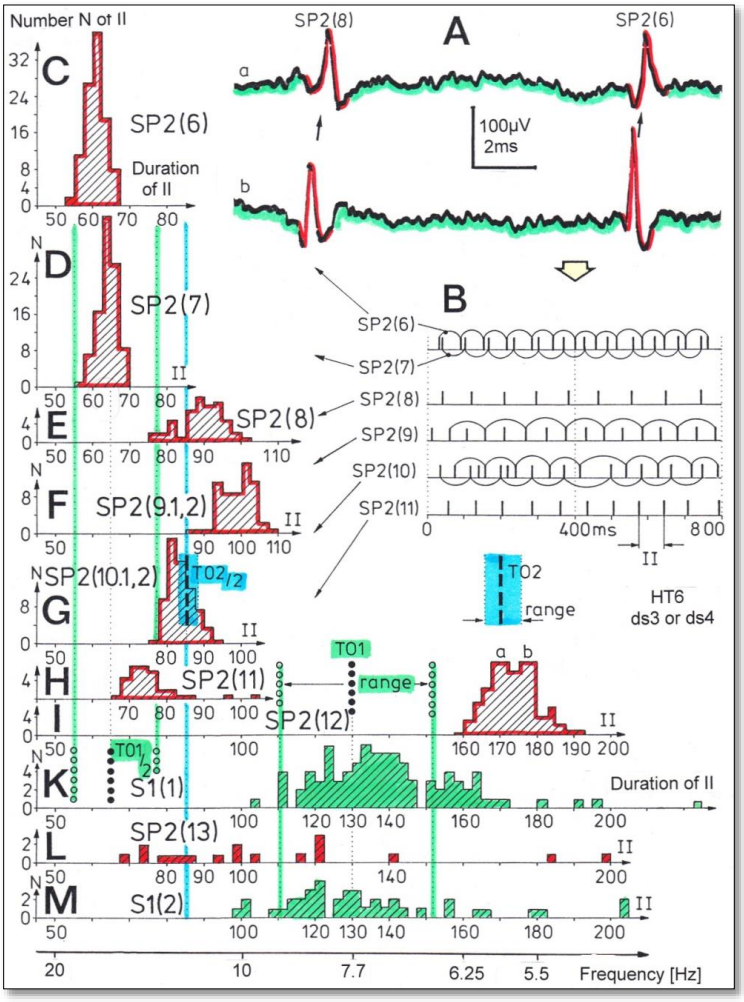

Figure 31. Measurements from brain-dead human HT6 from different spinal cord segments after retrograde bladder filling (700 to 800 ml), with the exception of "I," which was obtained before filling. A. Sweep piece of a recording from a dorsal S3 or S2 root filament. It can be seen that the secondary muscle spindle afferent SP2(6) AP can be distinguished by the waveform on the two traces from the secondary spindle afferent fiber SP2(8) AP (different amplitude of the three phases of the triphasic APs). B. Simultaneously recorded impulse patterns of the six parent secondary spindle afferents SP2(6) through SP2(11) obtained from dS3 or dS2 root recordings. The impulse patterns of SP2(6) and SP2(7) fibers are not separated to show the similarity of the patterns. The impulse patterns of the parent spindle afferents SP2(9) and SP2(10) are split into patterns of the single endings (single ending activity partly connected by circle lines) with the assumption that single endings of parent secondary muscle spindle afferents should have interspike intervals of duration longer than 50ms. C to H. Interspike interval distributions of six simultaneously recorded single secondary spindle afferent endings. F, G. Interspike interval distributions of parent fibers, which are the sums of the distributions from the two activated endings. I. Interspike interval distributions of a secondary spindle afferent fiber (SP2(12)) of a coccygeal root. K, L, M. Interspike interval distributions of single-fiber afferent activity from a lower sacral dorsal root. In L, most likely the activity from a secondary spindle afferent fiber is shown. In K and M, most likely the interspike intervals from afferents (S1(1) and S1(2)), innervating stretch receptors of the urinary bladder wall, are shown. In G, H and K, the durations of the oscillation periods (mean and range) of the oscillatory firing α_2-motoneurons are indicated by thick dashed and dotted lines; the motoneurons innervate the external anal sphincter (TO2) and the external bladder sphincter (TO1). The sites of innervation of the oscillatory firing motoneurons are identified (and distinguished from each other) by anal reflex stimulation, bladder filling and catheter pulling. Note that the TO1 and TO2 ranges and their halves overlap with the interspike interval distributions of the secondary spindle and stretch receptor afferents (relative frequency coordination).

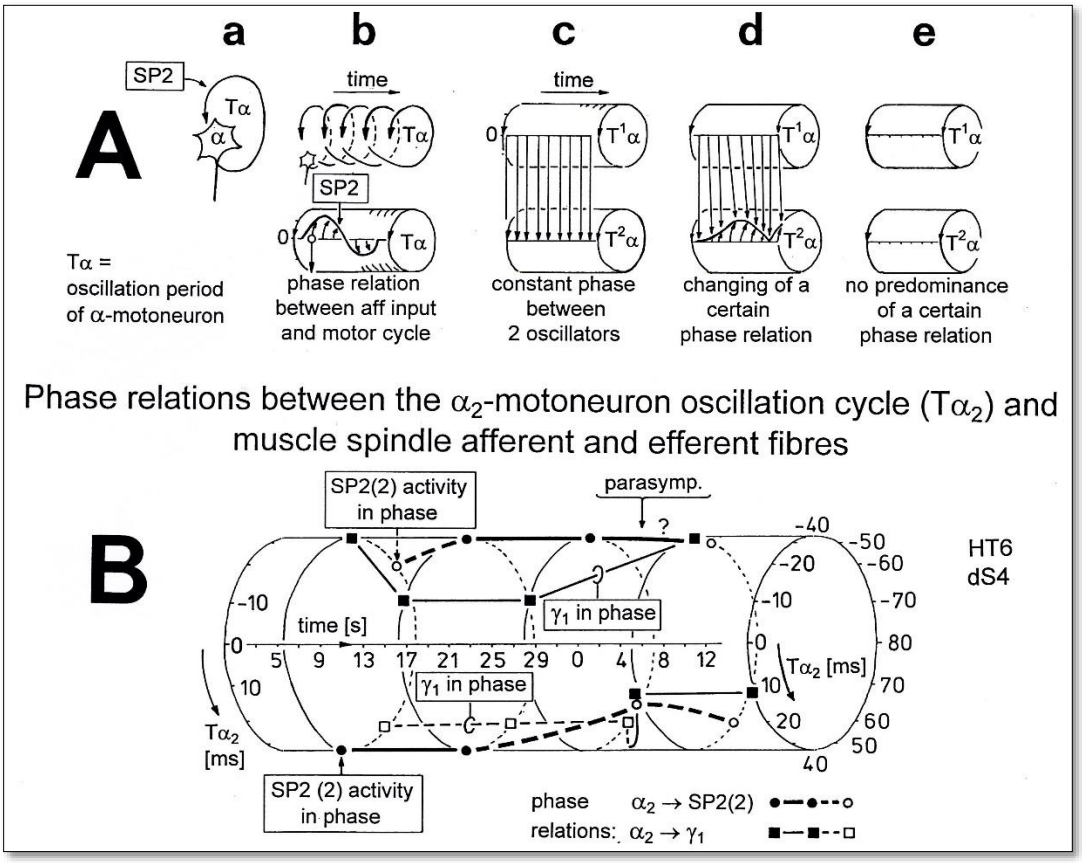

Figure 32. (A) Derivation of the simultaneous description of interspike intervals and phase relations. (a,b) The oscillation period of an oscillatory firing α-motoneuron is schematically characterized by the length of the loop (perimeter). Successive oscillation periods with ongoing time yield a cylinder. Flashing with a stroboscope on such a cylinder with the same frequency as that of the rotation of the cylinder would make a black spot on the turning cylinder not move up or down. If the frequency of the cylinder or the stroboscope changed slowly, the black spot would move up or down. If the black spot moves from left to right with ongoing time, a curve is obtained. By replacing the flashing of the stroboscope by the occurrence of the APs of the spindle afferent fiber (or another oscillatory firing motoneuron) with respect to the APs of the oscillatory firing motoneuron, phase relation changes are made visible in the lower part of "b" for a constant oscillation period (cylinder with no diameter changes). (c) A constant phase between two oscillatory firing motoneurons results to a constant line on the cylinder with ongoing time. (d) A changing phase gives a curve on the cylinder circumference. (e) If there is a loss of predominance of a certain phase between two motoneurons (the black spot gets diffused with ongoing time and is then lost), there is no line or curve. (B) Interspike interval and phase data from the brain-dead human HT6 (root dS4) are plotted in the representation of A. Filled dots and squares represent average phases (phase relations); thick and thin lines connect the dots to show trends. Note that the phase relations change only little; the frequency of the sphincteric α_2-motoneuron ($1/T\alpha_2$) changes only little - the cylinder does not change its diameter.

In **Figure 32Aa**, the loop excitation is pictured for this oscillator model. In **Figure 32Ab**, the phase relation between the SP2 fiber activity incidence and the oscillatory firing is pictured on the circumference of the oscillation period cylinder of the oscillator. **Figure 32Ac,d,e** shows different phase relations, namely a constant phase relation (c), a changing phase relation (d), and no phase relation (e). In **Figure 32B**, phase relation changes are plotted between an α_2-motoneuron and the activity of a secondary muscle spindle afferent fiber and between an α_2 and a γ_1-motoneuron. The data were taken from **Figures 4,5** of [62] of a brain-dead individual (probably normal with respect to the number of phases per oscillation cycle and with respect to phase changes). It can be seen that there were two phase relations per α_2-oscillation cycle and that the phase relation changed only little with time. The phase coordination between the

firings of the α_2 and a γ_1-motoneuron and the secondary muscle spindle afferent fiber was stable.

Unstable phase coordination in a patient with a spinal cord injury

In **Figure 33A**, B, different phase relation changes are with respect to the α_3-oscillation cycle (A) and the α_2-oscillation cycle (B). It can be seen that the different phase relations changed strongly in value over time (upon different stimulation) and that also the number of phase relations per oscillation cycle changed. The phase stability of the cooperative and competitive interplay among neurons became impaired. Whether the change of the number of phase relations from two to three following the activation of the parasympathetic nervous system in the sacral micturition center is physiologic or not is not clear.

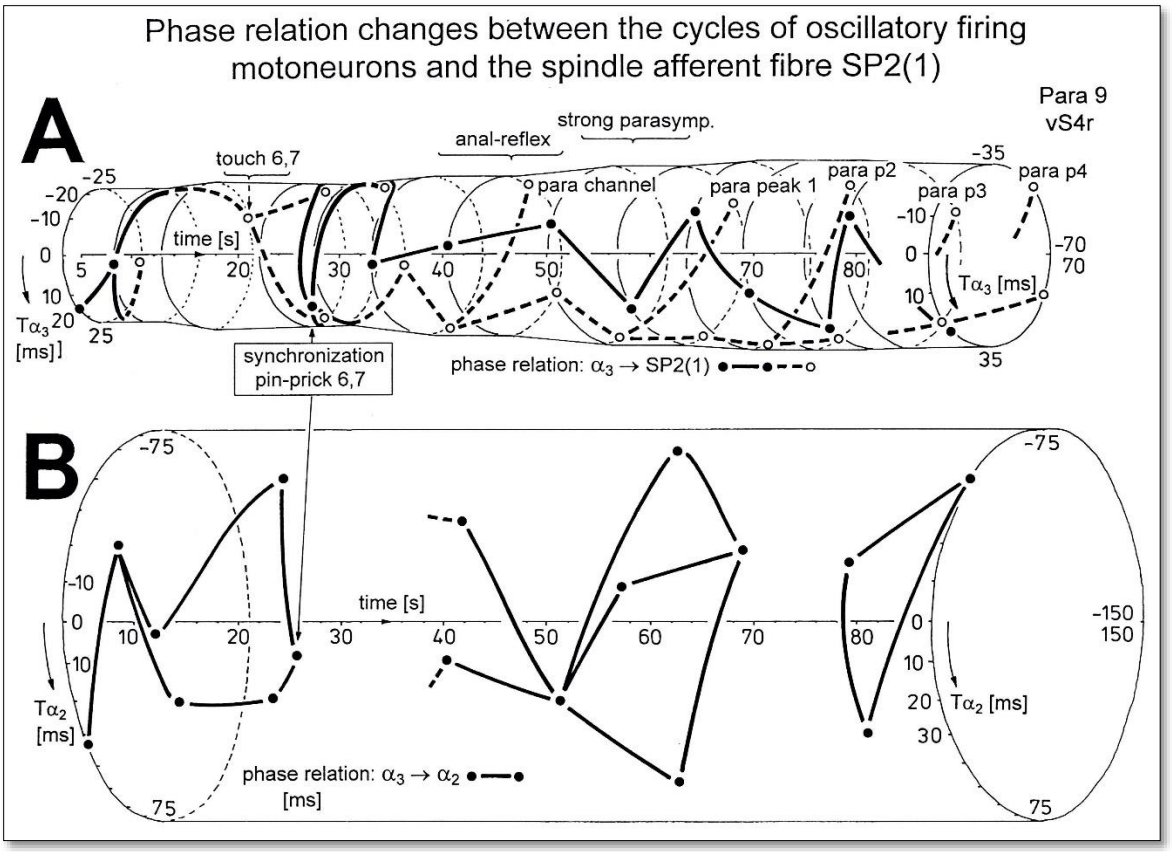

Figure 33. (A) Phase relations between the secondary muscle spindle afferent fiber SP2(1) and the oscillatory firing α_3-motoneuron, taken from **Figures 10-12** (and additional data), are plotted on the oscillation period cylinder Tα_3 (mean oscillation periods are taken from **Figures 11A,12A**) according to **Figure 21A**. The cylinder is changing its diameter (perimeter) because the oscillation period changes. Phase changes in ms are scaled on the cylinder circumference. The ongoing time (to the right) is scaled on the axis of the cylinder (time intervals are taken from **Figure 10A**). Existing phase relations are represented by dots (filled and open (back-side)); lines (filled and dashed (back-side)) only connect the phase relations to show trends. para peak 1, para p2, para p3, para p4 = activity peaks of the SP2(1) fiber due to parasympathetic activation (see **Figure 10A** right). (B) Phase relations between the α_3 and α_2-motoneurons plotted onto the oscillation period cylinder of the α_2-motoneuron. Dots represent phase relations, taken from **Figures 11B,12B**. Note that the phase relations of the paraplegic 9 are much more variable than those of the brain-dead human HT6 **(Figure 21B)**; also, the number of phase relations changes.

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

The most obvious difference of the phase relation changes between the above-mentioned brain-dead human and the paraplegic was that in the paraplegic. The phase relations varied very much, whereas they changed only little in the brain-dead human. The strong phase relation changes in the paraplegic can be interpreted as instability in the organization of neuronal networks. The correlation of neuronal subnetworks was instable in relation to those of the brain-dead human. Assuming that the neuronal network organization and functioning was rather physiologic in the brain-dead with respect to the firing

patterns of the premotor spinal oscillators, the functioning of the networks became instable following spinal cord injury.

The more frequent occurrences of changes of phase relations between the different nerve fibres in combination with the changing number of phase relations per oscillation may mean that subnetworks reacted and interacted more quickly and easily with others according to the afferent input. Especially because the oscillatory firing networks lost specific properties, their resonance frequencies changed from a narrow to a broad oscillator frequency band, which means that the oscillators were not excited at a certain frequency anymore but by a broad frequency band. They could now be excited at frequencies at which they physiologically would not be excited. Over-activation and mass effects could be the result. On the other hand, certain networks could escape from driving afferent influence by changing their phase by phase-escape to avoid interaction. Functionally far away networks are not reached anymore, which also would result in a loss of specific properties. Therefore, because of the loss of specific properties, some interactions could have occurred more easily and other ones not at all.

W.R. Hess tried, in 1944, to compare biological order and human society [63]. In a society, the upper behavior of spinal oscillators could be called "putting its flag to the wind." There could be similarities between the organizations of the human nervous system and the organizations between very many individual nervous systems.

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

Figure 34 shows such schematic natural simultaneous impulse patterns of a static and a dynamic γ-motoneuron, two secondary muscle spindle afferents and an oscillatory firing α_2-motoneuron O2 in a dorsal S4 nerve root (there are afferents and efferents in dorsal or ventral lower sacral roots) during continence pattern changes. The small arrows and the dotted lines indicate existing relative phase coordination's between the static and the dynamic γ-motoneurons and motoneuron O2, and between γ-motoneurons and secondary muscle spindle afferents. The dashed-circle line indicates a phase relation between the APs of the static γ-motoneuron (γ_1) and the cross-correlation between SP2(2)-fiber (single ending one of the mother fiber) and SP2(5)-muscle spindle afferent fiber.

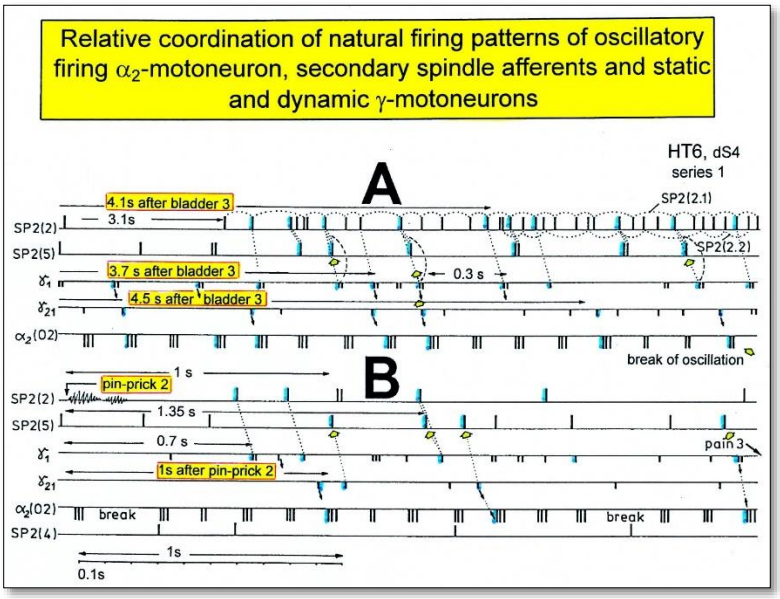

Figure 34. Impulse patterns of simultaneously recorded γ-motoneurons (γ_1 and γ_{21}), secondary spindle afferent fibers (SP2(2), SP2(4), SP2(5)) and oscillatory firing α_2-motoneuron O2 following bladder catheter pulling (bladder 3) (A) and pinprick 2 (B). B was recorded before A. In A, the impulse patterns of the two encoding sites SP2(2.1) and SP2(2.2) of the single parent fiber SP2(2) are indicated by the dotted curves. Times to the activity increases of γ-motoneurons and secondary spindle afferents following stimulation are indicated. Similar time intervals of the occurrence of γ-motoneuron APs and SP2(5) fiber APs (phase coordination) are indicated by the open arrows, and the similar time intervals of γ-motoneuron APs and α-motoneuron APs are indicated by small arrows. Similar time intervals of the APs of fibers SP2(2) and SP2(5) are indicated by the double dotted lines, those of γ_1-APs and the SP2(2) fiber APs by a dotted line, and those of γ_1-APs and the SP2(2)-SP2(5) correlation by a curved dashed line. HT6; dS4.

Including the phase relations between the firings of secondary muscle spindle afferents and the oscillatory firing motoneuron O2, we obtain interlaced loops of coordination's between the firings of γ-motoneurons and secondary muscle spindle afferents, and between secondary spindle afferents and α-motoneurons and between α-motoneurons and γ-motoneurons (co-activity of α and γ-motoneurons) **(Figure 35)**. It becomes obvious from the correlations between the natural impulse patterns (including those of single encoding sites of spindle afferents) that the γ-loop is not a single loop, but a network of loops, because of the divergent projections of γ-motoneurons onto muscle spindles and the probably divergent and convergent projections of secondary muscle spindle afferents into the neuronal network of the spinal cord, consisting of α and γ-motoneurons and interneurons.

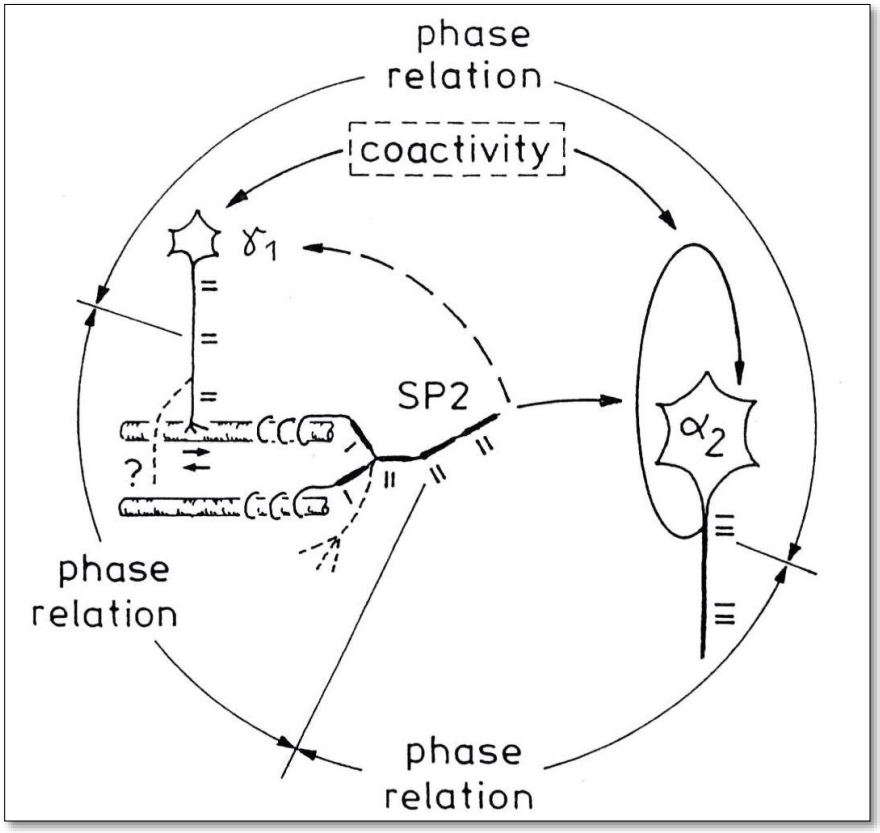

Figure 35. Schematized existing phase relation between α_2 and γ_1-motoneurons and a secondary muscle spindle afferent fiber (SP2). Parallel existing phase relations between other parent afferents and the α_2-motoneuron and between parent secondary spindle afferents are not shown. Phase relation means the increased occurrence of phases in milliseconds in a certain phase range between the action potentials (APs) of the two compared nerve fibers. The complex afferent and efferent muscle spindle innervation is not attempted to be shown. Small arrows at intrafusal muscle fiber indicate local contraction, which is in nuclear chain fibers readily transmitted to the place of afferent innervation. A possible reason of the doublet firing of the SP2 fiber is pictured to occur from single APs (schematized by bars) of two myelinated endings, not necessarily from pacemaker switching. More endings of the parent SP2 fiber and γ_1-motoneurons are indicated by dashed line branches. "Coactivity" indicates a correlation between γ and α-motoneuron spinal cord circuitries for higher activations.

More general, phase and frequency coordination can be seen among the natural firing patterns in the afferent and efferent fibres; this means that upstream in the CNS, there should also be phase and frequency coordination among neuron firing. Two phase relations have been observed to occur mostly between the APs of the secondary muscle spindle afferents and the oscillatory firing motoneuron per one oscillation period **(Figure 36)** (for somatic activation) in accordance with the "in phase" and "anti-phase" jumping on springboard and crawling. With this coordinated natural impulse traffic to and from the periphery, the change of integrative pattern states can also partly be understood from bladder to movement states.

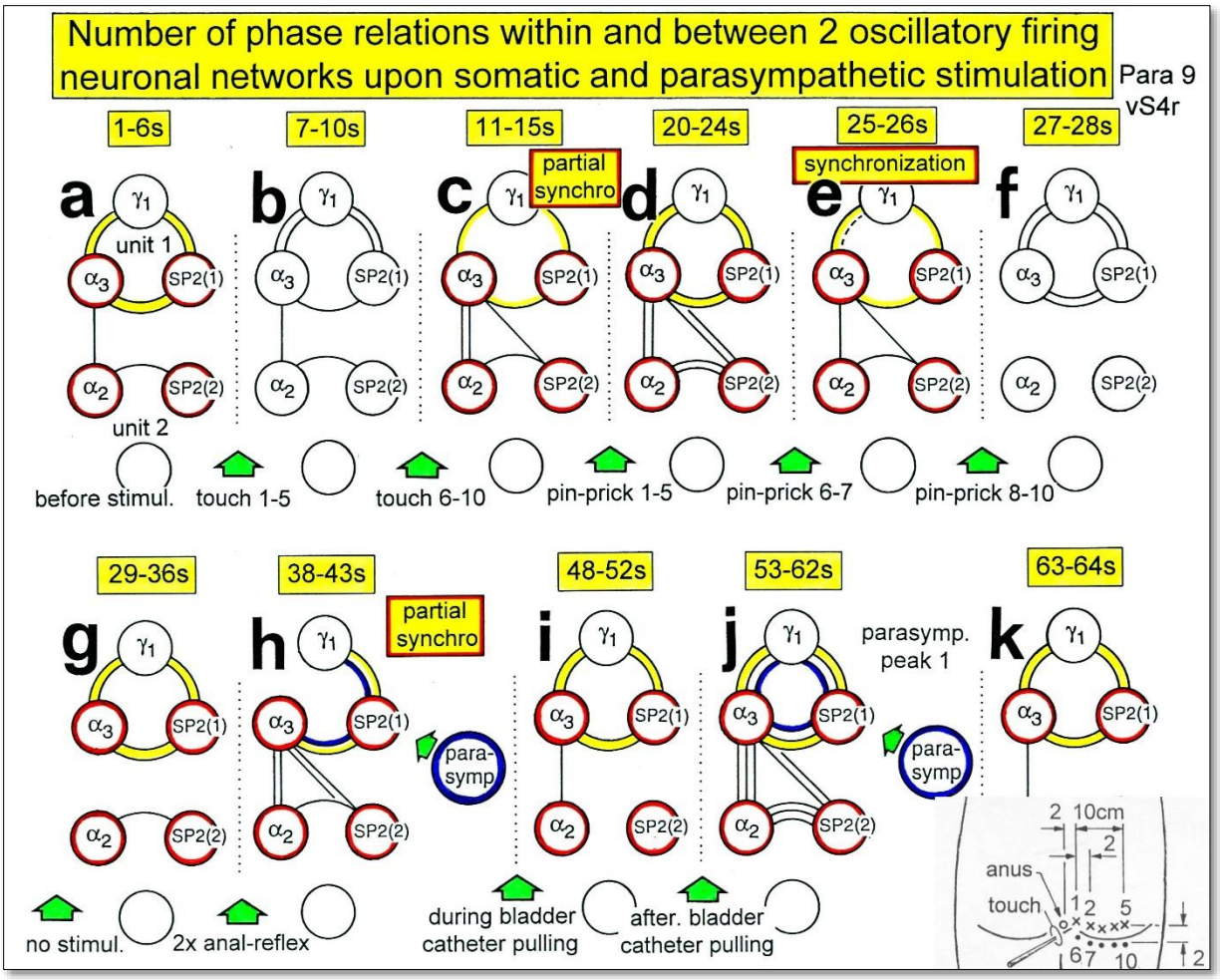

Figure 36. Number of phase relations within and between the two functional units α_3/γ_1/SP2(1) and α_2/-/SP2(2). Time intervals are those of **Figure 5A** of [1] (page 515). Note that in "a," the functional unit 1 is with two phase relations per oscillation period in a stage similar to those seen in the brain-dead individual; with synchronization, only one phase relation occurred (e) and the parasympathetic division channeled an extra phase relation to interact with the somatic division (j). The insert shows the sites of stimulation.

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

As shown in **Figures 11,12** of [1], the number (and the values) of phase relations changed between the firings of the different nerve fibers upon different stimulations. In the brain-dead human HT6, two phase relations were found between the α_2-motoneuron and the secondary muscle spindle afferent fiber SP2(2) and the α_2 and the γ_1-motoneuron (**Figure 5** of [62]). Also, in the paraplegic, two phase relations often existed between the firings of the different nerve fibers. Probably a third phase relation occurred when the activated parasympathetic division channeled an additional input to the oscillatory firing somatic neuronal network.

It may therefore be worthwhile to further analyze the number of occurring phase relations per oscillation cycle upon different somatic and parasympathetic stimulations.

Since two phase relation occurred per oscillation cycle between the α_3 and γ_1-motoneurons and the SP2(1) fiber in paraplegic 9, and also their IIs were rather similar, it is concluded that the neuronal networks of the α_3 and γ_1-motoneurons formed together with the spindle afferent fiber SP2(1) a part of a functional unit. The neural ensemble is built by efficiencies of synapses and projections between the convergence of several γ-motoneurons on one muscle spindle and by the divergence of muscle spindle projections onto several rhythmically firing populations of neurons driving α and

γ-motoneurons. Such a functional unit is partly pictured in **Figure 35** and schematized drawn by three circles in **Figure 36**. The α_2-motoneuron and the SP2(2) fiber belonged to another functional unit (another ensemble) (longer IIs and the existence of only one phase relation). The two functional units (ensembles) are characterized in **Figure 36** by two sets of three circles each. The two functional units interacted with each other, as there existed a phase relation between the α_2 and α_3-motoneurons (**Figure 36**).

Before stimulation (but with the anal and bladder catheters positioned), there were two phase relations in unit 1 (**Figure 36a**).

When touching sites, the skin outside the anal reflex area (**Figures 36**, inset), only slight changes occurred in the two units with respect to the number of phase relations **(Figure 36b)**. But when touching the skin of the anal reflex area, a partial synchronization occurred **(Figure 36c)**, and functional unit 1 reduced the number of phase relations to one. When pinpricking the skin outside the reflex area, two phase relations occurred again in unit 1 **(Figure 36d)**. Upon pinpricking sites inside the anal reflex area, the number of phase relations between all the components of the two units dropped to one **(Figure 36e)**, and synchronization occurred between the firing patterns. Since in the brain-dead human two-phase relations per oscillation cycle were observed in the functional units, it is possible that synchronization and the existence of only one phase relation for two to three seconds reflected a slight pathologic organization of the networks. Even though upon touching sites 6 to 10 **(Figure 36c)** or upon pinpricking sites 6 to 7 **(Figure 36e)** only one phase relation existed in unit 1, and synchronization occurred with both stimulations, it was shown (**Figures 8,9** of chapter V of [1]) that the touch afferent input organized a different functional state of unit 1 than pinpricking. The response time until the shortening of the oscillation period was longer than the oscillation period (≈ 100ms) for pinprick and shorter for touch. The repetitive touch stimulation (most effective inside the anal reflex area) reinforced the sustained stretch reflex of the anal sphincter (continence pattern), and repetitive pinprick stimulation replaced the continence pattern by the protection reaction of the anal sphincter. The number of phase relations alone therefore only provides limited information on the functional state of the organization of the neuronal networks of the human spinal cord. Measurements of a number of parameters are necessary to yield a rather complete description of the functional state of neuronal networks.

Following pinprick 8 and 10 and with no stimulation, two phase relations existed again in functional unit 1 **(Figure 36f, g)**, in some similarity to pre-stimulation status **(Figure 36a)**. Following two anal reflex stimulations, partial synchronization occurred in the components of the two units (**Figure 5** of [64]) and mainly two-phase relations existed (**Figure 36h)**. But the organizational state was still not very similar to the pre- **(Figure 36a)** or post-stimulation state in unit 1 **(Figure 36g)**, since the parasympathetic division was slightly activated following anal reflex stimulation, as was measured by the impulse pattern (increase of doublet activity) of the secondary muscle spindle afferent fiber SP2(1) (**Figures 5,7** of [8] (part 2)). Therefore, probably one phase relation was due to the somatic activation in similarity to **Figure 36c**, e, and the other phase relation was due to the activation by the parasympathetic division. During bladder catheter pulling **(Figure 36i)** and with no stimulation **(Figure 36k)**, the number of phase relations and possibly the functional organization was again similar to the pre-stimulation state **(Figure 36a)**. Following strong (painful) bladder catheter pulling with a strong activation of the parasympathetic division (time interval 53-62s **(Figure 36j)**), measured by the increased doublet firing (see **Figure 5** of [8] (part 2)) of the SP2(1) fiber, the functional organization of the sacral micturition center of the disconnected spinal cord changed completely. Functional unit 1 was now correlated by three phase relations per α_3-oscillation cycle. The functional unit 2 also showed three phase relations per an α_2-oscillation cycle, and interacted with functional unit 1 by three phase relations as well (between the α_3 and α_2-motoneurons; **Figure 36j** [53-62s]). Between the first and second parasympathetic peak at the time interval 63-64s **(Figure 36k)**, the organization form of the two functional units was similar to that before the first parasympathetic activation [49-52s] **(Figures 36)**, only the values of the phase relations changed **(Figure 12Bd** of chapter 5 of [1]). With the second strong activation of the parasympathetic division (parasymp. peak 2, time interval 65-72s), the functional unit 1 was bound together again by three phase relations), in similarity to the first strong activation of the parasympathetic division [62], measured by the burst firing of the secondary muscle spindle afferent fiber SP2(1) (**Figure 8** of [8]) and the increased doublet firing of the SP2(1) fiber (**Figure 5** of [8]). The functional unit 2 was disorganized, but phase relations still occurred between the α_3 and the α_2-motoneurons and the SP2(2) fiber [62]. The α_2-neuronal network and the γ-motoneuron networks, driving the SP2(2) spindle afferent fiber, were integrated differently. After the second strong parasympathetic activation, in the time interval 73-76s (**Figure 10A** of chapter V of [1]), the functional organization of the two functional units in the spinal cord was similar to that before the activation of the parasympathetic division. Functional unit 2 was slightly disorganized as the SP2(2) fiber strongly reduced its firing [62]. For further details see chapter V of [1].

This intricate analysis shows how complex neural network organization changes are. But such analyses are a first real step to understand human neural network organization and its consequences for disorders.

Surface Electromyography to measure motor programs, oscillatory firing and phase and frequency coordination among motor units through recording single-motor units

Another human electro-physiologic tool to measure natural impulse patterns of neurons is the surface electromyography (sEMG). With the same recording system used to record singe-nerve fiber APs, just replacing the wire electrodes with EMG surface electrodes, single-motor unit firing and motor programs can be recorded non-invasively. The sEMG recording arrangement is shown in **Figure 37** for recording motor programs from an infant.

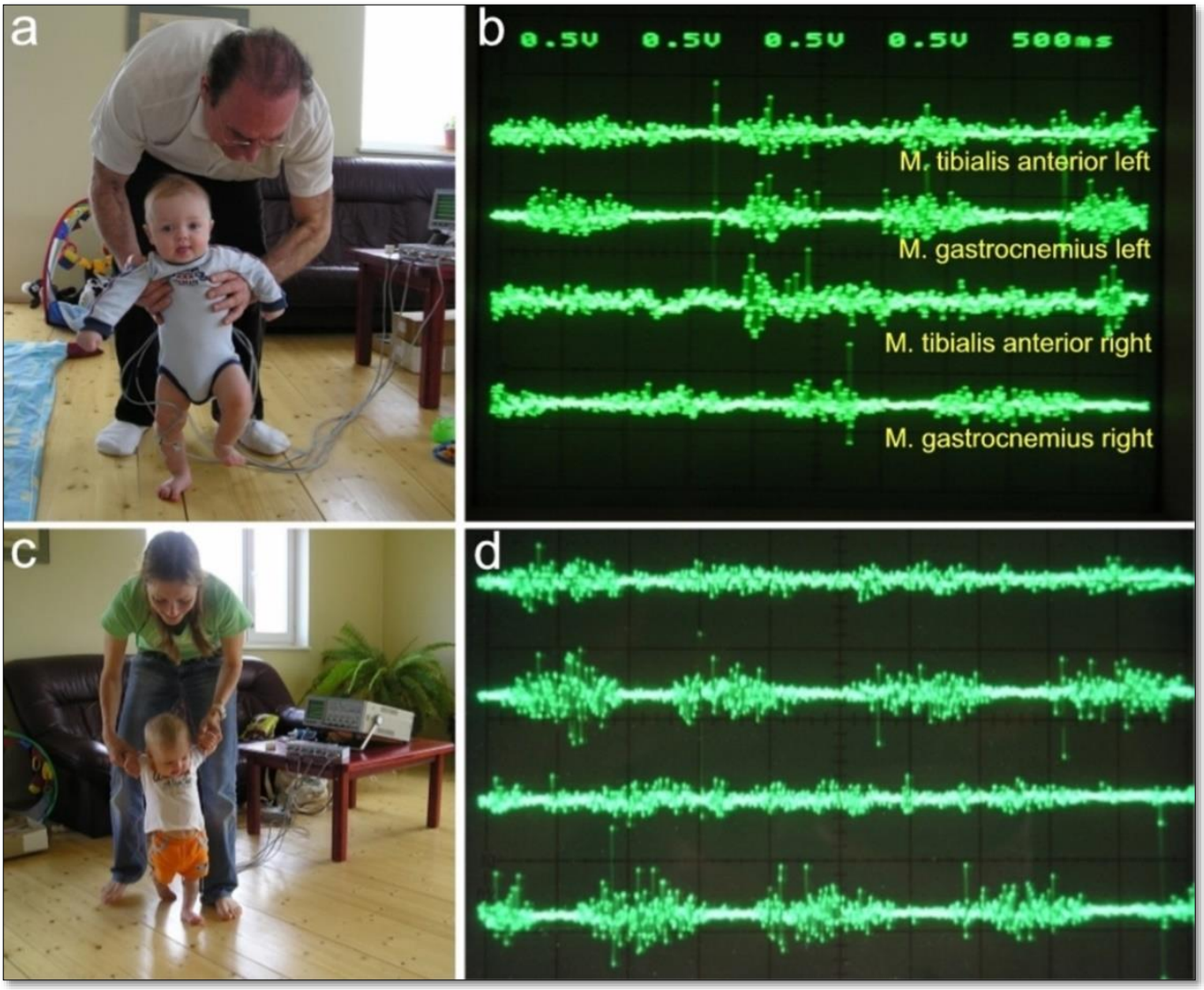

Figure 37. Surface EMG obtained from the healthy 5-months-old (a,b) and 8-months-old old "Jürgen" (c, d) during supported walking. a. Walking resembles automatic stepping, because of the strong lifting of the left knee. The toes of the right foot are plantar flexed, which is not physiologic. b. Surface EMG motor programs of left and right tibialis anterior and gastrocnemius muscles. Note that there is no antagonistic action between the tibialis 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).

When surface EMG is performed from a healthy person or child, coordinated motor programs can be recorded from the different muscles **(Figure 37)**. The patterns of recruitment of motor units cannot be seen in such a motor

program. Because the number of activated motor units is so high that single motor units cannot be followed. However, when only a few motor units can be activated in a certain muscle, then the pattern of activation of the motor units and the coordination between them can be seen. If the CNS of a patient with an incomplete spinal cord injury is functioning rather physiologically as a result of a long-lasting intensive coordination dynamics therapy, then an analysis of the generation of the motor program becomes possible based on single motor unit firing. **Figure 38** shows such sEMG recording. Some phase and frequency coordination's are indicated.

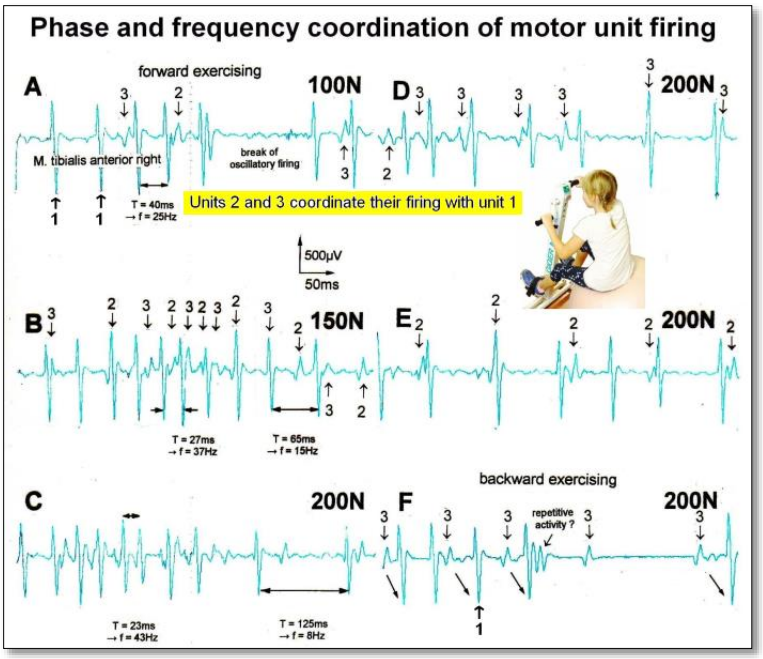

Figure 38. Phase and frequency coordination between oscillatory firing of 3 motor units (FF-type, motor units '2' and '3' are partly marked) during the generation of a motor program when exercising on the special coordination dynamics therapy device (see below) at loads increasing from 100 to 200N. Oscillation periods (T) and oscillation frequencies (f [Hz]) of oscillatory firing motor unit 1 (largest motor unit) are partly indicated. 'C, F' soleus electrodes shifted to gluteus muscles. In 'F', some coordination's between motor unit '3' and '1' are marked.

Entrainment of premotor spinal oscillator networks by rhythmic movement-induced afferent input and inputs from supraspinal centers

If one approximates for high activation spinal neuronal networks into premotor spinal oscillators (driving the motoneuron) and propriospinal oscillators, then premotor spinal oscillators can be handled in a first approximation as single linear oscillators. The premotor spinal oscillators and the spinal pattern generating networks are self-organized and driven by peripheral afferent and supraspinal inputs. When training rhythmic, dynamic, stereotyped movements, the premotor spinal oscillators, approximated as linear oscillators, are driven by movement-induced afferent input from the periphery (mainly the legs) and surrounding pattern generating networks and possibly supraspinal inputs. These spinal oscillators and most likely their neuronal network can be entrained at least by use of the external loop **(Figure 26)** for a better self-organization.

If one assumes that loop circuits do not only exist between the premotor spinal oscillators and the periphery, but are a general structure in the CNS, then motor learning involves the formation of loop circuits (or better loop network circuits) between the cortex and the periphery involving the sensory cortex and the thalamus. When a linear oscillatory system is driven by an external periodic input its response contains both frequency components. This is also, in general, true with nonlinear oscillators. However, in this case, if the external frequency is close to the Eigenfrequency of the oscillator itself, then it is possible to have a response at the external frequency only. This phenomenon is known as entrainment or synchronization. It is of paramount importance with respect to biological oscillators because it allows them to "latch on" to the environment. Thus, a rhythm with a free-running period of 24.7 h may be synchronized to 24 h when exposed to the natural sequence of day and night.

Need for improving the stability of phase and frequency coordination to allow specific patterns formation and learning transfer

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

In severe cervical spinal cord injury, the jumping on springboard **(Figure 26g)** is not sufficient for bladder repair (the biggest problem in spinal cord injury). First, of course, the patient has to regain movement functions back (especially the trunk stability) to be able to perform the jumping on springboard. Further, the self-organization of CNS networks by phase and frequency coordination has to be improved to make learning transfer [65] from movements to bladder functions possible, since in every CNS injury, the phase and frequency coordination is impaired. Large instabilities in phase and frequency coordination will not allow specific pattern formation as a basis for learning transfer. However, the stability of phase and frequency coordination can be improved when the patient is exercising on special coordination dynamics therapy devices, especially the one shown in **Figure 39**.

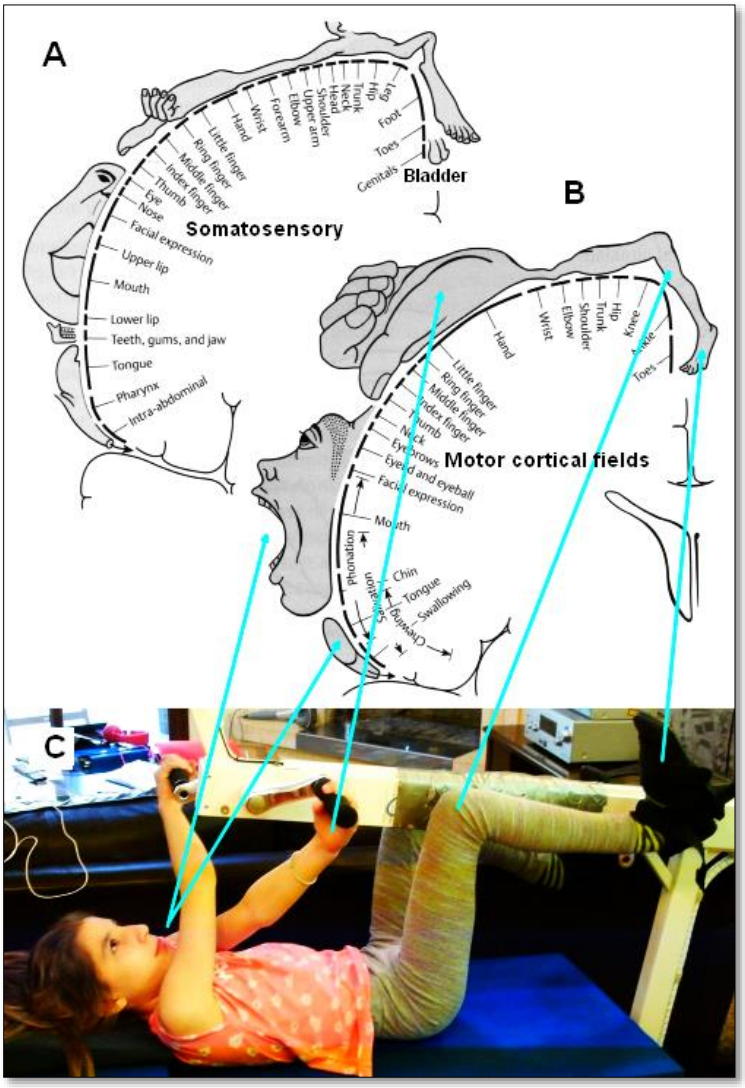

Figure 39. Relative sizes of cortical representations of different parts of the body which are activated when exercising on special CDT devices in coordination with instructions. Nearly the whole somatosensory (A) and motor cortical fields (B) are activated. When moving only the legs, as in case of a fitness bicycle, the activated areas are relatively small. Note, the cortical representation of the urinary bladder is close to the representation of the toes, and during jumping **(Figure 26g)**, the toes are activated. The patient Nefeli in 'C' suffered a spinal cord injury during a cancer removal by medical malpractice and had also the urinary bladder to be repaired. The crossing of the arms trains the corpus callosum. - This special CDT device for measuring and therapy (int.pat.) is produced by the firm: Giger Engineering, Martin Giger dipl.Ing.ETH/SIA, Herrenweg 1, 4500 Solothurn, Switzerland, www.g-medicals.ch.

The importance of stable phase and frequency coordination to allow specific pattern formation and in consequence learning transfer to other patterns can be understood at the collective variable level (System Theory of Pattern formation (see below) and at the neuron level. The behavioral information F_{inf} of the coordination pattern dynamics, characterized by equations of motion of collective variables, $dX/dt = F_{intr}(X) + \sum c_{inf}F_{inf}(X,t)$, affect the whole coordination pattern dynamics, including stability, rather than only certain coordination patterns. If the behavioral information includes the exercising of extremely coordinated, integrative movements, like exercising on the special CDT device for turning, then the quality of the CNS self-organization can be enhanced by improving the exactness of self-organization, namely the precision of phase and frequency coordination between neuron and neural assembly firing. By improving the precision of organization of the intrinsic dynamics $F_{intr}(X)$, that is, the specific variability of the injured networks, certain patterns do then already reappear (Chapter V of [1]).

Neurons often serve more than one network pattern at the same time by time sharing of neuron firing and, in this way, give rise to learning transfer among the activated patterns. If subnetworks are improved in the organization of one pattern, the organization of the other pattern will also improve. Neurons involved in the organization of breathing and activating intercostal muscles, for example, are also involved in the organization of trunk stability. By reducing spasticity of the trunk (in patients with Parkinson's disease), the breathing will also improve. Similarly, sphincteric motoneurons are involved in continence and pelvic floor weight bearing. If during pregnancy the (non-trained) pelvic floor is not trained, sometimes stress incontinence occurs after birth.

Human repair-neurophysiology demonstrated on continence repair in human patients

Pathologic bladder functioning following spinal cord injury

When measuring from lower sacral nerve roots, natural stimulated afferent and efferent impulse patterns are recorded simultaneously. The organization of the neural networks of the sacral micturition center is measured through the efferent output in connection with the input from the receptors of bladder and rectum. The input from the urinary bladder can be identified by filling the bladder or pulling the bladder catheter and the input from the anal canal can be identified by pulling the anal catheter or changing the catheter from thin to thick. The communication between the CNS and the changing periphery is monitored online at the single-neuron level **(Figure 40)**.

Activity of bladder afferents induced by retrograde bladder filling

For measuring bladder afferent activity increase upon retrograde bladder filling, the bladder was emptied and then filled while recording. With the groups of nerve fibers identified from conduction velocity distribution histograms **(Figure 41B)**, the increase in activity of the urinary bladder stretch (S1) and tension receptor afferents (ST) to retrograde bladder filling was measured. **Figure 41** shows the activity increases following filling of the bladder of Para 7, via a catheter, with up to 400 ml fluid. The bladder was filled to the maximal acceptable value as determined pre-operatively by compliance (bladder filling volume / bladder pressure) measurements. **Figure 41B** shows the sum of the individual velocity distributions for different filling stages for afferents and efferents. The peaks are identified by two calibration relations; α_2-motoneurons conduct with the same velocity as the secondary muscle spindle afferents (~50 m/s); and α_3-motoneurons conduct approximately with the same group velocity as the stretch receptor afferents S1 (41 m/s) at about 35.5°C. **Figure 41A** gives velocity distributions for certain bladder filling stages. The most important obvious feature is that the bladder stretches and tension receptor afferents fire considerably even with no bladder filling.

By setting up conduction velocity borders of the S1 and ST groups according to the distribution curve, the activity of each group could be measured for different filling volumes and plotted **(Figure 42A)**. As can be seen in **Figure 42A**, the stretch (S1) and tension receptor afferents (ST) in the left root S5 fired with 15 APs during 0.2s at no bladder filling. The bladder afferents increased their firing with the increasing bladder storage volume. At 160 ml filling, a transient very strong firing of ST afferents occurred. This was the filling volume at which before the surgery the detrusor was activated in a urodynamic measurement. It was not possible to activate the detrusor with retrograde bladder filling during surgery, even though the anesthesia was light, as paraplegics with a complete spinal cord lesion feel no pain.

Comparison of bladder afferent activity increase to retrograde bladder filling between a paraplegic and a brain-dead human

The pathology of the bladder afferent activity in the paraplegic 7 analyzed in **Figure 42A**, with dyssynergy of the bladder, is fully revealed by a direct comparison with the activity increase of the bladder afferents following retrograde bladder filling in brain-dead human HT6 **(Figure 42B)**. The dependence of the bladder afferent activity on the bladder filling volume in paraplegic 7 shows four main differences in comparison to those in HT6. (1) The bladder afferents fired already with no

bladder filling which was not the case in HT6. (2) The activity increased more smoothly in HT than in the paraplegic, even though bladder filling was stopped twice in HT6 but was not stopped in Para 7. (3) In the Para 7 the tension receptor afferent activity was higher than the stretch receptor afferent activity which was not the case in HT6. (4) The bladder afferent activity was higher in the paraplegic than in the HT6. This increased afferent activity will have consequences on the excitation of the CNS activating the striated sphincters of the bladder and the rectum.

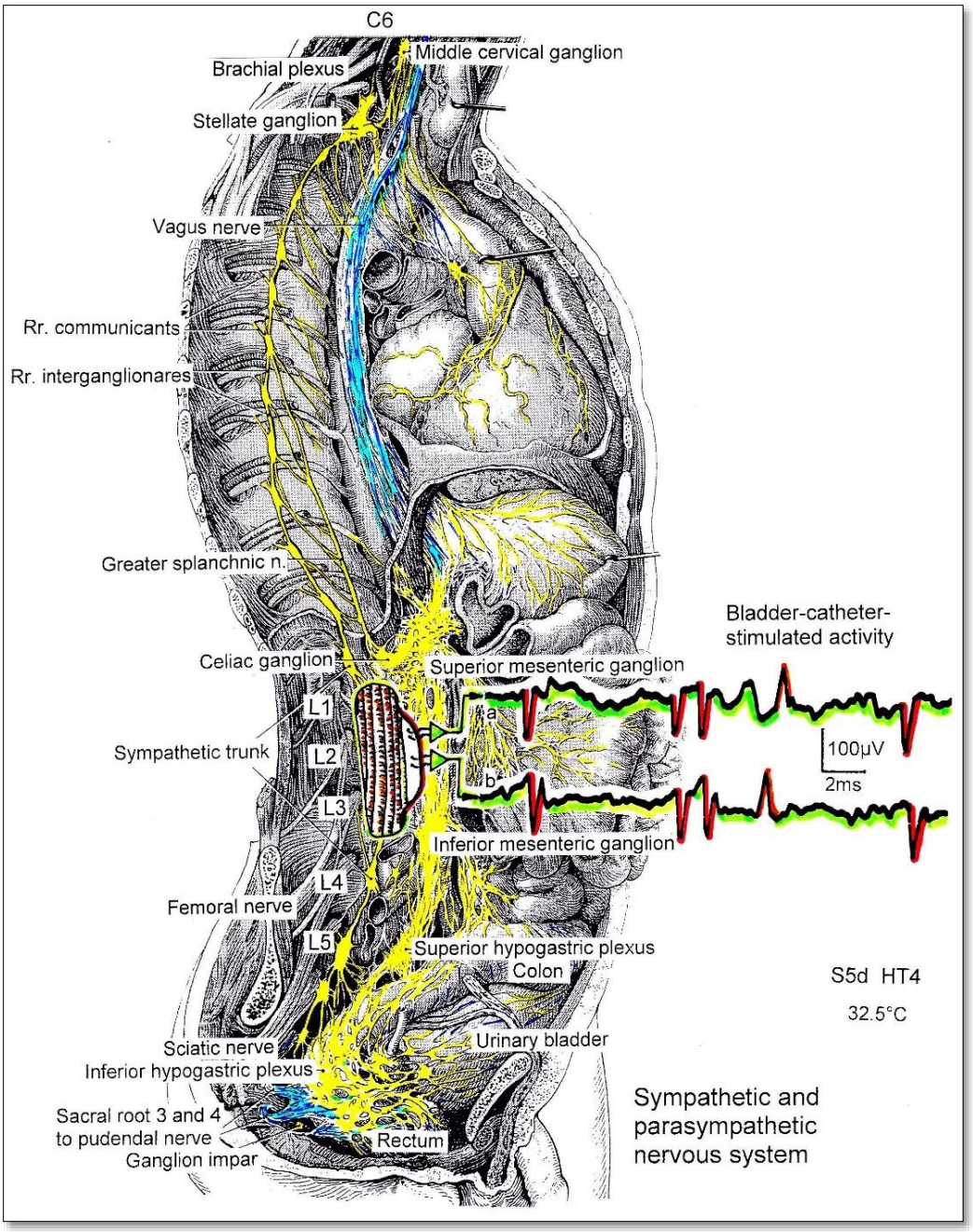

Figure 40. The picture illustrates the complexity of the autonomic nervous system. Connections of the different plexuses bypass the spinal cord and offer the structure for a functional repair of vegetative (and may be of somatic) functions like urinary bladder control, cardio-vascular performance and breathing. The recording of single-nerve fiber action potentials from human nerve roots, on the other hand, shows that in this complexity of human nervous system structures it is possible to record single-nerve fiber activity from several single identified neurons under rather natural conditions. Yellow = sympathetic, blue = parasympathetic.

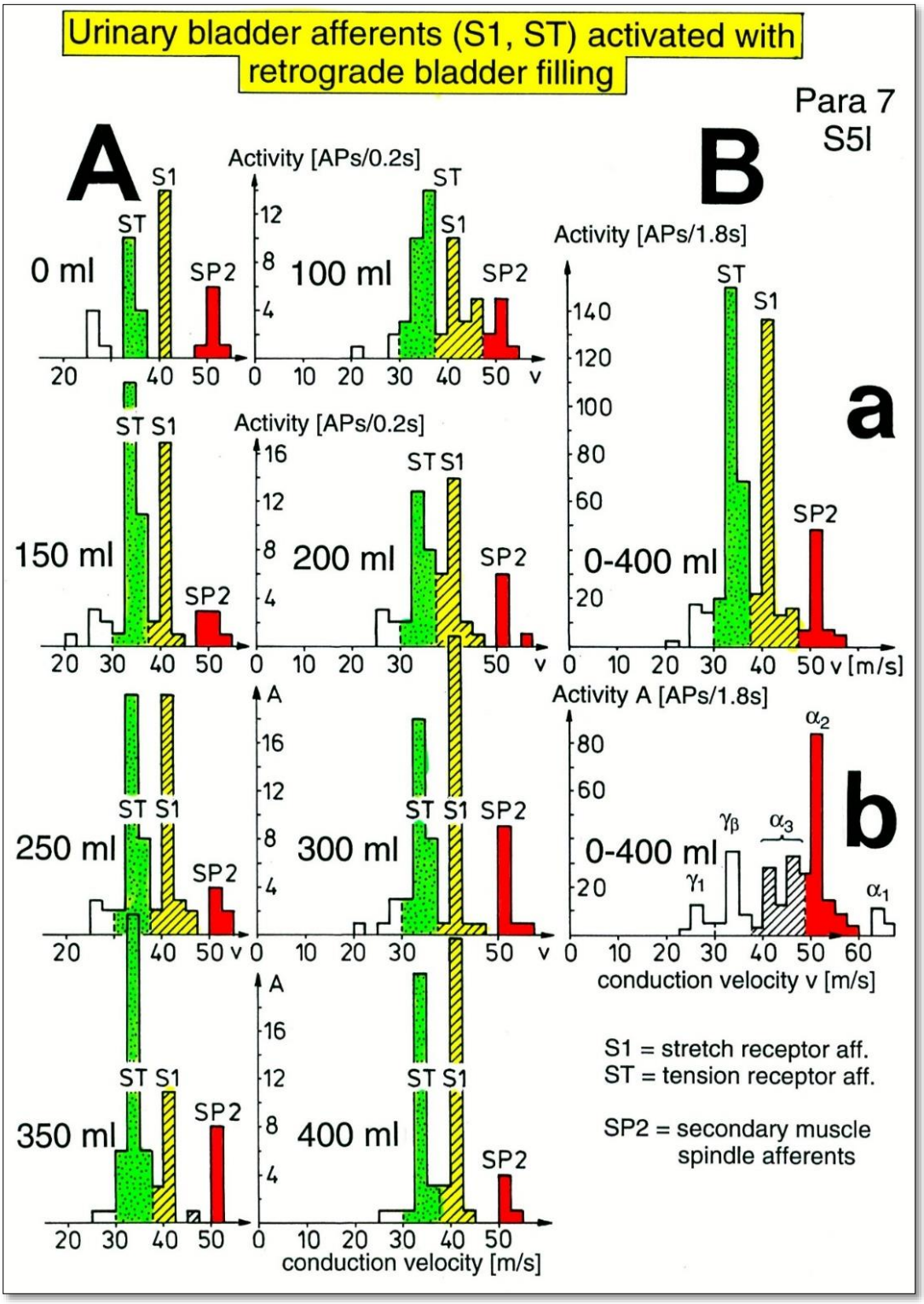

Figure 41. Conduction velocity distribution histograms for stretch (S1) and tension receptor afferents (ST) and secondary spindle afferents (SP2) for different retrograde filling stages of the urinary bladder (A). Summed histograms for afferents (a) and efferents (b) are plotted in B. α_1, α_2, γ_β, γ_1 represent velocity distributions of α_1, α_2, γ_β and γ_1-motoneurons. Para 7, left nerve root S5.

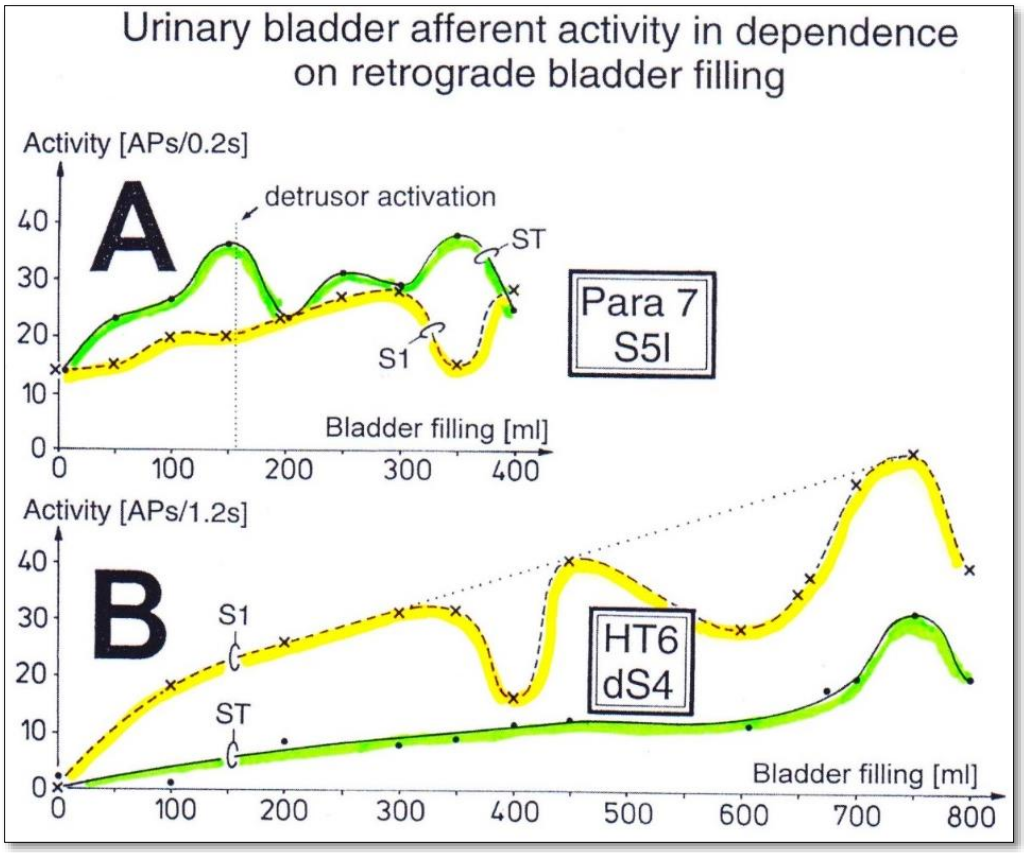

Figure 42. Afferent activity increases of stretch (S1) and tension receptor afferents (ST) to retrograde bladder filling in paraplegic 7 (left root S5) in relation to those of the brain-dead human HT6 (dorsal root S4). APs = action potentials. The speed of filling was 130 ml/min in para 7 and 100 ml/min in HT6.

Increased bladder afferent activity as a reason for urinary bladder dysfunction

A dramatic increase in the activity of the stretch (S1) and tension receptor afferents (ST) was shown with certainty in two paraplegics **(Figure 42)**. Also, in several other patients' bladder afferent activity seemed increased, as the bladder afferent activity was prominent for even small bladder filling volumes. Nearly all patients who underwent surgery had a much smaller storage volume of the urinary bladder, but not necessarily a reduced compliance (filling volume / pressure ratio). Following urinary bladder de-afferentiation the bladder storage volume increased as did the compliance. However, there are also paraplegics with a storage volume of 50 ml and no increased compliance. They are said to have hyper-reflexia of the bladder. Thus, there are patients with a stiff and infected bladder in whom the afferent activity of the bladder is much higher. The afferent activity is even often present with an empty bladder. The increased bladder afferent activity causes the detrusor being activated too early. On the other hand, there are patients with no increased compliance and no infection, and a detrusor which already contracts at filling volumes of 50 ml. It will be shown that there are important changes in the somatic and parasympathetic neuronal network of the sacral micturition center and in the coordination between them; this can account for an early activation of the detrusor and the external sphincter. Most of the complications of urinary bladder functions can be avoided and urinary bladder functions be cured if CDT is started early after spinal cord injury.

Premature activation of sphincter motoneurons in paraplegics following too high input from tension and stretch receptor afferents

Specific properties of sphincter motoneurons could be revealed separating impulse patterns of single motoneurons from the summed impulse traffic by waveform comparisons [47] **(Figure 14)**. **Figures 43A,B** illustrates the activity increase of motoneurons, innervating the external bladder sphincter, upon retrograde bladder filling and illustrates simultaneously the activity increase of motoneurons with tension receptor afferent activity changes in a brain-dead individual and in the paraplegic 7.

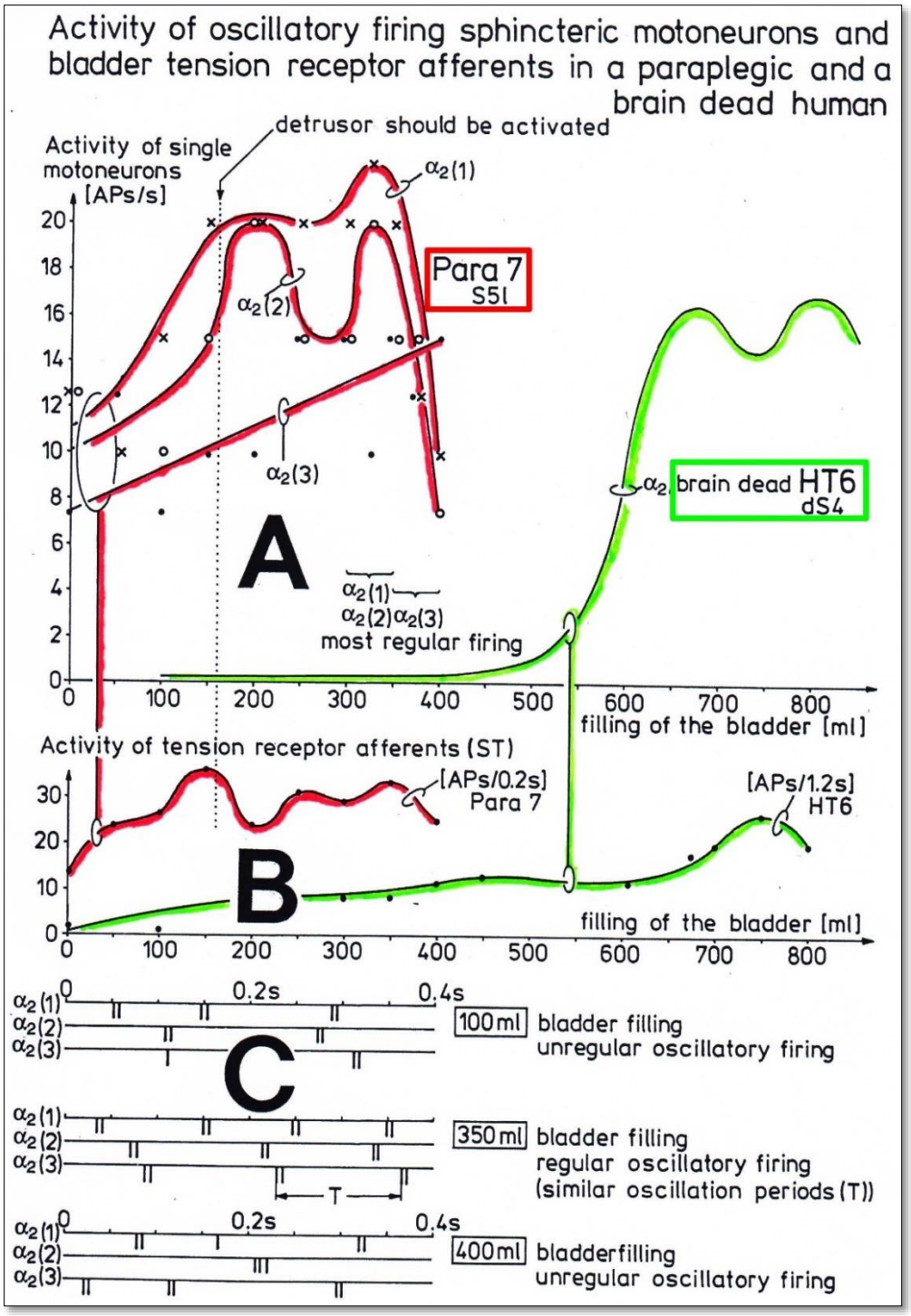

Figure 43. A. Activity of single α_2-motoneuron (FR) in dependence on retrograde bladder filling, in paraplegic 7 and brain-dead human HT6. B. Activity of tension receptor afferent fibers (ST), recorded simultaneously with the motoneuron activity in "A" in paraplegic 7 and the brain-dead human HT6. Note that the $\alpha_2(1)$ and $\alpha_2(2)$-motoneurons in paraplegic 7 show similar activity increases as the α_2-motoneuron in the brain-dead individual, with only the storage phase of the bladder being lost. Note further that with respect to the activity levels of the tension receptor afferent fibers (B), the $\alpha_2(1)$ and $\alpha_2(2)$-motoneurons in paraplegic 7 are not activated earlier than the motoneuron in the brain-dead human HT6 (A). C. Discharge patterns of the single $\alpha_2(1)$, $\alpha_2(2)$ and $\alpha_2(3)$-motoneurons at 100, 350 and 400ml bladder fillings. Paraplegic 7, nerve root S5.

In the brain-dead human, the sphincteric motoneurons show only a little activity in the occasional firing mode for a bladder filling smaller than 500 ml (storage phase). The activity of the bladder tension receptor afferents is nearly zero for no bladder filling. In paraplegic 7, the sphincteric motoneurons $\alpha_2(1)$ and $\alpha_2(2)$ fired already oscillatory to generate high activity levels when the bladder was still empty. Since in the paraplegic the activity of the tension receptor afferents was already very high for the empty bladder, the high excitement of the sphincteric motoneurons was most likely caused by a high bladder afferent activity, especially from the tension receptors of the bladder wall.

With increasing bladder filling, the activity of the sphincteric motoneurons increased in a manner similar to that observed in the brain-dead individual, if only at much smaller filling volumes. By comparing the activity increases of sphincteric motoneurons and tension receptor afferent fibers in paraplegic 7 with those in the brain-dead individual, it is concluded that the sphincteric motoneurons in the paraplegic behaved similar to the motoneuron in the brain-dead, the latter possibly representing the physiologic case in this respect. Only the sphincteric motoneurons in paraplegic 7 were activated too early because of a too high afferent input. The too high activity of the bladder afferents in the paraplegic mimics a rather full bladder, even though the bladder is still empty. The storage phase of the bladder is lost because of the too high afferent input. If the detrusor is also activated at certain bladder afferent inputs, similar to the sphincteric motoneurons, then the detrusor will also be activated at too small storage volumes. This means that the detrusor in this paraplegic was activated too early because of the too high bladder afferent activity at small bladder filling. The so-called hyper-reflexia of the bladder, namely the automatic detrusor activation for too small bladder volumes in this case, can be explained by the too high bladder afferent activity, especially from the stretch receptors of the bladder wall.

In the brain-dead human the sphincter α_2-motoneuron fired in the occasional firing mode at low bladder filling, in the transient oscillatory firing mode at bladder fillings between 500 and 600 ml, and in the continuous oscillatory firing mode at high bladder filling **(Figure 23)**. In the paraplegic, the $\alpha_2(1)$ and $\alpha_2(2)$-motoneurons, innervating the external bladder sphincter, fired continuously oscillatory for any bladder filling.

The sphincteric motoneurons normally are activated strongly at high bladder filling to secure continence. At those bladder fillings, the urge to void is probably high. If in paraplegic 7 the bladder sensibility had been preserved, the urge to void would have been strong for small storage volumes. The relative extensive de-afferentation of the bladder - cutting of dorsal roots S2 to S5 for implanting an electrical bladder stimulator (S5 root was sometimes not cut, if many parasympathetic fibers were contained), ventral root afferent fibers and possible bladder afferents running through the plexus hypogastricus remain preserved - increased the storage volume from 160 to 500 ml and the compliance from 19 to 38.

In **Figure 43A**, there is another α_2-motoneuron ($\alpha_2(3)$) that increased its activity upon bladder filling. Since this α_2-motoneuron (FR) showed a different activity increase than the $\alpha_2(1)$ and $\alpha_2(2)$-motoneurons, it is likely that this motoneuron did not contribute to continence. It was activated by reflex or response generalization. In **Figure 43C**, the impulse patterns of the $\alpha_2(1)$, $\alpha_2(2)$ and $\alpha_3(3)$-motoneurons are shown for different bladder fillings. The motoneurons fired mainly rhythmically with impulse trains consisting of two action potentials (APs), in accordance with the expected pattern of bladder sphincter motoneurons (**Figure 1 & Table 2** of [54]). In accordance with the measurements in the brain-dead individual **(Figure 23)**, the oscillatory firing is most regular for the highest motoneuron activation and less regular for smaller bladder fillings and probably overfilled bladders. But the oscillatory firing neuronal network, driving the motoneurons, was dysfunctional, as the oscillation period was strongly changing. In paraplegic 9 the disorder in the neuronal network of the functionally disconnected spinal cord was so grave that even the oscillation period and the number of APs per impulse train changed.

In the next section, the interaction between the somatic and the parasympathetic neuronal networks will be considered at points where the detrusor activation is expected to inhibit the motoneurons innervating the striated (external) bladder sphincter. Again, recordings obtained from the brain-dead individual HT6 with bladder synergia will be compared with those from a paraplegic with detrusor-sphincter dyssynergia [66].

Impaired neural network organization of the sacral and pontine micturition centers following spinal cord injury

Coordination impairment between the somatic and parasympathetic nervous system divisions in the human sacral micturition center following spinal cord injury

After having shown that the identification of somatic and parasympathetic nerve fibers by the group conduction velocity and the group nerve fiber diameter is possible **(Figure 17)** and had not changed following spinal cord injury (SCI) [1], it will be analyzed here, on the basis of natural impulse patterns, travelling into and out of the sacral micturition center, what became pathologic in the organization of the CNS following spinal cord injury.

Normal voiding is a voluntary act which results in sustained contraction of the bladder (detrusor) and relaxation of the urethra until the bladder is empty. To enable fluid flow along the urethra it is necessary that the pressure in the urinary bladder exceeds that within the urethra lumen. Under normal circumstances, in order to initiate micturition, a fall in urethral pressure immediately precedes a rise in pressure within the lumen of the bladder. Usually, this pressure rise is produced by active contraction of detrusor smooth muscle at the onset of micturition. The extensive vesical part of the pelvic plexus **(Figure 40)** and the profuse distribution of autonomic motor nerves emphasize the importance of the autonomic nervous system in initiating and sustaining bladder contraction during micturition. Immediately prior to the onset of micturition, the tonus of the striated external bladder sphincter is reduced by central inhibition of its somatic motor neurons located in the third, fourth and fifth sacral spinal segments. This inhibition is mediated by descending spinal pathways originating in higher centers of the CNS probably mainly the pontine micturition center. The central integration of the nervous control of the bladder and urethra is essential for normal micturition.

Immediately following complete SCI there is a period of spinal shock that lasts about three weeks or longer. This period is characterized by muscular flaccidity and a loss of spinal reflexes. The recovery of reflex activities below the level of the injury occurs at different times. If bladder reflexes reappear, they differ in some important respects from those in a normal individual. The 'autonomic bladder' contracts in response to distension, but the power is rarely that of the normal bladder, and the residual volume is increased. Injuries above the level of the brain stem centers lead to involuntary voiding in which the detrusor contraction is coordinated with sphincter relaxation (detrusor-sphincter synergy). Injuries below the level of the brain stem centers, but above the lumbosacral spinal cord, lead, after a period of bladder paralysis associated with spinal shock, to involuntary reflex voiding in which the detrusor (bladder) contraction is not coordinated with sphincter relaxation (detrusor-sphincter dyssynergy). The coordination between the detrusor and the external bladder sphincter will now be compared between a paraplegic patient with an injury below the brain stem and a detrusor-sphincter dyssynergy (pathologic) and a brain-dead human with partly destroyed brain stem and an at least partial detrusor-sphincter synergia (partial physiologic) [66].

If the SCI is complete, it is believed that paraplegics develop vesico-sphincteric dyssynergy because of the disconnection from the pontine micturition center which is responsible for the coordination of the detrusor and the external bladder sphincter. In cases in which no detrusor-sphincter dyssynergy has developed, the spinal cord injury is believed to be incomplete, so that supraspinal centers can still coordinate bladder functions. The external bladder sphincter will not be 'co-activated' with the detrusor in response to distension. The view that the important function of coordination is performed by spino-bulbo-spinal pathways has incorporated anatomical ideas of a hierarchy of functions of increasing complexity, the further rostral one goes in the CNS. Still, the coordination for the mutual inhibition of detrusor and external bladder sphincter may be located in the sacral micturition center. This dyscoordination problem shall now be analyzed using the single-nerve fiber action potential (AP) recording method.

For animals, reviews by de Groat [67] provide a basis for understanding how the filling and voiding functions work. He states that the primary stimulus for micturition is bladder distension, which induces reflex activation of the parasympathetic excitatory outflow to the bladder, depression of the sympathetic inhibitory outflow, and depression of the somatic efferent output to the external sphincter; secondary reflexes elicited by the passage of urine through the urethra may reinforce these primary reflexes and facilitate the complex emptying of the bladder. When the micturition reflex is exceeded, the parasympathetic reflex pathway through the brain stem is active. For an introduction to the physiology of the lower urinary tract, see [68].

Time course comparison between the proposed parasympathetically induced muscle spindle afferent activity and the detrusor pressure

In detrusor-sphincter dyssynergy of the urinary bladder, the somatic external bladder sphincter is activated at the same time as the detrusor (smooth muscle) with the consequence that the bladder cannot be emptied. This dyscoordination between the somatic and parasympathetic nervous system divisions in the human sacral micturition center is reflected urodynamically (clinically) in the simultaneous increase of the detrusor pressure and the electromyographic activity of the pelvic floor (**Figure 60B** of [29]). Before analyzing the detrusor-sphincter dyssynergia at the neuron level an important correlation between muscle spindle activity and detrusor pressure, measured urodynamically, has to be done, namely that muscle spindles, also driven by the autonomic nervous system, show very similar activity changes than the detrusor pressure.

It was shown that the activity in parasympathetic efferents can be measured, identified and distinguished from the activity of γ-motoneurons in conduction velocity distribution histograms **(Figure 21)**. Since the action potential amplitudes of parasympathetic efferents is small, it would still be very difficult to analyze the organization of the parasympathetic nervous system and it's coordinated functioning with the somatic nervous system

as in the control of the urinary bladder. But if some secondary muscle spindles in the parasympathetic range are also innervated by parasympathetic efferents besides somatic efferents (γ-motoneurons), then the activation of the parasympathetic nervous system can also be measured by the activity of secondary muscle spindle afferents. Since the action potentials of secondary spindle afferents are comparably large (thick fibers), the activation of the parasympathetic nervous system can be easily indirectly assessed. It will be shown now that at least some secondary muscle spindles, in the parasympathetic range, are innervated by parasympathetic efferents (parasympathetic fusimotors, with reassignment sympathetic fusimotors) [69-72]. The evidence is obtained by measuring the parasympathetic activation of the detrusor by detrusor-pressure changes and by measuring activity changes of secondary muscle spindle afferent fibers and compare the form of the changes of detrusor pressure with the activity changes of a secondary muscle spindle afferent fiber.

Figure 44 shows the regulation circuits for muscle length (A) and muscle tension (B). The Author does not know how morphologically the muscle spindles of external bladder and anal sphincters are innervated by the autonomic nervous system. Dr. Gladden [72], the specialist for muscle spindles, including human ones, tried to clarify it, but gave in for organizational reasons. When the Author tried at an international conference 29 years ago [74] to discuss with animal physiologists the human muscle spindle with respect to autonomic innervation, they refused it and complained later on that the Author cannot behave properly.

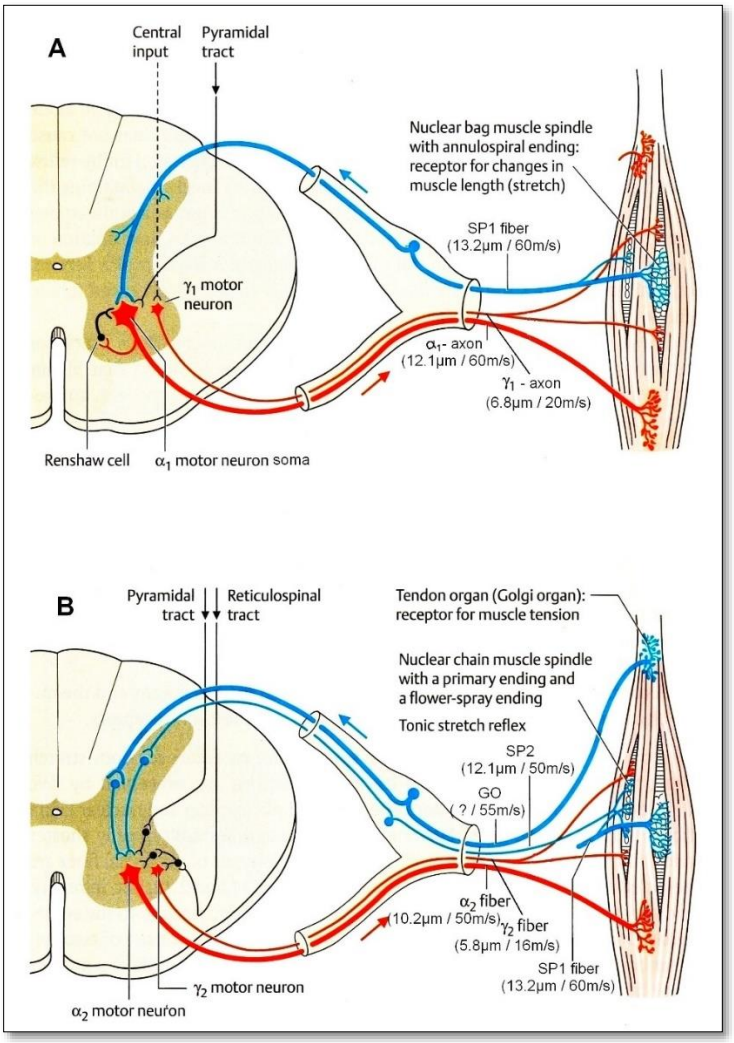

Figure 44. Regulation circuits for muscle length (A) and muscle tension (B). Nerve fibers are partly designated according to the classification scheme of human peripheral nerve fibers. This picture of muscle spindle innervation is not showing the real complexity of muscle spindle innervation. The innervation of the muscle spindles by the autonomic nervous system is missing. Figure partly taken from [73].

Upon retrograde bladder filling in patients with complete spinal cord injuries, the detrusor was reflex activated at rather small storage volumes, as could be measured through urodynamics by the detrusor pressure. In paraplegic 5, the detrusor was automatically activated at a bladder filling volume of approx. 350 ml, and in paraplegic 9 at approx. 10 ml. The reasons for the limited storage volumes are the increased afferent input from the bladder due to a bladder infection, for example, and the strong disorganization of the neuronal networks in the spinal cord. It was found for the paraplegics 7 and 11 that the first high bladder afferent activity occurred at bladder filling volumes in the operation, at which the detrusor was activated pre-operatively. In Para 7 the first high afferent input occurred at a filling volume of 150ml; the detrusor was activated at 160ml. In Para 11 the first comparatively high afferent input occurred at 50ml filling volume; the detrusor was activated at 80ml.

During surgery under light anesthesia the detrusor never responded to the filling of the bladder in 120 patients. Also, quick filling with 4°C saline solution did not activate the parasympathetic division. Only in one instance, during surgery on a tetraplegic patient with a lesion sub C3 (artificial ventilation), with no tubes placed in the trachea and extremely light Propofol-anesthesia, there seemed to be a slight detrusor pressure increase upon retrograde bladder filling. On the other hand, strong (painful) bladder catheter pulling activated the detrusor to contract in paraplegics with no anesthesia, most likely activated the parasympathetic nervous system in the brain-dead human HT6 (no anesthesia, possibly partial spinal shock) and seemed to activate the parasympathetic division during very light anesthesia. It is concluded therefore that painful stimulation of the bladder under light anesthesia activated the detrusor.

In **Figure 45**, the increase in detrusor pressure upon retrograde bladder filling before surgery is compared with the activity increase of the secondary muscle spindle afferent fiber SP2(1) following 4 times bladder catheter pulling during the operation. **Figure 45A** shows the undulating activity increase of a SP2(1) fiber. In **Figure 45C** the cystogram is shown. Upon bladder filling spontaneous micturition occurred several times. If parasympathetic fibers really activated muscle spindles, then the activity increase of the secondary muscle spindle afferent fibers following bladder catheter pulling may have a similar time course as does the bladder pressure increase due to detrusor activation following retrograde bladder filling. To check this similarity of time course, one undulating increase of detrusor pressure **(Figure 45C)** has been brought to the same time scale as the measured changes in muscle spindle afferent activity **(Figure 45A)** and transferred into **Figure 45B** for a direct comparison with **Figure 45A**. By comparing **Figure 45A** with **Figure 45B**, it can be seen that the occurrence of activity peaks of secondary spindle afferents is very similar in its time course to that of the peaks of the detrusor pressure. From the similarity of changes of spindle afferent activity and detrusor pressure (4 peaks) it can be concluded that some muscle spindles in the domain of the sacral parasympathetic nucleus are partly controlled by the parasympathetic division and that the muscle spindle and the detrusor activation have similar time courses. The other retrograde bladder filling induced undulating transient increases in pressure, shown in **Figure 45C**, had a similar time course.

Thus, there is some indication that some muscle spindles are partly driven by the parasympathetic division. The drive can be by parasympathetic fusimotor activity or more indirectly by somatic fusimotors (γ-motoneurons). Since in HT6, the somatic fusimotors did not change their activity levels strongly with the activation of preganglionic parasympathetic fibres and the activity increase of the secondary muscle spindle afferent fibre SP2(2) followed the transient increase of parasympathetic activity, it is likely that some muscle spindles are directly controlled by parasympathetic fusimotors. The direct control of some muscle spindles by parasympathetic fusimotors is supported by the slow activity decrease following very high activation [66] and the similarity with the time course of the detrusor pressure decrease following electrical stimulation of the preganglionic parasympathetic fibres during the surgery. The slow spindle afferent activity decrease would be difficult to explain by somatic fusimotor activation only. For further details see Chapter V of [1].

Pathologic organization of neural networks in the sacral micturition center following spinal cord injury

The detrusor-sphincter dyssynergia is analyzed now by comparing the natural impulse patterns of secondary muscle spindle afferents (SP2) contributing to continence and sphincter motoneurons in a brain-dead human with those in a patient with spinal cord injury (SCI). In **Figure 45** it was shown that the changes of the SP2 fiber activity were similar to those of the detrusor pressure. We are therefore now in the position to measure indirectly the autonomic detrusor activation and compare it with the activity of the external bladder sphincter at the single neuron level.

In the brain-dead human the sphincter motoneurons, subserving continence, were inhibited at a time, when preganglionic autonomic efferents and a SP2 fiber increased their activity (physiologic). In the paraplegic the sphincter motoneurons were not inhibited (pathophysiologic). In the brain-dead human, an SP2 fiber showed doublet firing (interspike interval (II) 10 to 14ms) for low level parasympathetic activation and multi-ending regular firing for high parasympathetic activation. In one paraplegic with strong bladder dysfunction, the multi-

ending regular firing was replaced by a repeated burst firing with a shortest II of 0.2ms (transmission frequency = 5000Hz). After SCI, the pathologic firing patterns of the SP2 fibers, the detrusor-sphincter dyscoordination, and the hyper-reflexia in paraplegics are most likely a result of neuronal network changes in the parasympathetic and somatic nervous system divisions of the sacral and pontine micturition centers. In every CNS injury, the phase and frequency coordination become impaired. In a paraplegic this was shown above by a comparison with the phase and frequency variability in a brain-dead human **(Figures 32 & 33)**. In the brain-dead the variability was small and in the paraplegic high. It is now focused on the detrusor-sphincter dyssynergy.

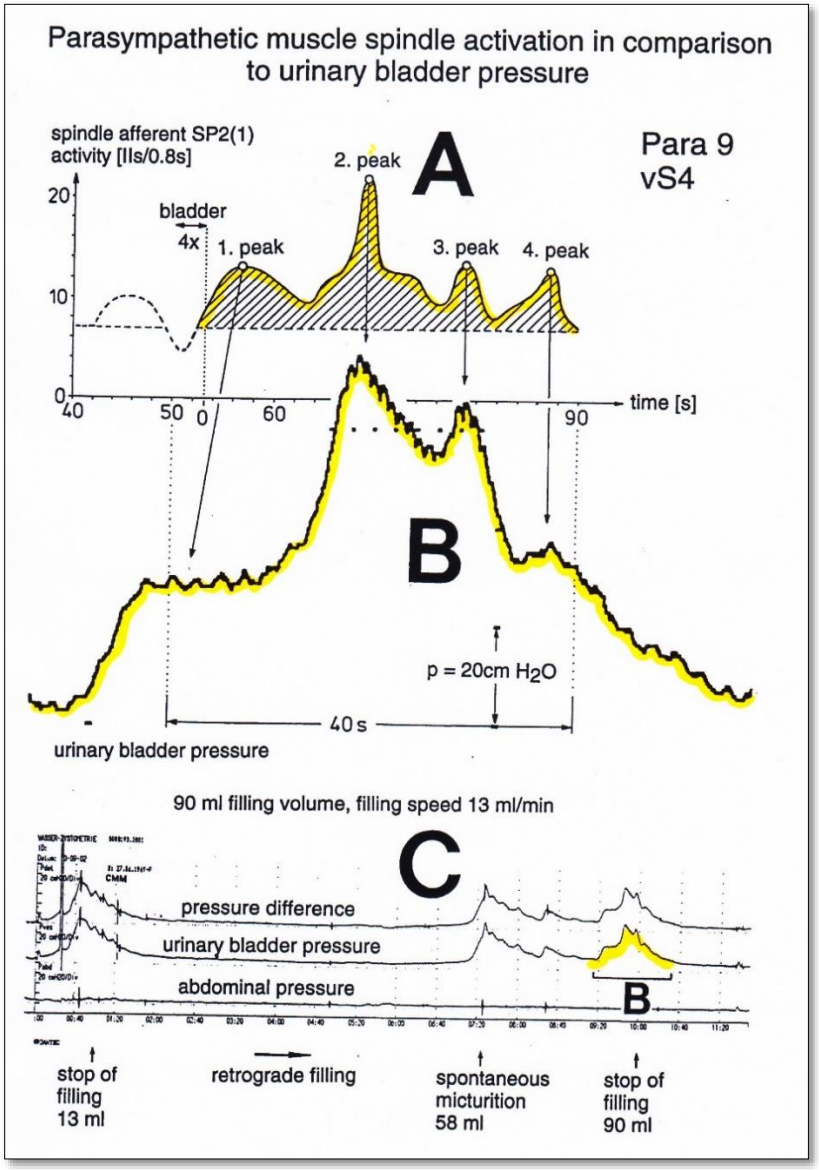

Figure 45. Comparison between changes in secondary muscle spindle afferent activity and detrusor pressure (measured before the surgery; for the implantation of an electrical sacral anterior root stimulator). Paraplegic 9.
A. Activity changes of the afferent fiber SP2(1) from **Figure 46A** following bladder catheter pulling. Approx. mean activity level is represented by a dashed line at 7.5 IIs/0.8s ((APs -1)/0.8s). The activity above the mean is cross-hatched and is proposed to be due to parasympathetic activation. Root vS4. B. Detrusor pressure (pressure difference) changes taken from 'C'. Note that changes in the detrusor pressure show almost exactly the same time course as do the activated changes of the secondary muscle spindle afferent fiber SP2(1) of 'A'. Corresponding peaks are correlated by arrows. C. Abdominal pressure (measured as rectal pressure), intravesical pressure (urinary bladder pressure) and detrusor pressure (pressure difference) during retrograde filling before the surgery. One transient detrusor pressure increases, marked 'B', is used, after enlargement in 'B', to compare with the spindle afferent activity.

Differences in the impulse patterns of secondary muscle spindle afferent fibres between paraplegics and the brain dead human HT6

The time course of the increase in the secondary muscle spindle afferent activity, induced by the sacral parasympathetic nervous system in muscle spindles contributing to continence, is very similar to that of detrusor pressure **(Figure 45)**. The detrusor-sphincter dyssynergy is therefore analyzed by comparing the natural impulse patterns of single secondary muscle spindle afferents (SP2) and sphincter motoneurons in a brain-dead human (physiologic) with those in patients with spinal cord injury (pathologic). The parasympathetic nervous system was activated by painful bladder catheter pulling.

Figure 46 shows the impulse patterns of parasympathetically driven secondary muscle spindle afferents in paraplegic 9 and the brain-dead human HT6. In the brain-dead individual **(Figure 46B)**, the activity was low before strong bladder catheter pulling and increased strongly continuously and regularly following stimulation. In paraplegic 9 **(Figure 46A)**, the activity level was higher before bladder catheter pulling and increased more slowly, in an undulating and irregular manner following catheter pulling. The burst-like firing seen in paraplegic 9 did not occur in HT6. The doublet firing was less regular in Para 9. Specific properties in the drive of the spindle seem to be lost in the paraplegic. Even though a burst-like firing also occurred once in HT6 **(Figure 46Ba)**, the afferent fiber in HT6 could generate a sustained high regular activity level, whereas the fiber in paraplegic 9 could not.

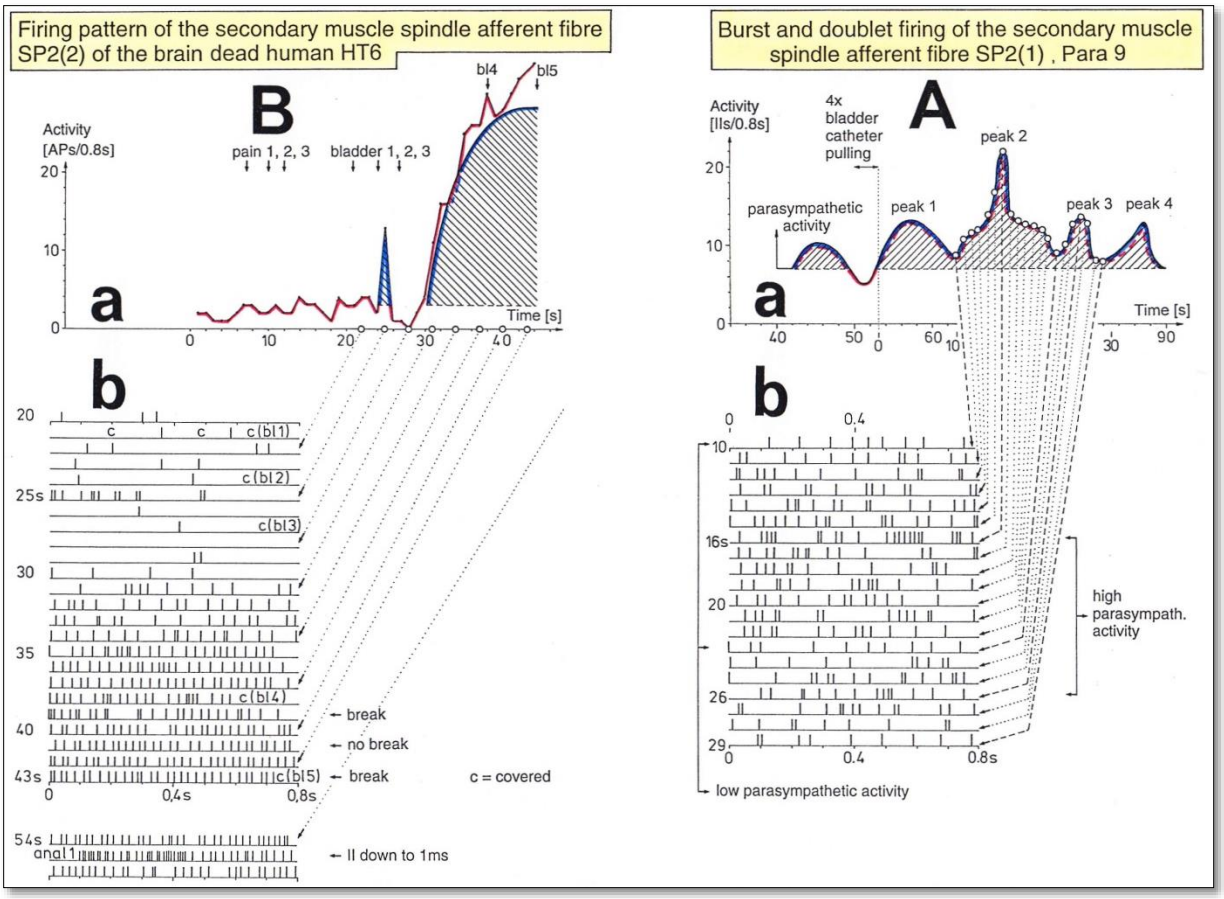

Figure 46. Comparison of the natural impulse patterns of single afferent fibers between paraplegic 9 with dyssynergia of the bladder (A) and the brain-dead human HT6 (B) with synergia of the bladder. Activity increase of the spindle afferent fibers following bladder catheter pulling (a) and the natural impulse patterns at different times following catheter pulling (b). A. Note that at activity peaks (a) there was burst firing in paraplegic 9, (marked by the arrows, 16s, 26s), and at low activity (a) there was no burst firing (10s, 23s). B. Note that even though burst firing appeared also in the brain-dead (25s), the activity increase sustained with similar interspike intervals (IIs). break = break of oscillation of sphincter motoneuron. c = covered = skin afferent action potentials covered SP2 fiber impulses due to bladder catheter pulling (bl 1 - bl 5).

The increase in the detrusor pressure in paraplegic 9 during retrograde bladder filling was very pathologic since there was nearly no storage phase and the pressure increased transiently and in an undulating way **(Figure 45C)**. It is satisfying that the results obtained with the single-nerve fiber AP recording method from impulse patterns of afferent and efferent fibers support the results obtained urodynamically. The impulse patterns however will provide additional insight into the organization of the human nervous system under physiologic and pathophysiologic conditions.

Detrusor-sphincter synergy of the bladder in the brain-dead human HT6, and dyssynergy in paraplegic 9

The measurement of parasympathetic activation of the detrusor by activity changes of secondary muscle spindle afferent fibers (the spindle is innervated by autonomic fusimotors) allows an analysis of detrusor-sphincter dyssynergy using the natural simultaneous impulse patterns of secondary muscle spindle afferents and sphincter α_2-motoneurons (and γ-motoneurons).

Figure 47A shows that in the brain-dead human HT6, whose parasympathetic preganglionic neurons increased activity **(Figure 47Ab)** upon bladder catheter pulling, the SP2(2) fiber activity increased strongly **(Figure 47Aa)**, whereas the α_2-motoneuron, innervating the external anal sphincter, discontinued its oscillatory firing **(Figure 47Ac)**, which is a measure for a strong activity decrease. An α_2-motoneuron, innervating the external (striated) bladder sphincter, was not activated. This means that with the activation of the detrusor, the sphincter motoneurons were relaxed by inhibition. Thus, the brain-dead human HT6 had a detrusor-sphincter synergy of the bladder.

In the paraplegic 9, the SP2(1) fiber showed no strong activity increase and there was no sphincter relaxation following bladder catheter pulling **(Figure 47B)**. The secondary muscle spindle afferent fiber SP2(1) increased its activity in an undulating manner **(Figure 47Ba)**. The parasympathetic fusimotors, driving the muscle spindle, innervated by the SP2(1) fiber, probably were not continuously active as suggested by **Figure 47Bb**, in contrast to the parasympathetic activity observed in the HT6 **(Figure 47Ab)**. The other secondary muscle spindle afferent fiber in paraplegic 9 (SP2(2), **Figure 47Ba**) slowly reduced its activity upon bladder catheter pulling. This spindle afferent fiber was not connected to the continence of the bladder. It is likely that its spindle was not parasympathetically innervated and was sited in leg muscles or parts of the pelvic floor muscles not contributing to continence. The α_2 and α_3-motoneurons **(Figure 47Bc)** showed a high activation, which is expressed in their oscillatory firing, and probably contributed to the continence of the bladder and the rectum. These likely sphincter motoneurons did not reduce their activity following parasympathetic activation, as can be seen from the SP2(1) fiber activity, monitoring parasympathetic activity. These motoneurons were not inhibited and the external sphincters were probably not relaxed. The somatic fusimotor γ_1 **(Figure 47Bc)** increased its activity transiently and slightly upon painful bladder catheter pulling, in similarity to a γ_1 fiber in HT6 [59]. The measurements in paraplegic 9 indicate a loss of the inhibitory action of the detrusor onto the sphincter motoneurons.

The time constant for the activity decrease of a spindle afferent fiber following parasympathetic activation was 31s in a paraplegic and approx. 40s in a brain-dead human (Chapter V of [1]). It is concluded that the muscle spindles are unchanged following spinal cord injury. The pathologic firing patterns of the SP2 fibers are thus probably a result of neuronal network changes in the parasympathetic and somatic nervous system divisions of the sacral micturition center.

In conclusion, in the brain-dead human the sphincter motoneurons sub-serving continence were inhibited at a time, when preganglionic parasympathetic efferents increased their activity (physiologic) for 10s and an SP2 fiber increased its activity for several minutes. In the paraplegic with a strong bladder dysfunction, the SP2 fiber activity increased, due to parasympathetic activation, lasted for approx. one minute, showed undulations, and its amplitude was smaller than that measured in the brain-dead human. There was therefore no powerful continuous parasympathetic activation. The sphincter motoneurons were not inhibited (pathologic).

Continence repair through coordination dynamics therapy (CDT) as a repair example

Cure of continence in 8 out of 10 patients through CDT

In 8 out of 10 patients with different diseases, continence could be repaired through CDT (Method) [29,30]. Based on human repair-neurophysiology, the patients continence disease could be cured. Therefore, human repair-neurophysiology is really medicine because the patients benefit from it.

Urinary bladder repair in spinal cord injury

The most important functions to be repaired in spinal cord injury (SCI) are firstly the bladder repair, followed by the sexual function. The walking is on place 3 followed by spasticity and scoliosis.

Spinal cord repair depends on the severance of the injury. In the patient with a 50% SCI (Sten) the bladder was fully repaired through 2 months of CDT. In the patient Kadri with 95% SCI 2.5 years were needed. In a 99% injury the

bladder was not repaired within 2.5 years. It is obvious from **Figure 48** that possible repair depends strongly on the severance of the injury.

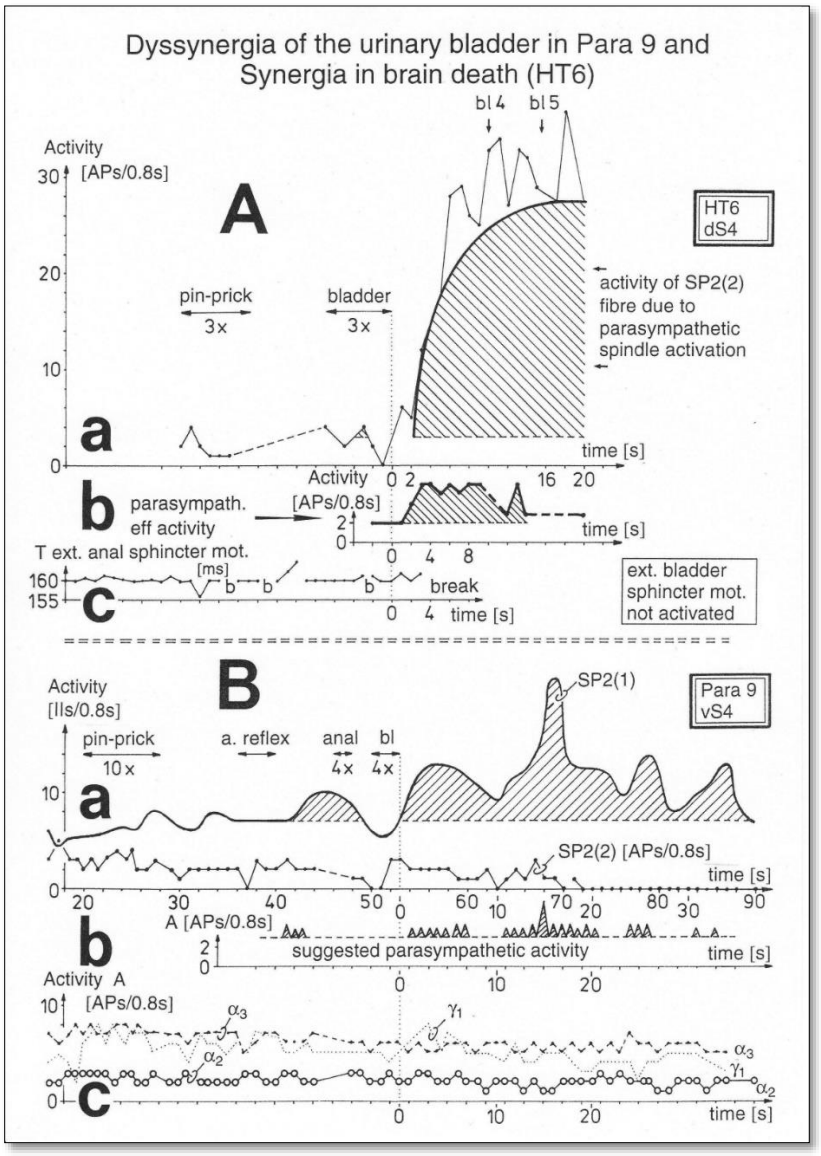

Figure 47. Direct comparison of secondary muscle spindle afferent activity and motoneuron activity between the brain-dead human HT6 with a synergia of the bladder (A) and the paraplegic 9 with a dyssynergia of the bladder (B). A. Simultaneous measurements of activities of secondary muscle spindle afferents (a), parasympathetic preganglionic motoneurons (b) and oscillatory firing (high activity mode) of a sphincter motoneuron innervating the striated anal sphincter (c). Note that with the transient activity increase of the parasympathetic fibers (b) the secondary muscle spindle afferent fiber increased strongly its activity (a) for minutes, and the oscillatory firing sphincter motoneuron discontinued its oscillation (c) to reduce strongly its activity. bladder 3x = 3 times bladder catheter pulling. T ext. anal sphincter mot. = oscillation period of the sphincter α_2-motoneuron innervating the anal sphincter. For further details, see Chapter V of [1]. B. Simultaneous measurements of activity of secondary muscle spindle afferent fibers SP2(1) and SP2(2) following anal (anal 4x) and bladder catheter pulling (bl 4x) (a), and the activity changes of an α_2-motoneuron (FR) and α_3-motoneuron (S) and a dynamic fusimotor fiber (γ_1) (c). Note that following bladder catheter pulling (and probably parasympathetic activity increase), the spindle afferent fiber SP2(1) (most likely contributing to continence) increased its activity in an undulating manner (a), whereas the SP2(2) fiber did not (probably not connected to continence) (a), and the α-motoneurons did not reduce their activity (c). The dynamic fusimotor γ_1 transiently increased its activity similarly as in HT6 measurements. In similarity to 'Ab', the suggested parasympathetic activity increase is pictured (b). a. reflex = anal reflex stimulation. IIs = interspike intervals; IIs/0.8s = (APS – 1)/0.8s (the activity measures IIs/0.8s and APs/0.8s differ by '1').

Because in 50% SCI the bladder is somehow functioning, animal researcher cut only 50% of the cord in animals to avoid urinary bladder problems, even though it is the most important function to be repaired in SCI.

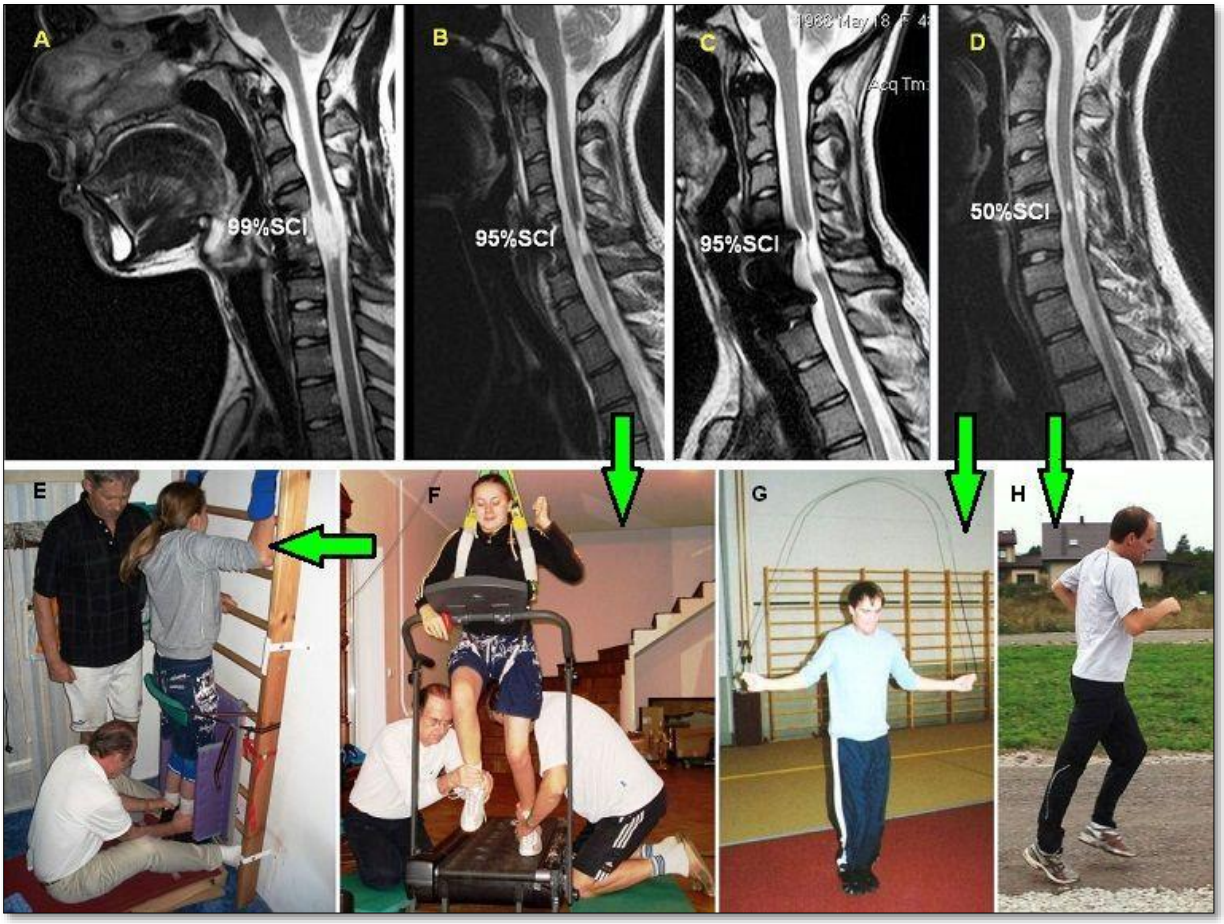

Figure 48. The outcome of a SCI repair depends strongly on the severance of the injury. A-D. MRI's of approximately 99%, 95% and 50% injury. C shows the 50% injury with titan fixation and B without. The severance of an injury can also be estimated with a fixation in place. G, H. In 50% injury, the patient can relearn walking, running and jumping. E, F. In 95% (and 99%) the patient cannot re-learn free walking and jumping.

In an almost complete cervical SCI, the caudal spinal cord is disconnected from the cerebral cortex and brain stem. With respect to urinary bladder functioning, the sacral micturition center is disconnected from the pontine micturition center **(Figure 3)**. Following the spinal shock some reflexes, such as the stepping automatism and urinary bladder reflex (similar to those in infants), may re-appear, especially when stimulated. Pathologic reflexes or automatisms also appear as for example extensor spasticity or spastic bladder. With very limited regeneration upon CDT, motor and vegetative functions partly re-appear in a cephalo-caudal direction and movements become controlled first proximally and then distally; spasticity reduces. This cephalo-caudal and proximal to distal scheme only partly holds, because the injured CNS uses all existing repair and adaptation mechanisms through movement-based learning, including plexus connections outside the spinal cord. But with respect to the improvement of trunk stability and breathing the repair in cephalo-caudal direction seems to hold.

To understand bladder repair through neural network learning and regeneration, the repair will be analyzed in the patient with a 95% injury Kadri **(Figures 48F,1A-D)**.

Urinary bladder repair in 95% spinal cord injury

The 17-year-old female patient Kadri suffered a severe cervical SCI 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 **(Figure 48B, C)**. 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. Urinary bladder functions were repaired. Details of the continence repair are given **(Figure 49)**. The connectivity over the injury site, according to the magnetic resonance imaging (MRI), may have increased to 8%.

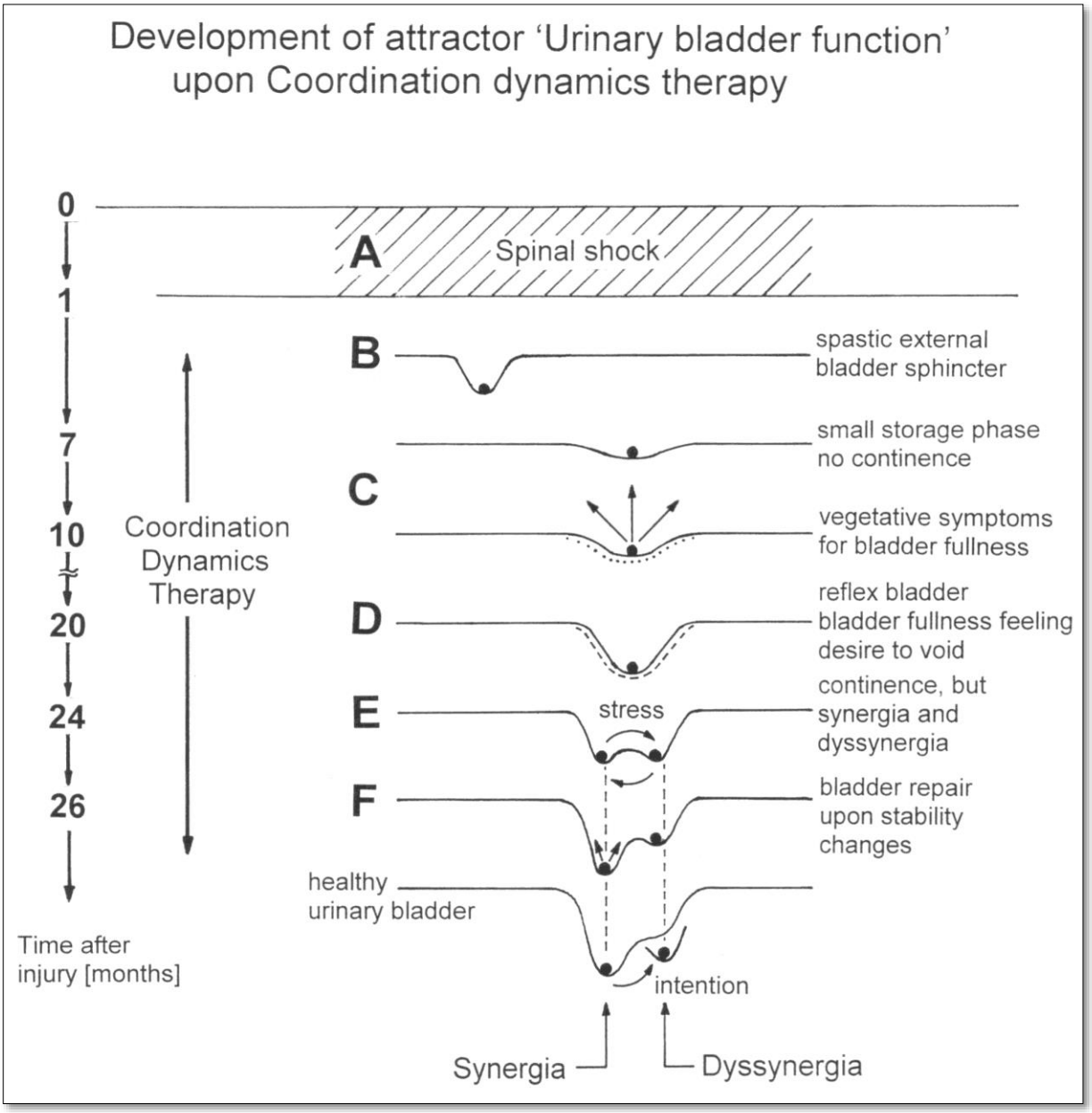

Figure 49. Evolution of the attractor layout of bladder functioning induced by learning transfer from movements to bladder functions upon CDT. The region around each local minimum of the potential landscape acts like a well that weekly traps the system into a coordinated state. Black balls correspond to stable minima of the potential. With learning, the pattern 'spasticity of the external bladder sphincter' vanishes and the patterns for bladder functioning ('synergy' 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 continuous CDT were needed for bladder repair.

Generally, a urinary bladder repair is very important in rather complete C5/6 SCI. The tetras are not able to perform intermittent bladder catheterization by themselves, because of the mainly lost finger functions due to the lost finger-function-motoneurons in C5/6 spinal cord segments. Through urinary bladder repair, the patients get their private sphere back.

The time course of the improvement of urinary bladder functions upon CDT

It is reported about the stages of bladder repair through 2 years of therapy. The 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 **(Figure 49)**.

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 antibiotics), patients were dying on such infections.

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 sudden bladder pressure increases (as for example during coughing), the rather fast-external sphincter (innervated by α_2-motoneurons and consisting of fast fatigue resistant muscle fibers (FR), **Figure 24**) is contracting to secure continence. If the striated external sphincter does not work 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 removed. 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 heard 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 (Zones of Head). Sometimes body positioning was used to influence the bladder reflex. With these maneuvers 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 this patient), it may not be possible to generate a good functioning reflex bladder. The neural networks of the sacral micturition center are working too pathologic.

6. After the appearance of the desire to void, the patient became able to hold the fluid for 30s till 1min. 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 SCI.

7. 24 months 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 (to reduce the residual urine, not to get bladder infections), the external sphincter contracted. The external sphincter co-contracted with the detrusor. Detrusor-sphincteric dyssynergia of the urinary bladder occurred **(Figure 49E)**. 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 residual urine was not measured.

At this stage of bladder repair two patterns existed: the synergy 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 **(Figure 49E)**. The synergy 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 both bladder emptying patterns do exist. The synergy pattern is for emptying the bladder and the dyssynergia function is for stopping the micturition. But both patterns are under volitional control.

8. Upon two years of CDT (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 **(Figure 48EF)** and exercising on the special CDT device. The strong improvement of urinary bladder functions occurred, when the coordination dynamics values strongly increased, indicating a bit of 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 h after 2 years of CDT.

The feeling of the lower abdomen, which was poor after the accident, improved also strongly at the time of nearly 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 **(Figure 48F)**. During walking on treadmill, and during other movements, the patient got goose-pimples all over the body. It seems that 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 (**Figure 49A**, only the pathologic bladder pattern 'spasticity of the external sphincter' was present **(Figure 49B)**. Six to 10 months later, the spasticity of the external sphincter reduced and a small storage phase of the bladder re-appeared as a first sign of bladder repair **(Figure 49C)**. 20 months after the operation, the reflex bladder pattern organized itself with bladder fullness feeling and the desire to void **(Figure 49D)**. 24 months after the accident, the attractor layout showed two attractors, the bladder synergy (the detrusor action inhibits the external sphincter) and the dyssynergia (co-contraction of detrusor and external sphincter) **(Figure 49E)**. The state of the system (pictured by the ball) switched easily from the attractor synergy to the attractor dyssynergia. 26 months after the accident, the stability of the attractor synergy had increased and the stability of the attractor dyssynergia had decreased **(Figure 49F)**. On volition (intention), the micturition could be induced and stopped as in healthy individuals.

As was shown in the patient Kadri with a 95% SCI, continence can be repaired by movement-based learning. The human nervous system has sufficient complexity for re-learning. Rats and cats may not have a sufficient network complexity for such repair [75-77]. They would not be able to exercise on a special CDT device **(Figure 50)**.

Figure 50. If the rat could be fixed to a special CDT device, it would not be able to turn continuously on it, because it could not generate the complicated patterns between pace and trot gait of coordinated arm and leg movements. But the rat is able to walk on hind limbs and could turn on the special CDT device with only the fore limbs or only with the hind limbs. Turning only with the hind limbs is something like exercising on a fitness bicycle.

Learning transfer is successful in repairing urinary bladder function, since the somatic and the autonomic divisions dovetail with one another with respect to jumping on springboard and exercising on the special CDT device. The necessary connection to the pontine micturition center for the coordination control of the detrusor and the external bladder sphincter is achieved upon CDT by limited regeneration of the human spinal cord, recruiting ectopic pathways through root connections, sympathetic chain or plexus connections (misdirected haphazardly during development) and re-organization of plexus outside the spinal cord. It is believed that the autonomic division of the nervous system is an elaborately organized division of the CNS with representations at all levels. At each level the somatic and the autonomic systems dovetail with one another.

Continence is most difficult to repair in patients with a real complete spinal cord injury. One of the patients, in whom continence could not be repaired was the famous Avo Leok, a motor cyclist, who suffered a real complete spinal cord injury in a competition. He had the mental discipline to go over all limits and would have been a suitable candidate to find out whether CDT can also cure continence in complete SCI. But, against the advice of the Author, he voted for "stem cell therapy", developed by animal researchers (below). When the miracle did not occur, he gave in to fight for a better future because he lost the believe in medicine, even though the sponsors would have paid further for his treatment.

Ethics of SCI research, treatment and clinical trials – False hope from animal treatment research

'Transplantation of both embryonic stem cells and embryonic stem cell-derived neural (neural or glial) progenitors is able to efficiently promote CNS regeneration in preclinical models of stroke, myelin deficiency, acute SCI [78,80] and Parkinson's disease [79]'. 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 has been 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 deliberately choose 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 [81]. I have learned in my medical study that medicine has something to do with the cure of diseases in human. Specialist 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 [81]. High ethical standards are required by researchers, clinicians and journalists to ensure that results are communicated to the general public in a manner that honestly reflects the safety and efficacy of a potential therapy [81].

Medicine is very successful if natural existing repair mechanisms are supported like in surgery or immunology. But if repair mechanisms do not exist, then medicine is not very successful. The repair of the nervous system is very limited and depends on the site of the injury. An exogenous stem cell therapy must be very sophisticated to be better than nature with respect to repair. The integration of new-born cells into the existing neuronal networks is by far not solved. Further, the scientific basis for doing neurobiology is out-of-date. The understanding of the functioning of the CNS in animals and humans has to be upgraded. In physics, for example, the basis is continuously upgraded. It was shown how complicated the innervation of two kinds of muscle cells by two kinds of motoneurons is (4-cell communication) [28]. The innervation and innervation changes during development and repair are probably much more complicated in the human CNS. It is a too simple thinking to believe that an addition of cells can repair the CNS what the CNS cannot do by itself. CDT, on the other hand, rests on learning which is natural for humans. Academically accepted articles are generating false hope by allowing authors to state that stem cells can potentially be used in different CNS diseases including SCI. The authors are stating it to get funding for their animal research, by making believe that their research has direct consequences for the treatment of human patients. No wonder that practitioners also want to participate in getting money. Instead of warning that some clinics in Asia may look more for profit than for qualified stem cell therapy, the editorials should first think over their own research policies which are giving rise to such unqualified medical treatment. It is not enough to state "The medical promise of stem cells remains real, but largely unrealized for now. The excitement must not be left to dissolve into a muddle of disappointment, frustration and fear because of the practices of a few irresponsible profiteers" [82]. There are principal problems to be solved for stem cell therapy in humans. A few years ago, there was a big propaganda in the TV and other mass media in Switzerland about the suppression of grow-inhibiting properties for the regeneration [83,84] of the spinal cord. It was stated that SCI could be cured in a year's time. It seems to be popular among neurobiologists to raise false hope in society concerning treatment in human patients, as if they have not understood much about treatment of human patients.

If we want to repair function, we also have to measure function in a qualified way and one powerful tool is the electrophysiology, because the nervous system is mainly functioning by electric currents and potentials. It is difficult to understand why electrophysiology has mainly been destroyed world-wide, even though this tool was very successful in neurophysiology in the past. One reason could be that although the younger generations are capable of handling computers or electronic equipment very good, they do not have the manual skill any more to perform complicated electrophysiology. Statistics are needed concerning treatment success beyond the placebo effect, including the occurrences of cancer and CNS instabilities (seizure disorders). But more is needed in medical research than just statistics. Hopefully the globalization does not give rise to the coordination in thinking (in German: 'Gleichschaltung der Denkweise').

It is depressing for a qualified therapist that 'there is an abundance of patients desperate for miracle cures, and one stem cell treatment can bring in tens of thousands of US dollars' [82]. Western scientists 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 [85]. 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 neuro-rehabilitation centers. More money can be earned with care.

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 humans. False hope also stops the patient from fighting for improvements which are needed for everyday life. Why should a patient fight for three years or more with a movement-based learning therapy to get urinary bladder and some motor functions repaired, if in a few years' time walking can be returned 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 an 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 (for example Christopher Reeve). Even monkey experiments are far away from human reality. A monkey cannot speak, write or read, and will never be able to solve 'differential equations' (mathematics). The power of the human CNS is its learning capacity, which is outstanding among different species. A fly demonstrates with how little brain matter sophisticated fly tasks are possible. Qualified human CNS research, including at the single-neuron level, is needed for understanding the functioning and repair of its neuronal networks.

Authors of recent review articles presented approximately 1000 citations on the repair of the human spinal cord following injury [79,85-87]. Less than 10% of the

citations were from human research. Interestingly, the author was not cited, even though his work is widely available online. 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' treatments are not the only dangerous for patients and the freedom in research. It is the worldwide research, treatment, and teaching system, that does not allow qualified human research, which is urgently needed to cure diseases and make humans live longer with a better quality of life.

METHOD OF COORDINATION DYNAMICS THERAPY (COORDINATED-MOVEMENT-BASED LEARNING)

Basic and clinical human research for CNS repair

For a repair of the injured, malformed or degenerating human central nervous system (CNS), firstly the impaired phase and frequency coordination of human CNS organization has to be improved to achieve efficient physiologic CNS organization again. This can mainly be achieved when the patient is exercising very coordinated movements on special coordination dynamics therapy (CDT) devices. Secondly, to achieve physiologic CNS functioning again, integrative coordinated movements like crawling, walking and running have to be trained so that other parts of the brain can take functions over from the injured ones by plasticity, which is especially strong in children under 10 years. Thirdly, movements have to be trained which stimulate the epigenetics for repair. In this article it is concentrated on the phase and frequency coordination of CNS organization and its consequences of improvement for neural repair and hopefully genetic disease repair.

Performed movements in CDT

The performed movements in CDT are creeping **(Figure 51)**, crawling **(Figure 52)**, up-righting, walking, running, jumping, old-learned and other movements, if the patient can perform them with or without support. The exercising on a special CDT device **(Figure 53)** is most important. The always impaired phase and frequency of CNS functioning can be repaired and the improvement of CNS functioning can be measured by a single value with ongoing therapy.

Figure 51. Sophie during creeping in interpersonal coordination (antiphase) with Nefeli (SCI). Sophie is overstretching (a) and overswinging the legs (b) in comparison to Nefeli. She had not fully learned to control the inertia and centrifugal forces of leg movement. She cannot stop leg movement on time. The spinocerebellum (vermis) had not been repaired sufficiently so far. In Sophie and Nefeli bladder functions were repaired.

Figure 52. Trot gate crawling of a cerebral palsy girl in interpersonal coordination with the therapist. The crawling performance of the therapist is not optimal. The right arm is leading with respect to the left knee.

Figure 53. Patient with SCI (Nefeli) during exercising on the special CDT device different movement patterns to improve phase and frequency coordination of neuron firing. In A and B also, trunk rotation is trained. When turning in the standing position (F), the performance of the right foot is pathologic (plantar flexed).

Measuring CNS functioning by the arrhythmicity of exercising (coordination dynamics value)

The impaired phase and frequency coordination at the single neuron level, the assembly level and the macroscopic level can be measured macroscopically when the patient is exercising on a special coordination dynamic therapy device **(Figure 54)** on which arms and legs turn with a slightly different frequency (transmission 19 (arms): 18 (legs)). The phase coordination between arms and legs is imposed by the device. The loss of phase and frequency coordination between arm and leg movements becomes visible and measurable by the arrhythmicity of turning. During a turning cycle the coordination between arms and legs changes between pace (P) and trot gait (K). According to the difficulty of the coordination, the turning frequency increases and decreases. This frequency variation (df/dt; f = frequency) can be recorded, quantified and displayed on a computer screen **(Figure 54A)** and is called coordination dynamics value. CNS functioning is therefore measured though pattern change (continuous pattern changes from trot gait to pace gait) according to the System Theory of Pattern Formation (below).

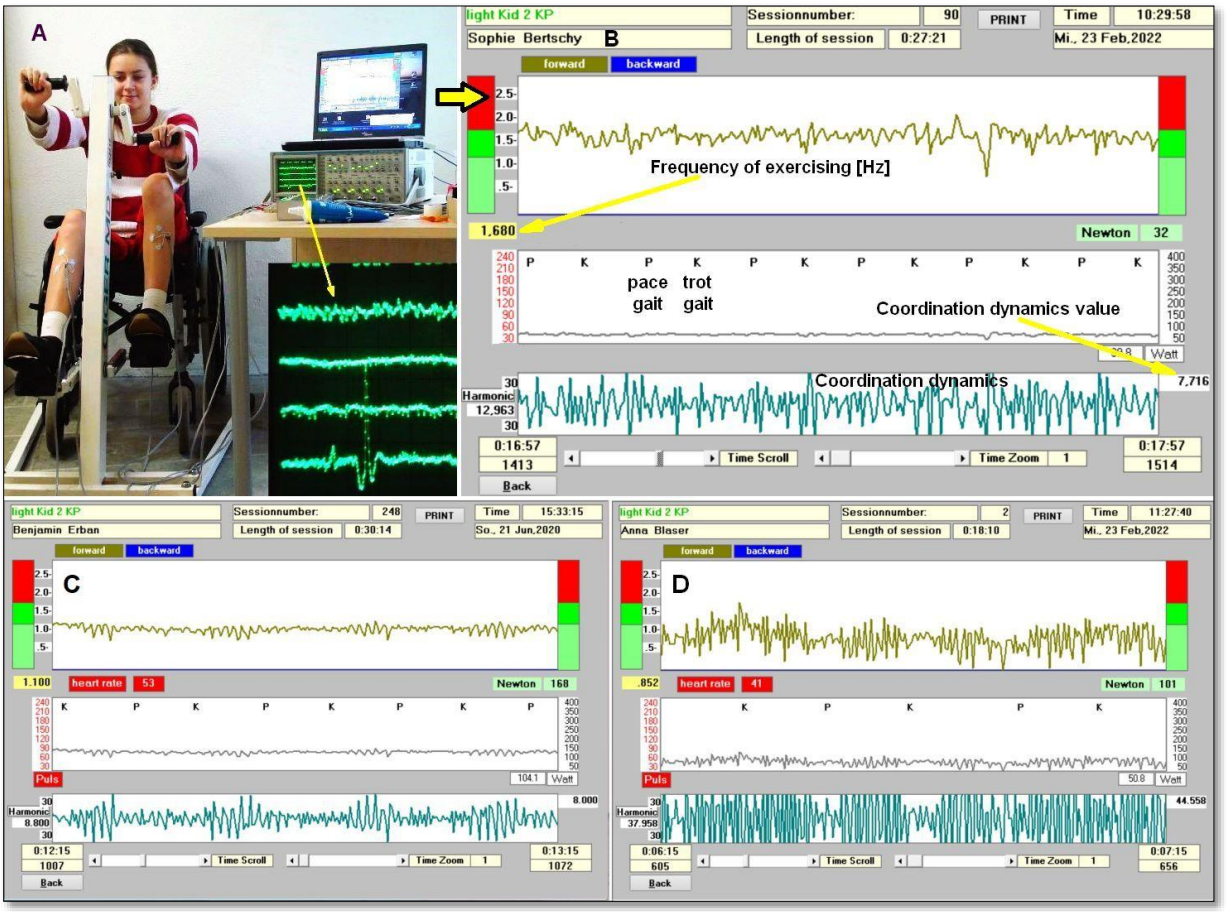

Figure 54. A. Layout for measuring coordination dynamics (arrhythmicity of exercising, (df/dt)) between arm and leg movements, displayed on the laptop, when exercising on a special CDT device. The recording of sEMG activity (displayed on the oscilloscope) from the tibialis anterior and other muscles is also shown. The inset shows a single motor unit action potential on the lowest trace. The recordings are taken from a patient (Kadri) with a motoric complete cervical spinal cord injury C5/6. B. Coordination dynamics measurements of the CP patient Sophie with repaired continence. C. In the brain-injured patient Benjamin, df/dt is higher between P and K but not between K and P. D. The sporty 10-year-old healthy Anna has problems for the difficult coordination's between P an K and K and P. Also, the healthy CNS needs CDT for improvement. The coordination dynamics value is the mean arrhythmicity value for 1min. P = pace gait, K = trot gait.

Brain-injured and healthy persons have problems with this difficult intermediate coordination's between pace and trot gait, especially for higher loads (Newton) **(Figure 54C, D)**, because the deep complexity of CNS organization is needed to generate these movement patterns. In reverse, if brain-injured patients learned to

generate these difficult coordination's, then their CNS improved its functioning in the deep complexity of CNS organization.

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

Unique properties of special CDT devices

The special CDT device has three important properties.

First, the patient performs coordinated arm, leg and trunk movements when exercising on it. The training of integrative patterns takes care of that the pathologic organization cannot escape from repair by shifting to another part of the CNS and the whole CNS, including the injured parts, is reorganized so that other CNS parts can take function over through plasticity. **Figure 39** shows for the motor cortical fields that nearly the whole brain is activated, if the patient is performing simultaneously speech therapy or if the patient is counting or speaking in coordination with the turning movement.

Second, neurons are coordination detectors **(Figure 55)**. Because the mechanical coordination between arm handles and leg pedals is extremely exact, the generated time-coordinated afferent input endplate potentials onto a neuron in the neural networks (approximately 5ms long) overlap more. The excitation threshold of the neuron is reached earlier. In this way, the efficiency of organization is improved. In spinal cord injury, for example, the transmission over the injury site will increase. If the mechanical coordination between arm handles and leg pedals of the device is not extremely exact any more, then the turning is only a muscle training and not a training through which the nervous system can learn from the device to function better. Maintenance of the device and supervision by an educated therapist is necessary.

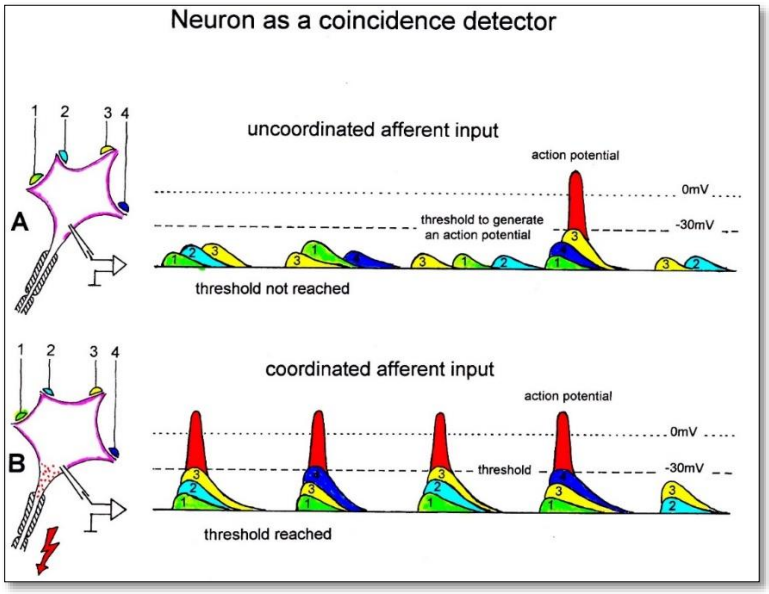

Figure 55. Neuron operating as a coincidence or coordination detector. A. Afferent input is reaching rather uncoordinated the cell soma. Only sometimes an action potential is generated, because the threshold of action potential generation is mostly not achieved. B. The action potentials in fibers 1 through 4 are reaching time-coordinated the dendrites or the cell soma. The postsynaptic potentials add up and the threshold is achieved at approximately - 30mV, and action potentials are generated time-coordinated at the axon hillock. In the real CNS mostly, many smaller postsynaptic potentials will contribute to the generation of an action potential and passive conduction from the dendrites to the cell soma has to be considered. Coordinated afferent input may thus induce or enhance (coordinated) communication between neuronal network parts following CNS injury.

Third, the coordination between arm and leg movements changes from pace to trot gait, imposed by the device. The intermediate coordination patterns between pace and trot gait are difficult to generate for the CNS neural networks. If the patients CNS learns to generate these intermediate patterns, imposed by the device, then the neural networks have learned to function better (more precise) in the deep complexity of CNS organization. The patient's nervous system learns by turning from the device, to function more physiologic through improving especially the phase and frequency coordination among neuron firings.

This phase and frequency coordination can be measured by single-motor unit surface electromyography non-invasively **(Figure 38)** and by the single-nerve fiber action potential recording method **(Figure 29)** invasively.

For understanding the details of neural network learning for repair through movement-based learning, it is necessary to give details of the 'System Theory of Pattern Formation' in connection with human neurophysiology and epigenetic aspects for repair. It will be shown that CDT is a scientifically based repair-method.

Integrative Physiology: System Theory of Pattern Formation

The System Theory of Pattern Formation for understanding Neuronal network organization and Learning

To understand the on-going changes of movement and other patterns in healthy humans and in patients with CNS injury, malformation and degeneration (aging), the System Theory of Pattern Formation is used. In a complex system like the human CNS, patterns are generated by a nervous system which seeks cooperative stability. Stability is what defines collective states. The system has the tendency to slip into the collective states to which it is attracted. When an infant crawl **(Figure 52)**, its arms and legs are strongly attracted to the 'pace' and 'trot' gait patterns. The attraction is so strong that intermediate crawling patterns seemingly do not exist, as if the patterns are hard-wired. But with the help of the special CDT device **(Figure 53)**, the CNS can generate intermediate coordination patterns. A patient with a CNS injury often crawls with intermediate arm and leg coordination patterns and has to re-learn the pace and trot gait coordination's for CNS repair and shifts in this way the attractors for crawling to the pace and trot gait coordination's. Attractive states and attractors of CNS organization can be pictured as a ball in a potential well or more generally in an attractor layout **(Figures 56 & 57)**. Changes in CNS functioning are characterized as continuous stabilization and destabilization, over time, of preferred attractor states.

Figure 52 shows a cerebral palsy girl who tries to relearn the attractor state patterns pace and trot gait crawling. A therapist is crawling in interpersonal coordination to speed up the learning process. The visual input from the exact crawling of the therapist into the CNS of the girl improves the performance of the in this case the trot gait pattern. For this supervised learning the cerebral palsy girl needs not to concentrate to it. It is working automatically. This interpersonal coordination is something like when soldiers march together. Once they got the rhythm among each other, the marching coordination works automatically. It was even reported that soldiers could march together in interpersonal coordination when half sleeping.

This supervised teaching of the therapist, so that the patient learns faster needs a lot of concentration. The therapist has to copy the pattern of the patient and has to drag her then into a better performance. In doing so, the therapist sometimes is also losing the own movement pattern. With the concentration on the patient and adapting partly to the pattern of the patient, the stability of the own movement pattern is reducing strongly and easily lost. With adaptation to the patient, her potential well of her movement pattern became shallower and more deformed and the ball jumps then easily out of the well.

To reduce for understanding the complexity of human neural networks of the many billions of neurons, order parameters or collective variables are introduced for the generation of certain movements. An equation of motion describes the coordination patterns dynamics. However, coordination patterns are not only determined by the task or biological function. Patterns adjust continuously to requirements from the environment (transmitted by impulse patterns from stimulated receptors in the periphery), memory, intention, and support given by a therapist. The specific requirements are captured by the concept of behavioral information and are made part of a vector field that attracts toward the required patterns. The coordination pattern dynamics, characterized by equations of motion of collective variables (the vector X), takes the general following form [88]:

$$dX/dt = F_{intr}(X) + \sum c_{inf} F_{inf}(X,t) \qquad (2)$$

where F_{intr} designates the intrinsic dynamics of the nervous system. These intrinsic dynamics capture the anatomical (neuronal network structure), physiological and pathological states of the CNS and its muscular-skeletal elements.

$\sum c_{inf} F_{inf}(X,t)$ represents the sum of external influences ($F_{inf}(X,t)$) with their relative strength (c_{inf}) pertaining to each influence. The so-called behavioral information $F_{inf}(X,t)$ includes cognitive states, emotional states, intentions, motivations, instructions, inter-personal

coordination, movement support etc. During motor learning or while applying therapy to a patient these extrinsic influences become extremely important, because the intrinsic (pattern) dynamics can be changed with these extrinsic influences by altering the equation of motion. By modulating the behavioral information, the intrinsic dynamics of the neuronal networks can be influenced further, that is if CDT is no longer efficient in repairing the injured CNS, the therapy has to be updated. With respect to a healthy athlete, the movement performance can be improved by modulating the behavioral information by for example including in the training program the exercising on a special CDT device to improve CNS functioning.

If the behavioral information includes the exercising of extremely coordinated, integrative movements, like exercising on the special CDT device, the quality of CNS self-organization can be enhanced by improving the exactness of self-organization, namely the precision of phase and frequency coordination between neuron and neural assembly firings. By improving the precision of organization of the intrinsic dynamics, that is the specific variability of the injured networks, certain patterns do eventually re-appear in the case of repairing the injured CNS by movement-based learning.

Learning implications for treatment derived from the equations of motion of the collective variables (Formula 2)

From the repair by learning in the severely injured CNS we can learn about learning in the healthy CNS.

1. Behavioral requirements F_{inf} (like intention, support, and instruction) affect the whole coordination dynamics, including stability, rather than only certain coordination patterns. The change of the whole coordination pattern dynamics of the CNS by the behavioral information is one scientific basis for learning transfer between different patterns and stability changes of patterns (as for example the reduction of spasticity). The other scientific basis for learning transfer is followed from human neurophysiology, namely that nerve cells or neural sub-networks are involved in different neural network organizations [1].
2. Intrinsic coordination tendencies captured by the intrinsic dynamics influence the performed pattern systematically because the degree to which intrinsic tendencies conflict or agree with the required patterns determines the variability of the performed coordination pattern.
3. A reduction in stability of movements and other patterns when intrinsic and informational requirements conflict, may lead to loss of stability and abrupt change while behavioral information is changing smoothly.
4. The intrinsic dynamics F_{intr} include vegetative and higher mental functions (these are also patterning of the coordination dynamics), which indicate that via exercising coordinated movements with support and/or instructions (F_{inf}), urinary bladder function, intelligence and speech may be partly repaired or improved following CNS injury or malformation.
5. When in an injured CNS with a certain set of behavioral information ($\sum c_{inf}F_{inf}$) the intrinsic coordination dynamics (F_{intr}) can no longer be influenced during coordination dynamics therapy, then this set of behavioral information has to be changed (using different F_{inf}), or balanced differently (using different c_{inf}), to further improve CNS organization dynamics.
6. However, the equations of motion of the coordination pattern dynamics (formula 2) provide no information about the specific behavioral information (F_{inf}) and training intensity (c_{inf}) with which the CNS can be efficiently repaired by learning in the patient. We need to have detailed knowledge of the human CNS at the single neuron and neural assembly level [1], as well as the knowledge at the integrative level, to find the specific behavioral information for the repair by learning of the human CNS.

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

Furthermore, we have means by which the stability of physiological network states can be increased (e.g., movements, continence, continuous concentration in performing certain tasks, speech etc.) and simultaneously the stability of pathological network states, like spasticity, decreased. The coordination (pattern) dynamics therapy, partly based on the System Theory of Pattern Formation in combination with human neurophysiology (including neuro-urology), thus offers us an important theoretical basis and a practical tool to diagnose, quantify and repair/improve the functioning of the human nervous system at the macroscopic level. Through neural network learning we can reach for repair the whole CNS, including the sacral and pontine micturition centers **(Figure 3)** and the plexuses outside the CNS.

Figure 40 shows that in the complexity of neural networks of the human body, including the plexuses, there is a unique location, the sacral nerve roots, where one can

measure and analyze CNS functioning at the single-neuron level. With this obtained knowledge, nervous system functions can partly be repaired through CDT in different diseases.

Geographical landscape of attractors

The drawback of the equation of motion of the order parameters (formula 2) is that it is normally not possible to find a mathematical solution to it. But by defining a potential function and by picturing the attractive states and attractors by a ball in a potential well or rather by a ball moving in a geographical landscape of attractors **(Figures 49, 56 & 57)**, we form a theoretical basis to understand and measure stability of certain coordinated movement patterns (i.e., the deepness of the potential well of an attractor) in patients with CNS injury who receive on-going therapy.

By studying the pattern change of certain highly coordinated arm and leg movements, while a subject is exercising on a special coordination dynamics therapy device **(Figure 53)**, pattern stability can be made visible and the mean stability per one minute can be measured by the arrhythmicity of exercising **(Figure 54)**. Such value, so-called coordination dynamics value, quantifies CNS functioning objectively, integrative, and non-invasively. The assessment of quality of CNS organization through pattern change is a second novel step in CDT.

To make the strategy of pattern formation, pattern stability, pattern assessment, and pattern picturing understandable, the procedure is demonstrated for the simple movement 'jumping on springboard', which is used during CDT, especially for the repair of the urinary bladder and training in the up-right weight-bearing posture (very important in patients with SCI, **Figures 26g & 56)**.

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

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

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

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

The mathematical solution of $d\varphi/dt = f_{intr}(\varphi)$ in the Haken-Kelso-Bunz model [89,90] (for the approximations being made) gives the equation of motion for jumping on a springboard for the space-time symmetry:

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

The so-called potential function is defined by

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

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

$$V(\varphi,t) = -a(t)\cos\varphi - b(t)\cos 2\varphi$$

For an easy understanding, the potential function can be developed approximately as follows. With the space-time symmetry $V(\varphi+2\pi) = V(\varphi)$ (time symmetry) and $V(\varphi) = V(-\varphi)$ (space symmetry) and using the first two terms of the Fourier series with sines and cosines we obtain $V(\varphi,t) = -a(t)\cos\varphi - b(t)\cos 2\varphi$ by regarding that only cosines are invariant when φ is replace by – φ. The minus signs allow to interpret the function, V, as a landscape with attractor states for positive values of a and b [88, page 55].

The potential function $V(\varphi,t) = -a(t)\cos\varphi - b(t)\cos 2\varphi$ can be plotted for different φ and certain ratios of the parameters a and b and is shown in **Figure 56**.

The potential function shows two attractor states, namely the jumping in in-phase ($\varphi = 0$) and the jumping in anti-phase ($\varphi = \pm\pi$). Especially for higher frequencies (smaller b/a) the jumping in-phase has a higher stability (the potential well is deeper) than the jumping in anti-phase. Asymmetry (not tackled mathematically here) strongly changes the stabilities of the attractor states (depths of potential wells) **(Figure 56)**.

The human CNS, seeking for cooperative stability, slips into the collective states to which it is attracted. For jumping on springboard these attractive states are the jumping in in-phase and in anti-phase. For crawling **(Figure 52)** (not creeping) the attractive states are the pace (in-phase) and trot gait coordination's (anti-phase).

Since such a potential function can no longer be derived from more general movements, especially when the CNS is injured, malformed or degenerating, the temporal stability of different movement patterns for a characterization of CNS functioning has to be measured. This is partly possible by measuring the so-called coordination (pattern) dynamics **(Figure 54)**.

Including the variability of phase and frequency coordination among neuron firing into the equation of motion of the collective variables

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

from the cooperative and competitive interplay between the behavioral information (supported jumping or walking of the patient) and the intrinsic dynamics.

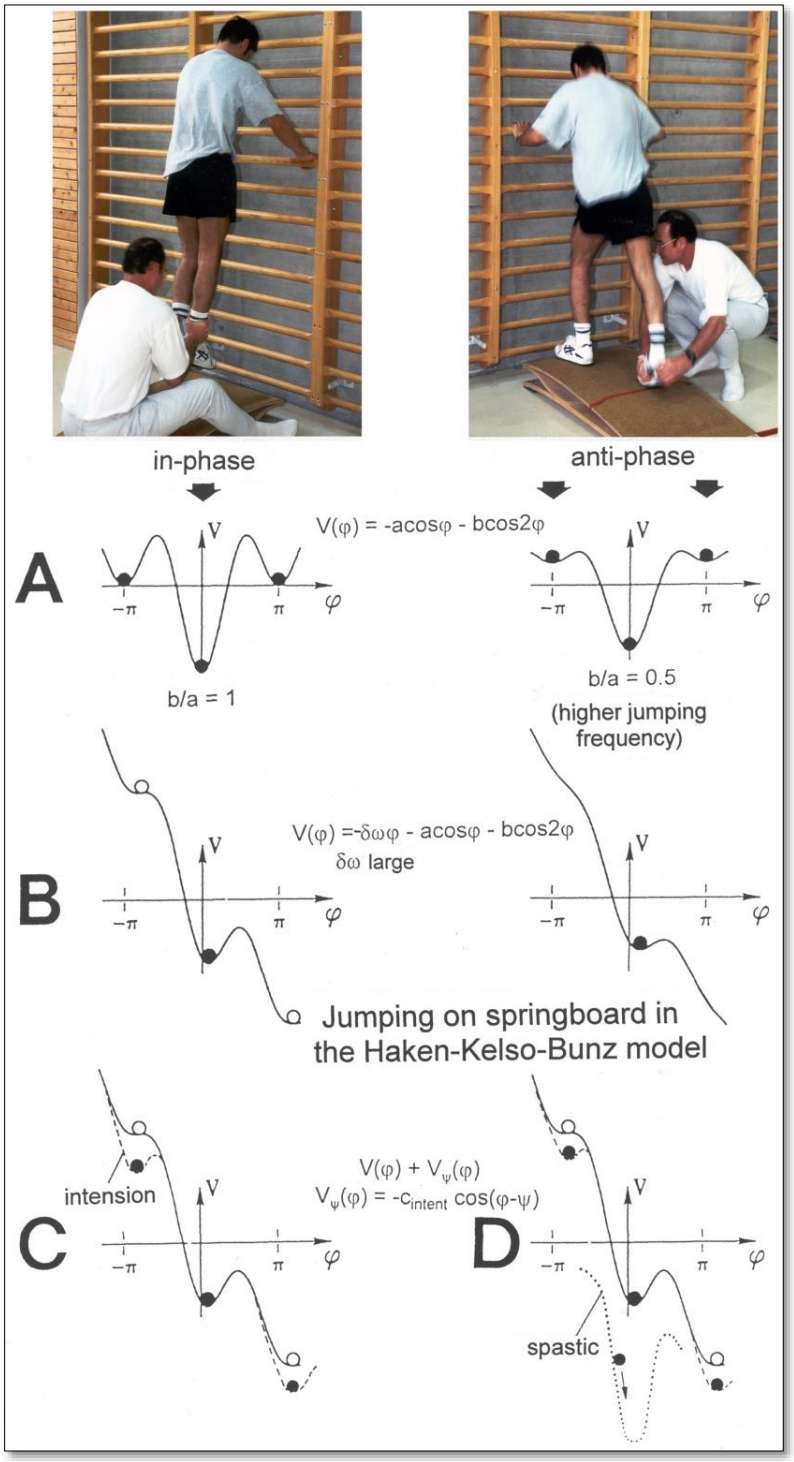

Figure 56. The jumping on springboard in in-phase and in anti-phase, analyzed by the Haken-Kelso-Bunz model in the framework of coordination dynamics. The stability of jumping patterns is represented by the potential wells (derived from the formulas) and a ball moving in the potential landscape. Dark ball = stable state (attractor state), white ball = unstable state. In 'A', the CNS injury is small (symmetry case); in 'B' and 'C' the injury is more severe with impaired symmetries. The Author is the therapist.

A completely different, additional nature of necessary learning is needed in the repair of CNS injury. The impaired phase and frequency coordination among neuron firing have to be repaired by re-learning for proper CNS self-organization. This perturbation of CNS self-organization produces deviations from the attractor states and changes the attractor layout because of altered hard-wiring due to injury. In a first approximation, this tremendously increased variability of phase and frequency coordination can be included into the equations of motion of the collective variables and gives further understanding of pattern change in patients with CNS injury as for example the switch from a movement pattern to a spastic pattern **(Figure 57B)**.

In the Haken-Kelso-Bunz model, the jumping on springboard **(Figure 56)** can be described in terms of relative phase between the rhythmically moving legs. Without specific behavioral information the dynamical description is defined by a vector field (a differential equation) expressing the rate of change in relative phase, dφ/dt, as a function of the derivative of its potential, V(φ):

$$d\varphi/dt = - dV(\varphi)/d\varphi + (Q\xi t)^{1/2} \quad (3)$$

where $V(\varphi) = - a\cos(\varphi) - b\cos(2\varphi)$ and $(Q\xi_t)^{1/2}$ is the phase and frequency variability of strength Q (where ξ_t is Gaussian white noise of unit variance). Zanone and Kelso [90] introduced noise in Equation 3 (from a logic point of view), because all real systems described by low-dimensional dynamics are coupled to many subsystems at a more microscopic level. One may view noise as a continuously applied perturbation that produces deviations from the attractor state. Such fluctuations are conceptionally important in dynamical modeling of phase transition or bifurcation phenomena and are essential in effecting transitions.

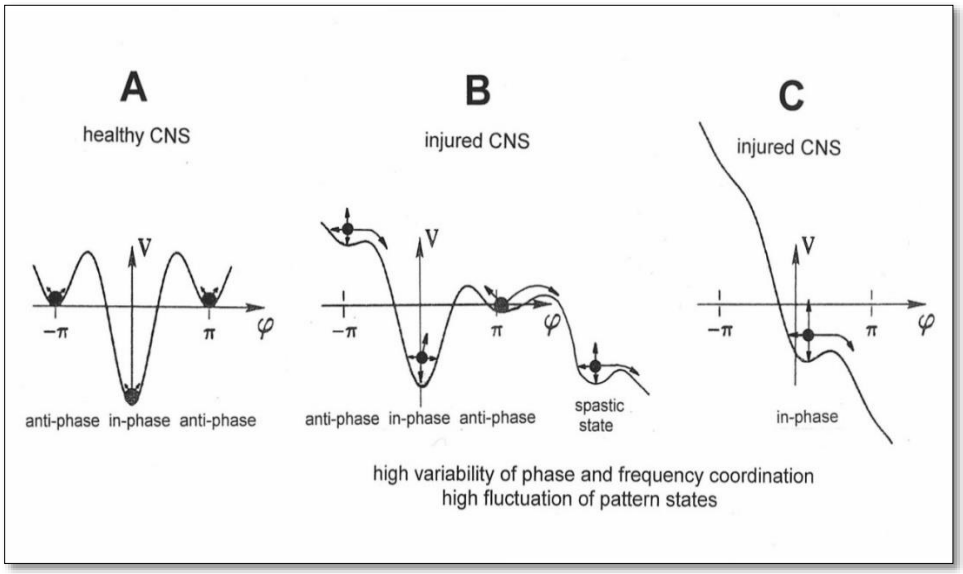

Figure 57. The potential, V(φ), of the coordination dynamics for jumping on springboard of a healthy (A) and injured CNS (B, C). The region around each local minimum act like a well that weakly traps the system into a coordinated state. Behavioral changes are represented by the over-damped movement of a rolling ball in the potential "landscape". High fluctuations (indicated by long arrows attached to the ball (network state)) in the stable state, due to high variability of phase and frequency coordination (in the injured case), will have a greater probability of "kicking" the system out of the basins of attraction (B,C) than for low fluctuations (short arrows) (A), due to small variability of phase and frequency coordination (in A). In B, the in-phase jumping is stable, even though the fluctuation is high. In C there is only an attractor basin for the in-phase jumping, but the fluctuation is so high that there is a high probability that the system is kicked out of the basin of attraction. The patient can no longer jump in anti-phase and has difficulty with jumping in-phase. The stability of jumping depends on the motor program (deepness of basin of attraction) and the fluctuation of the pattern state (moving of the ball) caused by the increased variability of phase and frequency coordination due to the injury.

I included noise in Equation 3 (from the experimental point of view) because of the measured increased variability of phase and frequency coordination among the coordinated firing of neurons and neural assemblies in the human CNS. This at the neuron level measured fluctuation of phase and frequency coordination is giving rise to phase transitions or bifurcation phenomena and is essential in causing transitions among attractor states under physiologic (small fluctuation; **Figure 25** (HT5 or normal Eigenfrequency distributions)) and pathologic

conditions (large range of the Eigenfrequency in **Figure 25**; Para 2 distribution). The relative stability of attractor states is, therefore, reflected by the depth of each potential well (I) and the strength Q of the variability of phase and frequency coordination (II), and the attraction of attractor states is reflected by the slope at each point of the potential curve.

The behavioral changes when jumping on springboard **(Figure 56)** are represented by the over-damped movement of a rolling ball in the potential landscape for the physiologic (**Figure 57 A**, Q small = little fluctuation of phase and frequency coordination) and the pathologic case (**Figure 57 B, C**, Q large = large variability). The increased fluctuation, due to increased variability of phase and frequency coordination, will have greater probability of "kicking" the system out of attractor the basin, especially in the asymmetric case **(Figure 57 C)**.

In the healthy CNS, the phase and frequency variability are small (short arrows) and the jumping in-phase and anti-phase is stable **(Figure 57A)**. Following injury, the potential landscape is deformed and the fluctuation of the network states, generating jumping, is high **(Figure 57B)**. The in-phase jumping is still stable in spite of the increased fluctuation, because the basin of attraction is deep. The jumping anti-phase became unstable because the basin of attraction is shallow and the increased fluctuation in the state has a greater probability of "kicking" the system out of the basin. A switch into a spastic state is also possible. In severe CNS injury or malformation, the patient cannot jump any more in anti-phase because of the missing of attractors for anti-phase jumping **(Figure 56 C)**. Support is needed for anti-phase jumping (**Figure 56**, upper right). The jumping in-phase is still possible but unstable (**Figure 56**, upper left).

Upon performing very exact coordinated movements, imposed by devices, the nervous system of the patient learns to reduce the variability of phase and frequency coordination and achieves in this way a small fluctuation of the network states again as shown in **Figure 57A**. The progress in treatment (learning) is that the in-phase jumping in **Figure 57C** and the anti-phase jumping in **Figure 57B** become stable **(Figure 57A)** again. Also, the potential landscape will change due to the reduction of the phase and frequency variability. The important consequence for treatment is that when exercising on special CDT devices and reducing in this way the variability of phase and frequency coordination, the patient can induce the formation of patterns again, without having trained them (learning transfer). Through improving the coordinated firing of neurons, a cerebral palsy child will become continent and my become able to speak or may develop social behaviors.

In conclusion, the impairment of phase and frequency coordination, measured at the neuron level in human (**Figures 32B-33**), can be included in the coordination dynamics at the collective variable level. The decrease of the variability of phase and frequency coordination (one kind of coordination repair) is an essential part of CNS development and repair by movement-based learning (neural network repair).

Repair strategies at the neuron membrane and genetic level

For the repair of the neural networks of the CNS it is likely that excitation-neurogenesis coupling [91-93] contributes, stimulated through CDT.

1. Repair depends on learning and memory formation, mediated or supported by epigenetic mechanisms. Epigenetics is the interplay between genes and the environment resulting in phenotype and epigenetic landscape.

2. Epigenetic mechanisms, like DNA methylation, are probably sensors for movement-based learning and memory formation and fine modulators of neurogenesis though CDT **(Figure 58)**.

3. The epigenome consists of non-coding RNA and chromatin, a proteinaceous matrix surrounding DNA. The dynamic interactions of post-translationally modified chromatin proteins, covalently modified cytosines inside DNA and non-coding RNA define the complex pattern of gene expression beyond the four bases of DNA.

4. The hippocampus plays an essential role in learning and memory. In the hippocampus there exists a specialized form of neural plasticity, which is the generation of new functional neurons from stem cells occurring throughout life. Adult hippocampal neurogenesis contributes to learning and memory formation.

5. New neurons are important for learning and memory formation (besides functional reorganization), i.e., for increasing the rate of repair, for the following reasons:

a. The insertion of new neurons helps to store the memory of the same activity that led to the creation of the neuron.

b. Activity-dependent neurogenesis enhances the learning of new memories and degradation and clearance of previously stored unwanted memories like spasticity, because the synapses, dendrites and axons can be devoted more fully to the newer memories. The old neurons with large and complex axon and dendritic trees are difficult to change. They can only be changed with sustained effort.

c. New neurons seem to improve the accuracy of relearned patterns (from model study [91]). This means that new neurons help to improve phase and frequency coordination of neuron firing and pattern stability.

d. The advantage of new neurons seems to be dramatically greater in networks that had been more active and had been required to store more memories [91]. The advantage of neurogenesis for memory storage in heavily active networks is that it provides an increased rate of repair if movement-based learning is administered aggressively and if different movements are trained.

6. Specific natural network activity is required for multiple aspects of repair. Specific activity is essential for correct migration of interneurons and it also controls the development and repair of their axons and dendrites. During repair there is a specific requirement of network activity in shaping the cortical integration of specific neural subtypes. Newly build neurons are likely electrically active shortly after their birth and participate in the early network activity that contribute to circuit maturation during repair by CDT.

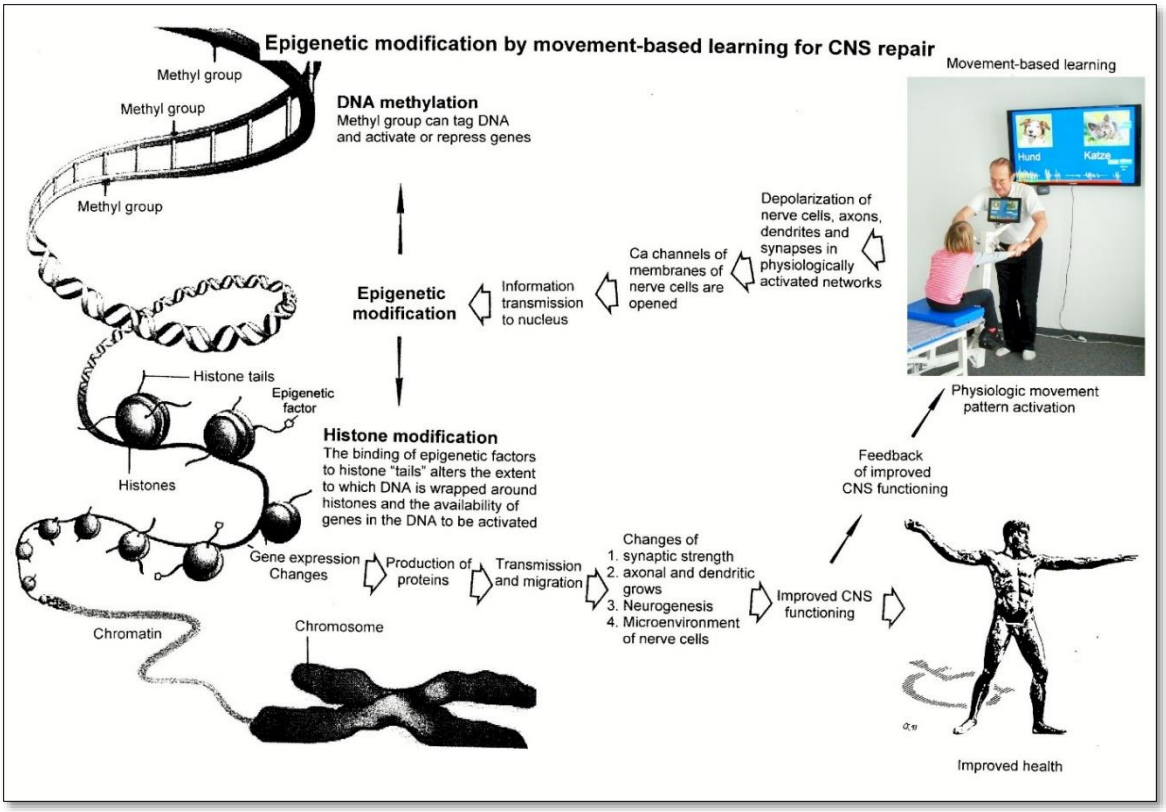

Figure 58. Epigenetic regulation for repair by movement-based learning. CDT-induced stimulation of the pathways that regulate neural network repair is a proven therapeutic and preventive tool. Epigenetic mechanisms, stimulated by physiologic network activation, are likely key players within signaling networks, as DNA methylation, chromatin remodeling and small non-coding RNAs super families are required for the fine-tuning and coordination of gene expression during neural network repair by learning.

7. Specific activity is required for migration and maturation at several stages of repair. A break in CDT may invalidate the whole chain of repair events. Specific interneuron subtypes require activity for migration and morphological maturation at two distinct stages of development [91]. Newly built neurons may even require specific activity for migration and maturation at several distinct stages of repair. During a break in CDT, the specific activity, required for neuron migration, maturation and network integration may not be supplied at one of these stages so that the chain of repair events is severed and the whole repair chain has to be started anew.

8. Drug application may undermine repair. Altering the level of neuronal excitability within genetically targeted neurons from drug application, for example antiepileptic drugs may have profound consequences on multiple aspects of the repair of select types of neurons within a population of neurons, as well as their associated gene expression. The pain-killer 'Contergan', taken during pregnancy, changed gene expression and the babies were born without arms.

9. Excitation-neurogenesis coupling [91]:

a. Excitation increases or decreases neuron production directly by excitation-neurogenesis coupling.

b. The excitation acts indirectly on the surrounding mature (hippocampal) cells through depolarization-induced release of growth factors.

c. Adult neurogenesis is enhanced by excitatory stimuli and involves Ca^{2+} channels and NMDA receptors.

d. The Ca^{2+} influx pathways are located on the proliferating stem/progenitor cells (NPCs), allowing them to directly sense and process excitatory stimuli. The Ca^{2+} signal in NPCs leads to rapid induction of a proneural gene expression pattern.

10. Integrative coordinated movements have to be trained to allow functional reorganization and new nerve cell integration across very large distances. CDT has to activate injured and uninjured networks to enhance physiologic CNS functioning and learning transfer.

11. Conclusion for optimal therapy according to the present stage of knowledge. If there is similarity between development and repair, animal (mice) data also hold in human and the principles of neurogenesis of the hippocampus also hold in other parts of the brain, albeit to a much lesser extent, then the patient has to be trained at his limits (1) to induce substantial building of new nerve cells [94]. The treatment has to be continuously administered (2) to support all stages of repair at the progenitor level as migration, maturation and integration. The networks requiring repair have to be activated specifically (3) to generate repair-friendly, micro-environmental properties in the networks. No drugs should be administered that change neuron excitability (4). The exercises have to include coordinated arm, leg and trunk movements (if possible) to improve the impaired phase and frequency coordination for CNS self-organization (5). The performed movements have to be as integrative as possible to reconnect distant brain parts and to induce learning transfer.

It is movement-based learning and learning transfer that achieves repair

It is learning and not simply training that elicits the survival effects of new neurons in the hippocampus. Learning appears to promote the survival of newborn neurons in cognitively unimpaired aged rats [95]. Learning elicits different influences on neural precursors at different developmental stages. The regulation of subgranular zone neurogenesis by hippocampus-dependent learning is complicated and can be affected by factors such as the age of the newborn neurons, the stage of learning and specific learning protocols [96].

When the human patient is exercising on the special CDT device, he should not just turn, but should try to turn more smoothly. He should try to reduce the arrhythmicity of exercising when especially exercising against higher loads. The patient should try to improve the performance of movements by learning. During learning, it is essential to concentrate and to be aware of what needs to be corrected. When the patient is well-practiced at exercising smoothly, the skill can be accomplished without conscious effort, much like in walking, swimming, cycling or skiing. Simply exercising will also improve CNS functioning. However, the rate of learning is significantly lower. This is the learning of automatic movements, in which the process is subconscious. A problem in some patients is that the cognitive functions are that much impaired that they cannot understand that they have to learn to improve their nervous system functioning. The hope in such cases is that the simple training improves their cognitive functions to a point that they can understand that they have to improve the performance of the trained movements to improve their CNS functioning. Older patients are intelligent and can understand that they have to perform movement-based learning. But according to their experience, they are not trusting the research and treatment systems any more.

With respect to the repair of continence functions, it is the learning transfer from the movements (and instructions) which repairs the bladder [65] because it was unsuccessful to train bladder functions through filling and emptying the bladder.

Movement-induced epigenetic modification for changing gene expression for repair

The mechanisms, or strategies, developed by the fetus, new-born, infant, or young child are not peculiarities or movement patterns which occur only in the neonatal or later period. They belong to one phase of the developmental course of the nervous system. These patterns are elements which have been tested and trained and which can be modified for use in more differentiated and complex motor behavior during later development. Their integrity must be regarded as a prerequisite for normal development during infancy. These pattern elements may partly originate in phylogeny (see below). Due to injury, malformation or degeneration, the learning process may be hampered by a deficiency of the neuronal structure on which they are dependent. Stimulating the patient to use uncommon modes of operation (as movements from phylogeny, see below) may enable him to achieve learning results which he cannot achieve spontaneously. If one recognizes which learning processes are deficient, one may then be able to offer the infant or patient a cue to start other learning processes or help him to eliminate errors and to progress in the right direction.

The early environment, consisting of both the prenatal and postnatal periods, has a profound effect on gene

expression and adult patterns of behavior [97]. The establishment of adult patterns of DNA methylation during the postnatal period suggests that critical periods exist after which levels of gene expression are relatively stable [97]. However, movement-based learning in adulthood is capable of targeting the epigenome and altering gene expression and hence repair; but the efficiency of repair may be much lower. CDT should therefore be started as early as possible in the event of CNS injury or malformation.

Movement-based learning for repair in patients

Problems of learning in the injured CNS

In severe brain injury some parts of the brain are damaged more than others and some parts are not damaged at all. Through CDT, the undamaged parts will try to become operational. Depending on the location, extent and type of the damage, it may happen that networks which in themselves are normal cannot bring about physiologic movement or other neural network patterns because some areas of the brain which are also necessary for the accomplishment of a particular motor function are deficient. For example, certain sub-functions which have been spared from the injury cannot be integrated into larger patterns because other elements of these larger patterns are missing or have not been sufficiently repaired through natural repair mechanisms. In general, both impaired and healthy parts of the brain change over time through therapy and this leads to increased complexity which has direct repercussions on the quality of the learning processes. In incomplete spinal cord injury, the main repair does not take place by a regeneration of the spinal cord but by a 'rewiring' of the remained tract fibers of the cord. It is the brain in cooperation with the autonomic **(Figure 38)** and enteric nervous system divisions which has pronounced plasticity.

The poor quality of movements, stereotypy of posture and motility, the inability to 'discover' new motor possibilities and deficits in higher mental functions in the first years following injury can all be traced back to a lack of learning as a consequence of deficient brain structure. In the case of an inability to 'discover' new motor possibilities, there may be a disturbance in the chain of events because errors in the self-organization of neuronal networks are not recognized (or not repaired), with the result that the processes of repair stop prematurely.

Problem solving therapy by learning during repair

It is of importance to recognize the deficiency or absence of particular functions and learning processes. If one recognizes which processes are deficient, one may then be able to offer the patient a cue to start other processes or help him to eliminate errors and to progress in the right direction. It may be sensible to 'teach' the patient specific modes of operation to avoid wrong postures or wrong movement patterns, or to stimulate him to use uncommon modes which may enable him to achieve results which cannot be achieved spontaneously. Below it is tried to find uncommon movements patterns for repair by considering the phylogenies and ontogenesis.

Motor learning and problem solving through error-elimination

Learning by problem-solving is a mean of repairing sub-networks which are necessary for functioning and learning. By inducing trial and error-elimination processes [3,98] in subunits of the changing nervous system, optimal repair may be achieved. To teach the injured CNS to repair itself by trial-and-error elimination processes, the CNS has, in similarity to development, to recognize through CDT, which sub-networks, regulation units or sub-loops are not functioning properly or missing and to repair them by error-elimination, including the possibility that other parts of the brain partly take over functions and sub-networks built anew to a limited extent upon structural repair.

Treatment principles embedded in the system theory of motor development

Because of the influence of many subsystems, many possibilities exist to facilitate (motor) behavior. All subsystems contribute to the enhancement or delay of motor behaviors and not only the motor system. In addition to exercising motor functions, instructions or self-instructions may contribute, for example, to the improvement of motor functions. Important questions remain. What degree of deprivation in any subsystem can be compensated by the other systems? Are some subsystems more important than others or is the severity of involvement the restricting factor? It seems that humans are resilient to minor disturbances within any subsystem. The nearly spontaneous repair in mild cerebral palsy and mild epilepsy provides support this assumption. Also, the injury, following a minor stroke, repairs mainly spontaneously. In degenerative diseases like Parkinson, the disease is only realized when the nervous system cannot compensate itself any more for the dying of nerve cells. The degree of resiliency is unknown. Even in severe brain injury there is some spontaneous recovery in the first- and second-year following injury.

Retarded, accelerated or deviant motor functions

Variability in motor performance is a characteristic of normal development. The impaired nervous system is not able to attain such variability in motor performance because the structure of the CNS is inadequate in enabling the patient with brain injury to use various modes of operation for single performance. When there is serious damage to the CNS it often happens that the usual modes cannot be achieved at all; the brain has to resort to unusual modes. Due to the deficiency of the 'hardware',

distorted motor patterns arise which fall outside the range of normal variability. These abnormal movements are stereotyped as they are the only movements which the injured hardware is capable of performing.

Due to the reduced variability in motor performance of the impaired nervous system, patients with CNS injury or malformation have great difficulty in exercising on the special CDT devices because the device imposes complex motor pattern variability. But motor pattern variability can partly be re-learned from the special CDT device. Some patterns are shown in **Figure 59**. Due to the deficiency of the neuronal structure, development of motor functions may be retarded, accelerated or deviant. Some functions may not develop at all, while others show only a decrease in variability.

Figure 59. Different training patterns realized when exercising on the special CDT device. The healthy 4.5-year-old boy Jonas exercises in the normal sitting position with pattern change (A), the pace gait (B) and trot gait pattern (C) with no pattern change and two standing positions with pattern change from pace to trot gait (D, E, F).

Learning for repair by recapitulating development

Learning for repair from the ontogeny

According to the ontogenetic landscape for locomotion **(Figure 60)**, in the framework of system theory of pattern formation (attractor layout), newborn stepping, crawling and climbing staircases are important.

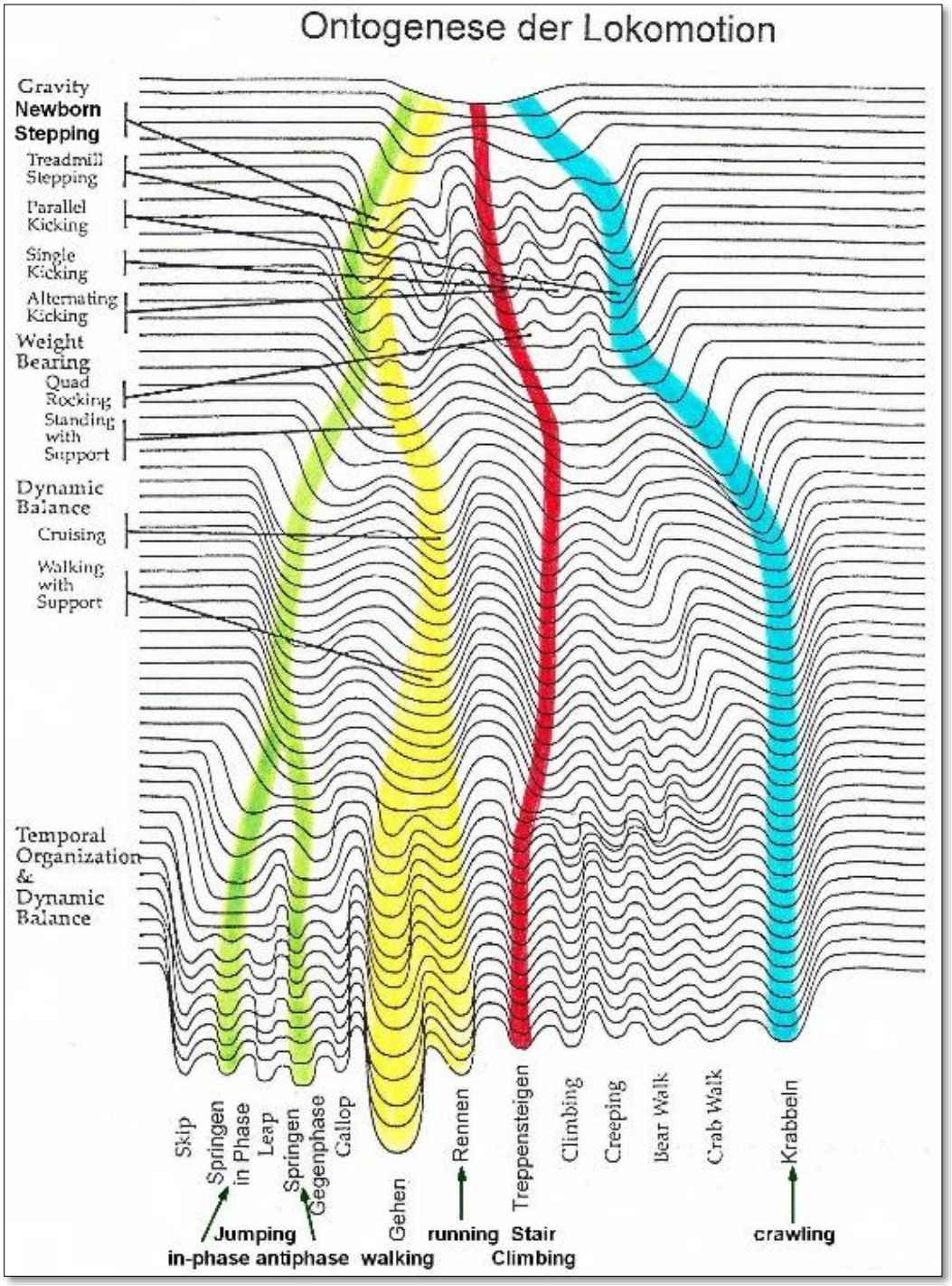

Figure 60. Ontogenetic landscape for locomotion. The evolution of the attractor layout (see System Theory of Pattern Formation) for the different movements. With permission of Esther Thelen (†) [99].

The neural network for the pattern 'newborn stepping' is mainly located in the intumescentia lumbosacralis, because in cervical spinal cord injury the stepping automatism can be induced by heel strike or bumping the forefoot. During physiologic development the stepping automatism network is brought under supraspinal control and is changed into the walking pattern. The change from newborn-stepping to walking can be seen in **Figure 61**. In A and B the newborn Juliane steps automatically. Characteristic is high lifting of the knees. In C the 4-month-old healthy Jürgen performs a pattern intermediate between newborn stepping and walking and in D the now 8-months-old Jürgen nearly walks. sEMG motor programs of the walking of Jürgen can be seen in **Figure 37b, d**.

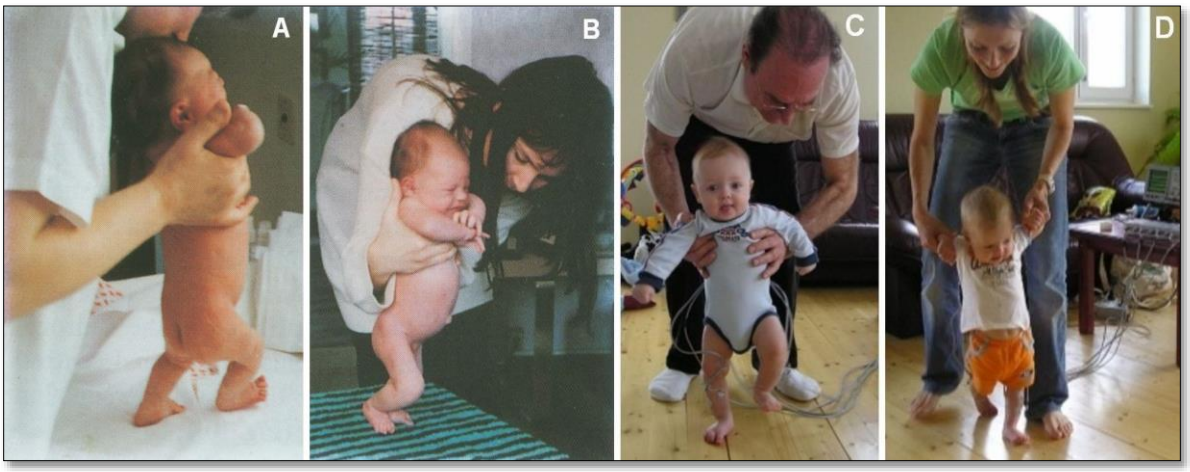

Figure 61. Development from newborn-stepping to walking. A, B. Automatic stepping in a newborn infant. A. The 5-day-old healthy infant, Juliane, performing primary automatic stepping; slight backward posture. The heel of the right foot touched the ground first. B. Infant Juliane, 8-day-old, performing automatic stepping. C, D. Supported walking of the healthy 5-months-old (C) and 8-months-old old "Jürgen" (D). In C the 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.

The stepping movement (automatism) of the new-born **(Figure 59A, B)** (characterized by the emphasized lifting of the knees) is partly re-appearing during repair in severe cervical spinal cord injury. After partial regeneration [11], induced through CDT, the stepping automatism partly changed again into volitional walking.

The aim of learning is not only to equip the deviant patterns of the infant or patient with just one efficient mode of motion for each motor performance, but to lay down a foundation in the CNS for adaptive responses to specific circumstances and to induce learning transfer to other movement patterns which cannot be trained. Jumping on springboard **(Figures 56)** and exercising on the special CDT device **(Figure 53)** improves continence in severe cerebral palsy [1] and spinal cord injury [12,29,30] by learning transfer [65]. Exercising walking in the backward direction on treadmill improves the forward walking in stroke patients by learning transfer.

The learning process may be hampered by a deficiency of the neuronal structure on which they are dependent. Stimulating the patient to use uncommon modes of operation may enable him to achieve results which he cannot achieve spontaneously. If an adult patient or child cannot jump in anti-phase on springboard **(Figure 56)** continuously, he may learn it by first jumping with both feet on the springboard in between anti-phase jumps, for example. Elements of function also have to be learned which are necessary for more complex motor patterns. Walking on knees **(Figure 62)**, for example, is a functional element of walking. If one recognizes which learning processes are deficient, one may then be able to offer the infant or patient a cue to start other learning processes or help him to eliminate errors and to progress in the right direction. If treatment strategies become more personalized to the needs of individual infants or patients, it may become more difficult to evaluate the effectiveness of any one treatment program. But if CDT were 10 times more efficient than conventional treatments, differences in effectiveness can be found. Proper treatment of the handicapped infant or patient consists of close co-operation between an active parent and an active therapist.

Learning for repair from the human development (phylogeny)

The strategy to repair the human CNS is the following. The impaired phase and frequency coordination of neuron firing is mainly improved when exercising on the special CDT device.

To compensate for the lost brain parts with their functions, the patient has to perform movements so that

other parts of the brain can take function over and hopefully some neural sub-networks at functionally important sites are made anew (plasticity). The simply adding of stem cells did not work. Automatisms and movements from the postnatal human development (ontogeny) were used for movement-based learning with the hope that genes will help in repair because of the importance of these functions. Such movements were creeping, crawling, up-righting, walking and running. Bear-walking and spider-walking (and old-learned movements) were also used. Jumping on springboard **(Figure 56)** (with an Eigen-frequency of approximately 1Hz) is used to repair premotor spinal oscillators (network oscillators), especially the α_3-motoneuron oscillators.

The learning process following CNS injury may be hampered by deficiencies of the neuronal structures on which they are dependent. Stimulating the patient to use uncommon modes of movements may enable him to achieve results which he cannot achieve spontaneously or when recapitulate postnatal development (ontogeny). Uncommon modes of movements may be related to the development of the embryo (phylogeny). Also, those movements have to be considered for repair which ancestors back till to the fish used.

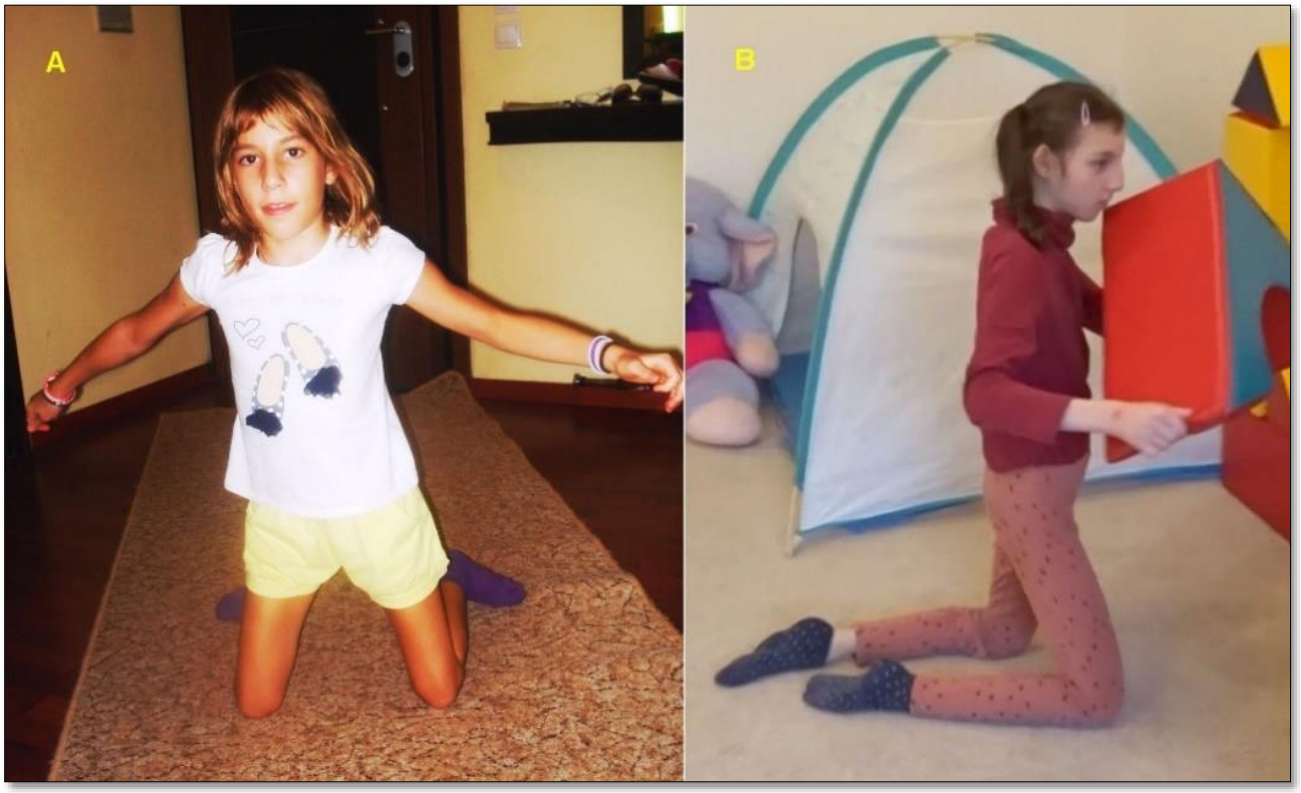

Figure 62. Patient with an incomplete spinal cord injury (A) and with a genetic disease (5p-) during walking on knees (B).

The first step into taking movements from phylogeny is the use of the stepping automatism, which is operational already before birth. The patient Benjamin suffered a severe brain injury in a car accident when he was 9.5 years old. He re-learned to walk **(Figure 63)** and run. But still the performance of the left arm and leg were poor. In **Figure 63** it can be seen that when Benjamin was walking with the Author in interpersonal coordination, the left hand was in spastic position. One year later the left hand was still spastic (and the left knee overstretched) during running. Further 15 years later, the left hand was still spastic during running in spite of therapy. Hand functions are difficult to repair because they are activated by very complex networks and complex networks are difficult to repair. But when Benjamin strongly lifted the knee during walking, the walking performance of the left foot improved strongly and the spasticity of the left hand reduced **(Figure 64A)**. When he was jumping against a step **(Figure 64B)**, the performance of jumping in anti-phase improved and the spasticity of the hand reduced. This higher lifting of the knees seemed to have improved the walking and jumping performance. The activation of the stepping automatism by lifting the knees strongly during training may therefore be useful to reduce the deficiencies of the neuronal structures and improve the pattern performance if the patient is able to induce the stepping automatism. The stepping automatism helps to repair, because this automatism is mainly located in the

neuronal networks of the spinal cord (intumescentia lumbosacralis) which are not damaged in brain injury.

Figure 63. The Author walking in interpersonal coordination with the 10-year-old patient Benjamin (severe brain injury). Note the spastic position of the left hand.

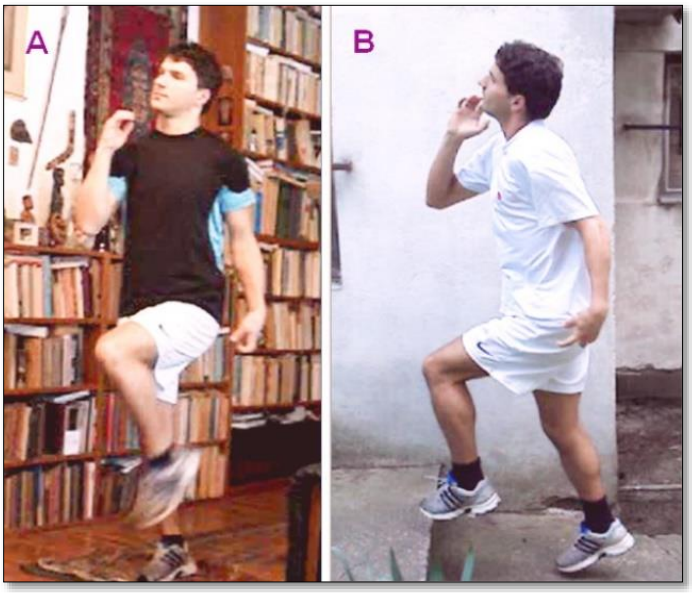

Figure 64. Walking (A) and jumping (B) of the 26-year-old patient Benjamin (severe brain injury). Note the only minor spasticity of the left hand (A) when lifting strongly the knees to activate the stepping automatism. Also, when jumping against a step the spasticity of the left hand is reduced.

In incomplete spinal cord injury, the use of the stepping automatism may also be helpful because most repairs are achieved by a functional reorganization of the brain. The patient Nefeli with an incomplete spinal cord injury at the level of Th10 was not able to activate the stepping automatism in the intumescentia lumbosacralis because of missing strength of the flexors. Even during walking with

sticks, she was not able to lift the knees and stimulate the stepping automatism **(Figure 65)**.

Figure 65. Nefeli with an incomplete spinal cord injury Th10 cannot lift the knees during supported walking to activate the stepping automatism.

But, on the other hand, Nefeli was able to activate the movement pattern salamander-walking (salamander-crawling) **(Figure 67)**. This salamander-walking **(Figure 66)** may be a pattern from phylogeny which helps to repair the CNS. How much such salamander-walking is helpful has to be seen? This movement pattern includes the trot gait crawling combined with a bending of the trunk and will be anyway helpful to reduce the scoliosis which was caused by the spinal cord injury. As can be seen from **Figure 67**, Nefeli can bend the trunk well to one side **(Figure 67A)** but only little to the other side **(Figure 67B)** because of the scoliosis and spasticity. Emphasizing the bending to the difficult side will reduce the scoliosis. A more efficient reduction of the scoliosis will be achieved when exercising the trunk rotation on the special CDT device in the lying position.

Figure 66. Moving of the salamander (Salamander-walking)

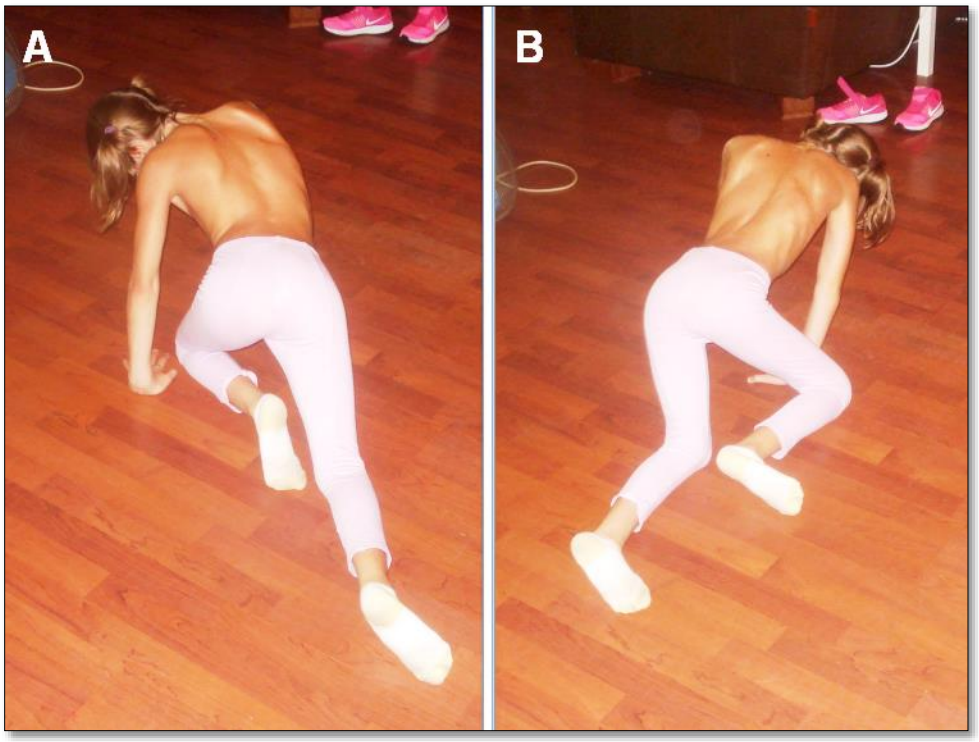

Figure 67. Salamander-walking (salamander-crawling) of the 10-year-old Nefeli with a spinal cord injury (Th10). In B the bending is disturbed because of the scoliosis and spasticity.

But why is it also important to look for repair movements which originate in phylogeny? First, anyway further movements are needed to find and repair the deficiencies of neuronal structures in different injuries. Second, it seems difficult to repair functions when old CNS structures, including the spinal cord, are injured and contribute to complex pathologic movement patterns. If, for example, the basal ganglia or the thalamus are damaged, a repair is difficult to achieve by movement-based learning. But maybe if movements of animals of the phylogeny are trained, we may reach more efficiently the injured old brain structures for repair. Gene expression changes may be activated then for further repair of the deficient neural structures.

Tiktaalik is a lobe-finned fish from the late Devonian period, about 375 million years ago, having may features akin to those of four-legged animals (tetrapods) **(Figures 68,69)** [100-102]. Tiktaalik has a possibility of being a representative of the evolutionary transition from fish to amphibians. It and similar animals **(Figure 69)** may

possibly be the common ancestors of amphibians, reptiles, birds, and mammals. Tiktaalik was gaining structures that could allow it to support itself on solid ground and breathe air, a key intermediate step in the transformation of the skull that accompanied the shift to life on land by our distant ancestors.

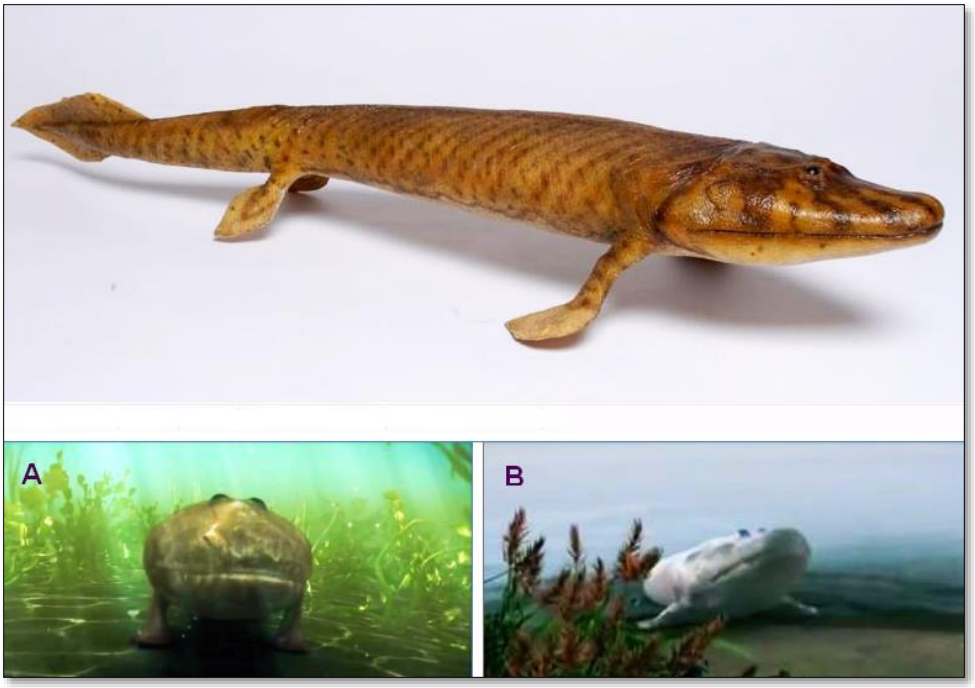

Figure 68. *Tiktaalik roseae*. Possible movements in shallow water (A) and when coming out of water (B).

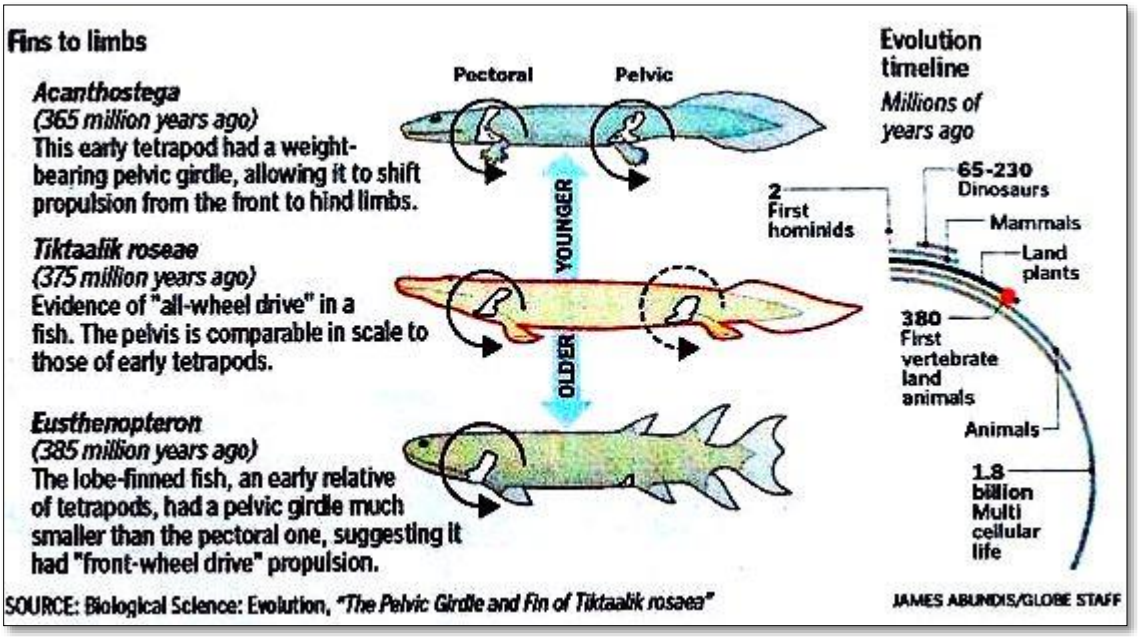

Figure 69. Evolutionary transition from fish to tetrapods.

The front fin was clearly weight bearing, being attached to a massive shoulder with expanded scapular and coracoid elements and attached to the body armor, large muscle facets, suggesting that the fin was both muscular and had the ability to flex like a wrist joint. The robust ribcage of Tiktaalik would have helped support the animal's body any time it ventured outside a fully aquatic habitat.

Tiktaalik also lacked a characteristic that most fishes have bony plates in the gill area that restrict lateral head movement. This makes Tiktaalik the earliest known fish to have neck, with the pectoral girdle separate from the scull. Neck movement can be trained, when exercising on the special CDT device in recumbent position with trunk rotation **(Figure 70)**.

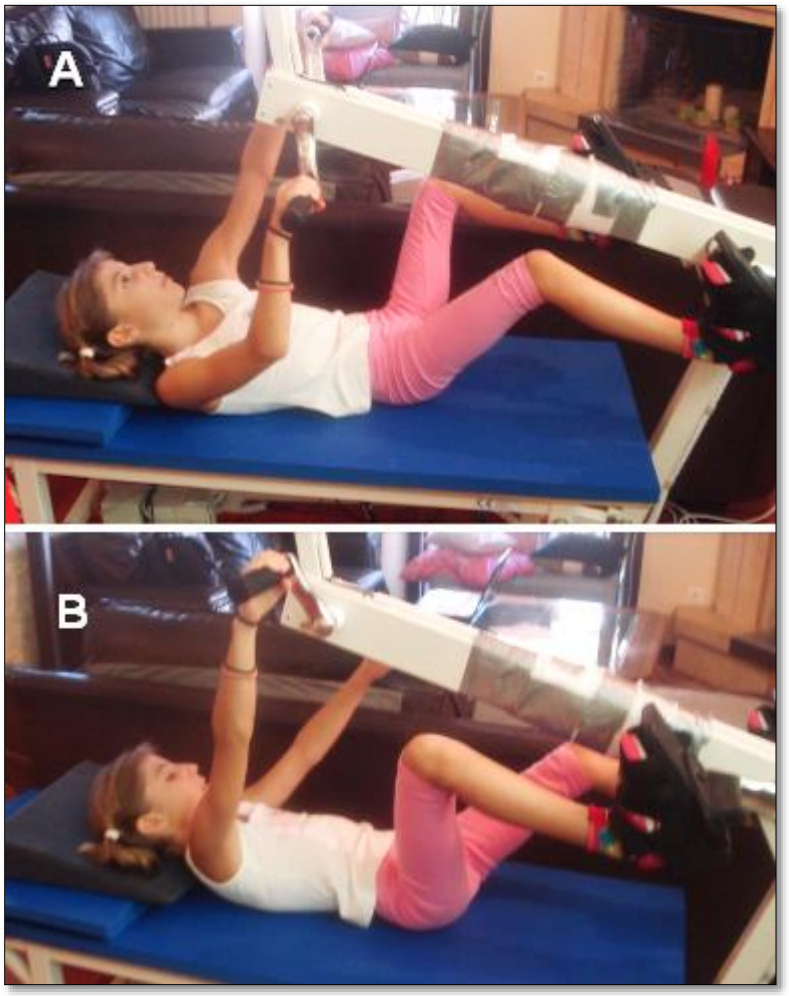

Figure 70. Training of neck, trunk and pelvis control of a patient with SCI (Th10) (Nefeli) during exercising trunk rotational movements on the special CDT device in the lying position. Due to the coordination changes of arms and legs between pace and trot gait all vertebra segments are trained.

Tiktaalik generally had the characteristic of a lobe-finned fish, but with front fins featuring arm-like skeletal structures more akin to those of a crocodile, including a shoulder, elbow, and wrist.

The skeleton of Tiktaalik indicates that it could support its body under the force of gravity whether in shallow water or on land **(Figure 68)**. The animal's pelvic girdle was strongly built, indicating that the animal could have used them for moving in shallow water and across mudflats. The important pelvis control can be trained on the special CDT device by rotating the trunk in the lying position **(Figure 70)** and during creeping **(Figure 51)**. Pelvis, trunk and neck control is necessary for many movements and positions especially during sitting, standing, walking and running.

One of the first new land movement of Tiktaalik **(Figure 71D)** may show similarity to the push-up movement (in German "Liegestütze") **(Figure 71E)**. Therefore, the lift-up movement should be included in the program of CDT. Also, the baby is using the push-up during the developmental course of its nervous system **(Figure 71F)**. Possibly the push-up movement activates key genes for the repair of finger, hand and arm functions especially in cervical spinal cord injury C5/6. Creeping, crawling and trunk rotational movements show similarity to the walking of the salamander **(Figures 66,67)** or similar animals and should be trained by the patient, if possible.

Trunk stability and pelvis control have anyway to be trained, because they are a prerequisite for walking and other movements.

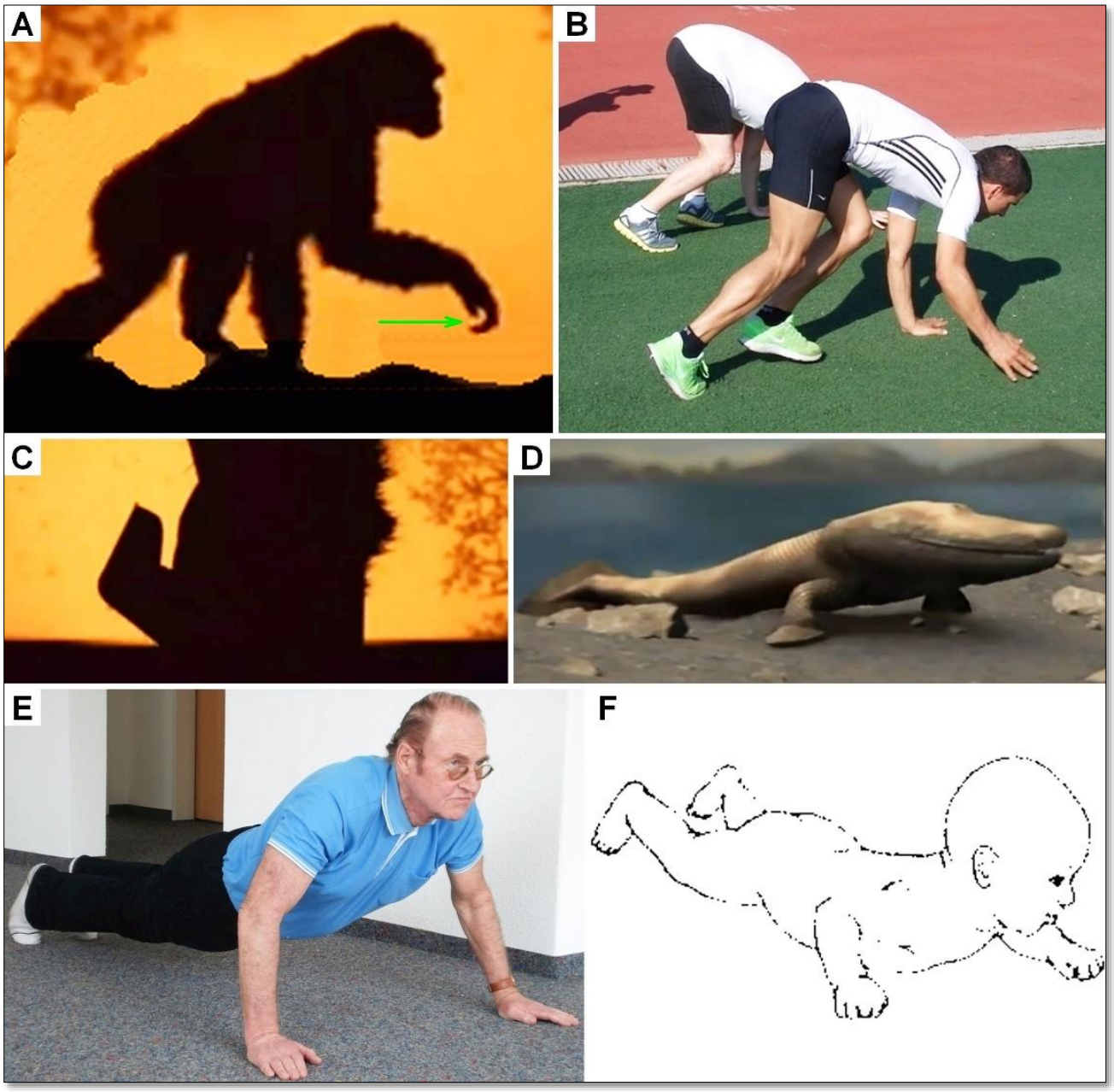

Figure 71. A. Four limb walking of the monkey; note, the palm of the hand is not touching the ground. B. Bear-walking of patients with brain injuries. C. Only the fingers and finger bones of the hands of the monkey are touching the ground. D. Tiktaalik (phylogeny between fish and Ichthyostega): the fish which is leaving the sea. Its movement on land bears similarity to push-up. E,F. Author and baby during push-up.

The Acanthostega appeared in the late Devonian period about 365 million years ago **(Figure 69)** and was also anatomically intermediate between lobe-finned fishes and those that were fully capable of coming onto land. It was among the first vertebrate animals to have recognizable limbs **(Figure 72)**. This early tetrapod had a weight-bearing pelvic girdle, allowing to shift propulsion from the front to the hind limbs. Young infants during ontogeny and patients may use this pattern for forward movement **(Figure 73)**.

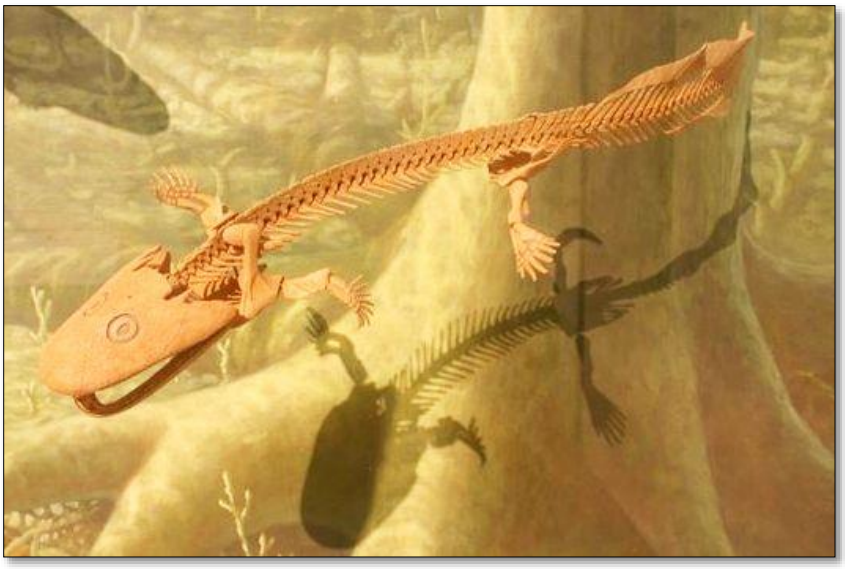

Figure 72. Acanthostega gunnari skeleton reconstruction. This tetrapod appeared about 365 million years ago.

Figure 73. Propulsion forward movement from the front to the hind limbs, performed by a patient with an incomplete spinal cord injury Th10 (Nefeli).

Performing gene analyses during movement-based learning may show whether really key genes are activated for CNS repair. For anti-cancer treatment, movement-based learning is beneficial because it seems that tumor-suppressor genes can be activated by exercise [22,102]. However, it has to be realized that with maturing of the CNS the strength of repair reduces and in animals like frog or salamander the power of repair is much higher than in humans. How the regenerative capacity was in Tiktaalik, Acanthostega or similar animals is unclear, but probably high.

The bear-walking **(Figure 71B)** is also an interesting movement with respect to the movement-induced afferent input. During coordinated arm and leg movement, the palm of the hand is touching the ground in difference to the four-limb walking of the monkey **(Figure 71A, C)**. In the monkey the dorsal fingers **(Figure 71A)** and finger bones **(Figure 71C)** are touching the ground during the four-limb movement. From brain-injured patients it is known that the input from the palm of the hand is important, in addition to the input from the soles of the feet, to reduce spasticity and generate a more physiologic movement pattern. The four-limb movement of the monkey, however, is no bear-walking and is not of interest for a repair of the human CNS.

Repair of CNS symmetry

The spider-walking **(Figure 74)** is also beneficial for CNS repair, because during arm and leg movement the sole of the foot and the palm of the hand get physiologic touch and joint induced afferent input. This coordinated movement has, of course, nothing to do with movement of a real spider. It is somehow the opposite movement of bear-walking **(Figures 71B)** with respect to symmetry. The symmetry of the injured CNS has also to be repaired by training the symmetry partner of a movement. Exercising on the special CDT device and crawling have to be performed in the forward and backward direction. The training of the backward walking, especially in interpersonal coordination, is in addition to forward walking important for improving the forward walking in stroke patients by learning transfer. A few years after stroke the poor forward walking of the patients becomes an old-learned movement, which is difficult to change. Whereas the backward walking, which has not been not used after the stroke, will improve the forward walking.

Figure 74. Trot gait spider walking on treadmill.

Recapitulation of development with respect to the repair of the development and improving CNS neural network functioning

Ontogeny and Phylogeny explores the relationship between embryonic development (ontogeny) and biological evolution (phylogeny) [103]. However, the development (ontogeny) of the brain has not only to be considered with respect to phylogenetic aspects. The development of the complexity of CNS organization and the connectivity of neural networks during maturing have also to be considered.

In the healthy new-born the stepping automatism is operational in the forward direction and can easily be induced by the heal strike **(Figure 61A,B)**. Later on, the infant learns to walk by getting the stepping automatism under supra-spinal control **(Figure 61C,D)**. The walking becomes first operational in the forward direction. Following complete or rather complete spinal cord injury in the adult patient, the stepping automatism re-appears and can be induced during supported walking. However, in difference to the development, the stepping automatism is operational in the forward and backward direction. The stimulation of the stepping automatism in the forward and backward direction during supported treadmill walking **(Figure 75)** is used for the repair of the spinal cord to get the stepping automatism under supra-spinal control, that means to change the stepping automatism into walking.

Figure 75. Supported treadmill walking in the forward and backward direction of a patient with a cervical spinal cord injury. The Author supports the walking on the right and a sport student on the left. During the supported walking, the stepping automatism could be induced in the forward and backward direction, when the patient or treadmill was turned. The stepping automatism was induced by heal strike or bumping the forefoot.

The difference between postnatal development and repair in adult patients stems similarity to problems of the evolution and the mechanics of recapitulation. If the evolutionary change occurs by the successive addition of stages to the end of an unaltered, ancestral ontogeny, then the length of an ancestral ontogeny must be continuously shortened during the subsequent evolution of its lineage.

Modes of locomotion revealed from CNS functioning, the skeleton of fish and tetrapod fossils and track ways

The evolution of tetrapods from sarcopterygian fish is one of the major transformations in the history of life and involved numerous structural and functional innovations, including new modes of locomotion, respiration and hearing. A landmark event in vertebrate history is the transformation of fish fins into tetrapod limbs. Limb skeletons differ from those of fins mainly by the presence of bones that comprise mobile wrists, ankles and digits. The fin of Tiktaalik was capable of a range of postures, including a limb-like substrate-supported stance in which the shoulder and elbow were flexed and the distal skeleton extended **(Figure 71D)**. The origin of limbs probably involved the elaboration and proliferation of features already present in the fins of fish such as Tiktaalik [100-102].

Many scientists regard Tiktaalik as the crucial animal between fish and the first tetrapods. But numerous track ways seem to show that first tetrapods appeared long before Tiktaalik **(Figure 76)**. Track ways were reflecting quadrupedal gait and diagonal walk. A model of Tiktaalik's skeleton could also produce a print much like the one published **(Figure 76)** if it's mushed into sand. Different consistencies or angles could produce an even closer match. There is nothing in Tiktaalik's described anatomy that suggests it didn't have a stride.

With respect to a repair of the human CNS by movement-based learning it is unimportant when tetrapods appeared. Important is whether there are movements which can repair old brain structures more efficiently. When a patient **(Figure 77)** or healthy person moves at beach, different track ways can be mashed into the sand, depending on what movement pattern is performed. The patient Nefeli can creep, crawl, salamander-crawl, bear walk, spider-walk, walk and hopefully can run in the future and can mush into sand many very different tracks ways. The movement pattern of **Figure 76** is the here named salamander-walking **(Figures 66 & 67)**. Crawling in pace or trot gait in the forward or backward direction can generate already many different track ways. What movements a nervous system can generate we only know when the nervous system is available and we can measure it up with basic methods.

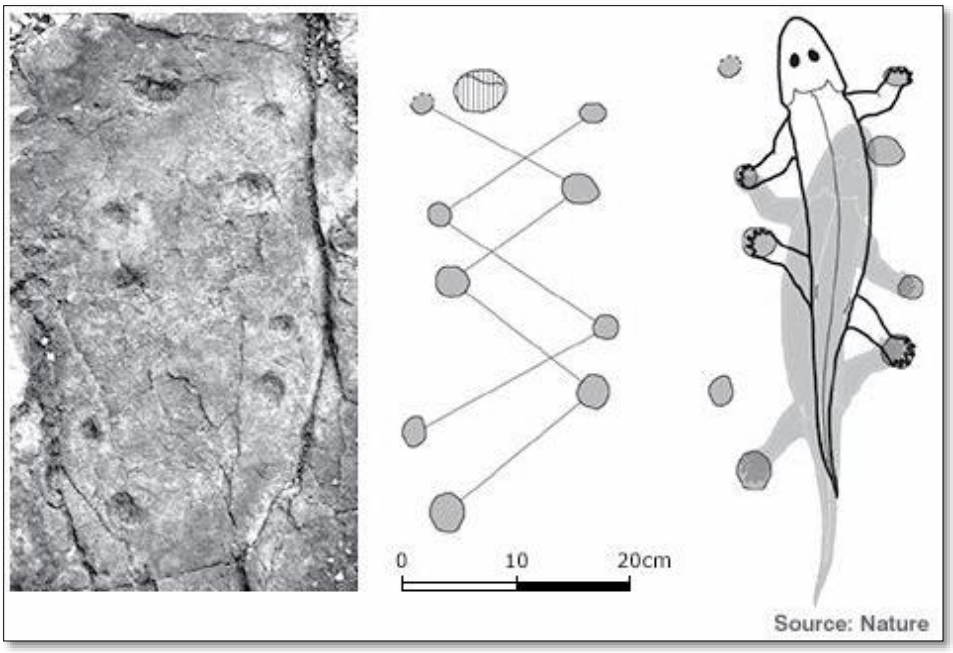

Figure 76. Footprints of tetrapods.

Figure 77. Track way of crawling of a patient with incomplete SCI Th10.

The cerebral palsy girl Sophie was not able to creep. When she learned to exercise by herself on the special CDT device, she suddenly could creep with quite a good performance **(Figure 51)**. Obviously, the creeping is an automatism. Interesting is, why does the pelvis rotate during the creeping movement? Is there an animal with a similar moving pattern? One possibility is that rotational movements occurred already in the Tiktaalik, Acanthostega or similar animals. Tiktaalik may have moved symmetrical with the front fins **(Figure 78A, B),** moved alternately with one front fin **(Figure 79A, B)** or moved with front and hind fins at different patterns. A repair of trunk stability is necessary in most CNS injuries. But especially in spinal cord injuries between the intumescentia cervicalis and lumbosacralis (thoracic SCI), the repair/improvement of the trunk stability is important. The possible different trunk movements of Tiktaalik or similar animals may contribute to the repair of the trunk.

The patient Nefeli with the incomplete spinal cord injury at Th10 could simulate with the arms the symmetrical front fin movements of Tiktaalik **(Figure 78C, D)** and also the alternating fin movements **(Figure 79C, D)** and trained in this way trunk stability. Still these movements are not suitable for trunk stability repair, because firstly, the patients do not like that movement, secondly, the movement is not very integrative and thirdly arm and leg movements have to be integrated in the movement to activate neural networks across the injury site. The creeping **(Figure 51)**, the propulsion from the arms to the legs (hopping, **Figure 73**) and the salamander crawling **(Figure 67)** are more suitable for the repair of spinal cord and brain injuries. May be, also Tiktaalik, Acanthostega or similar animals used these movements for locomotion.

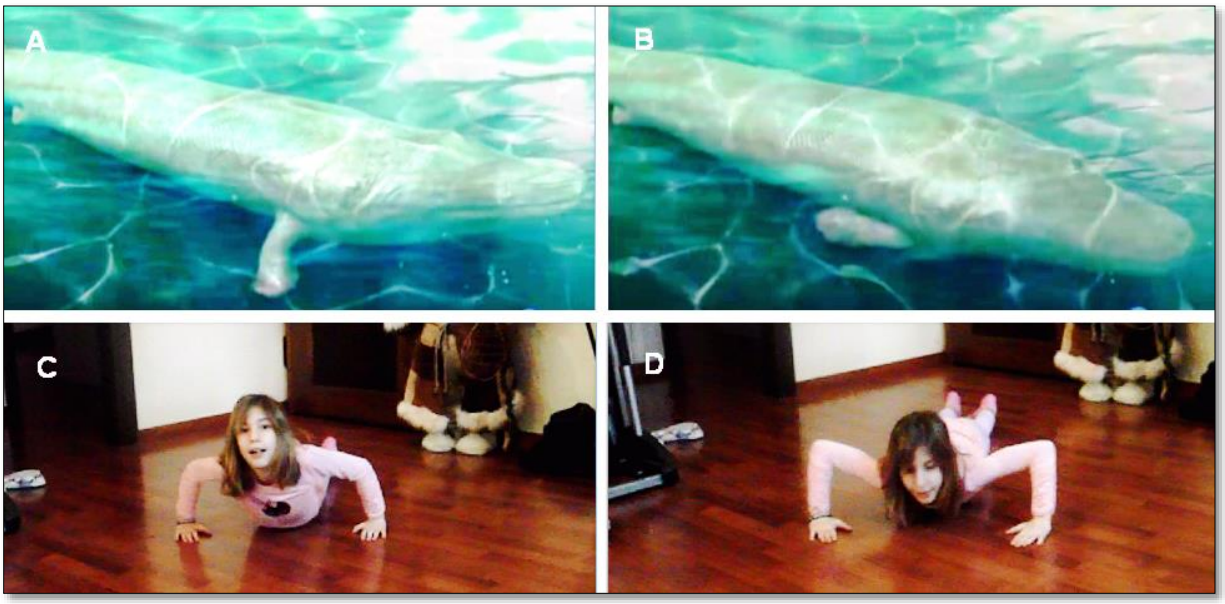

Figure 78. Possible symmetrical front limb movement of Tiktaalik (A, B), simulated for repair by the 10-year-old Nefeli with an incomplete spinal cord injury at the level of Th10.

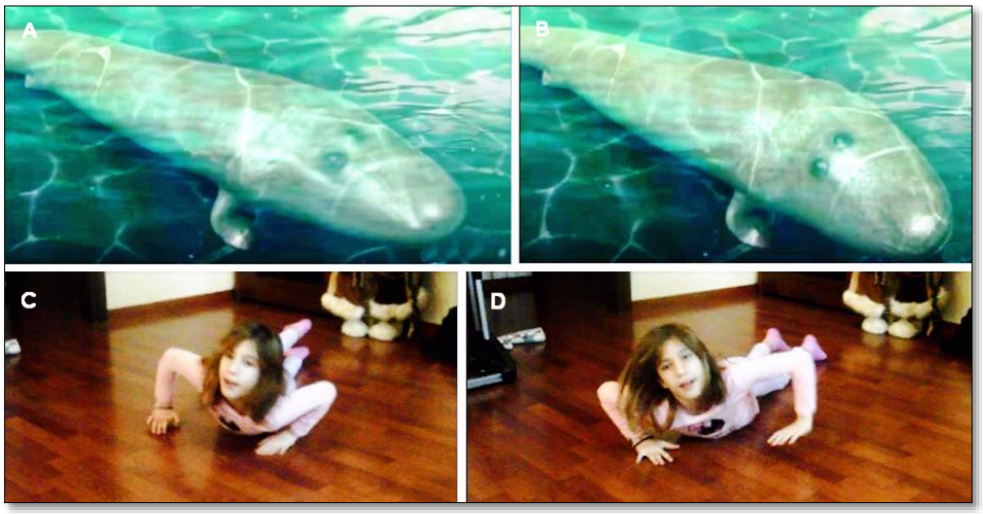

Figure 79. A, B. Possible rotational body movement of Tiktaalik, caused by alternately using one front limb for forward locomotion. C, D. This front limb movement is simulated by a patient with a spinal cord injury by using alternately the right and left arm.

In children with cerebral palsy, the performance of movements is often very pathologic. One gets the impression that there must be something pathologic with bones and tendons. But sometimes it can happen that for a short time the patient can walk quite normal, which indicates that the main pathology originates in the nervous

system. Only if the nervous system is not repaired in time, tendons and bones start to change. Treatment has therefore to be administered as early as possible; in diagnosed cerebral palsy after birth.

With respect to what different movement patterns distant ancestors could perform we need to analyze the functions of their nervous systems. Since movement patterns are influenced by the movement-induced afferent input, the environment needs also to be included in the considerations. Foot prints and even skeletons are not sufficient to know what different movements such animal could perform and learn.

Movement-based learning, accomplished by CDT, is successful in repairing the CNS through functional reorganization. However, in severe brain and spinal cord injuries (SCI), structural repair is also required, including the building of new neurons from stem cells. It was shown that new motoneurons could be built in SCI, but only to a very limited extent [94]. Cell physiology and genetics, especially epigenetics, have to be related to movement-based learning to further increase the functional and structural repair of the human CNS.

Genetic disease repair by learning and problem solving through error-elimination

Repair depends on learning and memory formation, mediated or supported by epigenetic mechanisms. Epigenetics is the interplay between genes and the environment resulting in phenotype and epigenetic landscape.

In genetic disease repair there are two problems. First, the malformed CNS (and body) has to be repaired and second, the pathologic development, caused by gene deletion, has to be made physiologic. But can the gene expression be changed in the way by the epigenome that other parts of the genome can take functions over from the lost piece of the chromosome, or can the therapy only repair continuously the gene defect malformed CNS and body?

But if there is genetic plasticity for CNS (and body) repair and repair of the pathologic development, the question is what trained movements can repair the CNS and what movements can induce genetic plasticity for the repair of the pathologic development. The standard movements of CDT, being successful in many diseases [1-23,27-30], will probably be able to partly repair the malformed CNS, even if there is a piece of the genome (and epigenome) deleted. But what training movements are able to improve the pathologic development? Are the standard movements sufficient and if not, what additional movements have to be used? In the patient Anna of below, different kinds of movements from phylogeny and ontogenesis are used additional to hopefully repair the CNS and body.

The answer of how much genetic plasticity exists in human can only come from the successful repair of human patients. For sure it must be an optimal movement-based learning therapy like CDT for years. The patient Anna is a suitable patient to answer the question of genetic plasticity, because she has a clearly defined chromosome deletion, she is cooperative in spite of many deficits especially of the cognitive functions, the mother is fighting strongly for her daughter and there is an older heathy brother and a healthy younger sister for comparisons with the healthy.

Learning by problem-solving is a mean of repairing sub-networks which are necessary for functioning, learning and physiologic development. Ideally, the malformed CNS should be repaired and the pathologic development made physiologic through gene expression changes. Is there sufficient plasticity in the genome and epigenome, so that other parts of the chromosome 5 or other chromosomes can take genetic function over of the deleted piece of chromosome 5? If there is such genome plasticity, then for example finger, toes, larynx and heart would become physiologic with further growing/development.

By inducing different trial and error-elimination processes in subunits of the changing nervous system, optimal repair may be achieved. To teach the injured CNS to repair itself by trial-and-error elimination processes, the CNS has, in similarity to development, to recognize through CDT, which sub-networks, regulation units or sub-loops are not functioning properly or missing and to repair them by error-elimination. What degree of deprivation in any subsystem can be compensated by other systems is unclear? Unclear is further, how much movement-induced epigenetic modification can change gene expression for repair and healthy development. Are the different movement-based learning strategies in the 9.5-years-old Anna are capable of targeting the epigenome and altering gene expression so that other parts of the genome can take function and development over?

In genetic disease some parts of brain and body are malformed more than others and some parts are not malformed at all. Through CDT, the not malformed parts will try to become operational. Depending on the location, extent and type of malformation, it may happen that networks/parts which in themselves are normal cannot bring about physiologic movement or cognitive functions because some areas of the brain which are also necessary for the accomplishment of a particular pattern are deficient. A large repertoire of movements has to be trained to eliminate errors and built new network parts to repair the genetic disease.

In general, both malformed and healthy parts of the brain and body change over time through therapy and this leads

to increased complexity which has direct repercussions on the quality of the repair processes.

How much plasticity exists in gene expression with respect to the repair of genetic disease will be clarified in the patient Anna. Actually, the therapy should have started earlier, when Anna was one or two years old **(Figure 79E)** or even after birth to have a better chance of repair because there may exist critical levels of gene expression after postnatal periods. Even in the prenatal period, the mother could have exercised on the special CDT device in the recumbent or standing position **(Figures 39,53)** to avoid also stress incontinence. Physicians did not inform the mother about the existence of CDT.

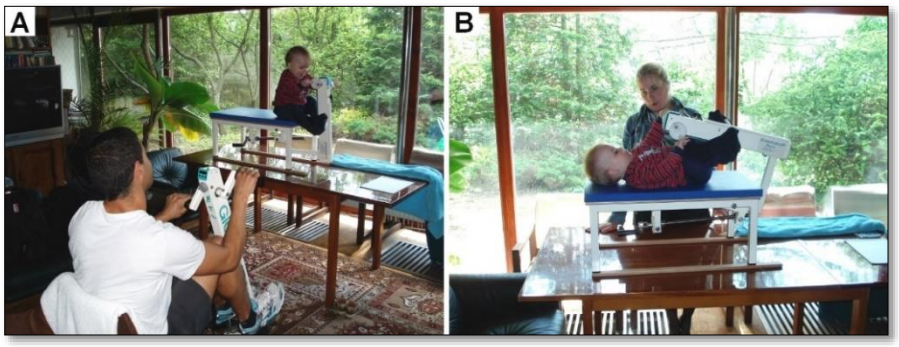

Figure 79E. Special CDT device for young infants and baby's including premature born ones. Age range of the device 0 to 3 years. Movements can be performed in the sitting (A) and lying position (B). The 18 months old healthy boy is already quite big for the device.

RESULTS

Case report of the patient Anna with cri-du-chat syndrome before optimal Coordination Dynamics Therapy (CDT) was started at an age of 9.5 years

Development of Anna with a 5p- chromosome deletion before optimal CDT was started

Anna was born in 2013 (26.3.) by a caesarian section. She was cat-like crying (Cri du Chat syndrome (CdCS)) and did not breath. By reanimation she started to breath. The physicians believed that no brain damage occurred through hypoxia. The reflexes and automatisms at birth were normal including the stepping automatism **(Figure 61A,B)**. At an age of 0.5 years a chromosome test (Karyotype analysis) was performed and a CdCS diagnosed **(Figures 80 & 81)**. This genetic disease results from a deletion of variable size occurring on the short arm of chromosome 5 (5p-).

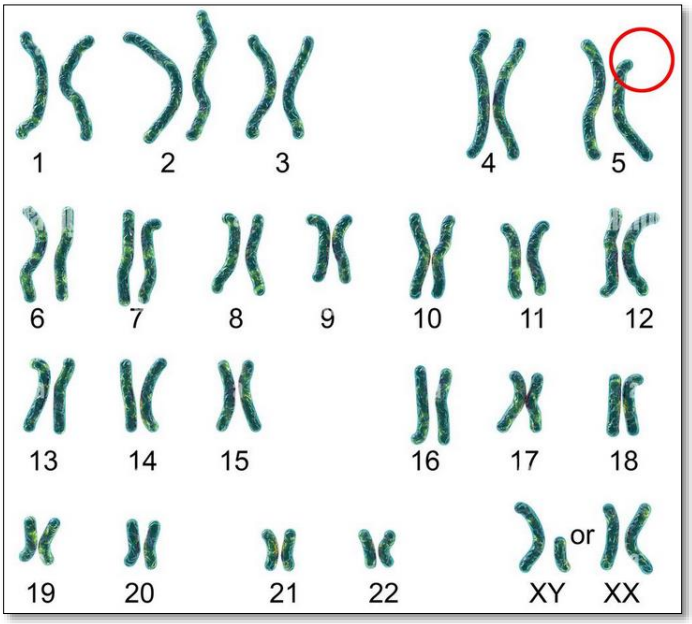

Figure 80. A Karyogram with the marked chromosome deletion.

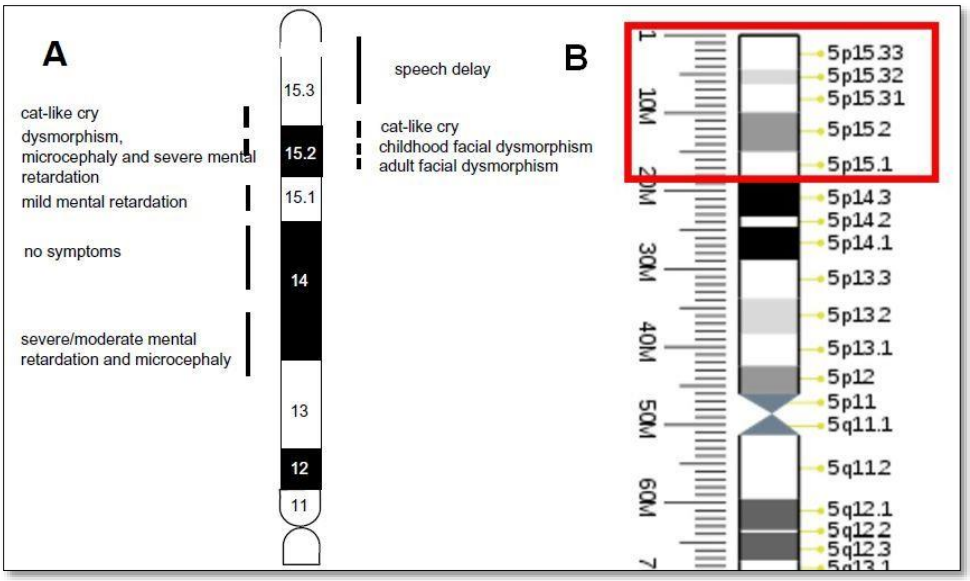

Figure 81. A. Phenotypic map of 5p. For further see [104]. B. The chromosome deletion of the patient Anna covers 5p15.1 till 5p15.33 as marked by the red box.

The actual diagnosis is shown in **Figure 81**: cat-like cry, dysmorphism, microcephaly, severe mental retardation and speech delay. There is no specific therapy for CdCS but early rehabilitative and educational interventions improve the prognosis and considerable progress has been made in the social adjustment of CdCS patients [104].

To improve the development and repair the brain malformation, the mother tried Bobath and Vojta, which did not help Anna. Later on, the exercising on the "Locomat" was tried **(Figure 82)**, which also did not bring progress. Anna was not able to walk.

Figure 82. Anna exercising on the Locomat. Since no progress was achieved, the exercising was stopped. The Locomat has no scientific basis and is approximate 20 times more expensive than the special CDT devices, which have a scientific basis.

At an age of 5 years, the mother tried low intensity coordination dynamics therapy (1.5 h per week) and Anna became able to walk a bit with poor performance (**Figure 83**, 5y 6m). The hands were hold upwards instead of moving them in coordination with the legs. With further low intensity CDT, the hands were held more downwards (**Figure 83**, 6y 1m). It is not clear whether the walking performance got better. Anyway, the CDT with 1.5 h per week helped a bit.

When comparing the walking performance of Anna with that of the 5-year-old younger sister Teresia, the tremendous lack of proper development of Anna becomes obvious. The healthy younger sister Teresia walked normally and Anna just managed to move on legs in the forward direction (**Figure 83**, 6y 1m).

Figure 83. Development of the patient Anna. Till to 5 years the patient could not walk without support (3y 7m). When low intensity CDT (1.5 h/week) was started, she became able to walk freely with poor performance (5y 6m). At an age of 6 years the hands were hold more downwards, but the leg movements were not much better (6y 1m). For comparison, the two-year-old healthy sister Teresia (2y) walked physiologically. y = year; m = months.

At an age of 9.5 years, the Author met Anna and the mother in the Slovak rehabilitation center "Harmony", when performing maintenance of the special CDT devices there. The mother was very much interested to get an efficient therapy for Anna and optimal Coordination Dynamics Therapy (CDT) was started with Anna. The 9.5-years.old Anna had at therapy start a healthy and clever 12-year-old brother (Teodor) and a healthy and clever 5-year-old sister (Teresia). When seeing the difference between Anna and her sister in motor, cognitive and social functions, the Author was getting depressed that the deleted piece of the chromosome 5 had such tremendous consequences on movements and cognitive functions. But since Anna was cooperative and has a nice character, she was/is a suitable child/patient to see whether fundamental progress in repair of genetic diseases is possible through CDT.

State of Anna when optimal CDT was started

Figure 84 shows the patient Anna during exercising on a special CDT device at the beginning of optimal CDT. Optimal CDT means, the therapy has to be efficient, intensive (aggressive) and long lasting. It took a few weeks of organization till 15 h therapy per week could be administered to her. The optimal therapy with 15 h per week was 10 times more intensive than the low intensity training with 1.5 h per week. But since already the low intensity training made Anna to walk with poor performance **(Figure 83)**, it can be expected that much more progress can be achieved with a 10 times more intensive therapy.

Figure 84. The 9.5-year-old patient Anna with a genetic disease (5p-) during exercising on a special coordination dynamics therapy device.

Anna had typical 5p- syndrome symptoms. Because of laryngomalacia, she had problems with breathing when becoming able to run or jump; she got also easily infections of the larynx. The cardiac defect was minimal. The mild ventricular septal defect should not cause problems during movement therapy. Fingers and toes had not the normal shape. The index finger and the second toe were too long, which can nicely be seen in a comparison with those of the healthy sister Teresia **(Figures 85 & 86)**.

Figure 85. Length of the fingers of the patient Anna with a 5p- syndrome in comparison to those of the healthy sister Teresia. The index finger of Anna is too long.

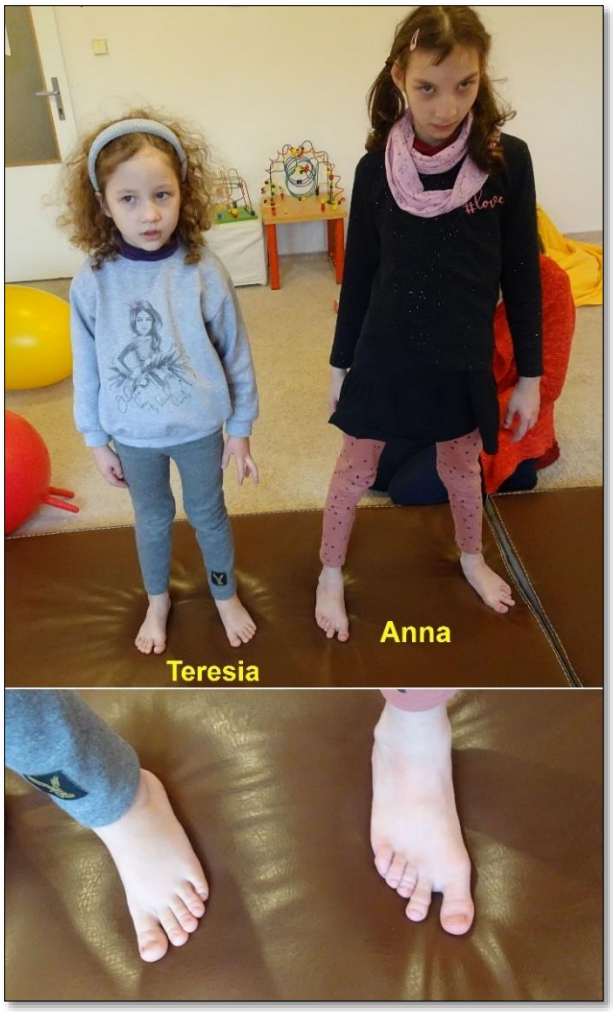

Figure 86. The toes of Anna in comparison to those of the healthy sister Teresia. The second toe is too long. Note, Annas legs are more apart during standing because of small balance problems.

The typical microcephaly is probably little, as can be seen when comparing the head of Anna with those of Annas mother **(Figure 87)**. An MRI was not available so far.

Figure 87. Comparison of the head of Anna (5p-) with those of the mother. No big difference can be seen to indicate severe microcephaly of Anna.

Anna had strange behaviors. She was addicted to babies. When she saw a baby, she was running to it. She needed a baby doll during therapy; otherwise, she would not be sufficient cooperative. Even when eating, there had to be a baby doll close to her.

At the beginning of optimal therapy, the patient Anna with the genetic disease could walk only with poor performance and had balance problems. She could not creep, but crawl in trot gate coordination with moderate performance. She could not crawl in pace gait coordination. Anna could not speak; her feelings were overemphasized and her cognitive functions very low. She needed the mother, but she did not listen to her. The mother estimated that her average developmental state was that of a 3-years-old girl. The 5-year-old healthy sister Teresia was much more developed than the 9.5-year-old Anna. During therapy, Anna was easily distracted from many things, which made it very difficult to stay for her in a certain pattern for longer times, even though she was cooperative. When the Author measured her coordination dynamics, he sometimes went with the computer to another room not to disturb the measurement.

Repair achieved within 6 weeks of rather optimal therapy

Balance training

Besides deficits in motor functions, Anna had balance problems, most likely caused by impaired motor patterns and a mild malformation of the cerebellum (below). Balance was trained and improved with many movements, but additionally with those shown in **Figure 88**. When sitting on the back of the Author or mother during their crawling, she trained balance and Author and mother could feel on the back her balance trials (A, B). When sitting on a ball during exercising on the special CDT device, she trained also balance (C). The mother could vary the balance difficulty by fixing more or less the ball with the right leg. When walking with the mother in the forest, the balance during walking on uneven ground was trained and improved (D). Before CDT was started, Anna could only move forward when supporting the upright movement with both hands like in **Figure 83** (3y 7m).

Training of walking and running

Walking and running improved, but Anna was not moving the arms in coordination with the legs **(Figure 89)**. The leg and foot performance patterns were physiologic and similar to the automatic stepping after birth **(Figure 61A, B)**. Normally, the stepping automatism is integrated later on into the developing walking pattern **(Figure 61)**.

Figure 88. Special balance training movements. Note in A that the patient is putting the legs around the trunk of the Author. When changing the crawling pattern from trot to pace gait enhances the difficulty of keeping balance.

Figure 89. Anna walked quite physiologically, but she did not move the arms in coordination with the legs.

But when walking with the mother (or the Author), one arm of Anna was pushed into the trot gait coordinated movement of the legs **(Figure 90)**. The not supported arm was not moving, but was downwards and not up. With supporting persons on both sides, both arms could be made moving. But the performance of such coordinated movement of three persons is very difficult.

Figure 90. Anna during walking with the mother. The mother pushes the right arm in coordination to the left leg of Anna during normal trot gait walking.

During running, what Anna liked very much, it was also tried to bring one arm into coordination with the movement of the legs **(Figure 91)**.

Figure 91. Author during running with the patient. He is bringing the left arm in coordinated movement with the right leg.

Free walking **(Figure 92)** and running became possible.

Figure 92. Free walking of Anna in the countryside.

Climbing staircases

Climbing staircases was difficult for the patient to learn. First, she succeeded to hold with both hands the rail. When becoming better, she managed to get up the staircases when holding only with one hand. Then the climbing staircases was trained and improved when the Author (or mother) supported her climbing by pushing one arm in coordinated movement with the legs. When the Author succeeded to bring Anna in a good climbing staircases pattern, she did not need to support the balance by touching the wall **(Figure 93)**. When the common staircase movement was not optimal, Anna had to touch the wall to keep balance. This means, climbing staircases is a learned pattern and the balance problem was mainly coming from a suboptimal pattern performance and cerebellum malformation. When the performed pattern was good, Anna could keep balance and when the pattern was poor, she needed balance support. The Author was counting the steps continuously in coordination to improve the rhythmicity. A running up the staircases was not possible so far. The Author tried it several times. The pattern of climbing staircases was still far from being optimal. What cannot be seen from the **Figure 93**, Anna stepped deep into the stairs, for safety reasons, and did not step onto the corners for getting a better rhythm input by stimulating the stepping automatism.

Figure 93. Anna during climbing staircases with the Author. When being able to bring Anna in a good rhythm, she did not need to touch the wall for keeping balance. A lot of concentration was needed, also for the patient. The Author was also counting in coordination with the stepping 1-2-3. Climbing in this way the staircases, Anna was not afraid and she liked it.

Jumping

Besides running, Anna liked very much the jumping, even though it was difficult for her. The jumping in phase was possible **(Figure 94)** and improved. The number of jumps in a series were counted to measure the progress of repair.

Figure 94. In phase jumping of Anna with the Author. As can be seen from her face, she liked it.

The jumping in rotation was so far not really possible **(Figure 95)**. The jumping in rotation is helpful for symmetry improvement and trunk muscle training to counteract scoliosis.

Figure 95. Anna trying to jump in rotation. Only little trunk rotation was achieved. Also, the legs are too much apart.

The jumping in anti-phase, which is the most difficult jumping pattern, was tried but not possible so far **(Figure 96)**.

Figure 96. Unsuccessful anti-phase by Anna. The Author was jumping in anti-phase, but Anna jumped in phase.

Crawling

At the beginning of optimal therapy, Anna could crawl in anti-phase, but the performance was moderate. With training, her trot gait crawling performance improved **(Figure 97)**.

Figure 97. Anna during crawling in anti-phase. The Author is crawling in interpersonal coordination to improve the performance of Annas movement. Such crawling in interpersonal coordination is difficult for the therapist. Often, he/she is losing the rhythm himself. Brain repair through interpersonal coordination is automatic and needs no effort by the patient. Only the trainer has to be in the field of vision of the patient.

Writing difference between the 9.5-years-old Anna and the 5-year-old sister Teresia

The Author got a gift from the 5-year-old sister Teresia (in Slovak Terezka) of Anna (Anicka). Terezka is thankful that the Author is trying to help her sister. It is beneficial that the healthy older brother and younger sister wanted also to help Anna. Even though it is good that all family members try to help Anna, but substantial progress, if possible, can only come from highly qualified treatment.

The difference of drawing and writing between Teresia and Anna was very large **(Figure 98)** and depressing for the Author again.

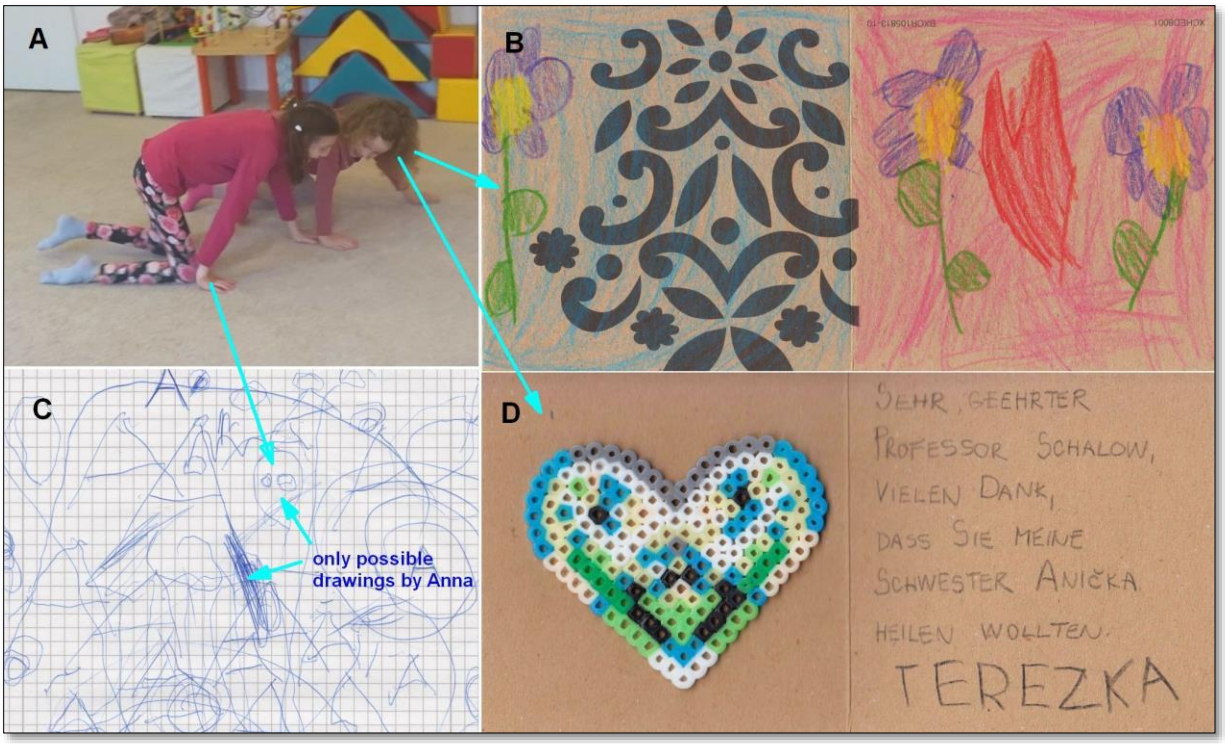

Figure 98. Drawing and writing difference between the 9.5-years-old Anna and the 5-year-old sister Teresia. Teresia was able to draw flowers and write letters, but Anna could only draw circles and not a single straight line to be able to write an A. In C Anna is performing repetitive lines, what is pathologic; the Author tried to stop her doing it.

Interesting is that Anna could not hold a pencil properly during development (**Figure 83** (3y 1m)) but at an age of 9.5 years she could hold the pencil physiologically (see below). The finger function patterns developed physiologically.

Playing

After 6 weeks of therapy, Anna became able to play a bit by herself **(Figure 99)**.

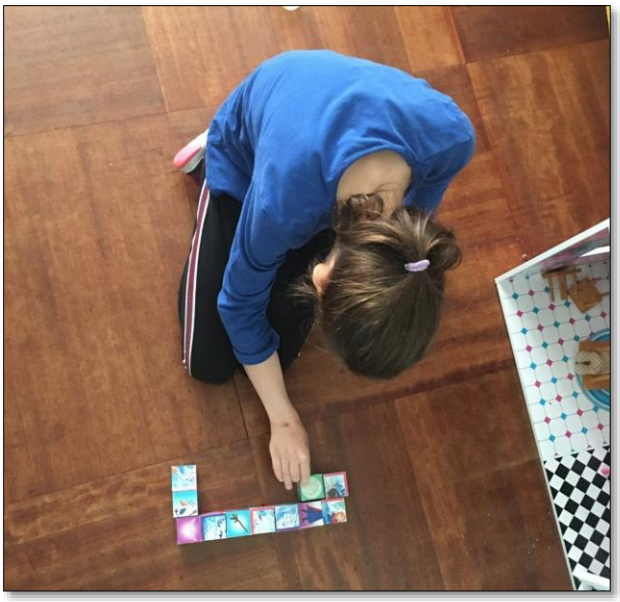

Figure 99. Anna starts to play also by herself.

Repair following 3 months of optimal CDT

Further improvement of walking, running and creeping

With continuing optimal CDT there was further substantial repair. Walking and running became better. On even ground there was no danger that she would fall. The movements seem to become more elegant **(Figure 100)**.

Figure 100. Running and walking of Anna (5p-). During running the arms moved a bit in coordination with the legs.

She learned to easily walk in stork step, jump with the sister and walk long distances on knees even on uneven ground **(Figure 101)**.

Figure 101. Anna during walking in the stork step pattern with the mother (A), jumping with the sister Teresia (B) and walking on knees on uneven ground (C).

With quite an effort Anna learned to creep **(Figure 102)**.
First the creeping was stepwise, but then continuously.

Figure 102. Anna during creeping.

Learning of push-up movement and robbing

The push-up movement was only partly successful, in spite of the big effort of the mother and Anna **(Figure 103)**. But it may be an important movement to improve ontogeny.

Figure 103. Annas mother helps Anna to train the push-up movement. In A the toes are in correct position, in B not.

Also, the learning of the possible robbing movement of Tiktaalik **(Figure 104A, B)** was not fully successful so far. The sister Teresia performed the movement pattern automatically when there was need for **(Figure 104E, F)**. Anna could not perform the pattern automatically and had to learn it. She was so far only partly successful **(Figure 104C, D)**.

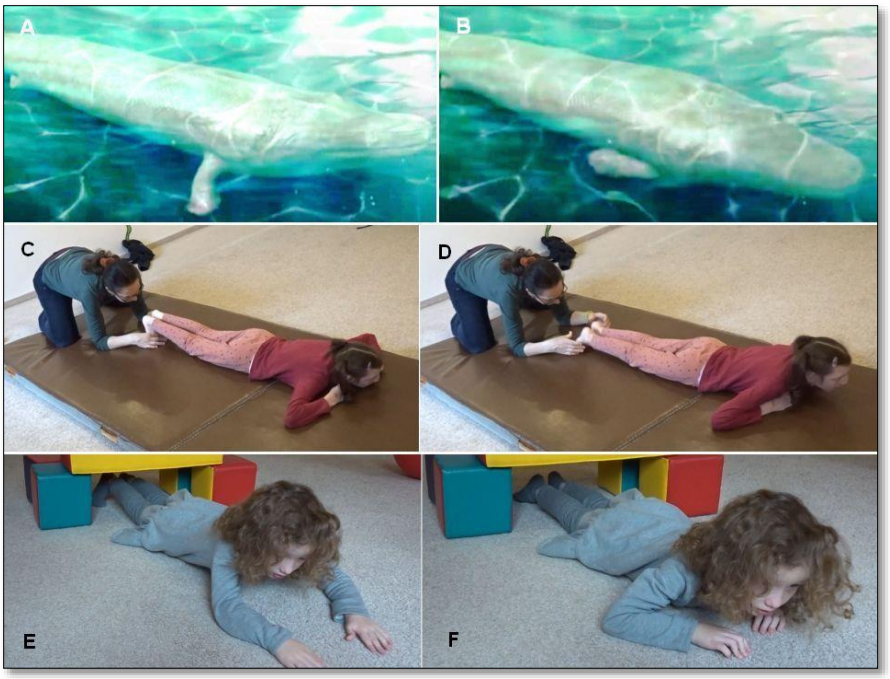

Figure 104. Robbing movement. A, B. Possible movement of Tiktaalik 375 Million years ago. E, F. The 5-year-old Teresia performed the robbing movement automatically. C, D. The 9.5-year-old Anna was only partly successful to learn this movement pattern so far (C, D).

Improvement of playing

But what about the hand functions. The too long index finger **(Figure 85)** caused no problems. She learned to eat properly, apart from the presence of a baby doll **(Figure 105)**. As was said before, Anna was baby-addicted.

Figure 105. Anna during eating with the left hand. The baby doll had to be there.

Anna learned and liked it, to put a baby doll clothes on. She could use her fingers nicely **(Figure 106)**.

Figure 106. Anna dressing a baby doll.

How excellent Anna learned to use hand and fingers can be seen from **Figure 107**. She became able to find in a game the corresponding color combination and put the game cards properly together. When thin cards are on the floor, it is not easy to pick them up. The too long index fingers were no problem. The fine control of hand and fingers became normal.

Figure 107. Anna manages to find the colored partner card and to put them together.

Improvement of cognitive functions

Most important of the treatment is the improvement of the cognitive functions. Anna learned to understand that she has to learn patterns to get better. When mother and Author succeeded that Anna managed a new movement pattern, they clapped the hands. When they forgot to clap hands, Anna did it. Clapping hands is anyway a good movement for nervous system repair, because the CNS gets exactly at the same time the input from the mechano-receptors of the skin **(Figure 18)** of the hands, which improve the symmetry and coordination of the neural networks.

So far Anna could not write and speak. The writing was trained in the way that the Author wrote with her together the capital "A" and then Anna should copy the "A" by herself **(Figure 108)**. This was not possible so far. But the writing trials improved **(Figures 98C,109)**. It seemed that Anna could not stop to draw a line to trace a short line. This missing drawing feature was may be hampered by a malformation of the cerebellum.

When the cerebellum is malformed or damaged, the patient has problems to stop a movement. The overswinging of the legs is shown in **Figure 51b** of the patient Sophie, with a cerebellum malformation, during creeping **(Figure 109)**.

Figure 108. The Author during drawing with the right hand of Anna an "A" (A). Then Anna should copy the "A" by herself (B). Note how nicely Anna can hold the pencil.

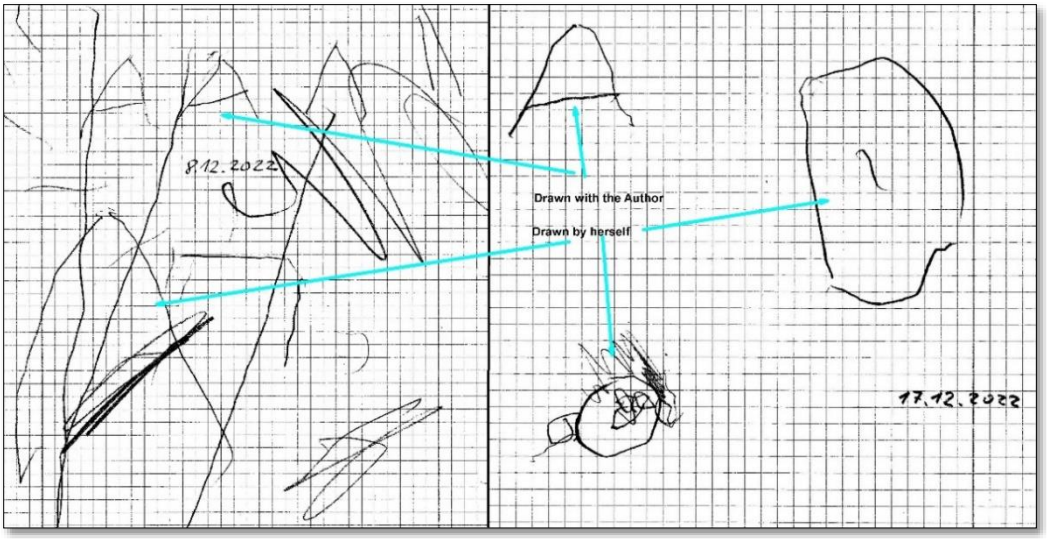

Figure 109. Drawing trials of the patient Anna. There is improvement from the 8.12. to the 17.12. Anna became able to stop drawing a line, even though the A is rudimental.

Variability of movement patterns performance was most likely present in the right and left hand. It is not clear whether Anna was right or left-handed. The connections to the higher mental functions seemed to be missing. The healthy younger sister Teresia was able to write TEREZKA **(Figure 98)**. Obviously, the higher mental functions have to be further repaired in Anna. With the writing it is tried to connect movement patterns to higher mental functions. In similarity to the saying "what was first, the hen or the egg", one may say "what was first, the movement or the intelligence"?

There is a similar situation in speech. After the three months of optimal therapy, Anna could only say mama, tata (papa) and baba (baby). As was diagnosed, the speech apparatus was working, but she could not speak. Anna was suffering on that. She wanted to speak, but it did not go. Her speech repertoire included only these three words, which was may be stored in the epigenome. When Annas higher mental functions improved, she could make understanding, even for the Author, what she wanted.

To repair the body and may be to make the development more physiologic, she had to explore the world. She had to 'discover' new motor and thinking possibilities. When she wanted to go around several houses, the Author went with her. When she wanted to go down the staircases backwards, even difficult for the Author, he did with her. Her memory and orientation became better. Anna was cooperative as long as the mother was close, best in her field of vision.

The progress in repair of the movements and cognitive function was obvious, but very far behind those of the younger healthy sister Teresia.

Now with the help of the continuously measured coordination dynamics, it will be tried to analyze, what could be wrong in the development of Annas CNS.

Coordination dynamics measurements

Figure 110 shows the measuring arrangement to record coordination dynamics. While Anna was turning, the mother was reading aloud from a book or shows her a video film to keep her in the turning pattern.

Figure 110. Layout of coordination dynamics measurements. The mother had to read aloud from a book (B) or show a video film on the smart phone while Anna was turning (A). Anna turns on a special CDT device type 1 (A) and type 2A (prototype) (B).

Figure 111 shows measurements at the beginning and end of these three months of optimal CDT. It can be seen that the coordination dynamics (arrhythmicity of turning) got better (smaller or smoother) with therapy. At the beginning of therapy, she got often stuck for the difficult intermediate coordination's between pace and trot gate and the arrhythmia of turning was large. At the end of the three months, she turned quite smoothly and did not get stuck for the difficult coordination's. She only stopped turning when she was distracted or she wanted to show something to the mother.

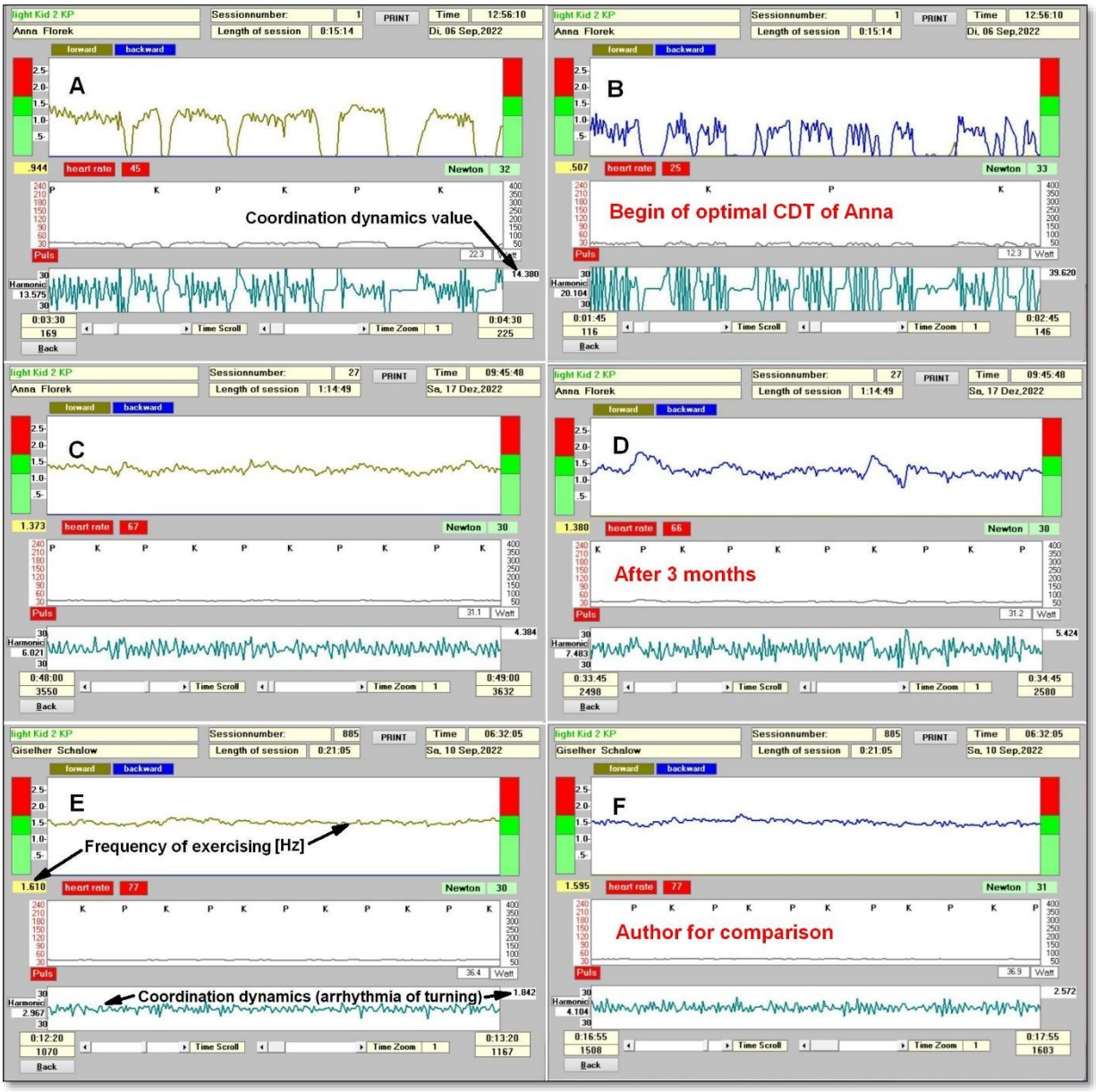

Figure 111. Coordination dynamics measurements of Anna at the beginning of optimal CDT (A, B) and after 3 months (C, D). For comparison, nearly ideal coordination dynamics of the Author (E, F). Left panel = forward exercising, right panel = backward exercising. P = pace gait; K = trot gait.

The repair progress of the nervous system can be seen more clearly when plotting the coordination dynamics values against ongoing therapy time and compare them with those of the healthy older brother and healthy younger sister **(Figure 112)**.

From **Figure 112A** it can be seen that that the low-load coordination dynamics values improved (reduced) strongly, whereas the values of the healthy brother and sister did not change much. Anna exercised on the special CDT device much more often than brother and sister, but their CNS worked physiologic. With respect to the coordination dynamics, Anna became as good as the brother and sister. The curve of value reduction is typical for brain repair. From the point of view of coordination dynamics, the curve of value reduction is an indication for ongoing brain repair.

This ongoing brain repair is supported by the transient reduction of the turning frequency **(Figure 112B)**. When during repair the neural networks re-organize, coordination dynamics values and turning frequency may get transiently worse, but improve again with ongoing therapy.

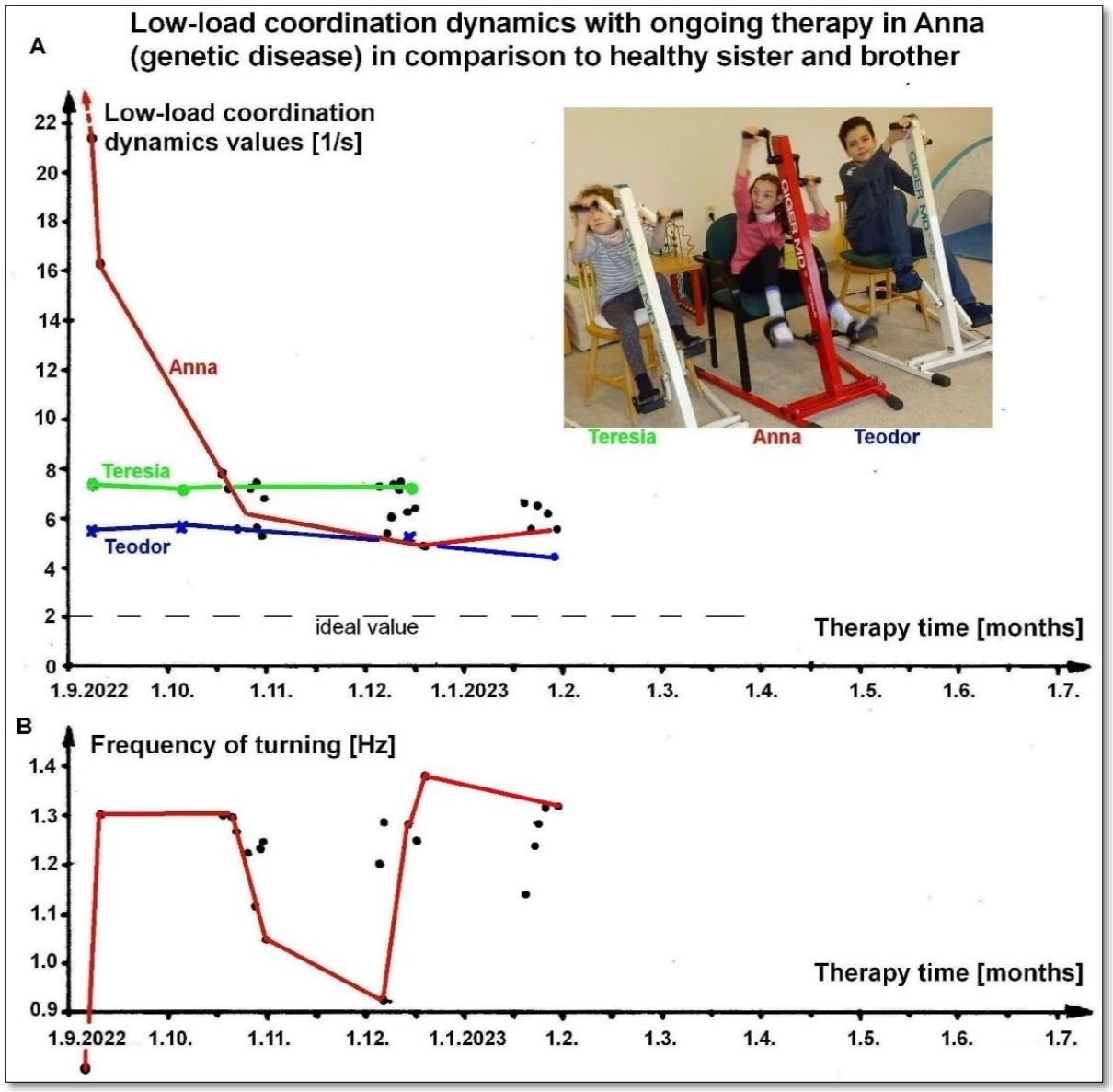

Figure 112. A. Improvement of the coordination dynamics values of Anna in comparison to those of sister and brother. B. Turning frequency of Anna.

The comparison with the healthy brother and sister helped to understand the progress of repair in Anna. But the comparison with healthy pupils further helped to understand Annas repair with respect to CNS repair and, may be, with respect to the repair of the pathologic development, caused by the lost piece of chromosome 5.

Figure 113 shows the average low-load coordination dynamics values for healthy pupils in the age range between 5 and 18 years for forward and backward exercising [1-3]. The CD values decrease with age, that means with on-going development. The frequency of exercising in the forward direction first increases strongly between 5 and 9 years of age and then deceases slowly **(Figure 114)**. This can be understood upon watching the pupils during exercising. The young children wanted to turn fast (sometimes they were even saying it) but they got stuck again and again at the difficult coordination's. The continuous exercising was hindered by the missing neural network maturation/complexity to be able to generate these changing movement patterns imposed by the device. Especially the complicated coordination patterns of arm and leg movements between pace and trot gait could not be sufficiently generated by their CNS neuronal networks. The network complexity and accuracy were not developed sufficiently in that developmental period.

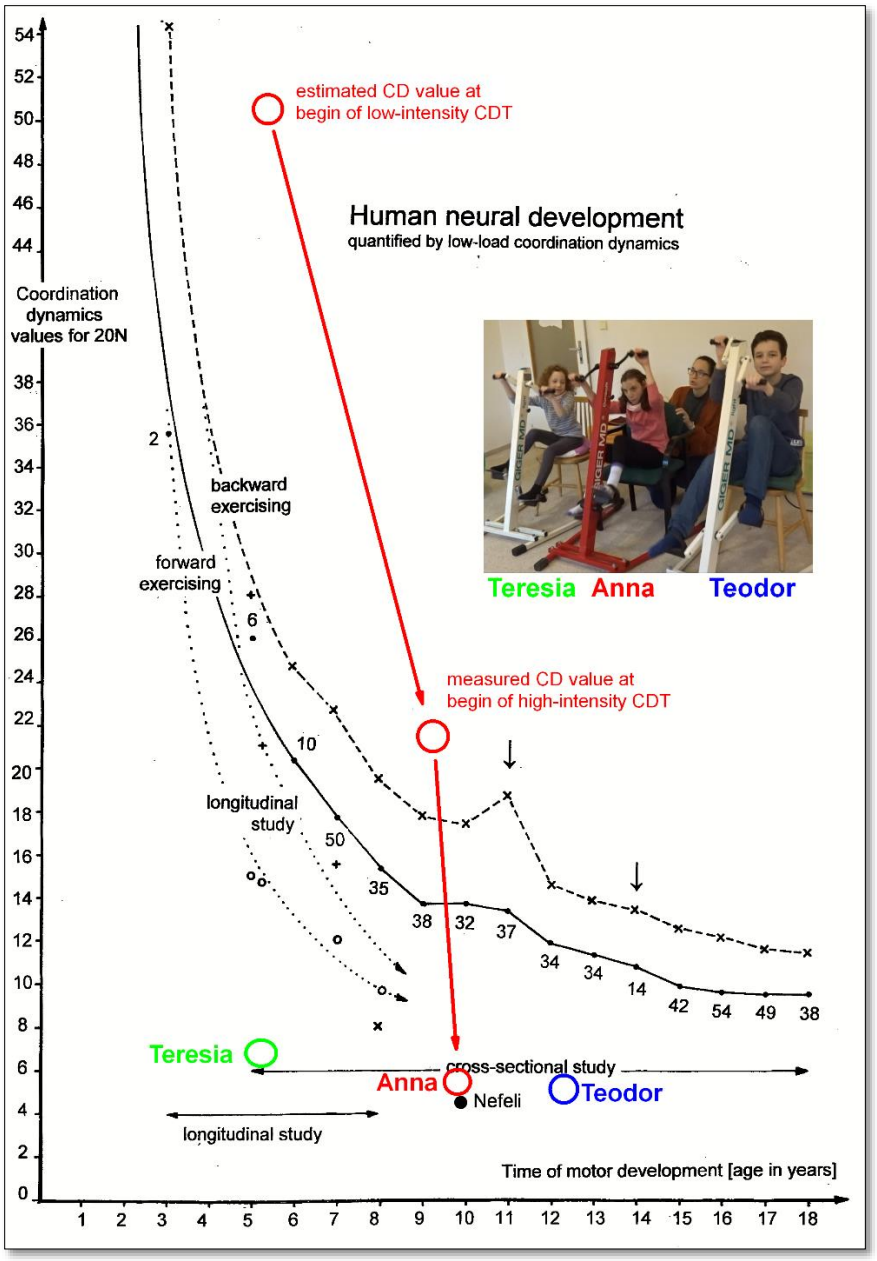

Figure 113. Coordination dynamics values of boys and girls (lumped together) to quantify human neural development. Note that the coordination dynamics values transiently increase at 11 years and that the group size (attached to the curve) is small at an age of 14 (puberty), as is indicated by arrows. Note further that the coordination dynamics (CD) values for backward exercising during the whole developmental period are worse (higher) and that in the longitudinal study (dotted lines) the CD values become smaller (better) than the average ones of the cross-sectional study due to the repeated assessment. Estimated and measured CD values of Anna, with a 5p- syndrome, during therapy and neural development are included. Note, according to the graph, a break-through in repair seems to come from the optimal therapy. Also, the values the healthy brother and sister are included.

The slow decrease of the exercising frequency with increasing age of healthy pupils, after the fast increase **(Figure 114)**, can also be understood. The high frequency of exercising was used by the CNS to improve its self-organization. The increased movement frequency improves the quality of performance because the kinetics are smoothening the movements and the improved movement-induced afferent input improves CNS organization by movement-based learning. With on-going maturing during development, this kind of movement-

based learning becomes less important and the frequency of exercising decreases. Fast moving can be observed in healthy children in everyday life. Generally, walking and running (especially when performed fast), jumping, and training balance seem to be necessary for a physiologic development of the nervous system.

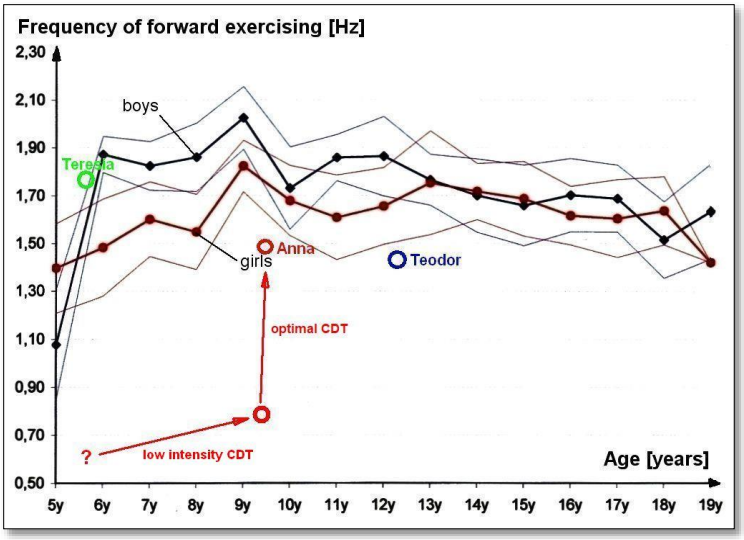

Figure 114. Frequency of exercising of healthy boys and girls in dependence on age when turning on a special CDT device ("■" are boys and "●" are girls). Note that the average group values are very similar; the standard deviations overlap strongly. Note further that the frequency of exercising is highest at an age of 9. The included frequency values of Anna indicate that she had problems to turn fast at the beginning of therapy.

The coordination dynamics values of Anna, Teresia and Teodor are related now to the average development of healthy pupils **(Figure 113)**. The healthy Teresia and Teodor had better coordination dynamics values (mean of forward and backward exercising) than the average pupils measured the first time (cross-sectional study). But Teresia and Teodor had exercised before. If the pupils would have exercised several times, for example in school sport, their coordination dynamics values would also have been lower/better as indicated by the longitudinal study **(Figure 113)**. The functioning of their CNS would have also improved in the pupils and they could have learned better at school.

When Anna started low intensity training (**Figure 83**, 5y6m), her estimated CD values were much worse than those of the healthy pupils because of her pathologic development **(Figure 113)**. The low intensity training improved her CD values, so that she could walk a bit without support **(Figure 83)**. But no substantial improvement occurred to indicate a repair of the pathologic development. Her CD values were still worse than those for the healthy pupils **(Figure 113)**. With the high intensity/optimal therapy, on the other hand, her CD values improved strongly **(Figure 113)** in accordance with the strong improvement of motor functions and partly cognitive functions. It may therefore be that a repair of the pathologic development started.

But to have a good CD value is only one parameter of good CNS functioning. The rate of improving the CD values (the rate of improving the CNS self-organization) would be a second parameter of good CNS functioning. There are most likely more parameters to quantify good CNS functioning in general. One has therefore to be extremely careful to draw conclusions of the quality of a person from some parameters of CNS functioning. Still, the CD value is an objective parameter and suitable for repair studies.

Even though the achieved CD value for low-load was very good (5 for a load of 20Newton), the CD values for higher load were much worse. When rising first time the turning load from 20N to 50N, her CD value increased from 5 to 50, that means the CD value got worse by a factor of 10.

Since with higher loads, the phase and frequency coordination of neural network organization is reaching more the deep complexity of CNS organization, it should also be exercised at higher loads if possible. The problem was that Anna had to stay cooperative for up to 5000 turns per day. Turning at higher loads is harder and needs more mental discipline and more effort by the mother to keep Anna motivated.

By increasing the load during longer periods of exercising, the slow muscle fibers (and the upstream networks, **Figure 24**) are trained which, for example, a marathon needs. To get sufficient oxygen, Anna had a malformation of the larynx, the cardio-vascular performance and the breathing had to be improved. The

vegetative nervous system had to be trained and improved in its functioning in general, especially because of substantial learning transfer to other not trained functions in the injured and uninjured CNS parts.

A comparison of Annas turning frequency with those of healthy pupils shows that Annas CNS repair can partly also be seen in the development of the turning/exercising frequency **(Figure 114)**.

Again, it seems that the low intensity training did not increase much the turning frequency to reach the higher turning frequency of healthy pupils. But with the 3-months-optimal training, she nearly reached the healthy turning frequency of her age. Her brother Teodor had a relative low turning frequency, because his neural network organization was already that good that fast exercising was not needed any more.

Transient fast turning on the special CDT device to judge healthy development

The learning from fast movements to improve CNS functioning, most likely by improving phase and frequency coordination, seems to be necessary during healthy development, because of increasing network complexity. The intention to move fast can nicely be seen by the transient fast turning when children exercise on the special CDT device, which is frequently observed in the age range between 6 and 9 years of healthy development **(Figure 114)** [1].

For a few seconds healthy young pupils turned very fast, just because they liked the feeling, as an older person with a slightly malfunctioning CNS explained. In this way the CNS is getting the input it needs for proper development. Such transiently fast moving can also be observed in patients with spinal cord injury, cerebral palsy, epilepsy and other CNS diseases.

This transient fast turning is used here to judge Annas development during optimal CDT. **Figure 115** shows the transient fast exercising of the 9.5-years-old patient Anna with the 5p- syndrome, her healthy 5.5-years-old sister, her healthy 12-year-old brother and the healthy Author. According to the by the coordination dynamics measured healthy development **(Figures 113 & 114)** [1], there should be plenty of transient fast exercising in Annas sister and Anna, if her development would be healthy.

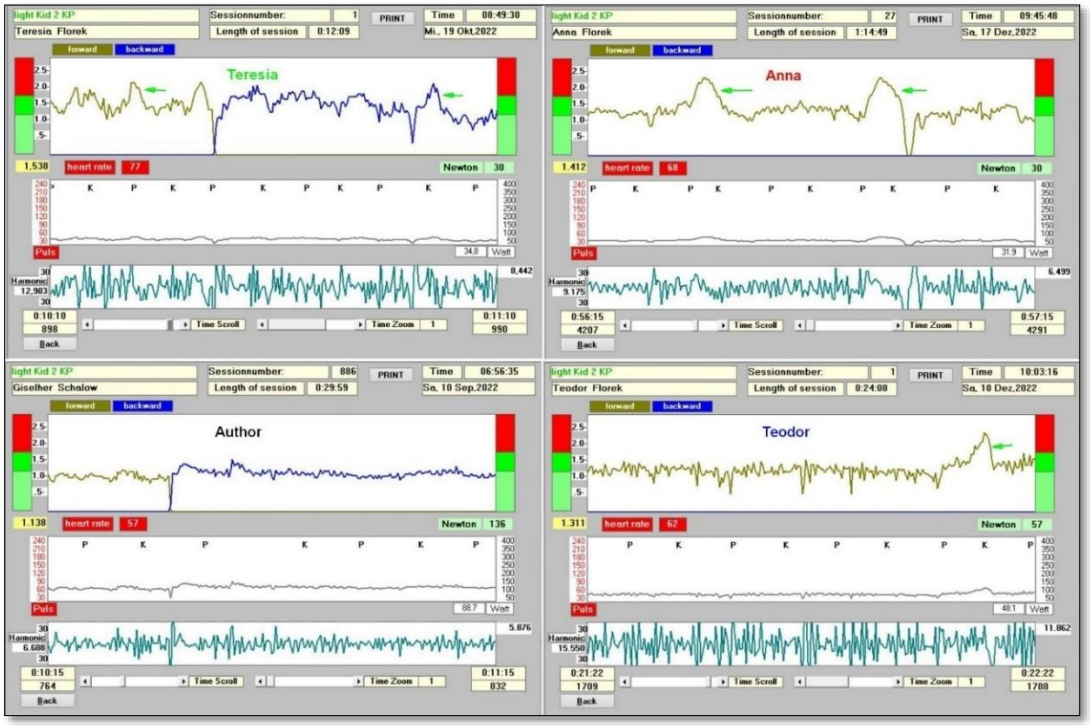

Figure 115. Transient fast exercising of the 9.5-year-old Anna with a 5p- syndrome and her healthy 5.5-year-old sister and 12-year-old brother. It can easily be observed in Teresia and Anna, but hardly in the 12-year-old Teodor and the Author; higher loads had to be used to observe them. Some transient fast exercising's are marked with an arrow.

The frequency of occurrence of transient fast exercising was measured and resulted to 95/h in Teresia, 31/h in Anna, 5/h in Teodor and 0/h in the Author for an exercising load of 20N. According to this transient fast exercising, Annas CNS developed in a healthy way under CDT treatment. But again, one has to be careful with judgement, because the measuring of CNS functioning through CDT is objective, but it measures only a certain aspect of CNS functioning. Here an example. According to coordination dynamics measurements, the Authors

CNS is functioning better than that of his former 34-year-old patient Benjamin, being a disabled athlete **(Figure 64)**. But he can run 100m in 14s. Such fast running is for the Author out-of-scope.

Still, it is beneficial that Annas CNS developed in a healthy way with respect to exercising on the special CDT device.

An important scientific question behind this so far successful treatment of Anna is: What degree of deprivation in chromosome 5 can be compensated by other chromosomes through coordination dynamics therapy?

With respect to Anna, with her deletion 5p15.1 to 5p1533, the question is what repair of body and development is still possible at an age of nearly 10 years. Are the gene expression changes the same as in healthy children, or is because of delayed development more time for substantial repair?

Repair following 4.1 months of optimal therapy

Transient interruption of treatment due to an infection

Shortly after the three months of CDT, Anna got an infection. The mother did not bring her to the kindergarten because of infection risk, but the brother brought the infection home from school (no Covid). The whole family got ill. Anna had 7 days fever over 39° and did not exercise for 9 days. She was eating nearly nothing in that period. When starting to train again, she had very little power. After 4 to 5 weeks following the begin of the infection the power was back as could be judged by the Author when running with her.

The drawing back of this infection for the treatment is the loss of training and the possibility that some repair stopped because the chain of events broke. A possible beneficial effect could be that the infection was a strong event for change. In literature it was reported that an infection stimulated a regeneration of the spinal cord. The development of the drug Piromen from the bacterium was not successful. The problem for therapy judgement is now that a disturbance of therapy progress may originate in that infection and/or a reorganization of the CNS.

Improvement of mental functions

Still some essential progress was achieved. At the 16.1.2023 she started to laugh very much and the next day she was crying for one to two hours without reason. The laughing and the crying patterns became fully operational when exercising on special CDT devices.

Anna was continent. But now she could be convinced to go to WC by herself.

When exercising on the special CDT device in the recumbent position, for protection against scoliosis, it can be seen that her facial impression changed a lot between nice looking **(Figure 116A)** and pathologic looking **(Figure 116B)**, indicating big changes in her mood. Quite often Anna pinched the Author strongly. When he complained, she showed that she was feeling sorry for that. A lot of changes seemed to go on in her mental status. It seemed that there was a repair of mental functions in progress.

Figure 116. Exercising on a special CDT device in the recumbent position to protect against possible development of scoliosis. Note the nice facial expression in A and pathologic one in B.

Often, she seemed to be stressed and disappointed that she could not speak, write, read and calculate and manage life like brother and sister. She knows very well that she was fully depended on the mother. She had good orientation in house, garden and town and remembered many things.

But she had problems to do something new as most patients with brain injury.

Training of variability of motor performance

When it was snowing, the snow was used to train pattern variability of crawling, walking on knees, walking **(Figure 117)** and running with the father. After some objection, Anna started to like it being in the snow. In the rather wet snow, it is more difficult to perform movement patterns than on even ground, because the snow has some resistance.

Figure 117. Anna during training of movement pattern variability with the father in the snow. The healthy sister Teresia joined the movements in interpersonal coordination.

Anna liked it very much to run. When being in bad mood, the running helped to clear her up. When the Author was running with her, he tried to speed up the running and improve the pattern performance. As shown in **Figure 118**, the Author was running in interpersonal coordination with Anna, pulled her to run faster and moved one arm in coordination with the legs. So far, she became able to run 13.5m in 7.30s. In case of falling, when not running straight or running on uneven ground, he could hold her.

Figure 118. Anna during running with the Author. He is running in interpersonal coordination with her and because he is running slightly in front of her, he is in the field of vision of Anna, so that Anna gets running support involuntary.

Anna learned bear-walking **(Figure 119)** and hopping **(Figure 120)**. Bear-walking is a good movement to get coordinated input from the hands and the feet and not overloading the knees as in crawling.

Figure 119. Anna during bear-walking.

Figure 120. Anna during hopping. A baby doll, marked with an arrow, is motivating her to hop.

The hopping, Anna learned easily **(Figure 120)**. To motivate her to cover a distance, a baby doll was waiting for her there.

When being the first time on a sky-walker **(Figure 121)**, Anna had problems. She was afraid. The sky-walking is a good movement to train the coordination between arms and legs, if the device is accurately made, and enhance the straight length, but it is no automatism. The jumping on springboard at wall bars has not been organized so far. The free jumping with the Author **(Figures 94-96)** did not improve so far even though Anna liked it.

Figure 121. Anna trying the first time to move on the sky-walker. A sky-walker is only helping to repair the CNS if the right-left coordination is exact, what is difficult to achieve when producing it.

Playing by herself

The playing of children by herself is part of healthy development. Anna became slowly able to play by herself. Not to connect Anna as a girl too much to babies, she got from the Author a car to play **(Figure 122)**. To connect the small doll to the car (and to the CDT device), he used sticky tape. Quickly Anna found a piece of sticky tape and also wanted to fix the doll with the tape. Certain things Anna learned and remembered quickly.

Figure 122. Anna during playing with a small doll and a VW-bus (beautiful old-timer). In the bus are marzipan sweeties. It was intended that Anna learns to transport the doll with the car.

No right- or left-handed

It could not be diagnosed whether Anna is right- or left-handed. When holding a pencil, she could use the right or the left hand similarly good **(Figure 108)**. When exercising on a special CDT device, she spontaneously used the right and left hand to show something **(Figure 123)**. The mother is left-handed and the father right-handed.

Figure 123. Anna during exercising on a special CDT device. She interrupts the turning to point something spontaneously with the left hand and a few minutes later with the right hand. This indicates that she is so far not right- or left-handed.

Coordination dynamics indicate progress in CNS repair

During healthy development children turn transiently fast on the special CDT device, especially in the age range between 6 and 9 years of age. Most likely this transiently fast exercising improves/optimizes neural network organization during development. This transiently fast exercising was also observed in Anna **(Figure 115)**. With further repair this transient fast exercising still occurred in Anna and of course in the healthy sister Teresia and brother Teodor **(Figure 124)**. The Author showed this transient fast exercising only for higher loads, indicating that neural network repair in aging is stronger when exercising against higher loads, which is harder work and needs more mental discipline. In Anna neural network repair would increase if she could be motivated to turn oftener at higher loads. But then she will not reach a sufficient number of turns, mostly 5000 per day. Another measure for sufficient neural network training is therefore the reached work in Joule per day or per week.

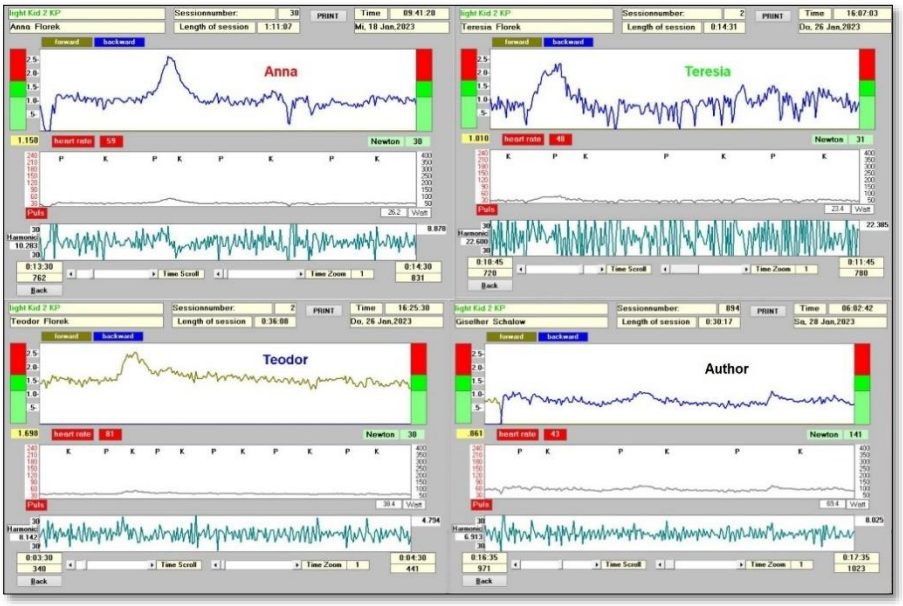

Figure 124. Transient fast exercising of Anna, Teresia, Teodor and Author. In the Author transient fast exercising is only occurring for exercising against higher load.

Pathologic in Annas neural networks is that often after transient fast exercising, she transiently stopped exercising **(Figure 125)**. This transient block of organization did not occur in Teresia, Teodor and the Author and is therefore pathologic. This pathologic neural network organization could not be repaired so far. This

block of neural network organization could be felt by the Author, when he supported Anna during turning.

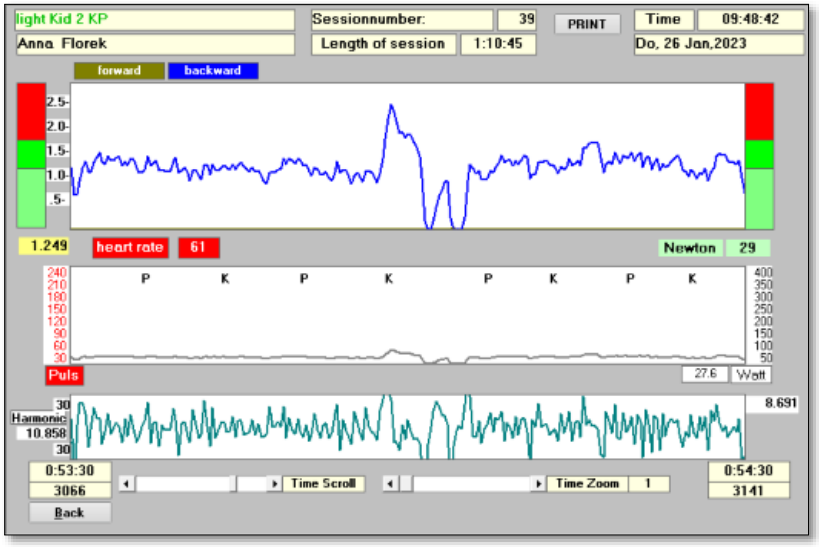

Figure 125. Block of turning following transient fast exercising in the patient Anna.

Physiologic in Annas neural network organization was the transient better turning after the change of the turning direction. In **Figure 126** it can be seen, that the Author turned transiently faster after changing from backward to forward exercising. Also, Anna turned faster when changing from backward to forward exercising.

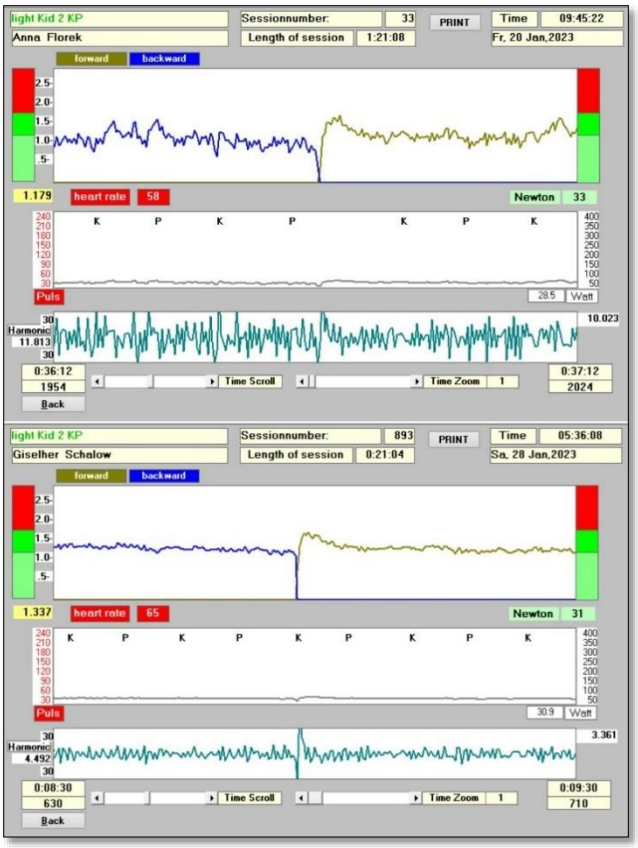

Figure 126. Faster and better exercising (better coordination dynamics values) on the special CDT device when changing the direction of turning. In Annas recording 3 transient fast exercising can be seen, two for backward exercising and one for forward exercising.

The transiently faster and better exercising directly after changing the direction of turning can be explained in the way that for a short time two pattern existed, namely the one for forward and for backward exercising, which improved neural network organization. A change of the turning direction enhances therefore the neural repair.

From **Figure 112** it can be seen that the coordination dynamics values got a bit worse (higher) following 4.1 months of therapy and the turning frequency lower, which indicates repair. During repair the neural networks reorganize and the coordinated firing among neurons is getting worse and the turning frequency decreases because the networks are not working optimal. With further CDT the coordination among neurons will improve again.

Super-coordination phase

A phase of super-coordination occurs after a few thousand turns and varies from subject to subject and other factors when exercising on the special CDT device. Earlier it was called super-compensation [2,3]. This super-coordination may be very important for genetic repair because the coordination and fine control in gene expression induced by the epigenome may be strongest then.

In the Author the super-coordination phase appears regularly when he reaches a turning number of between 1300 and 1500 in 35min. He can then turn easier at higher loads and mostly the spontaneous turning frequency increases. He then enjoys the exercising on the special CDT device.

At the end of this therapy period of 4.1months, the phase of super-coordination was measured in Anna by the Author and occurred after approximately 3500 turns during 1 h of exercising. It seemed that the number of transient fast exercising also increased then **(Figure 126A)**, indicating a better neural network repair. The problem with the patient Anna was that her CNS became slowly exhausted after 4000 to 5000 turns and she became unwilling to turn further, even though the mother tried all tricks to motivate her for further training. Annas CNS needed a rest. One can admire the mothers how patient they are when trying to motivate their child for CNS repair. In severe patients, a good motivated therapist would have little chance to motivate the child to train at limits without mother.

When the mother exercised with Anna on the device like in **Figure 110A**, the Author looked at the screen of the laptop to see in detail how the coordination dynamics value changed and compared that with the changing expression of Annas face. Anna got used to have the Author sitting in front of the laptop.

One could think what an effort is needed for this therapy. But if it becomes possible to induce gene plasticity through coordination dynamics therapy, that means that other parts of the DNA can take function over from the deleted p5 part, that will change the world. And Anna is a suitable patient for a prove and benefits from it. But it may take years of optimal therapy. Real progress in medicine comes from the cure or health improvement of human patients through therapies based on science.

Conclusion

In the nearly 10-year-old patient Anna with severe cru-di-chat syndrome, walking, running and jumping improved substantially through 4.1 months of coordination dynamics therapy. She learned running, walking, creeping, crawling and hopping. The climbing of staircases got better. Laughing and crying became operational. She learned a bit to play by herself. Even though cognitive functions improved, she did not learn to speak, write, read or calculate. But memory and learning improved. Obviously, coordination dynamics therapy is an available efficient treatment to repair the malformed CNS. The CNS repair is supported and quantified by the substantial improvement of the coordination dynamics values. But whether the pathologic development, caused by the chromosome deletion, can or could be improved is so far not clear. Much longer optimal treatment is needed.

DISCUSSION

Through four months of coordination dynamics therapy (CDT) motor functions could be improved in the nearly 10-year-old patient Anna with severe cru-di-chat syndrome. She learned to laugh and cry. Learning and memory improved. Still, she did not learn to speak, read, write or calculate. But one should not forget, frankly speaking, she is coming out of nothing.

Gene plasticity

The first step in repair was achieved. There is specific treatment available in genetic diseases. Also, in brain injury, malformation or degeneration [1-30] there would be CNS repair through CDT.

But in this chromosome deletion disease, also the development is pathologic. In addition to the brain malformation, including microcephaly, there is a pathologic development of brain and body. For a repair in the direction of cure, the pathologic development has to be made physiologic. A possibility would be if gene plasticity would exist and could be activated. In similarity to CNS plasticity, where other brain parts take function over from the injured ones through CDT, can also other parts of the DNS take function over from the deleted part? Is coordinated-movement-based learning (CDT) in children capable of targeting the epigenome and altering

gene expression and hence repair the CNS and pathologic development? In brain injury, other parts can nearly take all functions over at ages under 10 years. At ages over 10 years, the plasticity reduces. Anna was just under 10. Therefore, it was tried hard to administer to her optimal therapy immediately with different movements apart from the standard ones. For sure it would have been better to start CDT with her at an age of one or two years. Special CDT devices exist also for babies **(Figure 79E)**. But no physician informed the mother about CDT and she did not find CDT in the internet. Whether other parts of the DNA can really take functions over from deleted ones is unclear. Whether age periods exist is also not clear. Gene expression levels change strongly with age. Anyhow, it is tried in Anna at an age of just under 10 years to repair the CNS and the development.

Four months of optimal therapy are too short to see changes of development. The healthy development in human lasts in the range of 20 years. A permanent coma patient could be brought fully out of coma through 5 years of CDT (15 h CDT per week) and the patient started to speak again after 6 years of CDT [21,26]. He suffered a very severe traumatic brain injury and was older than 20 years, but he had no chromosome deletion. Fundamental repair seems to need long periods of optimal therapy.

From movements to higher mental functions

For learning, mostly one is showing a movement or other pattern to a child and it has to copy it with or without support. One proceeds therefore from the higher mental function, to realize the task, to the movement. During the therapy it was also tried the opposite, to go from the movements to cognitive functions. In **Figure 108** the Author was moving Annas hand to write an "A". He tried with Anna to proceeded from movement to intelligence. Anna then had to copy the "A", which was not possible so far. When Anna saw later on, among things of the Author, the page given rise to **Figure 108**, she pointed to it, that means, she remembered this action to try to make her writing. The same strategy to improve higher mental functions via movements was used when cleaning a car. As the mother reported, the cleaning pattern was existing in Anna and was operational. When in **Figure 127** Anna wanted to clean the car of the Author from snow, the Author took Annas hand and cleaned with a windscreen wiper the back window. She should realize that the cleaning is better with a windscreen wiper, which she cleaned with support. How successful this additional strategy is, to induce neural pattern organization/repair of cognitive function via movements, has to be seen in the future.

Figure 127. Anna getting used to play with snow and to clean a car window properly with leading support of the Author.

Real basic and applied medical research

Anna is a suitable patient to clarify whether there is gene plasticity. It is shown in this article that CDT was developed on the basis of basic medical research, by starting with human Anatomy, proceeding to human Neurophysiology and reaching than the Clinics via human Repair-neurophysiology, presented by continence repair (Introduction), and developing on the basis of this human basic medical research CDT to repair the brain (Method) and hopefully gene plasticity. If there is gene plasticity, then other parts of the DNA can take lost functions over from the deleted DNA part. Optimal therapy is probably needed for years. This possibly progress in repair of CNS functions and physiologic development is no theoretical game. From research point of view, it would change our thinking, also Darwin's theory may have to be adapted. But from the point of view of Anna and her family, a substantial progress would change their life's. Anna suffers very much that she cannot speak and communicate with the mother and the other members of the family.

Often, she is destructive, because certain things she understands very well but she cannot do certain things because other parts of the brain are not functioning well and she sees that the healthy brother and sister can do it. Most likely, she wants to be like brother and sister. Hopefully CDT, at an age of 10 years, is capable of targeting the epigenome and altering gene expression and hence repair.

Out-of-date of the clinical treatment system

The diagnostic in clinics is good till sophisticated, because it is organized and money can be earned. Sometimes too much diagnostic is performed. The cervical SCI patient Kadri (**Figure 48E, F**; now a lawyer) said, why should I go a neurologist. He is telling me what is wrong in my body, but he is not telling me how to repair the lost or impaired functions. Apart from exceptions, one cannot repair the human nervous system with drugs or operations. Movement-based learning, on the other hand, is a causal therapy which repairs the neural networks. But the physiotherapy (physical therapy) to repair the nervous system is mainly out-of-date and inefficient. When in Switzerland the physiotherapy education was upgraded from school to academy, only the names were upgraded, not the education. Physiotherapists do not learn, for example, to perform electromyography (EMG) on patients. When the Author demonstrated surface EMG to physiotherapists in a course, they all liked it, because one could really see pathologic motor programs and spasticity on the screen of the scope. When seeing their own volitional muscle activation, physiotherapists were impressed.

Being at the international conference for pediatric acquired brain injury (IPBIS2018), really interest was only coming from one physiotherapy student who wanted to do research, a physician who was interested in neural network learning and two lawyers, who were supporting and supervising the families of brain injured children. But all the physiotherapists, rehabilitation physicians, neurologists or neuropediatric did not want to get informed about new developments in CNS repair. Robotics were of interest to them. When the Author is seeing a picture where a child with a nervous system injury is in the wheelchair, he is getting angry and depressive. When the Author asked neuropediatric from New Zeeland whether they are not getting depressed when they diagnose all the deficits of a brain-injured child but cannot offer treatment, he did not get an answer and next day they did not come to the Authors poster **(Figure 128)** to get informed and discuss problems. The members of the conference seem to be afraid to see that the nervous system of children can partly be repaired. A physician, who treated Nefeli and Sophie **(Figure 1)** in a Swiss rehabilitation center, did not want to see the outcome of his former patients on the long-term. Interesting is further that no member of the conference wanted to try out the special CDT device placed besides the poster **(Figure 128)**. And no physician wanted to get a reprint or wanted to look in some publications or books **(Figure 128)**. When the Author exercised at the entrance of the conference building on the special CDT device, after some time he was pushed away by the administration (the organizer of the conference) so that nobody can see his exercising on the device (out of view-out of mind). Students and stuff of a nearby School for Management, who were passing the Author during exercising on the special CDT device, were more interested what the Author is trying to demonstrate than the members of the conference. When the Author gave long ago a talk at a Nobel institute for Neuroscience in Stockholm (Prof. Grillner, pattern generator), he was not allowed to discuss with all the assistances the human data, even though at that time they were thinking of a rat experiment to repair the spinal cord. They were planning at that time a rat experiment what the Author had already done on human.

At an international conference on continence repair in 2022, the Author got an e-Poster **(Figure 129)**. Only two physiotherapists were interested, even though there were treatment courses for catheterization of (spinal cord injury) patients. There was no real interest to repair continence through CDT (Introduction). There was no possibility to demonstrate the special CDT device. Even spinal cord injury patients in the wheelchair would be able to exercise on it. Nobody wanted reprints. Lucky that his abstract was in the abstract book.

When really some junior physicians get motivated to try new repair strategies of the brain, they are punished by the establishment. Why to develop new treatment to repair the human brain, when it is impossible to bring it to the patient? Moderators in TV are often open to new developments. But first, explanations have to be that simple that a differentiation between qualified research and hocus-pocus is not possible and secondly, the neuro-rehabilitation is still going on with their out-of-date treatment whatever the progress is in their field.

Often new organizations and predatory organizations arrange journals and conferences without sufficient knowledge. For both knowledge and money is needed. They screen the market and choose what sounds nice. But they are not blocking new developments. Researcher can now choose between not publishing or publishing in a new journal which may be predatory. But a real research worker has to publish because it is part of the profession and secondly, in human neurophysiology and clinical research, apart from statistics, many patients are suffering and dying and that puts load on clinical researcher. It was estimated that by shifting the new Berlin airport from the South of Berlin to the periphery of Berlin, approximately 11 inhabitants will die per year caused by aircraft noise.

By not using CDT, which improves health of patients in general, there may die a million people on earth every year.

Movement therapies are not popular because mental discipline is needed. Probably more than half of the population on earth has overweight. Especially young ones, who alternate between fast food and smart phone, have massive overweight. On Kriti (Greece), there are many children between 5 and 10 years which have already very much overweight and move therefore very little. In the class of Nefeli **(Figure 1)** there were 2 of the 18 children who had no overweight! But movements like walking, running, jumping and other movements are necessary for a healthy development. Many new diseases will therefore occur in the future due to the too little movements performed by children. Patients and healthy people only enjoy movements, if they have no overweight. Also, the elegance of walking is lost with overweight.

Figure 128. Poster of the Author Schalow G (Number 38) at the international conference IPBIS2018 in Belfast 2018: Pediatric acquired brain injury repair. The poster is not especially good because of lack of money. But the repair progress of the nervous system in children can clearly be seen. It is also shown that human anatomy and physiology is needed for repair.

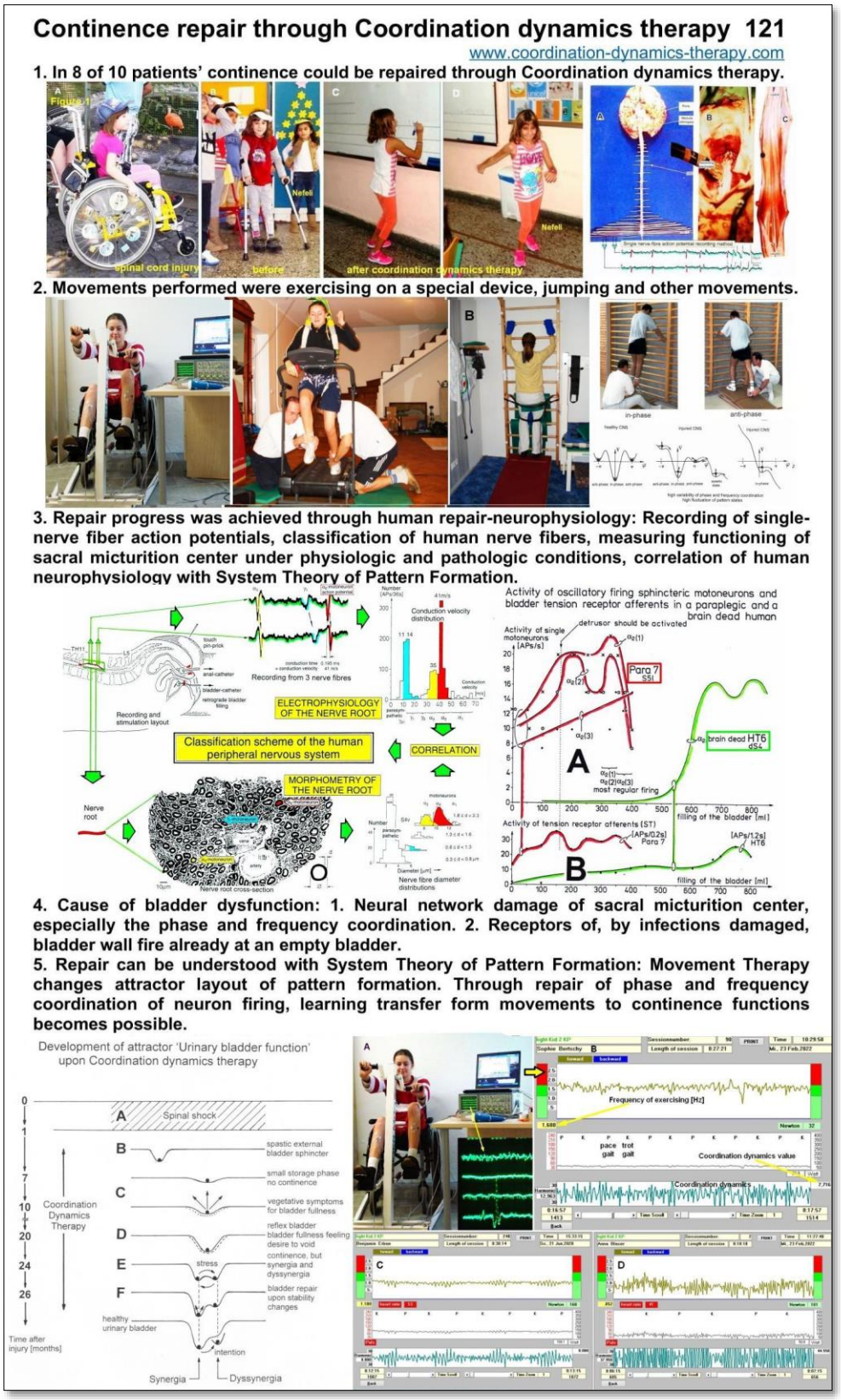

Figure 129. E-poster of the Author at the international conference on continence repair in Vienna 2022.

Universities and rehabilitation centers are with respect to human repair-neurophysiology approximately 30 years out-of-date. Just now an internet organization (academia.edu) tells what papers of the Author are read most. These papers are the ones which the Author published 10 to 20 years ago. That the neuro-rehabilitation is out-of-date is generally known. The Author was even told that for bringing progress to the rehabilitation an agreement with the devil is justified. But how is it, most likely, with the so-called progressive institutions? Astronauts are brought into space and because of missing gravity it has to be looked for their health. Astronauts get for example osteoporosis from which they do not recover again on earth. Their physical exercise in space is for the time being the walking on treadmill. Exercising on a special CDT device would at least also be needed. One could measure then additionally the organization of their CNS first on earth, then in space and afterwards on earth again and see what had changed of CNS functioning and health in space. By measuring at the same time heart rate variability and split it by Fourier analysis into sympathetic and parasympathetic contributions, one could see whether the astronauts have stress and reduce it, if possible, by exercising. Further, because CDT improves also coordinated finger movements, astronauts could better perform complicated experiments, in which finger coordination is needed.

Plenty of money is given to enhance artificial intelligence and necessary infrastructure is built. The highest intelligence is still by far generated in the human brain. Why the researchers in the field of artificial intelligence are not trying to learn from the organization of the human neural networks for their artificial neural networks? The human brain is very fast and is most likely not using iteration processes for network changes. It seems that not only disabled children have a "tunnel-view".

Aging men are worried to get prostate cancer. It is likely that prostate cancer growth can be inhibited by CDT in similarity to breast cancer [22]. In TV it was recently analyzed what operational strategy is better, to operate only with the hands or using additionally a robot. But on prevention of prostate cancer, namely to reduce the probability of prostate cancer occurrence by physical activity (including CDT), it was not reported of.

EPILOGUE

No financial support for human repair-neurophysiology

After an initial financial support of this research project to repair the human CNS by the "Deutsche Forschungsgemeinschaft" (DFG), further support was refused because of professional and ethical doubts. In spite of the support by the former German president Richard von Weizsäcker, the DFG did not change its mind and stated that the Author cannot apply any more for funding of this research project. Also, the "Swiss National fond" and the "Max Planck Institution" refused support. For the impossibility to get support for a research project to repair the human nervous system see also Epilogue of [1]. Because of the impossibility to get official funding for this research project, the Author went on with the research, mainly on personally saved money for 35 years to reach the present level.

When the Author wanted to work on brain-dead humans at the University of Greifswald (at that time German Democratic Republic, or Russian occupational zone), mainly at the neurosurgery department, an ethical committee was founded and this committee decided that it is justified to work on brain-dead humans for repairing the human CNS. For developing the "single-nerve fiber action potential recording method", the Author was supposed to get a professorship in Dresden (after being re-built). But after 10 years, with the fall of the Berlin wall, everything changed, the bad and the good things.

The ethics in research are important. But it is not only important what research on human is justified, but also what research is allowed to leave out. Here an important example. Through coordination dynamics therapy it is possible to live longer with a better quality of life for 10 to 20 years [25,26]. If every hundreds person (10^{-2}) on earth (world population = $8x10^{12}$) would have the mental discipline to train hard and live longer for 10 years (10^{-1}), then every year a few million lives could be saved when assuming a life time of 100 years ($8\times10^{12}\times10^{-2}\times10^{-1}= 10^{9}$ = 8 million). That means qualified research on human has tremendous consequences.

Disabled children also want help. The cerebral palsy girl Sophie **(Figure 1)** [15] trains with healthy cousins for motivation to further improve CNS functioning **(Figure 130)**.

War children (Kriegskinder)

Nightmares can partly be cured during CDT treatment of scoliosis and in cerebral palsy. (The following is not easy to write for the Author, but he feels responsible to partly analyze the past).

However, the CNS of children cannot only suffer damage from a traumatic brain injury, infection, or malformation, but also from the fallout of conflict zones, especially in the absence of parents. They can suffer nightmares which may last for the rest of their lives. **Figure 131** shows the ruins of Dresden following the bombing in 1945. Such situation may induce nightmares in those ones who survived.

Figure 130. The cerebral palsy girl Sophy trains with the healthy cousins. She is less concentrated than the other ones during exercising.

Figure 131. The Bombing of Dresden took place in the final months of the Second World War, when Hitler-Germany had lost already the war. In four raids between 13 and 15 February 1945 the bombing and the resulting firestorm destroyed over 6.5 km^2 of the city. An estimated 25,000 people were killed. There was no army in Dresden. A pilot of the United States Air Force refused to bomb Heidelberg, because he had studied in Heidelberg. Dresden was a cultural landmark and is sometimes referred to as "Florence on the Elbe". Culture is only protected by those ones who have culture.

To imagine the criminality done in the war in Ukraine, we need a comparison to other wars, as the first and second world war. This is not especially the duty of medical research, but first medicine is always involved in wars, second the public in many countries is avoiding such comparisons, third as Kant argues "if justice perishes, it is no longer worth living on earth", and fourth the Author's families from the father's side (Stettin) and mothers' side (Regentin) were displaced persons **(Figure 132)**, of which nobody wants to speak about. **Figure 133** shows refugees from east Prussia.

Figure 132. Parcellation of Germany according to the Potsdam conference. Germany was divided into 10 parts.

Figure 133. Photos made by Russian airplanes, showing tracks of refugees on the ice of the "Frisch Haff" from east Prussia in January or February 1945. (Upper photo a bit corrected).

In **Figure 134** some data of World War II are summarized with respect to Germany. There were 15 million German refugees, 3.5 million were killed on their way. The most well-known case was the sinking of the "Gustloff". 300 000 women were raped, abased, or killed. Seven million Germans starved on hunger or disease in between 1946-1947. Eisenhower forced German soldiers to dig diches in wet ground (Rheinwiesen) to stay in and stopped the red cross to bring them food. One million German soldiers died in the hands of the USA after the war according to the statement of three persons of **Figure 134**.

Der 8. Mai 1945 und der 8. Mai 2022

Feiern wir 77 Jahre nach Kriegsende unsere Befreiung?

Zur Erinnerung: Im Zweiten Weltkrieg fielen über 3 Mio. deutsche Soldaten für ihr Vaterland, ca. 1 Mio. nach dem Ende des Krieges in der Hand der USA. Mehr als 800.000 Zivilisten starben im völkerrechtswidrigen Bombenkrieg gegen deutsche Städte. 15 Mio. Deutsche wurden unter eklatantem Bruch des Völkerrechts vertrieben, davon 3,5 Mio. getötet – ein Völkermord! Ca. 300.000 deutsche Frauen und Mädchen wurden vergewaltigt, geschändet, erschlagen. Über 7 Mio. Deutsche starben 1946 -1947 an Hunger und Krankheiten. Deutschland wurde ca. ein Drittel seines Landes geraubt – auch dies ein eklatanter, absichtlicher Bruch des Völkerrechts.

Daran erinnert keine staatliche Gedenkstätte, bis heute – welche Schande! Nein: Wir feiern nicht! Ja, dies ist für uns ein Tag des Gedenkens und der Trauer.

V.i.S.d.P.: Dr. Hartmut Kluge - Alfred E. Zips, Oberstlt. Bundeswehr a.D. - Klaus Grotjahn BDA

Figure 134. Some data about the end of World War two. From "Junge Freiheit", 6.5.2022, Page 9.

Expulsion/refugees took place not only in the former east Germany (east Prussia, West Prussia, Silesia, east Pomerania (where the Authors father family is from)), but also in middle Germany, as for example, around Dresden **(Figure 131)**. Eisenhower, the head of US air force, gave the order for bombing. When refugees were running over the bridges of the river Elbe to escape, they were attacked by USA fighter pilots (photos I could not find so far). When we three children with our mother (and others) were fleeing in 1945 at Schönwalde, close to Berlin, Russian soldiers were shooting at us. In the war in Ukraine, it is distinguished whether military objects are attacked or refugees. Eisenhower's ancestors had to leave Baden-Württemberg (Germany) in 1792. It could well be that Eisenhower had also other motivations for bombing than to win the war.

It is therefore important that the USA is lay open all documents about World War two, what had not happened till now. Important facts are still in the archives. One cannot understand why the Australian Julian Assange is treated that hardly. Is the USA afraid that a whistleblower may open important documents of World War II?

Many refugees, especially from east Prussia, their children and grandchildren are still suffering on the loss of their home country and culture. On the graves they sometimes have the former home country **(Figure 135)**. When the Author drives with the car through the former East Germany **(Figures 132 & 135)**, he suffers by seeing the familiar old houses, small streets surrounded by tries, the old rails of the train, the lakes, and hills, what also parents and grandparents talked about, when sitting in the evenings at the warm oven (Kachelofen).

Figure 135. A grave of refugees from east Prussia in Berlin (Moltkefriedhof). These refugees wanted to keep their home country on the way to a better world.

Since the Author has been a theoretical nuclear physicist [105], he must state the following. The physicists Heisenberg (see also collected works of Heisenberg, especially section C, volume 5, page 164), Einstein and Bohr had the agreement not to tell politicians about the possibilities of nuclear forces with respect to build an atomic bomb. But Einstein convinced Roosevelt in a letter to build the (first) atomic bomb. Following Hiroshima and Nagasaki, he felt sorry for that. The German Heisenberg did not build an atomic bomb for Hitler. After the war, Adenauer did not use the knowledge of Heisenberg to build nuclear power plants and Heisenberg (the father of Quantum Mechanics) was disappointed because his expert knowledge was not used. Who knows how the development of nuclear power plants would have gone with his knowledge? Not only the Author made the experience that expert knowledge (for example human repair-neurophysiology) is often not of interest for various reasons.

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