Phase relation changes between the firings of $\alpha$ and $\gamma$-motoneurons and muscle spindle afferents in the sacral micturition centre during continence functions in brain-dead human and patients with spinal cord injury

G. Schalow

Summary

1. Single-nerve fibre action potentials (APs) were recorded with 2 pairs of wire electrodes from lower sacral nerve roots during surgery in patients with spinal cord injury and in a brain-dead human. Conduction velocity distribution histograms were constructed for afferent and efferent fibres, nerve fibre groups were identified and simultaneous impulse patterns of $\alpha$ and $\gamma$-motoneurons and secondary muscle spindle afferents (SP2) were constructed. Temporal relations between afferent and efferent APs were analyzed by interspike interval (II) and phase relation changes to explore the coordinated self-organization of somatic and parasympathetic neuronal networks in the sacral micturition centre during continence functions under physiologic (brain-dead) and pathophysiologic conditions (spinal cord injury).

2. In a paraplegic with hyperreflexia of the bladder, urinary bladder stretch (S1) and tension receptor afferents (ST) fired already when the bladder was empty, and showed a several times higher bladder afferent activity increase upon retrograde bladder filling than observed in the brain-dead individual. Two $\alpha_2$-motoneurons (FR) innervating the external bladder sphincter were already oscillatory firing to generate high activity levels when the bladder was empty. They showed activity levels with no bladder filling, comparable to those measured at a bladder filling of 600 ml in the brain-dead individual. A bladder storage volume of 600 ml was thus lost in the paraplegic, due to a too high bladder afferent input to the sacral micturition center, secondary to inflammation and hypertrophy of the detrusor.

3. In a brain-dead human, 2 phase relations existed per oscillation period of 160 ms between the APs of a sphincteric oscillatory firing $\alpha_2$-motoneuron, a dynamic fusimotor and a secondary muscle spindle afferent fibre. Following stimulation of mainly somatic afferent fibres, the phase relations changed only little.

4. In a paraplegic with dysynergia of the urinary bladder also 2 phase relations (less stable) existed per oscillation period of 110 ms in a functional unit between the APs of a sphincteric $\alpha$-motoneuron, a fusimotor and a secondary spindle afferent fibre. The phase relations changed with time following stimulation of mainly somatic afferents. A second functional unit organized by phase related interactions was phase related to the first functional unit.

5. Following painful bladder catheter pulling, the parasympathetic division was transiently activated several times in the paraplegic. At times of activation of the parasympathetic division, 3 broad phase relations occurred within and between the two functional units, indicating that the parasympathetic division in the sacral micturition and defecation center channeled an additional input to the somatic oscillatory firing neuronal networks driving motoneurons which innervate the external bladder and/or anal sphincters.

6. It is conceivable that the mutual inhibitory action of detrusor and external bladder sphincter has the capacity to recover, if the functional neuronal organization of the sacral micturition center is improved in the direction of more stable phase relations between the firings of neurons and neuronal ensembles by natural coordinated afferent inputs from continence organs, supraspinal neurons, and functionally connected neuronal networks.
For supraspinal control and improvement of neuronal organization some kinds of bulbo-spinal-bulbo pathways have to exist or to be reconstructed by regeneration.

7. It will be shown in a following article that the sacral micturition centre can be repaired after spinal cord injury by a functional reorganization and limited regeneration of the human spinal cord by administering coordination dynamics therapy.


**Introduction**

I have shown that the classification scheme for the human peripheral nervous system is preserved following spinal cord injury (57), and have analyzed the detrusor-sphincteric dyssynergia of the urinary bladder (58). Parasympathetically evoked impulse patterns of secondary muscle spindle afferents and sphincteric motoneuron activity were compared between paraplegics and a brain-dead human. It was shown that inflammation, hypertrophy and over-activated bladder stretch (S1) and tension receptors (ST) contributed to bladder dysfunction. The main reason for a detrusor-sphincteric dyssynergia of the bladder however seemed to originate from the central nervous system (CNS) itself. Following spinal cord injury, with the re-organization of the isolated sacral micturition centre the mutual inhibition of the detrusor and the external bladder sphincter is lost or impaired. The mechanism underlying the loss of the mutual inhibition of detrusor and external sphincter may be, besides other reasons, a false sacral reflex reorganization or disconnection from the pontine micturition center, which is believed to coordinate the activation of detrusor and external bladder sphincter. Intermediate stages of the coordination of detrusor and external sphincter are conceivable. Since in a brain-dead human the parasympathetic division inhibited sphincteric motoneurons with detrusor contraction, pathologic reorganization and adaptation of the CNS, caudal to the level of injury, probably takes place in the spinal shock phase and thereafter. Of interest are now the pathologic changes in the neuronal networks of the caudal spinal cord and whether those changes are reversible.

An electrophysiologic tool has been developed for analyzing CNS functions in humans with spinal cord injuries. Based on the classification scheme for the human peripheral nervous system (27,57) it is possible to construct with the single-nerve fibre action potential (AP) recording method simultaneously natural impulse patterns of single afferent and efferent nerve fibres and the phase relations among them. Functions of the CNS can be analyzed following natural stimulation by studying time correlations between the natural discharge patterns of secondary muscle spindle afferents and sphincteric motoneurons innervating the external anal sphincter, and those of urinary bladder afferents and sphincteric motoneurons innervating the striated bladder sphincter (Fig. 1 of (58)).

Even though the structure and the function of the neuronal networks of the human CNS are far from being even partly understood, progress in the understanding of spinal cord dysfunction is possible by making use of the discovered spinal oscillators (28). These spinal oscillators are functional units which organize themselves in the neuronal networks of the CNS by natural impulse patterns of the adequate afferents. They are characterized by the rhythm of firing, namely by the frequency of repeated firing with impulse trains and the interspike intervals of the impulse train (Fig. 1). If the adequate afferent input to the neuronal network is too low to fire oscillatory or if the neurons in the circuitry are inhibited, the sphincteric motoneurons are integrated in another organization form of network. Then, the motoneurons fire in the occasional firing mode (29,32,33) repeatedly every 3 s approximately, or they fire transiently oscillatory (28).

Fig. 1 summarizes what has been known so far about these spinal oscillators which, under physiologic conditions fire rhythmically with impulse trains (28,34). $a_1$ (FF), $a_2$ (FR) and $a_3$-motoneurons (S),
characterized by group conduction velocity and the group nerve fibre diameter, are integrated in their own neuronal network to fire oscillatory for high activation by their adequate afferent input, and to innervate their own muscle fibre type. In man there are mainly three organization forms of somatic neuronal networks in the sacral micturition center, which drive 3 kinds of striated muscle fibres (Fig. 1). The \( \alpha_2 \)-motoneurons for example, subserving continence functions, are integrated in neuronal network organization forms firing at 6 to 9 Hz; they innervate fast fatigue-resistant muscle fibres (FR) of histochemical type IIA which are fast oxidative glycolytic (FOG) (3-9,11,16,22,25,27,28,34,63,64). The \( \alpha_2 \)-motoneurons innervating the external bladder and anal sphincters are mainly specifically driven by oscillators which fire with 1 to 2 APs every 110 ms (8.7 Hz) and with 3 APs every 160 ms (6.25 Hz) respectively (Fig. 1). The neuronal network driving the external bladder sphincter is organized to fire oscillatory in response to the activity of bladder afferents from stretch (S1) and tension (ST), flow (S2) and other receptors. The neuronal network driving the external anal sphincter is channeled to fire oscillatory upon the activity of secondary muscle spindle afferent fibres (probably innervating the spindles of the anal sphincter) and skin and mucosa afferents innervating the anal canal. The oscillation period \( T \) of the spinal oscillators is related to the number of APs per impulse train \( n_{\text{AP}} \) by the relationship:

\[
T = \frac{70}{n_{\text{AP}}} + 30 \text{ ms}
\]

**Correlation of muscle fibre types, motor nerve fibre types, and oscillatory firing spinal neuronal circuitry**

![Correlation diagram](image)

Fig. 1. – Correlation of muscle fibre types, motor nerve fibre types, and oscillatory firing spinal neuronal networks, based on histochemical, morphological and physiological properties. This figure provides a simplified correlation between muscle fibre, motoneuron and sacral oscillator types. No additional subtypes have been included. The existence of \( \alpha_1 \)-motoneuron (FF) oscillators firing at 10 Hz has been predicted (34) and they have been identified in paraplegics (unpublished observation). \( \alpha \) = motoneuron, \( \gamma_1 \), \( \gamma_2 \) = dynamic and static fusimotors, parasympathetic = parasympathetic preganglionic motoneuron. S1, ST, S2 = stretch, tension and flow receptor afferents.
Further properties of the spinal oscillators have been discussed elsewhere (28,34). So far, preganglionic parasympathetic neurons and fusimotors could not be observed to fire oscillatory.

Since these spinal oscillators are essential organization forms of the neuronal network of the spinal cord, they can be expected to change their properties, when the neuronal network of the spinal cord is damaged or when there is some pathology in its functioning.

Early measurements of the dysfunction of spinal oscillators in paraplegics were used to study principal structures of their neuronal network (34).

In this paper mainly the interaction of the parasympathetic division with the somatic oscillators is under consideration, with the aim to tackle the problem of detrusor-sphincteric dysynergia. This approach uses measurements of interspike intervals (II) and phase distributions (synchrony of discharge (65)) between the oscillatory firing of motoneurons and the firing of secondary muscle spindle afferents following stimulation of the parasympathetic division.

It will be shown how powerful certain human CNS functions can be described by the use of these spinal oscillators. The rhythmic firing with impulse trains of the oscillators allows an easy recognition of the impulse patterns and opens possibilities for analyzing their circuitry (34).

I shall show in this paper that the parasympathetic division of the sacral micturition center interacts with the somatic neuronal circuitries, partly organized in oscillators, at points when the detrusor should inhibit the external sphincter.

In 1939 (17) and 1950 (18) E. von Holst criticized that the CNS was commonly regarded as a reflex apparatus, producing motor output. His ‘relative coordination’ of different rhythms (17) of the CNS from different species including man is very similar to recent findings on the correlation of human spinal oscillators (28,34,35). According to Moshe Abeles the nervous system is essentially a statistical machine (1). According to von der Malsburg (65) the information in this statistical machine is encoded not only in the number of active nerve cells and their mean firing rates (‘frequency code’) but also in interactions between neuronal and neuromuscular elements of cell assemblies expressed in correlation of their firing patterns. This author argues that the coordination of discharges has a strong influence on nervous system dynamics, since neurons essentially are ‘coincidence detectors’ (more generally coordination detectors (47)), because synchronous inputs excite a postsynaptic cell more effectively than do uncorrelated inputs. Temporal correlations, quantified by phase and frequency coordination, can therefore be processed by neuronal networks. Correlations with respect to time and space can be initiated in the network from an external source and then be propagated by ‘synfire chains’, as suggested by Abeles (1). The functional organization of the common brainstem system (21,26,61) and its dynamic changes is a consequence of afferent inputs and of the rhythmic properties of the common brainstem system network. The neuronal network reveals different types of functional organization. In the state of functional organization, in which the neurons discharge rhythmically, the phase relations between the different rhythms are essential in the transfer of information (21,26,39,58). For references concerning possible functions of the spinal cord, see (68).

With the analysis of natural impulse patterns of urinary bladder functions, by use of the single-nerve fibre action potential recording method, the pathologic functioning of the sacral micturition center is revealed. Possible clinical complications when the detrusor cannot inhibit the external bladder sphincter and the bladder cannot be emptied physiologically any more are also known: inflammation, detrusor hypertrophy, lost storage volume, repeated bladder infections which can reach the kidneys, destruction of the whole urinary tract system including the kidneys, extirpation of the urinary tract system and leading the urine into the colon which will ruin the electrolyte equilibriums (because the colon reabsorbs electrolytes). Before World War II most patients with spinal cord injury died on these complications. Depending on the degree of bladder dysfunction, neuro-urologists suggested the implantation of an electrical anterior root stimulator (according to Brindly (69)). The anterior root stimulator empties the bladder and avoids the upper urinary tract complications. But this operation is destructive because the bladder is deafferentiated (S2
through S5 dorsal sacral roots are cut and ventral roots are electrically stimulated later on), which means that the sexual function, running also through the lower sacral roots, is also destroyed or impaired. A natural causal repair of the spinal cord injury is not possible any more.

A substantial step further in this research project is that all these complications can be avoided by curing urinary bladder functions naturally by a movement-based learning therapy called coordination dynamics therapy (55,56,60). By using the System Theory of Pattern Formation for Repair (55) synergia and the dyssynergia of the bladder can be seen as two organizational patterns of the CNS with different stabilities. The causal therapy to cure urinary bladder function is to improve CNS functioning and to enhance the stability of the synergia pattern (the physiologic pattern) and to decrease the stability of the dyssynergia pattern (the pathophysiologic pattern) by learning transfer from certain movements (59). To create and understand this learning transfer for cure, the author needed 20 years of human neurophysiologic and clinical research. The learning transfer includes a functional reorganization and some structural repair, which means some regeneration of the human spinal cord (56,60).

In 4 recent articles (72-75) possible treatments in spinal cord injury were reviewed. The biggest problems in spinal cord injury, the urinary bladder and sexual functions, were not considered. Human research was not reviewed. More than 5% (up to 10%) of the society suffers on incontinence.

**Materials and Methods**

Measurements were performed in 9 patients with spinal cord injuries (paraplegics), dyssynergia of the urinary bladder, spastic pelvic floor and spasticity in general. The group of paraplegics was the same as that studied and described in two previous papers (57,58). Only those patients have been selected (paraplegics 7 and 9), in whom impulse patterns of oscillatory firing motoneurons could be extracted from the summed impulse traffic. The other cases were not used for this kind of analyses, because the recording conditions were unsuitable (small AP amplitudes, limited uniqueness of AP wave forms of certain fibres) or the obtainable impulse patterns did not contribute further information to this paper. Electrophysiologic measurements from the brain-dead human HT6 (and patients) were partly taken from previous analyses (34-39,57,58); in a few situations the original recordings were reevaluated. In basic clinical research one can only use available cases; and one reason why performing research in human neurophysiology is to develop treatment on the basis of those qualified measurements. It is extremely difficult to obtain suitable brain-dead humans for measurements, even though 5% of the society suffers on incontinence. After kidney explanation from brain-dead humans nervous system functions are lost, because of lack of sufficient blood supply. This one brain-dead human (HT6) is a reasonable control, since the results of the electrophysiologic measurements fit with the knowledge obtained from urodynamic measurements of healthy humans (for further discussion see section control group in (58)). The practical details for curing the urinary bladder in the patient with the motoric complete cervical spinal cord injury is given in a following publication (60).

**Electrophysiology**

Single-nerve fibre action potentials (APs) were recorded extracellularly from nerve roots with 2 platinum wire electrode pairs and stored on a video tape. Trace ‘a’ was the recording from the proximal electrode pair, and trace ‘b’ from the distal pair. APs from afferent and efferent fibres could clearly be distinguished since for the electrode arrangements used (differential electrodes) the main phase (second phase) from afferent fibres is upwards and that from efferent fibres downwards. Since the afferent and efferent APs reach the electrode pairs from opposite directions, also the conduction times for afferent and efferent APs are opposite. The conduction velocities of afferent and efferent nerve fibres were plotted in velocity distribution histograms for afferent and efferent fibres (Fig. 2B). The afferent and efferent nerve fibre groups were identified by peaks and ranges in the distributions (Fig. 2B), and by the calibration relations (e.g., α2-motoneurons (FR) conduct with the same velocity as the secondary muscle spindle afferents (SP2)). The fitting of a single-nerve fibre AP to a certain group was recognized by
the conduction velocity. The extraction of single-fibre impulse patterns from the multi-fibre recording of the whole nerve root was based on comparisons of conduction times and AP wave forms and on the recognition of reoccurring impulse patterns (for further details see (57,58)). Under physiologic conditions, probably present in brain-dead humans (HTs), motoneurons in the oscillatory firing mode can be identified by the rhythmic firing (Fig. 1). Under pathologic conditions the identification of the motoneuron type by the firing pattern is only possible if the pattern is not too much altered. Very pathologic oscillatory firing motoneurons can only be identified on the basis of group conduction velocities, since these velocities do not change following spinal cord injury (57). As group conduction velocity ranges overlap, the identification is then only safe to approx. 80% for a nerve root temperature of 36°C. The identification error can in principle be estimated from the overlap of drawn conduction velocity distribution curves of neighbouring nerve fibre groups of a substantial number of active nerve fibres. The conduction velocity distribution curves have a similar shape as the nerve fibre diameter distribution curves (Figs. 1,5,6,11 of (57)). Exact distribution curves however have to be determined in future research. Since group conduction velocities of different nerve fibre groups have different temperature dependence (57), the overlap of neighboring nerve fibre conduction velocity distribution curves depend also on the temperature. The overlap of the curves is smaller for higher temperatures (whereas the single-fibre AP amplitude is higher for lower temperatures (better recognition)).

Results

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

In Fig. 2A a recording from an S5 root of paraplegic 7 is shown. Conduction velocity distributions of afferent and efferent fibres were constructed (Fig. 2B) and nerve fibre groups were identified by the velocity ranges of the peaks. The identification of the nerve fibre groups rested upon the calibration relation, namely that secondary muscle spindle afferent fibres (SP2) conducted with the same velocity as the \( \alpha_2 \)-motoneurons (FR), and stretch receptor afferents (S1) conducted with the same velocity as \( \alpha_3 \)-motoneurons (S) (38,57).

The activities of bladder afferents and \( \alpha_2 \) and \( \alpha_3 \)-motoneurons during retrograde bladder filling are shown in Fig. 2C,D. The activity values of afferent and efferent fibre groups were obtained from histograms similar to those shown in Fig. 2B. It can be seen that the motoneuron activity slightly increased
during the bladder filling (Fig. 2D) as did the stretch and tension receptor afferent activities (Fig. 2C). The most important point, namely that bladder afferents fired already quite strongly when the bladder was empty, shows no characteristic consequences on the firing levels of the motoneurons. Most likely, the mixing of the activities from sphincteric motoneurons with those from other motoneurons, not associated with continence (and innervating e.g. leg muscles), weaned off specific properties. A similar loss of specific properties of the activities of motoneurons with different functions was observed in dog sacral nerve roots (Fig. 2 of (29), no specific properties in similarity to urodynamic recordings). In that case, motoneurons may have innervated leg, tail and continence muscles. The mixing of activities of the motoneuron firing in different modes, namely oscillatory and occasional, may have contributed to the loss of specific functions.

Specific properties of sphincteric motoneurons could be revealed separating impulse patterns of single motoneurons from the summed impulse traffic by wave form comparisons (39,58). Fig. 3A,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. In the brain-dead human, the sphincteric motoneurons show only 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 \( a_2 \) (1) and \( a_2 \) (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 (Fig. 2C), especially from the tension receptors of the bladder wall. With the 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 fibres 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.

![Fig. 3. – A. Activity of \( a_2 \)-motoneuron (FR) in dependence on retrograde bladder filling, in paraplegic 7 and brain-dead human HT6 (taken from Fig. 9 of Ref. 28). B. Activity of tension receptor afferent fibres (ST), recorded simultaneously with the motoneuron activity in ‘A’ in paraplegic 7 and the brain-dead human HT6 (taken from Fig. 6 of (35)). Note that the \( a_2 \) (1) and \( a_2 \) (2)-motoneurons in paraplegic 7 show similar activity increases as the \( a_2 \)-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 fibres (B), the \( a_2 \) (1) and \( a_2 \) (2)-motoneurons in paraplegic 7 are not activated earlier than the motoneuron in the brain-dead human HT6 (A). C. Discharge patterns of the \( a_2 \) (1), \( a_2 \) (2) and \( a_2 \) (3)-motoneurons at 100, 350 and 400 ml bladder fillings. Paraplegic 7, nerve root S5.]( Attached Image )
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, similarly as the sphincteric motoneurons, then the detrusor will also be activated at too small storage volumes (see below, Fig. 2B). 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 hyperreflexia 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 sphincteric $\alpha_{2}$-motoneuron fired in the occasional firing mode at low bladder filling, in the transient oscillatory firing mode at bladder fillings between 300 and 600 ml, and in the continuous oscillatory firing mode at high bladder filling (Table 2 of (28)). 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 motoneurons innervating the external bladder sphincter are rather specifically driven by the bladder afferents (Fig. 1). The secondary muscle spindle afferents (SP2), activating motoneurons that innervate the external anal sphincter (Fig. 1), did not increase their activity with the increasing bladder filling (Fig. 2C) and, for little bladder filling, did not contribute to the high activity of the $\alpha_{2}$ (1) and $\alpha_{2}$ (2)-motoneurons innervating the external bladder sphincter. The little understood $\gamma_{2}$-motoneurons (Fig. 2D) showed no specific properties upon bladder filling.

During the surgery, the detrusor was not activated upon bladder filling (see discussion in (58)). Before the surgery the detrusor was activated at approx. 160 ml bladder filling (Fig. 2E), at a volume when the sphincteric motoneurons $\alpha_{2}$ (1) and $\alpha_{2}$ (2) showed their first activity peak. If the parasympathetic division had not been suppressed by anesthesia, it is likely that the detrusor would have been activated at that filling volume during the surgery. The 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 deafferentation of the bladder (cutting of dorsal roots S2 to S5 (S5 root was sometimes not cut, if many parasympathetic fibres were contained), ventral root afferent fibres 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 (Fig. 2E).

In Fig. 3A there is another $\alpha_{2}$-motoneuron ($\alpha_{2}$ (3)) that increased its activity upon bladder filling. Since this $\alpha_{2}$-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. Probably, it was activated by reflex or response generalization.

In Fig. 3C 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 sphincteric motoneurons (Fig. 1 and Table 2 of (28)). In accordance with the measurements in the brain-dead individual (Table 2 of (28)), 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, is dysfunctional, as the oscillation period was strongly changing. In paraplegic 9 (Fig. 6) 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 (Fig. 1).

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-sphincteric dyssynergia.

Phase relations between the APs of the $\alpha$ and $\gamma$-motoneurons and secondary muscle spindle afferents in the brain-dead individual

In Fig. 4A impulse patterns of fusimotors ($\gamma_{1}$, $\gamma_{2}$), secondary spindle afferent fibres (SP2(2),
SP2(5)) and an \( \alpha_2 \)-motoneuron (\( \alpha_2(O2) \)) innervating the anal sphincter after bladder catheter pulling at the beginning of a strong activation of the parasympathetic division are shown. Small arrows, open arrows, dotted lines, doublet lines and dashed lines mark similar phases (in ms) between the APs (represented by bars) from the different fibres. Phase relations seem to exist. Half quantitative analysis of phase relations has been performed earlier. Here, the phase analysis is extended to include a full analysis over long periods of time. In the impulse patterns of Fig. 4Ba, phases (P) are defined between the APs of the motoneuron \( \alpha_2 \) (O2) and the spindle afferent fibres and the fusimotors. Phase histograms (Figs. 4Bb,4Cb) were drawn from the measured phases of the 0.8 s long impulse patterns (Figs. 4Ba,4Ca). In the histogram of Fig. 4Cb two phase relations seem to exist between the APs of the \( \gamma_1 \)-motoneurons, the SP2(2) fibre and the \( \alpha_2 \)-motoneuron (O2). To better quantify existing phase relations, phase histograms, such as those in Fig. 4Bb,Ch, of selected time intervals were lumped together (see Fig. 5).

It can be seen from Fig. 5 that two phase relations existed per oscillation period of the \( \alpha_2 \)-motoneuron between the \( \gamma_1 \)-motoneuron (dynamic), the secondary spindle afferent fibre SP2(2) and the \( \alpha_2 \)-motoneuron, for times up to 32 s (indicated by the long arrows). The phase relations in the three time intervals are rather constant. This means that the firings of the \( \gamma_1 \)-motoneuron, the SP2(2) fibre and the \( \alpha_2 \)-motoneuron were on average time-synchronized. With respect to the excitation output the
neuronal networks producing the $\gamma_1$ and $\alpha_2$-motoneuron activities had on average a constant phase against each other. The activities in the organized neuronal network were time-related. On the average, there was certain timing in the excitation of interneurons between these subneuronal networks. Since the secondary muscle spindle afferent fibre will get additional fusimotor drive different from that of the $\gamma_1$ fibre, some other fusimotor neuronal network organizations will, in general, also have fired in a phase related manner to the oscillatory firing $\alpha_2$-motoneuron circuitry. The firing of the static fusimotor $\gamma_21$ and the secondary spindle afferent fibre SP2(2) was not tightly correlated to the firing of the $\alpha_2$-motoneuron, since their phase relations were less pronounced.

With the activation of the secondary muscle spindle afferent fibre SP2(2) (see Fig. 9B of (58)) by the parasympathetic division, the phase relations between the different fibres were lost. Most likely, a rearrangement in the organization of the neuronal network of the sacral micturition occurred. The important conclusion is that in the brain-dead human some motoneuron circuitries had synchronous output firing. Probably, the firings of the interneurons in the subneuronal networks were, on the average, time related to each other. With the painful bladder catheter pulling, the strong afferent input rearranged the functional units.

**Interspike intervals of, and phase relations between, the APs of the $\alpha$ and $\gamma$-motoneurons and secondary muscle spindle afferents in paraplegic 9 with a dysfunction of the bladder**

Impulse patterns of $\gamma$ ($\gamma_1$), $\alpha$-motoneurons ($\alpha_2$, $\alpha_3$) and secondary muscle spindle afferent fibres (SP2(1), SP2(2)) in paraplegic 9 are shown in Fig. 6b-g. To show the activation of the parasympathetic division, the activity (Hz=0.8 s) level changes of the SP2(1) fibre are given in Fig. 6a. The times are indicated of selected impulse pattern sampling and the time intervals are marked for which interspike intervals and phase relations were lumped together.

The $\alpha_3$ and $\alpha_2$-motoneurons fired rhythmically with impulse trains consisting of one AP, in contrast to the physiologic firing patterns (Fig. 1), in which $\alpha_3$ and $\alpha_2$-motoneurons fired with impulse trains consisting of more than one AP. The identification of motoneurons by the conduction velocity is not
absolutely safe, since group conduction velocity ranges overlap (57). It is very unlikely nevertheless that one of the motoneurons was an $a_1$-motoneuron (FF), even though they fire physiologically rhythmically with impulse trains consisting of one AP. Oscillatory firing $a_1$-motoneurons are driven by time locked primary spindle afferent fibres (Fig. 1, 40). The firing patterns of the $a_2$ and $a_2$-motoneurons are strongly pathologic with respect to the length of the oscillation period and the impulse train length so that it is impossible in this paraplegic 9 to identify the motoneurons by their discharge patterns of oscillatory firing; this is possible if the neuronal network driving the motoneurons were to fire in a physiologic manner. The dysfunction of the neuronal networks could originate in interneuron cell death, false functional organization due to loss of natural afferent input or other reasons (see Discussion).

The time-correlation of afferent and efferent impulse patterns was easy to detect in the brain-dead individual as the $a_2$-motoneuron O2 fired regularly like an inner clock. The phases of fusimotor and spindle afferent APs could be defined with respect to the impulses of that inner clock. In paraplegic 9, the rhythmic firing was very irregular. The motoneuron firing could therefore not be used as a time reference basis. More phases between the impulses of the different fibres are necessary to fully describe the correlation between the simultaneous impulse patterns. In Fig. 6d,g the mutual phases between the APs of the different fibres are defined. In Fig. 6h,i are drawn the corresponding phase distribution histograms. Since too few phases occurred in a sweep piece of 0.8 s duration, phases occurred at certain time intervals were lumped together and plotted in Fig. 7.

In Fig. 7 the interspike intervals (IIs) and the phases are shown for similar time intervals. Before stimulation in the time interval 1-6 s, the $a_3$-motoneuron fired every 100 ms, the $g_1$-motoneuron every 100 to 130 ms, and the SP2(1) fibre every 80 to 150 ms (Fig. 7Aa). The $a_3$-motoneuron mostly fired every 300 ms and the SP2(2) fibre every 250 ms. At that particular time interval, increased similar phases (phase relation) occurred 2 times per an $a_3$ oscillation period between the APs of the $a_3$ and $g_1$ fibres, between the $g_1$ and the SP2(1) fibres and between the $a_3$ and the SP2(1) fibres (Fig. 7Ba). One phase relation occurred between the impulses of the $a_3$ and $a_2$-motoneurons, and one between the $a_3$ and the SP2(2) fibres. Existing broad phase relations between motoneuron discharge patterns are interpreted as interactions between populations of neurons.

Since $a$ and $g$-motoneurons are partly correlated (58, Fig. 8) and muscle spindle receptors integrate and may correlate somatic and vegetative drive, motoneuron driving circuitries are both a source and a target of rhythmical events; thus, the rhythmical events are both means for, and consequences of, functional organization.
Fig. 7. – A. Interspike interval (II) distributions of secondary muscle spindle afferent fibres SP2(1) and SP2(2), α2 (FR) and α2-motoneurons (S) and the dynamic fusimotor γ1 for different time intervals, as indicated in Fig. 6, before and after painful bladder catheter pulling. IIs were collected from sweeps of 0.8 s duration per second. Paraplegic 9, root vS4. In ‘f’, the interspike interval distribution of the secondary muscle spindle afferent fibre SP2(2) following parasympathetic activation in the brain-dead human HT6 is drawn for comparison.

B. Histograms of the phases between α2 and γ1-motoneurons and a secondary muscle spindle afferent fibres (SP2) (defined in Fig. 6d,g) for time intervals (as indicated in Fig. 6a) before and following painful bladder catheter pulling. The phases were collected from several histograms (defined in Fig. 6h) of sweeps of 0.8 s duration per second. Paraplegic 9, nerve root vS4.
Differences in the phase relations of motoneuronal and spindle afferent discharges between paraplegic 9 and brain-dead HT6

In the brain-dead individual, the phase relations between the impulses of the dynamic fusimotor $\gamma_1$, the secondary spindle afferent fibre SP2(2) and the $\alpha_2$-motoneuron O2 changed only little upon different stimulations. Two phase relations existed per $\alpha$-motoneuron oscillation period (160 ms) (Fig. 5).

With the activation of the parasympathetic division (time interval 33-74 s, Fig. 5) the stable relation between the $\gamma_1$ and the $\alpha_2$-motoneuron was lost. A detailed analysis of the phases between the APs of the SP2(2) fibre and the $\alpha_2$-motoneuron O2 was not performed.

Also in paraplegic 9, two phase relations existed between the activity of the $\alpha_3$, $\gamma_1$ and SP2(1) fibres per oscillation period (100-140 ms) of the $\alpha_3$-motoneuron (Fig. 7Ba,b), but the phase relations changed with ongoing time (Fig. 7Ba,b). With the activation of the parasympathetic division three phase relations occurred per $\alpha_3$-motoneuron oscillation period (Fig. 7Bc 53-62 s)). At the peak '1' of parasympathetic activation (Fig. 6a (53-62 s)), 3 phase relations occurred, and only two phase relations were present with little parasympathetic activation (Fig. 7Bd (63-64 s)) (times between the peaks (Fig. 6a)) (Fig. 9). Upon strong parasympathetic activation (parasymp. peak '1' (53-62) and parasymp. peak '2' (65-72)), the somatic and parasympathetic nervous systems became functionally fully intertwined in the way that in the subnetwork, consisting of the coordinated activity of the $\alpha_3$-motoneuron neuronal networks and SP2(1) spindle afferent fibre, the number of phase relations changed from 2 to 3 per $\alpha_3$-motoneuron oscillation period. At least, the rhythmically firing $\alpha_3$-motoneuron is in itself already an ensemble, namely a network oscillator of which the $\alpha_3$-motoneuron is a part of.

To make the changing phase relations per oscillation period of the $\alpha_3$-motoneuron between the activity of the different $\alpha$ and $\gamma$-motoneurons and secondary spindle afferent fibres, occurring in the phase histogram of Fig. 7B, easier recognizable, the functional units, consisting of the coordinated activity of fusimotor and $\alpha$-motoneuron neuronal networks and spindle afferents fibres, were schematized drawn in Fig. 8. A possible parasympathetic spindle innervation is not pictured. With further schematization, the change of the number of phase relations in and between two functional units upon different stimulations, plotted in Fig. 7B, are made easy visible in Fig. 9.

In Fig. 9 it can be easily seen how the number of phase relations changed for the different time intervals and stimulations, defined in Figs. 6,7B.

The difference of network organization between the brain-dead human and paraplegic 9 is that the functional units, consisting of fusimotor and $\alpha$-motoneuron neuronal networks and spindle afferent fibres, were rather unstable in the paraplegic. Further, another (third) phase relation per $\alpha_3$-motoneu-

![Phase relation diagram](image_url)
ron oscillation period occurred with the activation of the parasympathetic division (Fig. 9). The activated parasympathetic neuronal network of the sacral micturition and defecation centre seems to have channeled input to the oscillatory firing somatic neuronal network. An analysis of the change of the number of phase relations in the brain-dead was not performed.

Location and stimulation of receptors for continence

The receptors of skin, urinary bladder and anal mucosa, the muscle spindles which were innervated by secondary spindle afferents, and the muscles which most likely were innervated by α-motoneurons in paraplegics 7 and 9 and in the brain-dead human HT6 are marked in Fig. 10 in the lower pelvis. The locations for the brain-dead human were taken from Fig. 6 of (35).

The (rhythmic) activation of these receptors by anal and bladder catheter pulling and skin stimulation of sacral dermatomes, to stimulate simultaneously the somatic and parasympathetic divisions to induce learning transfer, can be simulated and achieved during therapy, if a patient with severe cervical spinal cord injury is jumping rhythmically on springboard upon no weight support (Fig. 11A).

![Parasympathetic intervention of somatic circuitries](image_url)

Fig. 9. – Schematic drawing of the occurrence of phase relations (of and between two units, one pictured in Fig. 10A) following activation of the sacral parasympathetic division (parasymp) by bladder catheter pulling (Fig. 6a) between the APs of the $\gamma_1$, $\alpha_3$, and $\alpha_2$-motoneurons and the secondary muscle spindle afferent fibres SP2(2) and SP2(5). Note that an additional phase relation occurred per oscillation cycle with the activation of the parasymp division. The time periods are same as in Fig. 8.

![Location of receptors for the continence of the urinary bladder and the rectum](image_url)

Fig. 10. – Location of receptors and muscles for the continence of the urinary bladder and the rectum, innervated by motoneurons the activities of which were recorded, in the brain-dead human HT6 (dS4 root), paraplegic 9 (vS4 root) and paraplegic 7 (nerve root S5).

Stimulation of the parasympathetic and somatic division via their receptors of the pelvic floor and intestine to induce learning transfer from movements to urinary bladder functions for care

It was shown that the parasympathetic division can be activated besides the somatic one by anal and bladder catheter pulling (Figs. 6,7). The activated parasympathetic neuronal network channeled input to the rhythmically firing somatic neuronal network.
via an additional phase relation (Fig. 9). This joint stimulation of the somatic and parasympathetic division is used in ‘coordination dynamics therapy’ to use movements which substantially activate the somatic and the vegetative nervous system to induce learning transfer from movement to bladder patterns to cure urinary bladder function. Upon jumping on springboard, without weight support in severe cervical spinal cord injury (!) (Fig. 11A), the pelvic floor (including the sphincters) is mechanically stimulated (stretch of muscle spindles) under the weight of the intestine. Also the stretch and tension receptors of bladder and rectum are activated upon the rhythmic up and down movements.

The desire or urge to void is also strongly stimulated when the patient is exercising on the special coordination dynamics therapy device, especially in the lying position (Fig. 11B). But this stimulation of the parasympathetic and somatic divisions is related to the improvements in the short-term memory of the phase and frequency coordination of the neuronal networks of the sacral micturition centre including the functional units pictured in Fig. 9. This analysis will be picked up in a following paper (59).

Both, the rhythmic mechanical stimulation of the continence organs (Fig. 11A) and the improved CNS organization in the short-term memory upon exercising on the special device for turning movements (Fig. 11B) lead to a strong activation of the sacral micturition centre which may lead in turn to strong increases of the heart rate and blood pressure, which are vegetative symptoms to inform supraspinal centres about bladder fullness in complete spinal cord
injury, if the urinary bladder is filled and if there is plenty of material in colon and rectum. Before exercising the bladder should be emptied.

Discussion

Premature activation of sphincteric motoneurons

As can be seen in Fig. 3A, the sphincteric motoneurons \(a_2(1)\) and \(a_2(2)\) in paraplegic 7 were activated too early with respect to the extent of bladder filling (double peaked activation shape) in comparison to the sphincteric motoneuron in the brain-dead individual HT6. With respect to the input of the tension receptor afferents the sphincteric motoneurons in paraplegic 7 were not activated too early (Fig. 3B). Thus the activation in the paraplegic was rather normal, with only the too high bladder afferent input mimicking a too filled bladder. The third \(a_2\)-motoneuron \((a_2(3))\) in paraplegic 7 was also highly activated, but showed a different activation shape (Fig. 3A). It is likely that normally this motoneuron would not directly contribute to continence. Probably this motoneuron was activated by reflex generalization, and most likely innervated the pelvic floor. Since few motoneurons in S4 and S5 roots innervate also leg muscles (36), it cannot be excluded that this motoneuron innervated a leg muscle.

Even though in paraplegic 7 the too early activation of sphincteric motoneurons was caused by a too high afferent input from the bladder afferent fibres, there were also changes in the CNS as suggested at least by the detrusor-sphincteric dyssynergia. A too early activation of the striated sphincters is not in contradiction with detrusor-sphincteric dyssynergia. In normal women with a urinary bladder infection, the detrusor is activated too early, most likely because the infection activates bladder afferent fibres, but the external bladder sphincter still relaxes when the detrusor is activated (detrusor-sphincteric dyssynergia). Interspike intervals and phase relations will now be used to analyse pathologic functions of the spinal cord. It will be shown that the oscillatory firing of motoneurons (34) and the coordination of firing between motoneurons and secondary muscle spindles changed following spinal cord injury, which could be one reason for the development of detrusor-sphincteric dyssynergia.

Interspike intervals of, and phase relations between, the APs of the \(a_1\) and \(\gamma\)-motoneurons and secondary muscle spindle afferents in paraplegic 9 upon activation of the sacral micturition centre

Since two phase relation occurred per oscillation cycle between the \(a_1\) and \(\gamma_1\)-motoneurons and the SP(2) fibre (Fig. 7Ba) in paraplegic 9, and also their IIs were rather similar, it is concluded that the neuronal networks of the \(a_1\) and \(\gamma_1\)-motoneurons formed together with the spindle afferent fibre SP(2) a part of a functional unit. The functional unit is built by efficiencies of synapses and projections between the convergence of several fusimotors on one muscle spindle and by the divergence of muscle spindle projections onto several rhythmically firing populations of neurons driving \(a\) and \(\gamma\)-motoneurons. Such a functional unit is partly pictured in Fig. 8 and schematized drawn by 3 circles in Fig. 9. The \(a_1\)-motoneuron and the SP(2) fibre belonged to another functional unit (longer IIs and the existence of only 1 phase relation). The two functional units are characterized in Fig. 9 by two sets of 3 circles each. The two functional units interacted with each other as there existed a phase relation between the \(a_1\) and \(\gamma_1\)-motoneurons.

Following touch, pin-prick and anal reflex stimulation, but not painful catheter pulling, the functional organization in that subneuronal network of the spinal cord only changed slightly between the time intervals 1-6 s and 49-52 s (Figs. 6a,7Ab,7Bb), since the durations of IIs and the existing phase relations changed only little. Functional unit one, consisting of the \(a_1\) and \(\gamma_1\)-motoneurons and the SP(2) fibre, only changed the values of their phases. Functional unit two (\(a_1\)-/SP(2)) became disorganized as the phase relation between the APs of the \(a_1\)-motoneuron and the SP(2) fibre was lost (Fig. 9 (49-62 s). The neuronal network driving the \(a_1\)-motoneuron was still interacting with the neuronal network driving the \(a_1\)-motoneuron, since a phase relation existed between the impulses of the \(a_1\) and \(a_2\)-motoneurons.

Following strong (painful) bladder catheter pulling with a first strong activation of the parasympathetic division (time interval 53-62 s), measured by the burst firing (see (58)) of the SP(2) fibre, the functional organization of the sacral micturition center of the disconnected spinal cord changed com-
pletely. Functional unit $\alpha_2$/SP2(1) was now correlated by three phase relations per an $\alpha$-oscillation cycle. The functional unit $\alpha_2$/SP2(2) also showed 3 phase relations per an $\alpha$-oscillation cycle, and interacted with functional unit $\alpha_2$/SP2(1) by 3 phase relations as well (between the $\alpha_3$ and $\alpha_2$-motoneurons; Fig. 9 (53-62 s)).

Between the first and second parasympathetic peak at the time interval 63-64 s (Figs. 6a,9), the organization form of the two functional units was similar to that before the first parasympathetic activation (49-52 s) (Fig. 9), only the values of the phase relations changed (Fig. 7Bb,d).

With the second strong activation of the parasympathetic division (parasymp. peak 2, time interval 65-72 s) the functional unit $\alpha_2$/SP2(1) was bound together again by 3 phase relations (Fig. 9), in similarity to the first strong activation of the parasympathetic division, measured by the activity of the secondary muscle spindle afferent fibre SP2(1). The functional unit $\alpha_2$/SP2(2) was disorganized, but phase relations still occurred between the $\alpha_3$ and the $\alpha_2$-motoneurons and the SP2(2) fibre (Figs. 7Be,9). The $\alpha_3$-neuronal network and the fusimotor networks, driving the SP2(2) spindle afferent fibre, were integrated differently.

After the second strong parasympathetic activation, in the time interval 73-76 s (Fig. 9), 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 $\alpha_2$/SP2(2) was slightly disorganized as the SP2(2) fibre strongly reduced its firing (Fig. 6g).

As analyzed in a previous paper (58), the secondary spindle afferent fibre SP2(2) in the brain-dead HT6 also showed short IIs, but no IIs of long duration (Fig. 7Af) when activated by the parasympathetic division, as compared to the occurrence of also long IIs in the SP2(1) fibre in paraplegic 9.

**Neuronal network, synfire chains and reverberating circuits**

It was shown in the brain-dead human that the phases in the functional unit, consisting of the fusimotor $\gamma_1$, the secondary spindle afferent fibre SP2(2), and the sphincteric $\alpha_2$-motoneuron O2 and, probably, other fusimotors and secondary muscle spindle afferent fibres, changed only little in the time interval 0-32 s (Figs. 4,5). Since there was no strong phase relation between the static fusimotor $\gamma_2$, the secondary muscle spindle afferent fibre SP2(5), and the oscillatory firing $\alpha_2$-motoneuron O2, the sub-populations of the neuronal network driving those fusimotors contributed only little to the information transfer to the network driving the $\alpha_2$-motoneuron O2. The interspike interval and oscillation period distributions of the $\alpha_2$-motoneuron APs, suggest that the $\alpha_2$-motoneuron O2 was integrated in the organized neuronal network (34). As a second working hypothesis, based on the relation between the oscillation period T and the number of APs per impulse train $n_{AP}$, the periodic firing is generated by reverberations in neuronal circuits in which the $\alpha_2$-motoneuron O2 is integrated. Such reverberations travel in dynamically changing closed loop pathways, in which the excitation follows multi-interneuronal routes which are changing from time to time. In each cycle the reverberation traverses a certain chain of interneurons for certain duration of the oscillation period. If the $\alpha_2$-motoneuron fires with impulse trains consisting of 3 APs every 160 ms, the interneuronal chain is 3 neurons, or neuron units (including inhibition), long. If the motoneuron fires with 2 APs every 130 ms, the interneuronal chain is only two neuron units long (34). This simple working hypothesis that such reverberations travel well-defined anatomical circuits has to be given up, since single dedicated routes cannot explain the pathological firing of the oscillators as reported herein. Also, the excitation of inhibitory interneurons is not included (see page 81 of (40)). Without trying to improve the details of the oscillator model, some changes have to be discussed to understand the pathologic firing of sphincteric motoneurons in paraplegics with detrusor-sphincteric dysynergia.

The dedicated lines of the working hypothesis have to be replaced by synfire chains, which consist of chains of neuronal sets. Each neuron in one stage excites every neuron in the next stage. The excitation transmission in a synfire chain from stage to stage is secured by the synchronous firing of all the cells in one stage (1). The important point in the synfire chains is that they can cross. Two dedicated lines cannot cross over because once the cross-over point is excited there is no way to tell which direction the activity will proceed. In the synfire chain
the same neuron may participate in many different chains according to whether it fires synchronously with one set of cells or with another.

From Fig. 6 it can be seen that $a_1$ and $a_3$-motoneurons in paraplegic 9 fired with 1 AP per impulse train every 100 to 160 ms ($a_1$) or every 300 to 400 ms ($a_3$) (Fig. 7A) in complete contradiction to the physiologic firing mode (Fig. 1). In paraplegic 7 the sphincteric motoneurons fired often with 2 APs every 200 to 300 ms (Fig. 3C). The number of APs per impulse train of the motoneurons innervating the external bladder sphincter is in accordance with Fig. 1, but the duration of the oscillation period is not. Essential changes must have taken place in the oscillatory firing neuronal networks, in which the motoneurons are integrated. The functional organization into different subpopulations should be different, because the oscillation period became much more variable for a certain impulse train length and the necessary phase relations became unstable (Fig. 7B). On the basis of the dedicated line hypothesis, the changing oscillation period can be explained by many different pathways. But these changes cannot be understood on the basis of dedicated lines and interneuron cell death. The dedicated lines are very sensitive to failure of individual neurons. If one neuron in a chain dies, the chain becomes useless as a whole. The large loops with long dedicated lines and long oscillation periods will become useless first, because they consist of many interneurons. Long oscillation periods still occurred in the very pathologically functioning spinal cord network, even though they were quite irregular. Dedicated line neuronal network and interneuron cell death cannot explain the pathologic firing of $\alpha$-motoneurons. The hypothesis of dedicated lines has to be abandoned. Even if there were no interneuron cell death, one could not understand where the pathologic changes should come from, if networks are constructed of dedicated lines.

If one thinks of a neuronal network consisting of synfire chains which cross each other and changes of synaptic efficacies (see later), then the measured pathologic impulse patterns are conceivable. If for example synfire chain loops cross each other, integrated in a network or matrix of synfire chains, then the reverberating excitation may change several times the loop. An overexcitation of the spinal cord neuronal network, often present in paraplegics, can result in a block of transmission at synfire chain crossings. When two synfire chains become active together and they share neurons in the same network, they may destructively interfere with each other (1). Therefore the synfire processing may be limited to one process at a time. The dying of frogs at temperatures between 29 and 30°C (see previous paper (58)) when their nervous system gets over-excited, can be understood on the basis of synfire chain networks. The synfire chain is a good candidate for the carrier of high-level processing in the central nervous system.

The coupling of oscillatory firing networks to a different degree, called ‘relative coordination’ by E. v. Holst (17), could be understood on the basis of synfire chains. The size of each set in a synfire chain is small but there is a large subsynchronous fringe of neurons affected by the activity in the chain. A single neuron may be affected by many synfire chains and may even be a part of several synfire chains (1).

**Different neuronal network systems may show different degrees of pathology: more integrative network organizations get more impaired**

The common brainstem system integrates and regulates the activity level of the brain and the nervous activity for the cardiovascular and respiratory regulation and the regulation of the motor tone. With respect to the functional organization of the reticular formation of the lower brain stem, it is argued that exact frequencies or sharply defined frequency ranges are not very helpful because of the variability of the rhythmical events, as described above; their amplitudes and period durations depend on the functional organization of the system, the character of afferent inputs and phase relations between different, simultaneous rhythms (26). Also, in the sacral micturition center of humans the frequency of the oscillatory firing motoneurons and the number of APs per impulse train depends on the afferent input (35) and on the coupling with other oscillatory firing networks (35). Under physiologic conditions however the $\alpha_1$-motoneurons (FR) fire rather stably in the oscillatory mode, the $\alpha_2$-motoneurons (FF) probably very stably and the $\alpha_3$-motoneurons ($S$) unstably (28). Probably the stability under physiologic conditions depends on the size.
of the functionally organized subneuronal network, on the kind of the respective afferent inputs, and on whether the network serves faster or slower motor functions (activation against gravity). The neuronal networks in which the α1-motoneurons are integrated probably consist of many hundreds of interneurons, and different kinds of afferent inputs will contribute to the drive. The α1-motoneuron networks probably are most similar to brain stem networks with respect to the organization, because of the low and changing frequencies and multi-afferent drive. But even in α1-motoneuron firing there seems to exist a correlation between the number of APs per impulse train and the oscillation period (28).

Interestingly, rather physiologically firing α1-motoneurons could not be detected at all in paraplegics, even though they are easy to detect because of their firing with long impulse trains. The α1-motoneuron of Figs. 6, 7 fired so atypically (Fig. 1) that one has doubts that it really was an α1-motoneuron rather than an α2-motoneuron (the identification rests only on the conduction velocity and not on the firing pattern). The slow neuronal network systems (α1) seem to have changed more than the fast systems (α1, α2) following spinal cord injury. Since most likely the α1-motoneuron neuronal networks consist of many more interneurons than the faster motor systems, it seems that it were the more integrative functions of the neuronal networks in the spinal cord that underwent changes. These integrative functions can be understood within the framework of System Theory of Pattern Formation, measured non-invasively by the coordination dynamics and can be repaired by applying integrative coordinated input and reconstructing supraspinal control in motoric complete spinal cord injury (see below). Actually during regeneration of the cord, following cervical spinal cord injury, the integrative functions (quantified by the coordination dynamics) get transiently impaired (increase of coordination dynamics values) very much like following injury (Fig. 3 of 56).

Since the detrusor is activated more slowly than the α1-motoneurons, the parasympathetic neuronal network in the sacral micturition center is probably slower and more integrative in processing than the α1-motoneuron neuronal networks. Probably, numerous interneurons contribute to the activation of the preganglionic parasympathetic neurons. One can expect therefore quite much dysfunction of the parasympathetic neuronal network system of the sacral micturition center. The parasympathetically activated secondary muscle spindle afferent fibres in paraplegics fired quite differently to those of the brain-dead human HT6 (58). The parasympathetic neuronal network can be repaired by specific input to the parasympathetic division in coordination with the input to the somatic division. The jumping on springboard (Fig. 11A) activates rhythmically the pelvic floor (with the external anal and bladder sphincters), the bladder (detrusor) and the colon and rectum via dynamic movements (Fig. 10). The movement induced afferent input from the continence organs entrains parasympathetic (and somatic) neuronal networks.

It was shown in this paper (Fig. 6) and elsewhere (34) that the oscillatory firing mode of α2 and α3-motoneurons changed following spinal cord injury. It was further shown that following spinal cord injury in the occasional firing mode the α1-motoneurons were recruited before the α1-motoneurons (32) whereas physiologically (including the brain-dead individual) the α1-motoneurons are recruited before the α1-motoneurons (32). Therefore, also the coordination between different kinds of α1-motoneuron neuronal network systems have changed following spinal cord injury. The coordination between the different α1-motoneuron neuronal networks can be trained by changing the frequency of exercising and activating in this way the slow, the intermediate and the fast neuronal networks differently. It is likely that also the coordination between the α1-motoneuron neuronal network systems and the parasympathetic neuronal network system underwent changes. Based on this, detrusor-sphincteric dyssynergia in paraplegics is likely to occur, because the timing between α3 and α1-motoneuron systems changed following injury as probably also did the timing between the α1-motoneuron systems and the parasympathetic neuronal network system.

**Reasons for pathologic changes**

The question is now, why do the neuronal networks of the sacral micturition center organize themselves in a false way. What changes occur in the isolated spinal cord when it is disconnected from the
supraspinal control that is exerted by impulse patterns and trophic effects. Interneuron cell death, sprouting, changes in synapse efficacy (see below), and reorganizations of the automatized spinal cord are possible reasons for change. Obvious interneuron cell death has not been found so far. For cats it has been reported that there is no sprouting following spinal cord transection (24), even though it is generally believed that there is sprouting (23). One is therefore mainly left with the changes in the synapses, partial denervation of neurons, lost supraspinal control and the reorganization of the micturition reflex (automatism) for the understanding of dysfunctions in the sacral micturition center. Since humans with partial cervical spinal cord injury (tetraparetics) can reduce their spasticity and repair bladder functions when undergoing coordination dynamics therapy (55), dysfunctions in the organization of the neuronal network of the sacral micturition center are at least partly reversible (tetraparetics with some volitional bladder innervation left have bladder synergia). It seems possible to modulate the efficacy of synapses by natural impulse patterns from the periphery and from supraspinal centers to make the organization of the neuronal networks turn more physiologic again (plasticity). Since there is limited regeneration in motoric complete cervical spinal cord injury (tetraparetics) can reduce their spasticity and repair bladder functions when undergoing coordination dynamics therapy (55), dysfunctions in the organization of the neuronal network of the sacral micturition center are at least partly reversible (tetraparetics with some volitional bladder innervation left have bladder synergia). It seems possible to modulate the efficacy of synapses by natural impulse patterns from the periphery and from supraspinal centers to make the organization of the neuronal networks turn more physiologic again (plasticity). Since there is limited regeneration in motoric complete cervical spinal cord injury (56), pathologic changes of the sacral micturition center are reversible (60). But still we need to understand how this repair is taking place.

Long term changes in efficacy of synapses, as terminal sprouting, new synapse formation and nerve terminal retraction occur in untreated vertebrate muscle under physiologic conditions (66,67). The physiological remodeling allows the change of the architecture of synapses in response to different physiological and pathophysiological conditions. Physiological plasticity that operates in the millisecond or second range is facilitation, augmentation, potentiation, depression and desensitization (19). For neural models of plasticity see (10). Efficacy can be functionally defined as synaptic safety margin, or the likelihood that postsynaptic potentials will exceed threshold for generation of axon AP. Presynaptic remodeling might be caused by presynaptic axon activity, that means by training.

For patients with complete spinal cord injuries, some supraspinal control has to be reconstructed to allow voluntary micturition and voluntary training of the organization of spinal cord network.

**Phase escape of the somatic neuronal networks as a possible cause for detrusor-sphincteric dyssynergia**

It was shown that with the activation of the parasympathetic division in paraplegic 9 three phase relations occurred in the functional organization of the units driving the \( \alpha_2 \) and \( \alpha_3 \)-motoneurons (Figs. 7B,9). Since phase relations indicate information transfer, it is concluded that the parasympathetic neuronal network interacted with the somatic ones, driving the sphincteric motoneurons. In the brain-dead human HT6 (Fig. 5) the phase relations were lost in the functional units consisting of the \( \alpha \) and \( \gamma \)-motoneurons and the secondary muscle spindle afferent fibres, when the parasympathetic division was activated. In a previous paper (58) it was shown that upon the activation of the parasympathetic division the \( \alpha_2 \)-motoneuron \( O_2 \) strongly reduced its activity level by stopping firing oscillatory; in other words, the parasympathetic division inhibited the sphincteric motoneurons. In the paraplegic patients, the phase relations were not lost in the two functional units (Figs. 7B,9). Only the number of phase relations changed from 2 to 3 and the phases changed. In a previous paper (58) it was shown that the sphincteric motoneuron did not strongly reduced its activity upon the activation of the parasympathetic division. The sphincteric motoneuron in the paraplegic was not inhibited upon the activation of the parasympathetic division.

Upon the activation of the parasympathetic division in the paraplegic patient, parasympathetic neuronal networks interacted with the two functional units driving sphincteric motoneurons, since an additional phase relation was built up (Fig. 9). However, as phase relations in the somatic units still existed and the activity of the sphincteric motoneurons was not reduced, it is possible that the somatic functional units escaped the inhibitory action of the parasympathetic division by changing their phases (phase escape). The phase escape of the somatic neuronal networks driving the sphincteric motoneurons, from the parasympathetic inhibitory action could be a reason for the detrusor-sphincteric dyssynergia at
the level of the sacral micturition center, in terms of human neurophysiology.

**Detrusor-sphincteric synergia and dyssynergia in the framework of System Theory of Pattern Formation – The solution of the seemingly unsolvable urinary bladder coordination problem**

A completely different understanding of detrusor-sphincteric synergia and dyssynergia is obtained in the framework of System Theory of Pattern Formation for Repair (55). The synergia and the dyssynergia are neuronal network patterns (attractors) with different stabilities. Under physiologic conditions, the stability of the attractor ‘synergia’ is high and the stability of the attractor ‘dyssynergia’ is low. By intention a healthy subject or a patient with a repaired bladder can switch between both patterns (60).

Such a schematic continence attractor layout for the jumping on springboard (55) shows some similarity to the attractor layout for the ‘jumping in-phase’ has a higher stability (deep potential well) than the ‘jumping in anti-phase’ (more shallow potential well).

Even more similar is the antagonicity property of antagonistic muscles (extensor and flexor), as for example the gastrocnemius and the tibialis anterior muscles. During walking, the tibialis anterior is inhibited (not activated) upon contraction of the gastrocnemius muscle and vice versa. The motor programs show antagonistic action. But during standing, both muscles are activated. The motor programs show co-contraction. There are therefore attractors for antagonistic action and co-contraction. A healthy subject can choose by intention between the walking and the standing pattern, which means between the pattern of antagonistic action and co-contraction.

Following spinal cord injury, the patient can have the antagonistic action or the co-contraction pattern preserved. Intermediate, pathologic patterns do occur. When the patient’s CNS can partly activate the stepping automatism, often also the pathologic extensor spasticity occurs, which is some kind of co-contraction with emphasis on the extension. During supported treadmill walking, the patient’s CNS can improve the walking pattern in the short-term memory. The stability of the antagonistic pattern is increasing and the stability of the co-contraction pattern is decreasing. The patient can walk better and the spasticity reduces. The impairment of antagonistic muscle action is therefore a similar problem as the dyssynergia of the urinary bladder, but can be measured by electromyography (55). The important difference between the antagonistic muscle action and the synergia of the bladder is that the antagonistic muscle action can be trained and relearned directly by performing coordinated movements like walking, jumping (Fig. 11A) or exercising on special devices for turning (Fig. 11B). But for the improvement of the stability of the synergia pattern of the bladder, learning transfer from coordinated movements is needed.

During physiologic micturition, the detrusor contracts and the external sphincter relaxes. But the pattern that the detrusor and the external bladder sphincter contract simultaneously also exists; only its stability is lower. A healthy person can stop (interrupt) the micturition (for continence reason) by activating on volition the external sphincter. In this situation, the detrusor and the external sphincter contract simultaneously. That means, by intention a healthy person can also activate the dyssynergia pattern. The healthy person can choose between the patterns continence and voiding and can even switch between both patterns. But with the loss of supraspinal control, a subject with a complete spinal cord injury cannot choose any more between both patterns. According to the special injury situation and the stage of disorganization of the neuronal networks of the sacral micturition centre, both patterns (and intermediate patterns) do occur and the patient cannot choose any more by intention.

The fundamental progress is now that urinary bladder function can be repaired in severe cervical spinal cord injury (motoric complete injury, sensoric incomplete) by learning and learning transfer from special movements and some reinnervation of the caudal spinal cord for volitional control (56,60). Such structural repair can be achieved by a partial regeneration of the spinal cord and/or an establishment of connections via the plexus hypogastricus.

In the reported case 2 years of optimal coordination dynamics therapy were needed for bladder repair (56,60). The bladder repair included the reconstruction of some supraspinal control which seems to be necessary for physiologic bladder functioning.
In the last stage of bladder repair the female patient felt the synergia and the dyssynergia patterns. For emptying the bladder, she started the voiding with the synergia pattern that means the detrusor (bladder muscle) contracted and the external sphincter relaxed. Fluid was leaving through the urethra. But when she pressed to reduce residual urine (and generated stress in her CNS, which induces spasticity), she felt that the external sphincter co-contracted with the detrusor. No fluid was leaving the bladder any more. The organizational state of the CNS had switched from the synergia pattern to the dyssynergia pattern. But with intention and touch afferent input (behavioral information in the equation of motion of the collective variables, see Ref. 55) from the Head’s zone of the bladder (the patient touched the skin on top of the bladder), the pattern state switched back to the synergia pattern. This means, the external sphincter relaxed (was inhibited) and the detrusor could push further fluid out of the bladder by continuous contraction to reduce further residual urine. For further discussion and details see the following article on the cure of urinary bladder (60).

In conclusion, urinary bladder dysfunctions can be cured, including the dyssynergia of the bladder. Destructive operations are therefore not justified any more, especially in young patients who will have a further life expectation time of 50 years and who want to train hard for a better future. Till to the cure of the bladder in severe cervical spinal cord injury, catheters, urinals, and diapers have to be used.

By using human electrophysiology and integrative pattern formation strategies it is possible to understand and cure urinary bladder dysfunction. The understanding of bladder functions under physiologic and pathophysiologic conditions alone is not sufficient for cure; the system theory of pattern formation for repair is needed. On the other hand, with an understanding of the integrative CNS functions alone, one even cannot understand the problem of bladder dyssynergia and cannot develop behavioral information (treatment) to increase for example the stability of the synergia pattern. Human neurophysiology and a clinical understanding of the problem are also necessary. Already Eccles argued: “From mere behavioural descriptions we shall never come to understand how the brain is effective in the learning of motor skills” (70). With the knowledge of central pattern generators (62) we also cannot understand learning transfer, which is important not only for curing autonomic CNS functions but also for improving higher mental functions in cerebral palsy (48) by learning in the motor system.

In incomplete cervical spinal cord injury a bladder repair is not that difficult, because a partial regeneration of the spinal cord is not needed (55). Already a functional reorganization can cure bladder (and motor) functions. By using coordination dynamics therapy, the author himself cured urinary bladder functions in 4 patients with an incomplete spinal cord injuries (of different degree) in the cervical, thoracic, and lumbar regions (41,42,55,56,60).

**Learning transfer**

The most important step in the development of treatment (on the basis of human repair physiology) to cure human CNS functioning is to measure human CNS self-organization under physiologic (in brain-dead and healthy humans if possible) and pathophysiologic conditions (in patients) to know what became pathologic and what has to be repaired. The simultaneous recording of natural impulse patterns from several single human neurons was the key tool for that diagnostic which has also been shown in this article. But further knowledge is needed of such natural afferent and efferent impulse traffic of single neurons to improve such learning transfer, achieved by the exercising of certain motor patterns, to further develop this movement-based learning therapy for repair called ‘coordination dynamics therapy’. Before coming to the article on the cure of the bladder, therefore, the learning transfer is further analyzed on the single neuron level in human because this learning transfer is not only necessary to cure bladder and other autonomic functions but also to improve higher mental functions, including speech and memory for example in cerebral palsy (48). Learning transfer is a general property of CNS functioning and is probably also involved in memory, intelligence, and creativity. How limited would be the property of learning, if we could not generalize a problem and could not use learned knowledge in other circumstances or disciplines.
Spared fibre counts

The relationship between the number of axons spared by an incomplete spinal cord injury and the locomotor efficacy of the animal’s hindlimb has been studied. It was found that residual fibre counts in excess of 5,000 are associated with useful hindlimbs to assist locomotion (12,20). How many fibres have to spared (or repaired) to cure urinary bladder function is unclear.

An early treatment (6-8 hours) with methylprednisolone hemisuccinate may improve the neurological outcome after acute spinal cord injury (2), so that approximately 80% of the new spinal cord injuries are incomplete.

Need for qualified human research

It could be argued that the few measurements of this and the previous article (58) offers not enough safety to draw conclusions concerning the functions of the human CNS; especially since there is only one direct control measurement (HT6). Firstly, one has to remember that it is extremely difficult to get hold of such human measurements (humans cannot be taken from the stock for measurements) and that this kind of research is not organized. Second, the functional correlations between neurons, immanent in the sets of natural impulse patterns, may give more insight into the function of the human CNS than hundreds of animal experiments, partly summarized in recent review articles (72-75). The simultaneous measurement of further parameters, which can clinically be tested, could further improve the safety of the measured parameter dependences. Thirdly, since each spinal cord injury is different to the other one, statistical evaluations are doubtful. The task is not to destroy a developing human neurophysiology (or ignore it), but to compete with it by offering more and better human data. Fact is that these few measurements on the self-organization of parts of the human CNS have direct clinical consequences in the treatment after stroke (43), traumatic brain injury (44,50), hypoxic brain injury (49), cerebellar injury (51,52), spinal cord injury (42,45,55,56,60), in cerebral palsy (48), and in Parkinson’s disease (46,47).

References


Address reprint requests to:
Gisela Schalow
Dr.med.habil.,Dr.rer.nat.,Dipl.Ing.
Untere Kirchenmatte 6
CH-6207 Nottwil
Switzerland
www.cdt.host.sk
E-mail: g_schalow@hotmail.com