Effect of functional electrical stimulation on the central state of excitability of the spinal cord

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Abstract—**The recent years brought a growing awareness for the existence of complex neuronal structures within the spinal cord that act as movement controllers. The presented pilot study addresses an extension of pure non-invasive spinal cord stimulation by adding an afferent input from electrically stimulated peripheral nerve. The goal was to assess electrophysiologically the influence of peripheral nerve stimulation (peroneal nerve) on the function of the lumbar spinal cord neural circuitries.**

In a subject in supine position 3 series of conditioning stimulus trains (10 s, 30 Hz) at sub-threshold, sensory threshold and motor threshold intensity were applied to the peroneal nerve, immediately followed by a stimulus via a paravertebral electrode pair, positioned between the T11 and T12 spinal processes. The stimulus intensity at the lumbar spinal cord was tuned to just eliciting measurable posterior root-muscle (PRM) reflexes in four major muscle groups of both lower extremities.

The PRM reflex of the ipsilateral quadriceps was suppressed and with increasing peroneal nerve stimulation strength this effect spread to other muscles. Reduced amplitudes were observed in EMG-recordings from ipsilateral proximal and distal flexor and extensor muscle groups. Further studies on this effect are ongoing.

Present preliminary results suggest that measurement of modification of excitability with conditioning peripheral nerve stimulation or even brain generated residual input to the spinal cord can contribute to the therapeutical programs based on FES.

Keywords— **Spinal cord, afferent input, pattern generator, electrical stimulation, FES.**

I. Introduction

Functional Electrical Stimulation (FES) has been applied for restoration of lost movement functions since the 60s of the past century. With the exception of peroneal nerve stimulation to activate the withdrawal reflex pathways for inducing ankle dorsiflexion in combination with knee and hip flexion for gait correction in dropped foot impairments or for gait restoration in case of paraplegia, FES relied on stimulation of efferent (motor) nerves and direct control of paralyzed muscles in the functionality of a biological brace [1,2]. Though it is more or less impossible to avoid co-activations of afferent nerve structures in mixed peripheral nerves the occasionally observed resulting indirect effects, mediated through the spinal cord (SC)/central nervous system (CNS), were neglected or interpreted as artifacts. Later the concept of stimulation of motor nerves of peripheral nerve trunk and neglecting possible afferent input to the nervous system has been progressively replaced by the concept of simultaneous motor and sensory FES [3,4].

The recent years brought a growing awareness for the existence of complex neuronal structures within the SC that act as movement controllers. The Central Pattern Generator (CPG) or Lumbar Locomotor Pattern Generator (LLPG) were identified as programmed and programmable units that control movements under consideration of code signals arriving via various descending pathways and afferent signals from peripheral receptors (neural sensors). Recently the terminus "Spinal Brain" was introduced as generic term representing these structural and (multi-) functional capabilities of the SC [5].

It has been demonstrated that variation of frequency of tonic signals delivered to the lumbar SC (vertebral level T11/T12) with epidural or non-invasive surface electrodes is capable of inducing rhythmical (gait-like) or extension movements of the lower extremities [6,7,8]. It has further been shown in preliminary experiments that subjects with incomplete SC lesion can react to tonic spinal cord stimulation (SCS) with gait improvements respectively modifications [9].

To learn more about the underlying mechanisms of these observations our group started systematic electrophysiological studies to unravel interactions of afferent signals, neuronal networks at the spinal level and resulting efferent muscle activation. In a first series control properties of PRM reflexes, elicited via epidural or skin surface electrodes at the lumbar SC level were investigated. It was clearly seen that depending on conditioning stimuli and/or motor tasks, characteristic and reproducible modulations of the multisegmental PRM reflexes occur [10,11,12].

Based on preliminarily qualitative observations in three subjects showing signs of multisegmental suppression of motor nuclei excitability in conjunction with peroneal nerve stimulation, this paper describes a quantitative case study on control capabilities of electrical stimulation of peripheral afferent nerve fibers, where conditioning stimulus trains were applied to the peroneal nerve in combination with transcutaneous SCS and PRM reflex recording.

II. Methods

A. Stimulation and recording setup

One subject with intact nervous system was studied in supine position (Fig. 1).

Electrical stimulation was performed using commercially available self-adhesive transcutaneous electrical neural stimulation (TENS) electrodes (Schwa-medico GmbH, Ehringshausen, Germany). For SCS a pair of round electrodes with a diameter of 5 cm was placed over the paravertebral skin 1 cm apart on each side of the spine. This paravertebral electrode pair was positioned between the T11 and T12 spinal processes. A pair of rectangular electrodes (8 cm x 13 cm each) was placed longitudinally over the abdomen, one on either side of the umbilicus. Both electrode pairs were connected to function as a single electrode. Single rectangular biphasic stimulation pulses with pulse duration of 2 ms were applied (1 ms per phase). The electrodes were connected to the stimulator such that the paravertebral electrodes acted as the anode during the first phase of the stimulus pulse, with the abdominal electrodes as cathode.

A further disc shaped electrode (3 cm) was placed as cathode over the common peroneal nerve immediately next to the fibular head, the indifferent anode of the same size 5 cm more distally. 30 Hz stimulation was applied with rectangular monophasic stimulation pulses and 1 ms pulse width.

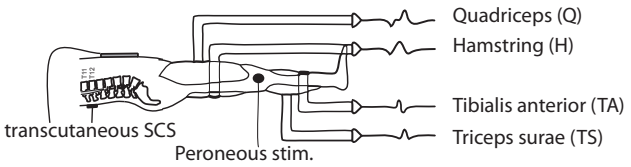

Fig. 1 Subject in supine position, stimulation electrodes above spinal process T11/T12 and above right common peroneal nerve, bilateral EMG recording from the 4 major muscle groups of the lower extremities.

The electromyographic (EMG) activity of stimulus-evoked compound muscle action potentials (CMAPs) of left and right quadriceps, hamstrings, tibialis anterior, and triceps surae muscle groups were recorded with pairs of silver-silver chloride surface electrodes. Each electrode pair was placed centrally over the corresponding muscle belly with an inter-electrode distance of 3 cm, and oriented along the long axis of the muscles.

B. Paradigm

PRM reflexes were used as test reflexes and the conditioning input was provided by peroneal nerve stimulation.

The paradigm consisted of three parts:
i) to obtain baseline responses 5 single stimuli with an inter-stimulus-interval of 10 s were applied to the spinal electrodes,
ii) after a delay of 10 s a series of 5 conditioning stimulus trains with continuous peroneal nerve stimulation (10 s, 30 Hz) immediately followed by a single stimulus to the SC where delivered with pauses of 5s and
iii) after a further break of 10s part i) was repeated.

The intensity for SCS was chosen above the common threshold, i.e. an intensity evoking PRM reflexes in all four muscle groups in both limbs.

The paradigm was performed independently with three stimulus intensities of conditioning trains (at peroneus):
i) 1 V below sensory threshold as reported by the subject,
ii) at the intensity of sensory threshold and
iii) at the motor threshold intensity, i.e. when tibialis anterior muscle showed initial signs of palpable reactions.

These three series where separated by breaks of 60s.

C. Data analysis

The hypothesis that the peak-to-peak amplitudes of the CMAPs of the PRM reflexes of the ipsi- and contralateral muscle groups differ between the baseline status before conditioning (control) and the conditioning sequence (test) was tested. The Kolmogorov-Smirnov test was used to test for normality. Equality of variances was tested with Levene's test. If the equality of variances was not given Welch's test for independent samples was used to compare control with test. Otherwise the Student's t-test for two independent samples was used. Results with $p < 0.05$ were deemed significant.

The correlation of the conditioned PRM reflex amplitude of every recorded muscle group and recording time was analyzed using Pearson's correlation coefficient, to exclude potential neural or muscular fatigue effects.

III. Results

The peak-to-peak amplitudes of the control PRM reflexes (control) and of the conditioned PRM reflexes, normalized to the mean of the control are depicted in Figure 2. The results of the statistical comparison between control and conditioned test are listed in Table 1.

Subsensory conditioning with peroneal stimulation depressed the ipsilateral quadriceps PRM reflex. With increasing stimulation strength of the conditioning the depression of the PRM reflexes spread to all ipsilateral muscle groups and increased in effect size. At motor level conditioning the amplitude of the contralateral hamstring was increased.

10 s after the conditioning sequence full recovery of the control status was observed, i.e. CMAPs achieved the same amplitude levels as the controls before conditioning.

No significant correlations between recording time and CMAP amplitude were identifiable in any muscle group and paradigm steps. This confirmed stable experimental conditions throughout the measurements.

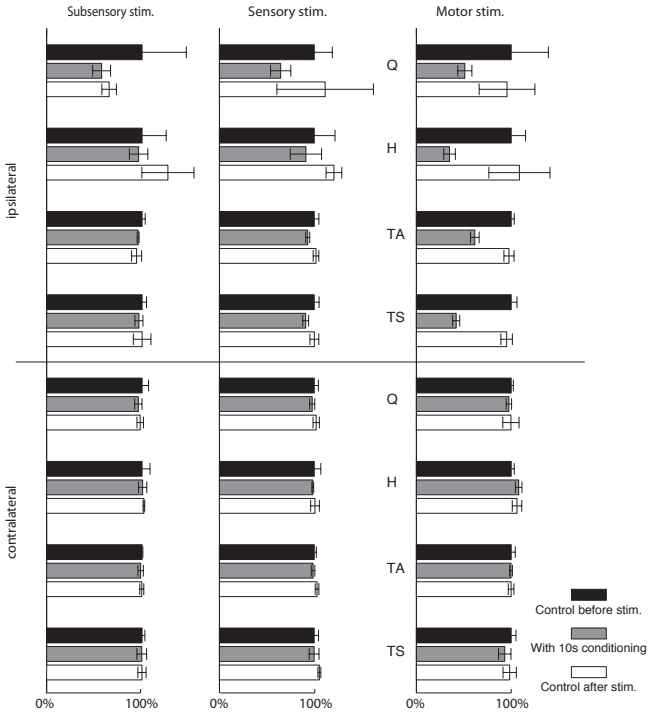

Fig. 2 Summary of the effects of 30 Hz / 10 s conditioning stimulation via peroneus nerve on the amplitude of PRM reflexes elicited in quadriceps (Q), hamstrings (H), tibialis anterior (TA), and triceps surae (TS) by transcutaneous spinal cord stimulation (36 V). The amplitudes are normalized to the mean value of the control PRM responses before conditioning. With increasing stimulation intensity the PRM reflexes are increasingly modulated. Ipsilateral depression increases with strength of peroneal nerve stimulation.

IV. Discussion

A suppression of the amplitude of the PRM reflexes is evident and is increased with increasing peroneal nerve stimulation strength. This effect occurs predominantly on ipsilateral proximal and distal flexor and extensor muscle groups. The attenuation of the excitability of the respective motoneuron pools is already evident even below threshold of muscle contraction. Furthermore, facilitation of the contralateral hamstrings was observed as well.

Table 1 Summary of effects between control and conditioned test

		Subsensory stimulation					
		μ (sd) cont.	μ (sd) test	t	df	p	sig.
ipsilateral	Q	0.49(0.09)	0.35(0.06)	2.90	8	0.020	*
	H	1.66(0.44)	1.68(0.17)	-0.09	8	0.931	
	TA	0.56(0.19)	0.54(0.01)	2.30	4.75	0.073	
	TS	3.55(0.18)	3.44(0.15)	1.05	8	0.326	
contralateral	Q	0.22(0.01)	0.22(0.01)	0.67	8	0.521	
	H	1.52(0.13)	1.55(0.07)	-0.40	8	0.703	
	TA	1.07(0.01)	1.05(0.03)	0.97	8	0.358	
	TS	1.96(0.06)	1.96(0.10)	0.12	8	0.904	

Stimulation at sensory level

		μ (sd) cont.	μ (sd) test	t	df	p	sig.
ipsilateral	Q	0.46(0.09)	0.30(0.05)	3.22	8	0.012	*
	H	1.73(0.43)	1.60(0.30)	0.59	8	0.574	
	TA	0.52(0.03)	0.49(0.01)	2.57	8	0.033	*
	TS	3.58(0.20)	3.24(0.11)	3.24	8	0.012	*
contralateral	Q	0.22(0.01)	0.21(0.01)	0.77	8	0.465	
	H	1.55(0.12)	1.52(0.01)	0.63	4.13	0.560	
	TA	1.06(0.03)	1.04(0.02)	0.82	8	0.437	
	TS	1.97(0.09)	1.95(0.10)	0.26	8	0.802	

Stimulation at motor level

		μ (sd) cont.	μ (sd) test	t	df	p	sig.
ipsilateral	Q	0.50(0.19)	0.25(0.04)	2.74	4.29	0.048	*
	H	2.12(0.32)	0.74(0.13)	8.89	8	0.000	***
	TA	0.54(0.02)	0.33(0.02)	15.44	8	0.000	***
	TS	3.74(0.23)	1.57(0.14)	18.09	8	0.000	***
contralateral	Q	0.23(0.01)	0.22(0.01)	1.49	8	0.175	
	H	1.49(0.05)	1.61(0.05)	-3.78	8	0.005	**
	TA	1.06(0.05)	1.05(0.02)	0.09	8	0.931	
	TS	2.15(0.11)	2.01(0.14)	1.83	8	0.105	

*: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$; Q: quadriceps, H: hamstrings, TA: tibialis anterior, TS: triceps surae, μ: mean, sd: standard deviation, df: degrees of freedom.

Of course we have to be careful with interpretation of first preliminary results of this study in progress. The results need to be confirmed by repetition of the experiment with a number of at least 10 subjects under same conditions, which is ongoing work. Furthermore we need more studies on the influence of variation of stimulation signals as frequency, intensity, train length etc. and on the control properties of various neural afferents. With view to future clinical treatment options inclusion of electrically stimulated afferents have to be considered.

The electrically and externally induced modification of altered neurocontrol in patients with upper motor neuron paralysis requires that stimulation is tailored according to the patient's residual motor control [5]. Therefore the measurement of the central state of excitability of spinal cord with PRM reflexes opens a new avenue in testing residual activity before application of external control approach.

Present preliminary results suggest that measurement of modification of excitability with conditioning peripheral nerve stimulation or even brain generated residual input to the spinal cord can contribute to the therapeutical programs based on FES. The question that needs to be answered is: What are capabilities of the nervous system for plasticity? In other words, we already learned that recovery capabilities in spinal-, head-injuries, strokes and other disorders depend on degrees of impairment, upper motor neuron dysfunction and the location of CNS lesion. How much these capabilities depend from residual motor control of spinal network is a question, which this new development allows to be addressed.

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