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RESEARCH ARTICLE

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Initiating extension of the lower limbs in subjects with complete spinal cord injury by epidural lumbar cord stimulation

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Abstract We provide evidence that the human spinal cord is able to respond to external afferent input and to generate a sustained extension of the lower extremities when isolated from brain control. The present study demonstrates that sustained, nonpatterned electrical stimulation of the lumbosacral cord—applied at a frequency in the range of 5–15 Hz and a strength above the thresholds for twitches in the thigh and leg muscles—can initiate and retain lower-limb extension in paraplegic subjects with a long history of complete spinal cord injury. We hypothesize that the induced extension is due to tonic input applied by the epidural stimulation to primary sensory afferents. The induced volleys elicit muscle twitches (posterior root muscle-reflex responses) at short and constant latency times and coactivate the configuration of the lumbosacral interneuronal network, presumably via collaterals of the primary sensory neurons and their connectivity with this network. We speculate that the volleys induced externally to the lumbosacral network at a frequency of 5–15 Hz initiate and retain an "extension pattern generator" organization. Once established, this organization would recruit a larger population of motor units in the hip and ankle extensor muscles as compared to the flexors, resulting in an extension movement of the lower limbs. In the electromyograms of the lower-limb muscle groups, such activity is reflected as a characteristic spatiotemporal pattern of compound motor-unit potentials.

Keywords Spinal cord injury · Spinal cord stimulation · Lower limb extension

Abbreviations *C:* Cervical · *CMUP:* Compound motor-unit potential · *EMG:* Potential · *CNS:* Central nervous system · *EMG:* Electromyography, electromyographic · *H:* Hamstring · *L:* Lumbar · *MLR:* Mesencephalic locomotor region · *PARA:* Paraspinal muscles · *Q:* Quadriceps · *S:* Sacral · *SCI:* Spinal cord injury, spinal cord-injured · *SCS:* Spinal cord stimulation · *T:* Thoracic · *TA:* Tibialis anterior · *TS:* Triceps surae

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Introduction

In several animal models, it has been shown that muscles which are paralyzed due to impaired upper motor neuron function can be induced to exhibit rhythmical activity and even to perform locomotion, by stimulating certain structures of the central nervous system (CNS). In 1966, Shik et al. reported that electrical stimulation (at 10–20 μA and 20–60 Hz) of the mesencephalic locomotor region (MLR) triggered a complete quadrupedal locomotor pattern in a decerebrate cat placed on a moving treadmill belt (Shik et al. 1966; Shik and Orlovsky 1976). Jordan et al. (1979) have moved one step further by demonstrating that a "fictive" locomotor pattern can be induced by

stimulating the MLR even when any phasic input from the periphery is excluded.

As long ago as 1910, Roaf and Sherrington used repetitive electrical stimulation of the feline cervical cord in studies on the neurocontrol of locomotion. Later in the century it was demonstrated in numerous preparations that stimulation with sustained, nonpatterned (i.e., tonic) electrical stimuli can be effective when applied to dorsal roots and/or columns of the spinal cord or to peripheral nerves (Grillner and Zangger 1979). The same authors succeeded in evoking alternating rhythmical electromyographic (EMG) activity and stepping patterns closely resembling the pattern of normal hind limb locomotion in deafferented acute and chronic spinal cats, who had received 3,4-dihydroxyphenylalanine (dopa) prior to the stimulation. A similar approach of studying spinal cord stimulation (SCS) for eliciting locomotor-like activity in spinalized and decerebrate adult cats has been used by Garcia-Rill et al., who suggest that stimulation of the lumbar enlargement may activate an intrinsically organized system (Iwahara et al. 1991). In 1983, Kazennikov et al. reported that stepping could be evoked in the decerebrate cat by electrically stimulating a specific portion of fibers in the dorsolateral funiculus at the cervical or thoracic level, also known as the "locomotor strip" (see also Shik 1997). Recently an effort has been made to elicit movements in different spinal preparations (frog, rat, cat) by direct electrical (micro-)stimulation of the interneuronal network within the lumbar gray matter (Giszter et al. 1993; Bizzi et al. 1995; Tresch and Bizzi 1999). Mushahwar et al. (2000) have reported functional movements by stimulating the spinal cord through electrodes (microwires) implanted in the lumbar cord enlargement of the intact cat.

In this way, animal experiments have revealed that sustained electrical stimulation of the MLR, the gray matter of the lumbar cord enlargement, or the posterior roots or columns of the lumbar cord, can induce rhythmical motor activity. From these three approaches of stimulating the CNS, the latter is closest to the already well-established clinical procedure for spasticity control in humans after a spinal cord injury (SCI) by electrical stimulation of the posterior cord from the epidural space (Barolat et al. 1995). For this effective method of treatment to be successful, it is crucial to evaluate the optimal stimulation settings (site, strength, and frequency) on a case-by-case basis. Stimulation below the SCI—particularly of the lumbar cord segments—controls spasticity more effectively than stimulation above the injury level (Richardson and McLone 1978; Barolat et al. 1995; Dimitrijevic 1998). Pinter et al. (2000) have demonstrated that SCS would be effective for the control of spinal spasticity if: (1) the stimulating electrode is located over the upper lumbar cord segments (L1–3), and (2) the applied stimulus train has a frequency of 50–100 Hz, an amplitude of 2–7 V, and a pulse width of 210 μs.

When SCS was the clinical choice for spasticity control in a patient with complete SCI, we took advantage of the available clinical practice and, while evaluating the optimal parameter configurations, recorded the motor effects elicited by the stimulation. In the course of the evaluation procedure, we noticed that the stimulation sometimes evoked rhythmical, locomotor-like EMG activity in the patient's paralyzed lower-limb muscles. This happened when we applied frequencies somewhat lower than the ones effectively controlling spasticity *without* changing the site of the stimulation (Rosenfeld et al. 1995; Gerasimenko et al. 1996). Meanwhile, we have performed several retrospective and prospective studies on the potential effect of SCS in eliciting motor activity in the lower extremities of complete SCI subjects. These studies have shown that a frequency of 25–50 Hz and a strength of 7–10 V (210 μs pulse width) had to be applied to the upper lumbar cord segments to initiate and retain rhythmical stepping-like hip-knee flexion movements of the subject's paralyzed limbs (Dimitrijevic et al. 1998a, 1998b, 2001; Pinter et al. 1998). Moreover, while evaluating the optimal settings for spasticity control, a strong and brisk extension movement of the lower limbs was evoked by stimulus

Table 1 Demographic and clinical data for subjects included in the study. (*SCI* Spinal cord injury)

Subject No.	Sex	Date of birth (month/year)	Date of SCI (month/year)	Cause of SCI	ASIA classification	Year data collected
1	F	12/1965	04/1996	Car accident	A	1999
2	M	04/1973	01/1997	Skiing accident	B	1999
3	F	07/1975	01/1996	Car accident	A	2001/2002
4	M	04/1973	01/1995	Car accident	A	2001
5	F	03/1978	12/1994	Car accident	A	2002

Table 2 X-ray documentation of injury level and epidural electrode position

Subject No.	Vertebral level of fracture	Stabilization of vertebrae	Electrode position (vertebral level)
1	T5/6, T10	T4-7, T9-11	T12/L1
2	C5/6	C4-7	T12
3	T7	T6-8	T12, slightly left
4	C4/5	C3-6	L1
5	T4/5, with dislocation	T3-6	T12

Table 3 Results of the neurophysiological evaluation. [*LSEP* Lumbosacral evoked potentials, *RP* root potential, *SP* stationary potential, *SSEP* somatosensory evoked potentials (+/− evoked potential present/absent), *Voluntary* voluntary movement, *Hip–Knee* unilateral leg (hip and knee) flexion and extension, *Ankle* unilateral ankle dorsi- and plantar flexion (+/− EMG response present/absent), *Tendon jerk: Knee* patellar tendon tap, *Ankle* Achilles tendon tap; *Withdrawal* plantar withdrawal reflex, *W supp* the subject was instructed to attempt to suppress any reflex movement, *W/o supp* without attempting to suppress the reflex movement (+/− reflex response present/absent in the EMG), R/L Right/left lower limb]

Subject No.	LSEP				SSEP		Brain motor control assessment											
							Voluntary				Tendon jerk				Withdrawal			
	RP		SP				Hip–Knee		Ankle		Knee		Ankle		W/o support		W support	
	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L
1	+	+	+	+	−	−	−	−	−	−	+	+	+	+	+	+	+	+
2	+	+	+	+	+	+	−	−	−	−	+	+	+	+	+	+	+	+
3	+	+	+	+	−	−	−	−	−	−	+	+	+	+	+	+	−	−
4	+	+	+	+	−	−	−	−	−	−	+	+	+	+	+	+	+	+
5	+	+	+	+	−	−	−	−	−	−	+	+	+	+	+	+	−	−

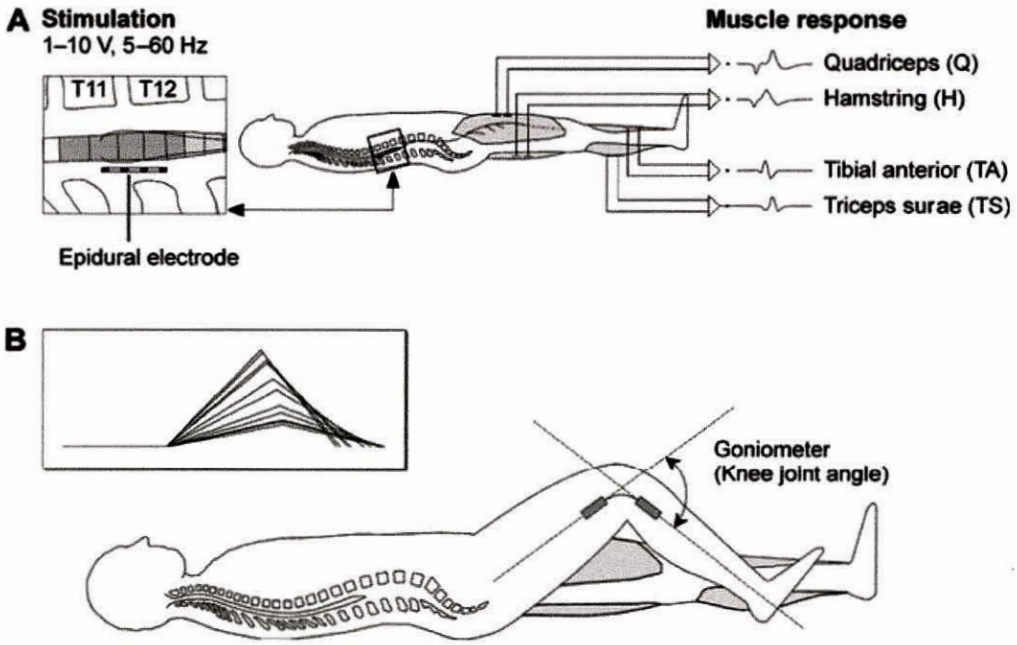


Fig. 1A, B Outline of the clinical assessment design. **A** The subjects were placed in supine position. Pairs of surface EMG electrodes were placed over the bellies of the lower-limb muscle groups to record the effects of epidural stimulation. **B** Goniometers were applied bilaterally to the knee to monitor leg movements. The stick figure (*inset*) illustrates how the position of the lower limb is shifting during induced movements

trains involving even lower frequencies (less than 15 Hz; Jilge et al. 2001).

From these observations it was clear that the lumbosacral cord isolated from supraspinal input would be capable of generating at least three different types of motor output in response to epidural stimulation at the same segmental level but different frequencies (and an adjusted stimulus amplitude). They led us to speculate that different stimulus frequencies would "open" different inhibitory and/or excitatory spinal pathways controlling: (1) the suppression of excitability within particular motor nuclei (thus reducing spasticity after SCI)—induced at stimulus frequencies between 50 and 100 Hz; (2) the generation of rhythmical locomotor-like activity (Minassian et al. 2001a, unpublished work)—induced at stimulus frequencies of approximately 30 Hz; and (3) the generation of sustained lower-limb extension—induced at stimulus frequencies below 15 Hz (Jilge et al. 2002). In the present study we investigated the effect of SCS at frequencies between 5 and 15 Hz. We analyzed previously recorded EMG data with respect to the question whether and under what conditions it was possible to initiate and retain lower-limb extension in subjects with trauma-related SCI whose lumbosacral cord was isolated from brain control.

Methods

Subjects

The analyses performed in this study are based on EMG and goniometric data collected while routinely conducting a clinical protocol for the evaluation of the optimal site and parameters of SCS for spasticity control in subjects who were resistant to other treatment modalities. For the present retrospective study, we selected recordings obtained in five subjects who were neurologically classified as having a complete (ASIA A, four subjects, and ASIA B, one subject) spinal cord lesion at the cervical or thoracic level, with no motor functions below the lesion. Pertinent demographic and clinical data are listed in Table 1.

At the time of data collection, the subjects met the following criteria: (1) they were healthy adults with closed posttraumatic spinal cord lesions; (2) the lesion was at least 1 year old; (3) no antispastic medication was being used; (4) the stretch and cutaneomuscular reflexes were preserved; (5) there was no voluntary activation of motor units below the level of the lesion, as confirmed by brain motor control assessment (Sherwood et al. 1996), while lumbosacral evoked potentials were present (Beric 1988); and (6) there was no sensory function below the level of the lesion in four of the subjects studied, while one subject showed tactile impairment below the level of the SCI, and unaltered cortical somatosensory evoked potentials elicited by stimulation of the peroneal and tibial nerves.

To control their spasticity, all subjects had an epidural electrode array implanted (see Methods) at a vertebral level ranging from T12 to L1, as verified by X-ray picture (Table 2). The implantation as well as the clinical protocol to evaluate the optimal stimulation parameters was approved by the local ethics committee. All subjects gave their informed consent.

Evaluation procedure

Within the Clinical Program of Restorative Neurology, a neurologist examined the subjects' spinal cord functions and assessed their functional status. In addition, the following clinical neurophysiological procedures for the assessment of motor and sensory functions were applied:

1. Simultaneous recording of compound motor-unit potentials (CMUPs) from muscle groups of the limbs and trunk using 16 pairs of surface electrodes and EMG channels, while a standardized protocol for the evaluation of voluntary and reflex motor tasks was executed (Sherwood et al. 1996).
2. To assess posterior column functions, cortical evoked potentials elicited by tibial and peroneal nerve stimulation were conducted (Dimitrijevic et al. 1983).
3. Lumbosacral evoked potentials were used to assess the functions of the spinal gray matter. They were recorded after tibial nerve stimulation (Beric 1988; Lehmkuhl et al. 1984) with silver–silver chloride surface electrodes placed at the T12, L2, L4, and S1 spinous processes referenced to an electrode at T6.

Results of the neurophysiological evaluation are listed in Table 3.

Stimulation procedure

For spasticity control, quadripolar electrode arrays (Pisces-Quad, model 3487A; Medtronic)—hereinafter referred to as "electrodes"—were percutaneously placed in the posterior epidural space at vertebral levels T12–L1 under local anesthesia. The implantation procedure has been described in detail previously (Murg et al. 2000). The position of the electrode relative to the vertebral column was monitored intraoperatively by fluoroscopy and elicitation of muscle twitches. The position of the electrode relative to the spinal cord was verified based on the previous finding that the spatial relation between the active cathode of the electrode and the corresponding segmental input–output of the spinal cord can be usefully monitored by EMG recordings of muscle twitch patterns (Dimitrijevic et al. 1980; Murg et al. 2000). During the postoperative test phase, the stimulus threshold values for muscle twitches were measured. Single muscle twitches were elicited with the epidural electrode connected to an external stimulator (model 3625; Medtronic) and the amplitude of the generated stimulus being increased to the point of eliciting brief muscle contractions. As mentioned above, the results of these routinely performed measurements provided the basis for estimating the position of the stimulating electrode relative to the spinal cord (see Data recording and analysis, below). Finally, the electrode was connected to the implanted pulse generator (Itrel 3, model 7425; Medtronic) to form a fully integrated closed system.

The four independent contacts of the quadripolar electrodes were set at a distance of 9 mm. They were labeled 0, 1, 2, 3, such that contact 0 was at the top and contact 3 at the bottom of the electrode. The stimulator was operated in bipolar mode by connecting the cathode and anode to a pair of contacts. The motor output elicited by SCS was captured for stimulus frequencies of 5–60 Hz (incrementally increased by approximately 5 Hz between 5 and 20 Hz, and by approximately 10 Hz between 20 and 60 Hz), amplitudes of 1–10 V (increased in 1-V steps; bipolar electrode impedance of approximately 1 kΩ), and pulse widths of 210 and 450 μs. However, intensities which caused discomfort to the subject under examination were never applied. An overview of the used parameter configurations is given in Table 4.

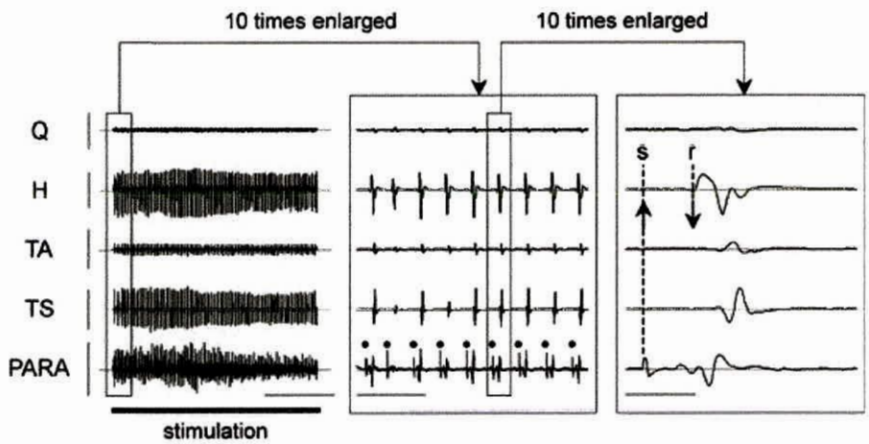


Fig. 2 Presentation of electromyographic (EMG) recordings. EMG recording from the lower limb (*Q* quadriceps, *H* hamstring, *TA* tibialis anterior, *TS* triceps surae) and paraspinal (*PARA*) muscles, presented on three different time scales. The *bar at the bottom on the left-hand side* indicates the time interval when spinal cord stimulation (SCS) was applied. On the intermediate scale, it is apparent that each pulse within the stimulus train triggered a single compound motor-unit potential (CMUP; in each muscle group). The stimulus artifacts (*dots*) recorded from the paraspinal muscles were used as indicators of the moments when the stimulus pulses were applied. The labels *s* and *r* on the *right-hand side* denote the application of a stimulus pulse and the onset of an evoked response, respectively. The time between these two moments will be referred to as the latency time of the evoked CMUP. Vertical markers: 2,000 μV (Q, H); 3,000 μV (TA, TS); 400 μV (PARA). Horizontal markers: 2 s, 200 ms, 20 ms. The EMG was recorded in subject 1 (estimated segmental level of stimulation: L4/5) in response to the following stimulation parameters: polarity of the active contacts 2+ 3–, 7 V, 14 Hz, 210 μs pulse width

Table 4 Overview of the stimulus parameters used and of the results recorded in the subjects under study. Parameter configurations tested and settings effectively inducing the EMG extension pattern

Subject No.	Initial position[a]	Polarity[b]	Tested[c]			Effective[d]		
			Strengths	Frequencies	*n*	Strengths	Frequencies	*n*
1	Extended	2− 3+	5–10 V	10–31 Hz	33	8–10 V	10–21 Hz	12/14
		2+ 3−	5–8 V	14 Hz	5	5–8 V	14 Hz	4/5
			1–10 V	21 Hz	11	6–10 V	21 Hz	5/5
		1− 2+	1–10 V	21 Hz	10	–	–	
		1+ 2−	1–10 V	21 Hz	10	9–10 V	21 Hz	2/2
2	Extended	0− 3+	6–8 V	10–60 Hz	18	7–8 V	10 Hz	2/2
						6–8 V[f]	16–60 Hz	11/13
		0+ 3−	6–8 V	10–60 Hz	18	7–8 V	16–21 Hz	4/4
3[e]/Session 1	Extended	0− 3+	1–10 V	10 Hz	10	7–10 V	10 Hz	5/5
	Flexed	0− 3+	5, 10 V (210 μs)	5–50 Hz	30	10 V	5–10 Hz	6/6
						10 V[h]	5–50 Hz	15/15
			5, 10 V (450 μs)	5–50 Hz	12	5, 10 V	5–16 Hz	5/6
						5, 10 V[f]	5–21 Hz	7/8
						5, 10 V[h]	5–30 Hz	9/10
		0+ 3−	5, 10 V (450 μs)	5–50 Hz	10	5 V	10–20 Hz	3/3
						10 V	5–10 Hz	2/2
						5, 10 V[f]	5–31 Hz	9/9
3/Session 2	Extended	0− 3+	6–10 V	5–50 Hz	35	8–10 V	5–16 Hz	9/9
						7–10 V[f]	5–50 Hz	23/27
						7–10 Vh	5–50 Hz	28/28
		0+ 3−	4–9 V	5–50 Hz	42	4–9 V	10–21 Hz	13/16
						4–9 V[h]	5–50 Hz	40/40
	Flexed	0− 3+	7–10 V	10–51 Hz	21	9–10 V	10–16 Hz	5/5
		0+ 3−	8, 10 V	16–50 Hz	7	8 V	16 Hz	1/1
						8, 10 V[f]	16–31 Hz	5/6
4	Flexed	0− 3+	5, 7 V	5–50 Hz	14	7 V	10–31 Hz	4/4
						5, 7 V[f]	5–50 Hz	12/14
						5, 7 V[h]	5–50 Hz	14/14
		0+ 3−	5, 7 V	5–50 Hz	12	5 V	16–21 Hz	2/2
						5, 7 V[f]	5–50 Hz	11/12

Data recording and analysis

Figure 1 shows the patient setup used, according to the clinical protocol, for the evaluation of the optimal stimulation parameters for spasticity control, with the stimulating electrode placed in the epidural space, and the recording sites for the surface EMG of the thigh and leg muscles (Fig. 1A). Goniometers were bilaterally applied to the knee (Fig. 1B). The subjects were placed on a comfortable examination table in a supine position and covered with soft sheepskin. This configuration allowed flexion/extension movements of the lower limbs to unfold smoothly and minimized friction between the heel and the supporting surface.

The subject's lower limbs were manually moved to the point of complete flexion or extension before stimulation was applied at certain configurations of the stimulus parameters. Throughout the induced unilateral or bilateral extension movements, the subject's legs were manually protected by a technologist (when necessary) in order to prevent injury of the joints during electrically evoked extension of the lower limbs, which was rather strong and sudden, resembling a ballistic movement.

A typical evaluation session to systematically test the effect of different stimulation sites (i.e., contact combinations), intensities, and frequencies lasted 1–2 h. The stimulation cycles themselves, during which one parameter (usually the stimulus frequency) was varied while the others (site and strength) were kept constant, lasted 1–5 min and were followed by appropriate resting intervals of 2–4 min. Within each stimulation cycle, the individual stimulation trials were separated by intervals of at least 10 s.

The effects of SCS were captured by EMG recording of induced CMUPs using pairs of recessed, silver-silver chloride surface electrodes placed 3 cm apart over the midlines of the quadriceps (Q), hamstring (H), tibialis anterior (TA), and triceps surae (TS) muscle bellies on both lower limbs. Paraspinal (PARA) muscles were covered in the same way. The skin was slightly abraded such that an electrode impedance of less than 5 kΩ was reached to avoid artifacts. In subjects 3–5, goniometers (model XM-180, and K100 amplifier system; Penny & Giles Biometrics) were used to record knee movements (Fig. 1B). The measurements were performed with a Grass 12D-16-OS Neurodata Acquisition System (Grass Instruments), using a gain of 2,000 over a bandwidth of 30–1,000 Hz (−3 dB). The data were digitized at 2,048 samples/s for each channel at a bit depth of 12 bits using a Codas ADC system (Dataq Instruments). The amplified and processed EMG and goniometer signals were monitored on-line and stored for subsequent analysis. Figure 2 gives an example of EMG-recorded induced CMUPs. The same data are presented on three different time scales illustrating; (1)

Table 4 (continued)

Subject No.	Initial position[a]	Polarity[b]	Tested[c]			Effective[d]		
			Strengths	Frequencies	*n*	Strengths	Frequencies	*n*
5	Extended	0– 3+	4–6 V	5–31 Hz	15	–	–	
		0+ 3–	4–6 V	5–31 Hz	15	–	–	
						4–5 V[f]	5 Hz	2/2
						4–5 V[g]	5–16 Hz	6/6
	Flexed	0– 3+	4, 6 V	5–31 Hz	10	4 V	5–16 Hz	3/3
		0+ 3–	4, 6 V	5–31 Hz	10			
						4, 6 V[g]	5–10 Hz	4/4
						4, 6 V[h]	5–16 Hz	6/6

[a]Position of the subject's lower limbs prior to the stimulation.

[b]Electrode contacts used as anode (+) and cathode (−).

[c]Tested parameter values, where *n* is total number of recordings using different parameter configurations (unless otherwise specified, the stimuli had a pulse width of 210 μs).

[d]Parameter values which effectively induced an EMG pattern in which hamstring and triceps surae exhibited larger CMUP amplitudes than quadriceps and tibial anterior, respectively (*n* is the number of supportive recordings) e.g., 8–10 V/10–21 Hz/12/14 denotes that the EMG extension pattern was observed in 12 of 14 recordings in which a stimulus amplitude between 8 and 10 V, and a stimulus frequency between 10 and 21 Hz was used.

[e]In subject 3, the analyzed data had been collected in two sessions. Results for the right or left lower limb were arbitrarily chosen for each subject.

[f]Parameter values which induced the EMG extension pattern immediately after the onset of the stimulation, but not necessarily also during subsequent phases.

[g]Parameter values which induced the EMG extension pattern in the thigh muscles, but not necessarily also in the leg muscles.

[h]Parameter values which induced the EMG extension pattern in the thigh muscles immediately after the onset of the stimulation.

a whole series of EMG responses to SCS, (2) the stimulus-response relationship, and (3) characteristics of single responses.

The cord-based positions of the epidural electrodes placed in the five subjects under study were estimated as follows: subject 1, L4/5; subject 2, L3/4; subject 3, L4/5; subject 4, S1/2; subject 5, L5. As described under Stimulation procedure, we arrived at these positions by analyzing the muscle twitch patterns elicited by the electrodes. This workaround was necessary because, failing appropriate neuroimaging techniques, spinal cord segments cannot be visualized directly, nor can they be accurately mapped by fluoroscopic visualization of the vertebrae involved. X-ray imaging is only useful to the extent that it hints at the cord level of the epidural electrode if we assume that the spinal cord has "standard" spatial relations between vertebral and cord structures (Kameyama et al. 1996; Lang and Geisel 1983).

In the present study, a refined approach to this issue was used by combining two evaluation techniques that are described in detail elsewhere (Murg et al. 2000; Rattay et al. 2000). First, the muscle twitch patterns obtained by EMG recording were analyzed for the recruitment order of the lower-limb muscles in response to incremental stimulus amplitudes, based on the demonstration by Murg et al. (2000) of two distinct recruitment orders depending on whether the stimulating cathode was placed over the upper (initial response by quadriceps and/or adductor) or the lower (initial response by tibialis anterior and triceps surae) lumbar cord segments. Second, the muscle twitch patterns were additionally evaluated as described by Rattay et al. (2000), who used computer modeling techniques to analyze the segmental position of a bipolar electrode in relation to the recruitment order of lower-limb muscles. Depending on the rostrocaudal level of stimulation, the authors discriminated at least four distinct muscle recruitment patterns.

The recorded EMG potentials were analyzed off-line using Windaq Waveform Browser (Dataq Instruments). The responses induced by the external stimuli did not interfere with each other, regardless of the stimulus frequency, as long as it did not exceed approximately 30 Hz (examples at 5 and 21 Hz are given in Fig. 4B). Each CMUP could be related unequivocally (1:1) to the pulse which had triggered it. In other words, each (sufficiently strong) pulse within the applied stimulus train evoked one single EMG response per muscle group (Fig. 2). For the *integrated activity* of single responses, the original EMG record was divided into successive time windows of equal length, each covering a single muscle-twitch response. The margins of the time windows were defined by the moments when the external stimuli had been applied. These moments were reflected in the EMG as volume-conducted artifacts of the stimulus pulses recorded from the paraspinal muscles. Then the samples $V_1,\ldots,V_M$ of the EMG potential within each window were replaced by a single value $IA(V_1,\ldots,V_M)$, calculated as:

$$IA(V_1,\ldots,V_M) = \frac{l}{M}\cdot\sum_{k=1}^{M}|V_k| \tag{1}$$

where M depends on the length l of the time window, which was selected based on the stimulus frequency f:

$$l = \frac{1}{f}, \qquad M = 2048l, \tag{2}$$

if l is given in seconds. (Note that the EMG recordings were digitized at a rate of 2,048 samples per second.)

The goniometer recordings were used to quantify the degree of extension incorporated in the induced movements based on the maximum deflection of the knee-joint angle:

$$\Delta\varphi = \max\varphi(t) - \min\varphi(t), \tag{3}$$

where $\varphi(t)$ is the time course of the joint angle as it is given by the

goniometer curve. The *average slope* of this curve over an interval from $t=a$ to $t=b$ was calculated as follows:

$$\frac{\varphi(b) - \varphi(a)}{b - a.} \quad (4)$$

Results

Here we are going to demonstrate that rhythmical motor-unit activity, which is induced by SCS at frequencies of 25–50 Hz, is converted to a tonic one by lowering the frequency of the stimulus train to approximately 5–15 Hz *without* changing the site and intensity of the stimulation (see Fig. 3). As a visible correlate of this tonic output, the lower limbs undergo an extension that persists for as long as the external stimulus is sustained. In some of our recordings, the paralyzed limbs remained extended for up to 52 s of continuous stimulation, which readily happened when lower stimulus frequencies of 5–10 Hz were used.

In this context, "rhythmical" ideally refers to the periodic alternation of burst-like phases of CMUP activity with "silent" ones in which no EMG activity is observed in a given muscle group. A "tonic" pattern, on the other hand, is characterized by continuous CMUP activity without any interruption, the individual discharges within this pattern being separated by a constant time interval. During the transition from rhythmical to tonic motor-unit activity or vice versa, interference between these two elementary features is observed (see Fig. 4A, 21 Hz).

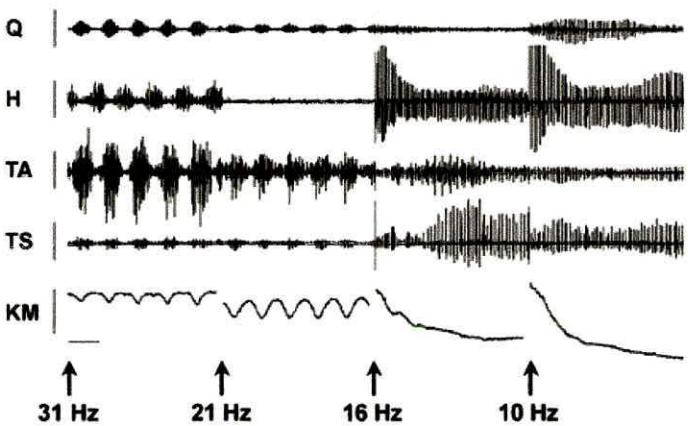


Fig. 3 Rhythmical and tonic EMG activity of paralyzed lower limbs induced by spinal cord stimulation. EMG recordings obtained from the lower-limb muscle groups during spinal cord stimulation at frequencies of 31 and 21 Hz (rhythmical activity) as compared to 16 and 10 Hz (tonic activity). The goniometer traces *below* illustrate the corresponding rhythmical and extension movements, respectively, of the lower limbs. The other stimulation parameters (site and strength) were never changed during the recording session. Note that during the "flexion phases" induced at 31–21 Hz the amplitudes in quadriceps and tibialis anterior are larger than the ones in hamstring and triceps surae, respectively. This dominance is reversed in response to stimulus frequencies of 16–10 Hz. Recorded in subject 3 (estimated segmental level of stimulation: L4/5); stimulation parameters: 0–3+, 10 V, 210 μs pulse width. Vertical markers: 500 μV (Q, H, TA, TS); 45° (*KM* knee movement). Horizontal marker: 1 s

Tables 4 and 5 survey the results obtained in each of the five subjects under study. The following sections give a detailed description of the evoked lower-limb extension, particularly in terms of the CMUP patterns induced in the thigh and leg muscles in response to specific stimulus parameters. As is apparent from Table 4, the findings we present were observed in a large number of recordings provided that appropriate parameter settings were applied.

Effect of stimulation parameters on EMG output and induced movement

When the subjects' lower extremities were manually moved to the point of complete (i.e., maximum possible) flexion and a train of electrical stimuli was subsequently applied to the posterior structures of the lumbosacral cord, at a frequency of approximately 5–15 Hz and a strength which was above the thresholds for twitches in the thigh and leg muscles (4–10 V), a sudden strong and brisk extension movement of the lower limbs occurred. When the endpoint of the actual movement was reached, and the stimulation was sustained, the limbs remained in the extended position, with the muscles visibly and strongly contracting. Any attempt to flex a limb in this condition manually in the knee and hip failed due to the strong muscle contraction induced by the stimulation. The strong and brisk extension was observed in the absence of any manual support of the lower extremities; it happened as soon as the appropriate stimulus parameters were applied. When the electrical stimulation was turned off, the lower-limb muscles relaxed immediately, and the limbs could be manually flexed and extended.

The parameter settings for which the goniometer recordings (and the annotations to these recordings) revealed a *sustained* extension of the initially flexed lower limbs in subjects 3–5 are given in Table 5. At the effective stimulus strengths, all four lower-limb muscle groups responded with muscle twitches. The corresponding EMG recordings confirmed the coactivation of (hip and ankle) flexors and extensors, with the CMUP amplitudes being larger in the latter as soon as specific stimulus frequencies were applied (see Fig. 2). With respect to the initiation of a goniometrically verified, sustained lower-limb extension, the effective frequencies ranged between 5 and 21 Hz. Frequencies above 21 Hz were effective only in subject 4 when low-intensity (5 V) stimuli were applied (using one particular combination of anode and cathode). However, a fleeting extension movement, i.e., one which was *not* sustained, *was* repeatedly evoked by 21- to 50-Hz trains (see footnote c in Table 5).

Figure 4A shows EMG recordings of subject 3, whose spinal cord was stimulated at the level of L3/4 (estimated segmental position of the cathode) at frequencies of 5–21 Hz and a stimulus strength of 10 V (210 μs pulse width). Figure 5A compares different recordings in the same subject using the same strength and a frequency of 10 Hz, whereas Fig. 5B was recorded in subject 4, who was stimulated at the segmental level of S1/2 (7 V, 16 Hz).

Table 5 Parameter settings which effectively induced an extension movement, and temporal changes in the EMG pattern observed during the movement (*NA* No goniometer recordings available)

Subject No.	Polarity	Effective[a]		Temporal changes in the EMG pattern[b]			
		Strengths (V)	Frequencies (Hz)	Immediate	Movement	Steady state	*n*
1		NA					
2		NA					
3/Session 1	0– 3+	10	5–16	+	–	±	8/9
		10[c]	21–50				
		5 (450 µs)	5–16	+	–	±	2/3
	0+ 3–	5, 10 (450 µs)	5–10	±	–	±	3/4
		5[c] (450 µs)	16–31				
3/Session 2	0– 3+	8–10	10–21	+ (10–16 Hz)[d]		±	6/9
				± (21 Hz)[d]		±	4/4
		10[c]	31–50				
	0+ 3–	–	–				
		8[c]	16–31				
4	0– 3+	5	5–50	+	–	±	8/8
		7	5–10	+	–	±	2/2
		7[c]	16–31				
	0+ 3–	5, 7	5–21	+	–	±	7/8
		5, 7[c]	31				
5	0– 3+	6	5–16	+	–	±	2/3
		6[c]	21–31				
	0+ 3–	–	–				

[a]Parameter values which effectively induced a sustained extension of the flexed lower limbs (as documented by goniometer recording)

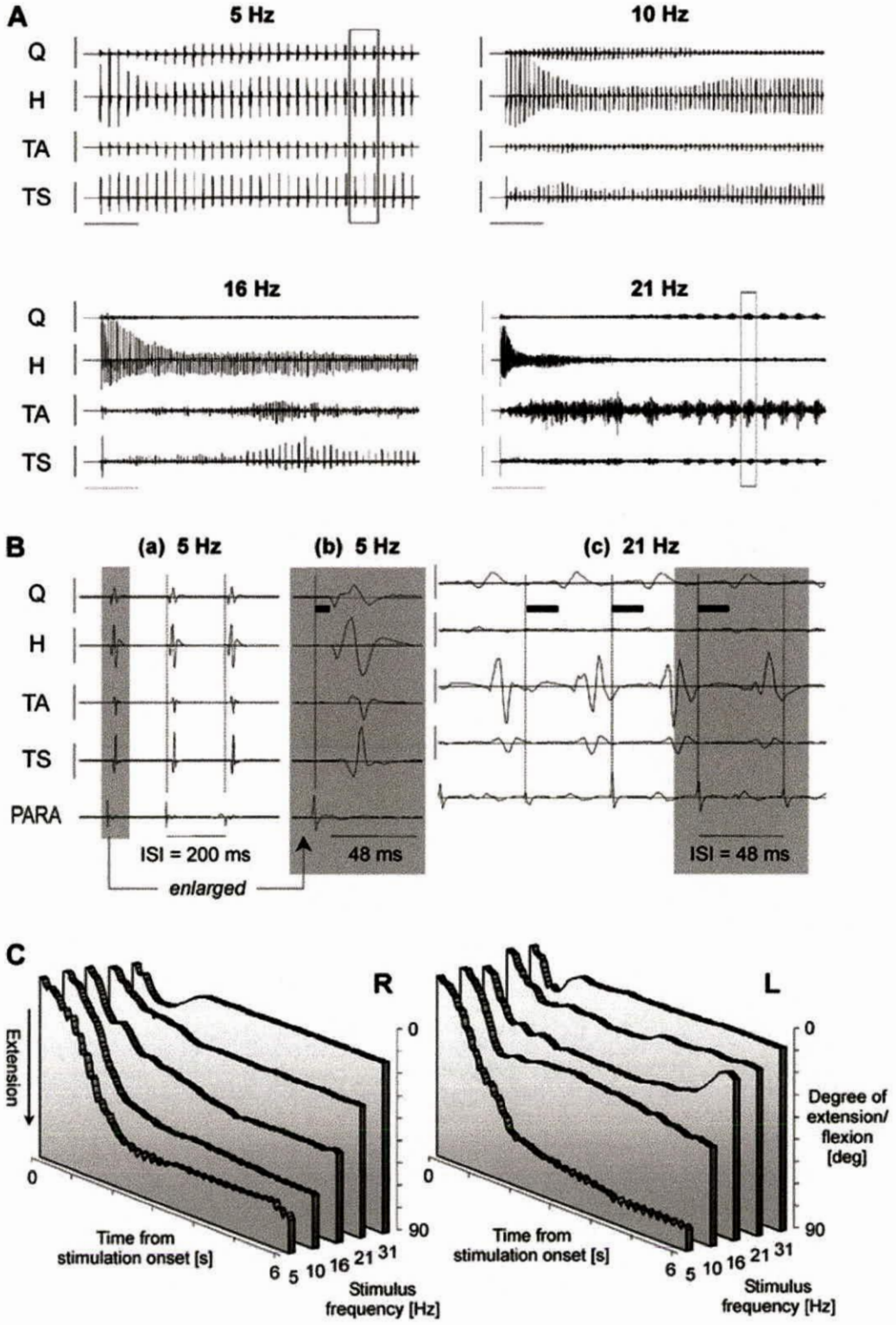
[b]Whether *H–Q* increased (+), decreased (–), or remained constant (±) during successive phases of the induced extension, where *H–Q* denotes the difference between the EMG amplitudes in hamstring and quadriceps, i.e. immediately after the onset of the stimulation (Immediate), during the actual movement (Movement), and as soon as the EMG output remained temporally stable (Steady state). *n* is the number of recordings in which the described modulations were actually observed, e.g., +/–/±/8/9 denotes that, in 8 of 9 recordings, *H–Q* first increased, then decreased, and finally remained constant.

[c]Immediately after the onset of the stimulation, an extension movement was induced, but it immediately reversed to a pronounced flexion.

[d]When a stimulus frequency of 10–16 Hz was applied, *H–Q* slowly increased until it remained fairly constant. At 21 Hz, the EMG amplitudes in the thigh muscles remained essentially constant throughout the recording.

The recordings for 5, 10, and 16 Hz (Fig. 4A), 10 Hz (Fig. 5A), and 16 Hz (Fig. 5B), respectively, revealed at least two distinct phases of the extension induced in the flexed limbs. In the first phase, the corresponding EMG pattern was characterized by substantial temporal modulation. The induced muscle contractions within the hamstring muscle group were immediately generated, resulting in a fast extension of the knee—as documented by the corresponding goniometer recording, Fig. 5A, B—and a progressive decrease in the EMG amplitude in the hamstring, while the one in the quadriceps gradually increased. During the following seconds, a steady amplitude relation was established between these muscles (second phase). In both phases, based on the amplitudes of recorded CMUPs, the hamstring had a larger output than quadriceps, and triceps surae had a larger output than tibialis anterior. By way of contrast, tibialis anterior dominated over triceps surae during the rhythmical activity induced at a frequency of 21 Hz. Moreover, by incrementally increasing the stimulus frequency, it was possible to demonstrate the transition from induced steady extension (Fig. 4A, 5 Hz) of the lower limbs to the onset of alternating flexion–extension movements (Fig. 4A, 21 Hz). Most interestingly, SCS which could effectively initiate stepping-like activity initially also evoked a tonic, "extension-like" CMUP pattern, with hamstring exhibiting larger amplitudes than quadriceps (and the limbs extending to a certain extent). Within 10–12 s, however, this tonic output turned rhythmical, with quadriceps and tibialis anterior dominating over hamstring and triceps surae, respectively (a "fleeting extension movement"). Figure 4B compares the CMUPs observed during implemented extension at 5 Hz with the ones during rhythmical activity elicited at 21 Hz. Apart from changes in shape and amplitude of the evoked CMUPs, they revealed significantly different latency times, the latter being prolonged by approximately 10 ms as compared to the former. A more detailed analysis of this observation will be presented in a separate communication.

In Table 4 the parameter configurations which induced an EMG pattern with hamstring and triceps surae dominating over quadriceps and tibialis anterior, respectively, are listed for each of the five subjects included in this study. We are going to refer to this characteristic



pattern of amplitude relations between antagonistic muscle groups as the EMG "extension pattern." It was generally observed in response to frequencies in the range of 5–15 Hz. However, on some occasions this range was slightly shifted toward higher frequencies (10–21 Hz). Applying stimulus trains above 21 Hz, the extension pattern could still be induced immediately after the onset of the stimulation, but it reversed very soon to one with the (hip and/or ankle) flexors dominating over the extensors (see Fig. 4A, 21 Hz and footnote a in Table 4).

Both the EMG output and the extension movement became increasingly weaker as the stimulus strength was reduced without changing the site and frequency of the stimulation. The minimum stimulus level inducing lower-limb extension would to be influenced by two factors: (1) the rostrocaudal position of the cathode based on spinal

Fig. 4A-C EMG and goniometric recordings in response to SCS at different frequencies. **A** EMG recordings in response to different stimulus frequencies (5–21 Hz). The subject's lower limbs had been placed in complete flexion prior to the stimulation. The stimulus trains at 5, 10, and 16 Hz evoked an EMG pattern with hamstring and triceps surae dominating over quadriceps and tibialis anterior, respectively, which is referred to as the EMG "extension pattern." In addition, the recordings reveal temporal modulation of the amplitude relation between quadriceps and hamstring as the induced extension movement unfolds: independently from the applied stimulus frequency, hamstring loses while quadriceps gains momentum until a fairly parallel course is established. At 21 Hz, in contrast, the extension pattern is replaced by a flexion/extension (i.e., stepping) pattern. Recorded in subject 3 (estimated segmental level of stimulation: L4/5); stimulation parameters: 0–3+, 10 V, 210 μs pulse width. Vertical markers: 800 μV. Horizontal markers: 1 s (5–16 Hz); 3 s (21 Hz). **B** CMUPs taken from the windows entered in **A** (see the recordings for 5 and 21 Hz, respectively) are shown on a larger time scale. The corresponding EMG recordings from the paraspinal muscles are also given. A magnification of the first CMUPs in *a* is given in *b*. *c* Although each phase of "burst-like" activity included approximately 15 CMUPs per muscle group, only 4 of them are illustrated. Note the prolonged latency time of the quadriceps responses at 21 Hz as compared to 5 Hz (see the *bars*). (The CMUPs under *b* and *c* are shown on the *same* time scale.) Vertical markers: 600 μV (5 Hz); 300 μV (21 Hz) (*ISI* interstimulus interval). **C** Goniometer traces covering the first 6 s of movements induced by SCS at different frequencies (5–31 Hz). The 5- to 21-Hz goniometer curves recorded from the left (*L*) limb belong to the EMG traces in **A**. The degree of flexion/extension is illustrated by a gradient of 0–90°. Downward deflection indicates lower-limb extension (*arrow*), upward deflection indicates flexion. As one can see, the degree of the induced extension was larger for lower stimulus frequencies. Trains at 31 Hz evoked a fleeting extension which was not sustained but quickly reversed to a pronounced flexion. The slightly different responses obtained in the right (*R*) versus left (*L*) lower limbs suggest that the posterior structures were not stimulated symmetrically from the midline of the spinal cord. Recorded in subject 3 (estimated segmental level of stimulation: L4/5); stimulation parameters: 0–3+, 10 V, 210 μs pulse width

cord segments, and (2) the electric contact between its active poles and the surrounding tissue influencing the impedance of the electrode. These two factors are also reflected in the routinely measured threshold values initiating single muscle twitches (see Methods); hence we used the results of these recordings as a reference in examining the relation between the segmental position of the stimulating electrode and the elicited CMUP output. The question within what segmental range the lumbosacral cord has to be stimulated to induce extension of the lower limbs was addressed by comparing the results obtained for different levels of the stimulating electrode. It emerged that there was no single "optimal" site to elicit and retain such extension. On the contrary: the cord-based locations at which stimulation was successful covered a relatively long distance, ranging from L2/3 to L5. In one case (subject 4), the electrode was placed as low as S1/2 and still evoked powerful extension movements at 5–50 Hz. In another subject, a strong extension was observed with the electrode at L4/5 when a stimulus of moderate strength (5 V) was applied at an increased pulse width (450 μs); again, the response remained essentially constant over a wide range of frequencies (5–31 Hz). Differences in the EMG output due to different levels of the stimulating cathode could be studied also *within* each subject to some extent by comparing the results obtained for different combinations of the electrode contacts used as anode and cathode. Curiously enough, using the 0– 3+ polarity (or 2– 3+, or 1– 2+, respectively) the lowest stimulus intensity required to evoke the EMG extension pattern was always higher than the one required for the reverse polarity (0+ 3–, 2+ 3–, or 1+ 2–, respectively; see Table 4). Whether this observation means that activation of the lower (rather than the upper) lumbar cord is required for lower-limb extension to be initiated needs to be investigated further.

The parameter configurations found to evoke the EMG extension pattern (as given in Table 4) largely coincide with the ones that the *goniometer recording* revealed to elicit sustained extension (as given in Table 5). We may therefore summarize that, in all five subjects included in this study, repetitive stimulation of the lumbosacral cord using particular parameter settings reproducibly induced lower-limb extension as documented by EMG and, in subjects 3–5, also by goniometer recording. Figure 5A demonstrates that the above-described characteristics of the induced sustained extension (particularly the dominance of the extensors, different phases of the movement, and the temporal modulations) were consistently observed in different trials under constant stimulation conditions. Applying the same protocol in different subjects revealed similar features, as can be seen by comparing Fig. 5A and B. If the same movement from full flexion to extension was, however, performed by passive (i.e., manually controlled) extension of the paralyzed limb instead of SCS, the EMG was of a quite different feature. It exhibited phasic–tonic stretch reflex responses of low amplitude (10–100 times below the ones in Fig. 5A) which were most prominent when the extended position of the limb had already been reached (Fig. 5C).

Degree and duration of the induced extension movement

The maximum deflection of the knee-joint angle, which was used to quantify the degree of extension obtained in our trials, depended on the frequency of the stimulus train. Figure 4 (R) illustrates a series of recordings in which a stimulus of 10 V was applied with the cathode placed over L3/4 (estimated segmental position). The frequency of the stimulus train was 5–31 Hz. Each recording was started with the subject's lower limbs in complete flexion. The goniometer recordings clearly confirmed that both the degree and the duration of the induced extension movements decreased as the stimulus frequency was increased. In response to 5-Hz stimulation, lower-limb extension was expressed at maximum degree. Figure 4C (L) represents the goniometric recordings which were obtained at the same time from the contralateral limb. The differences to the right limb, particularly in the traces at 10 and 16 Hz, can be explained by the asymmetric position of the stimulating cathode. In the five subjects under study, the best results, including the most powerful extension

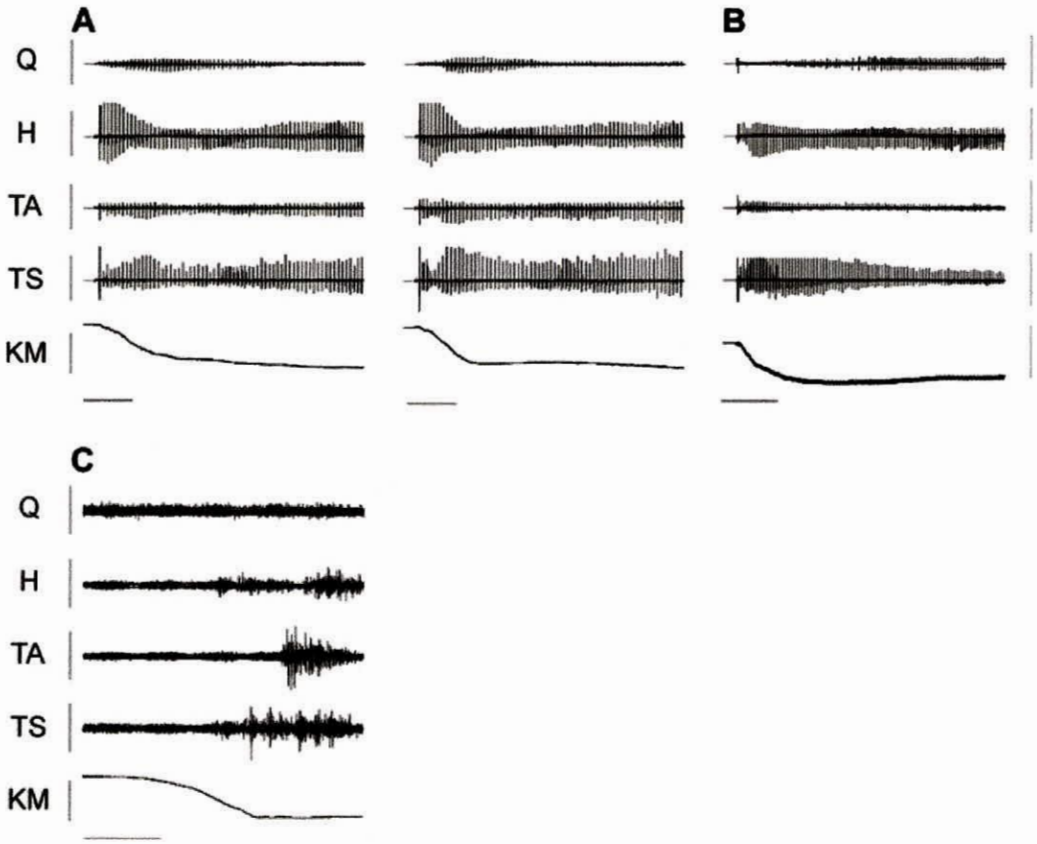


Fig. 5A-C EMG recordings during electrically induced versus manually controlled lower-limb extension. **A** EMG recordings during electrically induced lower-limb extension, obtained in two different trials using the same parameter settings (subject 3, estimated segmental level of stimulation: L4/5; stimulation parameters: 0– 3+, 10 V, 10 Hz, 210-μs pulse width). Note the similarities between the two recordings with respect to the dominance of the extensors over the flexors, and the temporal modulations during the actual movement. Vertical markers: 1,200 μV (Q, H); 600 μV (TA, TS); 60° (*KM* knee movement). Horizontal markers: 1 s. **B** EMG recording during electrically induced lower-limb extension obtained in a different subject (subject 4, estimated segmental level of stimulation: S1/2; stimulation parameters: 0– 3+, 7 V, 16 Hz, 210-μs pulse width). It reproduces the features observed in **A**. Vertical markers: 6,000 μV (Q, H, TA, TS); 90° (KM). Horizontal marker: 1 s. **C** EMG recording during manually controlled lower-limb extension (subject 3; stimulation off). In contrast to the frequency-following (stimulus-triggered) CMUPs observed in **A** and **B**, it reveals low-amplitude, phasic–tonic stretch reflex responses. (Note the different scaling of the vertical axes as compared to **A** and **B**.) Vertical markers: 80 μV (Q, H, TA, TS); 60° (KM). Horizontal marker: 1 s

movements, were obtained at frequencies of approximately 5–10 Hz.

Interestingly, the curves for all extension movements started with a steep slope (see Methods). In the curve shown for 16 Hz in Fig. 4C (left limb), it amounted to 36°/s based on the first 0.5 s. Although this initial slope was observed at all frequencies, the curves as a whole became increasingly flatter as higher frequencies were used. In the first phase of the extension movement, the slope of the goniometer curve was more or less constant, which implies that the average amount of extension *per muscle twitch* monotonically decreased as the stimulus frequency increased.

Although an extension movement was still observable at 31 Hz, this was, as pointed out above, a rather fleeting response immediately reversing to a pronounced flexion movement. A minor flexion peak right after the initial extension slope was also observed at 21 and 16 Hz, but the definitive flexion movement started markedly later in these cases (after approximately 5 and 3.5 s, respectively, compared with approximately 1 s at 31 Hz; see Fig. 4C, left limb).

Characteristic features of sequential EMG responses

Comparing Fig. 4A and C (the EMG traces in A belong to the 5- to 21-Hz traces in C, L), it becomes apparent that the temporal EMG pattern during induced lower-limb extension was well in accordance with the "movement trajectory," i.e., the time course of the joint angles during the induced extension movement. During the first phase, in which hamstring decreased and quadriceps increased in activity, the actual *movement* of the lower limb unfolded, while the subsequent phase could be related to the active *retention* of the extended position (see also Fig. 5A, B). The temporal changes in the CMUP patterns were further analyzed by calculating the integrated activity of single muscle-twitch responses during different phases of the movement.

Figure 6B illustrates the first 24 muscle twitches evoked in the thigh and leg muscle groups by a stimulus train of 5 Hz, which effectively induced an extension movement of the subjects' lower limbs. As can be seen from the goniometer curve, the first 12 of these responses covered the actual extension phase. It emerges that, after an initial phase of divergence (primarily due to certain augmentation in hamstring), the integrated activities of the thigh muscle groups tended toward each other during the extension movement, with hamstring losing and quadriceps gaining momentum (Fig. 6A). Once the limbs were in the final position, the activity within each muscle group remained fairly constant. Continued stimulation actively maintained this position, which was reflected in a stable EMG pattern, with the activity still being greater in hamstring than in quadriceps. For subjects 3–5, a qualitative description of the changing amplitude relations between these two muscle groups during induced extension is given in Table 5. In all analyzed recordings (except the ones during session 2 in subject 3 when the 0− 3+ electrode polarity was used), much the same spatiotemporal CMUP pattern was observed—as also illustrated in Fig. 5A, B.

As is apparent from Fig. 6C, the temporal modulations of the CMUP output during extension were not confined only to the EMG amplitude, but the shape of the individual responses elicited by repeated stimuli was changing also. Analyzing these changes was beyond the scope of this study but may help to understand the observed modifications. Preliminary studies of the EMG features of muscle responses during different types of induced activity have been performed. Results of these studies have been presented in abstract form (Minassian et al. 2001b, 2002; Jilge et al. 2002).

Effect of initial limb positioning

At that point in the study, the question remained to what extent the recordings revealing lower-limb extension may have been influenced by the initial position of the lower limbs. To address this question, we analyzed an extra set of recordings in which a different initial position was used: instead of being flexed, the subjects' lower limbs were moved to the point of complete extension and were left resting on the examination bed without manual support. The subsequently applied stimuli, while not evoking any visible extension *movements*, did raise the muscle tone due to isometric contraction, thus actively *retaining* the extended position of the lower limbs. Accordingly, the recorded EMG pattern was temporally stable, with hamstring and triceps surae showing a level of integrated activity of the single responses well above the one exhibited by quadriceps and tibialis anterior, respectively (Fig. 7B). This latter result was similar to the pattern observed in the regular recordings after the extension movement starting from complete flexion had been completed (Fig. 7A).

As we pointed out earlier, the extension phase in response to frequencies higher than approximately 20 Hz tended to be very short, quickly reversing to a flexion movement that, in some cases, was sustained until the limb was back to where it started from. Figure 7C illustrates the transition from the initially flexed position to extension and back to flexion again. The point where the integrated activity curves (i.e., the sequential histograms of integrated activity of single responses) for quadriceps and hamstring intersect coincides with the point where the corresponding goniometer curve for the knee joint angle has its valley, indicating the transition from the extension to the flexion movement. Tibialis anterior and triceps surae showed an analogous pattern (Fig. 7C). A similar EMG pattern and flexion movement were also induced when the stimuli were applied with the lower limbs fully extended (Fig. 7D). Overall, initial limb positioning did not have a noticeable effect on the characteristic EMG histograms once the induced movement (whether flexion or extension) had been completed.

Discussion

In the present study, we demonstrated that an extension of the lower limbs can effectively be initiated in subjects with complete SCI by using a train of electrical stimuli applied epidurally to the posterior structures of the lumbosacral cord at pulse frequencies between 5 and 15 Hz, an adequate pulse intensity between approximately 4 and 10 V, and a pulse width of 210 μs. Continued stimulation will actively maintain the extended position even when the endpoint of the actual extension movement has been reached. The amount of extensor motor-unit activity induced by SCS primarily depends on the frequency of the stimulus train, while the degree of the actual extension movement is higher when lower stimulus frequencies are used. Moreover, our EMG recordings revealed larger CMUP amplitudes in the hip and ankle extensors as compared to the flexors in response to the stimulation (referred to as the EMG "extension pattern"), and well-defined temporal modulations in the CMUP pattern toward joint stabilization as the actual movement unfolded.

Qualitatively equal results were repetitively obtained in different recording sessions (which were several months apart), both in the same subjects and in different subjects. The consistency of our findings only depended on the appropriate stimulus parameters. On account of this fact, it is particularly unlikely that the observed temporal modulations of CMUP amplitudes and shapes were basically a function of changing geometrical relations around the surface electrodes during the unfolding extension movement. Moreover, such an explanation cannot be reconciled with our finding that the EMG amplitude changed much more rapidly at higher frequencies of the stimulus train (compare Fig. 4A, 5 Hz and 21 Hz), whereas the initial velocity of the actual movement did not vary depending on the stimulus frequencies used. The

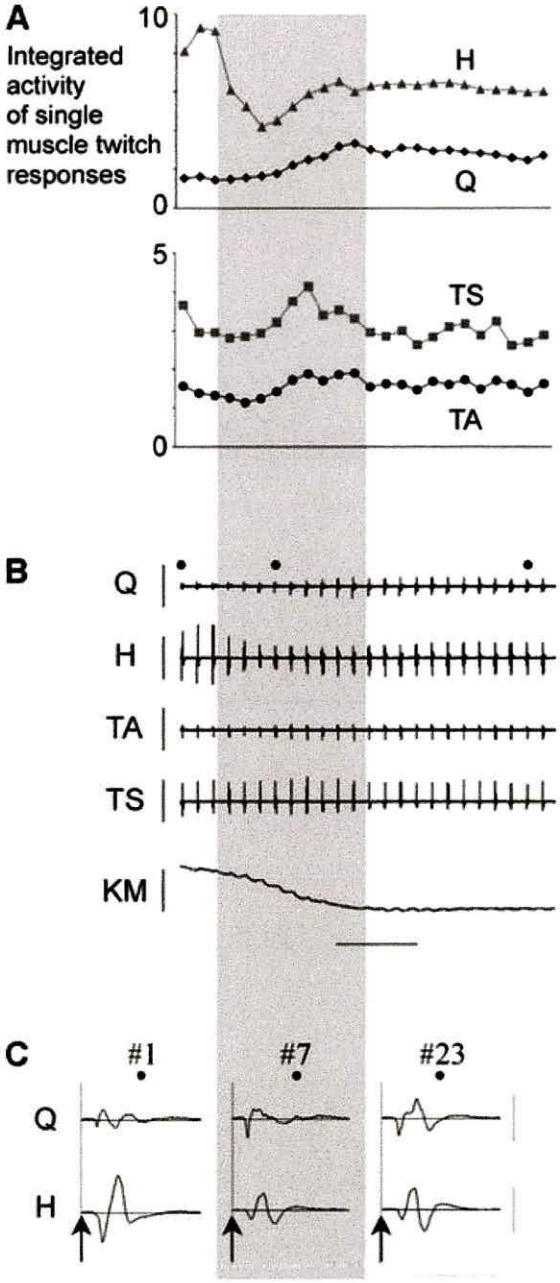


Fig. 6A-C EMG activity during the induced extension. Sequential EMG responses during the first 5 s of the induced extension. The first 12 CMUPs following the onset of the stimulation covered the actual movement phase, while during the next 12 CMUPs the extension was sustained. Recorded in subject 3 (estimated segmental level of stimulation: L4/5); stimulation parameters: 0– 3+, 10 V, 5 Hz, 210-μs pulse width. **A** Integrated activity [(in microvolt-seconds)=electric potential (in microvolts) × time (in seconds)] of single CMUPs. Note the difference in the amount of EMG activity in hamstring and quadriceps at the onset of the induced motor task. As the limbs approach the point of sustained extension, a parallel course is gradually established. **B** Original EMG data from which the histograms in **A** were calculated. Vertical markers: 1,600 μV (Q, H, TA, TS); 90° (*KM* knee movement). Horizontal marker: 1 s. **C** Presentation of single CMUPs, selected from the EMG record in **B**, on a larger time scale. CMUP 1 immediately followed the onset of the stimulation, CMUP 7 was taken from the actual movement phase, and CMUP 23 was recorded during sustained extension. The *arrows* indicate the moments when the external stimuli were applied. Note that the temporal modulations in the EMG pattern were not confined to the integrated activity of the individual responses, but their morphology (shape) was changing as well. Vertical markers: 400 μV (Q); 800 μV (H). Horizontal marker: 50 ms

latter argument follows from the observation that the goniometer curves recorded in parallel started with a slope which was more or less constant when different inter-stimulus intervals were applied (see Fig. 4C).

Primarily activated spinal cord structures

These observations immediately raise the question as to the mechanisms that are involved in the generation of the artificially induced lower-limb extension. First of all, which neural structures have been directly activated by the externally applied pulse train? It had been suggested by clinical observations (Maccabee et al. 1996; Troni et al. 1996) and demonstrated by theoretical studies (Coburn 1985; Strujik et al. 1993; Rattay et al. 2000) that specific geometric and electrical conditions would result in so-called "hot spots" for electrical stimulation (i.e., sites which have a low activation threshold). These sites would coincide with the entry points of the dorsal root fibers into the spinal cord. In fact, due to the dorsomedial position of the epidural electrode in the present study, the sensory afferents in the dorsal roots and their axonal branches in the dorsal columns are the largest fibers closest to the electrode, and therefore exceptional candidates among the possible targets for direct activation.

By analyzing EMG data which had been collected to define the segmental level of the epidural electrode in subjects with impaired sensory functions, Murg et al. (2000) have demonstrated that electrodes placed at vertebral levels T11–12 predominantly induce muscle twitches in quadriceps and adductors, while stimuli delivered from T12–L1 levels result in a stronger activation of tibialis anterior and triceps surae. A comparable relationship between the cathode level and the recruitment order of the lower-limb muscles has been obtained by Rattay et al. (2000) by assuming solely dorsal root stimulation in a computer model. Furthermore, the authors have provided evidence for the following conclusions: (1) with regard to the least stimulus strength ("threshold") required to initiate an action potential in a particular neural structure from the epidural space, dorsal root fibers have the lowest threshold values, while ventral root fibers do not respond until much higher stimulus intensities are applied; (2) for a cathode which is close to or above the entry level of a target fiber into the spinal cord, spike initiation putatively occurs at the border between the cerebrospinal fluid and the white matter. Cathodes positioned (essentially) below the entry level of a target fiber cause spike initiation at a point which is close to the cathode, in a region where the fiber follows the ascending/descending course within the cerebrospinal fluid.

By way of contrast, the activation of dorsal column fibers is general rather than localized to afferents of any specific segmental origins. This can be seen during

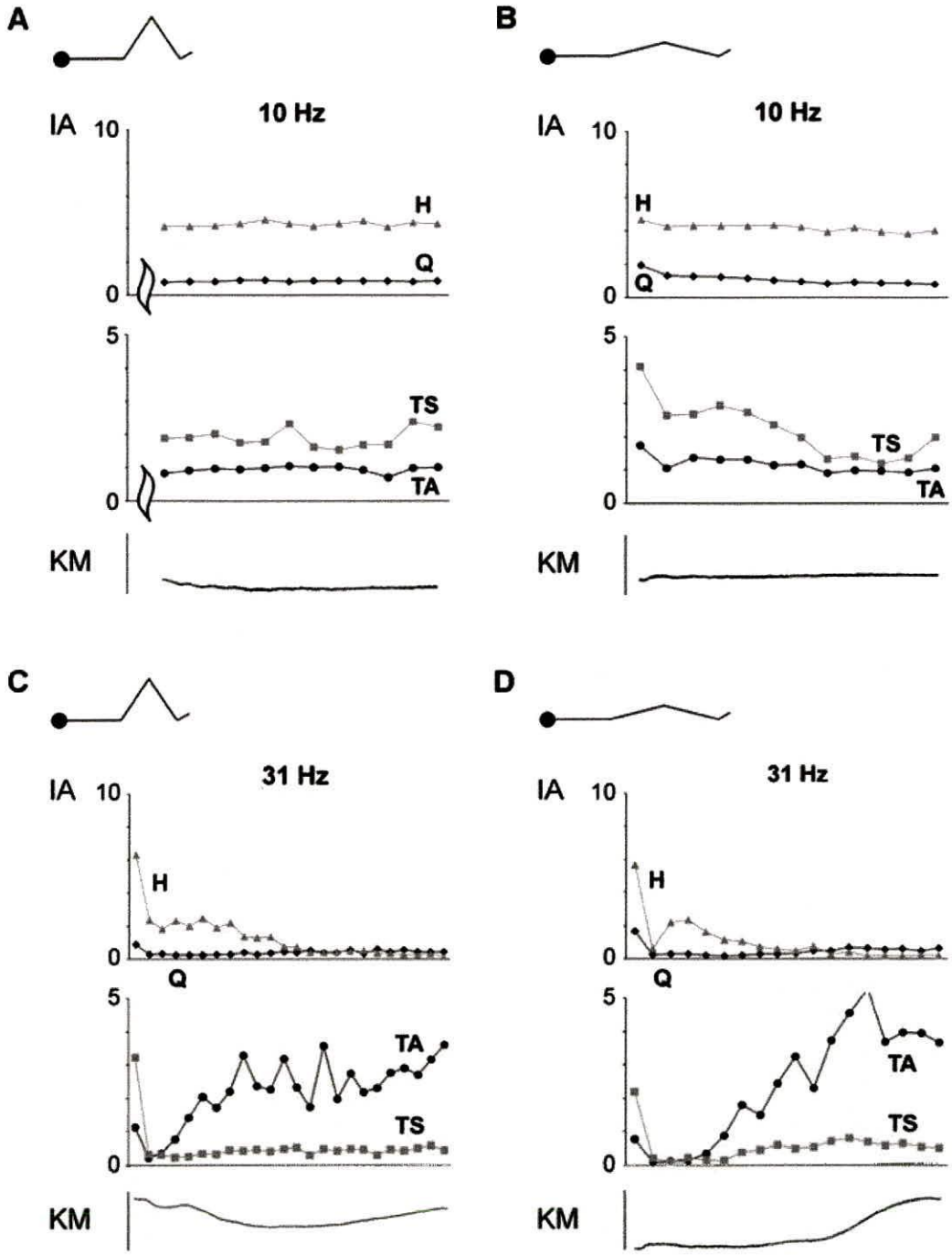


Fig. 7A-D Effect of initial limb positioning. **A** At low frequencies (10 Hz), when stimulation is started with the limbs *flexed*, extension of lower limbs is actively retained after the actual extension movement has been completed. The first 12 CMUPs, covering the movement from the flexed to the extended position, have been omitted from the diagram. **B** At low frequencies (10 Hz), when stimulation is started with the limbs *extended*, this extension is actively retained. **C** At high frequencies (31 Hz), when stimulation is started with the limbs *flexed*, the induced extension quickly gives way to flexion (developing stepping movement). **D** At high frequencies (31 Hz), when stimulation is started with the limbs *extended*, a flexion movement is induced. In the insets to the diagrams, the respective initial position of the lower limbs is indicated. Note the characteristic relationship between the integrated activities of quadriceps, hamstring, tibialis anterior and triceps surae when extension is induced (**A** and **B**), which is in contrast to the patterns obtained when flexion is induced (**C** and **D**). Vertical markers: 30°. (*KM* knee movement, *IA* integrated activity of single responses, in microvolt-seconds). The original EMG data were recorded in subject 3 (estimated segmental level of stimulation: L4/5) in response to the following stimulation parameters: 0– 3+, 10 V, 210-μs pulse width

application of SCS for control of pain. There, medially placed electrodes elicit a widespread distribution of paresthesia in body areas at the level of stimulation and well caudally to it (He et al. 1994). The reason is that at any cord level all dermatomes corresponding to that level and caudally are represented in the dorsal columns by ascending projections of their large cutaneous afferents. It has also been demonstrated that dorsal column stimulation can result in a nonselective, plurisegmental facilitation of motor neurons of different lower-limb muscles. Guru et al. 1987) and Hunter and Ashby (1994) have shown that thigh and leg muscles can be recruited with electrodes at T9–10 or even more rostral vertebral levels, at which point the cord segments and associated roots innervating the lower limbs are located well below the electrode. The authors attribute this nonspecific muscle activity to antidromic activation of the rostral projections of muscle afferents in the dorsal columns.

These findings demonstrate that the direct effect of epidural lumbosacral cord stimulation is typically restricted in two respects. First, the electric (cathodal) field generated by the epidural electrode (directly) affects neural structures within a specific, limited range of segmental levels. It is focused on the cord segment(s) in the vicinity of the cathode if the stimulation is applied at threshold level. Using higher stimulus intensities, adjacent rostrocaudal levels will be excited as well. Second, it is primarily the large axons within the dorsal roots which are

excited. If at all, activation of dorsal column fibers or interneurons plays a minor role. Meanwhile, there is further evidence that the muscle responses obtained by lumbosacral cord stimulation using a bipolar electrode placed dorsomedially in the epidural space are primarily due to the activation of large afferent fibers within the posterior roots (Minassian et al. 2001c). We therefore suggest that, in the present study, dorsal roots of a restricted range of lumbosacral cord segments were primarily recruited in response to different sites and strengths of the stimulation. Moreover, we expect that, within each recording session, those spinal structures which were *directly* activated by the stimulation were *the same* in response to a constant stimulus amplitude.

In this context, it is also important to ask if the occasional manual support applied in order to protect skin and joint injury could have contributed to the extension that was induced from the flexed limb position. The answer to this question is "no", which is immediately apparent from Fig. 5. It illustrates the differences in the EMG activity induced in the lower-limb muscles during electrically evoked (Fig. 5A, B), and passive (Fig. 5C), extension (with SCS off) of the lower extremities, respectively. The characteristic distribution of motor-unit activity within the lower-limb muscle groups, with the (hip and ankle) extensors dominating over the flexors, as well as the temporal modulations in the EMG amplitude during the electrically induced movement are absent if SCS is off. The outstanding differences in the EMG pattern suggest that epidural lumbar dorsal root stimulation on the one hand, and passive movement of the lower extremity on the other hand, provide quite different input to the spinal cord. Moreover, an actual extension of the lower limb was evoked only when appropriate stimulus parameters were applied. Even when we did not support the limbs during SCS, we were nevertheless able to observe a strong and brisk, ballistic-like extension movement. However, in order to prevent any limb injury, it was essential to add the protective—but not activating—manual antigravity support. Figure 7A demonstrates that the CMUP output in hamstring and triceps surae was larger than the one in quadriceps and tibialis anterior, respectively, also when the legs rested on the examination bed (without additional support) throughout the electrical stimulation.

We should recognise that the CMUP output induced in complete SCI persons by epidural stimulation in supine position is much larger than the one observed in the same category of subjects during locomotor training in vertical position with partial body weight support (cf., Dobkin et al. 1995; Harkema et al. 1997; or Dietz et al. 1997, where the reported EMG amplitudes are by a factor of 10–100 lower than the ones we recorded). This observation suggests that the mechanisms underlying these two approaches are very different, and further investigation to clarify this difference will be necessary.

Possible mechanisms underlying the induced extension

What about the possibility that the SCS-induced extension was the result of a series of massive reflex responses to the stimulation of several types of extensor and flexor afferents? Early studies on the motor control in subjects with chronic spinal cord injuries of different severity revealed that massive reflex extension is rare in complete SCI patients (Riddoch 1917; Walsh 1919; Kuhn 1950; Dimitrijevic and Nathan 1967; Dimitrijevic 1994). Even if such strong extensor reflex responses were after all evoked by the constant and regular stimulus pulses we applied, they would habituate rapidly due to the regular repetition of these pulses at the same site and with the same strength, rather than remaining present for 50 s or more of sustained stimulation (Dimitrijevic et al. 1972). Furthermore, it would be unusual to observe a massive reflex extension revealing EMG features within the thigh and leg flexors and extensors which were the same in subjects 3–5 on many occasions (cf. Tables 4, 5). In addition, a nonselective, strong activation of several types of extensor and flexor afferents—through the dorsal columns, for example—seems unlikely in the light of the described selectivity of lumbosacral cord stimulation.

The CMUPs recorded during SCS-evoked lower-limb extension were actually short-latency posterior root muscle-reflex responses. However, what mechanism could account for the dominance of the extensor forces which ultimately resulted in an extension of the limb? If a more complex interneuron system was not involved in its production, the higher forces in the antigravity muscles could, in principle, be generated at three different levels:

1. The extensor afferents could have been exposed to a stronger electric field than the flexor afferents. If this were the case one would expect the success of SCS with respect to the initiation of lower-limb extension to hinge on a particular rostrocaudal location of the stimulating cathode. However, our investigations did not reveal a single "optimal" site, but the spinal cord levels at which extension was effectively induced covered a relatively long stretch of lumbar segments (L2/3–5)
2. It could be an inherent property of the monosynaptic reflex arc of the extensors that the latter are activated stronger than the flexors in response to the same stimulus strength (and frequencies of 5–15 Hz).
3. It could be an inherent property of the extensor muscles to generate larger forces than the flexor muscles in response to the same level of input to the muscle fibers. Explanations 2 and 3, however, still leave the described temporal changes in the relationship between quadriceps and hamstring activity to be explained.

From the present study, it emerges that the human lumbar cord is capable of producing at least two very different functional movements in response to sustained nonpatterned stimulation. In other words, there are two different "codes" inducing the isolated lumbar cord to

respond with two different motor tasks (Fig. 3). It has previously been shown that a stimulus train with a frequency of 25–50 Hz can evoke rhythmical, even stepping-like activity in the muscles of the lower limbs (Dimitrijevic et al. 1998b; Dimitrijevic 2001). The presented results demonstrate that the lumbar spinal cord can also be induced to respond with a nonpatterned type of motor output in the form of sustained lower-limb extension. No less remarkably, this "reconfiguration" is brought about just by lowering the stimulus frequency and without departing from the same sustained and nonpatterned mode of input application *to the same spinal cord structures*.

During the transition between the two motor tasks (see Fig. 4A, 21 Hz), a new spatial and temporal distribution of excitation and inhibition is developed. In addition to the already discussed features of epidurally evoked lower-limb extension, several observations indicate that both peripheral *and central* mechanisms could be involved in the neurocontrol of the above SCS-induced movements: (1) the dominance of the EMG activity in the extensor muscles over the one in the flexors evoked at 5–15 Hz is reversed during the "flexion phases" of the induced rhythmical EMG patterns as frequencies of 25–50 Hz are applied (Fig. 3); (2) in contrast to alternating reciprocal activation of flexors and extensors during stepping-like activity, the lower-limb muscles are simultaneously activated during sustained extension. Thereby, the degree of coactivation is gradually reinforced as the movement unfolds in order to stabilize the involved joints and thus retain the extended position (Fig. 6A, B). Changes in the shape of the individual CMUPs recorded in parallel also suggest that a dynamic process takes place within the spinal cord (Fig. 6C); (3) the latency times of the CMUPs recorded from the flexor muscles during rhythmical activity are significantly (approximately 10 ms) longer than the ones during extension (Fig. 4B; see also Minassian 2001a, 2001b, 2002). Only the latter can be explained in a simple manner considering the respective length of the efferent part of the monosynaptic reflex arc and "a single synaptic time lag": During implemented extension, the thigh and leg muscle groups responded at a constant latency time of approx. 10 and 15 ms, respectively (see Figs. 2, right-hand side, 4B, 5 Hz, b; Murg et al. 2000). In contrast, necessary delays between flexor and extensor muscles are provided during rhythmical activity.

On the basis of this evidence, we hypothesize that the amplitude-modulated CMUPs observed during epidurally evoked sustained lower-limb extension actually reflect monosynaptic responses to the stimulation of large afferents in the posterior roots. However, the same primary afferent volleys will be synaptically transmitted to the intrinsic spinal circuitry which is involved in the generation of lower limb movement patterns. Stimulus trains at particular frequencies (namely 5–15 Hz) will configure this interneuronal network (or at least part of it) in such a way that it sets up—via presynaptic and synaptic mechanisms—the difference in the responsiveness between the flexor and extensor nuclei reflected in what has been termed the EMG "extension pattern." During the unfolding SCS-evoked movement, varying sensory feedback from the muscle, tendon and joint afferents will be integrated by the newly organized "functional units" of spinal interneurons (see Hultborn 2001) and thus control the observed temporal modulations in the excitability of flexor and extensor motoneurons (see Jankowska 2001). A speculative scheme to illustrate this hypothesis is given in Fig. 8.

Certain support for the existence of an interneuronal system within the mammalian lumbar cord which is—when properly stimulated—capable of generating extension movements has recently been provided by Mushahwar et al. (2000). They report to have elicited coordinated, weight-bearing, whole hind limb extensor synergies in healthy adult cats by stimulating the spinal cord through a microelectrode implanted in the caudal half of the lumbar enlargement. Following their argumentation, the induced multijoint movements were not due to direct stimulation of motoneurons but resulted from the activation of interneuronal networks within the motoneuronal pools (Mushahwar et al. 2002). A similar approach was used by Tresch and Bizzi (1999), who were successful in eliciting (isometric) forces which "drive the limb away from the body" in chronically spinalized rats by stimulation of a particular region within the posterior lumbar cord.

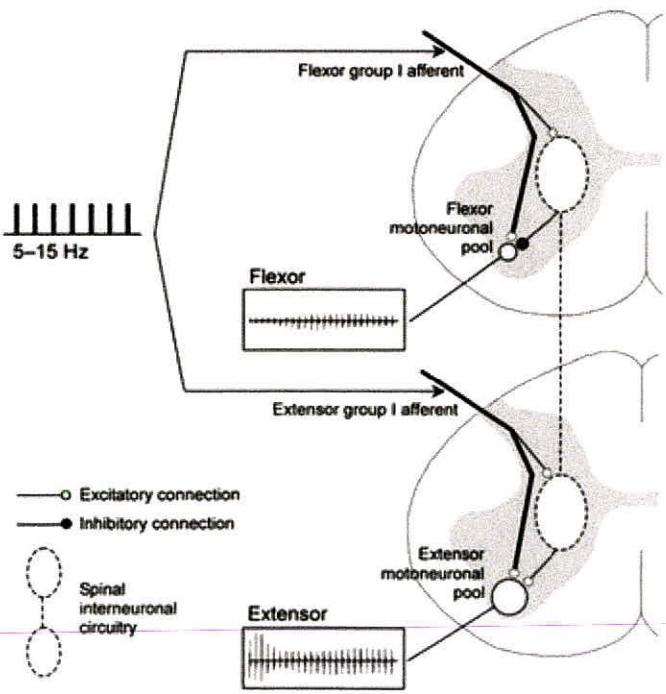


Fig. 8 Speculative scheme of the mechanisms underlying the induced extension. Probably both peripheral and central mechanisms were involved in the generation of the evoked lower-limb extension. We hypothesize that the CMUPs recorded during the induced motor task reflect monosynaptic responses to dorsal root stimulation of large primary afferents of flexor and extensor muscles. In parallel, the external stimulus would have triggered central processing via these afferents which gave rise to the observed amplitude relation between flexors and extensors and its modulation over time

One might finally ask how it can be that the same procedure of epidural lumbar cord stimulation is effective for both the suppression of spasticity and the implementation of lower-limb extension. It has to be noted, however, that distinct stimulus frequencies have to be applied to achieve these different goals. Partial elimination of afferent input has been shown to reduce spasticity (Dimitrijevic and Nathan 1967). Apparently, SCS at 50–100 Hz induces some kind of "electrophysiological rhizotomy" by strongly activating spinal interneurons which have an inhibitory—putatively presynaptic—influence on primary afferents of the lower limbs. In the control of several movement tasks, presynaptic mechanisms are known to play an important roll, being integral parts of their "central programs." Thus, presynaptic suppression of sensory transmission may be involved in the generation of SCS-induced lower-limb extension, too. Low-frequency stimulation (5–15 Hz), however, does not allow this mechanism to predominate the motor output. It is rather integrated in the organization which is induced by the regular train of stimuli. The *steady* difference in the excitability of the flexor and extensor motor nuclei during implemented extension is replaced by *alternating* excitation/inhibition of these nuclei during epidurally evoked rhythmical flexion/extension movements of the lower limbs.

Significance of the results

The question whether and how the ability to stand can be restored after spinal cord lesions has been addressed in the literature. Pratt et al. (1994) have investigated the effect of daily standing training on the weight-bearing capacity of a chronic spinal cat. De Leon et al. (1998) have revisited the same design to find out whether the observed recovery was really due to the training or whether it may have been spontaneous. They suggest that the improved standing ability seen after rote repetition of a specific hind limb task was due to the training, which presumably gave rise to long-term changes in specific spinal pathways. More recently, Harkema (2001) has shown that, after several weeks of step and standing training, chronic incomplete SCI subjects who had not been able to bear weight previously were eventually able to stand independently for several minutes.

Our results illustrate that a sustained extension of the lower limbs can be obtained by epidural stimulation of the lumbar cord in subjects who are resting in supine position. This approach does not require any preparatory (conditioning) procedure to be carried out, but the movement is elicited immediately after the onset of stimulus application. Moreover, the opportunity to induce an extension of the lower limbs by epidural cord stimulation remains intact even if the SCI occurred many years back (2–8 years in our population). However, the studies on the effect of SCS on spasticity, or with respect to the possibility to induce lower limb movements, respectively, were made in supine position. We did not have the opportunity to measure the forces actually generated in the lower-limb muscles in response to the stimulation. Although the extension induced in supine position was quite powerful, we are therefore not able to judge whether it would have been strong enough to support the subject's body weight in a standing position. Conversely, it has been shown that—at least during locomotion—the activity of both the leg and thigh muscles is powerfully controlled by afferents from load receptors (cf., Pearson and Collins 1993; Harkema et al. 1997; Dietz et al. 2002). Short-latency reflex responses occur in triceps surae at that point of the step cycle where the heel of the swinging leg hits the ground and becomes the center of weight bearing. In addition, Brooke and McIlroy (1985) have demonstrated that, during particular phases of the step cycle, short-latency pathways between extensors of the knee and ankle open in both directions.

Obviously, the artificial "code" externally applied to the posterior roots of the lumbar cord cannot replace the complex dynamic process that underlies postural control but in a fragmentary manner. The present study included only subjects whose lower spinal cord had been isolated from the brain by accidental trauma. Neurophysiological evaluation of their motor functions confirmed that they had no supraspinal control. All brainstem-derived descending tonic and phasic activity at the lumbosacral level had been eliminated by the injury. In particular, the presence of both the "driving" tonic input, which could provide postural tonus, and of the regulatory influences from higher centers was excluded. We have therefore not been able to address such critical questions as how to maintain balance or how to respond to unexpected postural disturbances (Mori 1987; Macpherson et al. 1999). Experiments in both decerebrate and spinal cats have shown that the brainstem and spinal cord cannot by themselves ensure postural equilibrium during stance. Such preparations may be capable of weight-bearing for as long as specific portions of the CNS are being stimulated, involving a short lag at best, but they cannot maintain lateral stability in the longer run (Mori et al. 1982; Pratt et al. 1994). Since the ability to stand is a prerequisite for locomotion, epidural stimulation of the lumbosacral cord at low frequencies might nevertheless be a useful neuroaugmentative tool to support locomotor training in subjects with SCI. However, further studies are needed to learn more about the mechanisms underlying our findings and to explore their full potential for clinical neurorehabilitation.

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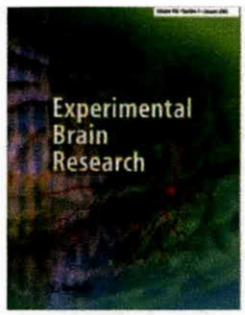

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