doi:10.1093/brain/awq370 Brain 2011: 134; 721–731 | 721

BRAIN
A JOURNAL OF NEUROLOGY

Locomotion in stroke subjects: interactions between unaffected and affected sides

Evelyne Kloter, Markus Wirz and Volker Dietz

Spinal Cord Injury Centre, Balgrist University Hospital, Forchstrasse 340, CH-8008 Zürich, Switzerland

Correspondence to: Prof. Dr Volker Dietz,
Spinal Cord Injury Centre,
Balgrist University Hospital,
Forchstr. 340,
CH-8008 Zurich,
Switzerland
E-mail: vdietz@paralab.balgrist.ch

The aim of this study was to evaluate the sensorimotor interactions between unaffected and affected sides of post-stroke subjects during locomotion. In healthy subjects, stimulation of the tibial nerve during the mid-stance phase is followed by electromyography responses not only in the ipsilateral tibialis anterior, but also in the proximal arm muscles of both sides, with larger amplitudes prior to swing over an obstacle compared with normal swing. In post-stroke subjects, the electromyography responses were stronger on both sides when the tibial nerve of the unaffected leg was stimulated compared with stimulation of the affected leg. This difference was more pronounced when stimuli were applied prior to swing over an obstacle than prior to normal swing. This indicates an impaired processing of afferent input from the affected leg resulting in attenuated and little task-modulated reflex responses in the arm muscles on both sides. In contrast, an afferent volley from the unaffected leg resulted in larger electromyography responses, even in the muscles of the affected arm. Arm muscle activations were stronger during swing over an obstacle than during normal swing, with no difference in electromyography amplitudes between the unaffected and affected sides. It is concluded that the deficits of the affected arm are compensated for by influences from the unaffected side. These observations indicate strong mutual influences between unaffected and affected sides during locomotion of post-stroke subjects, which might be used to optimize rehabilitation approaches.

Keywords: stroke subjects; spinal reflexes; quadrupedal coordination; locomotion; sensorimotor deficit; spastic hemiparesis

Introduction

Normal human locomotion is based on programmed activity within spinal neuronal circuits that is under supraspinal control and adapts to actual requirements based on multisensory feedback (Dietz, 1992). A defective reflex function is suggested to lead to impaired stepping movements, which are associated with an increased risk of falls and are a prominent clinical feature in patients suffering movement disorders such as Parkinson's disease or stroke (Lamontagne *et al*., 2007). Modulation of homonymous (Zehr *et al*., 1998; Tanabe *et al*., 2006; Schindler-Ivens *et al*., 2008) and heteronymous (Dyer *et al*., 2009) spinal reflex activity is impaired in stroke subjects and leads to abnormal inter-joint coordination (Finley *et al*., 2008; Dyer *et al*., 2009).

Recent evidence suggests that bipedal gait involves arm movements, corresponding to quadrupedal locomotion, to stabilize the body (Dietz, 2002; Michel *et al*., 2008) and to keep balance during obstacle avoidance movements (Michel *et al*., 2007). This persistent quadrupedal limb coordination during locomotion is also reflected in the behaviour of spinal reflexes (Zehr and Stein, 1999;

Received April 26, 2010. Revised October 1, 2010. Accepted November 9, 2010. Advance Access publication February 8, 2011

Dietz *et al*., 2001). For example, during locomotion—but not during stance—reflex responses to tibial nerve stimulation appear in the proximal muscles of both arms. In addition, neuronal activity coupling arm and leg movements is upregulated prior to swing over an obstacle (Michel *et al*., 2008). Surprisingly, appropriate activation of arm muscles is preserved during locomotion of subjects with Parkinson's disease, although arm movements are attenuated (Dietz and Michel, 2008).

Arm movements are also reduced on the paretic side of stroke subjects, which might have an influence on stepping performance. However, arm swing remains synchronized with stride frequency (Ford *et al*., 2007) and post-stroke subjects are able to adapt interlimb coordination of the legs to walk at different speeds on a split-belt treadmill (Reisman *et al*., 2007). Nevertheless an abnormal coupling of upper and lower limb muscles was described in subjects following stroke (Debaere *et al*., 2001; Kline *et al*., 2007; Barzi and Zehr, 2008; Stephenson *et al*., 2010) or cervical spinal cord lesions (Calancie *et al*., 1996). The disturbed inter- and intra-limb coupling is assumed to contribute to falls in post-stroke subjects (Marigold *et al*., 2004; Marigold and Eng, 2006; Lamontagne *et al*., 2007; Finley *et al*., 2008; Divani *et al*., 2009; Lamontagne and Fung, 2009).

The use of reflex testing to investigate quadrupedal coupling of limb movements during locomotion may offer more insight into several aspects of movement disorder in stroke subjects. First, recording bilateral arm muscle reflex responses to unilateral tibial nerve stimulation prior to normal and obstacle swing allows the study of the task-modulated processing of afferent input from the unaffected and affected legs. Second, bilateral arm muscle activation during normal and obstacle swing allows the study of automatic efferent control of arm movements. In healthy subjects, this arm muscle activation follows the preceding pattern of reflex activity (Michel *et al*., 2008).

In stroke subjects, it is hypothesized that arm muscle reflex responses to leg nerve stimulation and arm muscle activation during normal and obstacle steps are impaired on the affected side. This is thought to be especially true when the nerve of the spastic leg is stimulated and when the affected leg swings over the obstacle.

Materials and methods

This study was approved by the Ethics Committee and conformed to the standards set by the Declaration of Helsinki. All subjects were informed about the experiment and gave written consent for their participation.

Subjects

Seventeen subjects with stroke were included in this study (Table 1). The inclusion criteria were a hemiparesis due to ischaemic or haemorrhagic stroke 6 months or longer before enrolment, age >18 years, the ability to walk independently (Functional Ambulation Category $\geqslant 3$) (Holden *et al*., 1986) for at least 10 min and cognitive function sufficient to follow the instructions. In addition, the 10 m walk test was applied (Rossier and Wade, 2001). The clinical Fugl-Meyer test (Fugl-Meyer *et al*., 1975) was used to assess the sensorimotor deficits in the affected upper limb. Subjects with pre-existing or concomitant conditions interfering with the ability to walk (e.g. total joint replacement, severe osteoarthritis or cardiopulmonary disease) or epilepsy were excluded. Subjects were recruited from an outpatient rehabilitation centre and from a subject database (convenience sample).

Table 1 Clinical data of the stroke subjects included in the study

No.	Age	Duration (months)	Side affected	Fugl-Meyer	Functional ambulation category
1	61	8	Right	16	4
2	44	10	Left	32	4
3	46	8	Right	51	5
4	47	24	Right	47	4
5	61	7	Right	54	5
6	42	13	Left	35	5
7	58	8	Left	49	4
8	44	12	Left	35	3
9	69	162	Left	52	4
10	46	17	Right	30	4
11	68	11	Right	7	5
12	36	14	Right	33	5
13	60	98	Right	17	4
14	53	81	Right	26	4
15	38	133	Left	23	5
16	53	65	Right	52	6
17	60	70	Left	46	5

Fugl-Meyer test: maximum score for upper limbs = 66.

General procedures and conditions

In order to ensure inclusion and exclusion criteria, the motor capacity of each subject was assessed using the Functional Ambulation Category and Fugl-Meyer tests prior to experimental testing. Subjects walked with full vision on a split belt treadmill (Woodway, Weil am Rhein, Germany) with both belts running simultaneously at 1.4–2.8 km/h. In this range the individually most comfortable speed was chosen. Subjects' arms moved freely during walking. Force sensors located under the right and left treadmill belts detected 'heel strike' and 'toe off' for both feet. Two custom-built obstacle devices were placed on either side of the treadmill (Fig. 1A) (Erni and Dietz, 2001; van Hedel *et al*., 2002). The experimental details have been described previously (Dietz and Michel, 2008; Michel *et al*., 2008).

In short, the obstacle consisted of a foam stick placed 7–14 cm above the treadmill belt, according to the individual patient's ability. The stick was attached to the obstacle machine in such a way that it passively fell off if the subject touched it while attempting to overstep it. The heel strike signal randomly triggered the obstacle machine at either the right or left side to release the obstacle. After release, the obstacle moved at the same speed as the belt and the subjects could step over the obstacle with either foot without changing their rhythmic walking cadence. At the end of the treadmill, the obstacle folded up and moved back to its starting position at the front of the treadmill.

Before the experiment, subjects adapted to walking on the treadmill without obstacles and stimulation for ~8 min. The experiment itself lasted 25–30 min including a break after ~10 min of walking.

The protocol comprised 70 trials, with seven different experimental conditions. Each condition was recorded 10 times in random order,

with time intervals that varied between 11 and 16 s (i.e. every 4–8 step cycles).

The seven measurement conditions included: (i) normal steps without tibial nerve stimulation, for the analysis of background EMG activity; (ii) normal steps with tibial nerve stimulation of the unaffected; or (iii) affected leg during mid-stance, for the analysis of spinal reflex activity as the EMG responses appearing in upper and lower limb muscles to non-noxious electrical leg nerve stimulation; (iv) obstacle steps with the unaffected; or (v) affected leg without nerve stimulation, for the analysis of background EMG activity during swing over the obstacle; (vi) obstacle steps with ipsilateral nerve stimulation of the obstacle-crossing unaffected; or (vii) affected leg during mid-stance, for the analysis of spinal reflex responses prior to swing of the respective leg over the obstacle.

Biomechanical and electromyography signal recordings

Bilateral arm swing was recorded using flexible potentiometers fixed at the shoulder and the lateral aspect of the upper arm (Biometrics, Cwmfelinfach, UK). EMG recordings were made using surface electrodes placed over the tibialis anterior muscles of both legs and the anterolateral part of the deltoideus and biceps brachii muscles of both arms (Dietz and Michel, 2008; Michel *et al*., 2008). EMG signals were amplified, band-pass filtered (30–300 Hz) and rectified. Afterwards they were transferred together with biomechanical signals (shoulder excursion in the sagittal plane, heel strike and toe off) to a personal computer via an analogue-to-digital converter. All signals were sampled at 1000 Hz.

Spinal reflex recording

Spinal reflexes were defined as polysynaptic reflex responses to non-noxious tibial nerve stimulation (Dietz *et al*., 2009). Spinal reflexes were evoked 250 ms after heel strike, i.e. around the mid-stance phase (depending on the individual walking speed) of either leg prior to both normal swing or swing over an obstacle (i.e. at a time when the subject was aware of the approaching obstacle) (Fig. 1B). At this phase of the step cycle no relevant tibialis anterior EMG activity was present, neither in the unaffected nor the affected leg. The contralateral leg was in the initial part of the swing phase.

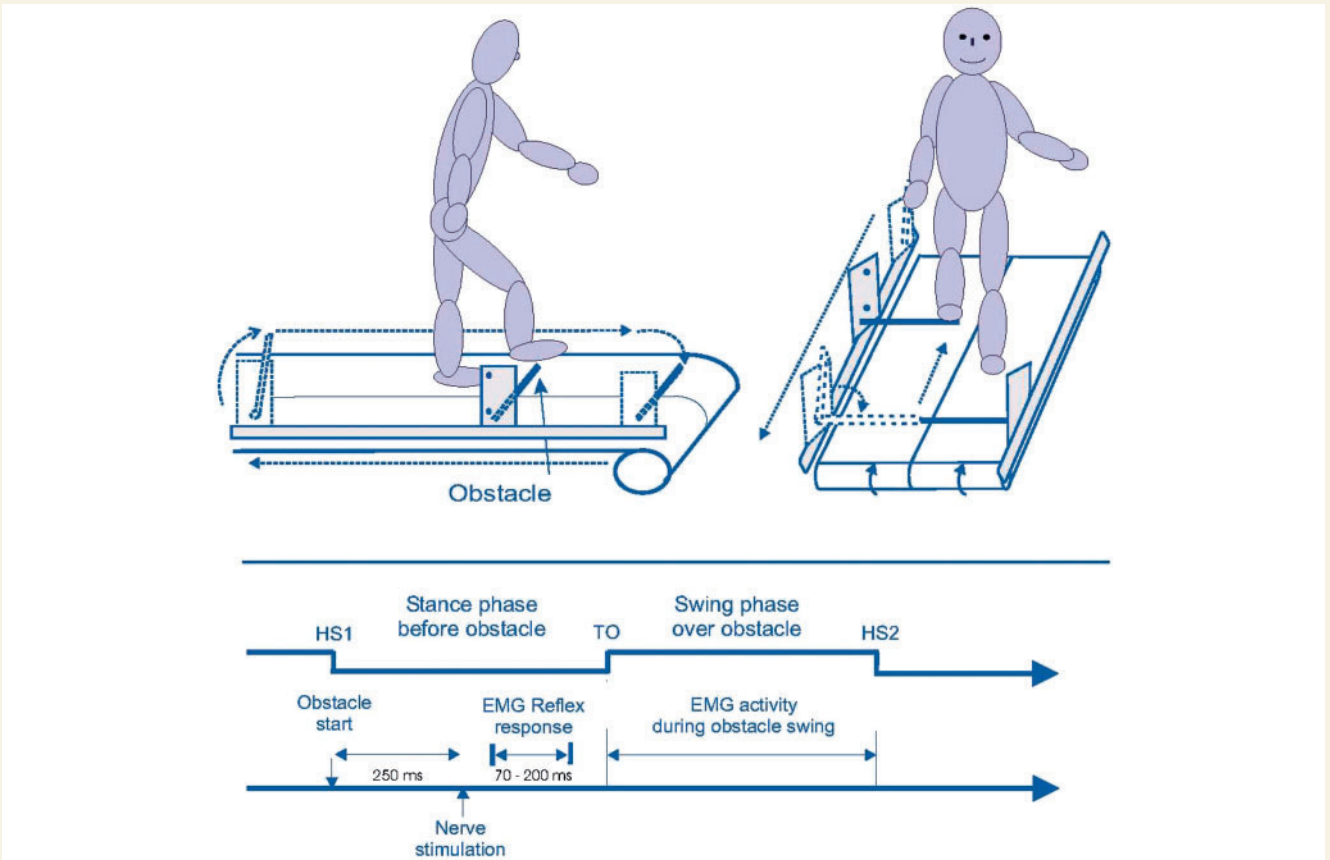

Figure 1 Experimental set up. (**A**) Schematic experimental setup illustrating a subject on a treadmill stepping over an obstacle with the right leg leading and freely moving arms. (**B**) Illustration of the events during an obstacle step cycle. At right or left heel strike (HS), the obstacle on the right or left side was randomly released and moved backwards with the treadmill belt. The reflex was evoked 250 ms after heel strike during mid-stance before swing over the obstacle. The following calculations were performed: (i) the root mean square value of the reflex response prior to obstacle swing was determined (window of analysis: 70–200 ms after stimulation). The background EMG activity prior to normal and obstacle swing was calculated for the same time interval of the step cycle (without nerve stimulation); and (ii) the EMG activity during the swing phase of normal or obstacle steps was analysed by calculating the root mean square during the swing phase [i.e. from toe off (TO) to heel strike].

A stimulation electrode (Ambu, Oelstykke, Denmark) was placed on the medial side of each ankle, where the posterior tibial nerve is closest to the skin (Roby-Brami and Bussel, 1987). The electrical stimulus consisted of a train of eight biphasic rectangular pulses with 2 ms durations and a frequency of 200 Hz. This stimulus paradigm has been shown to reliably evoke spinal reflex responses in subjects with Parkinson's disease (Dietz and Michel, 2008) and healthy subjects (Michel *et al*., 2008). In another study (Duysens *et al*., 1990), the perception threshold was used to standardize the stimulation intensity used to evoke spinal reflexes. Here, the motor threshold was used, as this might provide a more objective criterion in stroke subjects suffering spastic hemiparesis (Hiersemenzel *et al*., 2000; Dietz *et al*., 2001; Michel *et al*., 2008). The motor threshold of the abductor hallucis muscle was determined by increasing the stimulus intensity until the muscle twitched visibly. This was done with the subject standing. The stimulation intensity was set to 150% of motor threshold. This intensity is known to evoke non-nocioceptive cutaneous reflexes (Yang and Stein, 1990). After the optimal stimulation site was determined, the electrode was firmly attached with surgical tape. Using this procedure, constant stimulus conditions can be expected (Duysens *et al*., 1990). The stimulus constancy was checked during the break (after about 10 min of walking) and after the experiment. Habituation of the spinal reflex response was avoided by introducing a sufficient time delay between consecutive nerve stimulations (Shahani and Young, 1971).

Data analysis

The EMG activities of tibialis anterior and arm muscles during stance (reflex response) and swing (muscle activation) phase were analysed separately. For the reflex response, the root mean square of EMG signals was calculated by including all samples within a time window of 70–200 ms after stimulation (i.e. 320–450 ms after heel strike). A fixed time window was taken for the reflex analysis as it became obvious that distinct EMG responses could hardly be detected when the affected leg was stimulated. The window was chosen according to the appearance of the reflex responses in healthy subjects (Michel *et al*., 2008) and those suffering Parkinson's disease (Dietz and Michel, 2008). For the swing phase, EMG samples of the arm muscles from the entire period between toe off and heel strike were used to calculate the root mean square value. Ten EMG recordings from each condition were screened for outliers (greater than two standard deviations). After outliers were removed, the recordings of the remaining steps were averaged. Afterwards the mean root mean square values were normalized in the following way: (i) the root mean square values calculated for stance phase with stimulation of the unaffected and affected leg were divided by the values calculated without stimulation; and (ii) the root mean square values calculated for the swing phase while stepping over the obstacle with the affected or unaffected leg were divided by the values of deltoideus and biceps brachii of the unaffected arm calculated for the swing phase of the unaffected leg during normal steps (i.e. without the obstacle). This approach might be regarded as critical as the electrode placement and other variables may influence EMG amplitude on the contralateral arm. However, as shown earlier (Dietz and Michel, 2008), in healthy subjects and patients suffering Parkinson's disease, EMG amplitude differs very little between the two sides during walking.

In order to assess the effects of the side of tibial nerve stimulation, as well as the condition (i.e. normal versus obstacle steps), the root mean square values of EMG signals from the arms and legs of both sides (unaffected and affected) were compared using the Wilcoxon signed-rank test. Accordingly, the EMG amplitudes of the arm muscles during the swing phase were calculated from the unaffected and affected arm. Their mean values were compared between normal and obstacle steps. The signals of the potentiometers were taken to calculate the maximal forward-backward amplitude of arm swing during normal and obstacle step cycles. The mean values obtained were compared between unaffected and affected arm.

PASW statistics 17.0.2 (SPSS Inc, Chicago/IL) was used for the statistical calculations. Graphs were created using Excel 2003 (Microsoft, Redmond, WA, USA).

Results

The stroke subjects who participated in the experiment were selected with regard to their ability to step over an obstacle with a height of at least 7 cm. The range of individual walking speed was 1.4–2.8 km/h (mean 1.7 km/h). The self-selected walking speed during the recordings had no influence on the reflex behaviour. The force signals under the two belts indicated a symmetric stance phase duration of the unaffected (1.202 $\pm$ 357 ms) and affected (1.129 $\pm$ 328 ms) leg of the stroke subjects during the step cycle. They were therefore not severely disabled. This was also evident from their Fugl-Meyer and Functional Ambulation Category scores (Table 1). Nevertheless, the severity of spastic hemiparesis varied considerably among the stroke subjects. A sensorimotor deficit, spastic muscle tone and exaggerated reflexes were present on the affected side in all subjects.

Reflex activity in normal steps

Figure 2A shows the mean values of the averaged reflex responses in deltoideus muscles of the unaffected and affected arm following tibial nerve stimulation together with the background EMG of non-stimulated steps of the unaffected (Fig. 2A-a) and affected (Fig. 2A-b) leg prior to the normal swing phase of the stroke subjects. The arm muscle responses were of similar size on both the unaffected and affected side, independently whether the tibial nerve of the unaffected or the affected leg was stimulated (Fig. 2A and Table 2). The arm muscle responses to tibial nerve stimulation at the affected leg were usually small or sometimes even inhibitory on the background EMG. Therefore no response latency could be determined. The amplitudes of deltoideus (Fig. 2A) and biceps brachii EMG responses on both sides were greater when the nerve stimulation was applied to the unaffected leg (Table 2). In this condition the latencies from the onset of the stimulus train varied between 75 and 113 ms for the deltoideus muscle (unaffected arm 98.6 $\pm$ 8.8 ms; affected arm 91.2 $\pm$ 10.3 ms).

There was considerable variability in the EMG responses, especially when the unaffected leg was stimulated. However, in the majority of subjects the arm muscle responses were greater in amplitude on the unaffected (13/17) and affected (11/17) side when the tibial nerve of the unaffected leg was stimulated (Table 2). The EMG responses were only slightly larger in amplitude on the unaffected (Fig. 2A-a) compared with the affected (Fig. 2A-b) arm (not significant) in both stimulation conditions.

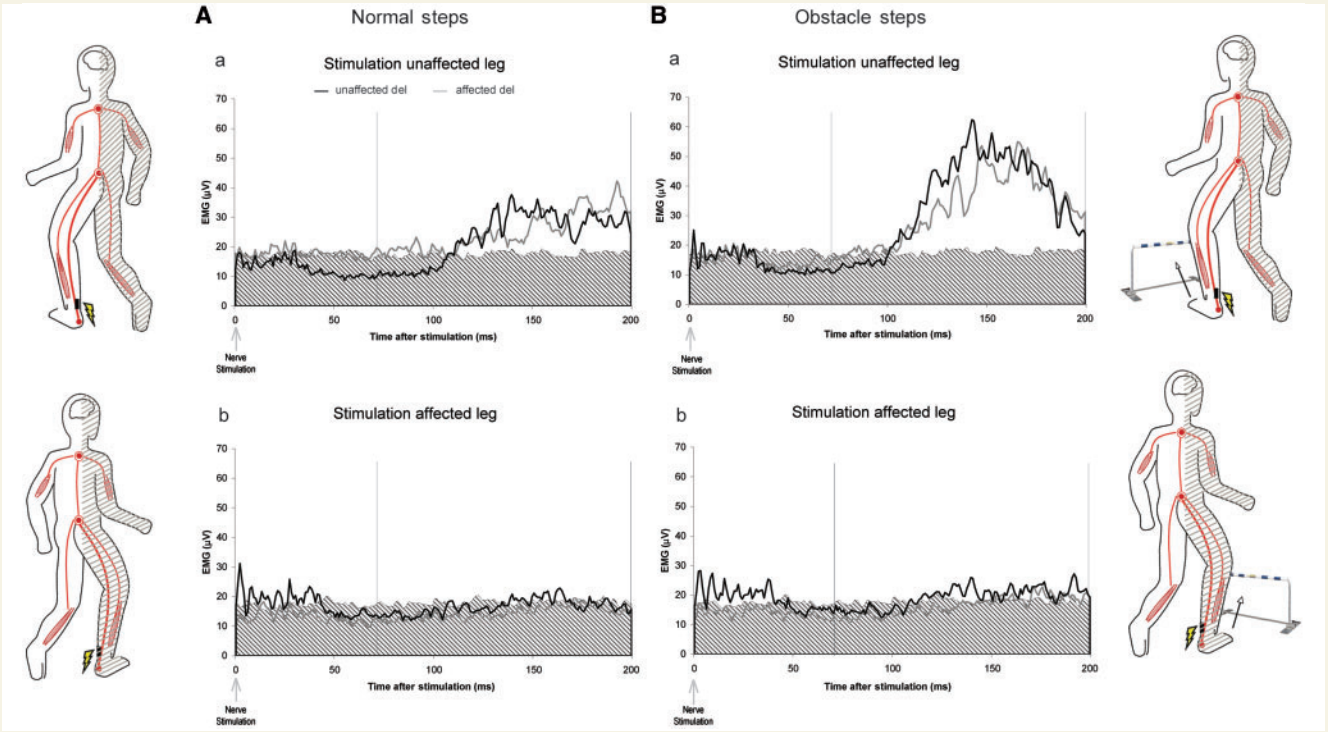

Figure 2 Reflex responses in the deltoideus (Del) muscle to tibial nerve stimulation. Grand means of the rectified reflex EMG responses in the unaffected (black lines) and affected (grey lines) deltoid muscles to tibial nerve stimulation at the unaffected (a) and affected (b) leg prior to normal (**A**) and obstacle (**B**) swing. In addition, the background EMG activity of non-stimulated steps of the unaffected (upper graphs) and affected (lower graphs) sides are displayed (hatched areas).The reflex was randomly evoked by unilateral tibial nerve stimulation around mid-stance. The reflex response was determined by the EMG activity level in the window from 70–200 ms after stimulation onset (indicated by vertical lines) and was quantified by calculating the root mean square. The stimulus train (artefact) starts at 0 ms (vertical arrow) and lasts up to 40 ms. The schematic drawings indicate the side of nerve stimulation (affected side: hatched area) and the walking conditions.

Table 2 Arm muscle reflex responses (M. deltoideus and M. biceps brachii) to tibial nerve stimulation at the unaffected and affected leg, respectively during normal and obstacle steps

	Normal steps			Obstacle steps			Reference unaffected leg	Reference affected leg
	Stimulation unaffected leg	Stimulation affected leg	*P*-value between side of stimulation	Stimulation unaffected leg	Stimulation affected leg	*P*-value between side of stimulation		
Unaffected arm	1.81 (2.13) *37.69 (43.55)*	1.11 (0.76) *25.39 (22.34)*	0.062	2.40 (2.85) *47.95 (54.38)*	1.29 (0.86) *29.85 (30.13)*	**0.019**	*27.18 (32.88)*	*27.53 (33.55)*
Affected arm	1.45 (1.54) *27.88 (27.94)*	0.86 (0.37) *22.89 (33.39)*	0.113	2.59 (3.43) *49.98 (71.71)*	1.03 (0.42) *32.11 (59.29)*	**0.039**	*22.47 (18.68)*	*21.05 (15.83)*

Reference values were recorded during stance of normal walking without stimulation. The figures displayed on the second row of the unaffected and affected leg represent the mean values of both arms. Numbers are presented as normalized and absolute (in µV below the normalized values in italic) root mean square values (SD). *P*-values were calculated using the Wilcoxon Signed Ranks Test. Significant values in bold.

Reflex activity in obstacle steps

Figure 2B shows the averaged EMG responses of both arms following stimulation of the unaffected (Fig. 2B-a) and affected (Fig. 2B-b) leg prior to swing over an obstacle. The deltoideus EMG responses in both arms were significantly greater when the nerve of the unaffected leg was stimulated prior to swing over an obstacle as compared with the stimulation prior to normal swing (Table 2). As in the normal steps, almost no reflex response could be detected when the nerve of the affected leg was stimulated. The reflex behaviour did not depend on the individual obstacle height.

In Fig. 3 the normalized and quantified reflex effects of nerve stimulation of the unaffected and affected leg on arm muscle EMG responses of the unaffected and the affected sides during normal (Fig. 3A) and obstacle (Fig. 3B) steps are shown. Because of the

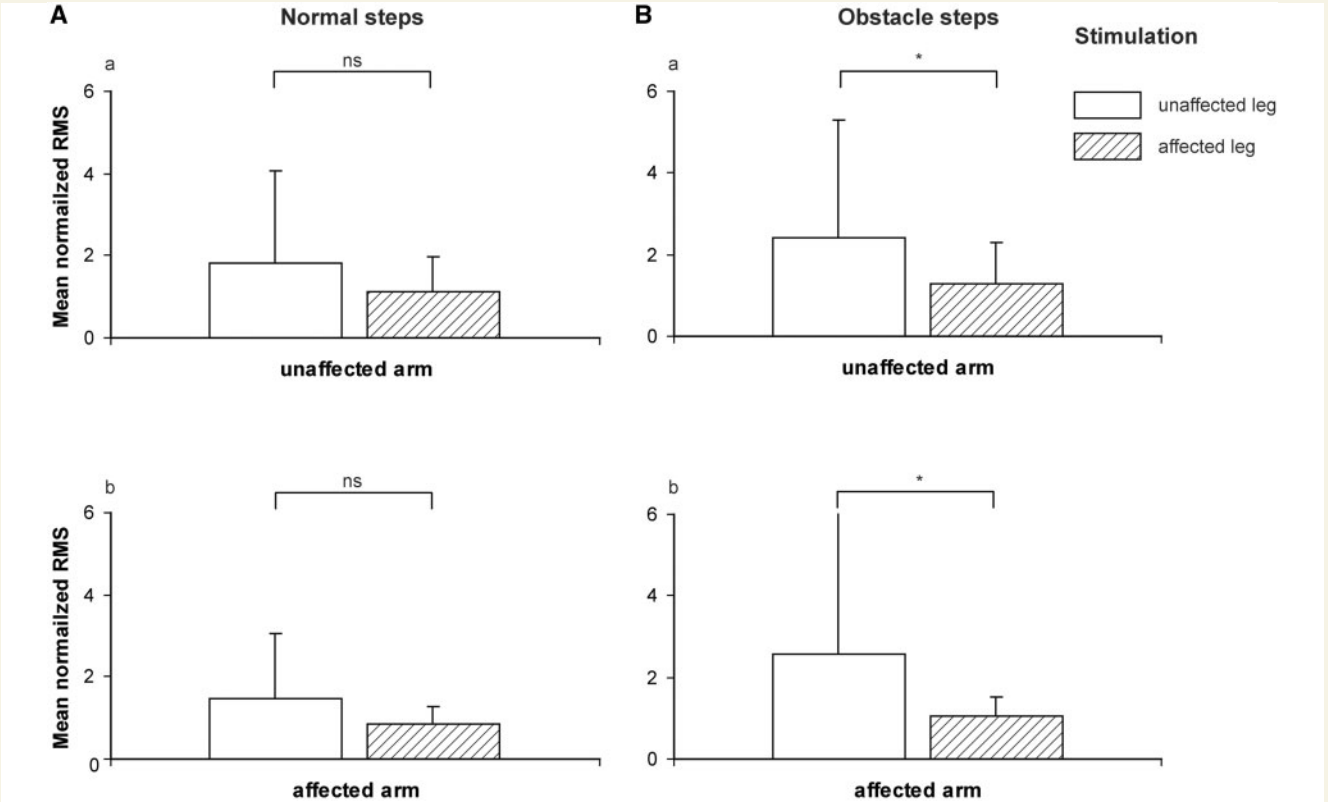

Figure 3 Effect of tibial nerve stimulation of the unaffected and affected leg, respectively, prior to normal (**A**) and obstacle (**B**) swing on arm muscle EMG responses (EMG responses of deltoideus and biceps brachiii were taken together) of the unaffected (a) and the affected (b) arms. Significant differences are indicated by an asterisk; ns = non-significant difference. RMS = root mean square.

similarity between deltoideus and biceps brachii responses, their root mean square values were taken together for further analysis.

In obstacle steps, the EMG response amplitudes were significantly greater on both arms (Table 2) when the nerve of the unaffected leg was stimulated as compared with the affected leg (Fig. 3B). In contrast when the affected leg was stimulated, the normalized root mean square values of the reflex amplitude in normal as well as obstacle steps remained ~1, i.e. was in the range of, or below, the background activity (Fig. 3A, Table 2). Nevertheless, due to the smaller variability, differences in EMG amplitudes were also present during obstacle compared with normal steps (Fig. 3B).

EMG responses in the tibialis anterior muscles of both legs were also recorded. A reflex response was only seen in the tibialis anterior of the stimulated leg. This tibialis anterior response was greater during obstacle than during normal steps (unaffected leg stimulation: $P = 0.028$; affected leg stimulation: $P = 0.053$). However the amplitude of the tibialis anterior reflex response was the same when either leg was stimulated.

Arm muscle activation during the swing phase

Figure 4A shows the mean values of the averaged EMG activity of the unaffected and affected arm muscles (deltoideus and biceps brachii together) from all subjects during a normal swing phase of the unaffected (Fig. 4A-a) and the affected (Fig. 4A-b) leg. In addition, Fig. 5A shows the quantified and normalized deltoideus and biceps brachii EMG activity (root mean square values were taken together) of both sides from all subjects during a normal swing phase of the unaffected (Fig. 5A-a and Table 3) and the affected (Fig. 5A-b) leg. In both conditions, EMG amplitude between the two arms was slightly smaller on the affected side, corresponding to the slightly reduced arm swing on the affected arm. The maximal forward-backward amplitude of arm swing was calculated for the normal step cycle [unaffected arm: mean 17.3° (SD 10.5°); affected arm: mean 10.6° (SD 7.3°); difference not significant].

Figure 4B shows the mean values of the averaged deltoideus EMG activity of the unaffected and affected arm during swing over the obstacle of the unaffected (Fig. 4B-a) and affected (Fig. 4B-b) leg. In addition, Fig. 5B shows the arm muscle activation during swing of the unaffected (Fig. 5B-a) and affected (Fig. 5A-b) leg over the obstacle. The EMG activity in the proximal arm muscles was significantly greater on both sides when the unaffected leg crossed the obstacle compared with normal swing (Fig. 5B-a and Table 3). The same was true when the affected leg crossed the obstacle (Fig. 5B-b and Table 3). Correspondingly, arm swing was more pronounced during obstacle steps than during normal steps [amplitude of unaffected arm swing during obstacle steps: 18.2° (SD 11.5°); amplitude of affected arm swing during obstacle steps: 13.4° (SD 9.9°); difference between the arms and between normal

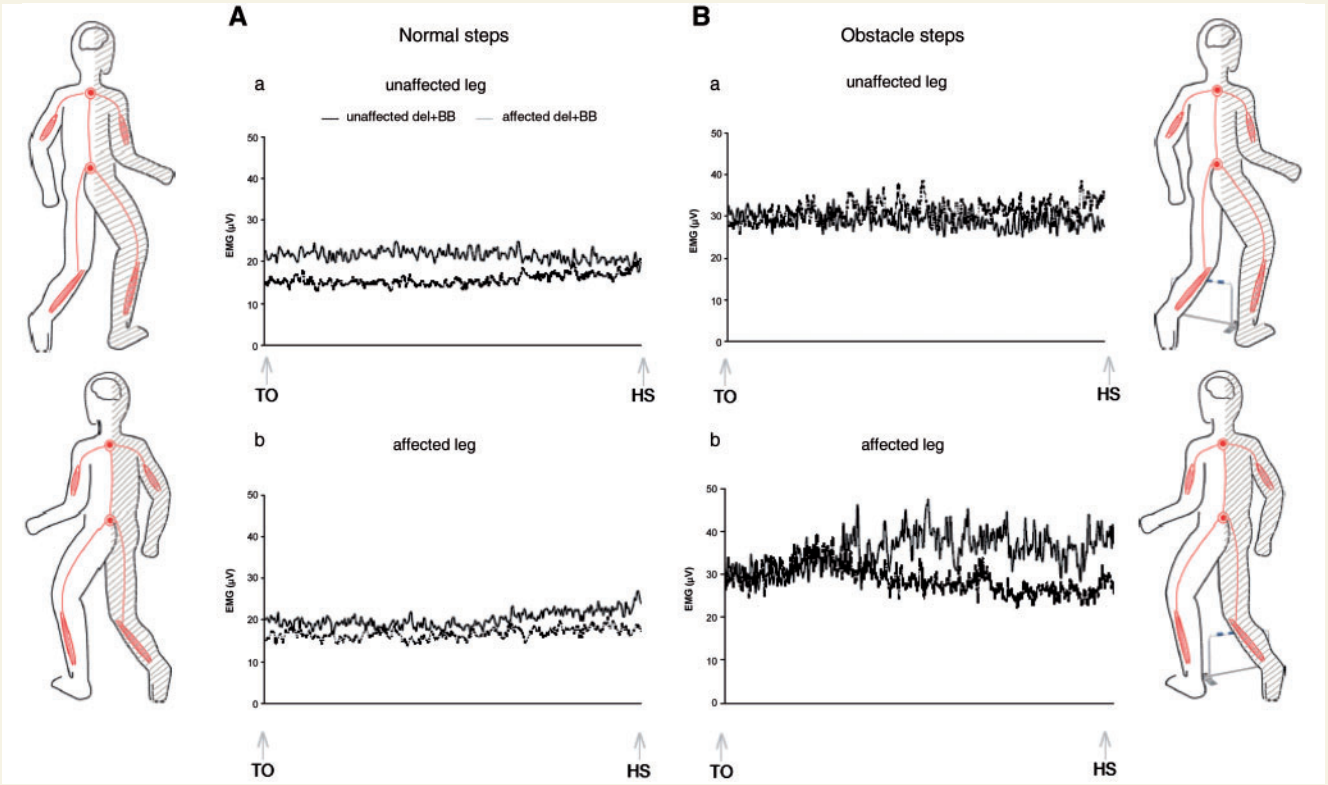

Figure 4 Grand means of the rectified deltoideus EMG activity (root mean square values) of the unaffected and affected sides during the swing phase (from toe off to heel strike; *cf.* Fig. 1) of the unaffected (a) and affected (b) leg in normal (**A**) and obstacle (**B**) steps. BB = biceps brachii; Del = deltoideus; HS = heel strike; TO = toe off.

and obstacle steps not significant]. There was no significant difference in the strength of arm muscle activation between unaffected and affected sides (Table 2B). This was the case even though arm swing appeared to be slightly attenuated on the affected side.

Relation to clinical/functional measures

The sensorimotor deficits in the affected upper limb were assessed by the Fugl-Meyer test. No relationship between the severity of the deficit and the reflex dysfunction was found. Also the Functional Ambulation Category showed no relation to the reflex behaviour. However, the maximal individual walking speed (10 m walk test) was related to the arm muscle reflexes. The reflex responses (average of the reflex responses in deltoideus and biceps brachii of both sides to nerve stimulation of the unaffected and affected leg) of the four fastest walkers were larger ($P < 0.05$) compared with those of the four slowest stroke subjects.

Discussion

The experimental approach used in this study is based on the observation that reflex responses to unilateral tibial nerve stimulation during locomotion appear in proximal arm muscles on both sides (Michel *et al*., 2008). This approach allows the testing of the effects of a non-noxious afferent volley from the unaffected or affected leg on the upper limb muscles of both sides during locomotion of post-stroke subjects.

The main results were as follows: (i) the reflex responses in the arm muscles were greater on both the unaffected and affected sides following tibial nerve stimulation of the unaffected leg compared with nerve stimulation of the affected leg; (ii) the arm muscle responses on both sides were larger in obstacle steps than in normal steps when the stimulus was applied to the unaffected leg, while little amplitude modulation occurred when the nerve of the affected leg was stimulated; and (iii) arm muscle activation was stronger on both sides during swing over an obstacle than during normal swing, with no difference in EMG amplitude between the two sides. These observations will be discussed with regard to their pathophysiological and clinical relevance.

Quadrupedal limb coordination

During locomotion of healthy subjects, unilateral tibial nerve stimulation results in EMG responses in the ipsilateral tibialis anterior and in proximal arm muscles with short latency (70–80 ms), with similar amplitude on both sides (Michel *et al*., 2008). The reflex latencies were somewhat longer in the stroke subjects, similar to subjects suffering Parkinson's disease (Dietz and Michel, 2008). This reflex behaviour supports the assumption of the persistence of quadrupedal coordination in human locomotion (Zehr and Stein, 1999; Wannier *et al*., 2001; Zehr and Kido,

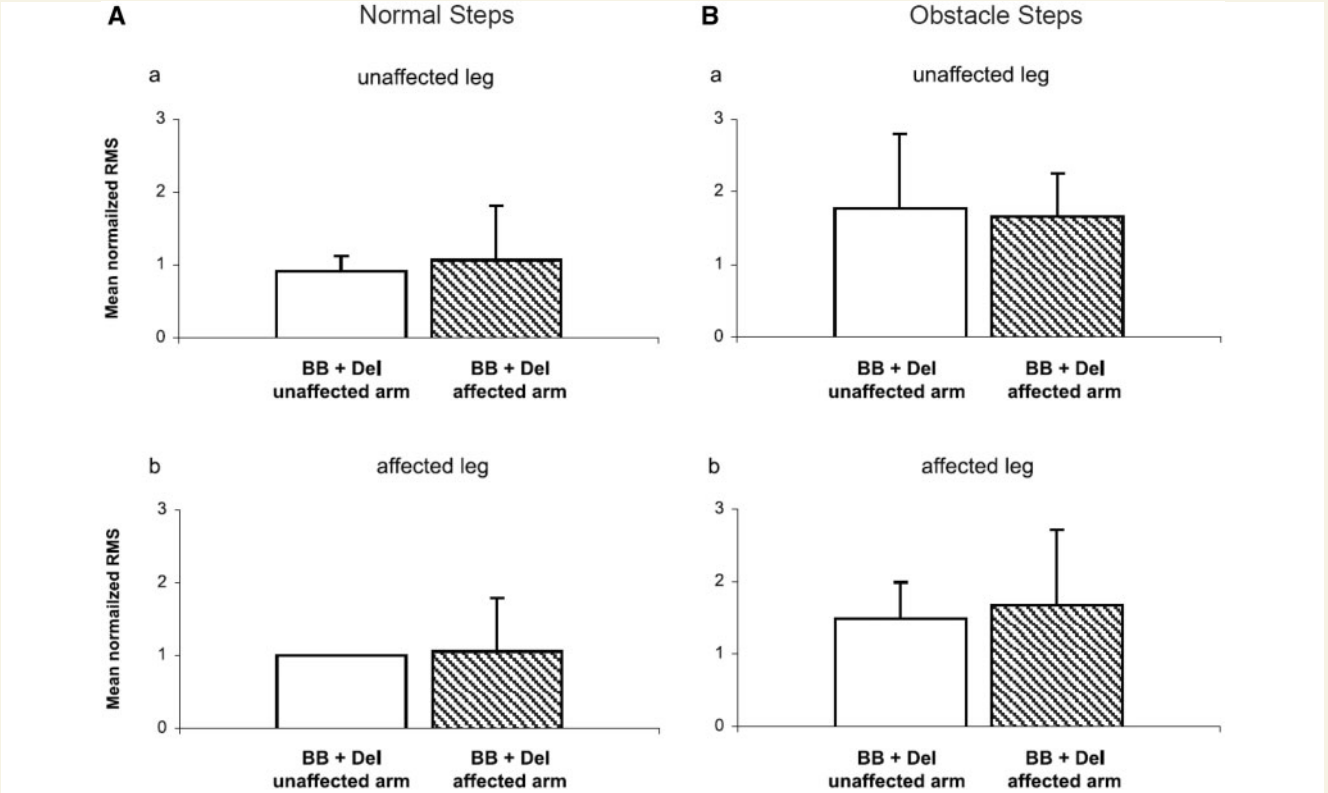

Figure 5 Arm muscle activation of both unaffected and affected sides during swing of the unaffected (a) and affected (b) leg in normal (**A**) and obstacle (**B**) steps. Values of deltoideus (Del) and biceps brachii (BB) EMG were taken together. The EMG activity was normalized to the deltoideus EMG activity of the unaffected side during normal swing. RMS = root mean square.

Table 3 Differences in arm muscle activation during the swing phase between unaffected and affected arm and between normal and obstacle steps

	Normal steps			Obstacle steps			
	Unaffected arm	Affected arm	*P*-value between arms	Unaffected arm	Affected arm	*P*-value between arms	*P*-value between normal and obstacle steps
Unaffected leg	1.00 (0.00) *26.80 (32.41)**	1.08 (0.60) *20.33 (15.50)*	0.831	1.50 (0.51) *37.18 (40.77)*	1.70 (0.80) *38.97 (59.94)*	0.758	
	1.04 (0.30) *23.56 (23.95)*			1.60 (0.55) *38.07 (50.36)*			**0.004**
Affected leg	0.91 (0.17) *23.59 (27.04)*	1.08 (0.65) *20.63 (17.77)*	0.653	1.80 (0.91) *36.25 (35.33)*	1.67 (0.46) *34.66 (35.06)*	0.492	
	1.00 (0.34) *22.11 (22.41)*			1.73 (0.59) *35.46 (35.19)*			**0.001**

The figures displayed on the second row of the unaffected and affected leg represent the mean values of both arms. Numbers are presented as normalized and absolute (in μV below the normalized values in italic) root mean square values (SD). The value marked with an asterisk represents the value that served as reference for the normalization procedure. *P*-values were calculated using the Wilcoxon Signed Ranks Test. Significant values in bold.

2001; Dietz, 2002). The quadrupedal coupling of the limbs during locomotion might be mediated by long propriospinal neurons (Calancie *et al*., 1996; Michel *et al*., 2008). Observations made in animals indicate that the mesencephalic locomotor region is involved in such coupling. In vertebrates, a unilateral activation of the mesencephalic region produces symmetrical bilateral locomotion (Brocard *et al*., 2010). Correspondingly, in our approach, a unilateral afferent volley from the leg applied during locomotion might be translated by the mesencephalic locomotor region into EMG responses in arm muscles on both sides. Consequently we

assume that the reflexes described here are in fact mediated by the brainstem. Nevertheless, a contribution by supraspinal centres cannot be excluded.

Impaired processing of afferent input

Essentially new observations were made in stroke subjects. The arm muscle responses were small or even inhibitory on both the unaffected and affected sides when the tibial nerve of the affected leg was stimulated. In contrast, they were larger in arm muscles of the affected side when the tibial nerve of the unaffected leg was stimulated. This indicates impaired processing of an afferent volley from the tibial nerve of the affected side, resulting in attenuated reflex responses in the arm muscles of both sides. We cannot exclude a contribution of kinematic changes of the affected leg to the difference in the reflex responses.

However, we would favour the idea that the disrupted corticospinal control represents an important factor for the impaired processing of the afferent volley (Lemon, 2008).

As a functional consequence, a defective sensorimotor integration, which is assumed to be responsible for the disturbed inter- and intralimb coupling (Finley *et al*., 2008; Dyer *et al*., 2009), could essentially be due to the impaired processing of afferent input. The novel aspect of this research is that the reflex effect evoked by a non-noxious volley concerned both the affected and unaffected arm of stroke subjects. The therapeutic consequence of this finding is that an enhanced afferent input from the unaffected side during functional training should lead to stronger muscle activation on the spastic side of stroke subjects.

Compared with the impaired processing of afferent input from the affected leg, the efferent part of the reflex pathway to the muscles of the affected arm was only slightly impaired. In other words, the arm and leg muscle EMG responses were only slightly smaller on the affected side compared with the unaffected side. The assessment of the neurological deficit in stroke subjects (e.g. by the Fugl-Meyer score) includes both parts of sensorimotor dysfunction—the efferent deficit and the impaired afferent processing. In addition, the study here concerns the automatic movement control of locomotion, which differs from voluntarily performed movements.

Task-dependent reflex modulation

The release of reflex responses during locomotion can also be used to probe the excitability of spinal neuronal circuits. In healthy subjects (Michel *et al*., 2008), enhanced anticipatory spinal neuronal activity mediating quadrupedal limb coordination prior to obstacle steps was described.

In stroke subjects, enhanced spinal neuronal activity was also present, as reflected in greater arm muscle reflex amplitudes on both sides in obstacle steps as compared with normal steps, when the nerve of the unaffected leg was stimulated. In contrast, when the nerve of the affected leg was stimulated, the difference in reflex amplitude between normal and obstacle steps was small; in other words, bilateral arm muscle responses were attenuated and only slightly modulated by the task. In addition, the tibialis anterior reflex amplitude was smaller in normal steps as compared with obstacle steps, but did not differ between the unaffected and affected leg.

The mutual interactions between the unaffected and affected sides of stroke subjects might explain the following observations. First, while the depression of presynaptic Ia inhibition is removed during the step cycle in patients with spinal injury, it is almost normal on the affected side in cerebral lesions (Faist *et al*., 1999). Second, in a static condition an abnormal stretch reflex activity is present not only on the affected but also on the unaffected side of stroke subjects (Thilmann *et al*., 1990).

Arm muscle activation during normal and obstacle steps

In healthy subjects, arm muscle activation is stronger during swing over an obstacle in order to maintain body balance (Grin *et al*., 2007; Michel *et al*., 2008). The stronger reflex responses prior to swing over an obstacle reflect the enhanced anticipatory neuronal activity (Michel *et al*., 2008).

The observation that increased arm muscle activation is preserved in stroke subjects during obstacle steps on both sides is at odds with the reflex behaviour observed when the nerve of the affected leg is stimulated. In post-stroke subjects, the defective processing of afferent input from the affected leg can be compensated for by a dominance of the neuronal function arising from the unaffected leg. It remains unclear when this behaviour emerges after a stroke.

Despite the strong bilateral arm muscle activation observed during swing over an obstacle, arm swing was slightly reduced on the paretic side. A similar observation was made in subjects with Parkinson's disease, who also showed normal arm muscle activation, although arm swing was reduced compared with healthy subjects (Dietz and Michel, 2008). The assumption of biomechanical restraints might also apply to the spastic paretic arm of stroke subjects (Dietz and Sinkjaer, 2007).

Clinical and functional significance

With regard to the lacking relationship between clinical assessment and reflex dysfunction one has to be aware that, (i) the group of stroke subjects studied was high functioning and quite homogeneous in their deficit, as they had to perform obstacle steps; and (ii) the reflex dysfunction is not well reflected in clinical tests as it primarily concerns automatically performed stepping movements. Consequently it makes sense that walking speed was related to the size of the reflex responses.

The present observations might have an influence on the recovery of gait and the effect of functional training in stroke subjects (Werner *et al*., 2002; Pohl *et al*., 2007; Forrester *et al*., 2008; Luft *et al*., 2008). The combination of walking at maximum speed and having body weight support leads to marked speed-related improvements of locomotor ability, especially in low-functioning stroke subjects (Lamontagne and Fung, 2004; Plummer *et al*., 2007; Hornby *et al*., 2008).

These effects might be achieved due to sensorimotor interactions of the unaffected and affected sides during functional training. According to the present results, the effects of this

training might be enhanced by providing additional afferent input from the unaffected side, especially in phases of the step cycle where balance reactions from the arms are required.

Acknowledgements

The authors would like to thank Prof. A. Luft and K. Campen from the 'Zentrum für ambulante Rehabilitation (ZAR)' in Zürich for allowing them to make recordings from stroke subjects under their care and for providing clinical data. The authors are grateful for the editorial service provided by Aimee Schultz.

Funding

The Swiss National Science Foundation (32-105324).

References

Barzi Y, Zehr EP. Rhythmic arm cycling suppresses hyperactive soleus H-reflex amplitude after stroke. Clin Neurophysiol 2008; 119: 1443–52.

Brocard F, Ryczko D, Fenelon K, Hatem R, Gonzales D, Auclair F, et al. The transformation of a unilateral locomotor command into a symmetrical bilateral activation in the brainstem. J Neurosci 2010; 30: 523–33.

Calancie B, Lutton S, Broton JG. Central nervous system plasticity after spinal cord injury in man: interlimb reflexes and the influence of cutaneous stimulation. Electroencephalogr Clin Neurophysiol 1996; 101: 304–15.

Debaere F, Van Assche D, Kiekens C, Verschueren SM, Swinnen SP. Coordination of upper and lower limb segments: deficits on the ipsilesional side after unilateral stroke. Exp Brain Res 2001; 141: 519–29.

Den Otter AR, Geurts AC, Mulder T, Duysens J. Gait recovery is not associated with changes in the temporal patterning of muscle activity during treadmill walking in patients with post-stroke hemiparesis. Clin Neurophysiol 2006; 117: 4–15.

Dietz V. Human neuronal control of automatic functional movements: interaction between central programs and afferent input. Physiol Rev 1992; 72: 33–69.

Dietz V. Do human bipeds use quadrupedal coordination? Trends Neurosci 2002; 25: 462–7.

Dietz V, Fouad K, Bastiaanse CM. Neuronal coordination of arm and leg movements during human locomotion. Eur J Neurosci 2001; 14: 1906–14.

Dietz V, Grillner S, Trepp A, Hubli M, Bolliger M. Changes in spinal reflex and locomotor activity after a complete spinal cord injury: a common mechanism? Brain 2009; 132: 2196–205.

Dietz V, Michel J. Locomotion in Parkinson's disease: neuronal coupling of upper and lower limbs. Brain 2008; 131: 3421–31.

Dietz V, Sinkjaer T. Spastic movement disorder: impaired reflex function and altered muscle mechanics. Lancet Neurol 2007; 6: 725–33.

Divani AA, Vazquez G, Barrett AM, Asadollahi M, Luft AR. Risk factors associated with injury attributable to falling among elderly population with history of stroke. Stroke 2009; 40: 3286–92.

Duysens J, Trippel M, Horstmann GA, Dietz V. Gating and reversal of reflexes in ankle muscles during human walking. Exp Brain Res 1990; 82: 351–8.

Dyer JO, Maupas E, de Andrade Melo S, Bourbonnais D, Fleury J, Forget R. Transmission in heteronymous spinal pathways is modified after stroke and related to motor incoordination. PLoS One 2009; 4: e4123.

Erni T, Dietz V. Obstacle avoidance during human walking: learning rate and cross-modal transfer. J Physiol 2001; 534: 303–12.

Faist M, Ertel M, Berger W, Dietz V. Impaired modulation of quadriceps tendon jerk reflex during spastic gait: differences between spinal and cerebral lesions. Brain 1999; 122: 567–79.

Finley JM, Perreault EJ, Dhaher YY. Stretch reflex coupling between the hip and knee: implications for impaired gait following stroke. Exp Brain Res 2008; 188: 529–40.

Ford MP, Wagenaar RC, Newell KM. Phase manipulation and walking in stroke. J Neurol Phys Ther 2007; 31: 85–91.

Forrester LW, Wheaton LA, Luft AR. Exercise-mediated locomotor recovery and lower-limb neuroplasticity after stroke. J Rehabil Res Dev 2008; 45: 205–20.

Fugl-Meyer AR, Jaasko L, Leyman I, Olsson S, Steglind S. The post-stroke hemiplegic patient. 1. a method for evaluation of physical performance. Scand J Rehabil Med 1975; 7: 13–31.

Grin L, Frank J, Allum JH. The effect of voluntary arm abduction on balance recovery following multidirectional stance perturbations. Exp Brain Res 2007; 178: 62–78.

Hesse S. Treadmill training with partial body weight support after stroke: a review. NeuroRehabilitation 2008; 23: 55–65.

Hiersemenzel LP, Curt A, Dietz V. From spinal shock to spasticity: neuronal adaptations to a spinal cord injury. Neurology 2000; 54: 1574–82.

Holden MK, Gill KM, Magliozzi MR. Gait assessment for neurologically impaired patients. Standards for outcome assessment. Phys Ther 1986; 66: 1530–9.

Hornby TG, Campbell DD, Kahn JH, Demott T, Moore JL, Roth HR. Enhanced gait-related improvements after therapist- versus robotic-assisted locomotor training in subjects with chronic stroke: a randomized controlled study. Stroke 2008; 39: 1786–92.

Kline TL, Schmit BD, Kamper DG. Exaggerated interlimb neural coupling following stroke. Brain 2007; 130: 159–69.

Lamontagne A, Fung J. Faster is better: implications for speed-intensive gait training after stroke. Stroke 2004; 35: 2543–8.

Lamontagne A, Fung J. Gaze and postural reorientation in the control of locomotor steering after stroke. Neurorehabil Neural Repair 2009; 23: 256–66.

Lamontagne A, Stephenson JL, Fung J. Physiological evaluation of gait disturbances post stroke. Clin Neurophysiol 2007; 118: 717–29.

Lemon RN. Descending pathways in motor control. Annu Rev Neurosci 2008; 31: 195–218.

Luft AR, Macko RF, Forrester LW, Villagra F, Ivey F, Sorkin JD, et al. Treadmill exercise activates subcortical neural networks and improves walking after stroke: a randomized controlled trial. Stroke 2008; 39: 3341–50.

Marigold DS, Eng JJ. Altered timing of postural reflexes contributes to falling in persons with chronic stroke. Exp Brain Res 2006; 171: 459–68.

Marigold DS, Eng JJ, Timothy Inglis J. Modulation of ankle muscle postural reflexes in stroke: influence of weight-bearing load. Clin Neurophysiol 2004; 115: 2789–97.

Michel J, van Hedel HJ, Dietz V. Facilitation of spinal reflexes assists performing but not learning an obstacle-avoidance locomotor task. Eur J Neurosci 2007; 26: 1299–306.

Michel J, van Hedel HJ, Dietz V. Obstacle stepping involves spinal anticipatory activity associated with quadrupedal limb coordination. Eur J Neurosci 2008; 27: 1867–75.

Plummer P, Behrman AL, Duncan PW, Spigel P, Saracino D, Martin J, et al. Effects of stroke severity and training duration on locomotor recovery after stroke: a pilot study. Neurorehabil Neural Repair 2007; 21: 137–51.

Pohl M, Werner C, Holzgraefe M, Kroczek G, Mehrholz J, Wingendorf I, et al. Repetitive locomotor training and physiotherapy improve walking and basic activities of daily living after stroke: a single-blind, randomized multicentre trial (DEutsche GAngtrainerStudie, DEGAS). Clin Rehabil 2007; 21: 17–27.

Reisman DS, Wityk R, Silver K, Bastian AJ. Locomotor adaptation on a split-belt treadmill can improve walking symmetry post-stroke. Brain 2007; 130: 1861–72.

Roby-Brami A, Bussel B. Long-latency spinal reflex in man after flexor reflex afferent stimulation. Brain 1987; 110 (Pt 3): 707–25.

Rossier P, Wade DT. Validity and reliability comparison of 4 mobility measures in patients presenting with neurologic impairment. Arch Phys Med Rehabil 2001; 82: 9–13.

Schindler-Ivens S, Brown DA, Lewis GN, Nielsen JB, Ondishko KL, Wieser J. Soleus H-reflex excitability during pedaling post-stroke. Exp Brain Res 2008; 188: 465–74.

Shahani BT, Young RR. Human flexor reflexes. J Neurol Neurosurg Psychiatry 1971; 34: 616–27.

Stephenson JL, De Serres SJ, Lamontagne A. The effect of arm movements on the lower limb during gait after a stroke. Gait Posture 2010; 31: 109–15.

Tanabe S, Kamiya A, Muraoka Y, Masakado Y, Tomita Y. Disorder of phase-related modulation of soleus H-reflex during hip movement in stroke patients. Electromyogr Clin Neurophysiol 2006; 46: 241–6.

Thilmann AF, Fellows SJ, Garms E. Pathological stretch reflexes on the "good" side of hemiparetic patients. J Neurol Neurosurg Psychiatry 1990; 53: 208–14.

van Hedel HJ, Biedermann M, Erni T, Dietz V. Obstacle avoidance during human walking: transfer of motor skill from one leg to the other. J Physiol 2002; 543: 709–17.

Wannier T, Bastiaanse C, Colombo G, Dietz V. Arm to leg coordination in humans during walking, creeping and swimming activities. Exp Brain Res 2001; 141: 375–9.

Werner C, Von Frankenberg S, Treig T, Konrad M, Hesse S. Treadmill training with partial body weight support and an electromechanical gait trainer for restoration of gait in subacute stroke patients: a randomized crossover study. Stroke 2002; 33: 2895–901.

Yang JF, Stein RB. Phase-dependent reflex reversal in human leg muscles during walking. J Neurophysiol 1990; 63: 1109–17.

Zehr EP, Fujita K, Stein RB. Reflexes from the superficial peroneal nerve during walking in stroke subjects. J Neurophysiol 1998; 79: 848–58.

Zehr EP, Kido A. Neural control of rhythmic, cyclical human arm movement: task dependency, nerve specificity and phase modulation of cutaneous reflexes. J Physiol 2001; 537: 1033–45.

Zehr EP, Stein RB. What functions do reflexes serve during human locomotion? Prog Neurobiol 1999; 58: 185–205.