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CORTICO-SPINAL TRACT FUNCTION IN INCOMPLETE HUMAN SPINAL CORD INJURY

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Summary

Remarkable recovery is observed in patients suffering from acute incomplete spinal cord injury (iSCI) and the majority of patients who initially present with some motor function below the level of lesion regain some walking ability. At present, no pharmaceutical or surgical interventions are available that enhance and promote neural repair after a spinal cord lesion. Thus, it is assumed that this recovery process is mainly due to plasticity occurring at the spinal, subcortical and cortical level of the central nervous system (CNS), as well as to compensatory adaptations occurring at both the level of motor units and in movement behaviour. In the future, regeneration therapies might be available that further enhance recovery from iSCI by either directly targeting the damaged fibre tracts or allowing for detour pathways. Evaluating the effectiveness of such therapies requires not only the identification of the fibre tracts that are the most promising in enhancing a patient's functional capacity, but also sensitive assessment tools that can detect the expected changes. The relevance of the cortico-spinal tract (CST) as a potential target for regeneration therapies has been scarcely investigated in humans, particularly in the lower limb. In addition, the sensitivity of the current clinical assessment of motor recovery from iSCI has been repeatedly criticized. Thus, the aim of this thesis was to study the impact of CST function on lower limb motor recovery by combining an advanced measurement protocol of motor evoked potentials (MEPs) with new clinical tests.

For this purpose, a new test was developed (auditory-paced repetitive ankle dorsi- and plantar- flexion movements at 3 frequencies) that assessed ankle dexterity (accurate timing of dorsiflexion movements) and maximal movement velocity (MMV), which assesses a patient's ability to generate dynamic muscle strength. Dexterity and movement velocity are two aspects of motor control that have been associated with CST function. The experimental protocol was complemented by static strength tests (maximal voluntary contraction (MVC)), manual muscle testing, neurophysiological measures of CST function (MEPs) and gait tests. Using this paradigm, motor control of (acute and chronic) iSCI patients and matched healthy subjects was compared. In addition, the course of the neurophysiological and clinical parameters was studied during the first 6 months after iSCI to evaluate the degree to which changes in CST function were related to clinical recovery. For further validation of the paradigm, and to integrate the results of the iSCI patients in the larger context of CNS lesions, stroke patients were also tested.

The results show that dexterity, when assessed as in the presented paradigm within the extent of the remaining muscle strength, was well preserved in acute and chronic iSCI

patients and was not related to the MEP measures. However in stroke patients, dexterity was significantly reduced in the hemiparetic leg, but was preserved in the non-affected leg. MMV, in turn, was significantly reduced in acute and chronic iSCI patients, as well as after stroke. This impairment persisted even in well-recovered iSCI patients, where only MMV, but not MVC was reduced compared to healthy subjects. In addition, MMV related better to the MEP measures than MVC and manual muscle testing. During recovery from acute iSCI, MEP latencies remained prolonged, while MEP amplitudes and all clinical parameters of muscle strength and ambulation increased. Again, the recovery in MMV was the only clinical parameter that was related to the increase in MEP amplitudes.

These results advance the current knowledge of motor control in iSCI. The dissociation between the impairments of motor strength and dexterity shows that iSCI patients can rely on surprisingly well-preserved control of the remaining muscle function, and indicates that augmenting a patient's dynamic muscle strength should be a key goal for both rehabilitation and regeneration strategies in iSCI. With a view to rehabilitation, appropriate strength training strategies might beneficially complement the current gait-specific rehabilitation approach (body-weight supported treadmill training). As for regeneration therapies, strategies that aim at remyelinating damaged CST fibers might be particularly promising, since the deceleration of CST conductivity was closely related to the reduced movement velocity. For the evaluation of the effectiveness of such new interventions in iSCI, enhancing the sensitivity of the current clinical assessment protocol by introducing a dynamic assessment, such as the presented paradigm, is essential.

Zusammenfassung

Nach einer inkompletten Querschnittlähmung zeigen die meisten Patienten eine beträchtliche motorische Erholung und die Mehrheit der Patienten, die initial unterhalb des Verletzungsniveaus auch nur geringfügige Muskelfunktion haben, wird wieder gehfähig. Gegenwärtig gibt es weder medikamentöse noch chirurgische Therapien, welche die Nervenverletzungen nach einer Querschnittlähmung zu reparieren vermögen. Es wird deshalb angenommen, dass Plastizität im zentralen Nervensystem (auf spinaler, subcorticaler und corticaler Ebene), aber auch Anpassungsvorgänge in den motorischen Einheiten der Muskeln und im Bewegungsverhalten zu diesem Erholungsprozess beitragen. In Zukunft werden Therapieformen, welche die beschädigten Nervenbahnen direkt zu reparieren versuchen oder die Entstehung von Umgehungsbahnen ermöglichen, die Erholung nach einer inkompletten Querschnittlähmung vermutlich weiter verbessern. Die Beurteilung der Wirksamkeit solcher Therapien verlangt einerseits die Identifikation der Nervenbahnen, deren Regeneration die grösste klinische Verbesserung eines Patienten zu bewirken vermag. Andererseits braucht es aber auch sensitive Tests, welche die erhofften Verbesserungen nachweisen können. Die Bedeutung der Corticospinalbahn als möglicher Angriffspunkt für solche Therapien wurde bisher im Menschen, vor allem in der unteren Extremität, nur spärlich erforscht. Im Weiteren wurde die Sensitivität der bisherigen Tests zur Erfassung der motorischen Erholung nach einer inkompletten Querschnittlähmung mehrfach kritisiert. Ziel dieser Arbeit war es daher, den Einfluss der Corticospinalbahn auf die motorische Erholung der unteren Extremität nach einer inkompletten Querschnittlähmung zu untersuchen. Dazu wurde ein erweitertes Messprotokoll von motorisch evozierten Potentialen (MEPs) in Kombination mit neuen klinischen Tests durchgeführt.

Zu diesem Zweck wurde ein neuer Test entwickelt (repetierte Dorsi- und Plantarflexionen zu vorgegebenen Tönen in 3 verschiedenen Frequenzen), der Geschicklichkeit (zeitliche Steuerung der Bewegungen) und maximale Bewegungsgeschwindigkeit des Fusses, ein Mass für die Fähigkeit eines Patienten, dynamische Kraft zu erzeugen, erfasst. Geschicklichkeit und Bewegungsgeschwindigkeit sind zwei Aspekte der Motorik, welche in Zusammenhang mit der Corticospinalbahn gebracht werden. Das Messprotokoll wurde durch Messungen der statischen Muskelkraft, manuelle Muskeltests, neurophysiologische Messungen der Corticospinalbahn (MEPs) und Gehtests ergänzt. Mit diesem Protokoll wurde die motorische Kontrolle von Patienten mit einer (akut und chronisch) inkompletten Querschnittlähmung und gesunden Probanden verglichen. Zusätzlich wurde der Verlauf der neurophysiologischen und klinischen Parameter während der ersten 6 Monate nach einer

inkompletten Querschnittlähmung untersucht, um festzustellen, inwieweit Veränderungen in der Funktion der Corticospinalbahn mit der klinischen Erholung in Verbindung standen. Schliesslich wurden auch Patienten nach einem Hirnschlag getestet, um das Testprotokoll weiter zu validieren und um die Resultate der querschnittgelähmten Patienten im erweiterten Kontext von Läsionen des Zentralnervensystems zu beurteilen.

Die Resultate zeigen, dass die Geschicklichkeit, wenn sie wie in der vorliegenden Arbeit im Rahmen der verbleibenden Kraft erfasst wird, bei akut und chronisch inkomplett querschnittgelähmten Patienten gut erhalten war und nicht mit den MEPs korrelierte. Die Geschicklichkeit der Hirnschlagpatienten war im betroffenen Bein signifikant vermindert, im nicht-betroffenen Bein aber erhalten. Die Bewegungsgeschwindigkeit war hingegen sowohl nach einer akut und chronisch inkompletten Querschnittlähmung als auch nach einem Hirnschlag reduziert. Dieses Defizit persistierte sogar bei inkomplett querschnittgelähmten Patienten, die sich so gut erholt hatten, dass die statische Kraft gleich gross war wie bei den gesunden Probanden. Zusätzlich korrelierte die Bewegungsgeschwindigkeit, verglichen mit der statischen Muskelkraft und den manuellen Muskeltests, am stärksten mit den MEPs. Während der Erholung nach einer akuten inkompletten Querschnittlähmung blieb die Latenz der MEPs verlängert, wohingegen sich die Amplitude und alle klinischen Messparameter für Kraft und Gehfunktion verbesserten. Die Bewegungsgeschwindigkeit war wiederum der einzige klinische Parameter, dessen Zunahme mit der Verbesserung der Amplitude der MEPs in Verbindung stand.

Die Resultate dieser Arbeit tragen zur Erweiterung des derzeitigen Wissens über die Motorik nach inkompletter Querschnittlähmung bei. Die Erfassung von Geschicklichkeit unabhängig von Muskelschwäche zeigt auf, dass Patienten nach einer inkompletten Querschnittlähmung über eine erstaunlich gut erhaltene Kontrolle der vorhandenen Muskelkraft verfügen und dass es daher das Hauptziel von Rehabilitation und Regenerationsversuchen sein sollte, die dynamische Muskelkraft eines Patienten zu verbessern. In der Rehabilitation könnten geeignete Krafttrainingsmassnahmen den gegenwärtigen gangspezifischen Rehabilitationsansatz (Laufbandtraining mit Gewichtsentlastung) sinnvoll ergänzen. Im Hinblick auf Regenerationsversuche könnten Strategien, welche auf die Remyelinisierung von verletzten Corticospinalbahnfasern hinzielen, besonders erfolgsversprechend sein, weil vor allem deren reduzierte Leitfähigkeit eng mit der reduzierten Bewegungsgeschwindigkeit verbunden war. Für die Beurteilung der Wirksamkeit von solch neuen Therapien ist es unerlässlich, die Sensitivität des gegenwärtigen klinischen Testprotokolls durch die Einführung eines dynamischen Tests, wie er in dieser Arbeit präsentiert wurde, zu verbessern.

1. Introduction

1.1. Spinal cord injury

1.1.1. Epidemiology

Within the neurological disorders, spinal cord injury (SCI) is an infrequent, but very debilitating and costly injury (O'Connor 2006). Its consequences are manifold. Aside from the physical afflictions, which include not only paralysis, but also pressure sores, urinary tract infections and pain, the social and economic costs are also great (Manns and Chad 2001; Kennedy et al. 2006; Whalley Hammell 2007). In the United States, the annual incidence per 100'000 people is 183 for stroke, 101 for traumatic brain injury and 4.5 for SCI (Hirtz et al. 2007). Similar incidence rates occur in Switzerland, with the annual number of SCI cases reported to be between 350 to 400 (Eberhard 2004). Yet, such statistics have often only focused on SCI of traumatic etiology. These lesions are mainly caused by traffic accidents, occupational and sport accidents, and suicide attempts (Dietz 1996). Current trends however suggest that the percentage of traumatic injuries to the spinal cord have decreased, while non-traumatic injuries, mainly due to spinal stenosis, tumor compression or vascular ischemia, have increased and amount for about 40 to 50% of all lesions to the spinal cord (McKinley et al. 1999; Eberhard 2004). Patients with a non-traumatic SCI are more likely to have an incomplete SCI (iSCI) (McKinley et al. 1999), which means that some motor and/or sensory function is preserved below the lesion (ASIA 2002).

1.1.2. Classification of spinal cord lesions

Two main features of a spinal cord lesion lead to its classification, namely its level and its completeness. The classification of the level of lesion is based on the neurological level, which is defined as the most caudal segment of the spinal cord with normal sensory and motor function (ASIA 2002). Importantly, the neurological level is not congruent with the skeletal level, which refers to the level at which the greatest vertebral damage is found by radiographic examination (ASIA 2002). Particularly in the thoracic and lumbar spine, these levels deviate considerably due to the fact that the spinal cord ends at the level of the second lumbar vertebral body. Lesions within the cervical part of the spinal cord result in quadriplegia (motor and sensory deficits in upper and lower limbs and in the trunk, and autonomic dysfunction affecting the cardiovascular system, bladder, bowel and sexual function). Lesions in the thoracic, lumbar or sacral parts of the spinal cord result in paraplegia (similar dysfunctions as in quadriplegia, but motor and sensory deficits in lower limbs and

trunk only). Within paraplegia, a distinction is made between the conus syndrome and the cauda equina syndrome. A conus syndrome results from an injury to the spinal cord at its caudal ending and is mainly associated with impairments on bladder, bowel and sexual functions. The term cauda equina syndrome refers to lesions of the lumbosacral nerve roots below the caudal ending of the spinal cord. It is in fact an injury of the peripheral nervous system (PNS) and leads, in contrast to lesions of the spinal cord itself, to flaccid instead of spastic paralysis of the lower limbs.

The completeness of SCI is classified according to the neurological standard protocol set by the American Spinal Injury Association (ASIA) (ASIA 2002). A complete injury is defined by the absence of sensory and motor function in the lowest sacral segment S4/S5 (category ASIA A). An incomplete injury, in turn, is defined by partial preservation of sensory and/or motor function below the neurological level including the lowest sacral segment (ASIA 2002). Based on the extent of the preserved function below the neurological level, 3 categories (categories ASIA B-D) have been established within the incomplete injuries, while the category ASIA E refers to iSCI patients, who have normal sensory and motor function (Tab. 1.1). Sensory function is quantified by testing the sensitivity to two aspects of sensation (pin prick and light touch) at 28 defined points (dermatomes) on both sides of the body (scores 0 to 2 for each dermatome), which results in a maximal sensory score of 112 points for sensitivity to pin prick and light touch, respectively. Motor function is quantified by manual testing of the muscle strength of 10 key muscles on both sides of the body (scores 0 to 5; Tab. 1.2), which results in a maximal motor score of 100 points. The assessment of motor function will be described in more detail in section 1.3.1.

Tab. 1.1: Categories of spinal cord injury.

Classification		**Description**
A	complete	No sensory or motor function is preserved in the sacral segments S4-S5
B	incomplete	Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-S5
C	incomplete	Motor function is preserved below the neurological level, and more than half of key muscles have a muscle grade less than 3
D	incomplete	Motor function is preserved below the neurological level, and at least half of key muscles have a muscle grade greater than or equal to 3
E	normal	Sensory and motor function are normal

Tab. 1.2: Assessment of muscle strength according to the American Spinal Injury Association.

Classification	Description
0	Total paralysis
1	Palpable or visible contraction
2	Active movement, full range of motion with gravity eliminated
3	Active movement, full range of motion against gravity
4	Active movement, full range of motion against moderate resistance
5	(normal) active movement, full range of motion against full resistance

1.2. Recovery from incomplete spinal cord injury

1.2.1. Mechanisms of recovery

Patients with iSCI often show considerable recovery of sensory and motor functions (Waters et al. 1994a; Waters et al. 1994b). A recent study showed that 92% of patients with iSCI who had little motor function below the neurological level (category ASIA C) at 2 months post injury were able to walk independently at 6 months post injury (Dobkin et al. 2006). Furthermore, 100% of patients with iSCI who showed strong motor function below the neurological level at that time (category ASIA D) regained their walking ability after 6 months (Dobkin et al. 2006). Little is known about the mechanisms that underlie this recovery process (Weidner et al. 2001). However, it is theoretically thought to arise either via neuronal and/or compensatory mechanisms (Fig. 1.1) (Curt et al. 2004).

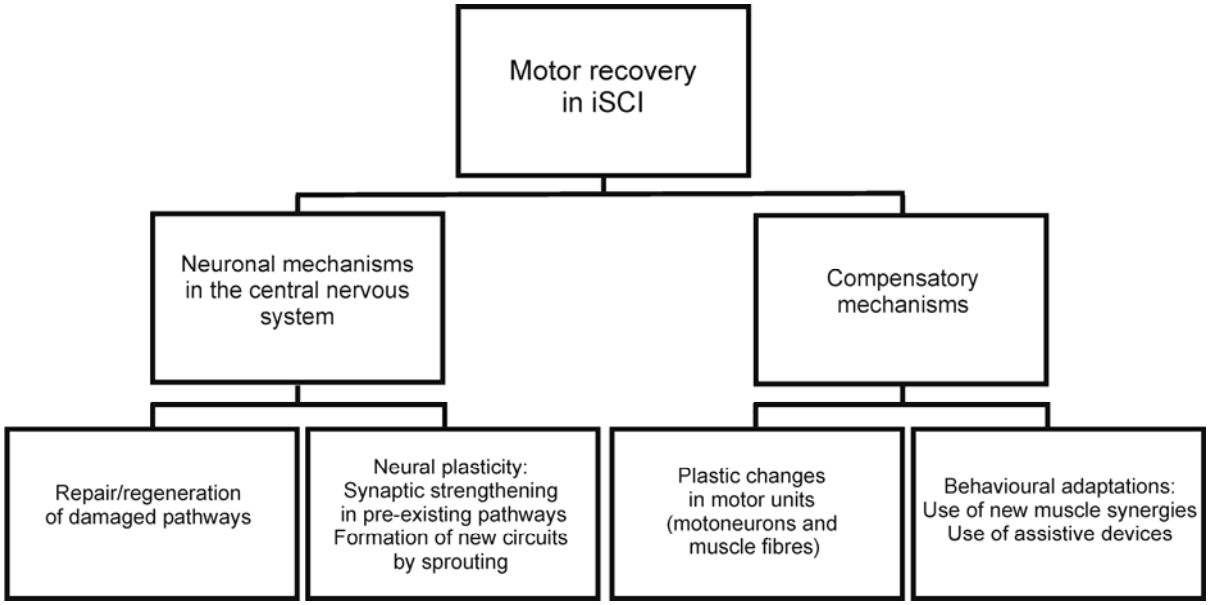

Fig. 1.1: Possible mechanisms underlying motor recovery after an incomplete spinal cord injury (adapted from Curt et al. 2004).

Neuronal mechanisms

Neuronal mechanisms are changes within the central nervous system (CNS) itself. They can be subdivided into (i) mechanisms that involve repairing damage to the injured neural structures and (ii) mechanisms involving neural plasticity, which refers to reorganization processes in both the intact and damaged pathways. In comparison to the PNS, neurons of the mammalian CNS typically fail to regenerate their axons after injury. This failure in regeneration is largely due to inhibitory molecules that are produced by two sources: the myelin-forming glial cells (oligodendrocytes) produce Nogo, myelin-associated glycoprotein (MAG) and oligodendrocyte myelin glycoprotein (OMgp), while the reactive astrocytes at the site of injury form a glial scar and produce various chondroitin sulphate proteoglycans (CSPGs). Various strategies to overcome these barriers to regeneration are actively being researched (for review see (Fawcett 2002; Kwon et al. 2005; Ramer et al. 2005; Fawcett 2006). For example, in animals, the intrinsic growth potential of axons is augmented by administrating neurotrophic factors and by targeting the neurite growth signaling pathway through increasing intracellular cyclic adenosine monophosphate (cAMP) (Cai et al. 2001) and/or inhibiting the Rho pathway (Dergham et al. 2002). Furthermore, neutralization of the axon growth inhibitory molecules has been attempted by administration of antibodies, such as anti-NogoA (Chen et al. 2000; Buchli and Schwab 2005). Another repair approach is focusing on transplanting cells that may bridge the site of injury and facilitate axonal regeneration across the hostile environment of the scar. Candidate cells include Schwann cells (Paino and Bunge 1991), which promote axonal regeneration in the PNS, and olfactory ensheathing glia cells (Li et al. 1997) that mediate continual axonal growth from the olfactory epithelium into the olfactory bulb throughout adult life. Another strategy involves transplanting autologous macrophages, activated by prior exposure to degenerating peripheral nerve segments, to promote axonal regeneration in the rat spinal cord (Rapalino et al. 1998). Attempts at cellular transplantation for remyelination of the regions surrounding the lesion have been made in several laboratories using implantation of oligodendrocyte precursor cells, which may be derived from embryonic stem cells or neural stem cells (Keirstead et al. 2005). While none of these approaches has entered clinical practice yet, it should be noted that three procedures (including the use of a recombinant protein Rho GTPase antagonist, activated autologous macrophages and anti-Nogo-A antibodies) have entered phase 1 and 2 clinical trials.

Contrary to neural regeneration, neural plasticity, which can be defined as the compensation of damaged structures by reorganization of the preserved lesioned or unlesioned structures, spontaneously occurs after spinal cord lesions. It involves the strengthening or weakening of

pre-existing circuits, as well as the formation of new circuits through collateral sprouting. After iSCI, plasticity is supposed to take place not only at the cortical level but also at the subcortical and the spinal level, as well as in descending pathways.

At the cortical level, areas of the motor cortex controlling muscles rostral to the spinal cord lesion tend to expand (Bruehlmeier et al. 1998) and to displace in the direction of the disconnected regions (Mikulis et al. 2002). However, the importance of these changes for the recovery of function after iSCI is not clear (Curt et al. 2002; Jurkiewicz et al. 2007).
At the subcortical level, plasticity of the cortico-spinal tract (CST) has been reported to occur to a substantial degree during development, but to be limited in the adult CNS (Raineteau and Schwab 2001). Nevertheless, in a study that completely lesioned the dorsal cortico-spinal motor pathway (containing 95% of all cortico-spinal axons) in rats, spontaneous sprouting from the ventral CST (containing less than 5% of all cortiospinal axons) was shown. This sprouting was paralleled by an improvement in performance in a skilled forelimb reaching task (Weidner et al. 2001). Another study reported that in adult rats, transected hindlimb CST axons formed detour circuits by sprouting into the cervical gray matter and contacting propriospinal neurons located there (Bareyre et al. 2004). In addition to plastic changes within the CST itself, particularly the rubrospinal system was shown to be able to take over some function of the lesioned CST in monkeys (Lawrence and Kuypers 1968).
At the spinal level, plasticity has been proposed to take place in the central pattern generator (CPG), which is a spinal network that is able to generate a reciprocal rhythmic activation pattern of flexor and extensor muscles for simple locomotion even when it is disconnected from its descending input (Grillner 2002; Dietz 2003). Although in humans the elimination of all peripheral and supraspinal inputs is not possible, there is however accumulating evidence that the human spinal cord also possesses a rhythm-generating network (Duysens and Van de Crommert 1998; Edgerton et al. 2004). Plasticity at the level of the CPG might involve the global enhancement of spinal excitability as well as some reorganization in pre-existing circuits through the stimulation of cutaneous receptors and muscle proprioceptors (Raineteau and Schwab 2001). Thus, enhancing neural plasticity is another target for pharmacological treatments and most of the aforementioned strategies also promote axonal sprouting of intact axons or collateral sprouting in the injured spinal cord (for review see (Fawcett 2002; Kwon et al. 2005; Ramer et al. 2005; Fawcett 2006). These include antibodies inhibiting NogoA molecules (Buchli and Schwab 2005) as well as the enzyme ABC chondroitinase that digests inhibitory proteoglycan molecules in the dense perineuronal extracellular matrix and in the astrocytic scar (Bradbury et al. 2002). In addition, some molecules like inosine or brain derived neurotrophic factor (BDNF) stimulate axonal sprouting in the spinal cord even when

applied to the cell bodies of the spinal cord projection neurons in the brain (Vavrek et al. 2006).

Compensatory mechanisms

Besides mechanisms that directly affect the injured CNS, compensatory mechanisms, which do not influence the CNS itself, also contribute to the considerable recovery after iSCI. These mechanisms involve changes in the motor units (=α-motoneurons and the innervated muscle fibres) as well as changes at the level of motor behaviour.

Force gradation in voluntary contractions is based on the recruitment of motor units and the modulation of their firing rate. In the thenar muscles of iSCI patients, motor unit recruitment was shown to occur over a wider range of force than in healthy subjects (up to 85% of maximal voluntary contraction (MVC) in contrast to 30% in the healthy subjects), while the firing rate modulation was limited (Zijdewind and Thomas 2003). Furthermore, motor units with unusual strength were observed after iSCI, which was explained by partial motoneuron loss and subsequent sprouting of the axons of the preserved motoneurons (Thomas et al. 1997). In addition, a relative muscle hypertrophy that restored the size of the muscle fibres from below normal to normal values was reported to be induced by body weight supported treadmill training (Stewart et al. 2004) as well as resistance training (Gregory et al. 2007) in chronic iSCI patients. In healthy subjects, a training-induced increase in muscle strength is, at an early stage, mainly based on neurological adaptation processes (improved intermuscular coordination of agonists, antagonists and synergists; controversial discussion of an increase in supraspinal drive and motoneuron excitability) and at a later stage on muscle hypertrophy (Folland and Williams 2007). Thus, also in iSCI patients, recovery of muscle strength might partly be based on training effects in preserved motor units.

Lastly, at the behavioural level, the training of new muscle synergies by using uninjured systems to compensate for injured pathways, as well as the use of assistive devices, also contribute to the recovery in function that is observed after iSCI (Curt et al. 2004).

1.2.2. The role of the CST in normal motor function and in recovery from iSCI

The role of the CST in normal motor function

The CST has several functions that can be summarized by one feature: it modulates spinal cord activity (Lemon and Griffiths 2005). In more detail, its main functions in motor control are (1) control of afferent inputs, (2) selection and gating of spinal reflexes, and (3) (direct and indirect) excitation and inhibition of motoneurons. It contributes to skilled motor behaviour (dexterity), particularly in primates and humans, which might reflect the importance

of this tract in primates at the expense of other descending pathways, such as the rubrospinal tract (Lemon and Griffiths 2005). Dexterity, which can be defined as the ability to coordinate voluntary muscle activity to meet environmental demands (Canning et al. 2004), is thought to be dependent on a rapid transfer of sensorimotor information between the cerebral cortex and the spinal cord (Darian-Smith et al. 1996). Morphological analyses of the CST terminations within the spinal gray matter across species showed that in cats, CST termination was restricted to the dorsal horn and the intermediate zone, while a ventral shift with direct projections to the motoneuron pool was observed in the macaque monkey and, more noticeably, in the chimpanzee (Kuypers 1973; Armand 1982). The location of CST termination was related to an animal's capacity for relatively independent finger movements (Kuypers 1973). Similarly, in a comparative morphological study of 69 mammals, digital dexterity corresponded most closely to the place of termination of pyramidal tract fibres within the spinal cord and, to a lesser extent, to the size of the tract itself (Heffner and Masterton 1975). As for the lower limbs, relatively little is known about the role of the CST in the control of walking. Cortical involvement in obstructed walking (obstacle avoiding) has been shown in several studies (Drew 1988; Drew et al. 1996). Unobstructed locomotion, in contrast, is highly automated. Spinal networks are involved in the generation of a reciprocal rhythmic locomotor pattern, which ensures an appropriate timing of muscle activation (Dietz 1992; Grillner et al. 1998). Nevertheless, there is some cortical involvement in simple, unobstructed locomotion. During locomotion of rabbits on a flat surface, for example, the cortical cells of layer five, which form the origin of the CST, were active, predominantly in the first half of the swing phase (Beloozerova et al. 2003). Furthermore, the pyramidal tract neurons of the cortex in cats showed increased activity during the swing phase (Drew et al. 2002; Lavoie and Drew 2002). In humans, the activity of the spinal network depends even more on supraspinal influences than what has been observed in rabbits and cats. Weak transcranial magnetic stimulation (TMS) that activated only inhibitory cortical interneurons, and thus inhibited the activity of the corticomotoneuronal cells, depressed the ongoing electromyographic activity in leg muscles during human walking, demonstrating that the motor cortex is directly involved in the activation of the lower limb motoneurons (Petersen et al. 2001). Furthermore, facilitation of the motor evoked potentials (MEPs) (elicited by TMS) of the tibialis anterior muscle was shown to be maximal prior to the swing phase (Schubert et al. 1997; Schubert et al. 1999). Cortical projections to the motoneurons of the tibialis anterior are more pronounced than to other lower limb motoneurons (Perez et al. 2004) and are comparable to that of finger muscles. This might be explained by the high precision needed for adequate toe clearing during the swing phase, which is comparable, in terms of motor control, to a precision grip task between index finger and thumb (Petersen et al. 2003). In summary, human bipedal and animal quadrupedal walking is based on the integration of the

spinal network with sensory feedback and descending commands from the cortex. However, in bipedal walking, the interaction has been modified towards a greater dependency on supraspinal control (Nielsen 2003).

The role of the CST in recovery from iSCI

After unilateral complete CST lesion, rats showed some transient locomotor deficits (asymmetry in gait), but recovered to normal, symmetrical locomotion within 5 to 7 days (Muir and Whishaw 1999). Cats, in turn, regained unassisted walking ability without difficulties in supporting body weight within 10 days after the lesion, but showed a paw drag, which is the inability to adequately lift the paw during swing phase and indicates an impaired control of the ankle dorsiflexor muscles (Drew et al. 2002). Similarly, the most obvious deficit in motor function after an unilateral lesion to the CST in non-human primates (monkeys) was foot drop (Courtine et al. 2005). However, despite this, all monkeys were able to walk unaided quadrupedally on a treadmill after one week of recovery albeit, as a result of paw drag, gait kinematics were altered in terms of step cycle duration. In addition, their lower limb manual dexterity (tested by a foot grasping task) was completely abolished. Twelve weeks post lesion, no paw drag occurred during testing, and the gait parameters were approximately comparable to pre-lesion values at that time. The ability to retrieve items with the foot also showed substantial, though incomplete recovery (Courtine et al. 2005). The finding of a long-lasting deficit in lower limb dexterity after unilateral CST section is in accordance with studies investigating manual dexterity of the upper limb in monkeys after unilateral section of the cervical spinal cord (Galea and Darian-Smith 1997). In humans, lastly, there is limited data regarding the effect of selective pyramidal tract lesion (Nielsen 2003). In patients with congenital CST dysgenesis, the temporal coordination between different muscles that are involved in dexterous finger movements was impaired (Duque et al. 2003). Regarding the lower limb, correlations between the location and the extent of the incision in the spinal cord and the motor function were made post mortem in patients who underwent cordotomies for relief of the pain of cancer (Nathan 1994). One patient with severe bilateral damage to the lateral CST was thereby reported to have eventually regained walking ability after the cordotomy, although with severe spastic paraparesis. The overall conclusion from 44 patients in that study was that any clinical evidence for CST damage meant that CST was indeed damaged when examined in histology. On the other hand, the CST could be damaged without clinically manifesting any evidence of a lesion (Nathan 1994). After SCI, CST conductivity (assessed by TMS, for more details see section 1.3.1.) was reported to be unchanged during the first year of recovery (Curt et al. 1998; Smith et al. 2000). Nevertheless, an increase in the function of spared cortico-spinal pathways (increased

response to TMS) after 3 to 5 months of intense treadmill training was proposed in chronic iSCI patients (Thomas and Gorassini 2005), which is supported by the earlier finding that treadmill training can induce reorganization of cortical leg representation (Dobkin 2000).

1.3. Assessment of motor function in incomplete spinal cord injury

1.3.1. Current clinical assessment protocol of motor function

Studying and understanding the mechanisms of recovery in iSCI requires precise monitoring of the recovery process. In the framework of the International Classification of Functioning, Disability and Health (ICF) (WHO 2001), the assessment of motor function in iSCI takes place at the level of body function, and at the level of activities and participation. At the level of body functions, muscle strength and CST function are measured, while at the level of activities and participation, several timed gait tests and tests for the quantification of independence in the activities of daily living are conducted. The following paragraphs give an overview of the assessment tools that are currently used in clinical practice.

Muscle strength

Muscle strength is quantified by a 6 level scale according to the protocol set by ASIA (ASIA 2002) (Tab. 1.2). Briefly, an examiner judges a patient's muscle strength by quantifying whether full range of motion can be performed without gravity, with gravity, or even against the resistance of the examiner. The scale is of ordinal nature and ranges from 0 points (=total paralysis) to 5 points (=normal active movement, full range of motion against full resistance). The classification within iSCI is based on this scale and consists of the categories ASIA A – E (Tab. 1.1).

Cortico-spinal function

The function of the CST is assessed by means of the neurophysiological method of TMS. This non-invasive, safe and – unlike transcranial electrical stimulation – painless method to stimulate the cortex and peripheral nerves was developed in the United Kingdom in 1985 (Barker et al. 1985). The principle of this technique is as follows: A coil of wire, enclosed in plastic, is held to the head of a subject. The coil is energized by the discharge of a large capacitor. This produces a rapidly changing current in its windings, which induces a magnetic field. This magnetic field then passes unimpeded through the skin and the skull and induces a current in the brain, which activates nearby neurons (Barker 1991). The elicited action

potential is then transmitted by normal nerve conduction and can be measured as a so-called motor evoked potential (MEP) by means of electromyography (EMG) at the limb that corresponds to the stimulated area in the motor cortex. A MEP is thus represented by an excitatory EMG response and is characteristically followed by a pause in EMG activity (Fig. 1.2). This pause, the so-called silent period, is a period of inhibited cortical and spinal excitability, which lasts for a few hundred milliseconds and which occurs because inhibitory circuits are stimulated by TMS (Chen et al. 1999; Kobayashi and Pascual-Leone 2003). Mostly, a MEP signal is quantified by its latency, which is defined as the duration between the stimulus and the MEP. It is an indicator of conduction speed and thus of integrity of the CST, and suggests, if prolonged, demyelination of pathways and loss of fast-conducting fibres. In addition, the MEP amplitude might provide additional information, since it reflects not only integrity, but also excitability of the structures involved (Kobayashi and Pascual-Leone 2003). Particularly the MEP amplitudes, however, vary widely from trial to trial, possibly due to changes in the excitability of both the cortico-spinal pathway and the motoneurons (Kobayashi and Pascual-Leone 2003; McDonnell et al. 2004), which is why they are regarded to be of less clinical relevance (Diehl et al. 2006).

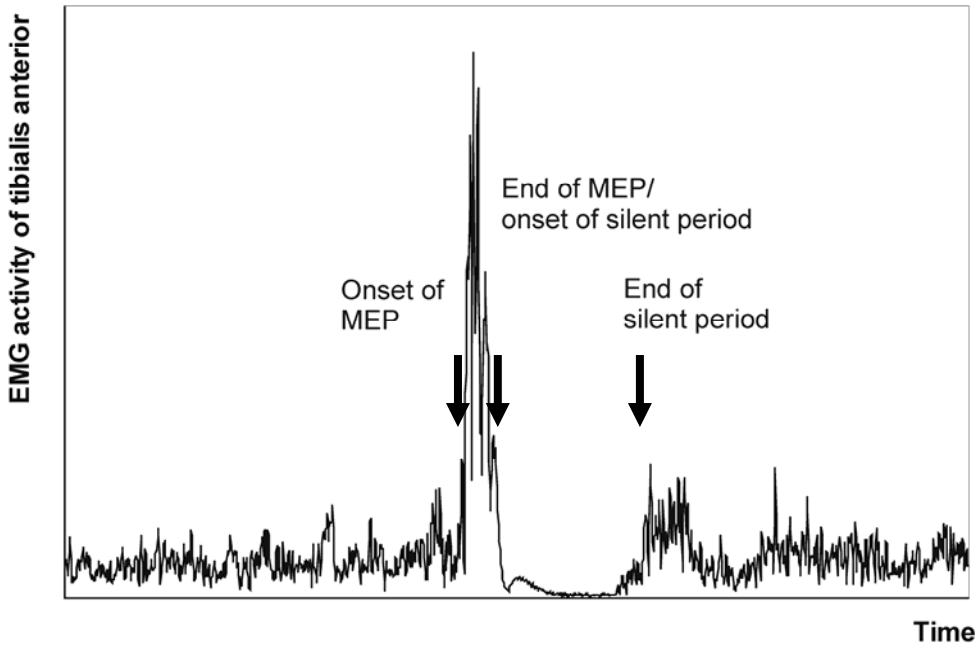

Fig. 1.2: Example of a MEP.

Gait tests

For the assessment of walking capacity, three timed walking tests and one test for assessing the assistive devices that a patient needs for walking are used in iSCI. The common timed

walking tests are the 10 Meter Walk Test (10MWT), the 6 Minutes Walk Test (6MWT) and the Timed up and go test (TUG). The 10MWT measures the time that a subject needs for walking 10 meters, while the 6MWT measures the distance that a subject covers during 6 minutes. The TUG measures the time it takes a subject to rise from an armchair, walk 3 meters, turn, walk back to the chair and sit down (Podsiadlo and Richardson 1991). All of these tests were not particularly designed for iSCI patients (Guyatt et al. 1985; Cahalin et al. 1996; Rossier and Wade 2001), but all of them were shown to be valid and reliable in iSCI (van Hedel et al. 2005). However, the walking speed in the 10MWT was reported to be highly predictable for the walking speed in the 6MWT, which resulted in the suggestion to preferentially use the 10MWT to assess gait capacity in iSCI patients (van Hedel et al. 2007a). Usually, the timed walking tests are performed at a patient's preferred walking speed. Recently, however, testing also maximal gait speed has been proposed to give additional information about gait capacity in SCI patients (van Hedel et al. 2007a).

For the assessment of a patient's need for assistive devices during walking, the Walking Index for Spinal Cord Injury (WISCI) was developed (Ditunno et al. 2000) and the revised version, the WISCI II, is currently in use (Ditunno and Ditunno 2001). This test consists of a 21 level scale. The score 0 indicates that a patient is unable to stand or walk, while a score of 20 stands for a patient who is able to walk 10 meters without using any device (for more details see section 2.3.2; Tab. 2.1). The validity of the WISCI (and the WISCI II) has been demonstrated in several studies (Morganti et al. 2005; Ditunno et al. in press).

Activities of daily living

In (i)SCI, the recovery of independency in the activities of daily living is commonly assessed either by the Functional Independence Measure (FIM) (Keith et al. 1987) or by the Spinal Cord Independence Measure (SCIM) (Catz et al. 1997). Both scales test a patient's independency in the areas self-care, sphincter control and locomotion. However, the FIM was not developed specifically for patients with SCI and thus includes abilities that are of less importance to this patient group (i.e. cognitive functions and communication). This led to the criticism that the FIM lacked sensitivity (Marino et al. 1993; Middleton et al. 2006) and also its validity in SCI has not been proven (Dodds et al. 1993). For this reason, the SCIM was developed, which includes areas of particular importance for subjects with SCI. These areas are weighted according to their clinical relevance with regard to the overall activity of patients with SCI. A revised form of the SCIM, the SCIM II, had been shown to be responsive during the first year post injury, even in complete SCI patients (Wirth et al. in press-c) and is currently in use in several SCI centers in Israel, Europe and the United States (Catz et al.

2001b). Recently, a third version has been developed (SCIM III), which includes one new sub-item and some slight modifications in scoring (Catz and Itzkovich 2007).

1.3.2. Motor function during the course of rehabilitation

During the course of recovery after iSCI, muscle strength, as measured by the ASIA motor scores, continuously increases, though with a decreasing rate of improvement (Waters et al. 1994b; Waters et al. 1994a; Curt et al. 1998; Smith et al. 2000; Wirz et al. 2006). A plateau of recovery is reached at about 300 days post injury (Waters et al. 1994a; Waters et al. 1994b).
With a view to neurophysiology, a MEP is not evokable in all iSCI patients. A MEP of the tibialis anterior muscle was reported to be recordable in about 80% of iSCI patients (Curt and Dietz 1999). If a signal can be recorded, it is normal in only about 10% of the patients (Curt et al. 1998), but shows prolonged latency and reduced amplitude in most patients (Curt et al. 1998; Curt and Dietz 1999; Smith et al. 2000; Diehl et al. 2006). In follow-up records during rehabilitation, the alterations in signal latency do not change (Curt et al. 1998; Smith et al. 2000), while controversial results were reported for signal amplitude (Curt et al. 1998; Curt and Dietz 1999). Furthermore, whether a MEP can be evoked at all in the very first stage after iSCI was reported to have some prognostic value. Patients with an elicitable MEP within the first 4 days post injury showed best recovery and became at least functional walkers (Hirayama 1991).
Although the majority of iSCI patients of the ASIA categories C and D become functionally able to walk (Dobkin et al. 2006), their preferred and maximal walking speed is clearly reduced compared to control subjects (van Hedel et al. 2007a). The preferred walking speed of iSCI patients was reported to be about half of that of able-bodied subjects (Lapointe et al. 2001), although this value might be highly variable according to the severity of the spinal cord lesion. Relating maximal to preferred gait speed, the preferred gait speed in iSCI patients is closer to maximum than in control subjects (van Hedel et al. 2007a). An explanation for this finding might be that faster walking leads to a decrease in the duration of single stance phase, which is the most demanding part of the gait cycle in terms of equilibrium (Lajoie et al. 1993). During the course of recovery, the timed walking tests and the WISCI II have been reported to show improvement up to 6 months post injury in one study (van Hedel et al. 2007a), while another study that included only patients who became able to walk within the first month post injury found the WISCI II to be responsive only within the first 3 months after the spinal cord lesion (van Hedel et al. 2006b). This can be explained by the ceiling effects of the WISCI II score in groups of well-recovered patients, with most of these subjects achieving the maximum WISCI II score of 20 within the first 3 months post injury (van Hedel et al. 2007a).

Functional recovery, lastly, continuously increases up to 1 year post injury, even in patients with complete paraplegia – regardless of whether the FIM or SCIM II is used as assessment tool (Hall et al. 1999; Wirth et al. in press-c). The rate of functional recovery, however, analogous to motor recovery, is highest in the first 3 months and then rapidly declines (Hall et al. 1999; Wirth et al. in press-c). Nevertheless, the relationship between functional and motor recovery is complex and poorly understood. Particularly in patients with paraplegia, neurological recovery poorly predicts functional recovery (Bracken and Holford 2002; Wirth et al. in press-c). This non-linear relationship might partly be explained by the fact that functional tests assess what patients actually do rather than what they are capable of. Thus, factors such as age, depression and other infirmities can affect the results (Bracken and Holford 2002).

1.3.3. Deficits of the current assessment protocol of motor function

The assessment protocol of motor function in iSCI as it is currently used in clinical practice has several deficits. Firstly, the muscle strength measurement according to the scale by ASIA has an ordinal data structure. It has thus been criticized in various studies for lacking sensitivity because of ceiling effects (Herbison et al. 1996; Noreau and Vachon 1998) and for relatively poor inter-rater reliability (Cohen et al. 1998; Jonsson et al. 2000), which may have been improved by the latest revision in 2000 (Savic et al. 2007). Furthermore, several studies reported that particularly the speed of voluntary movements, but not necessarily muscle strength, is reduced in patients with diseases of the upper motor neuron (equivalent to the CNS) (Kent-Braun et al. 1998; Miller and Johnston 2005). It was even proposed to replace the Babinski sign, which is a clinically important diagnostic sign of damage to the CST, by assessing the speed of foot tapping (Miller and Johnston 2005). Nevertheless, neither the muscle strength test according to the ASIA protocol nor any other test in the clinical protocol of motor function in iSCI assesses movement speed. In addition, dexterity was shown in stroke patients to be a separate aspect of motor function that can be impaired independently of muscle strength in CNS lesions (Ada et al. 1996). Nevertheless, in upper limb studies with stroke patients, the loss of dexterity was found to contribute less to physical disability than the loss of strength (Canning et al. 2004). In iSCI, most upper limb tests focus on muscle strength and activities of daily living. Some tests for dexterity with time as the outcome parameter are available, but time is not necessarily valid as a measure for dexterity, since an increase in speed can result from a decrease in accuracy (van Tuijl et al. 2002). Altogether, no gold standard for measuring manual dexterity in iSCI exists (van Tuijl et al. 2002) and in contrast to stroke, no studies evaluating manual dexterity in iSCI are available, while dexterity of the lower limb is not addressed at all.

Regarding TMS, the MEPs were shown to be facilitated by various influences, such as the activation of the contralateral limb or the observation or imagination of a movement (Kasai et al. 1997). The main MEP facilitation in terms of amplitude, latency and stimulation threshold, however, was achieved by activating the target muscle at the time of stimulus delivery (Rothwell et al. 1987). Maintaining a stable contraction of low intensity was proposed to stabilize cortical and spinal excitability and thus to improve reliability of the MEP (Darling et al. 2006). In addition, for optimal facilitation, minimal MEP latency was proposed to be achieved at 10% of MVC, maximal amplitude at 30% of MVC (Han et al. 2001). Yet, in clinical practice, the most common technique for facilitating TMS is to voluntarily contract the target muscle during stimulus delivery without measuring the extent of muscle activation, although this influences facilitation (Diehl et al. 2006). For these reasons, a MEP measurement protocol has been developed that standardizes for the torque that is produced at the time of stimulus delivery and that differentiates between stimulus delivery in a static and in a dynamic motor task (Diehl et al. 2006). Using this protocol, it has been shown in iSCI patients that the facilitation of MEP by means of dynamic activation was reduced in comparison to control subjects, which might represent the impairment of the descending motor pathways (Diehl et al. 2006). In addition, by means of standardizing for the produced torque at the time of stimulus delivery, not only is the MEP latency useful, but the MEP amplitude becomes reliable and can be used to quantify cortico-spinal function in iSCI (van Hedel et al. 2007b). For these reasons, the MEP measurements in this thesis were performed according to this protocol.

1.4. Aim of the project

As described in the previous sections, various methods to overcome the barrier for regeneration and to promote plasticity in the different tracts of the CNS are under evaluation in both animals and human subjects. The amount of regeneration and plasticity that can be produced does not currently offer complete repair, but might be sufficient to produce a discernible improvement in the function of patients with SCI. The current challenge, however, is to translate these experimental therapies from what is now largely basic research into the clinic (Fawcett 2002). One important prerequisite is to have clinical assessment protocols that are able to carefully monitor any regenerative effects and which can show whether a treatment has produced any benefit or even harm (Fawcett 2002; Curt et al. 2004). Thereby, the most important aspect is to combine neurophysiological assessments to parameters measuring clinical outcome, since recovery in function after SCI is a multidimensional process and the application of only one assessment is insufficient to evaluate the clinical

significance of any new treatment (Curt et al. 2004). Nevertheless, there are only a few longitudinal studies that correlate neurophysiological parameters with clinical parameters throughout the course of rehabilitation (Smith et al. 2000).
The significance of the CST for locomotion as well as for manual dexterity has been described previously. However, relatively little is known about its role in recovery from iSCI in humans. Two longitudinal studies focusing on CST function following iSCI in the upper limb found that the ASIA motor scores progressively improved during recovery, but the MEP latency stayed prolonged (Curt et al. 1998; Smith et al. 2000). The results of the clinical muscle tests did thereby not correlate to the neurophysiological assessment (Smith et al. 2000). Controversial results were reported in terms of the course of MEP amplitude during recovery (Curt et al. 1998; Curt and Dietz 1999). Since the CST might be a target for regeneration, it is important to study its significance for motor function in order to estimate a patient's benefit from possible regenerative changes.

For these reasons, the overall aim of this project was to study the relationship of CST function to motor control of the ankle in iSCI by combining a neurophysiological CST assessment (advanced protocol of MEPs) with new clinical tests (Wirth et al. in press-b) that intended to assess changes in CST function. While the relevance of the CST for the upper limb has been investigated in detail, less is known about its influence on the lower limb. Maximal movement speed and dexterity have both been shown to be specific for CST function, but have not yet been investigated in the lower limb of iSCI patients. Thus, in the first part of this thesis, a test that assesses these two aspects of motor control has been developed and evaluated in healthy controls and in iSCI patients (chapter 3). In order to study whether these parameters were related to gait function and whether they might be superior in the clinical assessment of CST function compared to the current clinical muscle scores, the results were related to selected gait parameters (timing of ankle dorsiflexion during swing and gait speed) (chapter 4) and to the neurophysiological assessment of CST function (MEPs) (chapter 5). In order to estimate the importance of the CST as a possible target for regenerative therapies by gaining further insight into its significance in motor recovery after iSCI, the course of the neurophysiological and clinical test parameters was monitored in a longitudinal study (over 6 months) in iSCI patients and control subjects (chapter 6). Lastly, for further validation and for the integration of the results of the iSCI patients in the larger context of CNS lesions, movement velocity and dexterity of the ankle, as well as CST function were assessed also in stroke patients (compared to iSCI patients) (chapter 7).

2. Methods

The main aim of this thesis was to investigate the relationship of cortico-spinal tract (CST) function to motor control of the ankle in patients with an incomplete spinal cord injury (iSCI). The studies were based on an assessment protocol that combines advanced neurophysiological assessments with current and new clinical outcome parameters in order to most comprehensively cover changes that occur during motor recovery in iSCI. As for the clinical measures, the protocol involved a task for ankle motor control in the supine position that tests two aspects of ankle motor control, (1) dexterity, measured as the ability to accurately time ankle dorsi- and plantar-flexion movements and (2) the maximal movement velocity (MMV) achieved in this task. The protocol also included the measurement of maximal voluntary contraction (MVC) and the assessment of the motor scores according to the American Spinal Injury Association (ASIA). While MMV dynamically assesses muscle strength, MVC is a static measure. The ASIA motor score, in turn, assesses the completeness of muscle activation, but lacks information about its speed (Kent-Braun et al. 1998). In addition, assessments of proprioception and spasticity were conducted. With regard to gait, the protocol assessed maximal and preferred gait speed and the required assistive devices. In addition, in chapter 4, ankle kinematics during gait on the treadmill were analyzed. The neurophysiologic assessment consisted of transcranial magnetic stimulation (TMS) (motor evoked potentials (MEPs)) with standardization for the ankle dorsiflexion torque produced at the time of stimulus delivery. The following paragraphs describe in detail all experiments of the core assessment protocol used in the studies that will be presented in the next chapters. Any modifications to the following protocol are described in the relevant later chapters.

2.1. Ankle task

This task was performed while the patients were lying in the supine position. Their leg, except for the heel, was placed lengthwise on a pillow, the knee slightly flexed (10-20 degrees), in order to allow free dorsi- and plantar-flexion movements. The subjects were able to visually control the placement of their foot to compensate for impaired proprioception, but they were not explicitly asked to visually monitor the foot movements (Fig. 2.1).

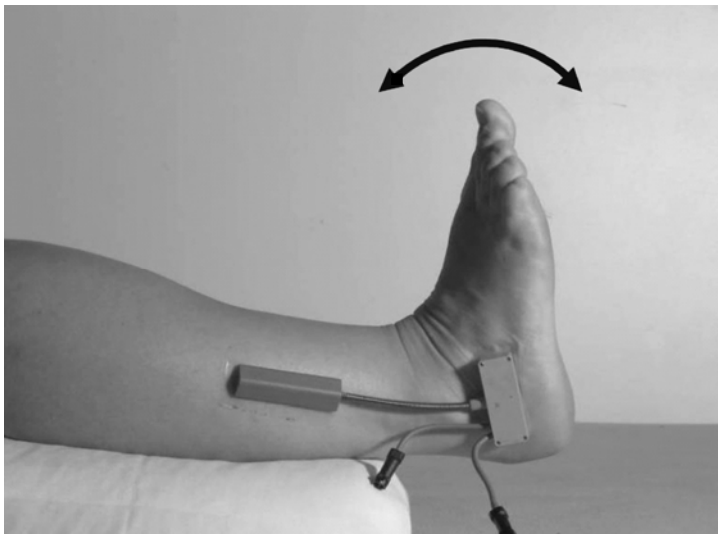

Fig. 2.1: Experimental set-up of the ankle task.

Computer-generated metronome sounds were presented to the subjects in blocks of different frequencies. In the first study, for exploration, the tested frequencies ranged from 0.8 to 3.2 Hz (at intervals of 0.4 Hz) (chapter 3) with breaks of about 30 seconds in between. Since the first task evaluation with healthy controls and iSCI subjects revealed that control subjects were able to accurately follow the tones up to 2.4 Hz, but significantly differed from the target frequency from 2.8 Hz onward (chapter 3), the test was performed only at 0.8 Hz, 1.6 Hz and 2.4 Hz in the subsequent studies. The acoustic signal consisted of two sinusoidal beeps of 0.05 seconds each: a high-pitched tone with a frequency of 1400 Hz and a low-pitched one of 700 Hz. The subjects were instructed (1) to perform alternate dorsi- and plantar-flexions by changing the movement direction as accurately as possible at the metronome sounds and (2) to do so with the largest range of motion (ROM) possible (Fig. 2.2). Whether the high- or low-pitched tone indicated dorsi- or plantar-flexion was not determined. For each frequency, the subjects had to perform 20 dorsi- and plantar-flexion repetitions. In addition, the maximal active and passive ROM was determined by averaging the results of 3 trials for each condition. All movements were recorded by means of an electric goniometer (Biometrics Ltd., Gwent, UK) with the sampling rate set at 1000 Hz.

Data from the first five movement cycles were not included in the analysis, since a minimum of 3 to 5 signals are required for picking up the beat (Aschersleben and Prinz 1995). From the remaining 15 ankle dorsiflexions and 15 plantarflexions, accuracy of timing was determined for each frequency by averaging the duration of movement cycles, converting the result to frequency and comparing it to the target frequency. The performed ROM was determined by subtracting maximum and minimum of each movement cycle and by averaging the results of each cycle. MMV of the ankle in dorsi- and plantar-flexion was

calculated by deriving the data of the goniometer and then averaging the maximal movement speed per cycle. For the analysis, Soleasy software (ALEA solutions GmbH, Zurich, Switzerland) and Matlab 6.5. (The MathWorks, Natick, Massachusetts, United States) was used.

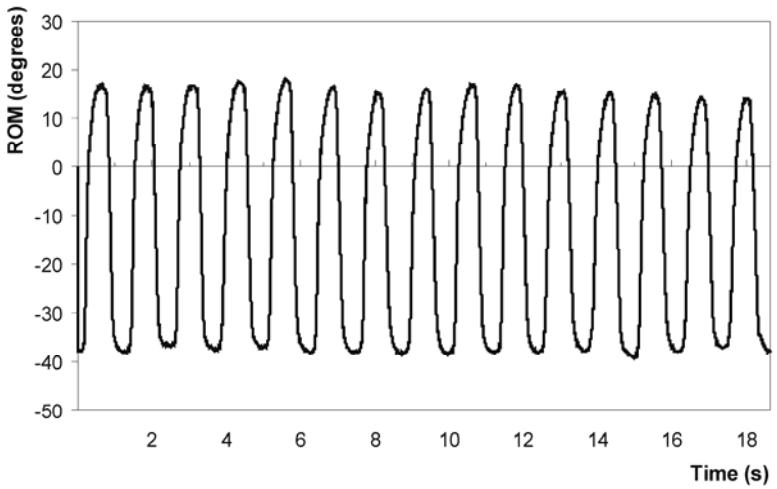

Fig. 2.2: Example of the performance (ROM) of a control subject in the ankle task at 0.8 Hz.
The positive y-axis indicates ankle dorsiflexion, the negative y-axis ankle plantarflexion.

2.2. Muscle strength assessments

2.2.1. Measurement of MVC

Maximal isometric torque (MVC) was measured in the supine position by a custom-built torque measuring device that prevented any movement at the ankle and any influence of the weight of the lower limb on the torque measurement (Diehl et al. 2006). As the axis of the measurement device was in line with the longitudinal axis of the leg, forces along the longitudinal axis of the lower leg did not result in torque. Strain-gauges, attached on both sides of the torque measuring device, recorded bending of the aluminum bar exerted by isometric plantar or dorsal torque (Fig. 2.3).

The output of the strain gauges was recorded with a sampling rate of 50 Hz, amplified and converted from V into Nm using Soleasy software (ALEA solutions GmbH, Zurich, Switzerland). The subjects were asked to isometrically pull their foot as forcefully as possible. The measurement was taken when the subject had been holding the isometric torque constant for about 2 seconds, while the torque was calculated over 0.2 seconds recording time. Finally, the torque data were normalized to body weight (Hsu et al. 2002).

Fig. 2.3: Experimental set-up of the measurement of MVC.

2.2.2. ASIA motor scores

The clinical assessment of strength of the dorsi- and plantar-flexor muscles was performed according to the standards of the ASIA (6 level scale), which was described in chapter 1 (section 1.3.1; Tab. 1.2) (ASIA 2002).

2.3. Gait assessments

2.3.1. Gait speed

Gait speed was assessed by the 10 Meter Walk Test (van Hedel et al. 2005; van Hedel et al. 2006b; van Hedel et al. 2007a). The subjects were asked to walk on a flat stretch of about 14 meters, once at their preferred gait speed and once at their maximal gait speed. The time taken for the 10 meters in the middle (to avoid effects of acceleration and deceleration) was manually measured using a stopwatch.

2.3.2. Assistive devices

The required assistance for gait, such as canes or physical assistance, were assessed by the Walking Index for Spinal Cord Injury II (WISCI II) (Ditunno et al. 2000; Ditunno and Ditunno 2001) that was described in chapter 1 (section 1.3.1), and consists of a 21-level scale (Tab. 2.1).

Tab. 2.1: The WISCI II scale: Assessment of assistance and assistive devices during gait.

Score	Devices	Braces	Assistance	Distance
0	Unable to stand or walk			
1	Parallel bars	Braces	2 persons	<10m
2	Parallel bars	Braces	2 persons	10m
3	Parallel bars	Braces	1 person	10m
4	Parallel bars	No braces	1 person	10m
5	Parallel bars	Braces	No assistance	10m
6	Walker	Braces	1 person	10m
7	2 crutches	Braces	1 person	10m
8	Walker	No braces	1 person	10m
9	Walker	Braces	No assistance	10m
10	1 cane/crutch	Braces	1 person	10m
11	2 crutches	No braces	1 person	10m
12	2 crutches	Braces	No assistance	10m
13	Walker	No braces	No assistance	10m
14	1 cane/crutch	No braces	1 person	10m
15	1 cane/crutch	Braces	No assistance	10m
16	2 crutches	No braces	No assistance	10m
17	No devices	No braces	1 person	10m
18	No devices	Braces	No assistance	10m
19	1 cane/crutch	No braces	No assistance	10m
20	No devices	No braces	No assistance	10m

2.4. Transcranial magnetic stimulation

TMS was applied in the supine position after ensuring that the subject had no contra-indication against the application of TMS (history of epilepsy, ferro-magnetic material in the head, cardiac pacemaker). TMS and electromyography (EMG) were performed analogous to previous studies (Diehl et al. 2006; van Hedel et al. 2007b). Single pulses of 200 µs were delivered by means of a magnetic stimulator (MagPro X100 Magnetic Stimulator (Dantec Medical A/S, Skovlunde, Denmark). For all measurements, a figure eight-shaped coil was used. Individual coil position and stimulation threshold were determined at the beginning of the recording (Fig. 2.4).

Threshold intensity was defined as the percentage of stimulator output that evoked a MEP amplitude of at least 50 µV in 50% of 10 consecutive stimuli. Stimulation intensity was set at 1.2 x threshold intensity and was kept constant throughout the experiment. TMS was performed in all patients at 20% of MVC using the above described torque measuring device, while visual feedback about the contraction level was provided on a computer screen. Excitability and facilitation of the MEPs was studied during a static and a dynamic contraction condition of the tibialis anterior muscle (TA). For the static condition, the examiner delivered

a TMS pulse after the patient had been holding the level of 20% MVC constant for about 2 seconds. For the dynamic condition, the patient continuously increased the isometric torque according to the given rate of 20% MVC/s (visual feedback on the screen). At 20% MVC, a TMS pulse was then delivered automatically. The average of 5 measurements per condition was analyzed.

The EMG electrodes were placed on the middle of the TA muscle belly (inter-electrode distance 2 cm) after skin preparation (shaving and cleaning with abrasive skin cleaning paste). The positions of the coil and the electrodes were measured and noted to ensure placement at the same location in the repeated measurements.

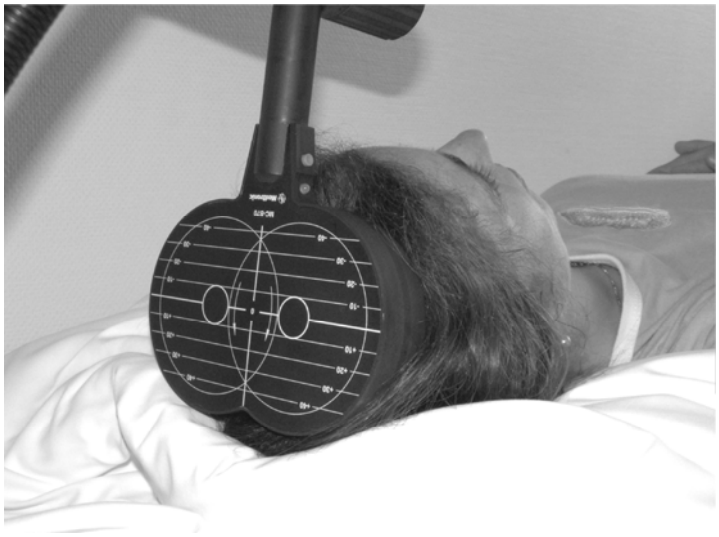

Fig. 2.4: Experimental set-up of the transcranial magnetic stimulation.

Data were recorded with a sampling rate of 2000 Hz and analyzed using Soleasy software (ALEA solutions GmbH, Zurich, Switzerland). The level of EMG background activity was calculated by the root mean square (RMS) of TA during 20 ms before the stimulus. MEP amplitude was determined by calculating the RMS over a time window of 20 ms from the onset of MEP and by subtracting the EMG background activity from the total MEP (van Hedel et al. 2007b) (Fig. 2.5). MEP latency was defined as the time between TMS trigger and the MEP response using the cumulative sum method, which facilitates the reliable determination of MEP signals (King et al. 2006). Lastly, the MEP latency was normalized by dividing latency by body height (van Hedel et al. 2007b).

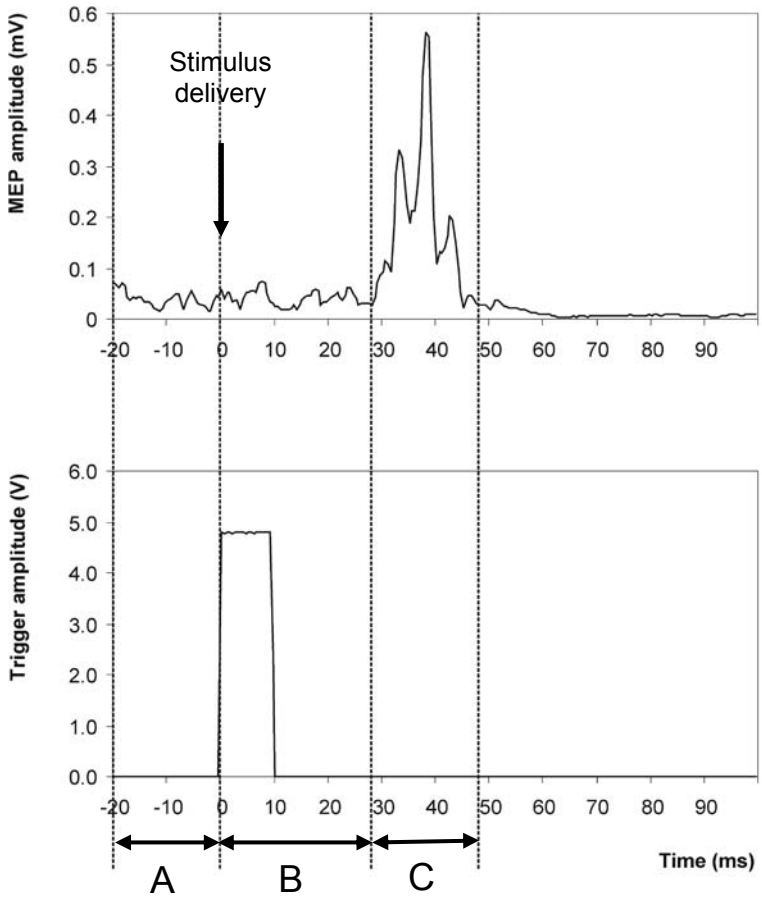

Fig. 2.5: Determination of EMG background activity, MEP latency and MEP amplitude.
(A) indicates the time window, where EMG background activity is calculated (20 ms before stimulus delivery) and (B) indicates MEP latency. MEP amplitude was calculated by subtracting the RMS over the time window (A) from the RMS calculated over the time window (C) (20 ms after MEP onset).

2.5. Assessment of proprioception

Since vibration sense and proprioception were found to be closely related (Freeman and Okun 2002), proprioception is assessed in clinics using a graduated tuning fork that is placed over a bony prominence (Rolke et al. 2006). For the studies in this thesis, the tuning fork (64 Hz) was placed over the malleolus medialis and the carpometacarpal joint of the first toe. A triangle and an arbitrary scale (ranging from 0 to 8) on the arms of the tuning fork allow for quantification of vibration threshold. Once the tuning fork vibrates at 64 Hz, the triangles appear double. The intersection of these two virtual triangles moves exponentially from 0 to 8, when the vibration of the arms decreases. Vibration threshold is considered the nearest value to the triangle intersection at the moment when the patient indicates that vibration was no longer perceived (Merkies et al. 2000).

2.6. Assessment of spasticity

Spasticity was assessed by the modified Ashworth test (Bohannon and Smith 1987). The examiner moved a patient's limb and scored the resistance on a 6 level scale (Tab. 2.2).

Tab. 2.2: Assessment of spasticity: Modified Ashworth Scale.

Classification	Description
0	No increase in muscle tone
1	Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of range of motion
1+	Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of range of motion
2	More marked increase in muscle tone throughout most of the range of motion, but the affected part is easily moved
3	Considerable increase in muscle tone, passive movement is difficult
4	Affected part is rigid

3. Study 1: Distinction between ankle paresis and dexterity in healthy subjects and patients with an incomplete spinal cord injury

This manuscript has been accepted for publication in the Journal “Neurological Research” under the title “Foot control in incomplete SCI: distinction between paresis and dexterity” (in press). The authors were Wirth B., van Hedel H.J., Curt A. All measurements and analyses were conducted by the first author. The manuscript was written by the first author and revised by the co-authors.

3.1. Abstract

Objectives: To complement the clinical assessment of motor impairment after incomplete spinal cord injury (iSCI) by introducing a test that reliably distinguishes between muscle weakness (paresis) and impairment of dexterity in a simple foot motor task.
Methods: Auditory-paced ankle dorsi- and plantar-flexion, in a supine position, was studied in 30 controls (to establish control values and to test reliability) and in 16 iSCI patients (test validation). The subjects were instructed to initiate dorsi- and plantar-flexion as accurately in timing and with the largest range of motion (ROM) possible. For each frequency, accuracy of timing, ROM, maximal movement velocity (MMV) in dorsi- and plantar-flexion and a time quotient for changing from dorsi- to plantarflexion and vice versa was determined. In iSCI subjects, these parameters were related to clinical measures of paresis, spasticity and proprioception.
Results: The test parameters showed good to very good reliability. The iSCI subjects were able to follow the target frequency with high accuracy, while ROM and MMV in dorsi- and plantar-flexion was significantly reduced. Furthermore, there was a strong correlation between ROM/MMV and motor scores within the iSCI patients.
Discussion: Repetitive foot dorsi- and plantar-flexion enables a distinction to be made between muscle weakness and reduced dexterity as the underlying cause of affected foot control. This distinction between, and quantification of, these two movement components complements the existing clinical examination, and in follow-up studies the recovery of these components may provide further insight into the mechanisms underlying motor function improvement after iSCI.

3.2. Introduction

Clinical recovery after a lesion of the central nervous system (CNS) is a multidimensional process that is based both on neuronal changes (regeneration of damaged pathways and plasticity within preserved neuronal structures) and functional (non-neuronal) compensation (e.g. training effects in preserved physical resources) (Schwab 2002; Curt et al. 2004; Ellaway et al. 2004). In CNS lesions, movement performance is limited by muscle weakness (paresis) as well as by deficits in movement dexterity that are not attributable to motor weakness (Canning et al. 2004; Krakauer 2005).

However, the clinical scoring of strength, such as proposed by the American Spinal Injury Association (ASIA), primarily addresses force generation, which is only one of the components involved in the recovery of motor function after SCI (Curt et al. 1998; Smith et al. 2000; ASIA 2002; Curt et al. 2004; Ellaway et al. 2004). Assessing the recovery of walking function (timed and qualitative walking tests) in patients with incomplete spinal cord injury (iSCI) (Asazuma et al. 1996; Marino et al. 1999) represents a complex outcome measure, which does not allow for a conclusion to be made regarding specific changes within the nervous system (Curt and Dietz 1997; Ditunno et al. 2000). To assess recovery of motor performance after iSCI, two important aspects should be addressed by a clinical test: 1) the assessments should be applicable soon after the initial injury (i.e. when patients are not (yet) capable of walking), and 2) the test should be able to distinguish between recovery of motor strength and improved movement dexterity. The latter can be defined as the ability to coordinate muscle activity to meet environmental demands (Canning et al. 2004) (i.e. optimized timing of muscle activation). As locomotion is a key function of the lower limbs, the focus of such an evaluation should be on functions that are relevant to gait. Ankle dorsiflexion was shown to be a critical component of the gait cycle in stroke and iSCI patients and was proposed as a potential marker for gains in motor control of the lower limb during rehabilitation (Dobkin et al. 2004).

Therefore, the present study assessed the ability of iSCI patients to switch the foot repeatedly from dorsi- to plantarflexion and vice versa, in a supine position. The aim was to provide a sensitive, simple motor task that can be used as a clinical test for evaluating impaired motor performance in iSCI and reliably distinguishes between paresis and deficits in dexterity.

3.3. Methods

All procedures were in accordance with the standards of the local ethics committee and with the Declaration of Helsinki. The subjects gave written consent to participate in this study. Two studies were performed: (1) To establish control values and to examine test reliability, 30 healthy volunteers were tested twice. (2) For feasibility and validation in iSCI, a cross-sectional study with iSCI patients and controls (matched for gender and age) was done.

3.3.1. Subjects

In the first study, 30 healthy controls (11 females, 19 males) were tested. All age groups were deliberately chosen for this study (range 18-74 years). The mean age of the females was 39 years (± standard deviation 16.8) and of the males, 43.3 years (± 16.8). For the second study, 16 iSCI subjects (5 females, 11 males), mainly ASIA C and D (one patient ASIA E) (mean age 53.6 ± 17.0 years), were recruited at the Spinal Cord Injury Center in Zurich, Switzerland. The participants did not suffer from any neurological diseases, apart from iSCI. The data of 16 of the 30 healthy control subjects (mean age 51.9 ± 14.4 years) were matched for gender and age to the iSCI subjects. For more detailed characteristics about the patients, see Tab. 3.1.

Tab. 3.1: Characteristics of the iSCI patients.

Age (years)	Gender	Time interval since SCI (years)	Cause of lesion	Level of lesion	ASIA category	Motor score DF	Motor score PF	Spasticity (modified Ashworth)
65	m	<1	Trauma	C 6	D	5	5	1
45	f	<1	Meningioma	T 8	D	5	5	0
65	m	4	Trauma	C 5	C	3	3	1
55	m	<1	Myeloma	T 8	D	NT	NT	0
59	m	3	Trauma	C 3	D	4	5	1
70	f	1	Stenosis	T 12	E	5	5	0
68	m	7	Myelopathy	T 9	D	4	4	1
46	m	2	Tumor intramedullar	T 5	D	2	4	0
60	f	<1	Myeloncompression	T 3	D	4	3	0
71	m	<1	Trauma	T 11	D	3	3	0
68	f	<1	Arteriovenous fistula	L 1	C	2	4	0
75	m	<1	Trauma	L 1	D	4	3	1
40	f	<1	Trauma	T 12	D	5	5	0
27	m	<1	Trauma	T 11	D	5	5	0
29	m	<1	Ischaemia	T 6	D	5	4	1
26	m	<1	Arteriovenous fistula	L 1	D	3	3	1

Legend:
DF dorsiflexion
NT not tested
PF plantarflexion

3.3.2. Experimental procedure

The assessment of the ASIA motor scores, spasticity and proprioception were conducted as described in chapter 2. Also the set-up of the ankle task was according to chapter 2, but the task included in this first study frequencies ranging from 0.8 to 3.2 Hz at intervals of 0.4 Hz.

3.3.3. Data analysis

In addition to the analysis of accuracy of timing, ROM and MMV that was described in chapter 2.1., additionally a quotient of the time spent in the upper- and lowermost 10% of the movement (division of the time spent in the lowermost 10% of plantarflexion by the time spent in the uppermost 10% of dorsiflexion) was calculated in this study. This quotient was determined to describe the ability to switch from dorsi- to plantar-flexion and vice versa. Furthermore, to establish reference values, 95% confidence intervals (CI) were calculated from the results of the 30 healthy subjects.

3.3.4. Statistical analysis

The deviations from the performance of the target frequency and from the time quotient for changing movement direction of 1 (equal duration of switch between dorsi- and plantar-flexion and vice versa) were determined by one sample t-tests. Differences in performance between the groups were analyzed using Wilcoxon rank sum tests. Age and gender dependency of the parameters was determined by multiple regression analyses. Reliability of the test was determined by intraclass correlation and Bland Altman plots. Multiple regression analysis and Spearman correlation were used to examine correlation between the outcome measures. The significance level α was set at 0.05 for all tests.

3.4. Results

3.4.1. Study 1: Control subjects

Control values

As the target frequency became higher, the healthy subjects accomplished the task by reducing both accuracy and ROM. They were able to follow the target frequency up to 2.4 Hz (no significant difference between the target frequency and the frequency performed in the test). At 2.8 and 3.2 Hz, the performed frequency differed significantly from the target

frequency (p = 0.015 at 2.8 Hz, p = 0.001 at 3.2 Hz) (Fig. 3.1 A). The mean of ROM continuously decreased as the target frequency increased. However, the CI for ROM remained approximately stable (Fig. 3.1 B). MMV in dorsi- and plantar-flexion showed significant increases up to a frequency of 2.4 Hz (i.e. for plantarflexion, 0.8 to 1.2 Hz ($p<0.001$) and 1.2 to 1.6 Hz ($p=0.03$); for dorsiflexion, 0.8 to 1.2 Hz ($p=0.001$) and 2.0 to 2.4 Hz ($p=0.04$); Fig. 3.1 C and 3.1 D). MMV in plantarflexion was significantly higher than in dorsiflexion at all frequencies ($p<0.01$ for all frequencies). The time quotient ranged between 0.90 and 1.12 and was significantly higher than 1 at 0.8 and 1.2 Hz ($p = 0.001$ and $p = 0.035$, respectively, Fig. 3.1 E).

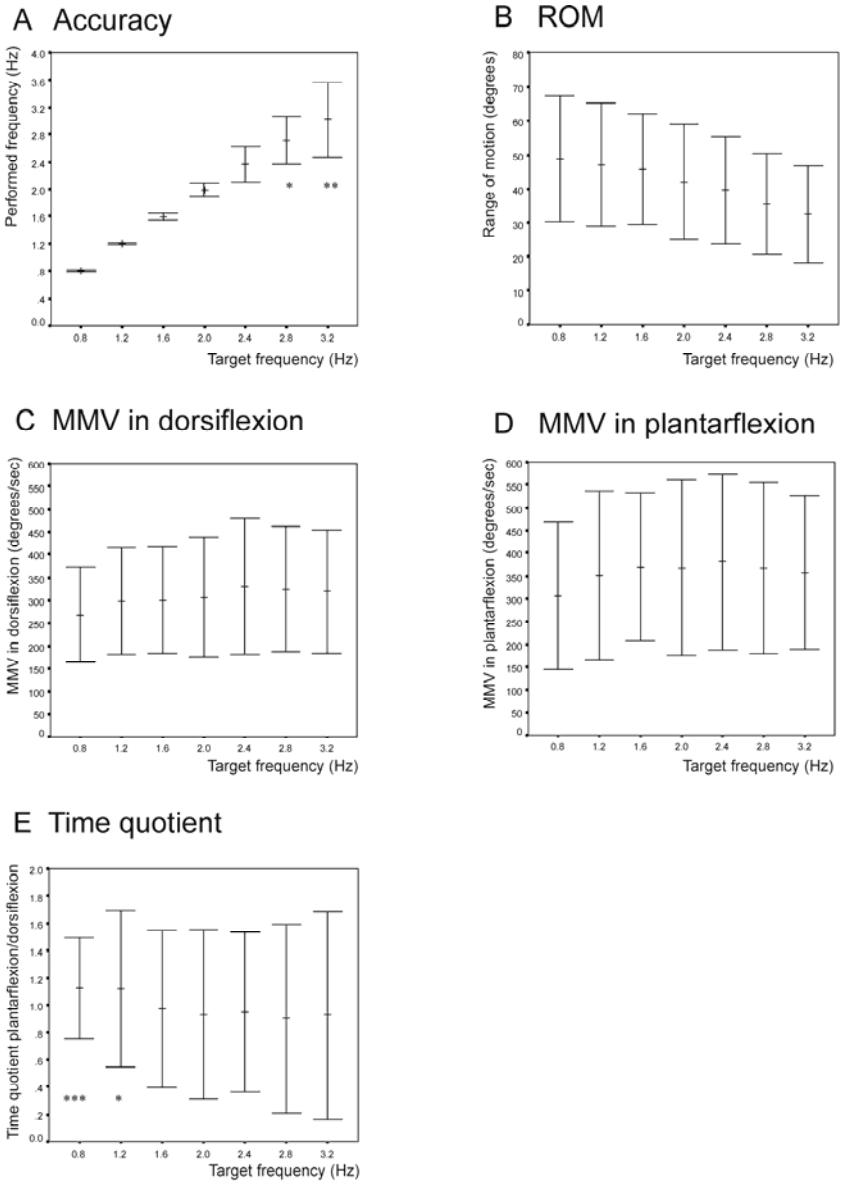

Fig. 3.1: Control values.

95% confidence intervals for 30 healthy subjects for the measurements of (A) accuracy, (B) ROM, (C) MMV in dorsiflexion, (D) MMV in plantarflexion, (E) the time quotient of movement alteration measured at all target frequencies (0.8 – 3.2 Hz). *p≤0.05 ; **p≤0.01 ; ***p≤0.001

Influence of age, gender and target frequency

All test parameters were significantly influenced by the target frequency, while age influenced ROM and MMV. Gender showed no significant influence on the test parameters.

The regression equation for the deviation of the performed frequency from target frequency (as dependent variable) and age, gender and target frequency as independent variables was: deviation from target frequency = -0.09 - 0.03 x gender ($p=0.09$) + 0.09 x target frequency ($p<0.001$); $R^2_{adj} = 0.299$. The parameter age was removed from the regression model.

The same analysis with ROM as dependent variable resulted in the regression equation: ROM = 61.39 - 0.14 x age ($p<0.001$) - 7.04 x target frequency ($p<0.001$); $R^2_{adj} = 0.379$. The parameter gender was removed from the model.

The regression equations for MMV in plantar- and dorsiflexion were: MMV in plantarflexion = 367.08 - 1.10 x age ($p=0.004$) + 17.94 x target frequency ($p=0.020$); $R^2_{adj} = 0.063$. MMV in dorsiflexion = 329.73 - 1.57 x age ($p<0.001$) + 21.33 x target frequency ($p<0.001$); $R^2_{adj} = 0.211$.

The time quotient showed neither dependency on age nor gender (Time quotient = 1.18 - 0.090 x target frequency ($p<0.001$); $R^2_{adj} = 0.055$).

Reliability

Test-retest reliability was determined in 31 healthy subjects and in 6 iSCI patients. In general, the second assessment was done within one week, and in some cases within 2 weeks, of the initial test. The intraclass correlation coefficients (ICC) are shown in Tab. 3.2. For the parameter accuracy, ICC could not be calculated for 0.8 and 1.2 Hz due to the low variation in the data. Instead, a Bland-Altman plot illustrated the low variability of the data and a paired samples t-test showed that the difference between the data of test 1 and 2 did not significantly differ from 0 ($p=0.88$ for 0.8 Hz, $p=0.09$ for 1.2 Hz) (Fig. 3.2 A and B). From 1.6 to 3.2 Hz, the ICC for accuracy were very good (>0.75) for all frequencies apart from 2.0 and 3.2 Hz (moderate to good, 0.5 - 0.75) (Dawson and Trapp 1994). The ICC for ROM were moderate to good for 2.4 and 2.8 Hz, and very good for all other frequencies. MMV in general (apart from 3.2 Hz) showed moderate to good ICC. They were very good for plantarflexion at 0.8 and 1.2 Hz and for dorsiflexion at 0.8 Hz. The ICC for the time quotients were moderate to good at 1.2, 1.6 and 2.0 Hz and very good for all other frequencies. ICC of the self-paced active ROM was 0.85.

Tab. 3.2: Intraclass correlation coefficients of all outcome measures.

Parameter	0.8 Hz	1.2 Hz	1.6 Hz	2.0 Hz	2.4 Hz	2.8 Hz	3.2 Hz
Accuracy	Bland Altman	Bland Altman	0.88	0.55	0.75	0.81	0.69
ROM	0.80	0.78	0.71	0.72	0.65	0.69	0.70
MMV in DF	0.80	0.71	0.71	0.60	0.61	0.70	-0.24
MMV in PF	0.84	0.82	0.67	0.65	0.68	0.69	-0.34
Time quotient	0.80	0.60	0.60	0.60	0.81	0.83	0.76

Legend:
DF Dorsiflexion
MMV Maximal movement velocity
PF Plantarflexion
ROM Range of motion

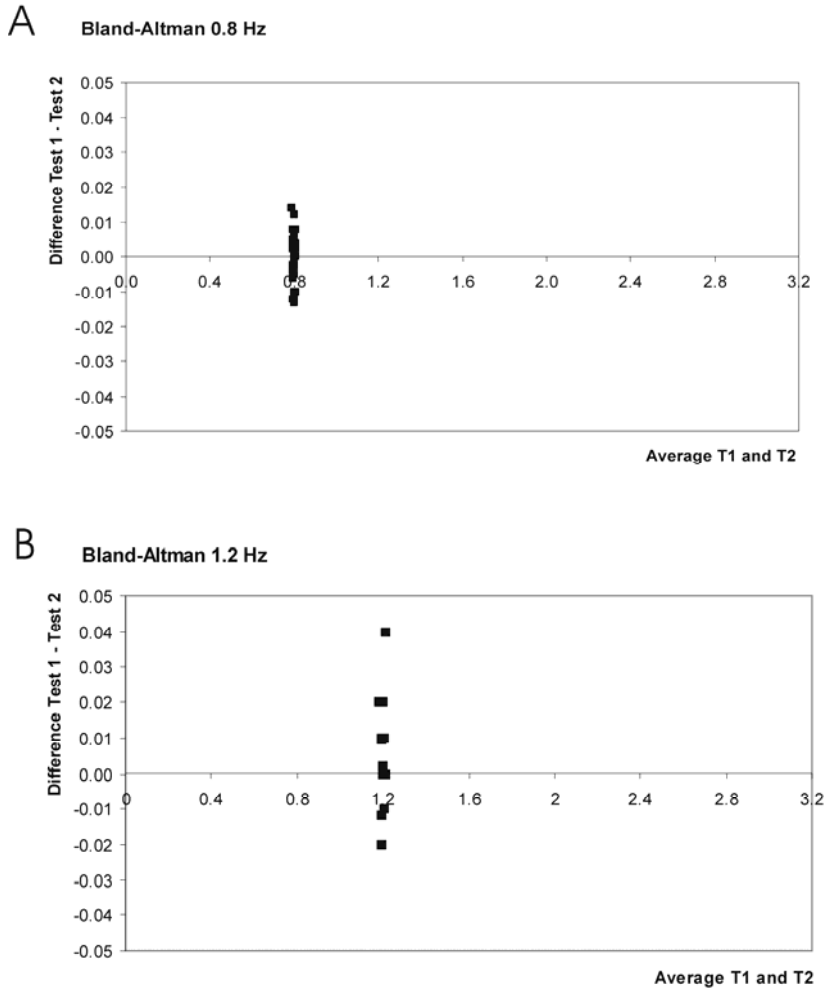

Fig. 3.2: Bland-Altman-Plots for the frequencies of (A) 0.8 and (B) 1.2 Hz.

Bland-Altman-Plots were used to determine reliability of accuracy at 0.8 and 1.2 Hz, as these two frequencies could not be calculated by the ICC method due to very low variability in the data. The x-axis shows the average of the two measurements, the y-axis the difference between the first and the second measurement.

3.4.2. Study 2: Healthy versus iSCI subjects

Characteristics of the iSCI patients

Muscle strength, sense of vibration and spasticity of the iSCI patients were as follows (Tab. 3.1): The median of the ASIA motor score for the tibialis anterior and the gastrocnemius medialis muscle was 4 (data ranged from 2 to 5 for the tibialis anterior and 3 to 5 for the gastrocnemius medialis muscle). The median of vibration sense was 5/8 at the malleolus medialis and 4/8 at the carpometacarpal joint of the first toe. Spasticity ranged between 0 and 1 (median of 0) for the modified Ashworth test.

Test results: Comparison of groups

The performance of the two groups differed in all outcome parameters, but most noticeably in ROM and MMV. The accuracy of the 16 healthy volunteers differed significantly from the target frequency at 2.8 Hz ($p=0.04$) and 3.2 Hz ($p=0.02$). In the iSCI subjects, accuracy deviated from the target frequency at 2.0 Hz and upwards (2.0 Hz: $p=0.03$; 2.4 Hz: $p=0.03$; 2.8 Hz: $p=0.004$; 3.2 Hz: $p<0.001$, Fig. 3.3 A). Yet, the difference in accuracy between the two subject groups was not significant prior to 3.2 Hz ($p=0.023$). The standard deviation of accuracy, which quantifies the intercycle variation, differed significantly between the two groups from 2.0 Hz and upwards ($p<0.05$, Fig. 3.3 B).

ROM and MMV in dorsi- and plantar-flexion differed significantly between control and patient groups at all frequencies (ROM: $p<0.001$ for all frequencies; MMV: $p< 0.01$ for all frequencies for both dorsi- and plantar-flexion, Fig. 3.3 C – E). At all frequencies, the iSCI patients spent more time in plantarflexion (range of the time quotient from 1.14 to 1.43 in the iSCI group and from 0.92 to 1.11 in the control group, respectively). However, the time quotient significantly differed only at a frequency of 1.6 Hz between the groups ($p=0.04$, Fig. 3.3 F).

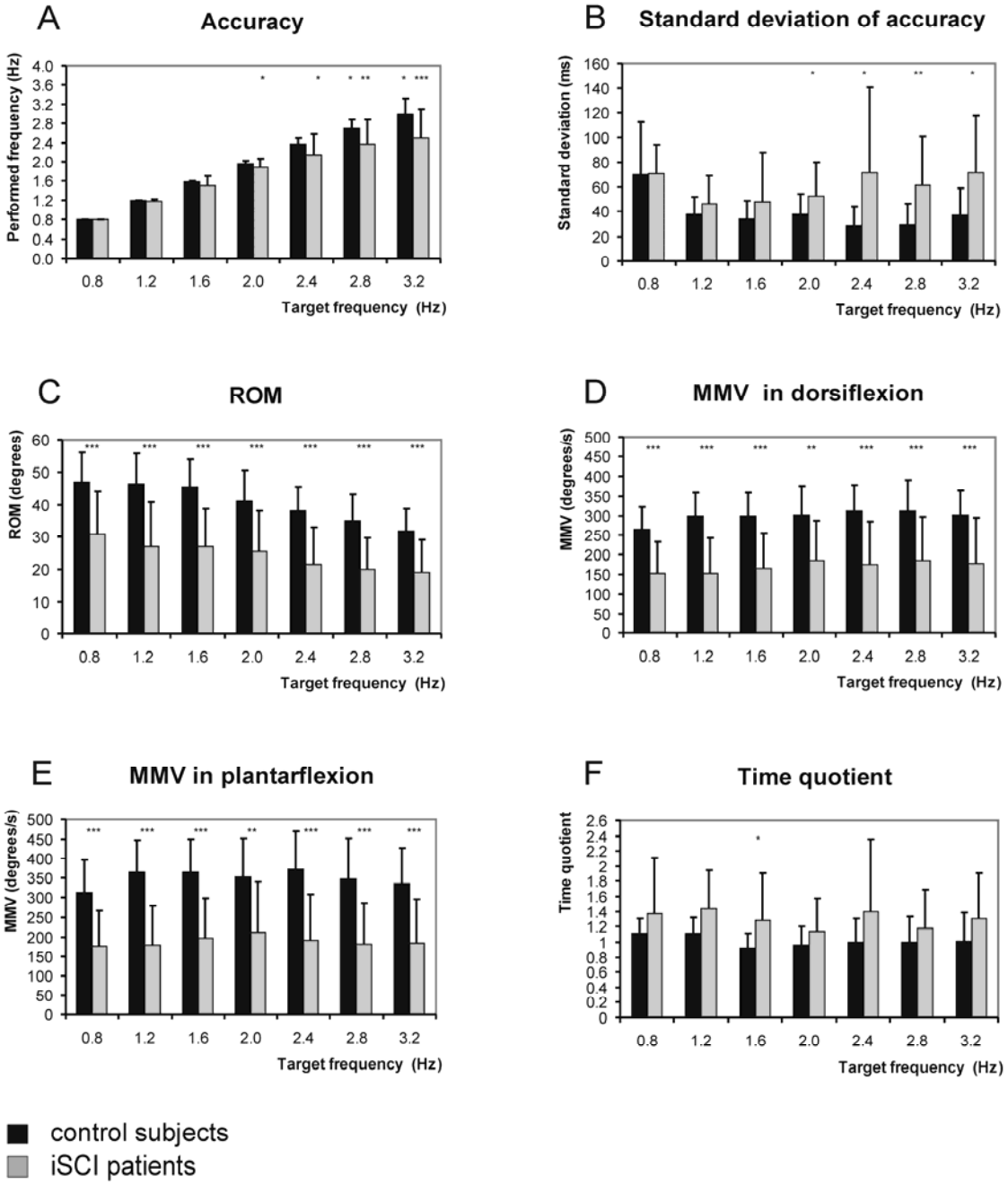

Fig. 3.3: Results of the cross-sectional study.

The results of the iSCI patients and the healthy subjects for (A) accuracy, (B) standard deviation of accuracy, (C) ROM, (D) MMV in dorsiflexion, (E) MMV in plantarflexion, (F) the time quotient of movement alteration. Please note that the differences were calculated from target values (A) and between the groups (B-F).

*p≤0.05 ; **p≤0.01 ; ***p≤0.001

Test validation: Correlation between outcome parameters

Muscle strength (ASIA motor scores) correlated well with the parameters of ROM and MMV (r_S: 0.71-0.83 and 0.72-0.86, respectively). Target frequency, MMV, proprioception and spasticity were used to explain the variation between the iSCI subjects in the parameters accuracy (deviation from target frequency), ROM and the time quotient. The regression model with the deviation from target frequency as dependent variable and standardized regression coefficients was: Deviation from target frequency = 0.043 + 0.567 x target frequency ($p<0.001$) – 0.163 x spasticity ($p=0.049$) - 0.501 x sum MMV in dorsi- and plantar-flexion ($p<0.001$). This model accounted for 42.9% of the variation in accuracy between the subjects ($R^2_{adj}=0.429$). The same regression analysis, using MMV in dorsiflexion, instead of the sum of MMV for both dorsi- and plantar-flexion, resulted in: Deviation from target frequency = 0.044 + 0.577 x target frequency ($p<0.001$) - 0.441 x MMV in dorsiflexion ($p<0.001$) ($R^2_{adj}=0.409$).

The multiple regression model to explain the variation in the parameter ROM (standardized regression coefficients) was: ROM = 0.009 – 0.384 x target frequency ($p<0.001$) + 0.908 x sum MMV in dorsi- and plantar-flexion ($p<0.001$) ($R^2_{adj}=0.920$). Replacing the sum of MMV by MMV in dorsiflexion resulted in: ROM = 0.010 – 0.424 x target frequency ($p<0.001$) + 0.883 x MMV in dorsiflexion ($p<0.001$) ($R^2_{adj}=0.869$).

The same procedure for the time quotient as dependent variable resulted in (standardized regression coefficients): Time quotient = -0.011 – 0.471 x spasticity ($p<0.001$) – 0.566 x sum MMV in dorsi- and plantar-flexion ($p<0.001$) ($R^2_{adj}=0.347$) and Time quotient = -0.010 – 0.431 x spasticity ($p<0.001$) – 0.542 x MMV in dorsiflexion ($p<0.001$) ($R^2_{adj}=0.335$), respectively.

Furthermore, a Spearman correlation between ROM and MMV showed high correlation for both movement directions (r_S for dorsiflexion 0.82-0.97, for plantarflexion 0.77-0.96).

3.5. Discussion

The purpose of the presented test was to distinguish between changes in muscle strength and dexterity of foot movements in iSCI subjects. The analysis of alternating foot dorsi- and plantar-flexions showed that dexterity was only slightly reduced after iSCI, whereas foot movements were severely affected by the reduced muscle strength. In addition, the transition from plantar- to dorsiflexion was prolonged in iSCI patients, regardless of movement frequency. As the derived parameters showed high reliability, follow-up measures during the course of iSCI will allow for quantifying changes in paresis and dexterity and for assessing their contribution to functional recovery.

3.5.1. Foot control in healthy subjects

The present study showed that healthy subjects were able to follow the target frequency with high accuracy up to 2.4 Hz. When the target frequency increased, ROM decreased, while MMV in dorsi- and plantar-flexion remained approximately constant. Only the muscle strength related measures ROM and MMV showed age dependency, which confirms the finding that older subjects favour accuracy over speed as has previously been reported in reciprocal hand tapping tasks (York and Biederman 1990).

3.5.2. Reliability of alternating foot dorsi- and plantar-flexion

Retest measurements showed a high reliability for all test parameters. The transient reduction of repeatability in accuracy at 2.0 Hz (ICC=0.55) might reflect a change in the mode of motor control. A change from a closed loop (continuous integration of sensory input into appropriate motor output) to an open loop strategy (intrinsic pattern of feed forward control) of motor control has also been reported in hand writing at 2.0 Hz (Siebner et al. 2001). Since the test performed in our study is newly developed, no reference values are available in the literature. Foot tapping tests have currently been used in various fields of neurology (i.e. cerebral palsy, Alzheimer's disease) to study the impairment of motor control (Toner et al. 1998; Franssen et al. 1999; Kauranen and Leppilahti 2001; Largo et al. 2001). In these tests, a sitting subject is asked to perform as many taps of the forefoot as possible in a given time period while the heel remains on the floor. However, such tests do not allow for a distinction to be made between foot dexterity and paresis. Furthermore, only limited data exists with regard to reliability (Miller and Johnston 2005). In children, values ranged between 0.15 and 0.82 (Spearman correlation coefficients) (Knights and Moule 1967; Largo et al. 2001), while no values are currently available for adults (Miller and Johnston 2005). Since these reliability values have been retrieved only by counting foot taps, the present parameters based on the more exact method of electrogoniometry show a very good reliability. The ICC for the isolated measurement of ROM of 0.85 confirms the previous finding that electrogoniometry is a reliable method for the measurement of ROM in the ankle joint (Rome and Cowieson 1996).

3.5.3. Foot control in iSCI subjects: Distinction between paresis and dexterity

Subjects with iSCI were able to maintain a high dexterity (i.e. accuracy of timing was reduced only at high frequencies with increased intercycle variation), while ROM and MMV of the foot movement were significantly reduced at all frequencies. It could be shown that ROM and

MMV were closely related to reduced motor scores and can be used to quantify paresis. The accuracy of timing was less influenced by motor weakness and was impaired only at higher levels of paresis. Therefore, parameters of paresis and dexterity are differently affected in iSCI and can be distinguished. The finding of reduced movement speed confirms the results of a study in patients with brain injuries, which reported slowness of speed in the foot tapping test to be very sensitive to CNS lesions, and it has been proposed that foot tapping should be included in the standard neurological examination (Miller and Johnston 2005). However, reduced speed in foot tapping tests can be influenced by both, muscle strength and movement control (i.e. dexterity), two components that have been demonstrated to be independently impaired in upper limb movements in stroke patients (Ada et al. 1996). Spasticity, another feature of CNS lesions, influenced the parameter accuracy only marginally in this sample of patients, which is in accordance with a finding in stroke patients that spasticity does not contribute greatly to motor dysfunction (Krakauer 2005). Nevertheless, all patients in this study had only limited spasticity (modified Ashworth test results of 0 or 1), and testing patients with greater degrees of spasticity would be expected to affect accuracy more significantly. Impaired proprioception was not found to influence accuracy. This is likely due to the fact that subjects could visually control their foot movements, as well as the implementation of an intrinsically patterned open loop movement strategy at higher speeds (Siebner et al. 2001).

The iSCI patients in this study spent, compared to the healthy subjects, slightly more time changing from plantarflexion to dorsiflexion than vice versa. The statistical analysis showed that spasticity and the strength-related parameter MMV in dorsiflexion were mainly responsible for this finding. This is in line with studies in patients with stroke and cerebral palsy, which reported plantarflexor stiffness and dorsiflexor paresis to be possible mechanisms for the failure to produce adequate dorsiflexion movements (Toner et al. 1998; Lamontagne et al. 2002). However, the statistical model only accounts for about a third of the observed variation in the data. This suggests that other mechanisms also contribute to the finding of impaired initiation of dorsiflexion and the prevalence of plantarflexor muscles. In gait, cortico-spinal input has been shown to have predominant input on the tibialis anterior muscle compared to the gastrocnemius muscle (Schubert et al. 1997; Capaday et al. 1999), thus cortico-spinal damage may result in a predominant use of the gastrocnemius muscle (in preference to the tibialis anterior muscle).

The measures ROM and MMV in dorsi- and plantar-flexion were highly intercorrelated, which may indicate redundancy. It is therefore likely that they develop in parallel during recovery of iSCI. However, gait analysis had previously shown no difference in ankle excursion between healthy and iSCI subjects, but did reveal significantly reduced ankle MMV in thoracic and lumbar iSCI patients (Krawetz and Nance 1996).

3.5.4. Relation of paresis and dexterity to gait function

Ankle dorsiflexion is a crucial part of locomotion and its accurate timing is highly important in initiating the swing phase. An impaired ankle dorsiflexion was shown to be a particular problem in stroke patients (Mandel et al. 1990; Lamontagne et al. 2002; Dobkin et al. 2004; MacIntosh et al. 2004) and a delayed initiation of dorsiflexion in the swing phase is a predictor of falls in elderly people (Kemoun et al. 2002). With a view to rehabilitation, ankle dorsiflexion has been proposed as a potential marker for gains in motor control of the lower extremity and as a substitute for multi joint walking movements of the affected leg in patients with stroke and SCI (Dobkin et al. 2004).

The parameter MMV in dorsiflexion has been shown to be a very sensitive measure in the present foot motor task, since it was significantly reduced at all frequencies. According to the finding that slowness of speed of foot tapping is a characteristic finding in upper motor neuron lesions (Miller and Johnston 2005), this parameter might be a reliable clinical indicator of cortico-spinal damage. However, the ability to perform a voluntary movement in a supine or sitting position can only be indirectly related to walking ability (Seitz and Wilson 1987; Capaday et al. 1999; Maegele et al. 2002). The basic locomotor rhythm in unobstructed locomotion is thought to be supported by spinal circuits and to be adapted by afferent feedback that is less dependent on voluntary activation (Drew et al. 1996). In monkeys, damage to the cortico-spinal tract was mainly represented by absence of proper initiation of the swing phase (dragging the hind paw in swing phase), an increase in cycle duration and an alteration in the relationship between stance and swing duration (Courtine et al. 2005). A possible correlation of some outcome measures, particularly of the parameter MMV in dorsiflexion, of this simple auditory-paced dorsi- and plantar-flexion task and gait parameters, and hence the possible predictive value of this task for walking ability, will be the subject of investigation in future studies.

3.6. Conclusions

This simple, auditory-paced ankle dorsi- and plantar-flexion task allows for a distinction to be made between motor strength and dexterity. In iSCI patients, mainly muscle strength was impaired, while dexterity was less affected. These findings, based on measurements in the supine position, will improve the clinical testing of motor impairment in iSCI by providing quantifiable measures of these two components. In longitudinal studies, changes in these parameters during the course of rehabilitation might provide further insight into the mechanisms underlying the improvement of motor function after iSCI.

4. Study 2: Ankle dexterity in supine position and during gait in patients with an incomplete spinal cord injury

This manuscript has been accepted for publication in the "Journal of Neurology" under the title "Ankle dexterity is less impaired than muscle strength in incomplete spinal cord lesion" (in press). The authors were Wirth B., van Hedel H.J., Curt A. Most measurements and analyses were conducted by the first author. The second author was also involved in some transcranial magnetic stimulations and the corresponding data analyses. The manuscript was written by the first author and revised by the co-authors.

4.1. Abstract

Background: The motor assessment after incomplete spinal cord injury (iSCI) currently consists of tests for muscle strength (manual muscle testing) and gait. The ability to adequately time a movement, an aspect of dexterity, is not tested. Thus, this study assessed the timing of ankle dorsiflexion in iSCI patients in supine position and during gait and examined its relation to measures for muscle strength, cortico-spinal conductivity and gait speed.

Methods: In 12 subjects with iSCI and 12 matched controls, timing of ankle dorsiflexion was tested by means of auditory-paced dorsi- and plantar-flexion movements at 3 frequencies in supine position and by determining initiation and termination of dorsiflexion in swing during gait. In addition, maximal movement velocity (MMV) in the ankle task, maximal voluntary contraction (MVC), cortico-spinal conductivity (motor evoked potentials (MEP)) and gait speed (10 Meter Walk Test) were assessed.

Results: The groups did not significantly differ in timing of ankle dorsiflexion, neither in the supine position nor in gait. However, they significantly differed in MMV at all frequencies, MEP latency, MEP amplitude and gait speed. In contrast to ankle timing in the supine position, the onset of dorsiflexion in swing during gait significantly correlated to the dynamic MEP parameters.

Conclusions: Although MMV and gait speed were significantly reduced, timing of ankle dorsiflexion, both in the supine position and during gait, was less impaired in iSCI patients. This indicates that the loss of strength, particularly of dynamic strength, is the major motor impairment in iSCI, which might be considered when assessing treatment interventions.

4.2. Introduction

Patients with iSCI often show considerable motor recovery (Waters et al. 1994a; Waters et al. 1994b) and the majority of patients who initially had some preserved motor function below the level of lesion become pedestrians (about 90% in traumatic iSCI) (Dobkin et al. 2006). The clinical assessment of motor deficits after iSCI currently consists of a measurement for muscle strength (manual muscle testing according to the American Spinal Injury Association (ASIA) (ASIA 2002)), of gait tests (Ditunno et al. 2000; Ditunno and Ditunno 2001; van Hedel et al. 2005; van Hedel et al. 2006b; van Hedel et al. 2007a) and of an assessment of independence in activities of daily living (Catz et al. 1997; Catz et al. 2001b).

Muscle strength, however, is only one component of motor function that can be impaired after a lesion of the central nervous system (CNS). In upper limb studies with stroke patients, dexterity, defined as adroitness and competency in use of the limbs (Canning et al. 2000), was shown to be a separate aspect of motor control, which is not restricted to manual tasks (Ada et al. 1996; Canning et al. 2004). In iSCI, a recent study showed that dexterity in the supine position, defined as the adequate timing of ankle dorsi- and plantar-flexion movements, was only slightly affected, while muscle strength was substantially reduced (Wirth et al. in press-b).

In the assessment of gait in iSCI patients, only gait speed and the usage of walking aids are currently being assessed (Ditunno et al. 2000; Ditunno and Ditunno 2001; van Hedel et al. 2005; van Hedel et al. 2006b; van Hedel et al. 2007a), while studies focusing on kinematic gait characteristics in iSCI patients have been rare (Krawetz and Nance 1996). Nevertheless, the swing phase of gait is particularly susceptible to cortico-spinal influence on the motoneuron pool (Schubert et al. 1997; Schubert et al. 1999). Thus, the control of ankle dorsiflexion during swing might be altered in iSCI patients, which could lead to impaired walking ability and enhanced risk for falls (Kemoun et al. 2002).

For these reasons, the aims of this study were to compare timing of ankle dorsiflexion as an aspect of dexterity in both, the swing phase during gait and in the supine position, between iSCI patients and control subjects and to relate it to cortico-spinal conductivity (MEP) (Curt et al. 1998; Diehl et al. 2006; van Hedel et al. 2007b)) and to measures for muscle strength and gait speed.

4.3. Methods

4.3.1. Subjects

All procedures were in accordance with the standards of the local ethics committee and with the Declaration of Helsinki. All subjects gave informed written consent to participate in the study. The 12 patients with iSCI (9 males; age = 58.3 years ± standard deviation 10.7 years) were recruited from the Spinal Cord Injury Center, Balgrist, Zurich, Switzerland. All of them had preserved motor function below the neurological level (ASIA C or D) and the spinal cord lesion occurred on average 2.65 years (± 3.53 years) ago, ranging from 1 to 117 months (Tab. 4.1). The elderly control subjects (matched for gender and age = 59.2 years ± 11.3 years) were recruited via the local university department for senior citizens. Data of the more affected limb of the iSCI patients were compared to those of the weaker limb of the controls, which was defined by the muscle strength of the dorsiflexor muscles, since these muscles were the focus of this study.

Tab. 4.1: Characteristics of the iSCI patients.

Age (years)	Cause of lesion	Lesion level	ASIA category	Time since SCI (months)	ASIA motor score DF	WISCI II
37	Epidural haematoma	T 6	D	1	3	16
44	Stenosis	C 5	D	15	5	20
53	Trauma	C 3	D	117	5	20
53	Trauma	T 10	D	112	5	20
57	Epidural phlegmona	T 11	D	7	4	19
59	Meningioma	T 9	C	5	3	16
60	Intramedullar ependymoma	T 12	D	1	4	16
61	Intramedullar neurinoma	C 2	D	57	5	20
63	Trauma	C 5	C	49	3	16
66	Trauma	C 6	D	22	5	20
70	Ischemia	T 7	D	1	4	16
76	Trauma	C 4	D	3	5	20

Legend:
ASIA American Spinal Injury Association
C cervical
DF dorsiflexion
T thoracic
WISCI II Walking Index for Spinal Cord Injury, 2nd version

4.3.2. Experimental procedure

The ankle task, strength assessments, transcranial magnetic stimulation (TMS) and gait tests were conducted as described in chapter 2. The gait speed data were normalized in this study by dividing gait speed by body height [s^{-1}] (Samson et al. 2000). In addition, the timing of

ankle dorsiflexion in the swing phase of gait was determined in this study. For this purpose, the subjects walked on a treadmill at 2.5 km/h. All patients (and the control subjects on request) wore a safety harness that was attached to the ceiling and all participants were instructed to hold the hand railings in parallel to the treadmill. Four force sensors underneath the treadmill recorded the phases of gait cycle, two electrogoniometers (Biometrics Ltd, Gwent, UK) the ankle movements. All subjects underwent a period of familiarization with treadmill walking under test conditions and subsequently, 20 consecutive complete step cycles (in order to avoid alterations of gait parameters due to fatigue) were collected. For analysis, the raw data were cut in single steps at the beginning of stance phase, averaged and normalized to 1000 samples. Initiation of dorsiflexion was determined by the time of the minimum in the ankle goniometer curve at the beginning of the swing phase (Kemoun et al. 2002), termination of dorsiflexion in swing by the maximum of the goniometer curve during swing.

4.3.3. Statistical analysis

With a view to the small sample size of the groups, differences in performance between the groups were analyzed using the non-parametric Wilcoxon rank sum tests. Spearman correlation was used to examine correlations between the parameters. The significance level α was set at 0.05 for all tests.

4.4. Results

4.4.1. Group differences in timing of ankle dorsiflexion

The groups did not significantly differ in the timing of ankle dorsiflexion, neither in gait (Fig. 4.1 A) nor in the supine position (Fig. 4.1 B). While walking, the iSCI patients initiated dorsiflexion during swing on average at 67.0% (± standard deviation 1.4%) and terminated it at 83.3% (± 3.3%) of the gait cycle. Swing phase in the control group started on average at 66.5% (± 1.4%) and finished at 87.5% (± 8.8%) of the gait cycle. In supine position, the deviation between performance and target frequency was larger in the iSCI group than in the control group at all frequencies, but the differences between the groups were not significant (deviation from target frequency in the iSCI group: 0.8 Hz: average = 0.009 Hz (± 0.015 Hz); 1.6 Hz: average = 0.067 Hz (± 0.127 Hz); 2.4 Hz: average = 0.280 Hz (± 0.358 Hz); deviation from target frequency in the control group: 0.8 Hz: average = 0.004 Hz (± 0.003 Hz); 1.6 Hz: average = 0.026 (± 0.040 Hz); 2.4 Hz: average = 0.142 Hz (± 0.157 Hz). Timing of ankle

movements in the supine position at all frequencies and initiation or termination of dorsiflexion in swing did not correlate.

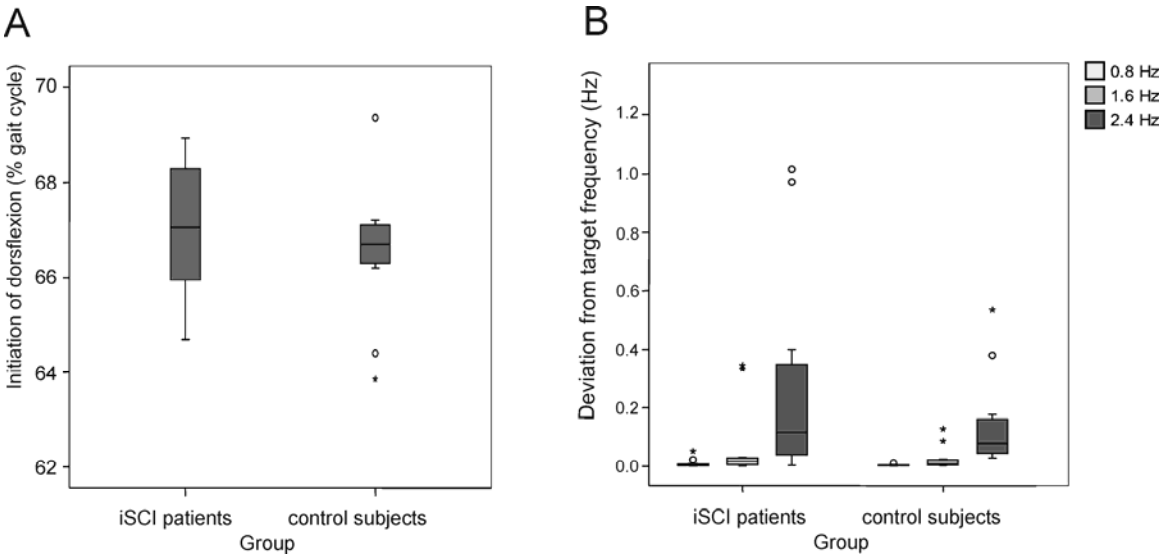

Fig. 4.1: Timing of ankle dorsiflexion.

The timing of ankle dorsiflexion in (A) swing phase of gait and (B) supine position, as assessed by 3 different frequencies (0.8, 1.6, 2.4 Hz) of audio-paced movements, was not significantly reduced in the iSCI group.

Circles in the boxplot indicate outlier values that are between 1.5 and 3 interquartile range from the end of the box. Stars indicate extreme values that are more than 3 times the interquartile range from the end of the box.

4.4.2. Timing of ankle dorsiflexion versus MEP

Static MEP amplitude was 0.065 mV (± 0.046 mV) in the iSCI group and 0.195 mV (± 0.176 mV) in the control group. Static MEP latency was 23.05 ms/m (± 4.3 ms/m) in the iSCI group and 20.33 ms/m (± 1.6 ms/m) in the control group. In the dynamic condition, the MEP amplitude was 0.089 mV (± 0.040 mV) in the iSCI group and 0.226 mV (± 0.173 mV) in the control group. Dynamic MEP latency was 23.64 ms/m (± 5.0 ms/m) in the iSCI group and 18.99 ms/m (± 2.0 ms/m) in the control group. The groups significantly differed in static ($p=0.006$) and dynamic ($p=0.006$) MEP amplitude as well as in static ($p=0.050$) and dynamic ($p=0.019$) MEP latency. In the iSCI group, the time of dorsiflexion initiation in swing correlated significantly to static and dynamic MEP latency (Spearman correlation coefficient $r_S=0.79$ ($p=0.006$) and $r_S=0.68$ ($p=0.02$), respectively). With a view to the supine position, the MEP parameters did not correlate to the deviation from target frequency.

4.4.3. Timing of ankle dorsiflexion versus MMV and MVC

MMV in the foot task was significantly higher in the control group at all frequencies (0.8 Hz: p=0.002; 1.6 Hz: p=0.001; 2.4 Hz: p=0.028) (Fig. 4.2 A). At 0.8 Hz, MMV in dorsiflexion was 145.9 degrees/s (± 50.0 degrees/s) in the iSCI group and 222.4 degrees/s (± 57.2 degrees/s) in the control group. At 1.6 Hz, MMV of the iSCI patients and the controls was on average 176.9 degrees/s (± 56.6 degrees/s) and 259.5 degrees/s (± 59.2 degrees/s), respectively. At 2.4 Hz, MMV was 180.4 degrees/s (± 54.8 degrees/s) in the iSCI group and 251.7 degrees/s (± 76.8 degrees/s) in the control group. However, the groups did not significantly differ in MVC in dorsiflexion (p=0.456) (Fig. 4.2 B). Isometric torque (normalized for body weight) was 0.35 Nm/kg (± 0.12 Nm/kg) in the iSCI group and 0.38 Nm/kg (± 0.07 Nm/kg) in the control group. Nevertheless, ankle timing in the supine position as well as the initiation and termination of dorsiflexion in swing were independent of MMV and MVC.

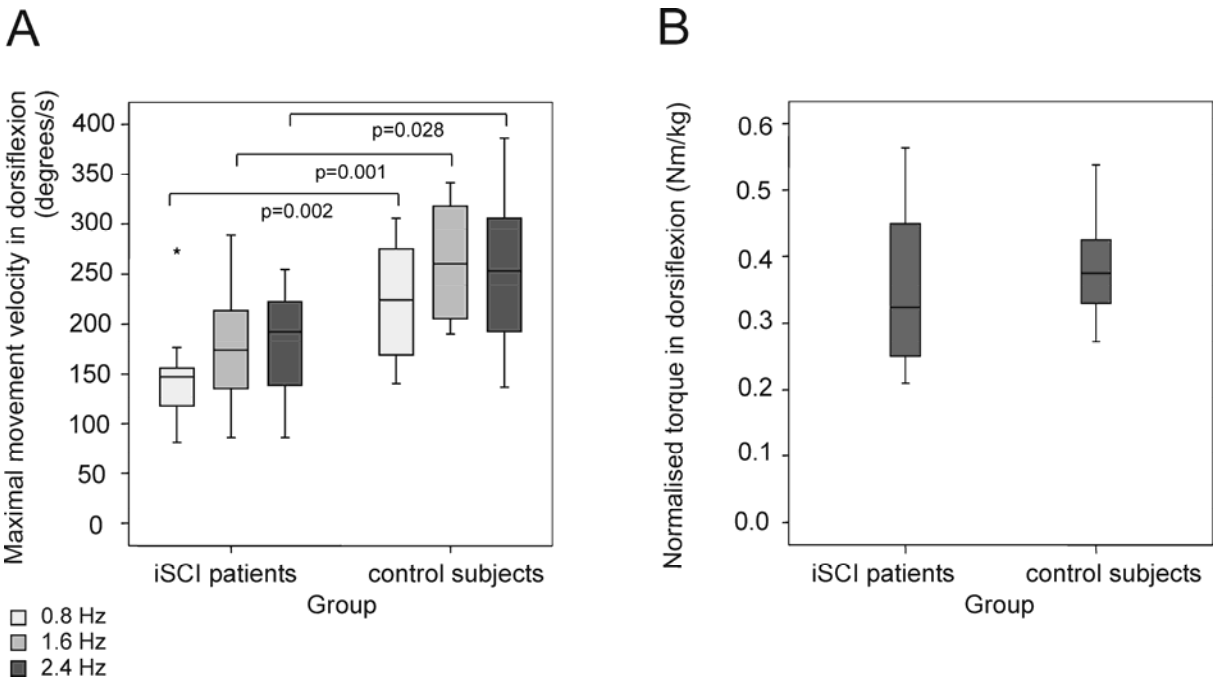

Fig. 4.2: MMV and MVC in dorsiflexion.

(A) MMV was significantly reduced in the iSCI group compared to healthy controls at all frequencies. (B) MVC did not significantly differ between the groups.

The star indicates an extreme value that is more than 3 times the interquartile range from the end of the box.

4.4.4. Timing of ankle dorsiflexion versus gait speed

In the iSCI group, preferred and maximal gait speed were 0.55 s^{-1} (± 0.18 s^{-1}) and 0.77 s^{-1} (± 0.29 s^{-1}), respectively. In the control group, preferred gait speed was 0.88 s^{-1} (± 0.09 s^{-1}), maximal gait speed was 1.39 s^{-1} (± 0.18 s^{-1}). Both, maximal and preferred gait speed

significantly differed between the groups ($p<0.001$). Neither accuracy in timing in supine position nor the time of initiation of dorsiflexion in swing correlated with maximal or preferred gait speed. However, within the iSCI group, MMV in dorsiflexion at 2.4 Hz correlated to gait speed ($r_S = 0.66$ and $p=0.02$ for maximal and preferred gait speed) as did MVC in dorsiflexion ($r_S = 0.80$, $p=0.006$ for maximal and $r_S = 0.83$, $p=0.003$ for preferred gait speed).

4.5. Discussion

The purpose of this study was to investigate timing of ankle dorsiflexion in iSCI patients and to study the impact of spinal cord damage on this aspect of motor control. Timing of ankle dorsiflexion was compared between iSCI subjects and healthy controls and related to measures for cortico-spinal tract (CST) conductivity (assessed by MEP), MMV, MVC and gait speed. Although gait speed, MEP parameters and MMV were significantly impaired in the iSCI subjects, there was no difference in timing of ankle dorsiflexion between iSCI patients and controls, neither during gait nor in the supine position. In addition, timing of ankle dorsiflexion was not related to muscle strength and gait speed.

4.5.1. Cortical control of ankle dorsiflexion

Ankle dorsiflexion was shown to be under large cortical control, both during gait and in the supine position. Enhanced CST activity in the swing phase of gait was reported in animals (Drew et al. 2002; Lavoie and Drew 2002; Beloozerova et al. 2003; Courtine et al. 2005) as well as in man (Schubert et al. 1997; Schubert et al. 1999). Nevertheless, spinal networks that are involved in the generation of reciprocal rhythmic movement pattern for simple locomotion substantially enhance cortical control of locomotion (Dietz 1992; Grillner et al. 1998; Butt and Kiehn 2003). In the supine position, a functional magnetic resonance imaging (fMRI) study in stroke patients using a paced dorsiflexion paradigm, which was very similar to the task presented in this study, showed strong cortical control of the ankle movement and reported an increase in fMRI activation in parallel to progress in gait speed and lower extremity motor control (Fugl-Meyer assessment (Gladstone et al. 2002)) (Dobkin et al. 2004). Therefore, timing of ankle dorsiflexion in supine position and during gait can be regarded as an aspect of dexterity, which is, apart from muscle strength, a separate aspect of motor control (Ada et al. 1996).

4.5.2. Dexterity in gait and in the supine position

Since initiation and termination of dorsiflexion in swing are dependent on gait speed (van Hedel et al. 2006a), the same walking speed was chosen for both the iSCI patients and the control subjects. Nevertheless, apart from a slight delay, none of these measures was significantly altered in the iSCI group, which indicates that gait cycle control was not considerably impaired. This is in contrast to other groups of patients with CNS lesions, where alterations in the duration of swing were reported (Chen et al. 2005; Gutierrez et al. 2005; Den Otter et al. 2006). In addition, in the elderly, a delay in ankle dorsiflexion in swing was shown to be predictive of falls (Kemoun et al. 2002). Although over-ground and treadmill walking were shown to be very similar in terms of kinematics and kinetic parameters (Riley et al. 2007), the sensory input provided by the driven walking belts might help to improve the timing of gait cycle. However, the time of initiation of dorsiflexion significantly correlated to MEP latency, which confirms the findings of a strong supraspinal (cortical) influence on the swing phase during gait (Schubert et al. 1997; Schubert et al. 1999).

In supine position, dexterity was only slightly reduced in the iSCI patients, but not significantly impaired. Although dexterity tests might be confounded by muscle strength, since a well controlled movement requires a certain amount of strength to be performed (Canning et al. 2000), the present motor paradigm in the supine position demonstrated that accuracy in timing did not depend on either MMV or on MVC. Thus, the iSCI patients and the controls were comparably able to switch from dorsal- to plantar-flexion and vice versa, although the MMV of the iSCI patients was significantly reduced. Furthermore, dexterity in the supine position did not correlate to the MEP parameters in the present study, despite previous evidence for a cortical involvement in ankle dorsiflexion tasks (Dobkin et al. 2004). This result shows that the ability to generate dynamic muscle strength is more responsive to an impairment of cortico-spinal pathways than dexterity (at least as dexterity was assessed in the present study). Although the iSCI patients showed considerable recovery of static muscle strength with preserved ankle dexterity, gait speed and dynamic strength were significantly reduced. This indicates that impaired ankle dexterity is not the main factor that leads to impaired limb movements after iSCI.

4.5.3. Maximal movement velocity and maximal voluntary contraction

The sample in the present study included iSCI patients with good recovery of static strength (no significant difference in MVC compared to controls) and walking capacity. Nevertheless, their MMV remained significantly reduced, which confirms slowing of movement to be a common feature after CNS lesions (Canning et al. 1999; Miller and Johnston 2005). The

dynamic measure MMV strongly correlates to muscle strength (Wirth et al. in press-b). Thus, the interesting result of similar static, but significantly different dynamic muscle strength in the two groups is in line with a recent finding that the rate of torque development was dramatically reduced in iSCI patients, while electrically elicited contractile properties did not differ compared to control subjects (Jayaraman et al. 2006). In addition, this finding emphasizes the need for a dynamic assessment tool to detect and follow motor deficits after iSCI (Miller and Johnston 2005).

4.6. Conclusions

The separate assessment of dexterity and paresis in the ankle showed that timing of ankle dorsiflexion was significantly less impaired than muscle strength in iSCI patients. This supports the assumption that the loss of strength, particularly of dynamic strength, is a major component leading to motor impairment of the lower limb in iSCI, which might be considered in the assessment of treatment interventions.

5. Study 3: Ankle paresis in patients with an incomplete spinal cord injury: Relation to cortico-spinal conductivity and ambulatory capacity

This manuscript is currently in revision at the Journal “Clinical Neurophysiology”. The authors were Wirth B., van Hedel H.J., Curt A. Most measurements and analyses were conducted by the first author. The second author was also involved in some transcranial magnetic stimulations and the corresponding data analyses. The manuscript was written by the first author and revised by the co-authors.

5.1. Abstract

Introduction: There is limited data on the relation of cortico-spinal tract (CST) conductivity to clinical measures in incomplete spinal cord injury (iSCI). This study evaluated the relationship of several muscle strength measures to CST conductivity (assessed by motor evoked potentials (MEPs)) and ambulation.

Methods: Dorsiflexor strength was measured by motor scores, maximal voluntary contraction (MVC) and maximal movement velocity (MMV) (acquired during auditory-paced ankle movements). MEPs were elicited during static (isometric, constant torque) and dynamic (isometric, continuously increasing torque) muscle activation. Ambulation was assessed by measures of gait speed and independence.

Results: Regression analyses showed that 1) there was no relationship between motor scores and MEPs, 2) MVC was related to the MEP latencies (static and dynamic condition), while 3) MMV was related to the MEP latencies and amplitudes in the dynamic condition and to the MEP latencies in the static condition. In contrast to any of the MEP parameters, all strength measures were comparably related to ambulation.

Discussion: The dynamic measure MMV allowed for the best estimation of CST conductivity as assessed by dynamic MEPs. Clinical studies on recovery and repair of CST function in spinal lesions might thus benefit from implementing dynamic measures in the clinical assessment protocol.

5.2. Introduction

After iSCI, substantial motor recovery can be observed in the majority of patients (Waters et al. 1994a; Waters et al. 1994b). However, little is known about the influence of neuronal changes (regeneration and plasticity) and physical compensation (e.g. training effects in preserved physical resources) on the observed improvement in humans (Schwab 2002; Curt et al. 2004). Motor recovery after iSCI has so far been assessed by 1) scoring muscle strength (6 level scale of manual muscle testing according to the protocol of the American Spinal Injury Association (ASIA motor scores) (ASIA 2002), 2) assessing CST conductivity (MEPs) (Curt et al. 1998; Smith et al. 2000; Ellaway et al. 2004) and 3) measuring functional outcome by means of timed and qualitative walking tests and tests for independency in activities of daily living (Asazuma et al. 1996; Marino et al. 1999; Catz et al. 2001a; Catz et al. 2001b).

However, particularly slowness of voluntary movements was reported to be a specific sign of weakness in patients with various lesions of the central nervous system (CNS) (Kent-Braun et al. 1998; Miller and Johnston 2005) and large deficits in the rate of torque development have been shown in iSCI patients (Jayaraman et al. 2006). Yet, manual muscle testing assesses only the completeness of voluntary muscle activation, but lacks information about its speed (Kent-Braun et al. 1998). In addition, the sensitivity of the 6 level ordinal scale of the ASIA motor scores has been criticized, particularly for grade 4 and higher (Herbison et al. 1996; Noreau and Vachon 1998). However, with a view to interventional studies in SCI, the impairment and recovery of motor function needs to be comprehensively assessed (Curt and Dietz 1997; Curt et al. 2004; Ellaway et al. 2004). Therefore, an ankle task was developed that assesses MMV and dexterity (defined as the ability to coordinate muscle activity to meet environmental demands (Canning et al. 2004), which is another element of motor control that is not addressed by the current motor assessment in iSCI. With regard to MEPs, their relation to function is unclear, since MEP latencies are pathologically prolonged and remain unchanged during recovery, while function remarkably improves (Curt et al. 1998).

For all these reasons, the aim of the present study was to determine and compare the relationship of dorsiflexor strength assessed by ASIA motor scores, MVC and MMV to CST conductivity (MEPs) and to ambulatory capacity in iSCI patients. Ankle dorsiflexion was chosen, since cortical projection to the lower limb is most pronounced to the motoneurons of the tibialis anterior (TA) muscle, most probably due to the high precision that is needed for toe clearance during the swing phase in gait (Perez et al. 2004).

5.3. Methods

5.3.1. Subjects

All procedures were conducted in accordance with the standards of the local ethics committee and with the Declaration of Helsinki and all subjects gave written consent to participate in this study. The iSCI patients were mainly recruited from the Spinal Cord Injury Center, Balgrist, Zurich, Switzerland and partly from the Klinik Hohe Warte in Bayreuth, Germany. All patients were ASIA category C or D (Tab. 5.1).

Tab. 5.1: Characteristics of patients.

Age (years)	Gender	Cause of lesion	Level of lesion	Time interval since SCI (years)
Assesssments: motor evoked potentials, strength, gait				
17	m	Trauma	C 4	<1
39	m	Epidural haematoma	T 6	<1
53	m	Trauma	C 3	2
53	m	Trauma	C 5	3
53	m	Trauma	T 10	9
57	f	Epidural phlegmona	T 11	<1
60	m	Intramedullar ependymoma	T 12	<1
65	m	Intramedullar tumour	L 1	<1
66	m	Trauma	C 6	2
76	m	Trauma	C 3	<1
Assesssments: motor evoked potentials, strength				
25	m	Arteriovenous fistula	L 1	<1
27	m	Trauma	T 11	<1
40	f	Trauma	T 12	<1
51	m	Intramedullar ependymom	T 6	<1
53	m	Trauma	C 3	9
63	f	Trauma	C 5	4
68	m	Myelopathy	T 9	9
Assesssments: strength, gait				
32	m	Trauma	C 3	<1
33	m	Myelopathy	C 4	<1
47	m	Trauma	T 10	<1
59	f	Meningioma	T 12	<1
60	f	Trauma	C 5	<1
61	m	Myeloncompression	T 7	4
65	f	Myelopathy	C 5	<1
65	f	Epidural haematoma	T 6	<1
74	m	Epidural haematoma	C 4	<1

Legend:
C cervical
T thoracic
L lumbar

The relationship between the strength measures and the MEPs was studied in 17 iSCI patients (14 male, 3 female) with an average age of 50.82 years (± standard deviation (SD) 16.46 years) and an average duration of iSCI of 2.4 years (±3.5 years). The relationship between the strength measures and gait speed was studied in 19 iSCI patients (14 male, 5 female) with an average age of 54.32 years (±15.22 years) and an average duration of iSCI of 1.0 year (±2.2 years).

5.3.2. Experimental procedure

The assessments (ankle task, strength assessments, transcranial magnetic stimulation (TMS), gait tests) were conducted as described in chapter 2. The gait speed data were normalized for body height [s^{-1}] (Samson et al. 2000).

5.3.3. Statistical analysis

Linear multiple regression analyses (backward method) were performed to describe the relationship between the strength measures ASIA motor scores, MVC and MMV and 1) the MEP parameters latency and amplitude and 2) the gait parameters (maximal and preferred gait speed, Walking Index for Spinal Cord Injury II (WISCI II)). To allow for direct comparisons between the regression coefficients, regression analyses with standardized regression coefficients were done. To determine whether MMV significantly differed between the 3 frequencies, a one-way analysis of variance (ANOVA) for repeated measures was conducted. Post hoc, the p-values were adjusted for multiple testing using Bonferroni's correction. The significance level α was set at 0.05 for all analyses.

5.4. Results

5.4.1. Strength measures in relation to CST conductivity

MMV significantly differed between the 3 frequencies ($F(2,32)=6.12$, $p=0.006$). Post hoc analyses showed that MMV at 0.8 Hz was significantly lower than MMV at 1.6 Hz ($p=0.02$) and MMV at 2.4 Hz ($p=0.009$), but MMV at 1.6 Hz did not significantly differ from MMV at 2.4 Hz. The average of MMV was 171.6 degrees/s (±68.1) at 0.8 Hz, 197.0 degrees/s (±77.7) at 1.6 Hz and 200.5 degrees/s (±93.6) at 2.4 Hz. The average of MVC (normalized to body weight) was 0.35 Nm/kg (±0.15), the median of the ASIA motor scores was 5 (ordinal data).

The amplitudes of the MEPs elicited during dynamic muscle activation were higher than those in the static condition, while the latencies were comparable (Fig. 5.1 A and B).

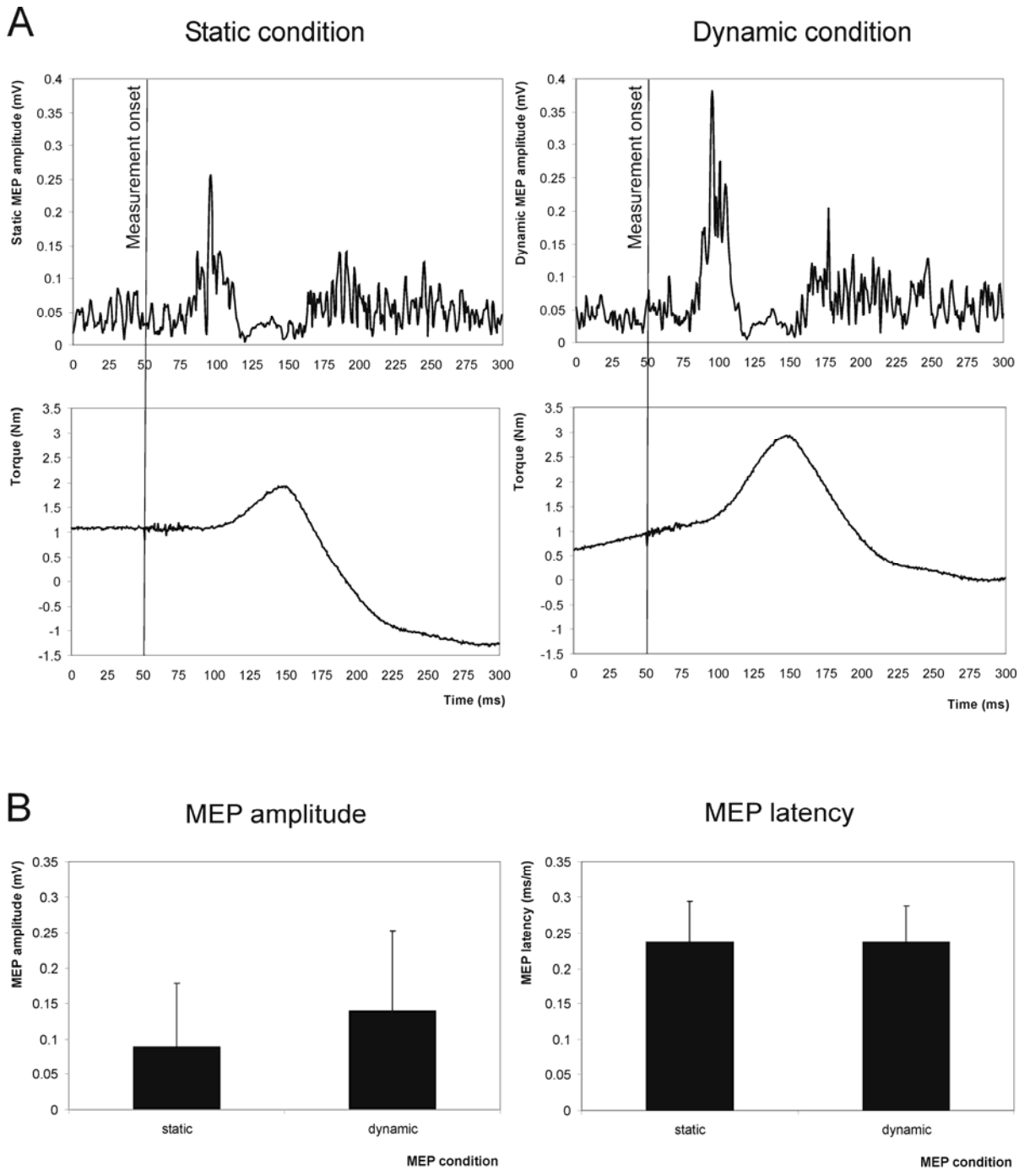

Fig. 5.1: Results of MEPs.

(A) Individual example of MEPs (top panel) and torque generation (bottom panel) elicited with static (left) and dynamic (right) muscle activation.

(B) Group results of MEP amplitudes (left) and MEP latencies (right).

The regression analysis showed that MMV, primarily MMV at 2.4 Hz, was the strength measure to be strongest related to the MEPs, particularly when the MEPs were elicited during the dynamic condition (Tab. 5.2). In the dynamic MEP condition, MMV was to be related to both, the MEP latency and the MEP amplitude ($R^2_{adj.}$ = 0.62) (Tab. 5.2, Fig. 5.2). In the static MEP condition, the relationship of MMV to the MEP amplitude was not significant. MVC was to be related only to the MEP latency in both, the static and the dynamic MEP condition ($R^2_{adj.}$ = 0.21). The ASIA motor scores were not to be related at all to MEP latency or amplitude. The details of the regression models are shown in Tab. 5.2.

Tab. 5.2: MEPs and strength measures.

Dependent variable	Static					Dynamic				
	MEP latency		MEP amplitude		$R^2_{adj.}$	MEP latency		MEP amplitude		$R^2_{adj.}$
	SRC	p-value	SRC	p-value		SRC	p-value	SRC	p-value	
MMV 0.8 Hz	-0.457	0.065	excluded		0.16	-0.435	0.046	0.542	0.016	0.37
MMV 1.6 Hz	-0.629	0.007	excluded		0.36	-0.571	0.013	0.367	0.091	0.35
MMV 2.4 Hz	-0.615	0.005	0.394	0.053	0.45	-0.606	0.002	0.589	0.002	0.62
MVC	-0.695	0.002	excluded		0.45	-0.505	0.039	excluded		0.21
ASIA scores	-0.428	0.087	excluded		0.13	excluded		excluded		

Legend:
ASIA American Spinal Injury Association
MEP motor evoked potential
MMV maximal movement velocity
MVC maximal voluntary contraction
SRC standardized regression coefficient

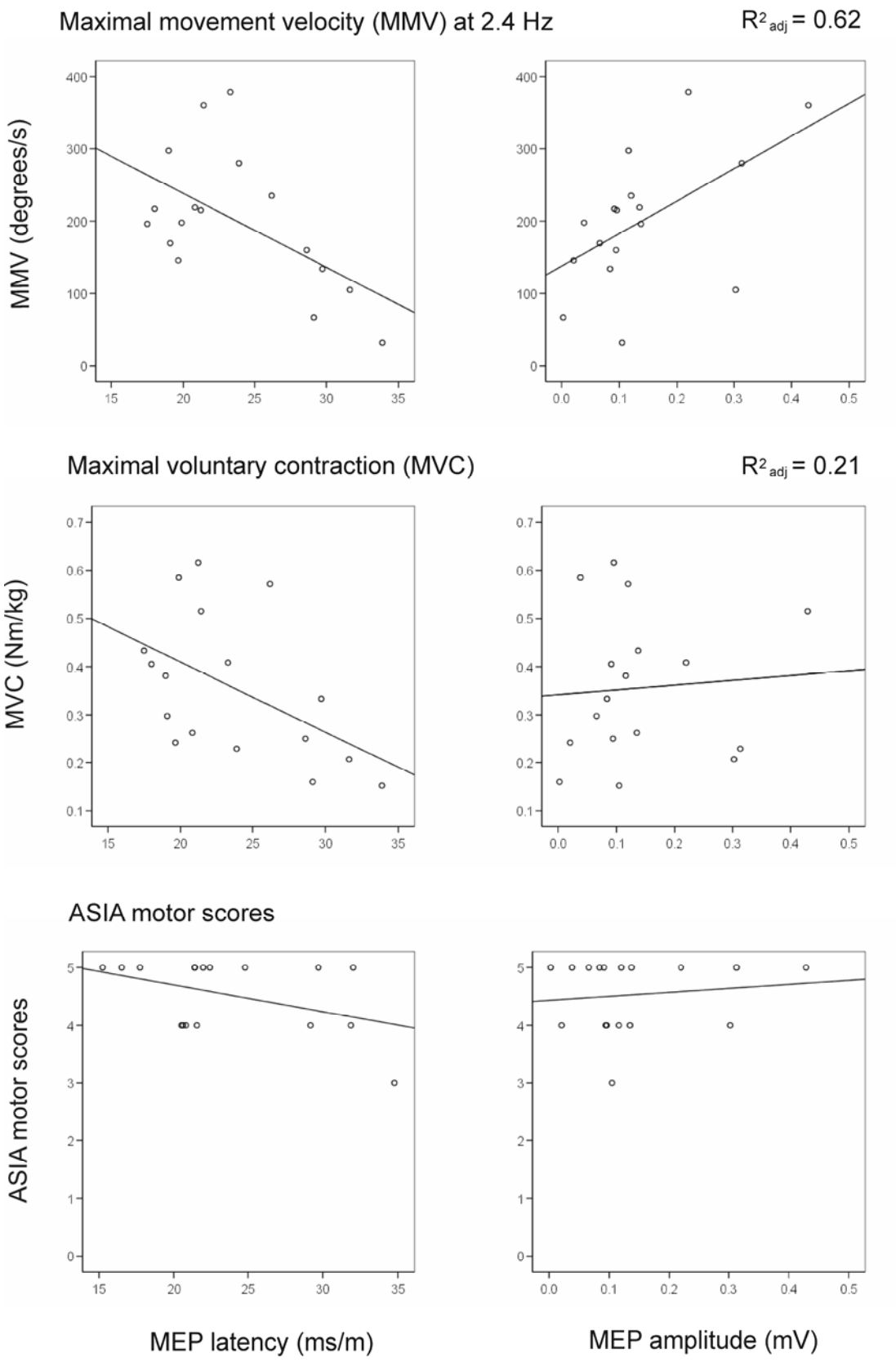

Fig. 5.2: MMV, MVC, ASIA motor scores in relation to CST conductivity.

Relationship between MEP latency (left column), MEP amplitude (right column) and MMV at 2.4 Hz in the dynamic foot task (top panel), MVC (middle panel) and ASIA motor scores (bottom panel).

5.4.2. Strength measures in relation to gait function

The sum of MMV in dorsiflexion of both legs was 307.1 degrees/s (±143.9) at 0.8 Hz, 343.0 degrees/s (±160.5) at 1.6 Hz and 361.9 degrees/s (±182.2) at 2.4 Hz. The average of the sum of MVC in dorsiflexion was 0.61 Nm/kg (±0.30), the median of the sum of the ASIA dorsiflexor scores was 9 (ordinal data). Averaged gait speed (normalized for body height) was $0.58s^{-1}$ (±0.38) (maximal) and $0.43s^{-1}$ (±0.28) (preferred).

MVC in dorsiflexion, the ASIA motor scores of the dorsiflexor muscles and MMV in dorsiflexion at 2.4 Hz (sum of both legs for each measure) were strongly related to gait speed. Multiple regression models showed that MVC had the strongest impact on gait speed, followed by MMV at 2.4 Hz and the ASIA motor scores. With a view to the WISCI II scale, the MVC in dorsiflexion, the ASIA motor scores of the dorsiflexor muscles and the MMV in dorsiflexion at 2.4 Hz showed a similar impact. The regression equations are shown in Tab. 5.3.

Tab. 5.3: Gait capacity and strength measures.

Dependent variable	Regression equation (standardized coefficients)	$R^2_{adj.}$	p-value
Normalised maximal gait speed	= -1.90 + 0.823 * sum normalised MVC	0.67	<0.001
	= -1.90 + 0.735 * sum MMV in dorsiflexion 2.4 Hz	0.53	<0.001
	= -0.093 + 0.655 * sum ASIA motor scores	0.50	<0.001
Normalised preferred gait speed	= -0.166 + 0.864 * sum normalised MVC	0.70	<0.001
	= -0.166 + 0.807 * sum MMV in dorsiflexion 2.4 Hz	0.61	<0.001
	= -0.066 + 0.676 * sum ASIA motor scores	0.51	<0.001
WISCI II	= 0 + 0.714 * sum normalised MVC	0.48	0.001
	= 0 + 0.762 * sum MMV in dorsiflexion 2.4 Hz	0.56	<0.001
	= 0.106 + 0.711 * sum ASIA motor scores	0.59	<0.001

Legend:
ASIA American Spinal Injury Association
MMV maximal movement speed
MVC maximal voluntary contraction
WISCI II Walking Index for Spinal Cord Injury, 2nd version

5.4.3. Gait speed in relation to CST conductivity

No correlation was found between the gait parameters and CST damage. Neither gait speed (maximal and preferred) nor the WISCI II scale showed any relationship to the MEPs. MEP latency and MEP amplitude were removed from all regression models.

5.5. Discussion

The purpose of the present study was to determine and compare the relationship of ankle dorsiflexor strength, assessed by different muscle strength measures (ASIA motor scores, MVC, MMV), to CST conductivity (MEPs) and ambulatory capacity in iSCI patients. It could be shown that the dynamic measure MMV was most closely related to the MEPs, while all strength measures were comparably related to gait function and no correlation was found between the MEPs and the gait parameters.

5.5.1. Paresis and slowness of movement in iSCI

Slowing of movements was reported to be a common feature in patients with various lesions of the CNS, in addition to reduced maximal peak torque generation (Canning et al. 1999; Miller and Johnston 2005). Also in the elderly, the ability to perform repeated rapid ankle dorsiflexions was significantly slowed, while isometric strength in a single contraction was unimpaired compared to young control subjects (Kent-Braun and Ng 1999). The basis of this slowing of movements is controversially discussed. In the elderly, no delay in the processes prior to the onset of activity in electromyography (EMG) was found in rapid isometric and isokinetic torque development, which led to the assumption that age-related differences in torque development might rather result from changes in muscle contraction mechanisms than from differences in central processing of motor commands (Thelen et al. 1996). In stroke patients, the phenomenon of slowness of movements was proposed to be the result of weakness and adaptation to poor muscle control in the sense of a speed-accuracy trade-off (favoring movement accuracy at cost of speed) (Ada et al. 1996). Other authors suggest that impairment in the recruitment of motor units and in the modulation of their firing rate might result in slowing of torque development (Desmedt and Godaux 1977; Kent-Braun et al. 1998; Kent-Braun and Ng 1999). The recent finding that the rate of torque development was dramatically reduced in iSCI patients, while electrically elicited contractile properties did not differ compared to control subjects (Jayaraman et al. 2006) as well as the findings of the present study (strong relationship between MEPs and MMV) further support the neuronal basis of this phenomenon and confirm the view of movement slowness as an upper motor neuron sign after CNS lesion (Kent-Braun et al. 1998; Miller and Johnston 2005).

5.5.2. Ambulation in iSCI

Gait speed was sufficiently related to all three strength assessments. The better correlation of gait speed to MVC than to the ASIA motor scores might be explained by the limited

sensitivity (Herbison et al. 1996; Noreau and Vachon 1998). Although a correlation between gait speed and the ASIA motor score of the TA muscle has been reported elsewhere (Kim et al. 2004), the present study shows that the sum of the motor scores of TA muscles of both limbs allows for an improved prediction of gait speed than the motor score of TA of just one limb (Kim et al. 2004). Yet, the results of this study show that the assessment of gait speed is limited in estimating changes of CST conductivity. This corroborates animal and human studies, which outline the influences of neuronal circuits in the spinal cord for the recovery of locomotor function (Dietz 1992; Grillner et al. 1998).

This study shows that an assessment of movement velocity complements the understanding of motor impairment of the lower limb after iSCI. Analogously to stroke patients, the isolated assessment of peak torque might lead to an overestimation of a patient's functional abilities since peak torque on its own might be functionally less relevant for iSCI patients in situations where torque has to be generated quickly (Canning et al. 1999). However, movement velocity can be compromised by several conditions, e.g. extrapyramidal disorders or joint diseases affecting the ankle (Wierzbicka et al. 1991; Miller and Johnston 2005), which implies that an accurate history and general physical examination, particularly of the ankle joint, is a prerequisite for reliable data. Nevertheless, the results of this study show that the ASIA motor scores and gait tests are not sensitive for assessing CST conductivity. Challenging dynamic motor tasks seem to be more dependent on the neuronal inputs provided by the CST and therefore allow for conclusions on CST function. These results implicate that the current clinical assessment of motor function after iSCI might be complemented by a dynamic assessment tool. Furthermore, training strategies in rehabilitation after iSCI, comparable to stroke, should promote the performance of daily-living activities by focusing not only on peak torque, but also on movement speed.

5.6. Conclusions

Although strength measures in general are predictive for the outcome of ambulation, the best relationship between CST conductivity and motor function was found between the MEPs with dynamic muscle activation and the dynamic measure MMV. These measures might thus be valuable complements for the clinical assessment protocol in iSCI.

6. Study 4: Changes in cortico-spinal function and ankle motor control during recovery from incomplete spinal cord injury

This manuscript has been submitted to the “Journal of Neurotrauma”. The authors were Wirth B., van Hedel H.J., Curt A. Most measurements and analyses were conducted by the first author. On the occasion of the first assessment, also the second author was involved in some transcranial magnetic stimulations. The manuscript was written by the first author and revised by the co-authors.

6.1. Abstract

Little is known about the mechanisms that underlie motor recovery after incomplete spinal cord injury (iSCI) in humans. This study assessed changes in cortico-spinal tract (CST) function by measuring motor evoked potentials (MEPs) and ankle motor control at 1, 3 and 6 months after acute iSCI. In 12 iSCI patients and matched controls, MEPs (evoked at 20% of maximal voluntary contraction (MVC)) were combined with a comprehensive ankle motor assessment protocol that measured ankle dorsiflexor strength (MVC, manual muscle testing, maximal movement velocity (MMV)), dexterity (the ability to accurately time ankle dorsiflexion movements) and gait (speed, walking aids). In the first 6 months after iSCI, all measures of muscle strength, gait and the MEP amplitudes significantly increased. The level of background electromyography (EMG) at 20% MVC remained stable, although absolute MVC increased. The delayed MEP latencies remained unchanged and dexterity was preserved throughout rehabilitation. The percentage increase in MEP amplitude was significantly related only to the percentage improvement in MMV. The finding of unchanged CST conductivity, as assessed by MEP latencies in acute iSCI patients recovering motor function, is in accordance with animal SCI studies, which did not show CST remyelination. The increased MEP facilitation at stable background EMG might indicate improved synchronization of the descending volley and/or responsiveness of motoneurons to supra-spinal input. The absence of a relationship between MEP amplitudes and recovery of ambulation and muscle strength implies that plastic changes in spinal neural circuits and preserved motor units might have contributed to the functional improvement.

6.2. Introduction

Within all spinal cord injury cases, the percentage of incomplete lesions is increasing and amounts nowadays to 40-50% (McKinley et al. 1999). Patients with iSCI show considerable recovery in muscle strength (Waters et al. 1994a; Waters et al. 1994b), gait function (van Hedel et al. 2007a) and independence (Catz et al. 1997), but little is known about the mechanisms that underlie this spontaneous recovery process (Curt et al. 2004).

Recovery after iSCI was proposed to be a multidimensional process based on neural plasticity (Raineteau and Schwab 2001) and compensatory (non-neuronal) mechanisms, such as training effects in the preserved motor units (Curt et al. 2004). For a comprehensive description of the course of recovery in iSCI, the combination of clinical and neurophysiological assessments was postulated (Curt et al. 2004), but only a few such studies have so far been conducted (Curt et al. 1998; Smith et al. 2000). Their results showed that the latencies of the MEPs remained unchanged, while muscle strength, assessed by the American Spinal Injury Association (ASIA) motor score, continuously increased (Curt et al. 1998; Smith et al. 2000). No relationship between muscle strength and neurophysiological data was found (Smith et al. 2000).

However, these studies did not use an accurate protocol for the control of torque generation in the target muscle during transcranial magnetic stimulation (TMS). Nevertheless, when applying the MEPs at a controlled level of background activity of the target muscle, reliable MEP amplitudes can be obtained (van Hedel et al. 2007b). In addition, the sensitivity of the ASIA motor score has been criticized because of its ordinal scale and ceiling effects (Noreau and Vachon 1998). Furthermore, movement speed rather than isometric maximal muscle strength was shown to be impaired in lesions of the central nervous system (Kent-Braun et al. 1998; Miller and Johnston 2005). Lastly, dexterity, defined as the ability to adapt muscle activity to environmental demands, has never been tested in iSCI, although it was shown in stroke patients to be an additional aspect of motor control, apart from muscle strength (Ada et al. 1996; Canning et al. 2004).

For all these reasons, the aim of the present study was to study motor recovery of ankle dorsiflexion in iSCI by combining the neurophysiological measurement of CST function (torque-controlled MEPs) with an extended ankle motor assessment protocol during the first 6 months after iSCI.

6.3. Methods

6.3.1. Subjects

All procedures were in accordance with the standards of the local ethics committee and with the Declaration of Helsinki. All subjects gave informed written consent to participate in the study. For a 17 year old patient, written consent was obtained from the participant and his parents. Twelve patients (6 male) with iSCI (mean age 53.7 ± standard deviation 18.5 years) and 12 control subjects (6 male; mean age 54.0 ± 18.0 years) were tested. Ten patients were recruited from the Spinal Cord Injury Center, Balgrist, Zurich, Switzerland, and two from the Klinikum Hohe Warte, Bayreuth, Germany. All of them had some preserved motor and sensory function below the neurological lesion level (ASIA C and D) and seven patients had an iSCI of traumatic etiology (Tab. 6.1). None of the patients had additional lesions to the peripheral nervous system (in the patients with lesions at T10-12, it was ensured that no additional damage to the conus medullaris and the peripheral nervous system existed). The elderly control subjects were recruited via the local university department for senior citizens and had no neurological, orthopedic or cardiologic diagnoses.

Tab. 6.1: Characteristics of the iSCI patients.

Age	Gender	Level of lesion	Cause of lesion
32	m	C 3	Trauma
76	m	C 3	Trauma
17	m	C 4	Trauma
60	f	C 5	Trauma
71	f	C 5	Trauma
30	m	C 6	Trauma
59	f	C 6	Trauma
74	f	T 2	Meningioma
50	m	T 9	Arteria spinalis anterior syndrome
56	f	T 10	Epidural abscess
59	f	T 12	Meningioma
60	m	T 12	Intramedullar ependymoma

Legend:
C cervical
T thoracic

6.3.2. Experimental procedure

The patients were tested at 1, 3 and 6 months after the onset of the spinal cord lesion. In general, the measurements took place within the timeframes set by the European Multicenter Study of Spinal Cord Injury (EM-SCI), which are 16-40 days after spinal lesion for 1 month

post injury, 70-98 days for 3 months and 150-186 days for 6 months post injury. For feasibility reasons (rehabilitation discharge), two patients were tested 1 week before the onset of the 6 months time window. The control subjects were tested at a self-selected first point in time and subsequently after 2 and 5 months, respectively.

The weaker leg of the patients (defined by MVC of the dorsiflexor muscles, which were the focus of the present study) were compared to the non-dominant leg of the control subjects, which was determined by asking which foot would be used to kick a ball (Gabbard and Hart 1996).

The assessments (ankle task, strength assessments, TMS, gait tests) were conducted as described in chapter 2, but only the maximal gait speed was measured in this study. With regard to the MEPs, the coil position and the electrode placement was measured and noted on the occasion of the first assessment to ensure placement at the same location in the repeated measurements. Stimulation intensity was set at 1.2 x threshold intensity on the occasion of the first assessment and was the same for all 3 measurements. The MEPs were evoked only in the dynamic condition (isometric, continuously increasing torque).

6.3.3. Data analysis

The MEP amplitudes of the subjects who showed no MEP response were considered to be 0 mV, while both the latencies and the background EMG activity at 20% MVC could not be determined. Thus, these measures were only analyzed in those patients whose MEPs could be recorded.

An analysis of variance (ANOVA) for repeated measures with 3 levels of the within-subject factor (1, 3 and 6 months after iSCI), 2 levels of the between-subject factor (iSCI subjects and controls) and their interaction was performed to determine differences between the various parameters (MEP amplitude, MEP latency, EMG background activity, dexterity and MMV in the ankle task, MVC, gait speed). The data for MEP amplitude and latency, EMG background activity and dexterity in the ankle task were transformed (square root transformation) to achieve normal residual distribution, which is a prerequisite of the ANOVA model (Sachs 1991; Riedwyl and Ambühl 2000). Post hoc, the p-values were adjusted for multiple testing using Bonferroni's correction. For the analysis of the assessments with ordinal data structure (ASIA motor score, score of the Walking Index for Spinal Cord Injury II (WISCI II)), a Friedman test was used to determine whether significant differences existed between the 3 measurements. If so, further analysis was done by Wilcoxon signed rank tests.

The relationship between the changes in the neurophysiological measures and those in the functional parameters were analyzed by linear regression analyses. The impact of the

percentages of change (quotient 1 month result / 3 months result and 1 month result / 6 months result) in MEP amplitude on the percentages of change in MVC, MMV at 2.4 Hz and gait speed was tested. Again, the neurophysiological data were square root transformed for the analysis in order to obtain normal residual distribution (Sachs 1991).
For the assessments using an ordinal data scale (ASIA motor score, WISCI II), a Spearman correlation between the percentage change in MEP amplitude (quotient 1 month result / 3 months result and 1 month result / 6 months result) and the differences in the ordinal scores (difference 1 month result minus 3 months result and 1 month result minus 6 months result) was calculated. The significance level α was generally set at 0.05. For the Wilcoxon signed rank tests α was adjusted for multiple testing and set at 0.05/3=0.0167.

6.4. Results

6.4.1. Changes in neurophysiological and functional parameters over time

TMS

In two patients, no MEP response was obtained at 1 month after iSCI. In a third subject, MEPs were recorded only at 6 months after iSCI, while MEPs could never be obtained in a fourth patient. *MEP amplitude* differed significantly between the groups ($F(1,22)=6.96$, $p=0.02$), the assessments ($F(2,44)=5.62$, $p=0.007$), and these factors significantly interacted ($F(2,44)=4.16$, $p=0.02$). Post hoc analyses showed that the MEP amplitude significantly increased in the patient group from 1 to 6 months (from 0.09 mV (± standard deviation 0.15) to 0.19 mV (± 0.14)) ($p=0.001$), but the increase between the first and third month (0.13 mV (± 0.10) was not significant ($p=0.28$) (Fig. 6.1 A, Tab. 6.2). The MEP amplitude was significantly reduced in the patient group at the first assessment ($p=0.01$). No significant changes in MEP amplitude were found in the control group (Tab. 6.2). An individual example of the course of MEP amplitude is shown in Fig. 6.1 B.
While the MEP amplitudes significantly increased in the patient group, EMG background activity at the time of stimulus delivery showed no significant differences between the groups and the assessments, neither in the patient nor in the control group (Fig. 6.2).
Overall, the *MEP latencies* were significantly prolonged in the patient group ($F(1,14)=11.65$, $p=0.004$), but showed no significant difference in assessment and interaction (Fig. 6.1 A).

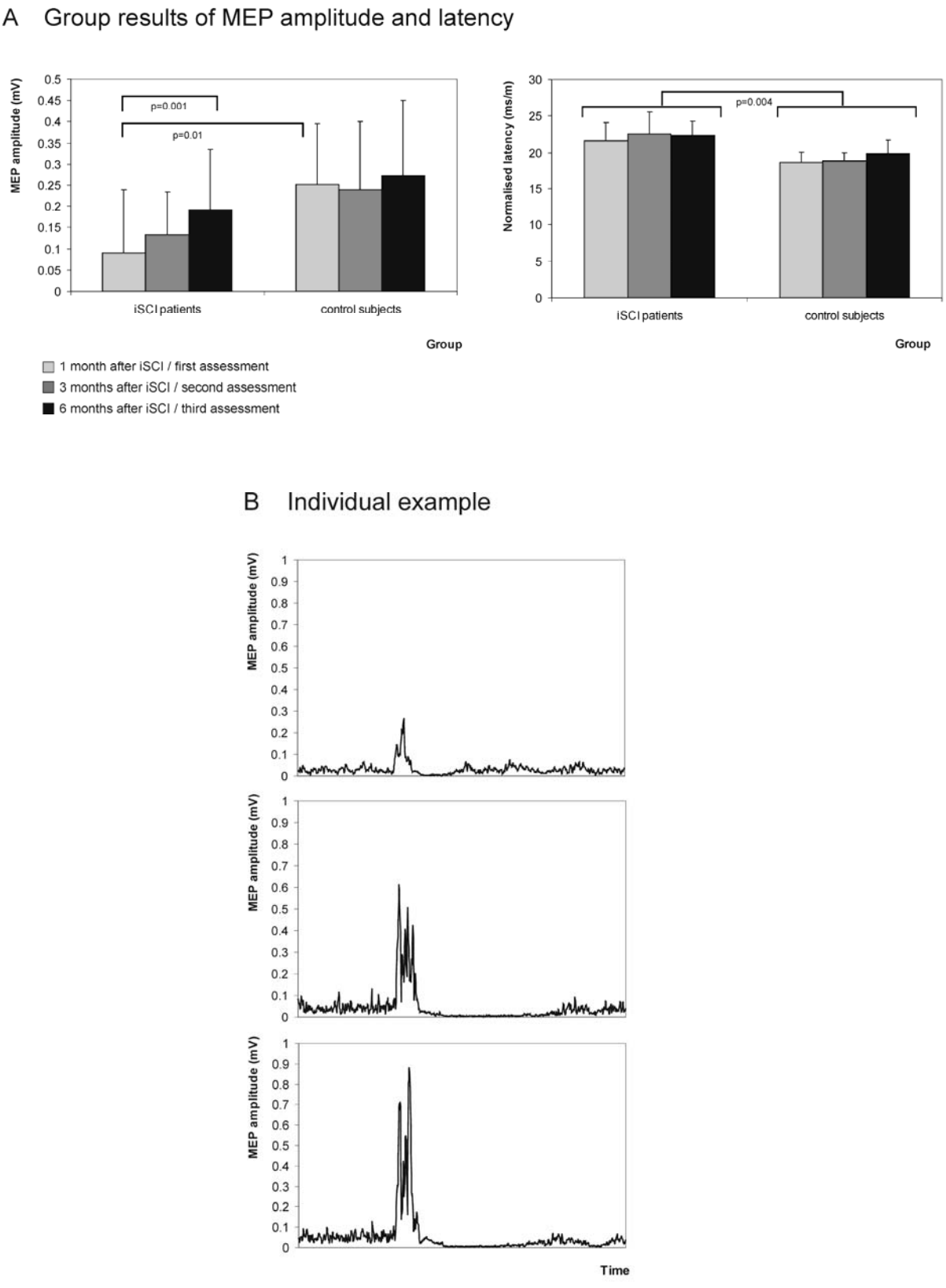

Fig. 6.1: Results of MEPs.

(A) Time course of MEP amplitude (left) and MEP latency (right) in iSCI patients and control subjects.

(B) Individual example of MEP amplitude of a 56 year old female patient with a non-traumatic iSCI at the level T 10 at 1 month (top panel), 3 months (middle panel) and 6 months (bottom panel) after iSCI.

Ankle dexterity

Ankle dexterity did not significantly differ between the groups, showed no change over time and no significant interaction. At the fastest condition (2.4 Hz), deviation from the target frequency continuously decreased in the patient group from 0.36 Hz (± 0.46) at 1 month post injury to 0.22 Hz (± 0.28) at 6 months post injury (Tab. 6.2), but this progress was not significant (p=0.15). No significant changes over time at all frequencies were observed in the control group (Tab. 6.2).

Muscle strength

MMV showed significant results for group, assessment and the interaction at all frequencies (0.8 Hz: group $F(1,22)=25.34$, $p<0.001$; assessment $F(2,44)=4.42$, $p=0.02$; interaction $F(2,44)=4.20$, $p=0.02$; 1.6 Hz: group $F(1,22)=26.33$, $p<0.001$; assessment $F(2,44)=5.75$, $p=0.006$; interaction $F(2,44)=5.65$, $p=0.007$; 2.4 Hz: group $F(1,22)=27.73$, $p<0.001$; assessment $F(2,44)=6.31$, $p=0.004$; interaction $F(2,44)=5.65$, $p=0.007$). Post hoc analyses showed that MMV significantly increased from 1 to 6 months after iSCI in the patient group at all frequencies (0.8 Hz: $p=0.003$; 1.6 Hz: $p<0.001$; 2.4 Hz: $p=0.002$), while the increase from 1 to 3 months was significant only at 2.4 Hz ($p=0.04$) (Fig. 6.2, Tab. 6.2). In addition, MMV was significantly reduced in the patient group in all assessments at all frequencies (0.8 Hz: $p<0.001$, $p<0.001$ and $p=0.002$ at 1, 3 and 6 months post injury, respectively; 1.6 Hz: $p<0.001$; $p<0.001$ and $p=0.001$; 2.4 Hz: $p<0.001$; $p=0.002$ and $p<0.001$ at 1, 3 and 6 months post injury, respectively). MMV in the control group was stable over time (Tab. 6.2).

MVC (normalized to body weight) differed significantly between the groups ($F(1,22)=16.84$, $p<0.001$) and the assessments ($F(2,44)=10.67$, $p<0.001$) and these two factors significantly interacted ($F(2,44)=4.48$, $p=0.02$). MVC significantly increased in the patient group from 1 to 3 months ($p=0.002$) and 1 to 6 months post injury ($p<0.001$) (Fig. 6.2, Tab. 6.2), but the increase between the third and sixth month was not significant. MVC differed between the groups at all assessments (assessment 1: $p<0.001$; assessment 2: $p=0.02$; assessment 3: $p=0.03$), while no changes over time were found in the control group (Tab. 6.2).

Accordingly, the *ASIA motor score* of the dorsiflexor muscles significantly increased over time (Friedman test: DF=2, $\chi^2=16.19$, $p<0.001$). Its median improved from 3.5 points at 1 month post injury to 4 points at 3 months and to 5 points at 6 months post injury. Post hoc tests showed that the increases from 1 to 3 months and from 1 to 6 months post injury were significant ($p=0.015$ and $p=0.004$, respectively).

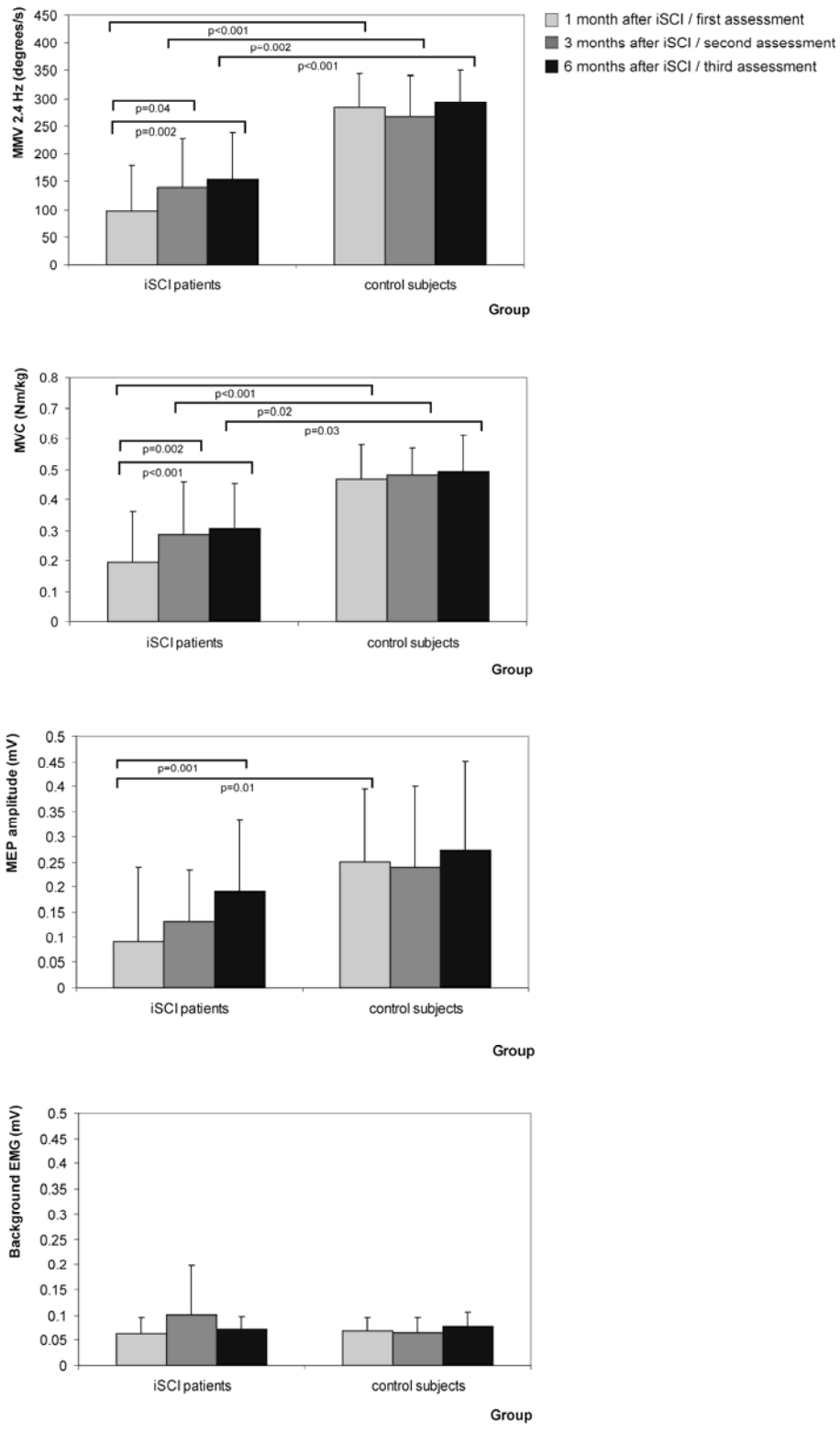

Fig. 6.2: Results of MMV, MVC, MEP amplitude and EMG background activity.

The figure shows a summary of MMV at 2.4 Hz (top panel), MVC (second panel), MEP amplitude (third panel) and EMG background activity (bottom panel). At stable EMG background activity, not only the MEP amplitude, but also MMV and MVC in dorsiflexion significantly increased in iSCI patients as the time after the injury increased.

Ambulatory capacity

Maximal gait speed significantly differed between the groups ($F(1,22)=37.80$, $p<0.001$) and the assessments ($F(2,44)=14.76$, $p<0.001$) and their interaction was significant ($F(2,44)=6.70$, $p=0.003$). In the patient group, maximal gait speed increased between the first and the second ($p=0.0007$) and the first and the third assessment ($p<0.0001$), but the improvement between the second and the third assessment was not significant (Tab. 6.2). Also, the WISCI II score increased over time (Friedman test: $DF=2$, $\chi^2=15.94$, $p<0.001$). The median increased from 13 points at 1 month post injury to 16 points at 3 months and to 20 points at 6 months after iSCI. This increase was significant between the first and the third assessment ($p=0.005$) and almost significant between the first and the second assessment ($p=0.017$; α in the post hoc tests = 0.0167).

Tab. 6.2: Results of the iSCI patients and control subjects.

Parameter		iSCI patients			Control subjects		
		1 month after iSCI (average ±SD)	**3 months after iSCI** (average ±SD)	**6 months after iSCI** (average ±SD)	**Assess-ment 1** (average ±SD)	**Assess-ment 2** (average ±SD)	**Assess-ment 3** (average ±SD)
MEP amplitude (mV)		0.09 (±0.15)	0.13 (±0.10)	0.19 (±0.14)	0.25 (±0.14)	0.24 (±0.16)	0.27 (±0.18)
Normalised MEP latency (ms/m)		21.64 (±2.43)	22.59 (±2.99)	22.38 (±1.96)	18.62 (±1.48)	18.85 (±1.16)	19.83 (±1.92)
EMG background (mV)		0.06 (±0.03)	0.10 (±0.10)	0.07 (±0.03)	0.07 (±0.03)	0.07 (±0.03)	0.08 (±0.03)
Deviation from target frequency (Hz)	0.8 Hz	0.004 (±0.003)	0.005 (±0.007)	0.004 (±0.006)	0.004 (±0.004)	0.004 (±0.003)	0.003 (±0.002)
	1.6 Hz	0.10 (±0.22)	0.05 (±0.11)	0.04 (±0.09)	0.03 (±0.04)	0.04 (±0.05)	0.02 (±0.05)
	2.4 Hz	0.36 (±0.46)	0.26 (±0.35)	0.22 (±0.28)	0.17 (±0.16)	0.17 (±0.13)	0.19 (±0.18)
MMV (degrees/s)	0.8 Hz	98.09 (±84.20)	121.63 (±73.16)	139.92 (±72.28)	249.30 (±44.43)	243.63 (±54.15)	250.37 (±56.39)
	1.6 Hz	104.90 (±91.88)	139.06 (±85.17)	155.38 (±89.44)	284.08 (±48.83)	275.81 (±68.90)	286.57 (±49.68)
	2.4 Hz	97.95 (±79.82)	139.41 (±89.27)	154.20 (±84.11)	284.59 (±59.51)	266.70 (±75.11)	293.74 (±56.87)
Normalised MVC (Nm/kg)		0.19 (±0.16)	0.29 (±0.17)	0.31 (±0.15)	0.47 (±0.11)	0.48 (±0.09)	0.49 (±0.12)
Maximal gait speed (m/s)		0.71 (±0.59)	1.06 (±0.74)	1.19 (±0.68)	2.36 (±0.41)	2.43 (±0.56)	2.45 (±0.49)

Legend:
EMG electromyography
MEP motor evoked potential
MMV maximal movement velocity
MVC maximal voluntary contraction
SD standard deviation

6.4.2. Relationship between changes in neurophysiological and functional parameters

Between 1 and 3 months as well as between 1 and 6 months after iSCI, the percentage increase in MEP amplitude was significantly related only to the percentage increase in MMV at 2.4 Hz (R^2=0.45, p=0.03 from 1 to 3 months and R^2=0.48, p=0.02 from 1 to 6 months) (Fig. 6.3 A). The percentage increase in MVC tended towards a significant relationship (R^2=0.25, p=0.14 from 1 to 3 months and R^2=0.34, p=0.06 from 1 to 6 months), while no relationship was found to the differences in the ASIA motor scores (Spearman correlation coefficient r_S = 0.08, p=0.83 from 1 to 3 months and r_S = 0.29, p=0.39 from 1 to 6 months) (Fig. 6.3 A).

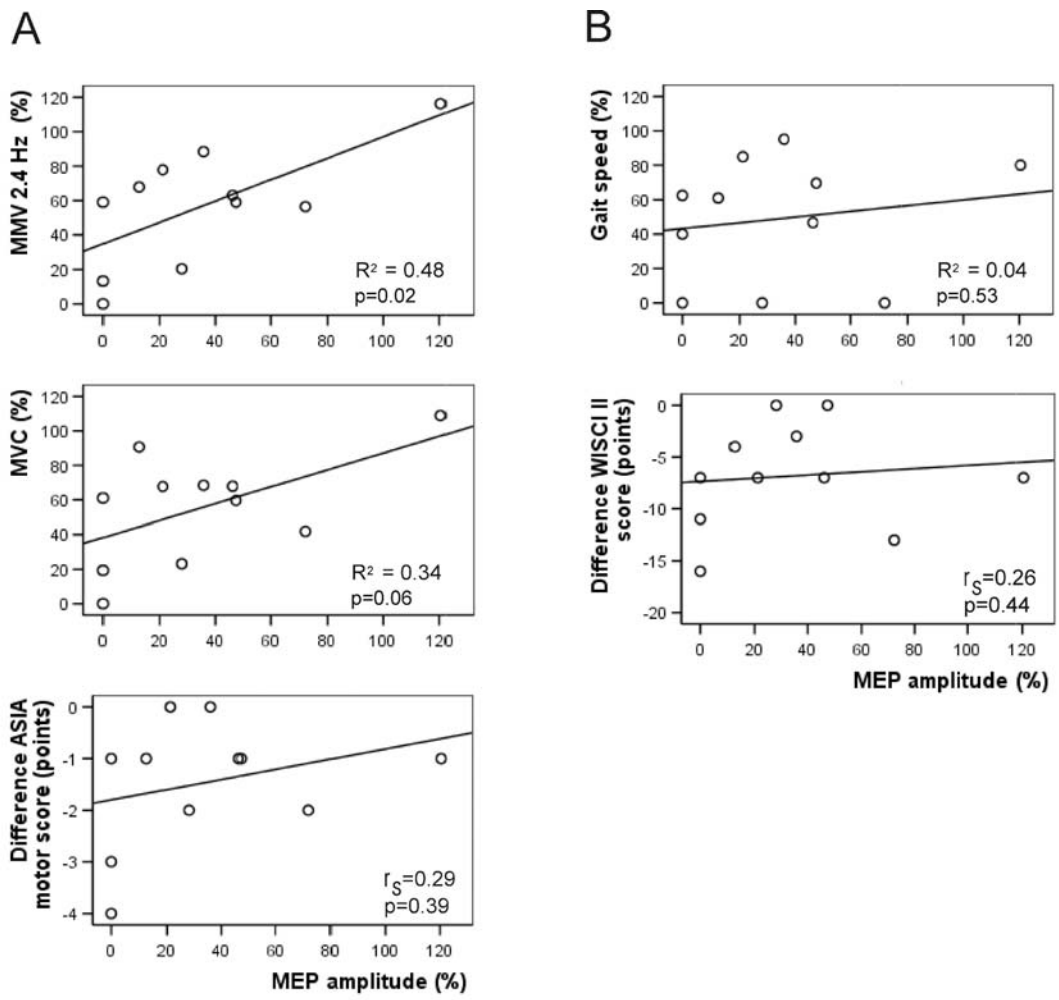

Fig. 6.3: Relationship between increase in MEP amplitude and all functional parameters from 1 to 6 months after iSCI.

The figure shows the changes in MEP amplitude in relation to (A) the changes in strength measures (MMV at 2.4 Hz (top panel), MVC (middle panel) and ASIA motor scores (bottom panel)) and (B) gait parameters (speed (top panel) and WISCI II score (bottom panel)). The data were calculated and displayed as percentages (quotient 1 month result / 6 months result) for MEP amplitude, MMV at 2.4 Hz, MVC and gait speed and as differences (difference 1 month result – 6 months result) for ASIA motor score and WISCI II score (ordinal data).

Also the improvement in ambulatory capacity was not related to the percentage increase in MEP amplitude, neither in terms of gait speed (R^2=0.06, p=0.48 between 1 and 3 months, R^2=0.04, p=0.53 between 1 and 6 months) nor walking aids (r_S = 0.17, p=0.65 between 1 and 3 months and r_S = 0.26, p=0.44 between 1 and 6 months after iSCI) (Fig. 6.3 B).

6.5. Discussion

In general, acute iSCI patients show substantial motor recovery, with the majority regaining some walking ability (Dobkin et al. 2006). However, the underlying mechanisms of this process are not entirely clear. Thus, this study investigated the recovery of ankle dorsiflexion in acute iSCI by combining neurophysiological assessments of CST function (torque-controlled MEPs) with a refined assessment protocol of ankle motor function during the first 6 months after iSCI. As expected, motor function (measures of muscle strength and gait) significantly recovered and the MEP amplitudes increased within that time period. However, the MEP latencies stayed prolonged, and the level of EMG background activity at 20% MVC remained unchanged, though in parallel with increased torque generation. The increase in MEP amplitudes was related only to measures of ankle maximum movement velocity, while there was no relationship to measures of gross muscle strength and ambulatory capacity. These findings are discussed with regard to evaluating the contribution of changes in CST function to recovery of function after iSCI.

6.5.1. Changes in neurophysiological and functional parameters over time

All functional parameters, apart from ankle dexterity, significantly increased during recovery. The finding of a significant increase in muscle strength within the first 6 months after iSCI is in line with previous studies, which used the ASIA motor scores and found a plateau beginning not before 9 months post injury (Waters et al. 1994a; Waters et al. 1994b). Also ambulatory capacity (gait speed and the WISCI II score) was reported to increase within that time (van Hedel et al. 2007a). Interestingly, ankle dexterity, assessed in the present study as the ability to accurately time ankle movements independently from muscle strength, was unimpaired at 1 month after the spinal lesion and thereafter. This is in accordance with findings in chronic iSCI patients where ankle dexterity, evaluated within the range of preserved muscle strength, was not significantly affected (Wirth et al. in press-a).

A shortening of MEP latencies during recovery was not found, as reported elsewhere (Curt et al. 1998). Compared to MEP latencies, MEP amplitudes have been scarcely used as a diagnostic measure because of the large trial-to-trial variability (Calancie et al. 1999;

Kobayashi and Pascual-Leone 2003). Consequently, the course of the MEP amplitudes during recovery from iSCI has been rarely described (Curt et al. 1998). Therefore, the present study controlled for the level of background torque with a comparable level of pre-activation at the time of stimulus delivery in order to provide reliable MEP amplitudes (van Hedel et al. 2007b). In addition, the reliability of the MEP amplitudes was confirmed by a very high intraclass correlation coefficient (ICC=0.81) within the healthy subjects. Furthermore, the magnitude of the MEP amplitude was calculated as the increase in net MEP amplitude (EMG background activity subtracted), while the level of EMG background activity in patients and controls did not change over time. Thus, the applied MEP protocol revealed a reliable increase in MEP amplitudes in the first 6 months after iSCI at a comparable level of facilitation.

The present study focused on changes in *voluntary* motor control, but did not include reflex measures, although extensive modulation of spinal reflex responses in both incomplete and complete SCI are well appreciated (Calancie et al. 1993; Hiersemenzel et al. 2000). However, the relevance of these reflex modulations for the recovery of motor function has not yet been conclusively established (Lee et al. 2005; Nakazawa et al. 2006).

6.5.2. Relationship between changes in neurophysiological and functional parameters

In general, the measures of CST conductivity and function were rather poorly correlated. A relationship between measures of MEP amplitudes and function was found particularly for ankle MMV, which confirms that movement speed as one aspect of motor control is most closely related to CST integrity (Kent-Braun et al. 1998; Miller and Johnston 2005). TMS studies in chronic iSCI patients showed that different reinforcement maneuvers can be successfully applied to improve the sensitivity of the assessment of descending motor tracts (Hayes et al. 1991; Wolfe et al. 1996). The present task- and torque-controlled MEP aimed at providing a standardized reinforcement maneuver. As this paradigm focused on the fast conducting descending motor fibres, changes in slow conducting or oligo-synaptic pathways, which might arise from the formation of CST detour circuits by collateral sprouting and enhancement of proprio-spinal connections as shown in rats (Bareyre et al. 2004) would not be assessed. Nevertheless, the present results of a significant increase in MEP amplitude over time are in line with a recent study that investigated the effect of intense treadmill training on CST function in chronic iSCI patients (Thomas and Gorassini 2005). In contrast to our findings, that study reported a high correlation between the increase in CST function and training-induced improvements in gait. Besides some methodological differences, this might

be mainly due to the different stage of recovery of the participating patients (chronic patients, who might have passed the time window of spontaneous recovery, versus acute patients).
In the present study, additional factors to changes in CST function might have contributed to the observed motor recovery from acute iSCI. At the brain level, extended cortical and subcortical changes in sensory-motor areas rostral to the spinal lesion evolve, as revealed by TMS (Topka et al. 1991) and neuro-imaging studies (Curt et al. 2002; Jurkiewicz et al. 2007). However, the implication of these changes to functional recovery is yet to be clarified (Curt et al. 2002; Jurkiewicz et al. 2007). Furthermore, other descending fibre systems than the CST, e.g. the reticulo-spinal (Ballermann and Fouad 2006) and the serotonergic (Oatway et al. 2005) system, were reported in animal studies to enhance motor function after iSCI. At the spinal level, it has been shown that plastic changes in spinal neuronal circuits can be trained and fostered by specific rehabilitation strategies (e.g. body-weight supported treadmill training) (Dietz et al. 1994; Grasso et al. 2004). In addition, besides changes in the central nervous system, the present study suggests additional mechanisms, such as changes in muscle properties to likely be involved in the increase in motor strength during recovery from acute iSCI. In healthy subjects, the magnitude of intra-individual EMG recordings was reported in the majority of studies, but not unanimously, to increase particularly during the first 3-4 weeks of strength training (Folland and Williams 2007). In the present study, MVC and motor scores significantly increased during the first 6 months after acute iSCI, while the produced EMG background activity at a comparable level of activation remained statistically unchanged. Few studies describing muscle function after iSCI exist (Jayaraman et al. 2006; Gregory et al. 2007). Unusual strong motor units were observed in iSCI patients (Thomas et al. 1997) and an increase in the prevalence of type IIa muscle fibres was reported to start as early as 4 to 6 weeks after the onset of a complete spinal cord lesion (Burnham et al. 1997). It is unclear, however, whether such fibre type shift also occurs in iSCI (Jayaraman et al. 2006). Further research is thus needed that investigates muscle plasticity after iSCI and its impact on function.

6.6. Conclusions

CST function improved during the first 6 months after an incomplete spinal cord lesion and contributed to the recovery in movement velocity. However, there was no obvious relationship between changes in CST function and measures of gross muscle strength and gait capacity. These findings imply that other mechanisms, such as plastic changes in spinal neuronal circuits and muscle properties most likely contributed to the functional recovery in iSCI. With regard to interventional studies either based on novel training approaches or cell-

based therapies, a multimodal assessment protocol (neurophysiological, neurological and functional assessments) is recommended.

7. Study 5: Ankle dexterity in incomplete spinal cord injury versus stroke

This manuscript has been submitted to the Journal “Brain” under the title “Ankle dexterity remains intact in incomplete spinal cord injury in contrast to stroke patients”. The authors were Wirth B., van Hedel H.J., Curt A. All measurements and data analyses were conducted by the first author. The manuscript was written by the first author and revised by the co-authors.

7.1. Abstract

Patients with incomplete spinal cord injury (iSCI) and stroke suffer from impaired muscle strength and ambulation. The assessment of motor control in iSCI has focused on measures of muscle strength (manual muscle testing), while in stroke extensive research has been directed towards upper limb motor control. With regard to ambulatory deficits, the ability to coordinate muscle activity in the lower limb is crucial. Slowness of movements was reported to be a common motor impairment of patients with lesions of the central nervous system (CNS). It may result from muscle weakness and deficits in dexterity, which are two aspects of motor control that are dependent on cortico-spinal tract (CST) integrity. Thus, this study investigated the impact of CST damage either at spinal (iSCI) or cortical level (stroke) on ankle control and locomotion.

Ankle motor control was tested in groups of 12 iSCI, stroke and control subjects. The patients were matched for gender, age and maximal voluntary contraction (MVC) in dorsi- and plantar-flexion. Timing of ankle dorsiflexion as a measure of dexterity and maximal ankle movement velocity (MMV) as a marker for dynamic muscle strength were tested in the supine position. CST conductivity was assessed by motor evoked potentials (MEPs) and ambulatory capacity by gait speed and the need for walking aids.

In both patient groups, MMV and ambulatory capacity were significantly reduced and MEP latencies and amplitudes were comparably deteriorated. However, dexterity was preserved in the iSCI group, but reduced in the hemiparetic stroke leg. The non-affected stroke leg showed intact dexterity and normal MEPs, but some muscle weakness (reduced MVC).

Although muscle weakness and CST conductivity were comparably deteriorated in both patient groups, only the stroke patients showed reduced dexterity of the hemiparetic limb. In contrast, the iSCI patients could sufficiently control the preserved muscle strength, but were predominantly impaired by lower limb weakness. These results indicate that rehabilitation

programs and cell based treatments in iSCI can build on preserved motor control while targeting at increasing muscle strength.

7.2. Introduction

Lesions of the CNS, such as those after stroke or spinal cord injury, are often associated with severe motor deficits. Particularly slowness of movement is a common motor impairment after CNS lesions (Miller and Johnston 2005), which may result from muscle weakness and deficits in dexterity. Dexterity can be defined as the ability to coordinate muscle activity to meet environmental demands and is not restricted to manual tasks (Canning et al. 2004). Impairments in muscle strength and dexterity account for the majority of disability observed in stroke patients (Ada et al. 1996; Canning et al. 2000). In upper limb studies, reduced maximal torque, a decreased rate of torque development (Canning et al. 1999) and deficits in manual dexterity have been demonstrated (Ada et al. 1996), even in the limb ipsilateral to the brain lesion (Wetter et al. 2005). In lower limb studies of iSCI patients, muscle weakness and slowness in the development of voluntary torque was found (Jayaraman et al. 2006), while dexterity, assessed by accurate timing of ankle movements, was only slightly reduced (Wirth et al. in press-b).

Aside from the aforementioned studies, little is known about the ability of iSCI and stroke patients to coordinate muscle activity in the lower limb. In addition, studying motor control in patients with a CST lesion at either the cortical or spinal level using the same paradigm might be useful for gaining deeper insight into the mechanisms underlying motor disability. Thus**,** the aim of the present study was to compare the impact of CST damage on motor control of the lower limb between iSCI and stroke patients (hemiparetic and non-affected leg) by combining measures of movement performance and CST conductivity as by means of MEPs.

7.3. Methods

7.3.1. Subjects

All procedures were in accordance with the standards of the local ethics committee and with the Declaration of Helsinki. All subjects gave informed written consent to participate in the study. The stroke patients were recruited from the Neuro-rehabilitation hospitals of Valens and Wald, Switzerland, the iSCI patients from the Spinal Cord Injury Center of Balgrist University Hospital, Zurich, Switzerland. The control subjects were recruited via the local

university department for senior citizens in Zurich, Switzerland. Twelve stroke patients (6 females; mean age = 65.75 years ± standard deviation 10.54), 12 iSCI patients (category C or D according to the American Spinal Injury Association (ASIA, 2002)), matched for gender and age (62.25 years ± 8.25), and 12 control subjects, matched for gender and age (63.25 years ± 10.71), were tested (Tab. 7.1).

Tab. 7.1: Characteristics of the stroke and iSCI patients.

Age	Affected limb (stroke)/ Level of lesion (iSCI)	Time since lesion (months)	Diagnosis	WISCI II	Maximal gait speed (m/s)	Spasticity (modified Ashworth)
Stroke patients						
39	left	5	CVA middle cerebral artery	18	1.3	0
57	left	1	CVA capsula interna	20	2.3	0
61	right	75	CVA middle cerebral artery	20	1.3	1
63	right	2	CVA middle cerebral artery	18	0.7	2
65	left	50	CVA fronto-parieto-occipital	20	1.1	0
65	left	2	CVA striato-capsular	20	0.6	1
67	right	2	ICH basal ganglia	13	0.6	2
71	left	15	CVA middle cerebral artery	20	1.1	2
73	left	6	CVA middle cerebral artery	20	1.6	0
75	left	12	CVA middle and anterior cerebral artery	13	0.6	1
76	left	2	CVA middle cerebral artery	19	0.6	1
77	left	1	CVA middle cerebral artery	20	1.0	0
iSCI patients						
50	T 9	1	Arteria spinalis anterior syndrome	0	0	0
53	T 10	112	Trauma	20	1.1	0
56	T 10	1	Abscess	13	1.3	0
57	T 11	7	Epidural abscess	19	0.9	1
59	C 6	1	Trauma	17	0.5	0
60	T 12	1	Intramedullar ependymoma	16	1.0	0
60	C 5	1	Trauma	13	0.6	0
65	L 1	1	Arteriovenous malformation	0	0	0
66	C 6	22	Trauma	20	2.1	0
71	C 5	1	Trauma	0	0	0
74	T 12	1	Meningioma	13	1.1	0
76	C 3	5	Trauma	20	1.7	0

Legend:
CVA cerebro-vascular accident
ICH intra-cranial hemorrhage
WISCI II Walking Index for Spinal Cord Injury, 2nd version

The stroke and the iSCI patients were also matched for muscle strength. Thus, MVC (normalized for body weight (Hsu et al. 2002)) in dorsiflexion was 0.23 Nm/kg (± 0.11) for the stroke patients, 0.26 Nm/kg (± 0.15) for the iSCI subjects and 0.48 (± 0.10) for the control subjects. In plantarflexion, normalized MVC was 0.23 Nm/kg (± 0.14) for the stroke patients, 0.22 Nm/kg (± 0.15) for the iSCI patients and 0.35 (± 0.16) for the control subjects. The stroke patients suffered mainly from ischemic brain lesions (cerebro-vascular accidents of the cortical middle cerebral artery (MCA) area as assessed by computer tomography (CT) or magnetic resonance imaging (MRI)) with the exception of one patient who had an intracranial hemorrhage (Tab. 7.1). The cognitive functions were assessed by a Mini Mental State (Folstein et al. 1975) and only patients with scores above 24 points were included (Adunsky et al. 2002). In addition, patients with spasticity > 2 on the modified Ashworth scale, or with ankle contractures, were excluded from the study (Canning et al. 1999). Thus, spasticity ranged from 0 to 2 scores on the modified Ashworth scale in the stroke group and from 0 to 1 in the iSCI group (no significant difference between the groups). Time since the onset of injury was on average 1.2 years (± 1.9) in the stroke group and 1.1 years (± 2.6) in the iSCI group (Tab. 7.1).

7.3.2. Experimental procedure

The set of assessments (ankle task, MVC (for strength matching), transcranial magnetic stimulation (TMS), gait tests) was conducted as described in chapter 2. The hemiparetic leg of the stroke patients was compared to the more affected leg of the iSCI subjects (defined by MVC of the dorsiflexor muscles, which were the focus of the present study) and to the non-dominant leg of the control subjects. In addition, the non-affected leg of the stroke patients was compared to the non-dominant leg of the control subjects. The dominant foot was self-reported as the foot used for kicking a ball, as this is regarded the predominant test (Gabbard and Hart 1996).

7.3.3. Data analysis and statistical tests

To determine dexterity, the deviation between target and performed frequency was statistically analyzed using one sample t-tests. To compare the need for walking aids (ordinal scale) between the patient groups, a Mann Whitney U test was conducted. To compare the other outcome parameters, the non-parametrical Kruskal Wallis test and, post hoc, Mann Whitney U tests were used. The significance level α was set at 0.05 for all analyses and was adjusted to 0.05/3=0.0167, where 3 comparisons were performed (post hoc tests and one sample t-tests).

7.4. Results

7.4.1. Comparison of stroke (hemiparetic leg) and iSCI patients to control subjects

Ankle task

The deviation from the target frequency was largest in the hemiparetic leg of the stroke patients at all frequencies (Tab. 7.2, Fig. 7.1) and was significant at 2.4 Hz (p=0.001), while the iSCI patients and the control subjects could comparably follow all target frequencies with only minor deviations (no significant differences). Comparing the groups, dexterity in the stroke patients differed at 2.4 Hz (DF=2, χ^2=10.83, p=0.004) compared to the iSCI patients (p=0.012) and the control subjects (p=0.001).

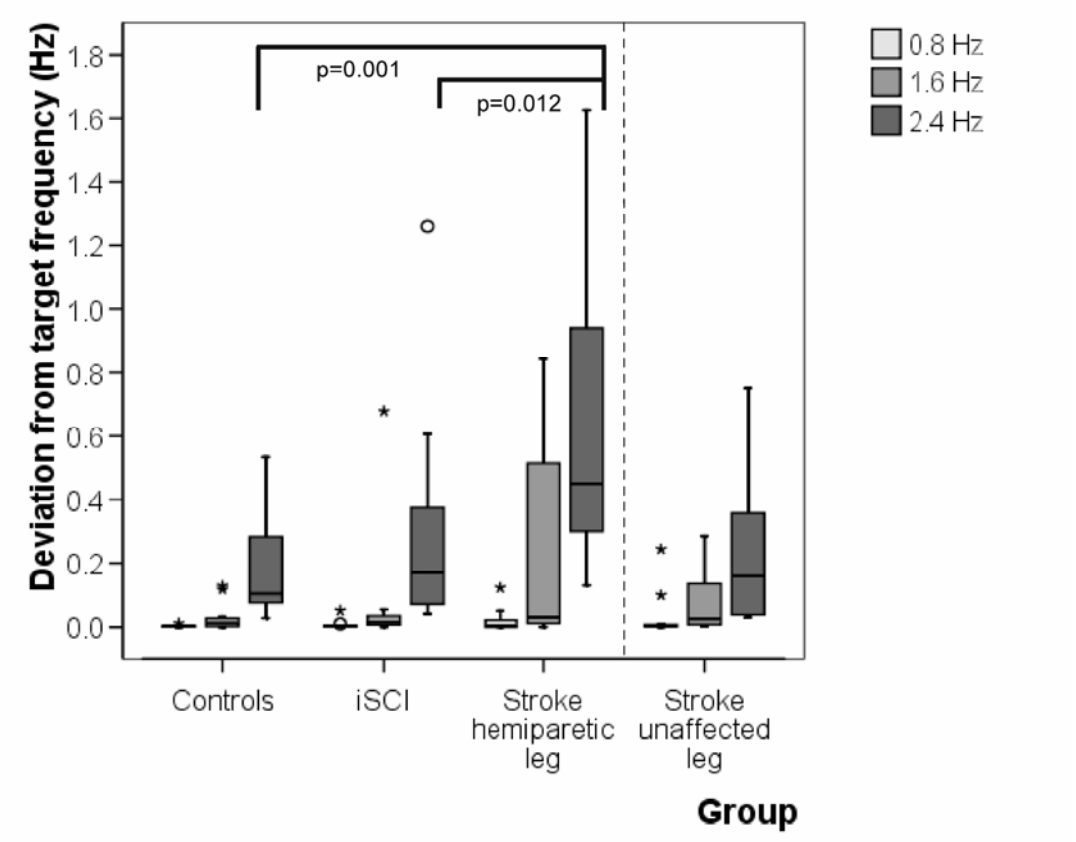

Fig. 7.1: Dexterity, group results.
The timing of ankle dorsiflexion in the supine position, as assessed by 3 different frequencies (0.8, 1.6, 2.4 Hz) of audio-paced movements, was significantly reduced in the hemiparetic limb of the stroke patients at 2.4 Hz.
Circles in the boxplot indicate outlier values that are between 1.5 and 3 interquartile range from the end of the box. Stars indicate extreme values that are more than 3 times the interquartile range from the end of the box.

For visualization, individual results of performance in dexterity of an iSCI patient and a stroke patient are shown in Fig. 7.2.

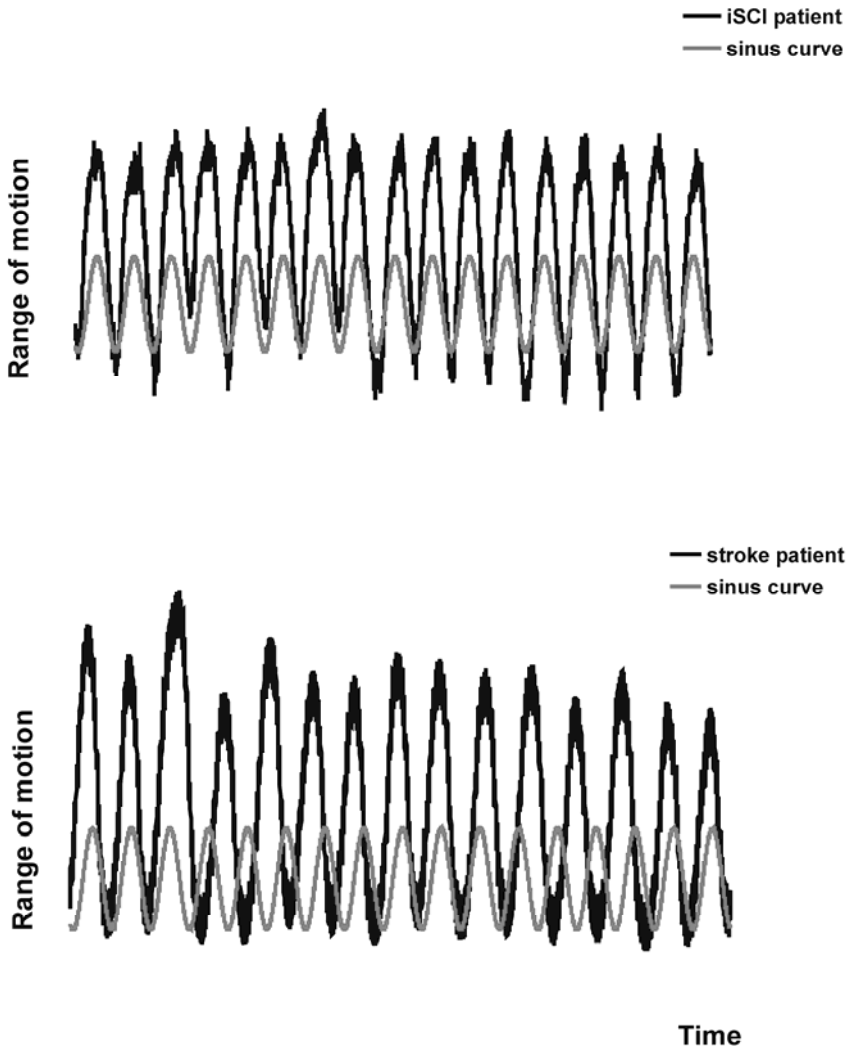

Fig. 7.2: Dexterity, individual examples.
Top: Individual results of dexterity at 2.4 Hz of an iSCI patient (female, 60 years, no spasticity, normalized MVC in dorsiflexion 0.34 Nm/kg) in comparison to the ideal sinus curve.
Bottom: Individual results of a stroke patient (left hemisphere) (male, 65 years, no spasticity, normalized MVC in dorsiflexion 0.22 Nm/kg) compared to the ideal sinus curve.

In terms of range of motion (ROM) and MMV, the 3 groups showed a similar pattern of task performance. They all showed a reduced ROM as the frequency increased, while MMV in dorsi- and plantar-flexion remained stable (no significant change of MMV between the 3 frequencies in all groups) (Tab. 7.2, Fig. 7.3 A and B). However, they differed in the following parameters: ROM (0.8 Hz: DF=2, χ^2=16.89, p<0.001; 1.6 Hz: DF=2, χ^2=21.32, p<0.001; 2.4

Hz: DF=2, χ^2=19.57, p<0.001), MMV in dorsiflexion (0.8 Hz: DF=2, χ^2=17.66, p<0.001; 1.6 Hz: DF=2, χ^2=21.26, p<0.001; 2.4 Hz: DF=2, χ^2=16.86, p<0.001) and MMV in plantarflexion (0.8 Hz: DF=2, χ^2=17.10, p<0.001; 1.6 Hz: DF=2, χ^2=20.16, p<0.001; 2.4 Hz: DF=2, χ^2=20.87, p<0.001). Post hoc analysis showed that the stroke and the iSCI patients were impaired in ROM and MMV (dorsi- and plantar-flexion) compared to the control subjects (p≤0.001). Comparing the stroke and the iSCI group, no significant difference was found in either ROM or MMV.

Motor evoked potentials

MEP latency was different between the groups in both the static and the dynamic condition (static latency: DF=2, χ^2=6.44, p=0.04; dynamic latency: DF=2, χ^2=13.48; p=0.001) (Tab. 7.2, Fig. 7.3 C). Post hoc analysis showed that the stroke and the iSCI patients had prolonged latencies compared to the control subjects in the dynamic condition (stroke: p<0.001; iSCI: p=0.008), while these differences were not significant in the static condition. In addition, no significant difference in MEP latency was found between the stroke and the iSCI patients. As for the MEP amplitude, the 3 groups did not significantly differ, neither in the static nor in the dynamic condition (static: DF=2, χ^2=4.33; p=0.12; dynamic: DF=2, χ^2=5.82; p=0.054) (Fig. 7.3 D).

Ambulatory capacity

All stroke patients were ambulatory. The median of the score of the Walking Index for Spinal Cord Injury II (WISCI II) was 20 and the maximal gait speed was on average 1.07 m/s (± 0.53), the preferred gait speed was 0.78 m/s (± 0.29). Of the 12 iSCI patients, 3 were not able to walk. The median of the WISCI II score was 14.5. Maximal and preferred gait speed in this group was 0.85 m/s (± 0.67) and 0.63 m/s (± 0.47). In the control group, maximal gait speed was 2.29 m/s (± 0.36), while preferred gait speed was 1.56 m/s (±0.13). Gait speed differed between the 3 groups for both the maximal (DF=2, χ^2=20.79, p<0.001) and the preferred (DF=2, χ^2=23.56, p<0.001) speed. Gait speed was thereby reduced in the stroke (maximal and preferred p<0.001) and the iSCI groups (maximal and preferred p<0.001) compared to the control subjects. Gait speed did not differ between stroke and iSCI patients, but the need for walking aids was significantly higher in the iSCI group (p=0.045).

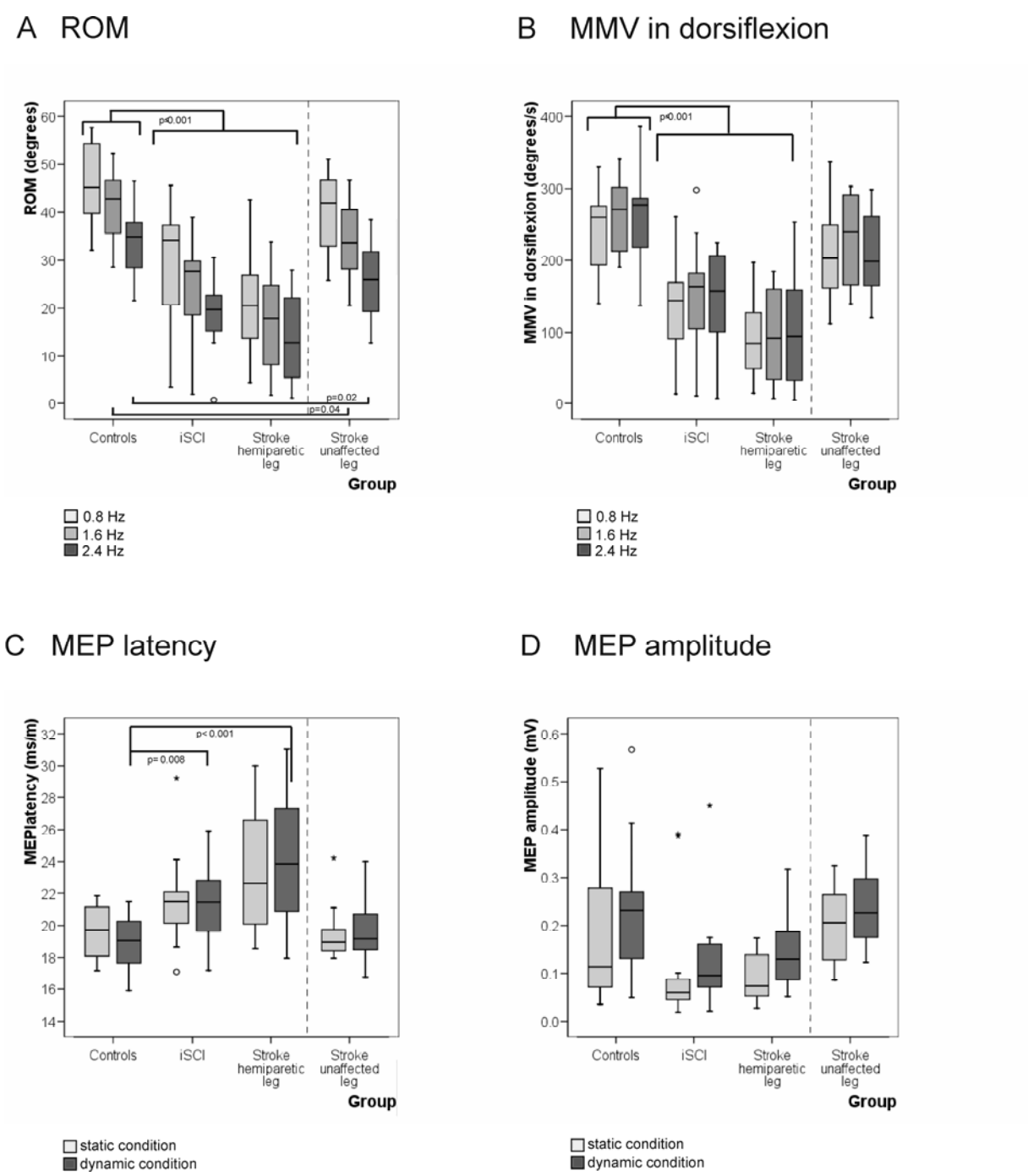

Fig. 7.3: Functional and neurophysiological outcome parameters.

(A) ROM and (B) MMV in dorsiflexion in the ankle task were significantly reduced in the hemiparetic limb of the stroke patients and in the iSCI group compared to the control subjects at all frequencies. ROM was also slightly reduced in the non-affected limb of the stroke patients. (C) Dynamic latency of the MEPs was significantly prolonged in the patient groups compared to the controls, while (D) MEP amplitude did not significantly differ between the groups.

Circles in the boxplot indicate outlier values that are between 1.5 and 3 interquartile range from the end of the box. Stars indicate extreme values that are more than 3 times the interquartile range from the end of the box.

Tab. 7.2: Outcome parameters of ankle task and transcranial magnetic stimulation in all groups.

Test parameter	Test condition	Controls	iSCI	Stroke hemi-paretic leg	Stroke non-affected leg
Deviation from target frequency (Hz)	0.8 Hz	0.004 (±0.003)	0.007 (±0.014)	0.02 (±0.04)	0.03 (±0.07)
	1.6 Hz	0.03 (±0.04)	0.07 (±0.19)	0.24 (±0.33)	0.07 (±0.09)
	2.4 Hz	0.18 (±0.16)	0.29 (±0.35)	0.66 † (±0.53)	0.25 (±0.26)
ROM (degrees)	0.8 Hz	45.79 (±8.34)	29.84 *** (±12.44)	21.83 *** (±11.59)	40.18 (±8.59)
	1.6 Hz	41.25 (±7.48)	24.64 *** (±10.03)	16.95 *** (±9.93)	34.09 * (±8.18)
	2.4 Hz	33.37 (±7.40)	18.79*** (±7.51)	13.87 *** (±8.91)	25.92 * (±7.61)
MMV DF (degrees/s)	0.8 Hz	238.81 (±58.09)	134.06 *** (±69.07)	91.92 *** (±57.06)	207.51 (±62.21)
	1.6 Hz	263.31 (±52.60)	150.45 *** (±79.77)	94.97 *** (±64.95)	229.60 (±62.83)
	2.4 Hz	256.34 (±67.58)	144.73 *** (±71.88)	99.53 *** (±76.09)	211.54 (±58.62)
MEP amplitude (mV)	static	0.18 (±0.15)	0.12 (±0.14)	0.09 (±0.05)	0.20 (±0.08)
	dynamic	0.23 (±0.14)	0.13 (±0.12)	0.15 (±0.08)	0.23 (±0.08)
MEP latency (ms/m)	static	19.64 (±0.17)	21.62 (±0.32)	23.49 (±0.41)	19.47 (±1.75)
	dynamic	18.94 (±0.16)	21.26 *** (±0.25)	24.08 *** (±0.39)	19.54 (±2.04)

Legend:
DF dorsiflexion
MEP motor evoked potential
MMV maximal movement velocity
ROM range of motion

* p<0.05 compared to control group
*** p<0.001 compared to control group
† p<0.05 between stroke and iSCI group

7.4.2. Non-affected leg of the stroke patients compared to the non-dominant leg of the control subjects

Dexterity in the non-affected leg of the stroke patients was slightly reduced compared to the non-dominant leg of the control subjects (Tab. 7.2, Fig. 7.1), but these differences were not significant. However, ROM was reduced in the non-affected leg of the stroke patients at 1.6 Hz ($p=0.04$) and 2.4 Hz ($p=0.02$) (Tab. 7.2, Fig. 7.3 A). MMV did not significantly differ in dorsiflexion (Tab. 7.2, Fig. 7.3 B), but was reduced in plantarflexion at all frequencies ($p=0.01$ at 0.8 Hz and 1.6 Hz; $p=0.02$ at 2.4 Hz). MVC was reduced in dorsiflexion ($p=0.006$) and was 0.36 Nm/kg (± 0.07) in the stroke group and 0.48 Nm/kg (± 0.10) in the control group. The MEP parameters were not altered in the non-affected leg of the stroke patients, neither in the static nor in the dynamic condition (Tab. 7.2, Fig. 7.3 C and D).

7.5. Discussion

The impairment of lower limb control after iSCI and stroke is clinically summarized as upper motoneuron (UMN) syndrome, which implies a similar impairment of motor function. However, similarities or divergences between iSCI (spinal lesion) and stroke (cortical lesion) patients in motor control of the lower limb have been less investigated so far. The purpose of the present study was to compare aspects of ankle dexterity and the ability to generate muscle strength in a dynamic ankle task between iSCI and stroke patients. To allow for comparison, the patients were matched not only for gender and age, but also for voluntary dorsi- and plantar-flexor strength. The study used a paradigm that requires minimal muscle strength to assess dexterity as an independent variable from muscle weakness. It could be shown that ankle dexterity was impaired only in the hemiparetic leg of the stroke patients, while the iSCI patients performed comparably to the control subjects. Although movement speed in the ankle task, gait speed and the MEPs were significantly deteriorated in the patient groups, the spinal CST damage in iSCI had only limited influence on dexterity when accounted for muscle weakness. Therefore, the UMN syndrome of the lower limb in iSCI differs from stroke patients in respect to dexterity which should be considered for rehabilitation programs and interventional trials.

7.5.1. Ankle control in iSCI patients compared to the hemiparetic leg of the stroke patients

The results of reduced performance speed and impaired dexterity in the ankle of stroke patients are analogous to previously reported upper limb studies, where it was found that loss of strength, and particularly slowness to develop peak torque, was a more significant contributor to disability than loss of dexterity (Canning et al. 1999; Canning et al. 2000; Canning et al. 2004). Also the results of the iSCI patients in terms of movement speed are consistent with previous results on this issue (Jayaraman et al. 2006; Wirth et al. in press-b). The reduction of maximal movement speed of the ankle and gait speed in both cortical and spinal lesions of the CST confirms that slowness of movement is a predominant characteristic in UMN syndrome (Miller and Johnston 2005). Interestingly, dexterity, as assessed in the present study as the ability to accurately time ankle movements, was only reduced in the stroke patients. This finding of more affected dexterity in the hemiparetic compared to the non-affected leg and the iSCI patients indicates that the applied paradigm is sensitive to assess differences in ankle dexterity. Although the performance in dexterity became physiologically reduced with the faster frequency in all groups, this effect was significantly more pronounced in the stroke patients, which is in line with studies on dexterity of the upper limb after stroke (Canning et al. 2004). Since the patient groups were matched for strength, this result cannot be accounted for by weakness. Also a deficit in movement planning cannot be the reason for the observed dexterity deficit in the stroke patients, since the non-affected leg showed no significant deficit in timing. Spasticity, in turn, could have influenced dexterity, since it was slightly (although not significantly) higher in the stroke group. To exclude that the finding of impaired dexterity was not simply based on spasticity, we analyzed the dexterity data excluding the three stroke patients with a modified Ashworth score equal to 2 (and the corresponding iSCI patients and control subjects) and came to the same result of impaired dexterity at high frequency compared to the control subjects and the iSCI patients. Another factor underlying low dexterity could be slowness of movement (Ada et al. 1996). Indeed, at the same level of strength, maximal movement speed was somewhat slower in the stroke than in the iSCI group (but not significantly different). Yet in the present study task, the patients were asked to first and foremost follow the target frequency accurately and secondly, to perform maximal ROM, requiring that accuracy be favored at the cost of ROM. Thus, reduced maximal movement speed did not necessarily have an impact on accuracy, but on ROM, which indicates that movement speed was unlikely to be the factor limiting accuracy in timing. More probably, in line with the results of two stroke studies using electromyography (EMG) during distinct upper limb (Ada et al. 1996) and cyclic lower limb movements (Kautz and Brown 1998), timing abnormalities (inaccuracy in an elbow tracking

task; prolonged and phase advanced muscle excitation during pedaling) have been attributed to an impaired ability to fine tune muscle activation. The rate of transmission of information from the cortex to the spinal cord was proposed to be the factor that limits dexterity (Darian-Smith et al. 1996). Prolonged MEP latencies of the hemiparetic limb in stroke have been reported elsewhere (Hendricks et al. 2003). Analogous in this study, MEP latency of the CST was prolonged in both patient groups with a slightly stronger delay (not significant) in stroke patients. Thus, reduced CST conductivity might be one factor that contributed to the finding of impaired ankle dexterity in stroke patients. Although muscle strength was reported to mainly determine gait speed in iSCI (Kim et al. 2004) and stroke patients (Hsu et al. 2003), rhythmic ankle re-education training with visual and auditory feedback during sitting, standing and walking led to a significant increase in walking speed in stroke patients (Mandel et al. 1990). Thus, the present findings are supportive to previous studies where training of ankle dexterity has been considered to be of value for optimizing gait outcome in stroke.

7.5.2. Ankle control in the non-affected leg of the stroke patients

Abnormal muscle activity in terms of strength and dexterity in the *non-affected* leg after stroke has been reported in several studies (Bohannon 1995; Andrews and Bohannon 2000). Abnormal descending signals (altered excitability of the opposite hemisphere) and changes in excitability of spinal reflexes are proposed to be underlying factors in this phenomenon (Yarosh et al. 2004). As for strength, impairments in various muscle actions have been observed in the non-affected leg after stroke (Bohannon 1995; Andrews and Bohannon 2000). Ankle dorsiflexion was thereby the least impaired muscle action and the reported strength values ranged between 92% (Bohannon 1995) and 75% (Andrews and Bohannon 2000) of normal, which is line with the present study, where the ankle dorsiflexor muscles of the stroke patients had 75% of strength of those of the control subjects. Also with a view to dexterity, the finding of no deficit in the non-affected leg in the present study is in line with previous results. Slowing and clumsiness after stroke were reported in the non-affected hand (Sunderland 2000), but these deficits were observed only in more complex tasks, such as the grooved pegboard and the maze coordination test (Haaland and Delaney 1981), while finger tapping and grip strength were normal (Haaland and Delaney 1981; Wetter et al. 2005).

7.5.3. Relevance for interventional treatments in iSCI

Recent therapeutic intervention studies in iSCI patients have mainly focused on task-specific locomotor training (Thomas and Gorassini 2005; Dobkin et al. 2006). However, a training strategy that aimed at increasing muscle strength by combining lower extremity resistance

training with plyometric training (high-velocity contractions) led not only to an increase in peak torque and the average rate of torque development, but also to enhanced gait speed in chronic iSCI patients (Gregory et al. 2007). Thus, task-specific rehabilitation strategies could be beneficially combined with interventions that aim at enhancing muscle strength.

In this context, also new cell based therapies that aim at neural repair after iSCI could be most effective by augmenting a patient's capacity to generate muscle strength. Furthermore, the preserved motor control, as evident by the intact dexterity, could be supportive to control recovered muscle activation where the increase of strength is accomplished by rather indirect and detoured neural regeneration (Bareyre et al. 2004).

8. General discussion and conclusions

This thesis investigated the role of the cortico-spinal tract (CST) in lower limb recovery after incomplete spinal cord injury (iSCI). It combined an advanced neurophysiological assessment of CST function (motor evoked potentials (MEPs)) with a new clinical test that separately assessed movement velocity and dexterity in the ankle, which are two aspects of motor control that can be attributed to CST function. These measurements were complemented by the assessment of static muscle strength (maximal voluntary contraction (MVC)), manual muscle testing and gait tests.
For a better understanding of the impairments in motor function after CST damage, these parameters were studied in acute and chronic iSCI patients and subsequently related to MEP latency and amplitude. In addition, both the neurophysiological and clinical parameters were studied over time in acute iSCI patients in order to estimate the extent to which changes in CST function contributed to motor recovery from iSCI. Lastly, for further validation and to integrate the results in the larger context of lesions of the central nervous system (CNS), stroke patients were also tested.

Reduced movement speed and impaired dexterity are regarded as the two main deficits in motor function of stroke patients (Ada et al. 1996; Canning et al. 2000). In the field of iSCI, these components of motor function have scarcely been investigated. Most iSCI studies rely solely on the motor scores according to the American Spinal Injury Association (ASIA) as a gold standard to assess motor function, though its sensitivity is insufficient (Herbison et al. 1996; Noreau and Vachon 1998) and it contains no information about movement speed. Dexterity has not been tested in the lower limb of iSCI patients so far.

The ankle paradigm that was developed in this thesis assesses ankle dexterity, defined as a patient's ability to accurately time repetitive dorsiflexion movements, and the maximal movement velocity (MMV) achieved in these movements, which assesses a patient's ability to generate dynamic muscle strength. Paced repetitive ankle dorsiflexion movements were shown in a study using functional magnetic resonance imaging (fMRI) to be an appropriate marker for measuring voluntary ankle motor control, due to the strong cortical projection to the motoneurons of the tibialis anterior muscle (Dobkin et al. 2004). The term 'dexterity' is often associated with skilled finger movements. Yet, it is not restricted to manual tasks, but rather defines a patient's general ability to co-ordinate muscle activity to meet environmental demands (Canning et al. 2004). Tests for dexterity are usually confounded by muscle weakness since their performance requires a certain amount of strength (Ada et al. 1996).

The task developed in this thesis quantifies dexterity within the strength capability of a patient. All patients who can move the ankle, if only a little, can be tested. Its application revealed a surprising dissociation between reduced muscle strength and preserved dexterity. Even in acute iSCI patients and in patients with severe paresis (ASIA motor score 2 or 3), dexterity was strikingly well preserved. However, dexterity was not related to either MEP latency or amplitude. This finding might indicate that within a given amount of preserved muscle strength, relatively few intact CST fibers are sufficient to provide the ability to accurately time ankle movements. In contrast to dexterity, MMV was closely related to the neurophysiological parameters of CST function. Movement velocity thus appears to be one aspect of motor control that is most susceptible to deficits in CST function in iSCI and hence most suitable for its clinical estimation. Furthermore, it was shown in this thesis that, in contrast to the reduction in static muscle strength, the reduction in MMV persisted even in well-recovered chronic iSCI patients. Compared to matched control subjects, MMV was significantly reduced in these patients, while static muscle strength did not differ between the groups.

During recovery, the MEP latencies remained stable suggesting that no remyelination of CST fibers took place. Nevertheless, an increase in CST facilitation (MEP amplitudes) was observed, which was related to the improvement in MMV, but which did not parallel recovery of static muscle strength and ambulation. Thus, changes in CST function (improved synchronization of the descending volleys) might have accounted for some improvement in motor function after iSCI. Nevertheless, the stable background activity in electromyography (EMG) in parallel to an increase in muscle strength implies changes in the neuromuscular properties. Furthermore, the lack of any relationship between the increase in the MEP amplitudes and the improvement in gait function might indicate plasticity in the central pattern generator (CPG). Of course, to unambiguously evaluate the contribution of these systems to the functional recovery from iSCI, each component would need to be targeted directly.

One limitation of this study is that the CST could have made further contributions to motor recovery, which might not have been detected by the assessment protocol used in this thesis. Transsected hindlimb CST axons of rats were shown to form detour circuits by sprouting into the cervical grey matter to contact propriospinal neurons, which most likely contributed to functional recovery (Bareyre et al. 2004). However, this study employed transcranial magnetic stimulation, which assesses only the fast-conducting CST fibres. Thus, it is questionable whether such sprouting could have been assessed by this technique. Furthermore, plastic changes at the spinal level (e.g. enhancement of spinal excitability (H-reflex)) might have contributed to the observed increase in MEP amplitude over time. H-

reflex latencies were shown to be normal or near-normal in acute and chronic iSCI patients (Brouwer et al. 1992; Calancie et al. 1993), while their amplitudes depend on time after injury (Calancie et al. 1993; Hiersemenzel et al. 2000). However, the H-reflexes can be modulated by movement observation and imagination (Baldissera et al. 2001; Clark et al. 2004), which implies that their facilitation is under considerable supraspinal control (Lemon and Griffiths 2005). In addition, the significance of such reflex modulations for *voluntary* motor control, which was the focus of this thesis, has not yet been conclusively clarified (Lee et al. 2005; Nakazawa et al. 2006), which is why they were not assessed. Nonetheless, for coherence, the results of this thesis might have been completed by the additional assessment of spinal reflexes. Lastly, this thesis exclusively investigated the role of the CST during recovery from iSCI and did not address other systems, which were reported to undergo plastic changes after iSCI and to contribute to motor recovery, such as the reticulo-spinal (Ballermann and Fouad 2006) and the serotonergic system (Oatway et al. 2005).

The application of the presented ankle paradigm in stroke patients revealed similarly slowed ankle movements as in iSCI patients, but significantly more deficiencies in ankle dexterity. These results disclose that the paradigm is capable of detecting dexterity deficits, if they exist, and is thus an appropriate tool for the assessment of ankle dexterity. Furthermore, these results clearly confirm the findings of upper limb stroke studies, which tested dexterity and movement velocity in an elbow flexion and extension paradigm, and which found that deficits in dexterity, in addition to deficits in generating dynamic muscle strength, contributed to physical disability (Ada et al. 1996; Canning et al. 1999; Canning et al. 2000; Canning et al. 2004). This consistency of upper and lower limb results further validates the presented ankle paradigm. Lastly, using the same paradigm in stroke and iSCI patients allowed for a comparison of motor impairments in the larger context of CNS lesions and confirmed the reduction of movement velocity as a common motor impairment in patients with CNS lesions (Kent-Braun et al. 1998; Miller and Johnston 2005).

In summary, the implications of the results of this thesis are manifold. From a clinical point of view, maximization of (dynamic) muscle strength seems to be a key goal to be strived for in iSCI patients. While a large body of literature addressed the issue of task-specific body-weight supported treadmill training and the efficacy of functional electrical stimulation, surprisingly few studies focused on the active therapy of muscle weakness (Hicks et al. 2003; Jayaraman et al. 2006; Gregory et al. 2007). Furthermore, these studies were all conducted in chronic iSCI patients only, and no assessment of acute iSCI patients was made. In these chronic patients, a combination of lower extremity resistance training with plyometric training (high-velocity contractions) led to an increase in peak torque, average

rate of torque development and gait speed (Gregory et al. 2007). Thus, the comprehensive investigation of the impact of similar training protocols on motor function in *acute* iSCI patients might lead to new rehabilitation strategies, which could beneficially complement the task-specific rehabilitation approach.

Furthermore, this thesis emphasizes that the assessment of the ASIA motor scores as the exclusive muscle strength test in iSCI patients is insufficient. Particularly in well recovered iSCI patients, only a dynamic test that assesses movement velocity is sufficiently sensitive to detect minor changes. Thus, there is a clinical need for a dynamic assessment tool that complements the current motor assessment protocol in iSCI. In order to enhance clinical practicability and data analysis, it is recommended to investigate whether the developed ankle paradigm could be simplified for this purpose. The speed of foot tapping was proposed to be a sensitive marker for upper motor neuron diseases (Miller and Johnston 2005). However, foot tapping has been sparsely explored in general (Largo et al. 2001) and has not been investigated at all in iSCI. Thus, studying validity, test-retest and inter-observer reliability, as well as sensitivity of foot tapping in adult subjects with iSCI (preferably in the supine position to ensure that the assessment tool is applicable from an early stage in rehabilitation) is required.

Also from a scientific point of view, with regard to the translation of basic research results into the clinic and vice versa, the need for a dynamic completion of the assessment of motor function in iSCI is strongly supported. By identifying MMV as the best clinical marker for CST function, the results of this thesis indicate that the implementation of a dynamic outcome measure is essential for monitoring the effectiveness of any regeneration therapy targeting the CST. Furthermore, the results suggest that regeneration approaches might be most effective by enhancing a patient's capacity to generate (dynamic) muscle strength. In this context, improving spinal conductivity by targeting the remyelination of damaged CST fibres could be a promising approach for further enhancing motor function in iSCI patients.

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10. List of abbreviations

ANOVA	analysis of variance
ASIA	American Spinal Injury Association
BDNF	brain derived neurotrophic factor
cAMP	cyclic adenosine monophosphate
C	cervical
CI	confidence interval
CNS	central nervous system
CPG	central pattern generator
CSPG	chondroitin sulfate proteoglycan
CST	cortico-spinal tract
CT	computer tomography
CVA	cerebro-vascular accident
DF	dorsiflexion
EM-SCI	European Multicenter Study of Spinal Cord Injury
EMG	electromyography
fMRI	functional magnetic resonance imaging
FIM	Functional Independence Measure
ICC	Intraclass correlation coefficient
ICF	International Classification of Functioning, Disability and Health
ICH	intra-cranial hemorrhage
iSCI	incomplete spinal cord injury
L	lumbar
MAG	myelin-associated glycoprotein
MCA	middle cerebral artery
MEP	motor evoked potential
MEPs	motor evoked potentials
MMV	maximal movement velocity
MRI	magnetic resonance imaging
MVC	maximal voluntary contraction
OMgp	oligodendrocyte myelin glycoprotein
PF	plantarflexion
PNS	peripheral nervous system
RMS	root mean square
ROM	range of motion

SCI	spinal cord injury
SCIM	Spinal Cord Independence Measure
SCIM II	Spinal Cord Independence Measure, 2nd version
SCIM III	Spinal Cord Independence Measure, 3rd version
SD	standard deviation
SRC	standardized regression coefficient
T	thoracic
TA	tibialis anterior muscle
TMS	transcranial magnetic stimulation
TUG	Timed up and go test
UMN	upper motoneuron
WISCI	Walking Index for Spinal Cord Injury
WISCI II	Walking Index for Spinal Cord Injury, 2nd version
10MWT	10 Meter Walk Test
6MWT	6 Minutes Walk Test

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- Wirth B, van Hedel HJ, Curt A. Ankle dexterity is less impaired than muscle strength in incomplete spinal cord lesion. J Neurol, in press.
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- Van Hedel HJ, Wirth B, Curt A. Accurate control of muscle strength after incomplete spinal cord injury: a future measure to assess reinnervation? In preparation.
- Van Hedel HJ, Wirth B, Curt A. Predicting walking function by initial strength, dexterity and corticospinal intactness. In preparation.

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