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UPPER EXTREMITY ACTIVITY MONITORING TO TRACK REHABILITATION PROGRESS IN SPINAL CORD INJURY

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presented by

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Summary

Spinal cord injury (SCI) leads to motor deficits such as paralysis of the upper limb (UL) if the damage occurs in the cervical spinal cord. Data from questionnaires have suggested that arm and hand function is the first functional priority in subjects with cervical spinal cord injury. Pre-clinical studies show that models of activity-based training facilitate neuronal regenerative growth and improve forelimb function. However, in humans, there is limited knowledge about the influence of UL activity on functional recovery. This is partly because quantification of UL activity is limited to subjective questionnaires or a wide range of indirect measures of muscle function and movement tasks capacity. Therefore, UL activity in cervical SCI subjects remains poorly investigated. To rectify these shortcomings, advances in wearable sensor technologies may offer a unique opportunity to assess UL activity objectively, during activities of daily living.

This thesis aimed to investigate UL activity during SCI rehabilitation using wearable sensors and its relation to clinical assessments. In order to achieve this goal, the present thesis aimed to develop and validate data analysis methods specific for SCI subjects based on ReSense, which is an inertial measurement unit designed for long-term movement and activity monitoring in patients with neurological conditions.

Data was collected in chronic community-dwelling SCI subjects and acute SCI patients during rehabilitation using several ReSense combinations. The set-up ranged from one module (placed on one wheel of the wheelchair) to four modules (placed on both wrists, on the chest, and on one wheel of the wheelchair), and with or without the gyroscope. In the second chapter, an algorithm able to classify self- and attendant-propulsion and to measure wheel kinematics was developed and validated in a “real-world” situation in 21 SCI subjects. The tested set-ups distinguished self-propulsion and estimated wheel kinematics with accuracy values as high as 92% for self-propulsion recognition and 99% for the estimation of wheel kinematics. In the third chapter, a methodology able to assess and quantify upper-limb use was validated in 12 tetraplegic subjects, and the prevalence of limb-use laterality was measured and related to clinical assessments. The methods demonstrated good construct and concurrent validity and the results showed that independence was negatively correlated to limb-use laterality. In the fourth chapter, measures of overall UL activity were collected in 30 acute SCI subjects and related to lesion characteristics, independence and function. Additionally, the prevalence of limb-use laterality was assessed. The results showed that overall UL activity was related to proximal muscle strength and independence, and that, compared to paraplegics, tetraplegics showed significantly higher limb-use laterality. In the fifth chapter, the value of the developed and validated methods was assessed during acute SCI rehabilitation in 31 SCI subjects. The changes in UL activity were measured and related to clinical assessments. The results showed that wearable-sensor methodologies are able to track clinical recovery of the UL. In later rehabilitation stages, the relationship between clinical measures and sensor-based metrics was attenuated as UL activity in tetraplegic patients matched that of their paraplegic counterparts regardless of their motor impairments. Finally, wearable sensors detected higher UL activity during therapy time compared to the time outside of therapy.

In conclusion, this thesis demonstrates that wearable sensor methodologies can assess recovery of UL activity concurrently to standardised clinical assessments and may be used to quantify the dose of UL activity during therapies. Additionally, sensors provide additional information on how the UL are used during activities of daily living and, at a later stage of rehabilitation, about the quantity of UL activities beyond the one that could be expected by judging the scores of clinical assessments. This thesis contributes to the rapidly growing field of long-term measurement with wearable sensors in providing the validity and the clinical meaning of these methods in SCI. The results advocate for the utilisation of these methodologies to track UL activity in the clinical routine, in clinical trials, and in outpatient care. With this knowledge, therapies and rehabilitation strategies may be tailored to the intervention and to the patient in order to fulfil improved recovery helping SCI subjects achieve higher functionality and independence.

Riassunto

Le lesioni al midollo spinale provocano dei deficit motori come la paralisi degli arti superiori. La ricerca svolta su questionari suggerisce che la priorità per persone tetraplegiche è il recupero della funzione delle braccia e delle mani. Studi preclinici dimostrano che le tipologie di riabilitazione basate sull'ampliamento dell'attività neurologica facilitano il ripristino neuronale migliorando la funzione degli arti superiori. Nell'ambito della ricerca su soggetti umani, la conoscenza sull'influenza di un'ampliata attività neurologica sul recupero funzionale è limitata poiché la sua quantificazione avviene tramite questionari, che vengono compilati in modo soggettivo e tramite misure indirette della capacità muscolare e dei movimenti funzionali. Per questo motivo questo ambito della ricerca su persone paralizzate necessita di supplementari investigazioni. Progressi recenti avvenuti nel ambito dei sensori portabili potrebbero offrire opportunità uniche per una valutazione oggettiva dell'attività degli arti superiori durante le attività quotidiane, rimediando in tal modo a questa carenza di informazioni.

L' obbiettivo di questa tesi è di investigare l'attività degli arti superiori tramite sensori portabili durante la riabilitazione di persone paralizzate e la valutazione della sua relazione con gli esami clinici. Per raggiungere questo obbiettivo, questa tesi ambisce a sviluppare e validare nuove metodologie di analisi specifiche per persone paralizzate. I metodi di analisi sono sviluppati per ReSense: un'unità di misura inerziale sviluppata per misurazioni di movimenti a lungo termine in pazienti che soffrono di problemi neurologici.

Soggetti cronici e pazienti acuti sono stati analizzati durante la riabilitazione usando svariate combinazioni dei moduli ReSense. Il setup variava tra un modulo (piazzato su una ruota della

sedia a rotelle) e quattro moduli (piazzati sui polsi, sul petto e su una ruota della sedia a rotelle) con giroscopio attivato o disattivato. Nel secondo capitolo, è stato sviluppato e validato su 21 pazienti paralizzati in una situazione del mondo reale un algoritmo capace di classificare autopropulsione e propulsione da parte di una terza persona e di stimare valori cinematici. I setup testati hanno rilevato l'autopropulsione con un'accuratezza con valori fino al 92% ed hanno stimato i valori cinetici della sedia a rotelle con accuratezza con valori fino al 99%. Nel terzo capitolo, una metodologia capace di misurare e quantificare l'uso lateralizzato degli arti superiori è stata validata su 12 persone tetraplegiche. In seguito la prevalenza dell'uso lateralizzato è stata misurata e messa in relazione con gli esami clinici. I metodi hanno dimostrato buona validità di costrutto e di criterio concorrente e i risultati hanno dimostrato che l'indipendenza è correlata negativamente con l'uso lateralizzato degli arti superiori. Nel quarto capitolo, l'attività totale delle braccia è stata misurata su 30 pazienti acuti. In seguito l'attività totale è stata messa in relazione con le caratteristiche della lesione al midollo spinale, con i risultati degli esami d' indipendenza e con i risultati degli esami della funzione muscolare. Inoltre, la prevalenza dell'uso lateralizzato degli arti superiori è stata quantificata. I risultati hanno dimostrato che l'attività totale delle braccia e delle mani è correlata con la funzione dei muscoli prossimali e con l'indipendenza. In fine, nei confronti dei paraplegici, i tetraplegici manifestano un uso lateralizzato superiore.

Nel quinto capitolo, l'utilità delle metodologie sviluppate e validate nei capitoli precedenti è stata valutata durante la riabilitazione studiando 31 pazienti paralizzati. I cambiamenti dell'attività degli arti superiori sono stati misurati e messi in relazione con gli esami clinici. I risultati dimostrano che le metodologie basate sui sensori portabili sono in grado di tracciare la guarigione clinica degli arti superiori. In una fase più avanzata della riabilitazione, la relazione tra gli esami clinici e le misurazioni dei sensori portabili è attenuata a tal punto che i pazienti tetraplegici raggiungono gli stessi livelli di attività degli arti superiori dei paraplegici indipendentemente dal loro handicap. Infine, i sensori portabili sono stati in grado di rilevare un’attività maggiore delle braccia e delle mani durante le ore della terapia rispetto alle ore al di fuori di essa.

In conclusione, questa tesi dimostra che le metodologie basate sui sensori portabili sono in grado di misurare l’attività degli arti superiori in concomitanza agli esami clinici standardizzati. Per questo motivo essi potrebbero essere utilizzati per quantificare la dose dell’attività degli arti superiori durante le terapie di riabilitazione. Inoltre, i sensori portabili forniscono ulteriori informazioni su come gli arti superiori vengono usati durante le attività della vita quotidiana. Nelle fasi più avanzate della riabilitazione questi forniscono informazioni supplementari sulla quantità dell’attività degli arti superiori al di là dell’attività che ci si può aspettare giudicando i risultati degli esami clinici. Questa tesi contribuisce al campo crescente dei sensori portabili per applicazioni di misurazioni a lungo termine dimostrandone la validità ed il significato clinico per persone paralizzate. I risultati sostengono l’utilizzazione di queste metodologie per monitorare le attività degli arti superiori durante la routine clinica, durante studi clinici e durate le cure ambulatoriali. Con questa conoscenza, le terapie e le strategie di riabilitazione potrebbero essere adattate all’intervenzione ed al paziente in modo da raggiungere una guarigione migliore migliorando la funzionalità muscolare e l’indipendenza dell’individuo.

1 General introduction

1.1 Cervical SCI

Spinal cord injury (SCI) involves a damage of nervous tissue within the spinal cord canal. The damage can occur following a traumatic contusion (e.g. motor vehicle accident) or a non-traumatic insult (e.g. ischemia) (McDonald and Sadowsky, 2002). Level of SCI is defined as cervical (neurologic level of injury C2 to T1) (Sunil, 2008a), thoracic (neurologic level of injury T2 to T11) (Wierbicky and Nesathurai, 2008) or lumbosacral (neurologic level of injury T12 to S4-S5) (Sunil, 2008b) depending on the location of the neural damage. Worldwide the incidence of SCI is 10-83 cases per million inhabitants per year (mean age: 33 years, male-female ratio: 3.8/1) and one-third of people suffering SCI have a cervical lesion (Wyndaele and Wyndaele, 2006).

The classification of the neurologic level of injury (NLI) is assessed according to the international standards for neurological classification of SCI (ISNCSCI), which it is used to determine the anatomical location of the spinal cord lesion by determining the most caudal intact sensory dermatome or myotome (Kirshblum et al., 2011a). Intact dermatomes have regular pinprick and light touch sensations (grade of two for each test). In the case of the myotomes, intact is defined as a score of at least grade three on the manual muscle testing provided that the segments above are intact. The spinal nerves C1-C7 emerge from the spinal canal above their associated skeletal level (vertebrae C1-C7). Starting from the spinal nerve C8, the neurologic and skeletal level of injury are different as the vertebra C8 do not exist. Therefore, spinal nerve C8 emerges from the spinal canal above vertebral level T1 but below vertebral level C7. Consequently, starting from the spinal nerve T1, the spinal nerves exit the spinal canal below their associated vertebrae (Figure 1.1). Along with the NLI, the ISNCSCI protocol assesses the extent of the lesion (i.e. completeness) according to the ASIA Impairment Scale (AIS) through some logical rules (Table 1.1). To be classified as incomplete, sensory or motor function should be preserved below the level of the injury or there must be some sacral sparing in the spinal cord sacral segment S4-S5 (Kirshblum et al., 2011a).

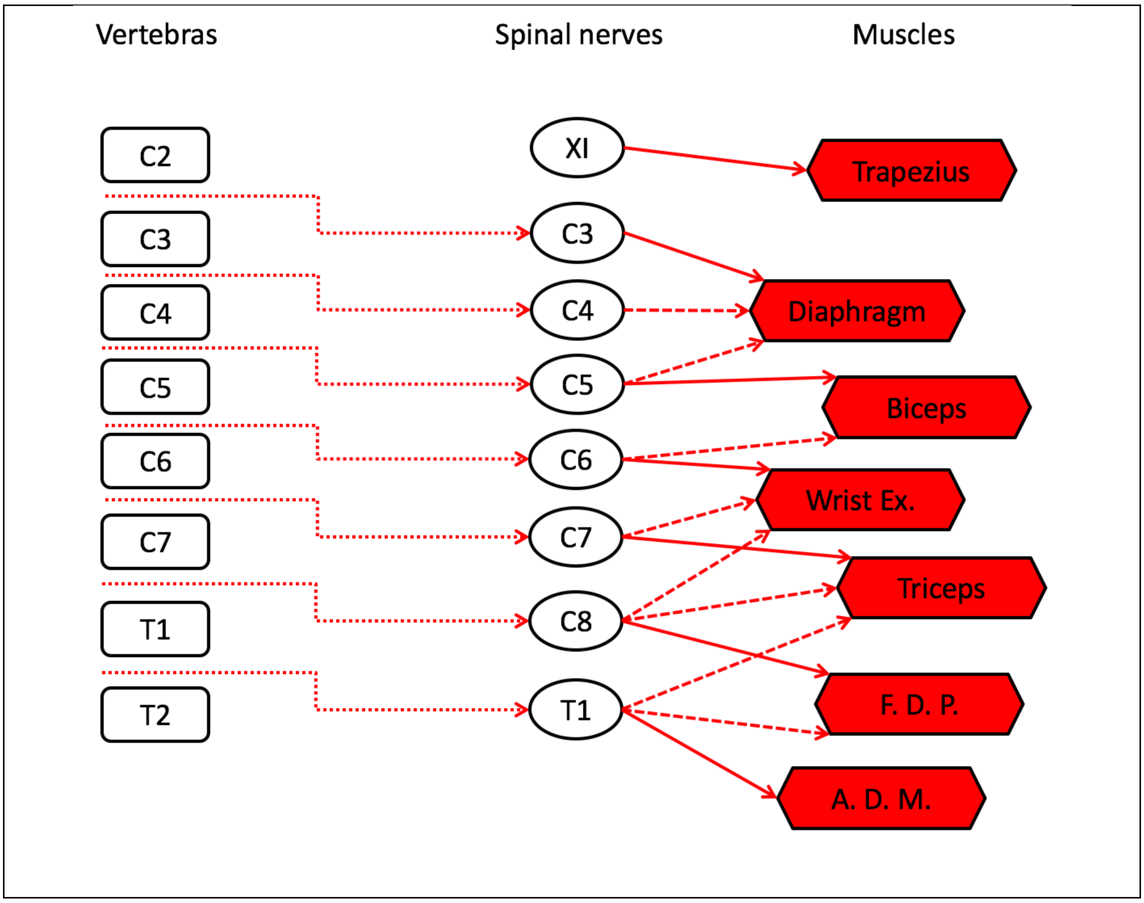

Figure 1.1. Overview on the neurologic and skeletal level of injury.

Spinal nerves are labelled with red dotted arrows. In the figure, the spinal nerves exit the spinal canal above (C3-C7) or below (T1-T2) their associated vertebra. Note that vertebral level C8 does not exist. As shown on the right, most muscles are innervated by different spinal nerves. The highest segment that innervated a particular muscle is labelled with a solid arrow, whereas lower segments that innervate the same muscle are represented by dashed arrows. Ex. = extensor; F. D. P. = Flexor Digitorium Profundus; A. D. M. = Abductor Digitorium Minimi. XI: the eleventh cranial nerve.

The symptoms of SCI are disorders of the autonomic nervous system, for example, bladder and bowel dysfunction, sensory impairment such as touch and proprioception, and muscle paralysis in the arms, trunk, and legs (Kirshblum et al., 2011a). This thesis focuses on cervical SCI (i.e. quadriplegia or tetraplegia) and the motor function of the upper limb (UL). Due to the segmental organisation of the spinal cord, the severity of muscle paralysis depends on the number of spinal nerves that are injured. Hence, the higher the NLI, the more spinal nerves are damaged and therefore the more functions are affected unless a zone of partial preservation exists or the lesion in not complete, in which case spinal nerves below the NLI may be intact. In contrast to dermatomes, which are innervated by a single spinal nerve, myotomes may be innervated by multiple spinal nerves. In the cervical region, this redundancy occurs through the plexus brachialis, which is a network of nerves composed of three trunks (upper, middle and lower trunk), which have their roots on multiple spinal nerves (C5-T1) and which split into multiple divisions (Figure 1.1). By way of illustration, the biceps is innervated from the upper trunk of the plexus brachialis, which originates from spinal nerve C5 and C6. In this case, a lesion of spinal nerve C6 will result in weakness of the biceps but not in a complete paralysis, as the nerve fibres of the spinal nerve C5 remain intact. In cervical SCI, the motor function of different segments is tested with a manual procedure called the manual muscle testing (MMT), which consists of the evaluation of the strength of individual muscles manually testing specific joint movements (i.e. testing muscle tonus, observing movement against gravity or applying resistance against movement) and grading the muscle function from 0 (total paralysis) to 5 (active movement against full resistance). The MMT is part of two SCI specific assessment protocols: the upper extremity motor scores (UEMS) of the ISNCSCI and the strength domain of the graded redefined assessment of strength, sensibility and prehension (GRASSP) (Kalsi-Ryan et al., 2012). Additionally, muscle function can be assessed with the hand held dynamometer (HHD), which is a device that measures isometric strength on a continuous scale (e.g. Newton) and may be used to replace the subjective judgment of assessors (Stoll et al., 2000). Table 1.2 displays motor impairments that result from various NLI.

Total or partial paresis of the UL has a significant impact on independence because in individuals with tetraplegia the sum of muscle strength of UL key muscles, according to the UEMS motor score, highly correlates with independence in self-care (Rudhe and van Hedel, 2009). Consequently, regaining partial arm and hand function may led to greater independence, hence increased quality of life (Anderson, 2004). In 2004, 500 individuals living with chronic SCI were asked to rank seven affected functions in order of importance to their quality of life. The data of this survey suggested that hand and arm function was the one that tetraplegic people would mostly like to regain (Anderson, 2004). Indeed, the same year in a different but similar survey, the majority of tetraplegic individuals thought that recovery of the arm and hand function, together with the recovery of control of bowel and bladder function, would make the most significant impact on quality of life (Snoek et al., 2004). Interestingly, 96.5% of participants indicated that exercise is an important aspect of functional recovery (Anderson, 2004). Hence, therapy of the UL in tetraplegics is of exceptional importance (Snoek et al., 2004). Rehabilitative plans for acute tetraplegics focus on adjustment issues after injury (e.g. emotional adjustment), mobility (e.g. wheelchair mobility and bed mobility), activities of daily living (ADL; e.g. feeding and dressing), and equipment needs for ADL (e.g. utensils with built-up handles and dressing equipment like dressing stick) (Kirshblum et al., 2007). This is because the primary goal of inpatient rehabilitation is to increase independence in a broad spectrum of physical skills (Whiteneck et al., 2011). This goal is achieved through physical therapy and occupational therapy, which when combined account for approximately 60% of the entire therapy time throughout the inpatient rehabilitation stay (Whiteneck et al., 2011).

Exercise not only improves independence but may help avoid numerous musculoskeletal complications, which include fractures due to large non-controlled movement in the full range of motion (e.g. elbow flexion and forearm supination fractures due to unopposed biceps activity) (Sunil, 2008a) and shoulder pain or rotator cuff problems such as impingement syndrome and rotator cuff tendinitis (Burnham et al., 1993, Bayley et al., 1987). The last one, in particular, may be prevented with wheelchair training exercising a circular propulsive stroke where the hand falls below the push rim after the stroke during the recovery phase (Boninger et al., 2005). These overuse syndromes are commonly seen in SCI subjects because this population relies entirely on their UL for ambulation (e.g. propulsion of a manual wheelchair) and on weight-bearing tasks such as transfers. However, the shoulder joint, with its greater range of motion and instability, is not designed for such strains (Apple et al., 1996).

Grade	**Extent of lesion**	**Rules**
A	Complete	Sacral segment S4-S4: no motor or sensory function preserved. Below the neurologic level: no motor or sensory function preserved.
B	Sensory incomplete, motor complete	Sacral segment S4-S4: no motor function preserved. Preservation or sparing of sensory function. Below the neurologic level: no motor function preserved. Preservation or sparing of sensory function.
C	Sensory incomplete, motor incomplete	Sacral segment S4-S4: sparing of sensory or motor function. Below the neurologic level: preservation of motor function, more than half of key muscles have a muscle grade less than 3.
D	Sensory incomplete, motor incomplete	Sacral segment S4-S4: sparing of sensory or motor function. Below the neurologic level: preservation of motor function, half or more than half of key muscles have a muscle grade of 3 or more.
E	Normal, no injury	No abnormalities in sensory and motor function (exception: abnormalities in reflex examination)

Table 1.1. Scoring of the AIS impairment scale.

Source: (Kirshblum et al., 2011a).

Level (NLI)	**Testable Innervated Muscles**	**Myotome's movements**	**Resulted UL impairment by complete lesion**	**Assessments**
T1	Finger abductors: - abductor digiti minimi	Finger abduction	Possible limitations in hand dexterity (Depending on the grade on the MMT the UL function may be fully intact)	GRASSP MMT, ISNCSCI UEMS
C8	Finger flexors: - flexor digitorum profundus	Finger flexion	Limitations in: - grasp release - hand dexterity	GRASSP MMT, ISNCSCI UEMS
C7	Elbow extensors: - triceps	Elbow extension, ulnar wrist extension, wrist flexion, finger extension, thumb flexion, extension and abduction	Limitations in: - grasp release - hand dexterity	GRASSP MMT, ISNCSCI UEMS, HHD elbow extension
C6	Wrist extensors: - extensor capri radialis longus - extensor capri radialis brevis	Radial wrist extension	Absence of: - elbow extension - wrist flexion - hand movements	GRASSP MMT, ISNCSCI UEMS
C5	Elbow flexors: - Biceps - brachialis	Shoulder flexion, abduction and extension, elbow flexion, forearm supination	Absence of: - elbow extension - elbow pronation - all wrist movements - all hand movements	GRASSP MMT, ISNCSCI UEMS, HHD elbow flexion

Level (NLI)	Testable Innervated Muscles	Myotome's movements	Resulted UL impairment by complete lesion	Assessments
C4	N/A	Shoulder shrug	Total paralysis of extremities Exceptions: shoulder elevation, retraction, downward rotation (Trapezius, XI)	N/A
C1-C3	N/A	Neck flexion, extension, rotation	Total paralysis of extremities and diaphragm Exceptions: shoulder elevation, retraction, downward rotation (Trapezius, XI)	N/A

Table 1.2. Simplified overview of the effect of NLI on key muscles and their related UL function.

UEMS: Upper Extremity Motor Score. ISNCSCI: International Standards for Neurological Classification of SCI. GRASSP: Graded and Redefined Assessment of Strength, Sensation and Prehension. MMT: manual muscle testing. HHD: hand held dynamometer. Source: (Kirshblum et al., 2011a, Mateo et al., 2015).

1.2 Activity based rehabilitative therapies

The primary goals of inpatient SCI rehabilitation include maximizing independence in a broad spectrum of physical skills such as bed mobility, wheelchair mobility, transfers, and ADLs (Taylor-Schroeder et al., 2011, Whiteneck et al., 2011). It has been shown that, compared to non-specialized rehabilitative programs, SCI specialized rehabilitative programs are superior in rehabilitative outcomes, reduced mortality, and reduced secondary complications, as specialized programs have better timing, higher therapy intensity, and longer therapy duration (Taylor-Schroeder et al., 2011). Recently, the relationship between treatment duration and the content of therapy to outcomes following SCI has been investigated, and researchers found that motor independence, according to the Motor Functional Independence Measure, was positively associated with more time spent in physical therapy (Teeter et al., 2012, Whiteneck et al., 2012). The positive association between length of treatment and independence may indicate that specialized SCI rehabilitation is designed to facilitate compensation of impairments and functional limitations (Teeter et al., 2012). This may occur at the expense of recovery of motor function, as the focus may be shifted toward the replacement of the impaired function (i.e. training compensation for deficit through equipment for ADL, such as using a fork with built in cuff) instead of the rehabilitation of motor function through neuroplasticity (Behrman et al., 2006), which may be induced by intense training of the lost function (Sadowsky and McDonald, 2009). It is believed that SCI rehabilitation may be influenced by scientific dogmas such as the impossibility of restoring damaged pathways (Curt and Dietz, 2005), which are justified by the fact that regenerative growth of damaged axons is extremely limited (Blesch and Tuszynski, 2009), and no effective treatment for human SCI currently exists (Alexander et al., 2009). Consequently, the compensation of motor function may be considered the most reasonable approach to regain independence. A shift in the rehabilitation paradigm, from compensation of deficit to regaining of function

(Behrman et al., 2006), may happen with advances in SCI treatments such as anti-Nogo (ATI-355) and neural stem cell transplant (HuCNS-SC) to name some that are currently conducted in clinical trial phase I and II in the European Multicentre Study About Spinal Cord Injury (EMSCI) (ATI-355 and HuCNS-SC, ClinicalTrials.gov identifier: NCT01321333 and NCT00406016). These advances in SCI treatments are not restricted to drugs (e.g. ATI-355) or biological material (e.g. HuCNS-SC) but may be achieved or combined with behavioural treatments such as activity-based restorative therapy (ABRT) (Sadowsky and McDonald, 2009).

ABRT, also referred to as activity-based therapies and activity-based rehabilitation, is a rather new approach that aims to increase the level of neurological activity to induce mechanisms of CNS plasticity, repair and regeneration (Sadowsky and McDonald, 2009). The volume and intensity of neurological activity may be increased with different approaches such as functional electrical stimulation, task-specific practice, and massed practice (Dolbow et al., 2015). The efficacy of ABRT is endorsed by several preclinical studies, which have shown some neuronal regenerative growth following this intervention (Brus-Ramer et al., 2007, Carmel et al., 2010, Maier et al., 2008, Song et al., 2016, Starkey et al., 2011, Starkey et al., 2014). By way of illustration, electrical stimulation, as a model for enhanced neurological activity of the UL, has been found to augment injury-induced plasticity after a complete lesion of one pyramidal tract below the ventral medulla, increasing the outgrowth of neurons from the contralateral into the ipsilateral denervated grey matter (Brus-Ramer et al., 2007, Carmel et al., 2010, Song et al., 2016). These models consisted in the electrical stimulation on the surface of the pyramid in the medullary region (Brus-Ramer et al., 2007), electrical stimulation of the motor cortex in the cerebral cortex (Carmel et al., 2010), and electrical stimulation of the motor cortex with co-activation of his target in the cervical enlargement in the spinal cord (Song et al., 2016). These mechanisms of plasticity are not restricted to electrical stimulation but may also be achieved with increased neurological activity induced by models of physical activity. Maier and co-workers showed that rats that underwent a unilateral pyramidal tract lesion showed growth across the midline at the cervical enlargement (C6–C8) after rehabilitative training of the affected forelimb done by forced limb use achieved by casting the spared limb (Maier et al., 2008). This region in the cervical enlargement is the part of the spinal cord where motoneurons innervate forelimb and paw muscles (McKenna et al., 2000), consequently, this growth of neurons suggests that voluntary activity may promote UL recovery. In a later study, Starkey et al. trained rats with two different task-specific training: either the single pellet grasping or the horizontal ladder task (Starkey et al., 2011). After receiving a unilateral pyramidotomy, the rats showed a significant increase in CST fibres that crossed the denervate grey matter at the midline, and more laterally, in the C2-T1 region, only after the training of the very demanding and complex single pellet reaching task. Interestingly, the gain in function was observed in both tasks, and in an additional new task that was not trained in both training groups, suggesting that different tasks may share the same recovered function and the same underlying motor program (Starkey et al., 2011). The results suggest that this fibres crossing is related to functional recovery, and that neuroplasticity may be induced by task unspecific physical activity. Further, Starkey and co-workers tested the effect of self-motivated motor training and task-specific training to functional improvements (Starkey et al., 2014). In this particular study, rats that received a thoracic bilateral hemisection were trained in two different training paradigms: self-motivated motor training in an enriched environment or skilled movement training such as pellet grasping and ladder walking. The study showed that rats that were housed in a complex natural habitat, enriched with self-training possibilities, outperformed rats that trained skilled movement task in functional abilities (Starkey et al., 2014). The results of this study suggest that self-motivated training leads to enhanced neurological activity that leads to functional recovery.

As outlined above, in preclinical research, it is well established that ABRT facilitates neurorehabilitation, yet in clinical research, studies that evaluate the effectiveness of exercise training in promoting recovery of UL function are lacking. Two recent reviews, which summarised evidence on the matter, suggested that training of the UL after cervical SCI seems to lead to improvements in muscle strength, UL function, ADL, and quality of life (Kloosterman et al., 2009, Lu et al., 2015). However, the authors discuss that the results are difficult to interpret. Two of the main factors that make interpretation difficult are the broad range of training methodologies, which differ in type, intensity, duration, and frequency, and the wide range of outcome parameters, which does not make it possible to perform a meta-analysis (Kloosterman et al., 2009, Lu et al., 2015). Neither review discusses the fact that the overall amount of UL activity, i.e., the activity that happened during and outside of therapy, was not assessed. This activity is indeed of crucial importance to the objective of improving function as pre-clinical research demonstrated that the amount of self-motivated motor training positively relates to functional outcomes (Starkey et al., 2014). Consequently, in order to avoid biased results, UL activity during self-training, leisure time, and therapy time, should be adequately and objectively assessed. Unfortunately, the assessment of UL activity outside of training sessions is often limited to subjective self-reported questionnaires that have been shown to overestimate the actual activity of the subject (van den Berg-Emons et al., 2011). In this context, advances in wearable sensors may offer a unique opportunity to monitor the type, quantity, and quality of UL activity round-the-clock (Dobkin and Dorsch, 2011). Similarly, wearable sensors may be used to evaluate UL rehabilitation efforts in clinical trials, which apply a behavioural treatment, such as ABRT, or other interventions such as drugs, cells and other biological products.

1.3 Wearable sensors and their applications in neurological conditions

“10,000 steps a day” is a slogan that has its roots in the late sixties / early seventies, when a research group led by Dr Yoshiro Hantano found that the amount of walking Japanese performed a day fluctuated between 3500 and 5000 steps (Tudor-Locke et al., 2008). The scientist assumed that doubling the steps to 10,000 a day would translate to burning approximately 300 Kcal a day through walking, resulting in a healthier lifestyle. Therefore, a pedometer named “manpo-key” (man = 10,000, po = step, kei = measure), developed by the Yamasa Corporation (Tokyo, Japan), began to be sold and became embraced by several Japanese walking clubs (Tudor-Locke et al., 2008).

Since then, the cut-off point of 10,000 steps a day has been endorsed by several authoritative and non-authoritative entities such as businesses in the fitness industry (Tudor-Locke et al., 2008). Wearable step counting devices are a straightforward and affordable means of tracking daily physical activity. Consequently, through observational studies, scientist-categorized physical activity cut-off points and public health guidelines based on steps/day for children and adolescents (Tudor-Locke et al., 2011b), adults (Tudor-Locke and Bassett, 2004, Tudor-Locke et al., 2011c, Tudor-Locke et al., 2008), and older adults. (Tudor-Locke et al., 2011a). For instance, Tudor-Locke and co-workers differentiated following cut-off points for several physical activity categories of healthy adults: sedentary (less than 5000 steps/day), low active (between 5000 and 7499 steps/day), somewhat active (between 7500 and 9999 steps/day), active (between 10000 and 12499 steps/day), and highly active (more than 12500 steps/day) (Tudor-Locke and Bassett, 2004). In a similar way, in the future, cut-off points based on wearable sensors may be produced for additional populations, such as the SCI community.

Recent advances in sensor technology such as increased battery runtime and hardware miniaturization allowed the implementation of additional sensing capabilities to wearable sensors. New sensing capabilities include, but are not limited to, three angular rate sensors, three accelerometers, and three magnetometers and provide additional monitoring benefit, which goes far beyond the objective quantification of total daily activity, which is often used to compare objectively performed physical activity to public health guidelines (Dobkin and Dorsch, 2011). Such wearable sensors, which are also called inertial measurement units (IMUs), combined with empirical approaches or trained algorithms are increasingly applied to monitor the quantity, the type, and the quality of activities in clinical research such as Parkinson disease and stroke (Dobkin and Dorsch, 2011).

In stroke, which is an injury to the brain caused by occlusion of a blood vessel (thrombotic or embolic ischemic stroke) or by a haemorrhage within the parenchyma of the brain (intracerebral haemorrhage) (Joel, 2008), wearable sensors have been mainly used to measure discrepancies between the motor capacity of the paretic UL and the non-paretic UL. The activity of the paretic UL can be compared directly (i.e. every second) or indirectly (i.e. at the end of a hours-long recording) to the activity of the non-paretic UL by measuring the quantity of impaired UL movement and divide it by the quantity of non-impaired UL movement (Bailey et al., 2014, Thrane et al., 2011, Uswatte et al., 2006, van der Pas et al., 2011). This ratio of impaired to non-impaired UL has been shown to correlate with clinical assessments such as the Actual Amount of Use Test and the Motor Activity Log (Uswatte et al., 2006, van der Pas et al., 2011), the Fugl-Meyer motor assessment of the most affected arm (Thrane et al., 2011), and motor capabilities according to the Action Research Arm Test (Bailey et al., 2015). Due to their suitability to capture movement characteristics related to stroke in multi-day recordings, wearable-sensor are starting to be used in clinical trials as the primary endpoint to decide whether there is an increase in arm use or daily walking after specific training interventions (Dorsch et al., 2015, Lemmens et al., 2014). For example, Lemmens et al. evaluated the change in the actual amount of arm use after an arm-training supported by a robotic device (Lemmens et al., 2014), whereas Dorsch et al. evaluated the change in daily walking time after training that provided quantitative feedback to the patients (Dorsch et al., 2015).

1.4 Wearable sensors in SCI

The use of wearable sensors in the daily life of someone suffering from SCI has not been established yet. One of the major challenges to the establishment of wearable sensors in SCI is that accelerometers are relatively expensive and require competent personnel to manage and manipulate the data in order to derive meaningful outcomes (Tudor-Locke et al., 2011c). For this reason, inexpensive pedometers are preferred in public health and clinical applications due to their simple step output that is readily available, displayed on a screen, and easily interpretable (Tudor-Locke et al., 2011c). Unfortunately, pedometers are not compatible with the majority of SCI subjects due to their dependence on a wheelchair for mobility. Consequently, the emerging step-based physical activity guidelines, such as the recommendations of the Ministry of Health Labour and Welfare of Japan, which recommends 8000 to 10000 step a day to promote health (Ishikawa-Takata and Tabata, 2007), can not be transferred to the SCI population.

SCI research has focused on developing and validating methodologies able to measure SCI specific movements such as wheeling (Coulter et al., 2011, Garcia-Masso et al., 2015, Hiremath et al., 2015, Hiremath et al., 2016, Ojeda and Ding, 2014, Postma et al., 2005, Sonenblum et al., 2012a, van der Slikke et al., 2015, Warms et al., 2008), test the feasibility of wearable sensors in real world recordings (Bussmann et al., 2010, Wilson et al., 2008), and observe physical activity (Nooijen et al., 2012, Sonenblum et al., 2012b, van den Berg-Emons et al., 2008). The clinical relevance of such studies is difficult to interpret because the measurements are usually conducted in the artificial and highly controlled laboratory setting, self-propulsion is not distinguished from attendant-propulsion, outcomes of wearable sensors are not put in clinical context (e.g. comparison to clinical assessments), measurements are not performed in standardised SCI timeframes, and the inclusion criteria are very narrow (e.g.

manual wheelchair user that can perform hand ergometer). One study used wearable sensor metrics as the primary outcome of a clinical trial, which investigated an intervention that aimed at changing the participants' behaviour toward a more active lifestyle (Nooijen et al., 2016). This primary outcome is used to measure general clinimetric proprieties, such as the change in physical activity, rather than ailment-oriented (disease specific) clinimterics proprieties such as muscle functioning (Fava et al., 2012). Consequently, the clinical ailment-oriented application of wearable sensors in SCI remains mainly unexplored. Table 1.3 summarises the methodologies described in the literature to measure SCI specific activities or movement characteristics (excluded are methods developed as part of this thesis). The list contains collected literature, regarding the use of wearable sensors (accelerometer and IMU) in SCI research, found using search engines such as PubMed from August 2012 to May 2016. Publications have been screened in order to decide whether they were considered relevant to the clinical study “Upper Limb Activity in Human SCI Rehabilitation” registered at the “ClinicalTrial.gov” register: NCT02098122. Additionally, the reference list of the selected articles has been manually searched for further relevant publications.

First and last author - Journal and year - Sample size	Study design and setting	Primary objective - Wearable sensors specification and placement - Additional assessments	Results/conclusion regarding wearable sensors - Clinimetric proprieties investigated
Postma – Stam, Spinal Cord, 2005. N = 10 SCI subjects. Five patients with poor triceps strength and five patients with good triceps strength.	Validation study. Standardised protocol: wheelchair propulsion and other propulsion activities. Patients performed each activity for 4 minutes. The measurement time was 45 min. Reference method: video recordings.	Objective: to detect hand-rim wheelchair propulsion and hand biking. Six uni-axial accelerometers attached to each thigh, to each wrist, and on the sternum. The sensors were connected to a data recorder (700g) with cables.	Hand-rim wheelchair propulsion can be validly detected in both groups. Agreement (92%), sensitivity (87%), and specificity (92%). No clinimetric proprieties investigated.
Wilson – Granat, Spinal Cord, 2008. N = 7 wheelchair-bound SCI subjects, 7 ambulant subjects, 5 healthy subjects.	Exploratory, feasibility study. 7 days of continuous monitoring in the free environment.	Objective: to explore the utility of the data collected by an activity monitor. Uni-axial accelerometer (20 g) attached to the wheelchair wheel or/and thigh. ActivPAL (PAL Technologies, Glasgow, UK).	The system was successfully used and provide useful information in a free-living environment. No clinimetric proprieties investigated.
Van den Berg-Emons – Stam, Archives of Physical Medicine and Rehabilitation, 2008. N = 40 SCI subjects.	Prospective cohort study. Measurements at the start of active rehabilitation, after three months after the start of the rehabilitation, at discharge, two months after discharge, and one year after discharge. Two consecutive weekday of recording (48h).	Objective: to assess changes over time in physical activity after SCI. Same activity monitor used by Postma et al. Metrics: duration of stationary and dynamic activities (e.g. manual wheelchair driving), average body motility (gravitational acceleration). Clinical assessments: binary group for plegia (tetraplegia: at or above T1, paraplegia: below T1) and binary group for completeness (complete: ASIA grade A and B, incomplete: ASIA grade C and D).	Overall, duration of dynamic activities increased significantly during inpatients rehabilitation and declined significantly after discharge. The level of lesion and completeness were determinant of the decline in physical activity after discharge. No clinimetric proprieties investigated.

First and last author - Journal and year - Sample size	Study design and setting	Primary objective - Wearable sensors specification and placement - Additional assessments	Results/conclusion regarding wearable sensors - Clinimetric proprieties investigated
Warm – Belza, Disability and Health Journal – 2008 N = 50 wheelchair-bound subjects (spinal cord injury, multiple sclerosis, brain injury, amputation, cerebral palsy, spina bifida, stroke, post-polio, and other neuro-muscular conditions)	Validation study. Seven days of real world recording.	Objective: to measure physical activity by means of wrist actigraphy and relate it to self-reported measures. Wrist worn tri-axial accelerometer. Metrics: AC, time spent in activities of various intensities. Physical activity assessment: physical activity record, Physical Activity Scale for Individuals with Physical Disabilities (PASIPD).	Wheelchair users do not meet health guidelines for physical activities. PASIPD and record scores of physical activity weakly correlated with daily AC, however not significantly. General clinimetric proprieties investigated.
Coulter – Granat, Spinal Cord, 2011. N = 14 SCI subjects.	Validation study. Indoor track and outdoor wheelchair skills course. Reference method: video recordings.	Objective: to validate a monitor system that measures wheelchair movements. Tri-axial accelerometer placed on the wheel (20 g). Metrics: wheel revolutions, absolute angle, distance travelled, duration of movements, and speed.	The methodology can accurately measure wheel revolutions (ICC > 0.999), absolute angle (ICC > 0.999), and duration of movement (ICC > 0.981) and is an objective tool for measuring wheelchair movements. No clinimetric proprieties investigated.
Sonenblum – Lopez, Medical Engineering & Physics, 2012. N = 2 able-bodied participants and 2 wheelchair user with SCI.	Validation study. Three test courses over multiple surfaces. Reference method: video recordings and 23m paths.	Objective: to validate a methodology for measuring manual wheelchair movement that can be applied to a variety of commercially available bi-axial accelerometers. Wheel-mounted tri-axial accelerometer. Additional input: wheel circumference. Metrics: binary label (moving vs. stationary), distance travelled.	Point-by-point and total time accuracy of distance travelled and moving labelling exceeded 90% in all tests. Accelerometers can accurately determine whether the wheelchair is moving, measuring the distance wheeled. No clinimetric proprieties investigated.

First and last author - Journal and year - Sample size	Study design and setting	Primary objective - Wearable sensors specification and placement - Additional assessments	Results/conclusion regarding wearable sensors - Clinimetric proprieties investigated
Sonenblum – Lopez, Rehabilitation Research and Practice, 2012. N = 28 manual wheelchair user (SCI subjects and participants with different diagnoses)	Observational study. 1-2 weeks of real world recording.	Objective: to describe how people move about in manual wheelchairs during everyday life. Wheel-mounted tri-axial accelerometer and seat occupancy switch. Metrics: daily distance (km), daily time moving (min), bouts per day, occupancy time (hours), percentage mobile, bouts per occupancy hour, and various bout metrics.	Participants wheeled in average 1.6 km a day over 54 minutes. Participants spent 10% of their occupancy time, which was 11 hours a day, wheeling. Seven days of recording are needed to achieve a reliability of 0.8 for all bout variables. No clinimetric proprieties investigated.
Bussmann – van den Berg-Emons, Spinal Cord, 2010. N = 10 SCI subjects	Experiments study. 7 days of real world recording. Reference method: rotation counter.	Objective: to assess the effect of wearing an activity monitor on the amount of manual wheelchair propulsion during daily life. Same activity monitor used by Postma et al.	Wearing the activity monitor does not influence the amount of daily manual wheelchair propulsion. No clinimetric proprieties investigated.
Nooijen - van den Berg-Emons, Spinal Cord, 2012. N = 42 SCI subjects.	A prospective cohort study. Measurements at the start of active rehabilitation, after 3 months after the start of the rehabilitation, at discharge, and 1 year after discharge. 48h of consecutive weekdays recording. Single maximal wheelchair exercise test.	Objective: to relate everyday physical activity to physical fitness and lipid profile. Three-axis accelerometers attached to each wrist to the sternum. Metrics: duration of wheeled physical activity and sedentary daytime, and average body motility (gravitational acceleration).	Increase in physical activity was significantly related to increase in physical fitness and therefore with a lower risk of cardiovascular disease. Increase in physical activity was not related with muscle strength.

First and last author - Journal and year - Sample size	Study design and setting	Primary objective - Wearable sensors specification and placement - Additional assessments	Results/conclusion regarding wearable sensors - Clinimetric proprieties investigated
		Other assessments: - physical fitness: aerobic capacity (peak oxygen uptake), peak power output (POpeak) - Blood lipid profile - UL muscle strength (hand held dynanometer)	General clinimetric proprieties investigated. Ailment-oriented clinimetric proprieties partially investigated.
Ojeda – Ding, BioMed Research International, 2014. N = 26 SCI subjects.	Validation study. Several trials of propelling the wheelchair on two different surfaces. Reference method: SMARTWheels (Three Rivers Holdings, LLC) and video recordings.	Objective: to estimate temporal parameters of wheelchair propulsion. Triaxis accelerometers placed on the upper arm, wrist, and under the wheelchair. Metrics: stroke number, push frequency.	Reasonable accuracy especially using the accelerometer placed on the upper limb for stroke number (ICC = 0.994) and push frequency (ICC = 0.916). No clinimetric proprieties investigated.
Hiremath – Ding, Medical Engineering & Physics, 2015. N= 45 SCI subjects.	Validation study. Structured laboratory, semi-structured National Veterans Wheelchair Games, and unstructured home environments. In all the environments the participants performed 10 standardised physical activities lasting 6 min that vary in levels of intensity. Reference method: protocol.	Objective: to validate an algorithm (machine learning technique) to detect wheelchair based activities. Two-axis gyroscope secured to the spokes, tri-axial accelerometer worn on the participant's right upper arm or wrist.	Overall classification accuracies were 89.3% for the sensor worn on the upper arm and 88.5% for the sensor worn on the wrist. No clinimetric proprieties investigated.

First and last author - Journal and year - Sample size	Study design and setting	Primary objective - Wearable sensors specification and placement - Additional assessments	Results/conclusion regarding wearable sensors - Clinimetric proprieties investigated
van der Slikke – Veeger, Journal of Biomechanic, 2015. N = 20 wheelchair basketball players (condition not know)	Validation study. Several laboratory agility tracks. Reference method: 3D infrared motion capture system.	Objective: to assess the reliability of a three inertial measurement unit (IMU) configuration to estimate wheelchair kinematics in wheelchair basketball match-like conditions. 3 IMUs placed on the frame's rear axis and on each wheel axis.	Except for brief moments of wheel skidding in truly vigorous tests, IMU based estimation of wheelchair kinematics provided reliable results: linear speed (ICC > 0.90), rotational speed (ICC > 0.99), and instantaneous rotation centres (ICC > 0.90). No clinimetric proprieties investigated.
Nooijen - van den Berg-Emons, Journal of Physiotherapy, 2016. N = 42 SCI subjects.	Randomised, controlled trial. 4 days of real world recording, two months before discharge, at discharge, and 6 and 12 months after discharge.	Objective: to test if a behavioural intervention promotes an active lifestyle after discharge. Three-axis accelerometers attached to each wrist and to the sternum. Metrics: duration of wheeled physical activity and sedentary daytime, and average body motility (gravitational acceleration).	The behavioural intervention was effective in promoting an active lifestyle according to wheeled physical activity. No clinimetric proprieties investigated.
García-Massó - Garcia-Casado, Spinal Cord, 2015. N = 20 paraplegic subjects (SCI and multiple sclerosis)	Validation study. Laboratory. The participants performed 10 physical activities for 10 min each. Reference method: protocol.	Objective: to validate classification algorithms to identify the activity type performed by manual wheelchair users with spinal cord injury. Four accelerometers placed on both wrists, chest and waist.	Individual activities were classified with lower classification accuracy (55–72.5%) whereas grouped activities were classified with high accuracy (83.2–93.6%). Best performance was obtained from four accelerometers. No clinimetric proprieties investigated.

First and last author - Journal and year - Sample size	Study design and setting	Primary objective - Wearable sensors specification and placement - Additional assessments	Results/conclusion regarding wearable sensors - Clinimetric proprieties investigated
Hiremath – Ding, Archives of Physical Medicine and Rehabilitation, 2016. N= 45 SCI subjects.	Validation study. Structured laboratory, semi-structured National Veterans Wheelchair Games, and unstructured home environments. In all the environments the participants performed 10 standardised physical activities lasting 6 min that vary in levels of intensity. Reference method: protocol.	Objective: to validate energy expenditure estimation models for manual wheelchair users with SCI. Two-axis gyroscope secured to the spokes, tri-axial accelerometer worn on the participant's right upper arm or wrist. In addition to this study, this research group published several article on the estimation of energy expenditure through wearable sensors in SCI. The researchers examined the validity of different accelerometers-based methodologies to estimate energy expenditure in SCI individuals such as proprietary commercially available algorithms (Hiremath and Ding, 2011), regression equations (Hiremath et al., 2012), and a combination of pattern recognition and machine learning algorithms (Hiremath et al., 2013, Tsang et al., 2015). All the publication are similar in their design and aims, which are the evaluation and validation of methodologies to estimate energy consumption.	Energy expenditure was estimated in 10 standardised daily activities with moderate to high ICC. Overall ICC was 0.81 for the accelerometer worn on the upper arm and 0.89 for the one worn on the wrist. No clinimetric proprieties investigated.

Table 1.3. Summary of the methodologies described in the literature to measure SCI specific activities or movement characteristics. Source: (Bussmann et al., 2010, Coulter et al., 2011, Garcia-Masso et al., 2015, Hiremath et al., 2015, Hiremath et al., 2016, Nooijen et al., 2012, Nooijen et al., 2016, Ojeda and Ding, 2014, Postma et al., 2005, Sonenblum et al., 2012a, Sonenblum et al., 2012b, van den Berg-Emons et al., 2008, van der Slikke et al., 2015, Warms et al., 2008, Wilson et al., 2008). (ICC) intraclass correlation coefficients.

1.5 ReSense: long-term activity monitor for patients with neurological conditions

The ReSense is a miniature low-power sensor with 10 degrees of freedom, which are a three-axis accelerometer, a three-axis gyroscope, a three-axis magnetometer, and a barometric pressure sensor. The ReSense was developed as part of a PhD thesis in 2011 for long-term monitoring (Leuenberger and Gassert, 2011). At the time, there was a lack of commercial hardware that could be used by scientists to write specific algorithms to analyse the motor behaviour of neurological patients in their daily environment and so ReSense was developed to address this shortcoming (Leuenberger, 2015). ReSense has many advantages over commercial devices: firstly, the ability to access raw data allowing the development of analysis algorithms for specific patient populations (e.g. SCI or stroke); and secondly, the ability to synchronise multiple modules enabling the placement of several sensors in positions needed to measure specific activities (e.g. sensor placed on the wheel to measure wheeling).

In 2014, Moncada-Torres and co-workers developed an algorithm that used the output of several ReSense modules, which were worn on each wrist, ankle, and on the trunk, to classify 16 ADL, which was a larger amount of activities compared to similar works (Moncada-Torres et al., 2014). The algorithm was trained and tested on six healthy subjects under laboratory conditions and performed better when the output of the wrist module was used, achieving overall classification accuracy rates of up to 93% (Moncada-Torres et al., 2014). Since this publication, ReSense has been used in different set-ups and neurological conditions.

In stroke, Leuenberger et al. developed an algorithm able to classify walking, out of several daily activities, testing 24 stroke patients in an indoor and an outdoor setting using the same sensor placement as Moncada-Torres and co-workers (Leuenberger et al., 2014, Moncada-Torres et al., 2014). The methodology consisted of a support vector machine classifier that classified walking and other daily activities, and a k-nearest neighbour classifier that subsequently classified stair ascent, level walking and stair descent. The algorithm reached the highest overall performance, with sensitivity and specificity values above 90%, using the input of the sensor units placed on both shanks and the trunk. Interestingly, the highest classification performance of a single module set-up was achieved with the module placed on the unimpaired shank, rather than with the module placed on the waist, as reported early by several studies on healthy and elderly subjects. The authors discuss that a condition-specific sensor placement may be beneficial for classification performance (Leuenberger et al., 2014). Detecting walking in stroke may be valuable in order to exclude walking phases to reliably assess activity levels in patients with lower UL function, as the measured UL activity may be overestimated due to arm swing during walking (Leuenberger et al., 2016). In a later study, Leuenberger and co-workers measured 10 subacute and chronic stroke patients for 48 h and compared AC of the paretic UL with the results of the Box and Block Test, which is a test that evaluates functional arm movements in stroke. The researchers found that when walking phases were excluded using the previously mentioned algorithm (Leuenberger et al., 2014), paretic UL activity correlated significantly better with the Box and Block Test compared to when walking phases were not excluded. The relationship was similar if paretic UL activity was calculated with a new methodology that counted UL activity only if the movement reached a significant magnitude and occurred around the sagittal plane and above the waist. In this way, paretic UL movements during ambulatory activities were not counted. Consequently, a single-sensor set-up may be used, increasing measurement simplicity and patient compliance (Leuenberger et al., 2016).

ReSense applications in SCI are reported in chapters 2 to 5 of the present thesis.

The successful integration of ReSense (hardware and methodologies) into several clinical research fields prompted Prof Armin Curt, Prof Roger Gassert, and Prof William Taylor to start the project “ZurichMOVE” (van der Haar, 2015), which aims to accelerate the development and implementation of wearable sensors into clinical routine and their application in clinical trials.

1.6 Thesis aims

Despite the vast availability of wearable sensors, UL activity in cervical SCI subjects remains poorly investigated. The goal of the present thesis was to evaluate spontaneous changes in upper limb activity using IMUs after human SCI. Such recordings may complement information from clinical assessments increasing the resolution and the objectivity. In order to achieve this goal, the thesis has been divided into three distinct aims.

The first aim was to develop and redefine data analysis methods specific for SCI subjects. More specifically, the goal was to develop an algorithm capable of differentiating self-propulsion from attendant-propulsion (second chapter) and to validate methodologies capable of assessing the prevalence of limb-use laterality in SCI subjects (third chapter).

The second aim was to evaluate the clinical application of wearable sensors in SCI. More specifically, the goal was to assess whether sensor metrics such as AC were related to scores of clinical outcome such as the GRASSP MMT (third and fourth chapter).

The third aim was to objectively measure the change in UL activity in tetraplegic and paraplegic subjects during SCI rehabilitation using the validated methodologies (fifth chapter) within three standardised time windows, specifically the acute I (one month), acute II (three months), and acute III (six months) time windows of the EMSCI.

1.7 Thesis outline

This thesis is organised with the following structure. As stated in the previous section, the second and third chapter provide the methods that have been developed and validated to measure wheeling kinematics and assess UL usage. These methods have been published in Medical Engineering & Physics and in the Journal of Neurotrauma, where the final publications are available. In addition to the validation of the methodology to assess UL use in SCI, the third chapter presents a first evaluation of the clinical application of these recordings. The clinical application of wearable sensors in SCI is further analysed in the fourth chapter in a multi-day recording. This analysis has been submitted to the Journal of Neurotrauma and is presented here in the pre-print version. Further, the fifth chapter evaluates the feasibility of the methods validated in the previous chapters in tracking UL activity during SCI recovery. This evaluation has been submitted to Frontiers in Neurology and is presented here in the pre-print version. The final chapter of this thesis discusses the accumulated findings in a broader context, highlighting clinical implications, and drawing general conclusions. Finally, areas for further research and consideration for clinical trials are formulated in the outlook section.

2 A novel algorithm for detecting active propulsion in wheelchair users following spinal cord injury[1]

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Detailed statement of individual contribution to this article. The study was designed by Werner Popp and Michael Brogioli supported by the co-authors. The manuscript was written by Werner Popp and Michael Brogioli and revised by the co-authors. The algorithm was written by Werner Popp. Data was analyzed by Werner Popp supported by Michael Brogioli. Michael Brogioli was responsible for data collection.

2.1 Abstract

Physical activity in wheelchair-bound individuals can be assessed by monitoring their mobility as this is one of the most intense upper extremity activities they perform. Current accelerometer-based approaches for describing wheelchair mobility do not distinguish between self- and attendant-propulsion and hence may overestimate total physical activity. The aim of this study was to develop and validate an inertial measurement unit based algorithm to monitor wheel kinematics and the type of wheelchair propulsion (self- or attendant-) within a “real-world” situation. Different sensor set-ups were investigated, ranging from a high precision set-up including four sensor modules with a relatively short measurement duration of 24 hours, to a less precise set-up with only one module attached at the wheel exceeding one week of measurement because the gyroscope of the sensor was turned off. The “high-precision” algorithm distinguished self- and attendant-propulsion with accuracy greater than 93% whilst the long-term measurement set-up showed an accuracy of 82%. The estimation accuracy of kinematic parameters was greater than 97% for both set-ups. The possibility of having different sensor set-ups allows the use of the inertial measurement units as high precision tools for researchers as well as unobtrusive and simple tools for manual wheelchair users.

2.2 Introduction

Regular physical activity is associated with positive health benefits following spinal cord injury (Washburn and Hedrick, 1997), but only 13-16% of affected individuals report being physically active (Nash, 2005). Wheelchair propulsion is one of the most intense activities performed by wheelchair-bound individuals, and the measurement of wheelchair mobility has therefore been proposed as a means of estimating and tracking physical activity in these individuals. Such activity measurements could be powerful tools to monitor rehabilitation progress and motivate these individuals to maintain an active lifestyle. Wheelchair mobility can be quantified through direct observation, questionnaires, satellite navigation systems, specialized wheel modifications (e.g. SmartWheel, Three Rivers Holdings LLC) or through accelerometers mounted to the wheels. Direct observation is a valid approach but it is not practicable in long-term settings as it requires that the subject is followed with a video camera for the entire recording and involves intensive post processing to label the videos. Questionnaires require less effort but are rather subjective due to the individual (possibly biased) perception of subjects making it difficult to objectively quantify mobility. Furthermore, well-established questionnaires regarding wheelchair mobility used in clinical set-ups such as the SCIM III (Itzkovich et al., 2007) do not reflect mobility in terms of physical activity but rather in terms of independence. A more objective way of describing mobility is to use a global positioning system (GPS) as described by Sindall et al. in a sport application (Sindall et al., 2013). However, one major drawback is the dependence on the availability of GPS signals via satellites and therefore indoor applications that likely reflect the majority of daily activities are challenged.

Dedicated wheelchair activity measurement devices such as the SmartWheel are very powerful tools, allowing the collection of not only kinematic parameters, but also interaction forces with the wheelchair push-rims. The SmartWheel has already been used in several studies, for example to investigate start-up and steady state velocity in experienced wheelchair users (Lawrence et al., 1997), or to investigate push frequency and stroke length in manual wheelchair users with SCI (Cowan et al., 2008). Although the SmartWheel is a very promising and powerful tool to measure wheelchair mobility, it is a costly solution that requires a mechanical modification of the wheelchair that might affect the dynamic behaviour (e.g. through increased weight and a shift in the centre of mass). Furthermore, it may not be applicable to subjects that need wheelchairs adapted to specific morphological characteristics (e.g. wheels with larger diameters), or that employ multiple wheelchairs (athletes).

A simpler approach to track mobility in manual wheelchair users is through the use of inertial sensors. In order to describe mobility in terms of distance travelled, velocity or number of wheel revolutions the angular velocity can be estimated through the use of accelerometers attached to the wheel (Coulter et al., 2011, Sonenblum et al., 2012a). This method has demonstrated a high accuracy of the estimated kinematic parameters such as distance travelled and has already been used for long-term monitoring (Sonenblum et al., 2012b). Whilst describing mobility and thus physical activity in terms of e.g. distance travelled is a good approach it has one major drawback, namely that it overestimates the mobility produced by the wheelchair user because it does not distinguish between the user moving the wheelchair himself ("self-propulsion") and being pushed by someone else ("attendant-propulsion"). The alternative is to use accelerometers attached to the upper extremity of the user to detect manual wheelchair propulsion. For example, during standardised mobility-related activities, Postma and co-workers were able to detect hand-rim wheelchair propulsion with a high accuracy, sensitivity and specificity (Postma et al., 2005). However, an estimation of wheelchair mobility based purely on activity measurements at the upper extremity might be misrepresented by upper limb activities unrelated to wheeling. Furthermore, complementary inertial sensors such as gyroscopes might provide a more accurate measure of wheel kinematics, as they directly measure angular velocity. In this direction, Hiremath and colleagues combined the two aforementioned approaches and showed that a multimodal system, consisting of a two-axis gyroscope fixed to the spoke of the wheel and multiple tri-axial accelerometers fixed to the upper extremity, were able to detect wheelchair activities (e.g. self-propulsion) with higher accuracy than with the individual components alone (e.g. only the accelerometers) (Hiremath et al., 2015). Although the system has been tested in a structured laboratory, semi-structured organizational and unstructured home environments (real-world), for the cross validation the three datasets were mixed together which limited the generalization (approximated to the real world) of the study's results.

The aim of this study was to develop and validate an algorithm to continuously monitor the type of wheelchair propulsion (self- or attendant-propulsion) and wheel kinematics using an enhanced inertial measurement unit (IMU) (Leuenberger and Gassert, 2011) within a “real-world” situation. Similar to the methodology used by Hiremath and co-workers (Hiremath et al., 2015), the algorithm fuses two approaches, i.e. using accelerometers attached to the human body to detected manual wheelchair propulsion (Postma et al., 2005) and accelerometers attached to the wheel to estimate kinematic parameters such as wheel revolutions, angular velocity or distance travelled (Coulter et al., 2011, Sonenblum et al., 2012a) and further allows the precise detection of wheeling phases and the distinction of self-propulsion from attendant-propulsion. The algorithm consists of two components, the first detects if the wheelchair was moved based on heuristic rules and the second component then determines whether the wheelchair was moved by the user itself based on a support vector machine (SVM) classifier. Six different sensor set-ups were investigated, ranging from a high precision measurement tool set-up involving multiple sensor modules and a relatively short measurement duration (around 1 day) where gyroscope data is included to a simple, less precise set-up with only one sensor module and an increased measurement duration exceeding one week (without gyroscope). In addition to kinematic parameters, the algorithm determines the percentage of wheelchair use which can be attributed to self-propulsion. The results obtained by this new approach provide a better insight into the effective mobility behaviour of wheelchair users, and the algorithm is especially suited for application both in acute in-patient rehabilitation through to discharge into the home environment (out-patient situation), and hence can provide information about mobility as patients progress from learning to use the wheelchair to eventually integrating the wheelchair into their activities of daily living.

2.3 Methods

2.3.1 Subjects

Seven paraplegic (age 61.85 ± 16.93 years, six male, one female, ASIA A, C and D) and 14 tetraplegic (age 38.71 ± 14.84 years, 12 male, two female, ASIA A-D) subjects in the chronic stage (at least 90 days post-injury) with traumatic SCI were recruited for this study. Inclusion criteria required that subjects were 18 years or older and were trained to use a manual wheelchair. Exclusion criteria were any neurological disorders, orthopaedic or rheumatological diseases affecting the upper limb (other than SCI) and pre-morbid or on-going major depression. Each participant provided written informed consent after having the experimental procedure explained to them. The measurements took place at the University Hospital Balgrist and the Swiss Paraplegic Center in Nottwil. The study was approved by the ethics committees of the cantons of Zurich (KEK-ZH 2013-0202) and Lucerne (EK 13018).

2.3.2 Measurement device

For this study an enhanced version of the ReSense module was used (Leuenberger and Gassert, 2011) (Figure 2.1). The new ReSense module is a miniature 10-degrees-of-freedom (DOF) IMU designed for long-term monitoring of human motor activities. It consists of a 3-axis accelerometer (ADXL345, Analog Devices), a 3-axis gyroscope (ITG-3050, InvenSense), a 3-axis magnetometer (MAG3110, Freescale) and a barometric pressure sensor (BMP 085, BOSCH). The electronics board is encased in a robust, water-resistant and biocompatible plastic housing. ReSense weighs 15g (including the battery and housing), measures 36x29x13mm^3 and can continuously record data for over 24h at a 50Hz sampling rate. An integrated power-management system can increase the operating time by a factor of 2-3. In addition, deactivation of the gyroscopes increases the operating time to 20 days. The collected data, which includes an absolute time stamp, is stored on an internal 2GB microSD card. An advantage of the ReSense is the possibility to synchronize the on-board clock across different modules with a host PC via a custom-built USB base station.

Figure 2.1.

A: Attachment of the sensor modules to the subject. One module is attached at each wrist, and an additional module is attached at the chest. The fourth ReSense module is attached to the wheel of the wheelchair B: Module worn at the wrist with the AlphaStrap Blue and Velcro Straps fixation. C: Custom made fixation plate for the wheel module.

2.3.3 Data collection

Participants were equipped with four ReSense modules (Figure 2.1) for up to six hours. One module was worn on each wrist, attached with AlphaStrap Blue (North Coast) and Velcro Straps (Velcro). The chest module was attached with a custom-made chest strap (BalgristTec AG, Switzerland). The fourth sensor was fixed between the spokes of the wheelchair using a custom-designed fixation (Figure 2.1). The subjects, who were all in-patients, were asked to carry on with their daily clinical routine during the entire duration of the measurement. In order to validate the algorithm, a video camera (GoPro Hero HD 2, GoPro Inc.) was attached to the back of the wheelchair to film the right wheel only. The frame rate of the camera was set to 30fps and it was synchronized with the ReSense modules prior to the recording.

To assess the accuracy of estimating the kinematic parameters with the wheel sensor two additional healthy subjects (age: 28.5 ± 2.12 years, both male) completed three pre-defined indoor courses and three outdoor courses set at Balgrist University Hospital. The courses were each completed two times and the subjects propelled the wheelchair at a self-selected speed. In addition to the measurement set-up described above, four additional sensors were attached at different distances from the center (5, 10, 15, 20cm) of the right wheel in order to identify the influence of sensor position. The indoor courses were performed along a straight corridor, and consisted of forward and backward segments during which the subjects had to travel in total 20m (20m forward), 20m (2x 5m forward and 5m backward) and 30m (10m forward, 5m backward and 15m forward, Figure 2.2). The outdoor measurements were performed on a 300m athletic track and subjects completed one, two and three laps (Figure 2.2).

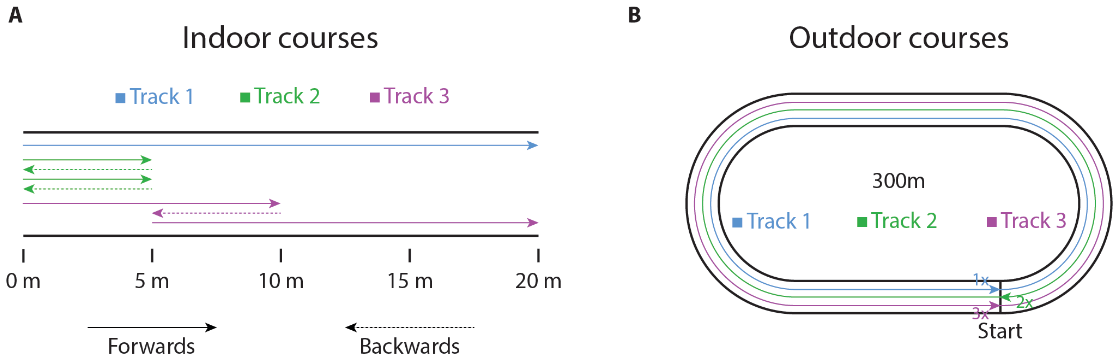

Figure 2.2. Illustration of the indoor and outdoor courses.

A: Indoor courses consisting of three different tracks with forward and backward segments. B: Outdoor courses with a length of 300m, 600m and 900m. The 600m long track 2 was performed in the opposite direction. For illustration purposes, the tracks are offset.

2.3.4 Data analysis and classification

The complete data processing, training of the SVM classifier and statistical analysis was performed using MATLAB R2013a (The MathWorks Inc). All processing steps were conducted offline.

In total three different sensor set-up combinations were investigated and trained. Set-up I included raw data from all four ReSense modules and was designed to be a high precision configuration. For set-up II, only raw data from three of the sensor modules were included in the analysis (left and right wrist and wheel sensor module). This set-up configuration was chosen because some of the participants complained about discomfort with the chest sensor module. The last set-up (Set-up III) contained only raw data from the wheel sensor module. The inclusion of this set-up was motivated by the fact that three sensor modules attached to body may disturb the user during certain activities of daily living and hence we wondered how accurate the data would be if only the wheel module were used. For each of the set-ups data was analysed separately once with the gyroscope data included (a) and once without the gyroscope data (b). The omission of the gyroscope recordings increases the operating time of our sensor modules from 2–3 days up to 20 days, which would be beneficial for long-term monitoring.

The final algorithm is split up into two different parts (Figure 2.3). The first part detects if the wheelchair was in motion by applying heuristic rules to the pre-processed data from the wheel module and the second part divides the wheelchair propulsion in active and passive phases by applying, depending on the selected set-up, different SVM classifiers.

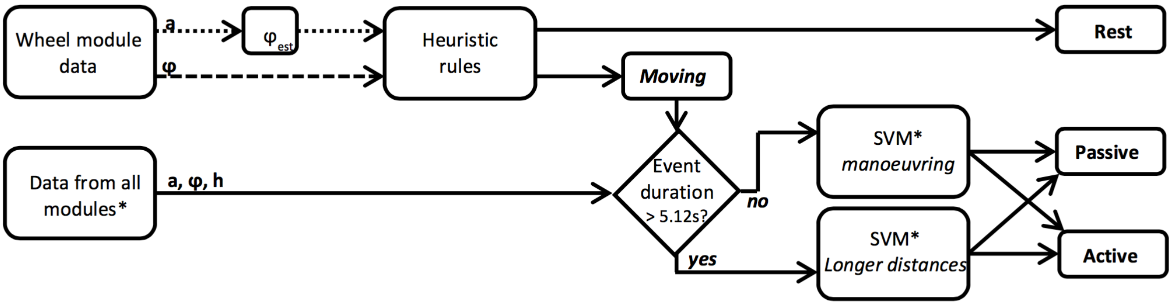

Figure 2.3. The flow chart of the presented algorithm.

First a classifier using heuristic rules identifies if the wheelchair was moving or not based on the angular velocity of the wheel. The angular velocity of the wheel can, depending on the set-up, be taken directly from the gyroscope of the wheel (dotted line) or estimated though the acceleration signal of the wheel sensor (dashed line). Then the data which was previously labelled as moving is separated into manoeuvring and longer wheeling distances. Depending on the set-up, acceleration (a), angular velocity (ϕ) and altitude (h) is fed into the support vector machine classifiers which distinguish between active and passive wheelchair motion. (* indicates the dependency from the specific set-up)

Labelling: The synchronized videos were labelled by two different raters with an inter-rater agreement of 0.99. A video editing tool (AVS Video Editor, Online Media Technologies Ltd.) was used for video labelling and the raters were asked to identify if the wheelchair was at rest, if it was moved passively ("attendant-propelled") or if it was moved actively ("self-propelled"). The only instructions the raters received were that wheelchair movement meant that the wheel should make at least a quarter turn. Furthermore, if the participant was not sitting in the wheelchair or if, due to the camera position, it was impossible to identify what the participant was doing, the activity was removed prior to the analysis.

Pre-processing: Data stored on the microSD cards of the ReSense modules were transferred to a PC via a custom made Basestation. The recordings from the modules were resampled at

50Hz using a cubic spline interpolation function. This step was necessary to ensure that all sensors had the same number of samples and that the data was temporally aligned.

Detection of wheelchair movement: For the detection of wheelchair movement, the angular velocity of the wheel was taken. For the set-ups I.a, II.a, III.a where the gyroscope data was included in the analysis, the angular velocity of the wheel was directly estimated through angular velocity of the wheel module (z-axis of the 3D gyroscope). The angular velocity was filtered using a 4th order Butterworth high-pass filter with a cut-off frequency of 0.3Hz. For the set-ups without gyroscope data (I.b, II.b, III.b) the angular velocity of the wheel was estimated using previously described methods (Coulter et al., 2011, Sonenblum et al., 2012a) where the gravity acting on the accelerometer is used to calculate the absolute angle of the wheel and therefore the angular velocity. The approach from (Sonenblum et al., 2012a) suggests a second order Butterworth low-pass filter with a cut-off frequency of 3.1Hz to filter the acceleration signals in order to measure wheelchair speeds up to 3 m/s. For higher angular velocities the presented filter design did not work. For angular velocities of around 500°/s and higher (=9.4 km/h with a wheel diameter of 0.6m), which can easily be achieved by wheelchair athletes, the centrifugal acceleration dominated the measured acceleration signals. Therefore, we changed the filter design proposed by Sonenblum and co-workers (Sonenblum et al., 2012a) to a second order Butterworth band-pass filter with lower and higher cut-off frequencies of 0.5 and 3.1Hz, respectively, as soon as the wheelchair starts moving. For a detailed description of the procedure used to estimate the angular velocity of the wheel, the reader is referred to the work of Sonenblum and colleagues (Sonenblum et al., 2012a).

To detect if the wheelchair was moving or not a threshold of 0.4°/s was applied to the angular velocity to identify possible movement windows. In order to classify such phases as a valid movement of the wheelchair the following rules were applied to each window separately:

- The angular velocity had to reach 10 deg/s at least once.
- The wheel rotation had to be at least 80 deg.
- The duration of a movement window had to be greater than or equal to 2s.

Finally, two consecutive windows were merged if they were separated by less than 2s. The events classified as "moving" were then used in the next step to distinguish between active and passive propulsion.

Pre-processing for the classifier: The different filters applied to the resampled signal are mostly based on previous work (Moncada-Torres et al., 2014). Firstly, the acceleration signal was filtered with a median-filter with a window size of 3 samples. Subsequently, the acceleration signal was passed through an infinite impulse response eight order elliptic low-pass filter with a cut-off frequency of 0.3Hz, a passband ripple of 0.02dB and a minimum stopband attenuation of 200dB in order to separate the static acceleration component due to gravity from the dynamic acceleration component resulting from body or wheel movement (Karantonis et al., 2006). The dynamic acceleration was obtained by subtracting the static acceleration component from the original signal. Gyroscope signals were filtered with a high-pass filter with a cut-off frequency of 0.3Hz with the same filter design as described above. The altitude signal was filtered with a second order low-pass Butterworth filter with a cut-off frequency of 0.07Hz.

Segmentation: Data that were previously labelled as "moving" were divided into two sub-sets, one containing short lasting "moving" events (less than 5 seconds, defined as "manoeuvring") and one containing longer periods of wheelchair movements (5 seconds or more).

Each manoeuvring phase was taken as a single event and was assigned as such using the video recording. For the longer wheelchair motion dataset the first and the last five seconds of the movement were cut because the acceleration and deceleration of the wheelchair adversely affected the training of the SVM classifiers. The remaining data were divided into windows of 5.12 seconds with an overlap of 50%. Again, a single label from the video recording was assigned to each window.

Feature calculation: Features were calculated from the pre-processed acceleration signal containing the static component; the acceleration signal containing the dynamic motion; the gyroscope data; and the altitude signal. It is important to note that features were taken from single axis data and also from the magnitude of the different sensor modalities. The complete overview of the data analysed can be found in Table 2.1. Features computed from the angular velocity or the acceleration signal were based on previously used features in activity classification studies (Curone et al., 2010, Ravi et al., 2005, Maurer et al., 2006, Bouten et al., 1997, Karantonis et al., 2006, Herren et al., 1999, Baek et al., 2004, Bao and Intille, 2004, Stikic et al., 2008, Leuenberger et al., 2014). Features calculated from the altitude signal were based on the work of Moncada-Torres et al. (Moncada-Torres et al., 2014). Additionally, the inter-sensor correlations of the acceleration magnitude were taken as additional features. Depending on the analysed set-up the number of features changed: e.g. for the full set-up (I.a) all 755 features where used; for the full set-up without gyroscope data (I.b) 579 features were used; for the full set-up with three sensors (II.a) 565 features were used; and finally for the data that did not contain gyroscope information (II.b) 433 features were used. The number of features for the single wheel sensor set-up with and without gyroscope data was 155 (III.a) and 111 (III.b), respectively.

Domain	Feature	Alt.	Acc. P.	Acc. A.	Gyro.
Time	Mean		X		X
	Standard Deviation	X	X	X	X
	Variance	X	X	X	X
	IQR	X	X	X	X
	RMS	X	X	X	X
	Interquartile Range	X	X	X	X
	Percentile (3, 10, 20, 97)		X	X	X
	Peak to Peak Amplitude	X		X	X
	Peak to RMS			X	X
	Counts		X	X	X
Frequency	Max Frequency Component			X	X
	Energy			X	

Table 2.1.
Features calculated for each sensor with Acc.P. being the acceleration with the gravity component and Acc.A. the acceleration including the movement components.

Feature selection: To reduce the set of features to a smaller subset the ReliefF algorithm (Kononenko, 1994) was used. For each of the set-ups investigated (I.a – III.b) the 15 most highly weighted features were selected for further investigations. For each of the set-ups the best feature combination was selected, in order to train the classifiers with a maximum of eight features.

Training SVM classifiers: In total 12 different SVM classifiers were trained. For each of the six different set-ups (I.a-III.b) two classifiers were trained: one for the manoeuvring and one for the longer wheelchair movements. For each of the SVM classifiers different kernel functions were evaluated and the one showing the best performance was chosen. The investigated kernel functions were linear kernel, quadratic kernel, Gaussian radial basis function kernel (scaling factor = 1) and a multilayer perceptron kernel (scale [1 -1]).

Testing SVM classifiers: The performance of the SVM classifier was analysed by using the leave-one-subject-out method. This means that the data of all participants except one was used to train the algorithm and the data from the remaining participant was used to evaluate the performance of the classifiers.

Classification example: To describe the overall algorithm, a single set-up will be presented in detail, i.e. set-up II.b which contains data from three ReSense modules without the gyroscope information. After pre-processing the angular velocity of the wheel is estimated using the acceleration signals. Next, using heuristic rules applied to the wheel sensor data, the algorithm classifies the wheelchair state as “rest” or “moving”. The events categorized as “moving” are then separated into “manoeuvring” or “longer wheelchair movements” and further classified into active/passive propulsion using the corresponding SVM. In the case of the “longer wheelchair movements” the previously cropped segments at the beginning and the end are classified. Finally, for each of the classified movement events, duration, speed and distance travelled are calculated.

Performance analysis: The performance of the complete algorithm and the different sub-parts was analysed in terms of:

accuracy

$$accuracy = \frac{TP + TN}{TP + TM + FP + FN}$$

sensitivity

$$sensitivity = \frac{TP}{TP + FN}$$

and specificity

$$specificity = \frac{TN}{FP + TN}$$

with TP as true positive rate, TN as true negative rate, FP as false positive rate and FN as false negative rate. Additionally, the kinematic parameters were analysed in terms of absolute mean errors. The estimation of the angular velocity of the wheel from the accelerometer data was compared to the values obtained through the gyroscopes using a paired t-test.

2.4 Results

The average length of evaluated data was 219.12 ± 83.24 min (range: 73.48 min - 335.29 min) per subject. The video showed that subjects were not moving the wheelchair for 87.54 ± 4.71% of the time (range 79.82% - 96.75%). On average a subject self-propelled the wheelchair 12.19 ± 4.47% of the time (range 3.02% - 20.18%), whereas 0.27 ± 0.37% of the time the wheelchair was attendant-propelled (range 0% - 1.38%). In total, 18 out of the 21 subjects had at least one phase where the wheelchair was attendant-propelled. Table 2.2 shows the performance of the classifier based on heuristic rules for the direct input of gyroscope data and for the modified approach based on Clouter et al. (Coulter et al., 2011) and Sonenblum et al. (Sonenblum et al., 2012a) where the angular velocity of the wheel was estimated through accelerometer data. Note that the accelerometer-based approach performed slightly worse in terms of specificity (1.11%).

	Gyroscope	**Accelerometer**
Sensitivity	95.80 ± 1.91%	94.69 ± 3.01%
Specificity	99.58 ± 0.29%	99.25 ± 0.43%

Table 2.2. Sensitivity and specificity of the classification if the wheelchair was moving compared to the data from the video recording.

The accelerometer-based approach is a modified version of the work presented from Coulter et al. and Sonenblum et al. (Coulter et al., 2011, Sonenblum et al., 2012a).

Table 2.3 shows the performance of the 12 trained classifiers in terms of overall accuracy, sensitivity and specificity as well as the number of features selected and the kernel function chosen for the evaluation. For training of the SVM classifiers to analyse the manoeuvring data a total of 376 time windows were generated. For the training of the SVM classifiers for analysis of the long motion periods a total of 4151 windows were included.

Set-up	Number of modules	data type analysed	Overall Accuracy	Sensitivity "passive"	Sensitivity "active"	Number of features	kernel function
I.a	4 modules	long mobility bouts	98.24%	90.38%	98.57%	4	rbf
		manoeuvering	90.77%	84.85%	98.11%	3	rbf
I.b	4 modules without gyroscope	long mobility bouts	98.24%	90.38%	98.57%	4	rbf
		manoeuvering	88.74%	85.61%	97.93%	2	rbf
II.a	3 modules	long mobility bouts	96.34%	87.21%	98.28%	4	rbf
		manoeuvering	88.54%	85.88%	97.91%	3	rbf
II.b	3 modules without gyroscope	long mobility bouts	96.34%	87.21%	98.28%	4	rbf
		manoeuvering	88.54%	85.88%	97.91%	3	rbf
III.a	1 module	long mobility bouts	87.68%	81.73%	85.08%	4	linear
		manoeuvering	88.36%	74.45%	84.35%	5	linear
III.b	1 module without gyroscope	long mobility bouts	87.68%	81.73%	85.08%	4	linear
		manoeuvering	84.52%	73.94%	84.16%	4	linear

Table 2.3.
Overall accuracy and sensitivity for the trained support vector machine classifiers are presented in this table. Additionally, the numbers of features used to train the classifier and the chosen kernel function are indicated (rbf = Gaussian radial basis function).

Table 2.4 shows the performance of the complete algorithm with the classification of moving or rest and the following part with the SVM classifiers.

		Overall accuracy
I.a	4 modules	93.29%
I.b	4 modules without gyroscope	91.12%
II.a	3 modules	90.96%
II.b	3 modules without gyroscope	90.51%
III.a	1 module	83.77%
III.b	1 module without gyroscope	82.07%

Table 2.4. The overall accuracy of the presented algorithm combining heuristic rules and a support vector machine classifier.

Finally, the results of the estimated distance travelled and the duration of movement for the additional measurements on the indoor and outdoor tracks are presented in Table 2.5. The statistical analysis showed no significant difference between the approach using the gyroscope data and the one using the accelerometer data for each of the estimated parameters.

	Real Distance	**Gyroscope estimated distance**		**Accelerometers estimated distance**	
		Average Distance	*Accuracy range*	*Average Distance*	*Accuracy range*
Indoor track 1	20m	19.8 ± 0.2	97.7-99.8%	20.1 ± 0.0	99.2-99.6%
Indoor track 2	20m	19.9 ± 0.3	98.5-99.1%	20.2 ± 0.0	98.7-98.9%
Indoor track 3	30m	29.7 ± 0.3	97.7-99.8%	30.2 ± 0.0	99.2-99.4%
Outdoor track 1	300m	303.1 ± 1.8	98.5-99.4%	302.9 ± 0.7	99.3-99.5%
Outdoor track 2	600m	605.3 ± 3.8	98.6-99.6%	604.1 ± 1.5	99.3-99.6%
Outdoor track 3	900m	908.0 ± 5.9	99.7-99.9%	907.9 ± 4.2	99.5-99.8%

Table 2.5. ***Estimation of the distance using the modified accelerometer based approach or directly using the gyroscope data.***

Data was collected from 5 sensors placed at different distances from the center of rotation of the wheel. Each trial was repeated twice. Note that there are no significant differences between the two estimation methods for the estimation of the distance.

2.5 Discussion

The aim of this study was to develop and validate an algorithm that could continuously monitor "real-world" wheelchair propulsion and distinguish attendant- or self-propulsion using an enhanced IMU. Here we present a valid method that, firstly estimates time-distance parameters of mobility, such as distance travelled and the speed and duration of movement, and secondly distinguishes passive (attendant-propelled) from active (self-propelled) wheelchair propulsion by using data collected from unobtrusive IMUs. Furthermore, we were able to show that even with a reduced number of IMU modules (one instead of four) and different set-ups (with or without the gyroscope) overall the accuracy remained high.

The full sensor set-up using four sensors with gyroscope data included in the analysis performed best with an overall accuracy of more than 93%. Reducing the set-up to only one sensor module still showed a sufficiently high overall accuracy (82%) and can thus be used as a basic, unobtrusive tool for monitoring subjects' overall mobility. The set-ups where gyroscope data was not included performed slightly worse than the set-ups where the gyroscope data was included with a maximal difference of around 2%.

The wheelchair algorithm developed by Sonenblum and colleagues (Sonenblum et al., 2012a) focused on evaluating overall wheelchair use (Sonenblum et al., 2012b). However, overall mobility data alone are less sensitive for describing the true physical activity of the wheel chair user, as it does not distinguish between self- and attendant-propulsion (being propelled by another person) and consequently the assessment of overall physical activity is limited. For wheelchair users it can be quite difficult to estimate their overall wheelchair activity both during the early phases of rehabilitation and after discharge when they are living in their home environment as they have no obvious parameters for comparison of their activity (i.e. meaningful thresholds of low or high wheelchair activity). In particular, this is of high relevance when after an SCI wheelchair activity replaces all the previous bodily activities (walking, running, stair climbing etc.) and a novel way of measuring activity needs to be developed. Therefore, it is important to be able to distinguish between active (self-) propulsion of the wheelchair from passive attendant-propulsion and to provide patients with feedback about active wheeling not only in parameters such as time-distance but also readouts that can be translated into dynamic values (acceleration, managing levels, ramps etc.).

For this purpose, the SVM classifiers showed a good overall performance. Interestingly, the features selected were mostly single axis accelerometer data containing the static components (3rd and the 97th percentile). In other words, the features selected were mostly related to the orientation of the IMU as none of the features with high frequency content were selected. This is in contrast to the previously reported findings of Hiremath and co-workers (Hiremath et al., 2015) where the features identified by the classification algorithm were mostly frequency-based , e.g. entropy of the velocity. This divergence may be attributed to the different nature of the environment where we performed our experiment, a real-world environment where activities are performed spontaneously, compared to the one used by Hiremath and colleagues which was a mixture of laboratory and real-world settings, where subjects performed artificially defined activities. By way of illustration, Hiremath and co-workers reported that in each case the same attendant was used and that because it was always the same individual this may have resulted in specific movement patterns that may have influenced the sensitivity of the developed algorithm. The pushing or propelling the wheelchair with a heterogenic speed or acceleration pattern may result in a more homogeneous frequency spectrum compared to a more natural and spontaneous propulsion, as observed in our set-up, which might shift the classifier feature selection toward placing a priority on frequency-based features. This

example may explain the importance of validating such methodologies in a real-world environment in order to achieve a higher ecological validity.
Most of the trained SVM classifiers did not include gyroscope data. From the six possible set-ups that included gyroscope data only two used gyroscope-related features in the final SVM classifier. To support this, it has been reported previously that gyroscopes do not include information that is valuable for the purpose of activity (Moncada-Torres et al., 2014). Also, it should be noted that the classification accuracy of propulsion is within the same range as previously published data (Postma et al., 2005).

The accuracy of our estimation of the distance travelled agreed with previously published studies (Coulter et al., 2011, Sonenblum et al., 2012a, Hiremath et al., 2013) both approaches to estimate the angular velocity of the wheel, i.e. the accelerometer-based approach and the gyroscope-based estimation of distance, have previously been shown to be valid. The adaptation of the algorithm presented by Sonenblum and co-workers (Sonenblum et al., 2012a) was necessary to match the requirements of a long-term monitoring device, i.e. for recordings longer than three days the gyroscope will need to be turned off to extend battery life. Additionally, although manual wheelchair users do not usually achieve a wheelchair speed of 9km/h in daily life, a future application might be to monitor highly active people, e.g., wheelchair athletes where speeds of 15km/h can be easily reached.

Some study limitations should also be mentioned. Firstly, for training of the SVM classifiers we had much more data from active wheelchair propulsion compared to passive phases which might result in a classifier rating slightly in favour of the active propulsion. Additionally, for this study we also had to separate between events classified as manoeuvring and longer events where the wheelchair was moving. This made an already complex algorithm even more complex. We reported small deviations between how an operator labelled the videos and how the data was labelled by the classifier based on heuristic rules. This discrepancy may be due to the fact that it was sometimes difficult to recognize wheelchair motion from the video. Alternatively, the synchronization between the video and the sensor data may not have been optimal.

2.6 Conclusion

The methods presented in this study allow for an accurate identification of active and passive wheelchair propulsion, as well as a valid estimation of kinematic parameters of wheelchair movement such as distance travelled. The possibility to switch between different sensor set-ups allows the use of the ReSense as a high precision tool for research and as an unobtrusive and simple tool which could be implemented on future commercial activity trackers for manual wheelchair users. Future work will focus on using this algorithm to gain new insights into the "true" mobility behaviour of manual wheelchair users with a special focus on elderly persons, wheelchair athletes and those in the acute stage of recovery from a spinal cord injury. This tool has the potential to help clinicians assess and motivate manual wheelchair users, to adapt therapy when needed or to promote a more active lifestyle. In addition, the presented tool could help identify if abilities as measured by clinical assessments are transferred into performance in daily life, e.g., self-propulsion.

3 Novel sensor technology to assess independence and limb-use laterality in cervical spinal cord injury[2].

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Detailed statement of individual contribution to this article. The study was designed by Michael Brogioli and Werner Popp supported by the co-authors. The manuscript was written by Michael Brogioli and revised by the co-authors. Data was analyzed by Michael Brogioli supported by Werner Popp. Michael Brogioli was responsible for data collection.

3.1 Abstract

After spinal cord injury (SCI), levels of independence are commonly assessed with standardized clinical assessments. However, such tests do not provide information about the actual extent of upper limb activities or the impact on independence of bi- versus uni-lateral usage throughout daily life following cervical SCI.

The objective of this study was to correlate activity intensity and laterality of upper-extremity activity measured by body-fixed inertial measurement units (IMUs) with clinical assessment scores of independence.

Limb-use intensity and laterality of activities performed by the upper extremities was measured in 12 subjects with cervical SCI using four IMUs (positioned on both wrists, on the chest and on one wheel of the wheelchair). Algorithms capable of reliably detecting self-propulsion and arm activity in a clinical environment were applied to rate functional outcome levels and were related to clinical independence measures during in-patient rehabilitation.

Measures of intensity of upper extremity activity during self-propulsion positively correlated ($p < 0.05$, $r = 0.643$) with independence measures related to mobility. Clinical measures of laterality were positively correlated ($p < 0.01$, $r = 0.900$) with laterality as measured by IMUs during “daily life” and increased laterality was negatively correlated ($p < 0.01$, $r = -0.739$) with independence.

IMU sensor technology is sensitive to assess and quantify upper limb-use intensity and laterality in human cervical SCI. Continuous and objective movement data of distinct daily activities (i.e. mobility and day-to-day activities) can be related to levels of independence. Therefore, IMU sensor technology is suitable not only to monitor activity levels during rehabilitation (including during clinical trials) but could also be used to assess levels of participation after discharge.

3.2 Introduction

Data from questionnaires have suggested that, of all affected functions, hand and arm functions are the ones that tetraplegic people would most like to regain (Anderson, 2004, Snoek et al., 2004). This is because functional and effective hand use is a key element influencing the quality of life of the sufferer (McDonald and Sadowsky, 2002). The importance of upper limb function for quality of life was investigated in earlier studies where independence, as assessed by the Spinal Cord Independence Measure (SCIM), was shown to be positively correlated with measures of upper limb function, such as the motor score protocol of the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI)(van Hedel and Curt, 2006, Rudhe and van Hedel, 2009) or more recently, the Graded Redefined Assessment of Strength, Sensibility and Prehension (GRASSP) (Velstra et al., 2015). Much of what we do everyday involves the use of both arms, for example for basic self-care skills (e.g. bathing, dressing, feeding, toileting), mobility functions (e.g. carrying objects, getting up from bed, driving) and instrumental activities (keyboarding, shopping, cooking) (McCombe Waller and Whitall, 2008). In this context most upper extremity tasks require both arms to work together to accomplish a goal even if one hand is only used as support (Bailey et al., 2014).

In the stroke field the negative effect of limb-use laterality on independence, upper extremity activity and upper extremity function is well documented (Uswatte et al., 2006, Thrane et al., 2011, van der Pas et al., 2011, Michielsen et al., 2012, Bailey et al., 2015). For example, subjects with chronic stroke were assessed with an accelerometer-based upper-limb activity monitor that compared the time of activity between the two arms (Michielsen et al., 2012). It was shown that they used their unaffected arm more than their affected arm, and that their affected arm was rarely used for unilateral tasks and almost only used during bimanual activities (Michielsen et al., 2012). In comparison, according to accelerometer-based upper-limb activity measurements, healthy subjects show equal usage of the dominant and non-dominant arm (Lang et al., 2007, Bailey et al., 2015, Michielsen et al., 2012). These studies also show that in healthy subjects the intensity of the activities of each arm during bimanual movements is higher than the intensity of the activities of each arm during unilateral movements whereas in stroke patients the intensity of the activities of the less-affected arm tends to be higher regardless of whether the subject is performing a bimanual or unilateral task (Michielsen et al., 2012, Bailey et al., 2015). Uswatte and co-workers showed that in subjects 3-9 months post-stroke the ratio of paretic to non-paretic arm use was strongly correlated with impairment according to the Motor Activity Log and the Actual Amount of Use Test, and showed a weak correlation with the Stroke Impact Mobility Scale, a measure of overall physical activity (Uswatte et al., 2006). In contrast, in the field of SCI no specific measures of laterality exist, besides the classification of the Brown-Séquard syndrome (Kirshblum et al., 2011b). Laterality can at best be inferred, for example from the ISNCSCI classification (Kirshblum et al., 2011b), where the severity of the injury is classified on two ordinal scales, one for the level of the injury (the spinal cord segment damaged) and one for the completeness of the injury (the degree of impairment), thus information about laterality can be extracted by comparing the scores of the two sides. Hence, a more sensitive indicator of laterality following SCI may help clinicians select treatments, evaluate progress or develop tailored rehabilitation strategies.

The purpose of this study was to examine limb-use laterality and intensity of use of the upper extremity in tetraplegic subjects during the normal clinical routine using ReSense (Leuenberger and Gassert, 2011), a miniature low-power IMU. Manual wheelchair propulsion has previously been shown to be a bilateral, symmetrical movement (Soltau et al., 2015).

Therefore, we used an algorithm previously developed by our group (Popp et al., 2016) that is capable of distinguishing active and passive wheelchair propulsion, and hence can be used to investigate upper extremity usage during ADL and manual wheelchair-propulsion (active wheelchair propulsion) separately. Using this methodology, we tested whether laterality in limb-use affects independence and whether the intensity of use of the upper extremity during manual wheelchair propulsion correlates with independent mobility in daily life.

3.3 Materials and methods

3.3.1 Subjects

12 tetraplegic subjects (age 37.92 ± 15.46 years, range 20-75 years, 11 male, 1 female, ASIA A-D, Table 3.1) were recruited from two specialized SCI centres (Balgrist University Hospital, Zurich and the Swiss Paraplegic Center, Nottwil). All participants completed the first rehabilitation but were at the time of the measurement in-patient. A complete overview of the participants can be found in Table 3.1. Inclusion criteria were subjects suffering from traumatic cervical complete or incomplete chronic spinal cord injury (defined here as >90 days after SCI). The mean time post-injury of the recruited subjects was 10.19 ± 7.89 years (range: 1.75 years – 22.34 years). Subjects either not using a wheelchair at all or using an electric- or a hybrid-wheelchair were excluded. Subjects with a neurological disease other than SCI and/or an orthopaedic or rheumatologic disease were excluded. The study was approved by the local ethics committee of the cantons of Zurich and Lucerne.

3.3.2 Assessments

The level of independence in daily life was assessed with the third version of the Spinal Cord Independence Measure (SCIM III) (Itzkovich et al., 2007). The SCIM III was used to assess overall outcomes in two domains dedicated to ADL and wheelchair mobility. The ADL domain comprises a total of nine items (scores range from 0 to 30) belonging to: 1) sub-scores of mobility (room and toilet), and 2) sub-scores of self-care. The domain of wheelchair mobility comprises six items (scores range from 0 to 30) belonging to sub-scores of mobility (indoor/outdoor). The level of neurological impairment (NLI) as related to the level and completeness of lesion was assessed using the ISNCSCI protocol (Kirshblum et al., 2011b).

Subject	Age	Gender	Neurological classification	SCIM III Mobility Outdoor [0-30]	SCIM III Room and Self-care [0-30]	GRASSP MMT Right [0-25]	GRASSP MMT Left [0-25]	Measurement time [h]	Distance active [km]	Peak velocity [km/h]	Time spent in active propulsion
1	20	male	A C6	4	8	15	17	5.7	0.202	6.62	2 %
2	42	male	D C7	9	28	38	41	5.2	1.327	6.83	10 %
3	20	male	B C5	6	26	NT	NT	4.6	0.953	6.75	7 %
4	44	female	A C6	7	20	22	28	5.0	1.032	7.86	9 %
5	20	male	B C4	3	8	9	15	4.7	0.618	3.25	9 %
6	75	male	D C7	5	17	45	49	5.4	1.467	4.93	16 %
7	45	male	B C6	7	16	17	17	4.1	1.682	6.32	18 %
8	42	male	B C5	6	15	17	15	3.6	0.185	5.45	3 %
9	43	male	C C5	8	15	18	20	3.8	0.788	7.67	8 %
10	27	male	D C7	9	29	50	50	4.3	1.479	10.74	11 %
11	35	male	A C6	7	29	21	20	3.7	1.270	7.53	15 %
12	42	male	A C5	7	20	20	21	5.8	3.029	7.14	17 %

Table 3.1. Demographics and self-propulsion kinematics of 12 cervical spinal cord injured subjects.

SCIM III: Spinal Cord Independence Measure. SCIM III Mobility Outdoor: SCIM III mobility indoor, outdoor and on even surface. SCIM III room and Self-care: SCIM III mobility room and toilet and SCIM III self-care. GRASSP MMT: Strength subset of the Graded and Redefined Assessment of Strength, Sensibility, and Prehension. NT = not testable.

The functional deficit of the upper limbs was assessed using the strength sub-test of the GRASSP (Kalsi-Ryan et al., 2012). The first sub-test of the GRASSP, manual muscle testing (MMT), assesses upper limb function unilaterally in 10 muscles (scores range from 0-50 per arm). This assessment was used to reveal clinical limb-use laterality. Laterality was calculated by dividing the scores of the right hand by the scores of the left hand. In order to have a symmetrical scale centred around 0 the ratio was log-transformed (natural logarithm), where a negative value corresponds to left limb-use and a positive value to right limb-use. The reason for choosing the MMT of the GRASSP was because it has been shown to have excellent responsiveness to changes over the course of recovery (Velstra et al., 2015) and because it is one of the most valuable outcomes for identifying clinically meaningful changes in the tetraplegic population (Velstra et al., 2015). The responsiveness of the GRASSP (the ability to detect changes) and its ability to identify clinically meaningful changes makes it suitable for addressing limb-use laterality in human SCI. The final sub-test of the GRASSP, quantitative grasping (QtG), tests the capacity of the subject to perform six unilateral, standardised ADL movements (scores range from 0-30 per arm) and therefore represents extreme limb-use laterality movements. This sub-test was filmed as described in the methods section “Data collection and procedure”.

3.3.3 Sensor device

An enhanced version of the previously published ReSense module (Leuenberger and Gassert, 2011) with more robust plastic housing, an upgraded gyroscope and a new magnetometer was used. The module has 10 degrees of freedom and consists of a three-axis accelerometer (ADXL345, Analog Devices, Norwood, MA, USA), a three-axis gyroscope (ITG-3050, InvenSense, San Jose, CA, USA), a three-axis magnetometer (MAG3110, Freescale

Semiconductor Inc., Hamilton, Bermuda) and a barometric pressure sensor (BMP 085, BOSCH, Stuttgart, Germany). The ReSense module is 36x29x13 mm^3 and weighs 15g (including the battery and the water-resistant plastic housing) (Figure 3.1). The sampling rate can be varied from 25 to 100 Hz, and was set to 50 Hz for these recordings. The collected data is stored on an internal 2GB microSD card. Through the absolute time stamp different modules can be synchronized via a custom-built base station (Figure 3.1). In this way several ReSense modules can be used in a multi-sensor set-up. For the purpose of this study the magnetometer and the barometric pressure sensor were not used.

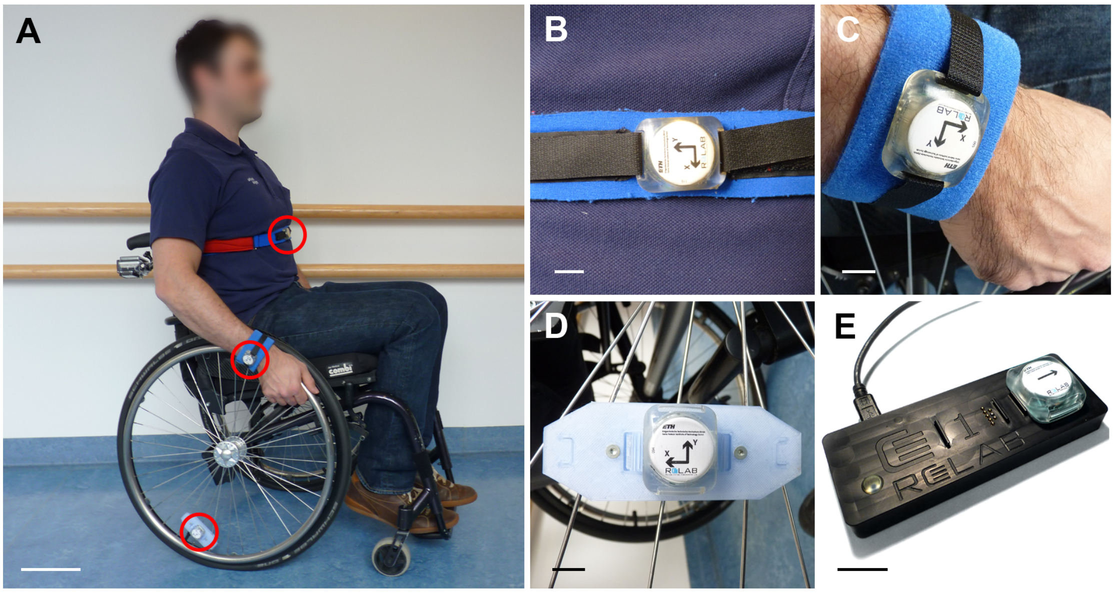

Figure 3.1. Set-up of ReSense IMUs for recording.

A: An investigator propelling a manual wheelchair equipped with 4 ReSense modules. Sensors can be seen on the right wrist, left wrist (not shown), chest and wheel (red circles). B: a ReSense module fixed to the chest strap. C: a ReSense module fixed on the right wrist of the subject. D: a ReSense module fixed on at the wheel of the wheelchair with a custom-designed fixation plate. E: ReSense module attached to a base-station for the extraction of recorded data. Scale bar (A) indicates 20 cm, scale bars (B, C & D) indicate 1 cm and scale bar (E) indicates 3 cm.

3.3.4 Activity categories

As the purpose of this study was to measure upper limb motor performances and their relationship to independence, two main categories of activities were distinguished based on the output of an algorithm previously developed by our group (see "Labelling"). Quantitative measures recorded during self-propulsion of the wheelchair and during any ADL or any UL activity not related to self-propulsion, were recorded during regular in-patient daily routines. Consequently the self-propulsion category (first category) included all upper extremity movements performed whilst the subject actively propelled the wheelchair, whereas, the ADL category (second category) encompassed all upper extremities movements occurring during any other day-to-day activities without any further differentiation.

An isolated recording, was performed in order to distinguish an additional category. This was done in order to test the validity of our methodology in discriminating limb-use laterality in two extreme and contrasting conditions consisting of non-cooperative single hand movements. Therefore, all subjects performed the QtG of the GRASSP wearing the ReSense modules and were filmed with an HD camera (Handycam, Sony, Tokyo, Japan) for later labelling of unilateral movements (unilateral condition, category GRASSP QtG Left & Right, third category).

3.3.5 Data collection and procedure

Participants had to complete standardized assessment protocols and thereafter were fitted with four ReSense modules (Figure 3.1) in order to first record the uni-lateral activities of the GRASSP QtG during a single assessment and secondly to complete a non-standardised real life recording. A ReSense module was worn with a strap (AlphaStrap Blue with Velcro, North Coast Medical Inc, Camino Arroyo, CA, U.S.A) on both wrists and with a custom-made chest strap (Balgrist Tec AG, Zürich, Switzerland) on the chest. The wheel sensor was fixed between the spokes of the manual wheelchair using a custom-designed fixation device produced by a 3D printer (MakerBot Replicator 2, MakerBot Industries LLC, Brooklyn NY, USA). For the real life recording subjects were instructed to wear the ReSense sensors for 3-6 hours while continuing with their regular daily routines. Subjects were not asked to perform any specific ADL but they were free to behave as they wanted and to follow the daily inpatient schedule.

3.3.6 Data analysis

Pre-processing. Following the completion of the recording session, data were transferred from the ReSense modules to a PC with a custom-designed base station. To ensure the temporal alignment of recordings from different modules, all data were resampled at 50Hz using a cubic spline interpolation function.

3.3.7 Labeling

An algorithm previously developed by our group (Popp et al., 2016) was used to label the acceleration signal with periods of active propulsion. In short, to detect if the wheelchair was stationary or moving, heuristic rules were applied to the acceleration and angular velocity signals from the wheel sensor. Secondly, previously trained Support Vector Machine classifiers were used to discriminate active (self-propelled) and passive (attendant-propelled) wheelchair propulsion from the acceleration and angular velocity signal coming from the sensors attached to the body. The algorithm is able to distinguish between the two propulsion categories with accuracy greater than 93%. In addition to classifying activities, the algorithm was used to estimate kinematic parameters of wheelchair movements (e.g. distance travelled). The estimation accuracy of the algorithm for kinematic parameters is greater than 97%. A more detailed description of the algorithm is provided elsewhere (Popp et al., 2016).

3.3.8 Deriving activity metrics of the upper extremity

Data were analysed offline using MATLAB R2013a (MathWorks, Natick, MA, U.S.A). Measurement gaps, such as when sensors were taken off during the measurement, were removed from the data by an observer and the exact start and stop times were set by visual inspection of the acceleration signal. The activity detected by the sensors was summarized as “activity count” (AC). AC was calculated by integrating the absolute acceleration signal and filtering it with a 2nd order Butterworth high pass filter with a cut-off frequency of 0.25 Hz, over an epoch of 2 seconds. The counts of all epochs were normalized by time and converted to AC per minute in order to enable comparison with other published data.(Chen and Bassett, 2005)

In order to calculate two variables: “Activity intensity” and “Laterality”, AC were further processed, using a similar methodology to Bailey and co-workers(Bailey et al., 2014), the differences being the way in which resting phases were detected (adapted to the ReSense hardware). Activity intensity is calculated by summing the ACs of the sensors of both arms where the upper extremities are active. In order to avoid the influence of rest phases, where the upper extremities are not active, epochs were only included if the rectified and filtered acceleration signal was more than three times the standard deviation of the noise. In doing so, only moments in which upper extremity movements occur are included in the data analysis. Thereafter, the summed counts were time normalized.

Laterality was calculated by dividing the AC of the right hand by the AC of the left hand. In order to avoid an indeterminate (e.g. 0/0 = indeterminate value i.e., when both hands are inactive) or undefined value (e.g. 3/0 = undefined value i.e., when one hand is inactive), 1

AC/min is added to all the data points of the AC vector of each upper extremity. The ratio was then log-transformed (natural logarithm). Therefore, values near zero indicate similar activity in the left and right arms, positive values indicate right-dominant laterality and negative values indicate left-dominant laterality. Density graphs (distribution of epochs in function of AC and laterality) were created in order to visually analyse laterality (bin width: 0.2 units) and activity intensity (bin width: 50 Activity Counts/min) during the three different activity categories (Self-Propulsion, ADL, GRASSP QtG Left & Right).

3.3.9 Statistical analysis

The statistical analysis of the data was performed using IBM SPSS Statistics version 19 (IBM, Armonk, NY, U.S.A). As the sample data of the two metrics derived from the ReSense modules were not normally distributed, the data shown is the median and interquartile range, unless otherwise stated. Laterality differences between different movement conditions were analysed using a one-way analysis of variance (ANOVA) with Bonferroni post-hoc correction. Due to the ordinal nature of the SCIM III subdomain scales, Spearman's rank-order correlation coefficient analysis was applied to investigate the relationship between independence scores and the activity metrics. A spearman-rho value larger than 0.60 was considered a strong correlation. Significance level was set to $p < 0.05$. For the analysis, the NLI (i.e. C4, C5) and completeness of the lesion (i.e. A, B) were assumed to be ordinal and were transformed into numerical values (i.e. C4 was transformed to 4 and C5 to 5, A transformed to 1 and B to 2).

3.4 Results

3.4.1 Description of participants' behaviour

ReSense data were recorded for all 12 tetraplegic subjects. After visual correction, the mean length of the analysed data was measured and found to be 4.63 hours (the shortest recording time was 3.57 hours and the longest recording time was 5.88 hours). The mean distance travelled was 1.17 km (the shortest distance travelled was 0.19 km and the longest was 3.03 km) with an average velocity of 2.31 km/h (the slowest mean velocity was 1.51 km/h and the fastest mean velocity was 3.24 km/h).

3.4.2 Activity intensity and laterality

In order to show the validity of both the intensity and laterality metrics and in order to facilitate the interpretation of the results the data of two subjects with different profiles in terms of laterality (subject 5 and 11 show two different extremes) are presented in frequency distribution and density plots (Figure 3.2), as an example. In Figure 3.2 A-C and G-I the frequency profile of AC of the two subjects is similar for the different activities, for example, ADL shows a strong positive skew (Figure 3.2 A & G), self-propulsion has a moderate skew to normal distribution (Figure 3.2 B & H), and GRASSP QtG left and right has a moderate positive skew (Figure 3.2 C & I). Accordingly, during the full range of upper extremity movements performed during ADL, the activity intensity varies considerably whereas less intensive movements seem to happen more often (Figure 3.2 A & G). As opposed to ADL, the distribution profile during self-propulsion represents a single specific upper extremity activity and therefore the frequency distribution is more symmetrical than for ADL (Figure 3.2 B & H). Subject 5 shows a strong left-sided laterality during ADL compared to subject 11. This can be seen in the two-dimensional density graph, which is shifted to the left in subject 5 compared to Subject 11 (Figure 3.2 J & D, respectively). Finally there were significant differences in laterality between the three conditions, F(1.215, 13.369) = 183.911, $p < 0.001$ (one-way RM ANOVA, Post-hoc tests with Bonferroni correction), GRASSP QtG Left: -4.254 ± 0.378, self-propulsion: -0.002 ± 0.021, GRASSP QtG right: 3.712 ±0.272; $p < 0.001$, giving support to the validity of this method for describing laterality.

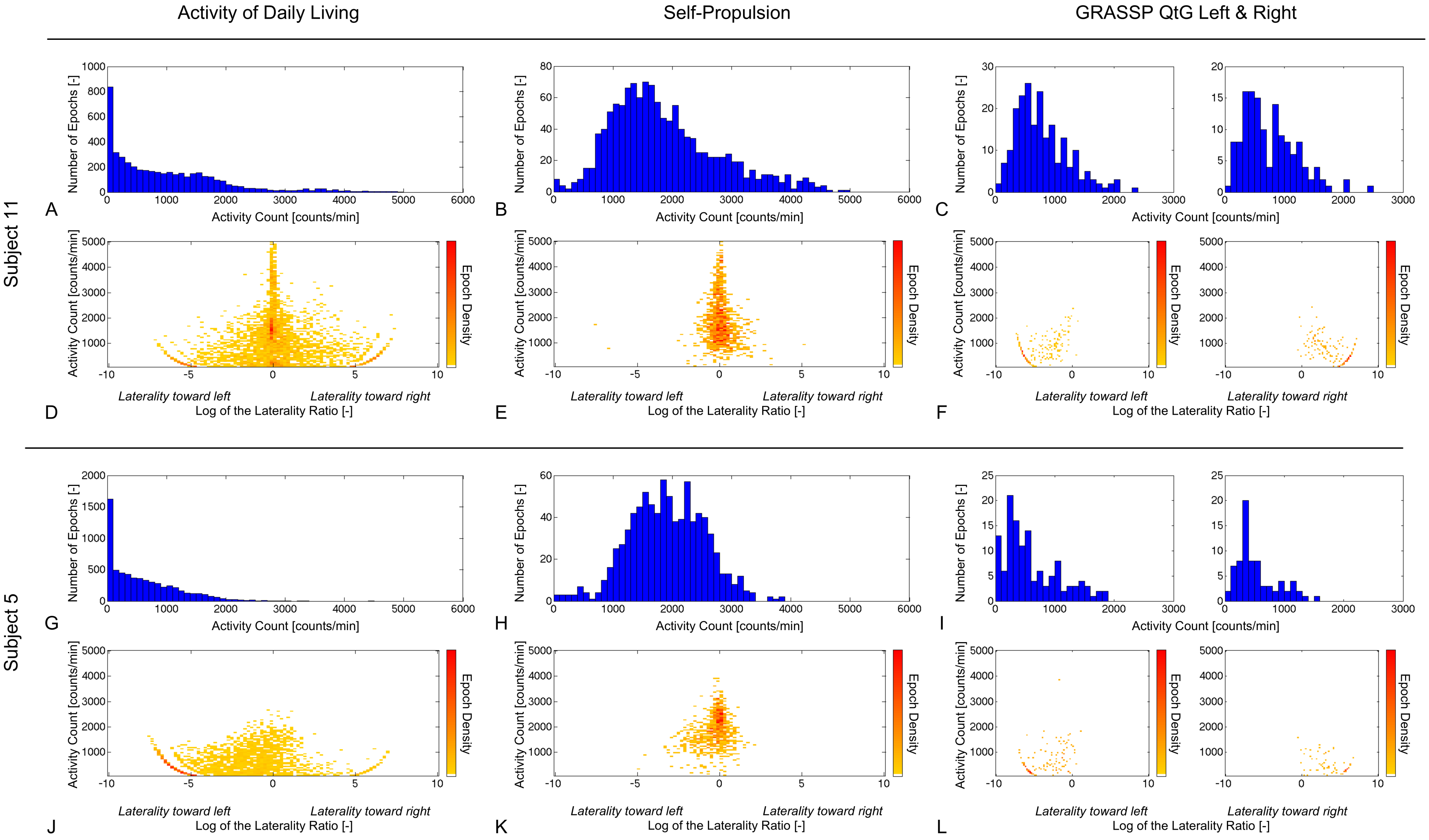
Activity of Daily Living
Self-Propulsion
GRASSP QtG Left & Right
Subject 11
Subject 5
A
B
C
D
E
F
G
H
I
J
K
L
Number of Epochs [-]
Activity Count [counts/min]
Epoch Density
Laterality toward left
Laterality toward right
Log of the Laterality Ratio [-]
0
1000
2000
3000
4000
5000
6000
-10
-5
5
10

Figure 3.2. Example data from two participants during different conditions.

Frequency distributions of Activity Counts (A, B, C, G, H & I) and density graphs of the distribution of epochs in function of AC and laterality (D, E, F, J, K & L), showing the data of two subjects with different laterality patterns (subject 11: lacking laterality, subject 5: pronounced laterality). The frequency distributions and density graphs are displayed for ADL (Activity of Daily Living; A, D, G & J), a condition of symmetrical activity (self-propulsion; B, E, H & K) and two conditions of laterality (GRASSP QtG left: left unilateral task; GRASSP QtG right: right unilateral task; C, F, I & L). The plotted shapes of the density graphs indicate the pattern of limb use laterality (bin width for laterality: 0.2 units; bin width for activity intensity: 50 Activity Counts/min; D-F, J-L). During the condition of ADL, subject 11 showed a more symmetrical pattern in the limb usage of both upper extremities compared to subject 5 that showed pronounced left-sided laterality (D & J). Diminished laterality was shown during self-propulsion for both subjects (E & K) whereas strong laterality is shown during the unilateral tasks (F & L). GRASSP: Graded and Redefined Assessment of Strength, Sensibility, and Prehension. QtG: Quantitative Grasping subset of the GRASSP.

3.4.3 Relationship between wheeling characteristics and independence in mobility

We assessed the intensity of self-propulsion. On average, a subject self-propelled the wheelchair 10.47 ± 4.59% (mean ± SD) of the recording time (range 1.93% - 16.94%). The average propulsion time was 29.12 ± 15.91 min (mean ± SD) (range 6.70 min - 58.70 min). We found a positive correlation ($P < 0.05$, $r = 0.643$, Spearman correlation, Figure 3.3) between the SCIM III sub-scores of mobility outdoor and AC during self-propulsion, suggesting that subjects performing more intense upper extremity movements during self-propulsion are more independent. No relationship was found between AC during self-propulsion and NLI ($P = 0.743$, $r = -0.106$, Spearman correlation) or completeness ($P = 0.344$, $r = 0.300$, Spearman correlation). These results suggest that, in the tested subset of patients, the ability to perform intense upper limb movements during self-propulsion is not affected from the severity of the injury.

To further analyse the relationship of other wheelchair mobility outcomes with independence, we correlated the SCIM III mobility outdoor with wheelchair kinematic metrics. We found that the maximal forward velocity was strongly, positively correlated with independence ($P < 0.05$, $r = 0.779$; Spearman correlation) whereas the distance travelled showed a trend towards a positive correlation ($P = 0.09$, $r = 0.507$, Spearman correlation). Finally we correlated the same kinematic metrics with the intensity of the self-propulsion and found that maximal forward velocity was strongly correlated with AC during self-propulsion ($P < 0.05$, $r = 0.832$, Spearman correlation) but not with the distance travelled ($P = 0.24$, $r = 0.371$, Spearman correlation).

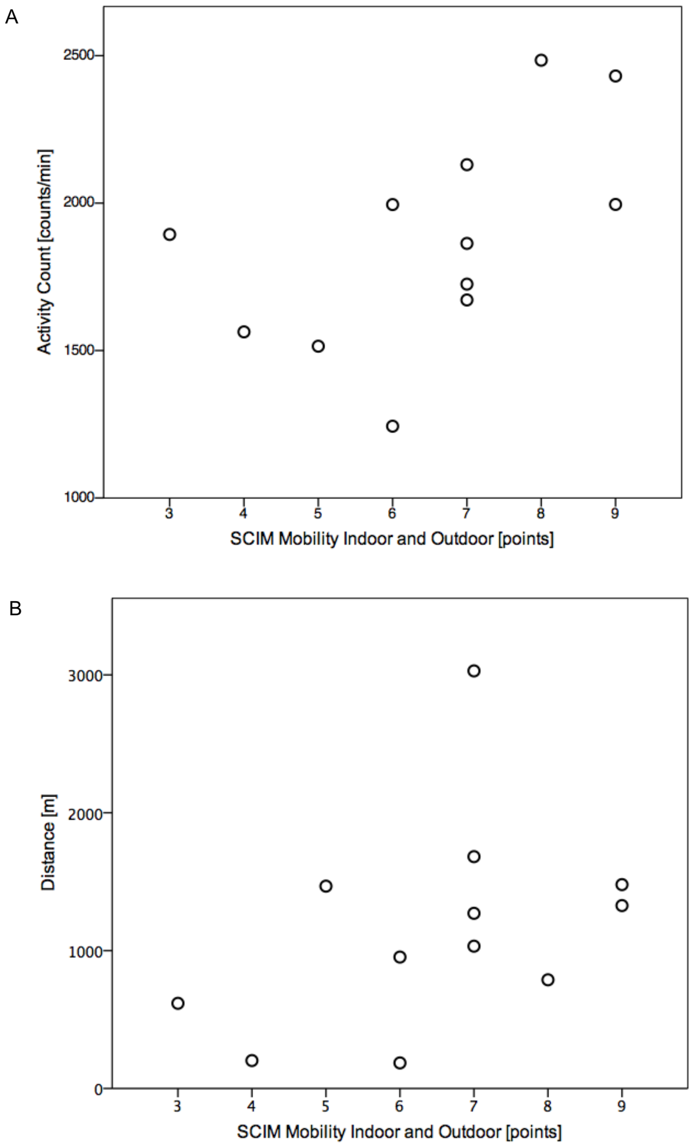

Figure 3.3. Relationship between independence and activity intensity and distance travelled.

A: The median of the Activity Count measured during self-propulsion was strongly positively correlated with the Mobility outdoor subdomain of the Spinal Cord Independence Measure ($P < 0.05$, $r = 0.643$, Spearman correlation). B: Distance travelled showed a trend towards a positive correlation ($P = 0.09$, $r = 0.507$, Spearman correlation). A & B: Open circles indicate individual subjects. SCIM: Spinal Cord Independence Measure.

3.4.4 Effect of laterality on independence

In order to investigate the effect of limb-use laterality on independence, the correlation between the laterality scored as part of the strength section of the GRASSP and the limb-use laterality measured by ReSense was investigated. The laterality derived by the ADL sensor recording (median of the log transformed ratio) was strongly correlated with the laterality derived by the GRASSP MMT (log transformed ratio), ($P < 0.01$, $r = 0.900$, Pearson correlation, Figure 3.4).

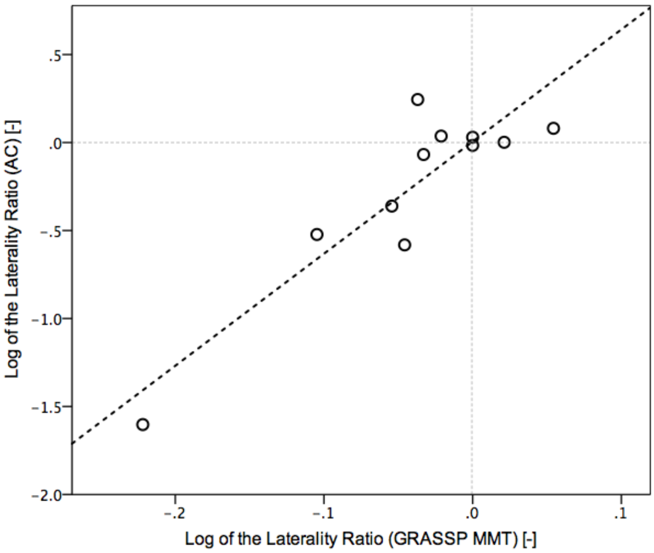

Figure 3.4. Relationship between two measures of laterality.
The log transformed laterality ratio calculated from the strength subpart of the Graded Redefined Assessment of Strength, Sensibility, and Prehension (GRASSP) was strongly correlated with the median of the log transformed laterality ratio of Activity Count measured during activity of daily living ($P < 0.01$, $r = 0.900$, Pearson correlation). Open circles indicate individual subjects. AC: activity count. MMT = manual muscle testing.

Next we investigated whether laterality, measured during ADL, influences independence in daily life. We correlated the SCIM items that are most closely related to ADL, i.e., SCIM mobility room and self-care, with sensor recordings during ADL activities (i.e. the data excluding self-propulsion). We found that laterality measured during ADL (log transformed laterality ratio) negatively correlated with independence during ADL (SCIM mobility room and self-care) suggesting that laterality negatively influences a subject's independence (P <

0.01, r = -0.739, Spearman correlation, Figure 3.5). Finally we investigated whether laterality, measured during ADL, was related to NLI or the completeness of the injury. No relation was found between laterality and NLI (P = 0.223, r = -0.380, Spearman correlation) or completeness (P = 0.937, r = 0.026, Spearman correlation).

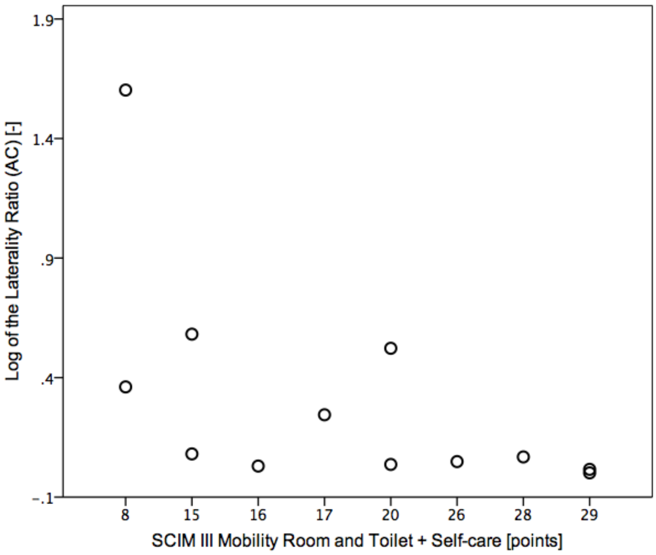

Figure 3.5. Relationship between independence and laterality.

Absolute laterality measured during activity of daily living was strongly negatively correlated with the Mobility room and self-care sub-domains of the Spinal Cord Independence Measure (P < 0.01, r = -0.739, Spearman correlation). Open circles indicate individual subjects. AC: activity count. SCIM: Spinal Cord Independence Measure.

3.5 Discussion

This is the first study to reveal that IMU technology can be applied to objectively assess the intensity and laterality of upper limb activities in cervical spinal cord injured subjects and that these assessments can sensitively differentiate between active and passive wheeling and other upper limb activities as required for ADLs. The findings of this study suggest that intense upper limb movements are required to achieve independence mobility-wise and that increased limb-use laterality negatively influences independence.

We assessed the relationship between the intensity of wheeling and the overall level of mobility according to the independence measure of mobility, distance travelled and peak velocity. To assess the intensity of self-propulsion, we analysed the data that was classified as manual, active wheelchair propulsion using our algorithm (Popp et al., 2016). We found a positive relationship between independence measures that are most closely related to wheelchair mobility, such as the SCIM III sub-score mobility indoor and outdoor, and the intensity of upper-extremity movements during self-propulsion. The results suggest that subjects that are able to perform more intense upper extremity movements during manual wheelchair propulsion are more independent mobility-wise. As the SCIM items that are most closely related to wheelchair mobility are all items that judge the ability of a subject to move independently for different distances (e.g. short distances, moderate distances between 10 and 100 metres and long distances longer than 100 metres), these results imply that intense movements are required in order to travel long distances. In this context, the positive relationship between independence in mobility and kinematic metrics (maximal forward velocity and distance travelled) supports the suggestion that subjects that can perform more intense upper extremity movements (i.e., those subjects that are more independent in mobility) can propel the wheelchair faster and for longer distances.

The correlation between the intensity of the self-propulsion and the maximal velocity suggests that the intensity of upper extremity movements during self-propulsion (i.e. those movements with larger amplitudes and higher acceleration) is a direct measure for velocity. This result is intriguing because it suggests that despite the use of different wheeling techniques (e.g. differences in the wrist orientation and force pattern during the pulling or pushing phases) upper-limb movements are performed without a substantial leak of kinetic energy in patients with a weak grip or poor hand function (i.e. despite a weak grip the hands do not slide on the hand rim). This means that cervical SCI subjects achieve high wheeling efficiency. This may be influenced by the effectiveness of gripping aids. Our results are equivalent to preliminary outcomes of a clinical evaluation protocol developed by Cowan and co-workers, which found that average peak force, measured by a device capable of measuring push forces on the hand-rim of a wheelchair, was a significant predictor of velocity (Cowan et al., 2008). Therefore clinicians may use our approach in order to evaluate wheelchair propulsion without the need to mechanically adapt the wheelchair (e.g. installing a wheel equipped with dynamometer).

In the field of SCI no specific measures of laterality exist and the effect of bi- versus unilateral usage of the upper extremities throughout the day has not been established. In order to test if IMU-measured laterality is a valid instrument to assess limb-use laterality in SCI subjects (construct validity), we firstly evaluated the differences between two conditions of laterality (left unilateral ADL and right unilateral ADL) and a condition of symmetrical activity (self-propulsion) and we found significant differences in laterality according to the ReSense recordings. This suggests that IMU-based methodologies are valid for assessing limb-use laterality because they discriminate between different degrees of laterality. In order to visually evaluate limb-use laterality, density graphs were produced. The density graphs of self-propulsion are centred, as would be expected because this is a bilateral movement for the most part, whereas the density graphs of unilateral activities (GRASSP QtG right and left) are, as expected, shifted to the respective side. Therefore, a density graph of a real-life recording can be used by therapists and medical doctors as a visual tool to assess limb-use laterality and intensity of the performed activities and to track changes over time.

Secondly we compared metrics derived from IMU measurements of limb-use laterality in daily life with independence measured with standardised clinical assessments and found that laterality measured clinically (MMT of the GRASSP) positively correlates with laterality measured by the IMUs worn in the clinical setting (concurrent validity).

We correlated independence measures most closely related to ADL (the “mobility room and toilet” and “self-care” sub-score items of the SCIM) with ADL IMU recordings (i.e. IMU recordings excluding periods of self-propulsion). In order to achieve this we removed the data that was classified as manual wheelchair propulsion from the IMU recordings. We found that limb-use laterality during ADL negatively correlated with independence suggesting that the more lateralised a person is, i.e. the more one side is affected compared to the other or the more one side is used compared to the other; the less independent they are in daily life. This finding makes sense because much of what we do in everyday life involves the use of both arms cooperatively (McCombe Waller and Whitall, 2008). Hence, if one arm is more strongly impaired than the other, the arms/hands cannot work together cooperatively to accomplish a task, for example as in a bimanual task like buttoning a shirt or a complimentary bimanual task like dishwashing, where one hand is used to stabilize the dishes while the other manipulates the dishwashing accessories. In this context, in some individuals the impairment of trunk balance may also lead to an increased usage of one side compared to the other, since in different situations one side may be used to stabilize the trunk (e.g. clamping one of the wheelchair's hand-grips between their upper- and forearm) while the other side is performing specific tasks.

Recently Bailey and colleagues measured adults with chronic stroke and found that decreased activity of the affected upper extremity was associated with increased severity of motor dysfunction and dependence in ADLs (Bailey et al., 2015). Contrary to the stroke field, in SCI there is no validated assessment that discriminates a more affected upper extremity, therefore we calculated the ratio between the right and the left hand. This means that our laterality metric ranged from negative to positive whereas the one used in stroke ranged from strong negative to weak negative (in the present study, values near zero indicated that there was similar activity in the left and right arms, whereas positive values indicated right-sided limb-use laterality and negative values indicated left-sided limb-use laterality). For comparison with Bailey and colleagues (Bailey et al., 2015), one should add a negative sign to all the positive laterality values in the present study. In this way our calculated laterality values range from -0.001 to -1.603 during ADL and from -0.004 to -0.124 during manual wheelchair propulsion. Having done this, as expected because strokes often affect people on one side, it appears that limb-use laterality is not as pronounced in SCI as it is in stroke where the median magnitude ratio for adults with chronic stroke was -2.2 (IQR = 6.2) but it appears to be more pronounced in SCI than in non-disabled adults were the median magnitude ratio was -0.1 (IQR = 0.3) (Bailey et al., 2015). Despite this, limb-use laterality remains an important issue in cervical SCI as it affects independence as supported by the fact that we found a strong negative correlation between laterality and independence. Additionally, because limb-use laterality does not seem to exist in non-disabled adults and because much of what non-disabled adults do everyday involves the use of both arms (McCombe Waller and Whitall, 2008), our results suggest that limb-use laterality is due to functional impairment and therefore may not be influenced by handedness.

We acknowledge a number of limitations. Firstly, we would like to point out that for the time-dependent outcome variable of distance travelled, a more extensive measurement time may be considered for future studies. The relatively short measurement time may in part explain the weak correlation between this metric and independence or intensity of self-propulsion. Secondly the low number of subjects included may not reflect all subsets of patients in regard to the characteristics of cervical SCI lesions. This fact limits the interpretability of the missing relationship between intensity of self-propulsion and NLI. Including a higher number of cervical SCI subjects might produce a stronger effect of NLI. Lastly we would like to state that the category “ADL” is an approximation of ADL, because with our sensor-based methodology we cannot identify every single ADL task. In this regard we would like to clarify that the aim of this study was not to detect if one subject performed more unilateral than bilateral tasks but to evaluate if there was a tendency toward an increased usage of one UL with respect to the other one. This was determined independently of whether unilateral or bilateral tasks were performed.

3.6 Conclusion

The present study demonstrates the ability of IMU-based upper-limb recordings to assess intensity and laterality in cervical SCI subjects. These methodologies reveal that the ability to perform intense movements during manual wheelchair propulsion may increase the independence of the subjects and that pronounced limb-use laterality may be associated with decreased independence in cervical SCI subjects. Novel IMU-based analysis methods can be used to assess clinically-relevant outcomes and may be used to gain insights into the long-term evolution of patients during recovery as well as into their independence in the home environment.

4 Multi-day recordings of wearable sensors are valid and sensitive measures of function and independence in human spinal cord injury[3].

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Detailed statement of individual contribution to this article. The study was designed by Michael Brogioli supported by the co-authors. The manuscript was written by Michael Brogioli and revised by the co-authors. Data was analyzed by Michael Brogioli. Michael Brogioli was responsible for data collection.

4.1 Abstract

Wearable sensor assessment tools have been proven to be reliable in measuring function in normal and impaired movement disorders during well-defined assessment protocols. Whilst such assessments can provide valid and sensitive measures of upper limb activity in spinal cord injury (SCI), none have yet been introduced into unsupervised daily recordings to complement clinical assessments during rehabilitation.

The objective of this study was to measure the overall amount of upper-limb activity in acute SCI subjects using wearable sensors and relate this to lesion characteristics, independence and function.

The overall amount of upper extremity activity counts, measures of wheeling (speed and distance) and limb-use laterality were measured in 30 in-patients with an acute cervical or thoracic SCI three months after injury. The findings were related to the international standards for neurological classification of SCI, the spinal cord independence measure and the upper extremity motor scores of the Graded and Redefined Assessment of Strength, Sensibility and Prehension.

Overall upper extremity activity counts were successfully recorded in all patients and correlated with the neurological level of injury and independence. Clinical measures of proximal muscle strength were related to overall activity count and peak velocity of wheeling. Compared to paraplegics, tetraplegics showed significantly lower activity counts and increased limb-use laterality.

This is the first cross-sectional study showing the feasibility and clinical value of sensor recordings during unsupervised daily activities in rehabilitation. The strong relationship between sensor-based measures and clinical outcomes supports the application of such technology to assess and track changes in function during rehabilitation and in clinical trials.

4.2 Introduction

Wearable sensor technology, such as accelerometers and inertial measurements units (IMUs), combined with empirical approaches or trained algorithms are increasingly applied by clinicians and researchers to monitor the type, quantity, and quality of everyday activities (Dobkin and Dorsch, 2011). Recently, accelerometers have been used to predict l-Dopa response in tremor patients (Imbach et al., 2014), to quantify limb non-use in chronic stroke sufferers (Michielsen et al., 2012) and to monitor changes in motor capacity during rehabilitation in children with cerebral palsy (Strohrmann et al., 2013). In the field of spinal cord injury (SCI), Postma and co-workers validated an accelerometer-based activity monitor in a laboratory-setting. This monitor was able to detect wheelchair propulsion with a moderate accuracy in SCI subjects. However, it was a multiple-sensor set-up requiring wired connections between the sensors and a 700g data recorder which was worn on the body, hence, such a system is not applicable in unobserved/uncontrolled observations of daily activities (Postma et al., 2005). Using a smaller and lighter tri-axial accelerometer, Sonnenblum and coworkers developed and validated a methodology to continuously measure wheelchair movements and distances travelled with an accuracy of about 90% (Sonenblum et al., 2012a). Recently, we have developed and validated a robust IMU-based assessment capable of distinguishing active and passive wheelchair propulsion with an accuracy greater than 93%, and kinematic parameters like distance travelled with an accuracy greater than 97% in a real-world setting (Popp et al., 2016).

So far, the use of such technology in SCI has been limited to studies that evaluate how much people who mobilize with a wheelchair move, tracking distance wheeled (Coulter et al., 2011, Sonenblum et al., 2012b) or that evaluate if physical activity recommendations are met (Warms et al., 2008) and if behavioral interventions help meet those recommendations (Nooijen et al., 2016). This is because it is well know that persons with disabilities are less likely to be physically active that healthy subjects (Heath and Fentem, 1997) and that people affected by SCI show a lower physical activity level than able bodied people (Dearwater et al., 1985). A sedentary lifestyle in wheelchair-bound subjects increases the risk of secondary conditions such as diabetes or cardiovascular diseases (Myers et al., 2007), consequently an active lifestyle may reduce risk-factors such as high density lipoprotein and cholesterol concentration (Brenes et al., 1986). The advantages of portable-sensor technology may not be limited to an objective evaluation of public health guidelines but may provide notable benefits if used as a functional assessment during and following rehabilitation (Rahimi et al., 2011). In a previous study the relationship between the level of physical activity and lesion characteristics during in-patient rehabilitation was found to be rather weak (van den Berg-Emons et al., 2008). However lesion characteristics were assessed in a binary fashion (e.g. below or above the segment T1) and, the level of physical activity was not compared to functional outcome. So far, a reasonable comparison between wearable sensors and functional or independence scores has not yet been established in SCI.

The purpose of this study was to prove the feasibility of wearable-sensor technology in a multi-center study design and to determine the relationship between sensor-derived upper limb activity-metrics and patients' characteristics according to sensitive, standardized clinical assessments in an inpatient cross-sectional set-up three months after injury.

4.3 Methods

4.3.1 Subjects

A total of 30 SCI subjects (age 46.43 ± 16.91 years, range 19-74 years, 21 male, 11 paraplegic and 19 tetraplegic subjects) were recruited from three specialized SCI centers in Switzerland: the Swiss Paraplegic Centre in Nottwil (13 patients), Balgrist University Hospital in Zurich (12 patients) and Rehab Basel in Basel (5 patients). Included in this study were patients with acute traumatic SCI (70-98 days post-injury) with any grade (A, B, C and D) of the ASIA Impairment Scale (AIS) undergoing primary in-patient rehabilitation and mobilized to undergo an active rehabilitation program. A complete overview of the neurological level of injury (NLI) and completeness can be found in Figure 4.1. Due to the broad inclusion criteria, patients with different extents of walking impairment were eligible, i.e. from those that were independently ambulatory or walking with devices to wheelchair-bound patients relying on a manual wheelchair or powered wheelchair. Consequently patients performed bouts of mobility according to their ability. 26 patients were wheelchair-bound (two patients relied completely on a powered wheelchair, three patients occasionally used a complete or partial power assist on their wheelchair), four patients were fully ambulatory. Sufficient cognitive ability to follow verbal instructions was required to participate in the study. Subjects with conditions, other than SCI, that were expected to affect UL function, such as neurological diseases (i.e. plexus paresis) as well as orthopedic or rheumatologic diseases (e.g. osteoarthritis) were excluded from the study. Subjects were also excluded in case that they were suffering a premorbid or an ongoing depression or psychosis.

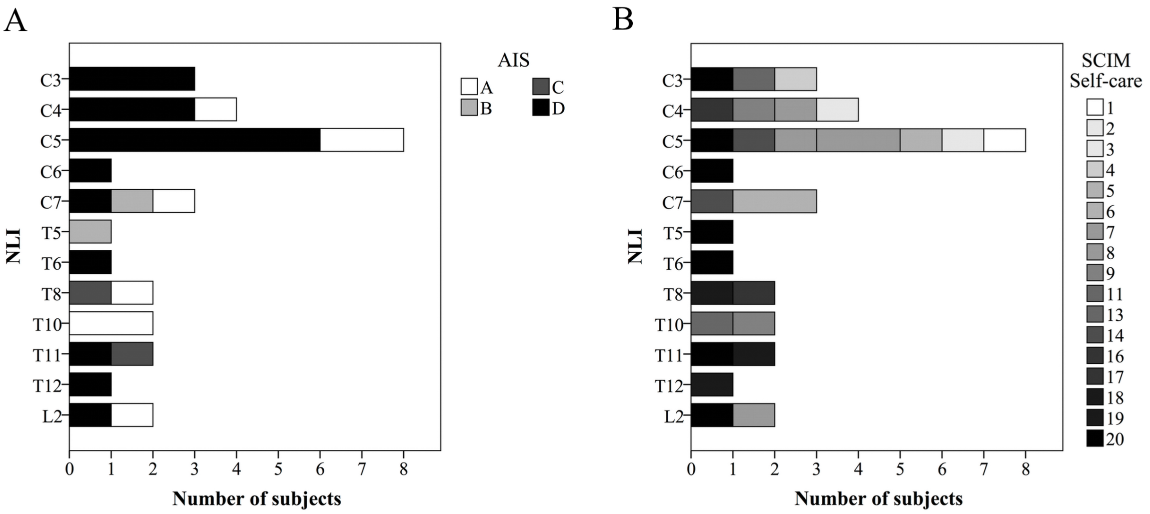

Figure 4.1. Description of the study sample.

The histogram shows the number of subjects belonging to each neurological level of injury (NLI). A: Boxes are color coded to indicate the ASIA Impairment Scale (AIS). Complete subjects (AIS A and B) are marked with white or light gray whereas incomplete subjects are marked with dark gray or black. B: Boxes are color coded to indicate the scores of the self-care domain of the Spinal Cord Independence Measure (SCIM).

4.3.2 Assessments

In order to report on neurological impairment, capacity of motor function and independence of patients, various standardized clinical assessments were performed. Neurological assessment was performed following the International Standards for Neurological Classification of SCI (ISNCSCI) (Kirshblum et al., 2011b) and summarized in the NLI and the extent of lesion according to the AIS. Upper limb muscle function was assessed using the motor domain of the Graded and Redefined Assessment of Strength, Sensibility and Prehension (GRASSP) (Kalsi-Ryan et al., 2012). This domain is assessed with the manual muscle test (MMT) of 10 upper limb muscles on both arms (scores range 0-50 per arm). In order to have a more sensitive measure of strength values from M3 to M5 (Noreau and Vachon, 1998), strength tests with a hand-held dynamometer (HHD) of three key UL movements, were performed: elbow flexion (biceps), elbow extension (triceps), shoulder flexion (deltoid) (Stoll et al., 2000). Finally, the Spinal Cord Independence measure (SCIM) was used to assess the level of independence in daily life (scores range 0-100) (Itzkovich et al., 2007).

4.3.3 Sensor device

The inertial measurement unit (IMU) used in this study was the ReSense module (Leuenberger and Gassert, 2011). This device records raw data with a 3D accelerometer, 3D gyroscope, 3D magnetometer and barometric pressure and with all sensing capacity turned on it can record for at least 24 h. For the analysis, signals coming from the magnetometer and the barometric pressure sensor were omitted.

4.3.4 Data collection and procedure

Research staff consisting of movement scientists, occupational therapists and physiotherapists were trained to ensure that the GRASSP and HDD examinations, as well as ReSense measurements, were performed correctly. Independent clinicians rated the SCIM questionnaire and the ISNCSCI protocols. For the ReSense measurement patients were fitted with one ReSense module on each wrist and one on the right wheel of the wheelchair as reported previously (Popp et al., 2016). Subjects were instructed to wear the modules continuously over the period of three weekdays (between Monday and Friday), covering their whole days, i.e. rehab program and daily off-times. The research staff was asked to start the ReSense measurement on Monday or Tuesday. Patients were told to remove the sensors only during bathing or any activity where the sensor would be submerged in water for long periods of time. The rehabilitation protocol was prescribed by independent clinicians at the separate centres and therefore, it was not influenced in any way by this study.

Due to battery-life the full sensing capacity of ReSense is limited to about one day and therefore the sensors needed to be exchanged daily with a new set of fully charged modules. In order to measure distance travelled and speed over an extended amount of time, an additional module with only the triaxial accelerometer enabled was fixed on the wheel, thereby increasing the recording time by up to seven days.

4.3.5 Data analysis

After completing the recording, data were transferred from the internal SD-card via a custom-designed base station to a PC. All data were resampled at 50Hz using a cubic spline interpolation function. This enables the temporal alignment of recordings from different sensor modules. The raw data was analyzed offline using MATLAB R2013a (MathWorks, Natick, MA, U.S.A). In order to ensure the integrity of the data, visual inspection was performed. Data recorded during sleep phases and phases when the sensors were taken off was removed prior to the analysis. As a consequence sensor-based metrics are derived from the time the patients are awake.

4.3.6 Calculation of upper limb activity metrics

An IMU-based multi-sensor set-up consisting of three ReSense modules (right wrist, left wrist and right wheel) and an accelerometer-based single sensor set-up (right wheel) were used (Table 4.1). The multi-sensor set-up was used to extract upper limb (UL) activity metrics and label behavioral events (i.e. active-propulsion). The long-lasting single sensor set-up was used to extract speed and distance parameters as wheelchair-mobility metrics require an extensive measurement time in order to achieve adequate reliability (Sonenblum et al., 2012b).

Set-up & sensing	Number of modules & position	Duration of recordings	Metrics calculated
IMU-based multi-sensor set-up - 3D accelerometer - 3D gyroscope - 3D magnetometer - Pressure sensor (altimeter)	3 ReSense modules - Right wheel - Right wrist - Left wrist	Up to 3 days (Modules are exchanged and charged daily)	Upper limb activity - Activity counts - Limb-use laterality (RSAL) Behavioral parameters - Percentage active/passive wheeling (RSWA) - Activity count ratio (self-propulsion/total counts)
Accelerometer-based single sensor set-up - 3D accelerometer	1 ReSense module - Right wheel	Up to 7 days	Time/distance parameter (RSWA) - Duration - Distance - Velocity Behavioral parameters (RSWA) - Percentage active/passive wheeling

Table 4.1. Overview and characteristics of the ReSense set-ups used for the recordings.

RSAL: ReSense Assessment of Laterality. RSWA: ReSense Wheeling Algorithm.

4.3.7 IMU derived outcome measures

4.3.7.1 Overall activity counts

Activity counts (AC) were used as a measure of UL activity. In order to derive AC, the acceleration signal of each wrist sensor was filtered with a 2nd order Butterworth high-pass filter with a cut-off frequency of 0.25 Hz. The magnitude was calculated and integrated over an epoch of one minute. In order to compute the total UL AC over the complete measurement, all AC epochs of the right and left arms were summed and normalized by time.

4.3.7.2 Limb-use laterality

Limb-use laterality was assessed with the ReSense Assessment of Laterality (RSAL), a new IMU-based methodology validated in stroke (Bailey et al., 2014) and in SCI (Brogioli et al., 2016a), capable of measuring the prevalence of limb-use laterality in day-to-day activities. Absolute laterality is scored from zero to infinite where the higher the value the more pronounced the limb-use laterality.

4.3.7.3 Speed-distance parameters and percentage active wheeling

Data were further analyzed with the ReSense Wheeling-Algorithm (RSWA, set-up II.a), an algorithm previously developed by our group (Popp et al., 2016) capable of reliably discriminating active (self-propelled) and passive (attendant-propelled) wheelchair propulsion and estimating speed and distance parameters. The labeling of active wheelchair propulsion allows the distinction of total UL activity compared to UL activity related to active wheeling and therefore allows the computation of the count ratio (self-propulsion counts divided by the total number of counts). Distance (in meters) and peak velocity (m/s) were also computed with the RSWA using the acceleration signal of the single-sensor set-up of the right wheel (RSMA set-up III.b). Peak velocity was computed using the 90th percentile (10th percentile for backward peak velocity) in order to have a more robust metric against outliers in peak velocity.

4.3.8 Statistical analysis

The statistical analysis was performed using IBM SPSS Statistics version 19 (IBM, Armonk, NY, U.S.A).

Sample size: We recruited 30 SCI patients who were heterogenic in terms of their mobility and impairments. Hence the number of subjects included in different analyses varies in order to permit robust, non-biased, statements. For example, to evaluate the relationship between muscle function and peak velocity, only wheelchair-bound subjects that did not use any kind of power assist were included. This is because power assist permits the user to reach higher velocities with less muscle effort. Sample sizes for each analysis are presented in Table 4.2.

Metric	**Number of patients included**	**Exclusion criteria**
Activity Count, limb-use laterality	30 (11 paraplegic, 19 tetraplegic)	N/A
Percentage active wheeling and counts ratio	24 (10 paraplegic, 14 tetraplegic)	Ambulant patients, patients using exclusively an electric wheelchair
Speed and distance parameters (active)	21 (10 paraplegic, 11 tetraplegic)	Ambulant patients, patient using exclusively an electric wheelchair, patients using a manual wheelchair with electro assist
Length of IMUs-based set-up recordings	30 (11 paraplegic, 19 tetraplegic)	N/A
Length of accelerometer-based set-up recordings	26 (10 paraplegic, 16 tetraplegic)	Ambulant patients

Table 4.2. Overview on the sample size and exclusion criteria corresponding to the metrics used for each statistical analysis performed.

Variable reduction: In order to reduce redundancy in the multiple GRASSP variables a Principal Components Analysis (PCA) was performed with the MMT values of the tetraplegic subjects. The set of variables was reduced into principal components. Each GRASSP item was analyzed as an individual ordinal variable scored from 0 to 5, and treated as interval scale variable because the number of levels for each variable is higher than 3-level items (Gorsuch, 1983).

Components were retained following subjective judgment by examining the leveling off of the eigenvalues and their meaning was analyzed. For this purpose, a rotated solution was computed with an orthogonal rotation. The interpretation of the extracted components was based on the component loading on the variables.

Finally, for each extracted component, component scores were computed in order to relate each component with overall upper limb activity.

Associations: Spearman’s rank-order correlation coefficient was used to inspect the associations between assessment scores and sensor metrics, due to the ordinal nature of the ISNCSCI protocol, the SCIM and the domain scores of the GRASSP. If the data were continuous and normally distributed, the Pearson product-moment correlation coefficient was preferred. Parameters were checked for normality with the Shapiro-Wilk test of normality. A Spearman or Pearson rho value larger than 0.60 was considered as a strong correlation, and the significance level was set to $p < 0.05$.

Differences between groups: The comparison between paraplegic and tetraplegic groups was performed with a Mann-Whitney U test or an independent samples T-Test, depending on the nature of the values being compared and their distribution. When the variable was not normally distributed and/or in the case of ordinal data the Mann-Whitney U test was preferred.

4.4 Results

4.4.1 Recordings

The mean length of the genuine data analyzed for the IMU-based set-up was 2.87 ± 0.35 days (shortest recording 2 days, longest recording 3 days) and for the accelerometer-based set-up 6.15 ± 1.12 days (shortest recording 4 days, longest recording 7 days). Patients were awake for 15.31 ± 1.09 (range: 13.38 – 17.76) hour/day) hours per day. Wheelchair users actively propelled the wheelchair for 95.70% ± 14.76% (range: 39.06% - 100%) of the wheeling time. They actively covered 2120.50 ± 1296.27 m per day (range: 46.03m - 4936.59m) wheeling forward and 167.62 ± 158.58 m per day (range: 5.06m - 812.01m) maneuvering or wheeling backwards.

4.4.2 Relation between independence and overall UL activity

In order to investigate the relationship between independence in daily living and overall UL activity, UL activity was correlated with the SCIM self-care subdomain, which is the subdomain that reflects upper limb activity. Overall UL activity strongly correlated with SCIM self-care ($N = 30$, $P < 0.01$, $r = 0.692$, Spearman correlation, Figure 4.2).

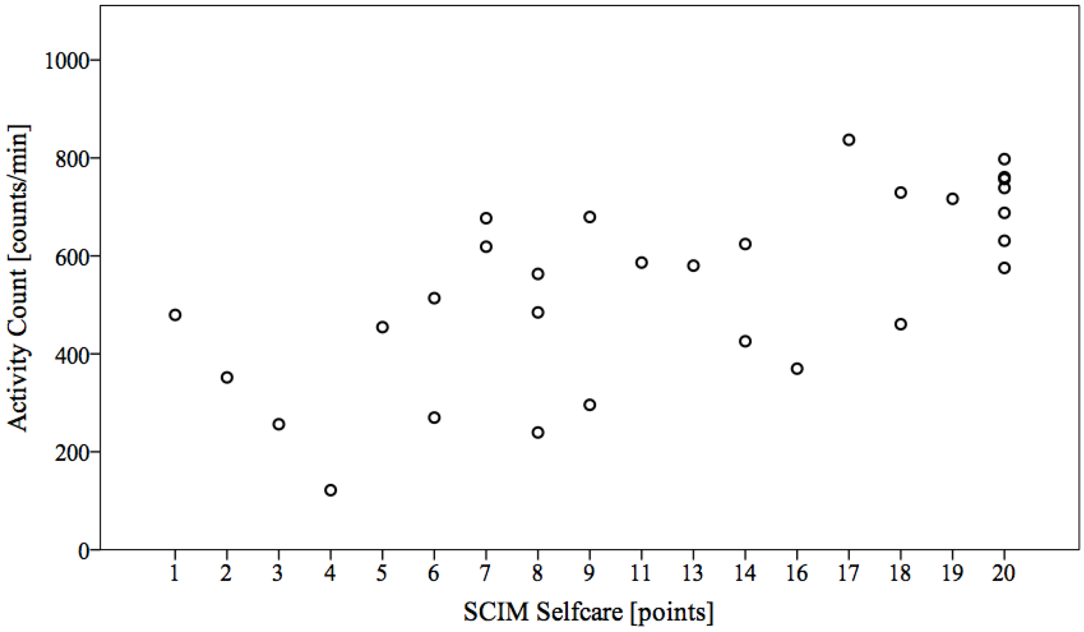

Figure 4.2. Strong correlation between overall upper limb (UL) activity and independence in daily living.

The graph shows the strong correlation between the overall amount of UL activity and the independence in self-care ($P < 0.01$, $r = 0.692$, Spearman correlation) for 30 SCI patients.

4.4.3 Relation between lesion characteristics and overall UL activity

In order to investigate the relationship between lesion characteristics and overall UL activity, correlations between the neurological level of the lesion and completeness scored as part of the ISNCSCI protocol were investigated. Overall UL activity moderately correlated with NLI ($N = 30$, $P < 0.05$, $r = 0.412$, Spearman correlation) but was not significantly related to completeness ($N = 30$, $P = 0.28$, $r = -0.203$, Spearman correlation).

4.4.4 Relation of upper limb muscle function and overall UL activity

The GRASSP MMT tests several proximal and distal upper limb muscles. In order to reduce multi-collinearity and therefore reveal variables that are rather closely correlated and identify variables that are less correlated, a PCA was performed with the MMT values of the tetraplegic subjects. Two principal components (PC1 and PC2), which explained 55.29% and 21.56% of the total variance, respectively, were retained (cumulative 76.85% of total variance explained). An orthogonal rotation was used in order to interpret the results and it revealed strong loading of distal muscle items on component 1 and proximal muscles items on component 2 (Table 4.3). The relationship between overall UL activity and component scores showed that the overall UL activity was not significantly related to PC1 ($N = 18$, $P = 0.580$, $r = 0.140$, Pearson correlation) but was strongly related to PC2 ($N = 18$, $P < 0.01$, $r = 0.649$, Pearson correlation). Note that one subject was excluded from this analysis because of missing MMT values.

GRASSP MMT items	PC1	PC2
Flexor pollicis left	**.962**	.012
Flexor digitorum profundus left	**.930**	-.074
Finger abductor 5 left	**.928**	.030
Opponens pollicis left	**.917**	.028
Finger abductor 2 left	**.897**	.121
Extensor digitorum left	**.879**	-.008
Finger abductor 5 right	**.868**	.249
Opponens pollicis right	**.834**	.290
Finger abductor 2 right	**.834**	.233
Flexor pollicis right	**.827**	.319
Flexor digitorum profundus right	**.767**	.317
Extensor digitorum right	**.724**	.427
Deltoideus right	.003	**.924**
Biceps right	-.093	**.918**
Extensor carpi radialis right	.151	**.841**
Deltoideus left	.211	**.821**
Biceps left	-.010	**.796**
Extensor carpi radialis left	.310	**.730**
Triceps left	.557	**.620**
Triceps right	.511	**.617**

Table 4.3. Rotated component matrix showing component loading for all the MMT variables of 18 tetraplegic patients.

GRASSP MMT items are visualized in the first column whereas the component loadings are visualized in the second and third column. Higher loadings are visualized in bold (if > 0.6). PC1 load mainly on distal MMT items, whereas PC2 load mainly on proximal MMT items.

4.4.5 Speed and distance parameters, activity count of self-propulsion and limb-use laterality

In the interest of evaluating the relationship between total distance travelled and peak velocity with muscle function, correlation analyses between kinematic metrics and muscle function according to the MMT and the HHD of three key muscles were performed (Table 4.4). The results show that muscle strength is most closely related to peak velocity and less related to distance suggesting that longer distances can be achieved with slow speeds and impaired muscle function.

	Distance travelled per Day		**(Peak) Velocity**	
	Active Forward	**Active Backward**	**90th percentile Active Forward**	**10th percentile Active Backward**
MMT Proximal	0.405	-0.331	0.463*	-0.388
MMT Distal	0.483*	-0.327	0.600**	-0.690**
HHD Shoulder Flexion (Delta)	0.391	-0.415	0.626**	-0.370
HHD Elbow Flexion (Biceps)	0.311	-0.421	0.633**	-0.414
HHD Elbow Extension (Triceps)	0.270	-0.332	0.461*	-0.546*

Table 4.4. Relationship between wheeling distance and peak velocity with muscle function for 21 SCI patients.

Forward and backward peak velocity is highly related to proximal and distal muscle function, according to the GRASSP MMT. Correlation analysis between forward and backward peak velocity and hand hold dynamometer (HDD) scores on 3 key muscles revealed that delta, biceps and triceps highly influences forward velocity but that only the triceps seems to play a role in backward velocity.

To determinate if there was a difference in behavioral parameters, such as limb-use laterality, between paraplegic and tetraplegic patients, comparisons between group means were performed. The mean count ratios (self-propulsion counts divided by the total amount of counts) were 0.27 ± 0.11 for paraplegic patients and 0.19 ± 0.12 for tetraplegic patients. A Mann-Whitney U test revealed that the count ratio of paraplegic subjects (mean rank = 15.90) was significantly higher than for tetraplegic subjects (mean rank = 10.07, U = 36, z = -1.991, $p <0.05$), meaning that in paraplegic patients a much higher amount of upper limb activity came from self-propulsion. The same two groups of patients showed a significant difference in overall UL activity, where paraplegic subjects performed an average of 656.24 ± 124.72 counts/min and tetraplegic subjects an average of 491.70 ± 166.19 counts/min ($t(22)=2.639$, $P < .01$, independent sample t-test) suggesting that self-propulsion counts make a high contribution to the overall UL activity.

Finally, mean absolute limb-use laterality was 0.17 ± 0.12 (range: 0.01 – 0.46) for paraplegic patients and 0.93 ± 1.11 (range: 0.03 – 3.57) for tetraplegic patients (Figure 4.3). A Mann-Whitney U test revealed that limb-use laterality of tetraplegic subjects (mean rank = 18.00) was significantly higher than for paraplegic subjects (mean rank = 11.18), U = 57, z = -2.044, $p <0.05$.

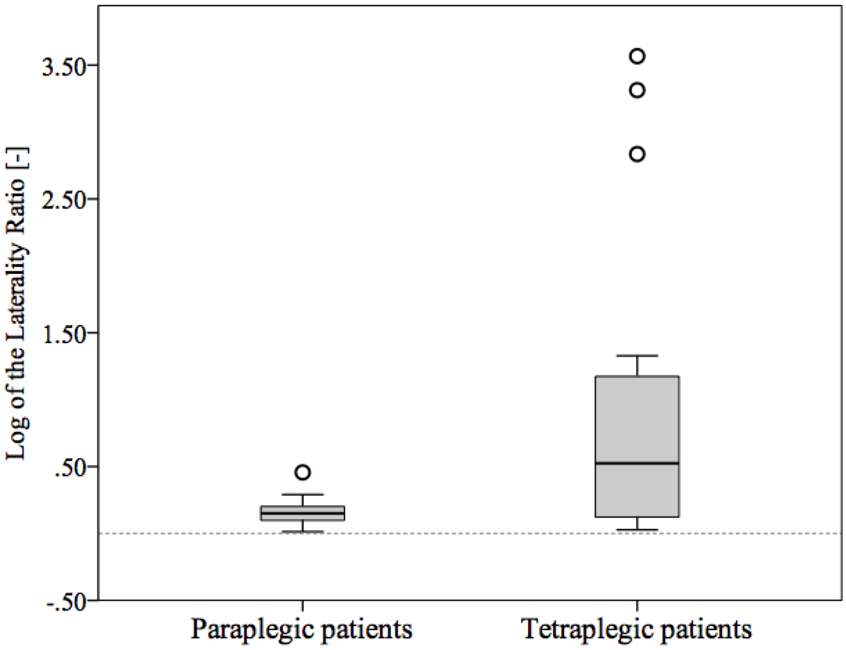

Figure 4.3. Absolute limb-use laterality between groups.

The boxplot shows the median (the bottom represents the first quartile, the top represents the third quartile and the whisker is 1.5 times the interquartile range) of limb-use laterality calculated as the absolute log of the laterality ratio for a group of 11 paraplegic subjects and a group of 19 tetraplegic subjects. A Mann-Whitney U test showed that the mean rank (18.00) for tetraplegic subjects were statistically significantly higher than for paraplegic subjects (mean rank = 11.18), U = 57, z = -2.044, p = 0.041.

4.5 Discussion

The aim of this study was to assess unsupervised upper-limb activity during rehabilitation in SCI using non-obtrusive wearable sensors and to relate this to clinical assessment scores. We showed that wearable sensors are feasible and provide valid and sensitive information about UL activity and function in SCI. Moreover, this is the first study to reveal that these measures strongly correlate with neurological impairment and are applicable for tracking clinical outcomes in SCI rehabilitation.

The relationship between lesion characteristics and the level of physical activity has been addressed before in acute SCI in-patients. Van den Berg-Emons and coworkers evaluated if the level of lesion (above or below the T1 segment) and completeness (motor complete or incomplete) were determinants of changes in physical activity during in-patient rehabilitation but found no relationship (van den Berg-Emons et al., 2008). However, the assessment of lesion characteristics in a binary fashion is rather less sensitive for analyzing the relationship between lesion characteristics and upper extremity activity in the heterogenic SCI population (Spiess et al., 2009, van Hedel and Curt, 2006). Therefore, we assessed lesion characteristics applying the ISNCSCI protocol that compiles multiple information about level of lesion, motor and sensory scores across all spinal segments. The latter approach showed a positive relationship between neurological impairment (level of lesion) and overall UL activity in contrast to the simplified distinction of AIS grades. This is not surprising because the AIS grades are biased towards the definition of sacral sparing and therefore do not necessarily reflect the overall impairment following SCI (Spiess et al., 2009).

The introduction of novel treatments in SCI has been challenging because of the need to target appropriate patients and providing satisfactory clinical efficacy (Alexander et al., 2009, Casha et al., 2012, Lammertse et al., 2012). In essence the latter depends on revealing meaningful improvements in neurological impairment and performance, such as independence during daily life (Steeves et al., 2012). For this purpose the SCIM is recommended as a comprehensive assessment of functional recovery as it assesses overall ADL (Alexander et al., 2009). The present study revealed a strong relationship between the SCIM self-care and sensor-based overall UL activity and indicates that activity measures, as measured by IMU during daily activities, can be used as a surrogate for ADL levels. While sensor-based measures are scored on a continuous scale, instead of the ordinal scale of the SCIM, they may be more sensitive at revealing even small differences and therefore are complementary to clinical scores for tracking changes in clinical trials. In addition, IMU measures are unsupervised and unobtrusive and therefore applicable over a longer and continuous time period and do not require the therapist or the patient to fill out a questionnaire.

In order to evaluate clinically meaningful changes, it is important to explore relationships between neurological function and performance-based outcome measures. Upper extremity motor scores either using the ISNCSCI or GRASSP key muscles, have been proven to assess recovery profiles of the UL over one year after injury (Steeves et al., 2012, Kalsi-Ryan et al., 2014, Velstra et al., 2015). Accordingly we showed that specifically the proximal motor scores of the GRASSP are strongly related to overall UL activity. Even more specific is the strong correlation between the peak velocity of wheeling and the function of specific muscles (i.e. biceps strength). Therefore, the combination of activity measures (i.e. activity counts in relation to independence) and measures of specific motor functions (i.e. detailed assessment of active wheeling) will enable a comprehensive evaluation of changes in upper limb function and an appreciation of the effectiveness of a therapeutic intervention.

Measures of limb-use laterality have been performed and show that upper limb activity is more lateralized in adults with stroke (median absolute magnitude ratio -2.2, IQR = 6.2) compared to non-disabled adults, where dominant and non-dominant upper limbs were active to a similar degree (median absolute magnitude ratio 0.1, IQR = 0.3) (Bailey et al., 2015). In a previous study we showed that limb-use laterality in tetraplegic subjects negatively influences independence as laterality values ranged from 0.00 to 1.60 and were negatively related to scores of independence in self-care (Brogioli et al., 2016a). These findings were also confirmed in the present study during unsupervised recordings with laterality values higher in tetraplegic subjects compared to paraplegic subjects who had laterality values in the same range as non-disabled adults. Our findings provide additional evidence that changes in everyday limb-use laterality are most likely caused by functional impairments rather than hand-dominance. This supports the assumption that in the healthy condition much of what we do every day involves the use of both arms regardless of handedness (McCombe Waller and Whitall, 2008).

4.5.1 Limitations

We acknowledge a number of limitations. For the analysis of the relationship between the structure of the lesion and the overall activity a more sensitive assessment may be considered (e.g. neuroimaging) as certain aspects of the ISNCSCI may be insensitive and highly variable. Secondly, upper-limb activity may be influenced, to some extent, by the clinical setting (e.g. therapies) or by decreased trunk control (e.g. some individuals use their arms to stabilize the upper body increasing UL activity or perform fewer UL movements due to the loss of balance) influencing the aforementioned relationships. Lastly, we would like to state that measures of overall upper limb activity and limb-use laterality measure the prevalence of UL activity and limb-use laterality during day-to-day activity but, with the exception of active wheeling, are not able to distinguish, in detail, the type of activity performed.

4.6 Conclusion

This study showed the clinical applicability of wearable sensors for measuring UL activity in day-to-day, unsupervised and non-obtrusive recordings in SCI. Sensor-based metrics allow a comprehensive evaluation of upper limb recovery as measures of overall UL activity and peak velocity were closely related to clinical assessments of function and independence. Wearable sensors are promising as complementary clinical assessments as they can quantify patients activities outside of rehabilitation sessions and thus provide novel insights into overall performance that likely have an impact on outcome in clinical trials.

5 Monitoring upper-limb recovery after cervical spinal cord injury: insights beyond assessment scores[4]

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Detailed statement of individual contribution to this article. The study was designed by Michael Brogioli supported by the co-authors. The manuscript was written by Michael Brogioli supported by Sophie Schneider and revised by the co-authors. Data was analyzed by Michael Brogioli and Sophie Schneider. Michael Brogioli was responsible for data collection. Creation of the figures in R was done by Sophie Schneider.

5.1 Abstract

Background: Pre-clinical investigations in animal models demonstrate that enhanced upper-limb (UL) activity during rehabilitation promotes motor recovery following spinal cord injury (SCI). Despite this, following SCI in humans, no commonly applied training protocols exist and therefore activity-based rehabilitative therapies (ABRT) vary in frequency, duration and intensity. Quantification of UL recovery is limited to subjective questionnaires or scattered measures of muscle function and movement tasks.

Objective: To objectively measure changes in UL activity during acute SCI rehabilitation and to assess the value of wearable sensors as a novel measure that is complimentary to standard clinical assessments tools.

Methods: The overall amount of UL activity and kinematics of wheeling were measured longitudinally with wearable sensors in 12 thoracic and 19 cervical acute SCI patients (complete and incomplete). The measurements were performed up to seven consecutive days, and simultaneously, SCI-specific assessments were made during rehabilitation sessions one, three, and six months after injury. Changes in UL activity and function over time were analysed using linear mixed models.

Results: During acute rehabilitation the overall amount of UL activity and active distance wheeled significantly increased in tetraplegic patients, but remained constant in paraplegic patients. The same tendency was shown in clinical scores with the exception of independence, which showed improvements at the beginning of the rehabilitation period, even in paraplegic subjects. In the later stages of acute rehabilitation, the quantity of UL activity in tetraplegic individuals matched that of their paraplegic counterparts despite their greater motor

impairments. Both subject groups showed higher UL activity during therapy-time compared to the time outside of therapy time.

Conclusion: Tracking day-to-day UL activity is necessary to gain insights into the real impact of a patient’s impairments on their UL movements during therapy as well as during their leisure time. In the future, this novel methodology may be used to reliably control and adjust ABRT, and to evaluate the progress of upper limb rehabilitation in clinical trials.

5.2 Introduction

Cervical spinal cord injury (SCI) results in profound and devastating life changes for the affected individuals due to the loss of arm and hand function (Lu et al., 2015). Consequently, this function is the one that tetraplegics would most like to regain (Anderson, 2004, Snoek et al., 2004). However, there is currently no effective treatment for SCI (Alexander et al., 2009, Casha et al., 2012, Lammertse et al., 2012), damaged axons do not repair spontaneously and regenerative growth is extremely limited, if it happens at all (Blesch and Tuszynski, 2009). Therefore, the functional recovery that is observed is either functional compensation and/or due to plastic changes in intact fibres (Curt et al., 2008). Preclinical data suggest that functional reorganisation of the adult mammalian central nervous system (CNS) can be promoted through activity based rehabilitative therapies (ABRT) (Sadowsky and McDonald, 2009), which has been shown to improve forelimb function and enhance plastic sprouting of undamaged corticospinal tract fibres in adult rats (Brus-Ramer et al., 2007, Carmel et al., 2010, Maier et al., 2008, Song et al., 2016, Starkey et al., 2011).

In clinical research, the influence of UL activity on functional recovery is less clear. This is on the one hand, because there are few studies investigating this issue and on the other hand because the results that do exist are contradictory (Kloosterman et al., 2009). Typical challenges to such studies are the limited sample size due to low incidence of SCI, frequent subject dropout and poor adherence due to a high frequency of secondary complications in cervical patients as well as the fact that UL movements are complex because they involve a variety of non-cyclic movements that are difficult to measure objectively (Lu et al., 2015, Spooren et al., 2009). The latter may be the reason why no commonly applied training protocols exist. The consequence is that ABRT are highly variable resulting in different protocols in terms of training characteristics (e.g. frequency, duration or intensity) and in terms of outcome measures used to test their efficacy (Spooren et al., 2009). Additionally, the assessment of UL activity outside of training sessions is often limited to self-reported questionnaires that have been shown to be rather imprecise, overestimating the actual activity of the subject (van den Berg-Emons et al., 2011). As a consequence the efficacy of ABRT, which can be evaluated in terms of increased quantity of UL movements, is difficult to assess. This is because functional improvements cannot be exclusively associated with ABRT-induced increases in neuronal activity, as the overall UL activity performed outside therapy sessions cannot be accurately assessed. Therefore, an objective daylong measure of performance is needed to assess the effect of an activity-based increase in neuronal activity on functional recovery, and to track the evolution over the inpatient stay.

The use of wearable sensors during SCI rehabilitation could be considered as a feasible solution for measuring total UL activity. Wearable sensors provide objective and continuous measures and outcomes can be compared between studies (Chen and Bassett, 2005). In this regard, wearable sensors have been used in the field of SCI research to determine everyday physical activity (Nooijen et al., 2012, Nooijen et al., 2016, van den Berg-Emons et al., 2008). However, as these studies focused exclusively on measuring physical activity rather than assessing functional recovery they were not performed within standardised time-frames and the activity outcomes were not compared with standardised clinical outcomes (Nooijen et al., 2012, Nooijen et al., 2016, van den Berg-Emons et al., 2008). For this reason, in a previous study we showed the feasibility and validity of sensor-based outcome metrics in measuring UL function and independence during cross-sectional recordings (Brogioli et al., 2016b). Given the validity and sensitivity of these measures, the purpose of this study was to assess the quantity of upper-limb activity and its changes during acute rehabilitation in a cohort of tetraplegic and paraplegic patients in standardised SCI-specific time frames.

5.3 Methods

5.3.1 Subjects

31 subjects with SCI (age 47.84, SD: ± 17.50 years, range: 20 to 77 years, ASIA A-D, 12 paraplegic and 19 tetraplegic subjects, 22 male and 9 female) participated in this study. Additional demographic information can be found in Table 5.1. Participants were recruited from the Swiss Paraplegic Centre in Nottwil, Switzerland, the Balgrist University Hospital in Zurich, Switzerland, and the Rehab Basel in Basel, Switzerland. Acute wheelchair-bound patients with a traumatic SCI were included in this study one month (Acute I, 16 – 40 days, 30 Subjects) or three months (Acute II, 70 – 98 days, 31 Subjects) after injury according to the time frames of the European Multicenter Study about SCI (EMSCI; www.emsci.org). Patients with a neurological disease other than SCI as well as those with an orthopaedic or rheumatologic disease were excluded from this study. Measurements were performed one month, three months and six months (Acute III, 150 – 186 days, 27 Subjects) after injury within the EMSCI time-windows. All patients were measured in at least two different time windows and 26 of these were measured in all three time windows. The study was approved by the ethical committees of the cantons of Zurich, Lucerne and Basel. All participants gave their written informed consent in accordance with the Declaration of Helsinki.

Subject	Age	Gender	Neurological level of injury	ASIA Impairment Scale
1	32	Male	C3	D
2	71	Male	C3	D
3	60	Male	C3	D
4	31	Male	C4	A
5	53	Female	C4	D
6	22	Male	C4	D
7	37	Male	C4	D
8	33	Male	C5	A
9	25	Male	C5	A
10	63	Female	C5	D
11	53	Male	C5	D
12	49	Male	C5	D
13	60	Female	C5	D
14	73	Female	C5	D
15	75	Male	C5	D
16	55	Female	C6	D
17	38	Male	C7	A
18	20	Male	C7	B
19	60	Male	C7	D
20	53	Female	T5	B
21	32	Male	T6	D
22	28	Male	T8	A
23	49	Female	T8	C
24	44	Female	T10	A
25	58	Male	T10	A
26	77	Male	T10	A
27	65	Male	T11	C
28	29	Male	T11	D
29	74	Male	T12	D
30	25	Female	L2	A
31	39	Male	L2	D

Table 5.1. Demographic characteristics of the 31 spinal cord injured subjects included in the study.

5.3.2 Clinical Assessments

Neurological impairment was assessed with the ISNCSCI protocol (Kirshblum et al., 2011b). This protocol classifies the neurological level of injury (NLI) and the extent of lesion by determining the most caudal intact myotome or sensory dermatome. Observed NLI levels range from C2 (cervical spinal cord segment) to S4-5 (sacral spinal cord segment). Cervical (tetraplegic; above T2) and thoracic (paraplegic; T2 and below) patients were grouped according to the NLI value at three months after injury, as this information was available for all patients. This information was used to define the two investigated groups as explained in the section "statistical analysis". The extent of lesion was assessed according to the ASIA Impairment Scale (AIS).

Motor function of the UL was assessed using the motor domain of the Graded and Redefined Assessment of Strength, Sensibility and Prehension (GRASSP) (Kalsi-Ryan et al., 2012, Velstra et al., 2015) that assesses the function of 10 upper limb muscles on both arms with the manual muscle test (MMT). The scores range from 0 to 50 per arm and the scores of both arms were summed together. In a previous study we showed that proximal motor scores of the GRASSP are strongly related to overall UL activity in acute in-patients (Brogioli et al., 2016b), therefore distal muscle scores were omitted from the analysis, resulting in a proximal score range from 0 to 20 per arm. Strength tests with a hand-held dynamometer (HHD) of four key groups of UL muscles were performed: elbow flexors (Biceps brachii, Brachialis and Brachioradialis), elbow extensors (Triceps brachii), shoulder flexors (Deltoid anterior part, Pectoralis major upper and middle part) and extensors (Lattissimus dorsi and Teres major) (Stoll et al., 2000). This assessment tool was chosen in order to obtain a more sensitive measure of strength values from M3 to M5 (Noreau and Vachon, 1998). Hand grip strength was measured with a hand dynamometer (van Tuijl et al., 2002).

Independence in self-care was assessed with the self-care subdomain of the Spinal Cord Independence Measure (SCIM) (Itzkovich et al., 2007) resulting in a score range from 0 to 20.

5.3.3 Data collection and measurement procedure

Patients were assessed three times during primary in-patient rehabilitation Figure 5.1. Each time frame consisted of three weekdays of wearable sensor recordings in conjunction with clinical assessments. The wearable sensor used in this study was the ReSense (Leuenberger and Gassert, 2011), an inertial measurement unit that records 3D acceleration, 3D angular velocity, 3D magnetic field strength and barometric pressure for at least 24 h at a time. If only 3D acceleration is measured then the battery life lasts for over 2 weeks. Signals coming from the magnetometer and the barometric pressure sensor were disregarded for the purposes of this study. For the recordings, patients were fitted with three ReSense modules, one on each wrist and one on the right wheel of the wheelchair. The wheel module remained fixed on the wheel for up to seven days, recording wheeling kinematics. More details about the ReSense set-up are presented elsewhere (Brogioli et al., 2016a, Popp et al., 2016). Patients were not asked to perform any specific activity but they were free to behave as they wanted following their daily inpatient schedule. ReSense had to be removed only during bathing or any activity involving long-term contact with water. GRASSP examinations were performed by trained research staff consisting of movement scientists, occupational therapists and physiotherapists. The SCIM questionnaire and the ISNCSCI protocols were rated by clinicians who were independent to the study.

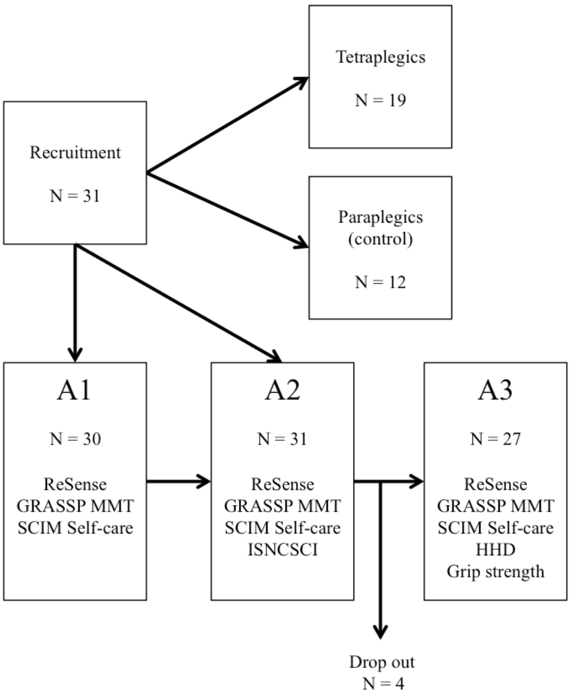

Figure 5.1. Flow diagram depicting the study groups and the measurement performed in each time frame.

Stage A1: 1 month after injury; Stage A2: 3 months after injury; Stage A3: 6 months after injury; GRASSP: Graded and Redefined Assessment of Strength, Sensibility and Prehension; SCIM: Spinal Cord Independence Measure; HHD: hand-held dynamometer.

5.3.4 Data analysis

ReSense data were transferred post-recording from the internal SD-card via a custom-designed base station to a PC and were analysed offline using MATLAB R2013a (MathWorks, Natick, MA, U.S.A). A cubic spline interpolation function was used to resample the data at 50Hz enabling the synchronization of recordings from different sensor modules. Visual inspection was performed in order to ensure that the data was genuine, removing data recorded during sleep phases and phases when the sensors were taken off prior to the analysis.

5.3.5 Sensor based outcome measures

In order to track changes in UL activity we used sensor-based metrics (overall activity counts (AC), distance wheeled, peak wheeling velocity and limb-use laterality index) that allow a comprehensive evaluation of UL recovery as they have been shown to be closely related to UL motor function and independence in an acute cross-sectional study (Brogioli et al., 2016b).

AC was used as a measure of overall UL activity. In order to calculate this metric the acceleration signal is processed with a 2nd order Butterworth high-pass filter with a cut-off frequency of 0.25 Hz. Subsequently the magnitude of the filtered signal was integrated over an epoch of one minute resulting in an output in counts/min. The counts of the right and left limb were summed together and normalized by time.

Limb-use laterality refers to the dominance in the usage of one UL over the other during day-to-day activities. Limb-use laterality was assessed with the ReSense Assessment of Laterality (RSAL) and is scored from zero to infinite where the higher the value the more pronounced the limb-use laterality (Brogioli et al., 2016a, Bailey et al., 2014). Lateralized patients were defined here as patients with limb-use laterality values above two standard deviations from the mean of paraplegic subjects at one month after injury (Z-score = 2).

Distance actively wheeled and peak velocity was calculated over an extended amount of time of up to seven days (Sonenblum et al., 2012b) with an algorithm previously developed by our group (Popp et al., 2016). In short, the ReSense Wheeling-Algorithm (RSWA, set-up II.a and III.b), reliably discriminates active (self-propelled) and passive (attendant-propelled) wheeling estimating speed (m/s) and distance (in meters). In this way, active distance wheeled and peak-wheeling velocity can be reliably measured. Peak velocity was computed using the 90th percentile in order to obtain a more robust metric against outliers in peak velocity.

5.3.6 UL activity categories

We split up overall AC into two distinct activity categories because overall AC during the whole day is a generic measure. In agreement with our previous study (Brogioli et al., 2016a), these two categories were distinguished based on the output of the RSWA (set-up II.a). The category “self-propulsion AC” included all upper extremity movements performed whilst the subject actively propelled the wheelchair, whereas the category “ADL AC” included all upper extremities movements that occurred during any other day-to-day activities excluding self-propulsion. In addition, the difference between AC performed during therapies and AC performed outside therapy sessions was evaluated by splitting a day into therapy time (from 9 am to 5 pm) and leisure-time (time outside the nine to five excluding sleep).

5.3.7 Statistical analysis

The statistical analysis was performed using IBM SPSS Statistics version 19 (IBM, Armonk, NY, U.S.A). Figures were prepared using the ggplot2 library for R (The R project for Statistical Computing, R Core Team, r-project.org). Two analyses were performed: a longitudinal analysis over all time frames (analysis of changes) and a cross-sectional analysis at six months after injury (analysis of the differences between groups). The measured subjects were divided into two groups according to the NLI value at three months after injury: a control group of paraplegic subjects in which no changes in UL activity are expected and a group of tetraplegic subjects in which improvements in UL activity are expected.

Sample size: We recruited 31 SCI patients who were heterogeneous in terms of their impairments and in how they mobilize. For these reasons the number of subjects included in different analyses varies depending on the aim of the analysis. If not otherwise stated, the sample size is 31 patients (19 tetraplegic patients and 12 paraplegic patients) for the longitudinal analysis and the cross-sectional analysis at stage A2, 30 patients (18 tetraplegics patients and 12 paraplegic patients) for the cross-sectional analysis at stage A1, and 27 patients (16 tetraplegic patients and 11 paraplegic patients) for the cross-sectional analysis at stage A3 (Figure 1). The sample size is stated in parenthesis in case of smaller sample sizes due to not tested items in the clinical assessment of some individuals.

Longitudinal analysis: Data has been analysed with a linear mixed model (LMM) due to inconsistent sample sizes across stages. The repeated-measures dataset was considered to be a two-level type, in which the second level represents the patient and therefore covariates measured at this level represent between-subject variation. The first level represents the repeated measurements made on each patient and therefore within-subject variation. To analyse each dependent variable, six statistical models were built: overall AC, active distance wheeled, peak velocity, limb-use laterality, GRASSP MMT proximal, and SCIM self-care. For all models subjects and intercept were included as random factors. Covariates, main effects and interaction effects were included as fixed effects. The following fixed effects were used to set up the statistical models: age and gender were treated as covariates. The main effect time was chosen as repeated measurement and its residual covariance matrix was set to uncorrelated and estimated with the restricted maximum likelihood. In order to test interaction effects, grouping variables were added to the model and defined as the category paresis (0 = paraplegic patient, 1 = tetraplegic patient) and the category limb-use laterality (0 = no UL lateralization, 1 = UL lateralization, limb-use laterality model only). The interaction time X paresis was added to all models. The interaction time X limb-use laterality was added to the limb-use laterality model.

The predicted means of each category (e.g. paraplegic patients) were computed for each time frame using the fitted model. In order to discover whether the mean of a group was equal over all time-windows a Univariate Test was performed. If the means were different, pairwise comparisons were employed to identify significant differences between specific time frames. For this purpose the alpha level was adjusted for multiple comparisons using Bonferroni correction. All p-values reported are corrected for multiple comparisons.

Cross-sectional analysis: The comparison between paraplegic and tetraplegic groups was performed either with an independent sample t-Test, in the case that the data were normally distributed, or with the non-parametric Mann-Whitney U test in the case of non-normally distributed data. Normality was checked with the Shapiro-Wilk test of Normality (Ghasemi and Zahediasl, 2012). Normality was not met for the values of limb-use laterality and all the scores of the clinical assessments. In case of multiple means comparisons (i.e. more than two), a one-way analysis of variance (1-way ANOVA) with Bonferroni post hoc test was performed.

A Spearman's rank-order correlation coefficient was used to inspect the associations between sensor metrics and assessment scores.

For all statistical tests, the statistical significance level α was set at 0.05.

5.4 Results

5.4.1 Changes in sensor metrics

The aim of this study was to examine changes in sensor-based measures across time among a group of paraplegic and tetraplegic subjects (Figure 5.2). For this purpose changes in six dependent variables (four sensor metrics and two clinical assessment measures) were analysed using LMM. The six dependent variables were overall AC, distance wheeled actively, peak wheeling velocity, limb-use laterality, GRASSP MMT proximal, and SCIM self-care. Results of pairwise comparisons of the estimated marginal means for sensor metrics over the three time frames for paraplegic and tetraplegic patients are summarized in Table 5.2.

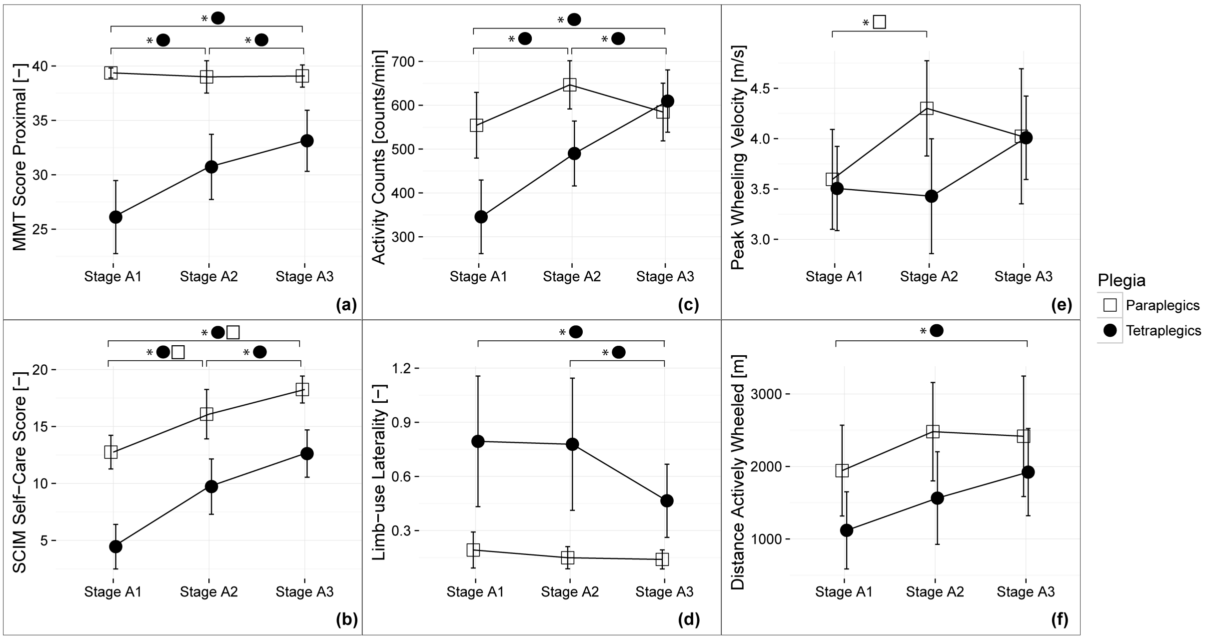

Figure 5.2. Changes in sensor-based and clinical measures over time among a group of paraplegic and tetraplegic patients.

Lines represent the means, error bars represent the 95% confidence interval. Paraplegic patients are displayed with empty squares whereas tetraplegic patients are displayed with full circles. Panels (a)-(b), illustrate the changes in clinical scores during rehabilitation, panels (c)-(f) changes in sensor-based metrics. Proximal muscle strength was assessed with the manual muscle testing (MMT); independence in self-care was assessed with the Spinal Cord Independence Measure (SCIM). Stage A1 – 1 month after injury; Stage A2 – 3 months after injury; A3 – 6 months after injury.

Group	**Time**	**GRASSP MMT [scores]**	**SCIM Self-care [scores]**	**Overall activity [counts/min]**	**Distance [m/day]**	**Peak velocity [m/s]**	**Laterality index [-]**
Paraplegics	1 month	39.464 (2.056)	12.706 (1.313)	552.617 (57.727)	1889.160 (376.139)	3.531 (0.259)	0.192 (0.233)
	3 months	39.100 (1.904)	16.039 (1.653)	644.973 (47.763)	2549.482 (407.526)	4.306 (0.277)	0.149 (0.213)
	6 months	39.099 (1.615)	18.206 (1.244)	589.342 (47.122)	2261.312 (473.384)	4.185 (0.318)	0.136 (0.111)
	Significant pairwise comparisons (p <.05*)	ns	t_1 - t_2, t_1 - t_3	ns	ns	t_1 - t_2	ns
Tetraplegics	1 month	25.715 (1.619)	4.361 (1.058)	331.316 (46.531)	1045.859 (320.275)	3.492 (0.263)	0.896 (0.186)
	3 months	31.046 (1.503)	9.791 (1.326)	495.693 (38.376)	1677.737 (360.708)	3.374 (0.263)	0.742 (0.170)
	6 months	33.853 (1.311)	13.003 (1.037)	627.111 (38.337)	2286.398 (424.393)	4.120 (0.307)	0.432 (0.089)
	Significant pairwise comparisons (p <.05*)	t_1 - t_2, t_1 - t_3, t_2 - t_3	t_1 - t_2, t_1 - t_3, t_2 - t_3	t_1 - t_2, t_1 - t_3, t_2 - t_3	t_1 - t_3	ns	t_1 - t_3, t_2 - t_3

Table 5.2. Summary of changes in overall upper-limb activity, distance wheeled per day, peak velocity and limb-use laterality.

* Bonferroni corrected; ns, not significant; t1, one month; t2, three months; t3, six months. Results are displayed as estimates ± standard errors.

* Bonferroni corrected.

The relationship between overall AC and proximal muscle function was analysed for each time frame (Figure 5.3). Overall AC and proximal muscle function were strongly related at one month ($P < 0.01$, $r = 0.562$, $N = 29$, Spearman correlation) and three months ($P < 0.01$, $r = 0.605$, $N = 29$, Spearman correlation) after injury, though not significant at six months after injury ($P = 0.178$, $r = 0.273$, $N = 27$, Spearman correlation).

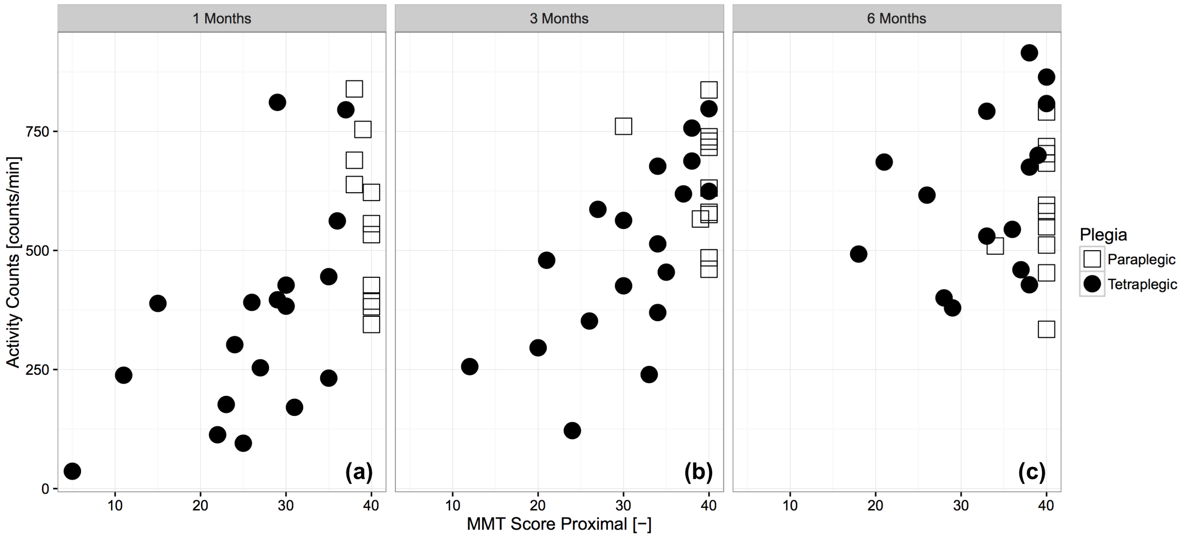

Figure 5.3. Cross-sectional relationship between proximal muscle function and overall upper-limb activity across time.

Paraplegic patients are displayed with empty squares whereas tetraplegic patients are displayed with full circles. The relationship at one (a) and three months (b) after injury was strong and significant ($N = 29$ and $N = 31$, $P < 0.01$, $r = 0.562$ and $r = 0.605$, Spearman correlation) whereas it was not significant at 6 months (c) after injury ($N = 27$, $P = 0.178$, $r = 0.273$, Spearman correlation). MMT = manual muscle testing.

5.4.2 Changes in limb-use laterality

As shown in Table 5.2, pathologically increased limb-use laterality significantly decreased in tetraplegic subjects whereas, as expected, it was normal throughout the study in paraplegic subjects. A Mann-Whitney test revealed that limb-use laterality of tetraplegic subjects was significantly more pronounced over the course of acute care one month and three months after injury (mean rank = 18.50, 18.44) than for paraplegic subjects (mean rank = 11.00 and 11.08;

U = 54 and 55; z = -2.286 and -2.244; $p < 0.05$ and $p < 0.05$). Limb-use laterality of tetraplegic subjects seems to recover at the end of the acute rehabilitation at six months after injury (mean rank = 16.25) as at this time it was not significantly different from the paraplegic subjects (mean rank = 10.73, U = 52, Z = -1.776, p = 0.07). In contrast to the 75th percentile (0.237 for paraplegic subjects and 1.110 for tetraplegic subjects), the 25th percentile (0.038 for paraplegics and 0.129 for tetraplegic) of the laterality index at one month after injury were comparable between paraplegic and tetraplegic subjects, meaning that some tetraplegic subjects showed the same limb-use laterality as paraplegic subjects. For this reason limb-use laterality was further analysed for a sub-cohort of lateralized subjects. Lateralized subjects were defined here as subjects whose laterality values at one month were above two standard deviations from the mean of paraplegic subjects (i.e. laterality index above 0.6127). Nine subjects (8 tetraplegic subjects and 1 paraplegic subject) showed lateralization. Limb-use laterality significantly decreased in these lateralized subjects (Table 5.2), but remained significantly different from their non-lateralized counterpart in all time windows, meaning that lateralized subjects recover some limb-use symmetry but remain impaired in terms of laterality (mean rank no lateralization = 10.50, 11.79 and 11.18; mean rank lateralization = 25.50, 21.10, and 17.89; U = 0, 34 and 37, z = -4.399, -2.799 and -2.129, $p < 0.01$, $p < 0.01$ and $p < 0.05$).

5.4.3 Group differences at six months

To determine if there was a discrepancy in UL activity between paraplegic and tetraplegic subjects at six months after injury, comparisons between group means were performed for different UL activity categories (overall AC, ADL AC and self-propulsion AC). An independent samples t-test revealed that overall AC (584.50 ± 132.83 counts/min for paraplegic and 609.60 ± 172.70 counts/min for tetraplegic, t(25) = -0.43, p = 0.67) and ADL AC (475.79 ± 85.93 counts/min for 9 paraplegic and 547.60 ± 112.17 counts/min for 12 tetraplegic, t(19) = -1.66, p = 0.11) were not significantly different between the two groups Figure 5.4. Finally, 27 paraplegic and tetraplegic subjects had higher counts during therapy times (618.28 ± 153.80 and 695.97 ± 193.99 counts/min) as opposed to leisure time (536.02 ± 122.16 and 514.47 ± 180.92 counts/min). The increase from leisure time to therapy time was slightly more significant in 16 tetraplegics (181.49 (95% CI, 99.04 to 263.95) counts/min, t(15) = 4.692, $p < 0.01$) compared to 11 paraplegics (82.26 (95% CI, 1.19 to 163.33) counts/min, t(10) = 2.261, $p < 0.05$).

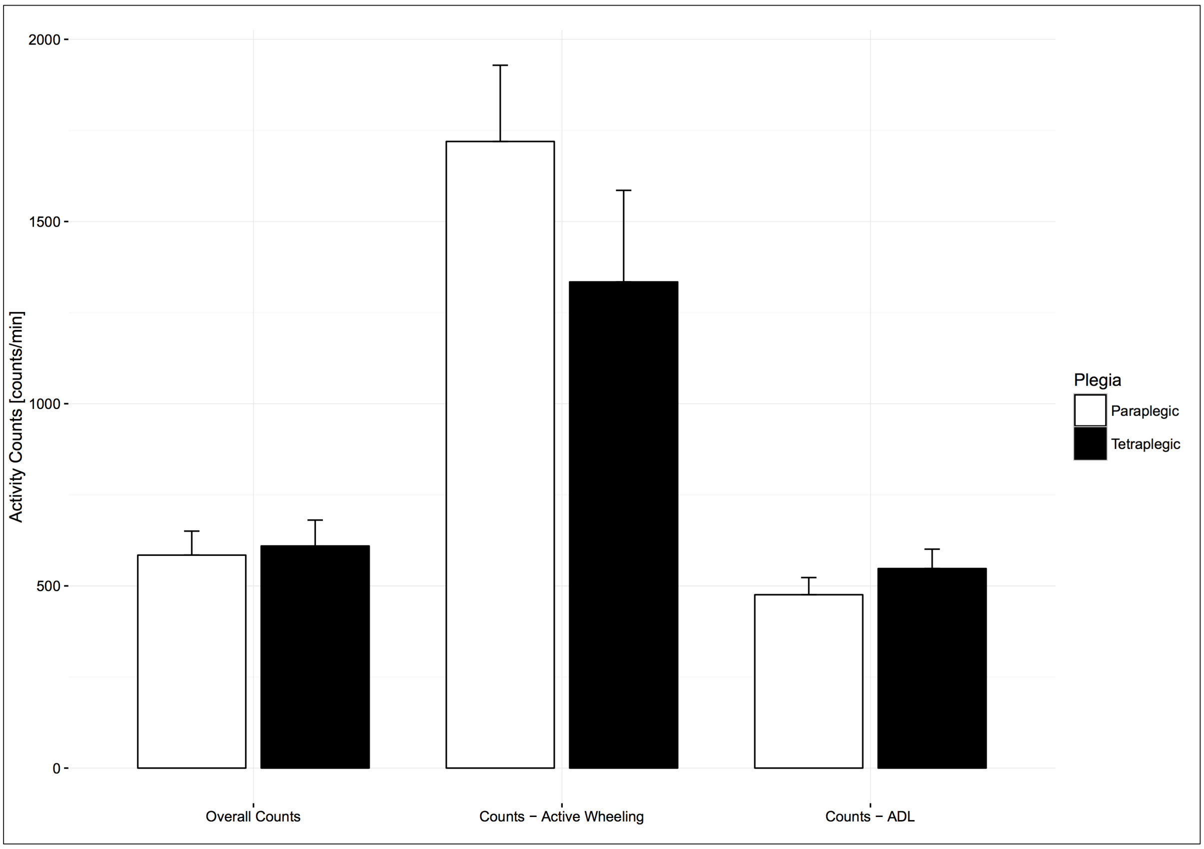

Figure 5.4. Comparison of activity count (AC) categories between paraplegic and tetraplegic patients six months after injury.

Bars represent the means, error bars represent the 95% confidence interval. Paraplegic patients are displayed in white whereas tetraplegic patients are displayed black. Differences are not statistically significant. ADL – activities of daily living.

Next, to determine if the similarity in UL activity between groups was due to similar motor impairments, comparisons between group means of muscle function were performed. A Mann-Whitney U test revealed that proximal MMT scores of paraplegic subjects (median: 40, IQR: 0, mean rank = 20.17) were significantly higher than for tetraplegic subjects (median: 36, IQR: 9.75, mean rank = 10.25, U = 28, z = -3.29, p <0.01), meaning that the tetraplegic subjects were significantly more impaired than their paraplegic counterparts. As shown in Figure 5.5, this was also the case for hand strength (mean rank paraplegics = 6.55 and tetraplegics = 16.45, U = 6, z = -3.58, p <0.001, 11 paraplegics, 11 tetraplegics) and independence in self-care (mean rank paraplegics = 19.83 and tetraplegics = 10.50, median paraplegics = 18, IQR 2, and tetraplegics = 13, IQR: 8; U = 32, z = -3.011, p <0.001, 12 paraplegics, 16 tetraplegics). However, a further analysis of four key proximal muscles in paraplegic subjects and tetraplegic subjects revealed that the HHD scores of antigravity muscles were equivalent in paraplegic subjects (mean rank elbow flexors = 17.45, mean rank shoulder flexors = 17.00) and in tetraplegic subjects (elbow flexors, mean rank = 11.63, U = 50, z = -1.87, p =0.06; shoulder flexors, mean rank = 11.94, U = 55, z = -1.63, p =0.11, Figure 5.5). This was not the case for elbow extensors (mean rank = 19.73 and 10.06, U = 25, z = -3.11, p < 0.01) and shoulder extensors (mean rank = 18.36 and 11.00, U = 40, z = -2.37, p < 0.05) where the HHD scores were significantly higher in paraplegic subjects compared to tetraplegic subjects (Figure 5.5). We investigated the relationship of the HHD scores with self-propulsion AC in order to evaluate if impairments in these muscles result in less AC because the HHD scores of shoulder and elbow extensors were significantly different between the two groups. This was the case for shoulder extensors (N = 18, P < 0.05, r = 0.529, Spearman correlation, Figure 5.5) but not for elbow extensors (N = 18, P = 0.28, r = 0.267, Spearman correlation).

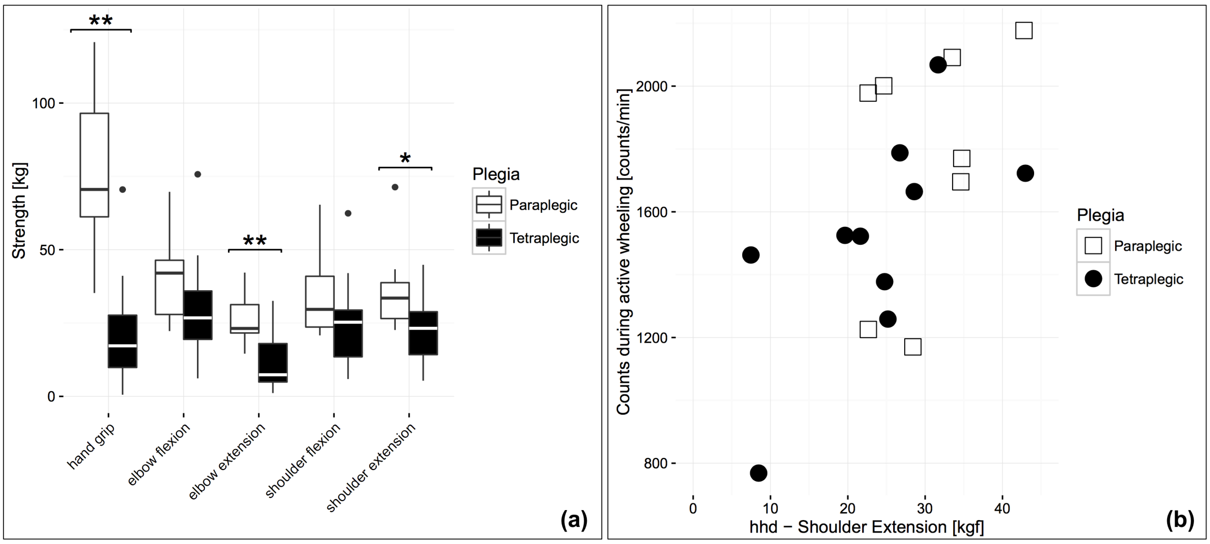

Figure 5.5. Comparison of strength values between paraplegic and tetraplegic patients six months after injury.

Panel (a): the boxplot shows the median of each strength measurement. The bottom represents the first quartile whereas the top represents the third quartile. The whisker is 1.5 times the interquartile range. Outliers are displayed with points. Significant differences are represented with stars (one star represents alpha <= 0.05, two stars represent alpha = 0.01). Panel (b): relationship between AC during active wheeling and HHD scores of shoulder extension. Paraplegic patients are displayed in white or with empty squares whereas tetraplegic patients are displayed in black or full circles. hhd = hand hold dynamometer.

5.4.4 Centre differences at 6 months

A one-way ANOVA was conducted to determine if overall AC was different for subjects in different centres. Subjects were separated into three groups: centre A (n = 11), centre B (n = 12) and centre C (n = 4). Note that the name of each centre is hidden from this analysis in order to guarantee centre-anonymity. The overall AC was statistically significantly different between the centres $F(2, 24) = 17.539$, $p < 0.01$. The overall AC was highest in centre B (730.07 ± 113.68), then centre C (521.48 ± 113.20) and lowest in centre A (485.12 ± 86.30). Bonferroni post hoc analysis revealed that the differences between centre A to B (244.94, 95% CI (134.19 to 355.70)) and between centre C to B (208.59, 95% CI (55.40 to 361.77)) were statistically significant ($p < 0.01$, Figure 5.6), meaning that subjects in centre B were significantly more active. The same analysis was performed for MMT proximal and SCIM self-care in order to determine if this difference between centres was due to differences in muscle impairments or independence. MMT proximal and SCIM self-care were not significantly different between the centres $F(2, 25) = 0.571$ and $F(2, 25) = 0.847$, $p = 0.572$ and $p = 0.441$. Due to the lower number of wheelchair users in centre C (three patients), an independent samples t-test was conducted to determine if active distance wheeled was different between centre A and centre B revealing that the distance wheeled in centre A (1682.32 ± 1687.83 m/day, n = 7) was not significantly different from centre B (2881.77 ± 1001.89 m/day, n = 10).

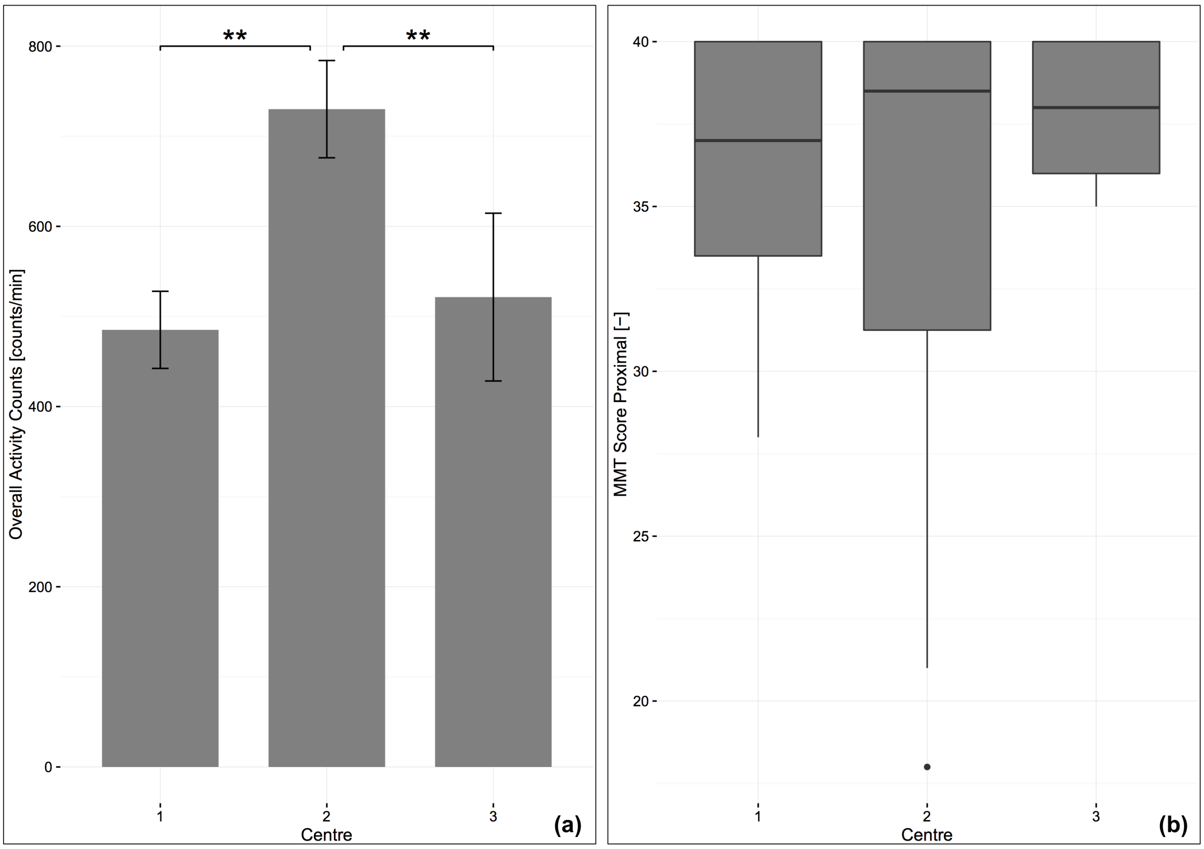

Figure 5.6. Centre differences in overall activity counts and in scores of proximal muscle strength at 6 months after injury for all patients.

Panel (a): the bars represent the means of overall activity counts, error bars represent the 95% confidence interval. Significant differences are represented with stars (two stars equal alpha = 0.01). Panel (b): the boxplot shows the median of each strength measurement. The bottom represents the first quartile whereas the top represents the third quartile. The whisker is 1.5 times the interquartile range. Outliers are displayed with points. MMT = manual muscle testing.

5.5 Discussion

This study assessed changes in UL activity with objective measures of performance at standardised time points during acute rehabilitation. We showed that subjects with cervical SCI significantly increased the overall amount of UL activity compared to their thoracic injured counterparts that did not experience significant changes. Moreover, six months after injury, subject with a cervical SCI showed a similar level of UL activity as subjects with a thoracic injury despite their greater motor impairment. Thus, at this time point post-injury, wearable sensors measure a different level of UL performance as would be predicted by clinical assessments.

Overall AC increased significantly in cervical SCI subjects during the course of acute rehabilitation, suggesting functional recovery of UL movements, which was confirmed by a similar trend in measures of strength and independence. On the contrary, UL activity in paraplegic subjects remained constant confirming that UL motor function is not affected in paraplegic patients, as confirmed by the score of proximal strength. Therefore, in these subjects, inpatient rehabilitative interventions focus on other physical skills (Whiteneck et al., 2011). Indeed, in this patient group active peak wheeling velocity increased significantly between one and three months after injury. This suggests that early rehabilitation focuses on wheelchair training (e.g. improvement of wheelchair handling) in paraplegic subjects compared to tetraplegic subjects. Tetraplegic subjects with high-level injuries are typically not able to propel a manual wheelchair (Taylor-Schroeder et al., 2011), and thus we did not see a significant improvement in peak wheeling velocity in this group. Our results complement previous findings that showed significantly more time spent on manual wheelchair mobility training for paraplegic subjects, compared to tetraplegic subjects where therapies focused primarily on improving UL function through strengthening and increasing ROM by stretching (Taylor-Schroeder et al., 2011).

In contrast to the overall AC and active peak velocity, there were no significant changes in active distance travelled between the groups. This may be due to the greater unpredictability of global kinematics metrics such as total distance wheeled (Sonenblum et al., 2012b) or due to various confounders, some of which are difficult to control. For example some subjects (i.e. AIS C or D) progress to functional ambulation as their primary mode of mobility, and thus become less dependent on a manual wheelchair (Taylor-Schroeder et al., 2011) and therefore such subjects most likely decrease their distance wheeled rather than increasing it. Walking detection through wearable sensors is challenging in SCI as ambulation is very heterogeneous in terms of lesions with a broad range of functional impairments that result in several walking alterations (Awai and Curt, 2014). Additionally, ambulant SCI subjects use many different assistive devices (e.g. crutches and rollers). For these reasons algorithms developed for walking detection in other neurological diseases (Moncada-Torres et al., 2014, Prajapati et al., 2011, Leuenberger et al., 2014) have not yet been validated in SCI.

We are aware of only one study that successfully measured distance wheeled in SCI subjects with the help of accelerometers (Sonenblum et al., 2012b). However, all participants were community dwelling and only two thirds of the enrolled participants were diagnosed with SCI. Additionally, the methods used were not able to differentiate between self-propulsion (active wheeling) or attendant-propulsion (passive wheeling). Therefore, the results of the present study extend the findings for acute SCI by confirming the high variability of global kinematic metrics that fluctuate around 2 km/day and do not change significantly during rehabilitation.

Our results show that there are pronounced inter-subject differences in limb-use laterality within the tetraplegic group, with some tetraplegic subjects showing pronounced limb-laterality soon after injury and others, similarly to paraplegic subjects, not showing any shift in limb-use laterality. Therefore, in order to correctly analyse limb-use laterality, tetraplegic subjects should be split into lateralized and non-lateralized subjects. A powerful method in assisting clinical decision making is the use of Z-scores (Chubb and Simpson, 2012). Z-scores are the conversion of individual values in terms of standard deviations from the means by taking into account a reference group. We arbitrarily chose a Z-score of two as 95.4% of the values fall within two standard deviations from the mean of paraplegic subjects. This is because we have previously shown that paraplegic subjects do not show any limb-use laterality (Brogioli et al., 2016b) and their limb-use laterality indexes are similar to healthy subjects (Bailey et al., 2015). In analysing only the lateralized-group, we showed that lateralized cervical subjects significantly decreased limb-use laterality but remained impaired with limb-use laterality values in the same range as a group of chronic tetraplegic subjects that we measured previously (Brogioli et al., 2016a).

Previously we showed that proximal muscle function was strongly related to overall AC during acute inpatient rehabilitation (Brogioli et al., 2016b). In the present study we extend these findings and show that this relationship becomes weaker over time. This means that at the beginning of acute rehabilitation overall UL movements are influenced by the motor impairment of proximal muscles. Therefore, subjects that are more impaired are less active with their upper limbs. Over time, as patients recover and learn how to perform different tasks through compensatory movement strategies (Curt et al., 2008), the impairment in some muscles may play a less pronounced role because their function is replaced by other muscles.

This is supported by the fact that at six months after injury, tetraplegic subjects showed significant differences in muscle impairment, according to the GRASSP MMT, but reached the same level of UL activity (in terms of AC) as paraplegic subjects. Despite the same level of UL activity the independence score in self-care was significantly different. This might be because, regardless of the ability to perform an activity (e.g. eating with or without a fork with built in cuff), tetraplegic patients are penalized in SCIM scores because they use adaptive devices. Consequently, at the end of the rehabilitation, overall AC may be a better measure of performance compared to clinical assessments. The effect of learning compensatory movement strategies may become obvious by analysing the change in overall AC compared to the two clinical measures, where the increase in strength and independence seem to stall after three months whereas UL activity keeps increasing.

The outcome measure of overall AC is a purely quantitative measure and does not enable us to evaluate distinct activities. If we split up the overall AC and look more closely into one distinct activity, in this case self-propulsion, we can see a trend towards higher values of self-propulsion AC in paraplegic subjects compared to tetraplegic subjects. Despite this, the difference is small and may not fully reflect the functional impairment of the UL. Therefore, we investigated the motor impairment between para- and tetraplegic subjects in more detail using the HHD. This analysis revealed that, compared to paraplegic subjects, tetraplegic subjects showed no significant difference in the strength of shoulder flexors and elbow flexors, which are muscles that work against gravity (Kloosterman et al., 2010). The contrary was true for shoulder and elbow extensors. Previously, it has been shown that functional elbow extensors may be crucial for the performance of activities of daily living including wheelchair propulsion (Welch et al., 1986). However, although tetraplegic subjects included in our study show a reduction in elbow extensor strength, they do not show a decrease in overall UL activity compared to paraplegic subjects with full elbow extensor function. This indicates that tetraplegic subjects may use other muscles to compensate for the functional deficit in the elbow extensor. It has been suggested that this compensation is mainly driven by scapulothoracic and glenohumeral movements (Mateo et al., 2015) triggered mainly by the shoulder flexors (Gefen et al., 1997). This may suggest that overall AC is directly influenced by these larger anti-gravitation muscles and not by proximal muscles like the elbow extensors where function can be very well compensated. However, we observed a significant difference between paraplegic and tetraplegic subjects in the shoulder extensor, which is also an anti-gravitation muscle. It has been shown that during ADL the position of the arms is essentially constrained around the sagittal plane (Howard et al., 2009) above the waist (Vega-Gonzalez et al., 2007). Therefore shoulder extensors may not influence ADL, which as shown in our data, is the main contributor to overall AC. In contrast, during wheelchair propulsion, the shoulder extensor is needed for the recovery phase (Rankin et al., 2011). Our data extend this finding, because activity counts during wheeling significantly correlate with HHD score of shoulder extensor.

Furthermore, we aimed to compare UL activity during therapy in contrast to UL activity during leisure time and we showed that all subjects have a significantly higher UL activity during therapy, whereas the increase was more pronounced in tetraplegic compared to paraplegic subjects. Therefore we assume that this is due to a major focus on UL therapy in tetraplegic subjects in contrast to paraplegic subjects (Taylor-Schroeder et al., 2011). This may be related to the fact that physical activity levels during inpatient rehabilitation are higher than after discharge (van den Berg-Emons et al., 2008), suggesting that high levels of UL activity may be confined to therapy time. Interestingly, a recent study demonstrated that this could be successfully counteracted using behavioural interventions that maintain similar physical activity levels after discharge (Nooijen et al., 2016). This may be the reason why UL activity during therapy and during leisure time was significantly higher in one rehabilitation centre compared to the other two, meaning that this specific centre may offer more successful interventions for increasing UL activity. This suggests that an increase in overall UL activity can be achieved by increasing the intensity of existing therapies as well as by offering better opportunities for patients to shape their leisure time in a more physically-active manner.

5.5.1 Limitations

We acknowledge a number of limitations. Firstly, the fact that we see no difference in scores of anti-gravitation muscles between paraplegic and tetraplegic subjects suggests a low stratification of included patients (i.e. low number of patients with high tetraplegia). Secondly, we could not control for certain confounds, e.g. the prevalence of ambulatory bouts of mobility, which limits the interpretation of global kinematics metrics (e.g. active wheeling distance).

5.6 Conclusion

This study has shown that tetraplegic subjects significantly improve UL activity during acute rehabilitation, so that by six months post-injury they have reached similar UL activity levels as their paraplegic counterparts. During acute care, sensor-based metrics correlate with UL motor function, whereas this relationship is attenuated later in rehabilitation. This may be due to the task-specific strategies tetraplegic subjects acquire to compensate for deficits in specific UL muscles. Therefore, tracking day-to-day UL activity is crucial to gain valuable insights into the actual impact of a subject's impairment on their UL movements. Future investigations should focus on controlling for the intensity of activity-based therapies and evaluating their impact on functional recovery as well as on acquiring reference data to set specific rehabilitation goals. In this way, sensor-based measurements of UL performance may become a powerful tool to tailor rehabilitative therapies to specific subjects.

6 General discussion

The general goal of this thesis was to monitor UL activity with wearable sensors to track rehabilitation progress in SCI relating it to clinical assessments. In order to successfully achieve the overall goal, three distinct aims were investigated. The first aim was to develop and validate wearable sensor methodologies to measure SCI-specific movements such as active wheelchair propulsion and limb-use laterality (second and third chapter). The second aim was to evaluate how such metrics could be used in a multi-centre set-up as a major outcome measure of UL function (third and fourth chapter). The third aim was to assess the quantity of UL activity and its changes during acute rehabilitation in standardised SCI-specific time frames (fifth chapter). In this thesis, and associated publications, wearable-sensor metrics were demonstrated to be valid and reliable in describing movement characteristics of the UL following SCI. Consequently, these methodologies have been successfully applied to track UL recovery after injury concurrently with clinical assessments. The findings of each study were discussed in detail in the context of the respective study goal in the discussion section of each chapter. Therefore, the present chapter discusses the accumulated findings in a broader context considering their clinical implications within the framework of the published literature. Finally, areas for further research will be formulated in the outlook section.

6.1 Activity classification

Activity classification based on IMUs placed on several body locations has previously been performed successfully in healthy subjects under laboratory conditions (Moncada-Torres et al., 2014). At the beginning of this project, the classification of several UL ADL in SCI subjects, such as brush teeth, was considered but abandoned for several reasons. Two of which are: the fact that it may not be clinically meaningful to quantify the prevalence of specific ADLs (e.g. peeling carrots) and the fact that SCI subjects could perform the same ADL using several movement strategies as their motor function is affected in many different ways. Consequently, this heterogenic way in doing the same task may decrease the classification performance. The focus of this thesis was instead shifted towards the classification of active wheelchair propulsion (self-propulsion) as this activity is the primary method of mobility for SCI subjects, and wheelchair-bound individuals wheel approximately one tenth of the time they sit in their wheelchair (Sonenblum et al., 2012b). Consequently, quantifying wheeling is clinically relevant as it may be the most widespread and intense activity SCI subjects perform with their UL. Several methodologies have been developed to track wheelchair mobility, but their implementation in the clinical setting is limited as they have two principal sources of error. Firstly, most methods are not able to distinguish between self-propulsion and assisted wheelchair movements (Coulter et al., 2011, Ojeda and Ding, 2014, Sonenblum et al., 2012a, Sonenblum et al., 2012b, van der Slikke et al., 2015, Wilson et al., 2008). Secondly, most methods that are able to classify self-propulsion are not validated within a "real-world" situation where activities are performed spontaneously (Garcia-Masso et al., 2015, Hiremath et al., 2015, Postma et al., 2005). To address these drawbacks, in the second chapter we developed a robust algorithm, which was able to classify self-propulsion with different module combinations, ranging from one module to four modules, and with or without the gyroscope, and validated it in a "real-world" situation. The algorithm was highly reliable and highly adaptable to several clinical needs. This flexibility was used successfully to analyse different datasets. The high precision set-up, set-up I.a (four sensor modules with gyroscopes turned on), was utilised in the third chapter, where the participants were able to wear all four modules because the measurement was limited to a few hours. Set-up II.a (three sensor modules with gyroscopes turned on) was utilised in the fourth chapter, where a significant number of patients were not able to wear the chest sensor in the evening and during sleep. Finally, a combination of set-up II.a and II.b (three sensor modules with gyroscope turned off) was utilised in the fifth chapter, where some patients were measured in the outpatient setting. As this setting did not allow the exchange of the modules every day the gyroscope was turned off to allow a multi-day measurement. Additionally, every multi-day measurement was performed with set-up III.b (one sensor module with gyroscope turned off) to track wheelchair kinematics up to seven days.

The clinical advantage of classifying self-propulsion is that, once classified, this activity can be isolated from the full dataset and either further analysed or discarded from the analysis. For example, in the third chapter, the intensity of UL movements during self-propulsion was investigated, and a positive relationship between the intensity of the UL effort during self-propulsion and independence in mobility was shown. Further, in the same study, self-propulsion was excluded from the analysis to evaluate the prevalence of limb-use laterality during day-to-day activities in tetraplegics. The in- or exclusion of particular wheeling events may be utilised to assess additional UL movements characteristics for example, it has been suggested that accelerometers placed on the UL may be used to measure temporal parameters of wheelchair propulsion, such as stroke number or push frequency, under laboratory conditions (Ojeda and Ding, 2014). In combination with the classification of self-propulsion, this analysis may be transferred to unsupervised measurements. A tool able to detect strokes using only the angular velocity input of ReSense placed on the wheel is already under development for ReSense. Such methodologies may provide clinicians and researchers with information about the efficacy of wheeling techniques (e.g. meters travelled for each stroke) allowing, for example, the objective judgment of the cause of possible overuse syndromes (e.g. high number of strokes per day despite a small distance travelled).

At the beginning of rehabilitation, the majority of SCI subjects are wheelchair-bound. One-year post injury, about half of incomplete tetraplegics and two third of incomplete paraplegics advance to some level of ambulation (Kirshblum et al., 2007). The first three studies of this thesis (chapter two to four) recruited and measured only wheelchair-bound subjects. However, a small number of patients participating in the fourth study (chapter five) became ambulant by the end of their rehabilitation. In stroke, it has been suggested that, if ambulatory activities are not excluded from the recordings, UL activity may be overestimated due to passive UL swinging during ambulatory activities (Leuenberger et al., 2016). Therefore, the classification of ambulation may give complementary information that could be used to evaluate the effect of walking on UL activity. The classification of walking performance in stroke has been shown to be more accurate when the IMU is placed on the unimpaired shank rather than on the impaired shank (Leuenberger et al., 2014). In SCI, the placement of sensors for walking detection should be carefully selected as walking in SCI is characterised by a broad range of disturbances (Awai and Curt, 2014), SCI subjects use several different assistive devices (e.g. crutches and rollers), and SCI usually affects both lower-limbs. Consequently, the placement of IMUs on both limbs seems reasonable and should be considered in future studies.

6.2 Limb-use laterality

The lack of a specific measure of laterality in SCI was the rationale and starting point for the validation of an accelerometer-based methodology, which was first proposed by Bailey and co-workers in stroke (Bailey et al., 2014). This method consists of calculating the ratio, which is log transformed, between activity of both ULs, which is measured by an accelerometer placed on both wrists. In this way, the prevalence of limb-use laterality in day-to-day activities is measured directly. The third chapter of this thesis showed, for the first time in a measurement of performance, that several community-dwelling tetraplegic subjects suffer from pathologically increased limb-use laterality, and that limb-use laterality is found in patient with rather low or decreased independence. The fourth chapter extended these findings and showed that, as expected, paraplegic subjects did not show lateralized limb usage. Finally, the fifth chapter showed that, during rehabilitation, several tetraplegic subjects recovered limb-symmetry, but for a significant number of tetraplegic subjects, pathological limb-use laterality did not recover. Consequently, the findings of this thesis highlight the importance of the involvement of both arms to accomplish ADLs in tetraplegics, and suggest that it is important to make researchers and clinicians conscious of taking limb-use laterality into consideration when developing therapy guidelines or prescribing therapy.

The proposed accelerometer-based measure of laterality may be more appropriate than clinical investigations in giving comprehensive information on the prevalence of this specific symptomatic. In the third chapter, the laterality index was calculated from the ordinal scores of the GRASSP MMT and was found to correlate strongly with the laterality index calculated from the sensor recordings. Despite the strong relation, assessment-based laterality indexes are difficult to interpret, as they are an indirect rather than a direct measure of limb-use laterality and they do not take into consideration several confounders such as the impairment of trunk balance. Therefore, laterality indexes calculated from the MMT of the GRASSP may not be representative of actual discrepancies in usage between the two ULs.

Secondly, limb-use laterality is difficult to judge if the minimally detectable value for the strength subset of the GRASSP, which is five points for the uniaxial assessment and seven points for the bilateral assessment (Kalsi-Ryan et al., 2016), is taken into consideration. This is a challenge because if the difference in scores between the two UL is less than five points, theoretically no limb-use laterality should be detected. Compared to assessment-based laterality indexes, the sensor-based laterality indexes are more sensitive as they are derived from two continuous scales rather than from two ordinal scales. For this reason, with the help of Z-scores, pathological limb-use laterality can be elegantly defined from a sample of control subjects, which in this case was a group of paraplegic subjects.

The laterality index may be calculated from the scores of assessments of functional movements, such as the GRASSP subset of quantitative prehension. However, as these items are tested unilaterally, the scores do not give information about how the ULs work together to perform a task. Further, as this subset is scored on an ordinal scale, it suffers from the same sensitivity issue as the GRASSP MMT. Consequently, wearable sensors seem to be the most straightforward and valid methodology for tracking limb-use laterality in cervical SCI subjects and may help clinicians to adjust treatment strategies by formulating limb-use specific rehabilitation goals, which help the subjects achieve independence.

6.3 Clinimetric characteristics of wearable sensors

Clinimetric are indexes or rating scales that describe, or measure, the physical signs and the symptoms of a disease or condition (Fava et al., 2012). One manifestation of SCI is UL paresis, which can be measured directly by motor scores (e.g. UEMS and MMT of the GRASSP) and indirectly by independence scores (e.g. SCIM). The relationship between clinical scales and wearable-sensor metrics have been tested in chapter three, four, and five, in order to investigate the clinimetric proprieties of wearable sensors. The rationale in investigating this, was the lack in advances in this topic in SCI limited by the lower number of studies investigating this relationship and by their inability to draw consistent conclusions. For example, Van der Berg-Emons et al. considered changes in physical activity, which were measured by an activity monitor, after SCI and during rehabilitation as clinically relevant (van den Berg-Emons et al., 2008). However, the researchers did not relate clinical scores to physical activity to back-up their suggestion (van den Berg-Emons et al., 2008). In a later study, Nooijen et al. investigated the correlation between physical activity and muscle scores and found no relationship (Nooijen et al., 2012). However, the results of this study are difficult to interpret because the researcher did not measure muscle strength with validated assessments (Nooijen et al., 2012). Recently, Zariffa et al. identified motor impairment scales that could be concurrently assessed by wearable sensors (Zariffa et al., 2016). The researchers found that motor scores, according to the GRASSP MMT, were highly predictive of scores of unilateral functional tasks in SCI, suggesting that wearable sensors may be used to measure impairment in muscle function (Zariffa et al., 2016). The present work extends these findings, as the fourth chapter of this thesis showed that, indeed, proximal muscle function is strongly related to UL activity, according to wearable sensors, in SCI patients three months after injury. However, this relation was not found for scores of distal muscles. Additionally, the fifth chapter of this thesis expanded this cross-sectional analysis to two additional timeframes, which were one month and six months after injury, and found that the relationship between proximal muscle scores and UL activity lost statistical significance over time and was not significant at six months. This discrepancy may be due to compensatory movement strategies that are not captured comprehensively by clinical assessments (Zariffa et al., 2016). Indeed, in the fifth chapter, the effect of learning compensatory movements strategies becomes apparent by evaluating the course of motor impairment scores compared to the course of sensor-based assessment of UL performance. Both indexes showed a positive trend, but after three months, impairment scores showed a gentler increase compared to performance counts. Altogether, these observations suggest that, in early rehabilitation, measures of UL activity are valid indexes of motor impairment and functional movements, whereas at later rehabilitation stages these measures comprehensively assess functional movements in their wholeness. The results of this thesis extend the young literature concerning wearable sensors incorporated into SCI research drawing consistent conclusions about clinimetrics characteristics of wearable sensors.

6.4 Activity-count based cut-off point to maintain neurological function

For many years, step-based goals have been proposed in order to help individuals pursue a healthy lifestyle by increasing or maintaining cardiorespiratory fitness (Tudor-Locke et al., 2008). Following a SCI, if the legs are impaired, the capacity to burn calories through physical activity is decreased as only the UL muscles, which have a small, total muscle mass, can consume energy voluntarily. Perret and co-workers proposed that, instead of overloading the UL musculoskeletal system, which suffers from overuse syndromes in more than 50% of SCI subjects, the necessary weekly energy expenditure of 1000–2200 kcal may be achieved through four to eight hours of functional electrical stimulated cycling (Perret et al., 2010). For this reason, it may be unreasonable to expect SCI subjects to reach such considerable energy consumption with their ULs alone, which questions the feasibility of a healthy-related cut-off point based on voluntarily UL activity only. Consequently, a tailored cut-off point for UL should be set as high as sustainable for the UL musculoskeletal system in order to slow down the onset of inactivity-related comorbidities and to maintain or improve motor function. Assuming that paraplegic subjects ULs are not impaired, a reasonable goal for tetraplegic subjects may be to match the UL activity of their paraplegic counterparts. The fifth chapter of this thesis showed that, at a later stage of rehabilitation, both patient groups performed UL activity that averaged 600 counts/min per day. Van den Berg-Emons and co-workers observed that SCI subjects significantly decreased the amount of physical activity after discharge (van den Berg-Emons et al., 2008). Consequently, a cut-off of 600 counts may reflect the most easily achievable motor function by the end of therapy and subjects should aim to maintain this level of activity after discharge. Future research should focus on tracking UL movements of SCI patients years after discharge to evaluate if higher activity counts are related to less functional losses and a lower prevalence of inactivity-related comorbidities.

7 Conclusion

This thesis contributed to the advancement of the research field in SCI in several ways. The developed and validated methodologies represent the foundations for developing an evaluation framework for the UL in SCI that provides information on clinically relevant movement characteristics. This thesis demonstrated that long-term monitoring of UL activity is feasible in a multicenter set-up and that wearable sensors can be used to reliably track UL recovery after SCI. Therefore, this thesis guides researchers in the implementation of such methods in the clinical setting and clinical studies. Additionally, the results give the first contribution to building a historical database of wearable-sensor metrics measured during spontaneous SCI recovery in standardised timeframes. Finally, this thesis extends knowledge about motor impairment in cervical SCI showing that there is pathological limb-use and higher as expected overall UL activity at later stages of rehabilitation. This knowledge contributes in a broader understanding of paresis in SCI and may help with tailoring therapies and rehabilitation strategies to improve functional recovery and independence.

Based on the results of the research performed as part of this thesis following general conclusions are drawn:

- This thesis developed and validated wearable-sensor methodologies that are able to assess proximal muscle strength and independence concurrently with standardised clinical assessments. These methods could be used in clinical trials to track UL recovery.
- At a later stage of rehabilitation, wearable-sensor methodologies provide comprehensive information about the quantity of UL activities beyond what is expected from clinical assessments.

- Sensor based assessments of limb-use laterality are more robust than their clinical counterparts as they are a sensitive measure of the prevalence of pathological limb-use laterality.
- Classification of wheelchair self-propulsion is advantageous in order to analyse its intensity and the characteristics of the movement and to exclude its influence on other activity metrics such as overall AC.
- During rehabilitation cervical SCI subjects significantly increase UL activity and reduce limb-use laterality. However, for some cervical SCI individuals, limb-use laterality is a pathological manifestation that does not recover.
- Wearable sensors detected significant differences in UL activity between centres during therapy times which backs up their application in tracking the dose of exercise during ABRT.
- Sensor-based UL activity cut-off points may be used to facilitate neurological and health benefits well beyond the first rehabilitation.

8 Outlook and future directions

This thesis showed the validity of wearable sensors as clinimetric indexes in SCI. Accordingly, the next step would be to define how these methodologies should be implemented in the clinical routine and in clinical trials as primary or secondary endpoints. Additionally, further research should evaluate if this technology can be used to measure additional movement characteristics.

8.1 Considerations for clinical trials

It has been proposed that wearable sensors could revolutionise the design of clinical trials by measuring outcomes with a higher frequency and beyond the official end of a trial, which is usually limited to one year (Dobkin and Dorsch, 2011). This thesis has shown that wearable-sensor measures are concurrent to some clinical assessments. Consequently, they may be used to track UL recovery, in an automated way, every week without limiting the evaluation of an intervention to a few timeframes (e.g. five timeframes over one year in SCI). A higher assessment frequency may be of particular importance in the evaluation of treatments, where the timing of the onset of rehabilitative therapies is of tremendous importance (e.g. anti-Nogo (Starkey and Schwab, 2012)), as recovery trajectories of motor function can be produced with higher time resolution. However, in contrast to what has been suggested by Dobkin and co-workers (Dobkin and Dorsch, 2011), in SCI the use of such technology may be limited to the first few months of rehabilitation. In later rehabilitation stages, as shown in the fifth chapter of this thesis, the concurrency between clinical assessments and sensors is not guaranteed. However, this discrepancy may give indirect insights into compensation furthering the understanding of UL recovery. In the event that the intervention is ABRT, therapy times should be properly labelled, in order to assess the actual dose of exercise compared to all other UL activity. Additionally, during ABRT interventions, fatigue should be adequately controlled.

8.2 Considerations for further developments

In order to provide proof of the robustness of these methodologies, additional psychometric properties of outcome measures, such as the responsiveness, sensitivity, and minimally detectable difference, should be collected. To ensure adequate power, this collection may require up to 60 tetraplegic subjects that should be measured longitudinally in an observational multicentre study (Kalsi-Ryan et al., 2016). As part of the further development of the clinical study “Upper Limb Activity in Human SCI Rehabilitation”, registered at the “ClinicalTrial.gov” register under NCT02098122, measurements are being expanded to an additional SCI centre in Germany in order to increase recruitment. Furthermore, the collection of spontaneous UL activity reference values, during rehabilitation and after discharge, may be advantageous to build a historical database to aid decision-making about personal cut-off points and to provide evidence on the amount of activity relative to neurological or health outcomes.

The establishment of new technology may require the collaboration with industry and other research groups to provide reliable measurement devices to several clinical units. ReSense has been shown to be robust and reliable, but its application in larger multicentre studies is limited as it is a prototype, whose production and support is managed by a small research team. For this reason, teams from ETH Zurich and the University of Zurich have initiated the project “ZurichMOVE” (van der Haar, 2015), which aims to accelerate the development, production, and clinical deployment of IMUs. With the help of this platform and the promising results of this thesis, SCI patients may benefit from a broader use of wearable sensors in the clinical routine, thereby increasing the chances of improving their rehabilitative outcomes.

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Abbreviations

- A. D. M.: Abductor Digitorium Minimi
- ABRT: activity-based restorative therapy (activity-based therapies, activity-based rehabilitation)
- AC: activity count
- ADL: activities of daily living
- AIS: ASIA Impairment Scale
- ASIA: American Spinal Injury Association
- ATI-355: monoclonal antibodies that inhibits NOGO
- CNS: central nervous system
- CTS: corticospinal tract
- Ex: extensor
- F. D. P.: Flexor Digitorium Profundus
- GRASSP: The Graded Redefined Assessment of Strength, Sensibility and Prehension
- HHD: hand held dynamometer
- HuCNS-SC: human central nervous system stem cells
- IMU: inertial measurement units
- ISNCSCI: international standards for neurological classification of SCI
- MMT: manual muscle testing
- NLI: neurologic level of injury
- SCI: spinal cord injury
- UEMS: upper extremity motor scores
- UL: upper limb
- XI: the eleventh cranial nerve

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