DISS. ETH NO. 26087

PHYSICAL ACTIVITY IN INDIVIDUALS WITH A SPINAL CORD INJURY:

TOWARDS OBSERVATIONAL-BASED RECOMMENDATIONS

A thesis submitted to attain the degree of

DOCTOR OF SCIENCES of ETH ZURICH

(Dr. sc. ETH Zurich)

presented by

SOPHIE SCHNEIDER

M.Sc. in Bioinformatics, University of Potsdam

born on 28.02.1987

citizen of Germany

accepted on the recommendation of

Prof. Dr. Roger Gassert (examiner)
Prof. Dr. Armin Curt (co-examiner)
Prof. Dr. William Taylor (co-examiner)

2019

Don't listen to the person who has the answers; listen to the person who has the questions.

—Albert Einstein

Acknowledgements

This thesis is the result of almost 4 years of work in the Spinal Cord Injury Center of the Balgrist University Hospital in Zurich and the close collaboration with the Rehabilitation Engineering Laboratory (Department of Health Sciences and Technology, ETH Zurich).
This work would not have been possible without the precious contribution of a number of people to whom I would like to express my genuine gratitude and appreciation.

First and foremost, I would like to sincerely thank my thesis committee, Roger Gassert, Armin Curt, and Bill Taylor. Thank you, Roger and Armin, for guiding, motivating, and challenging me throughout my PhD, while leaving me enough freedom to fully unfold my potential. I am deeply grateful for the possibility to work in such a close collaboration with the clinical and the engineering environment. Thank you Bill for co-refereeing my thesis, the valuable inputs during our meetings and, together with Armin and Roger, initiating the ZurichMOVE project of which I could be part of.

A special thank goes to Michelle Starkey, who hooked me up with this exciting project and supported me during the first steps of my thesis work.

I furthermore deeply thank our 'REACT' sensor group: Michael Brogioli for introducing me to the project and for the fruitful collaboration, Urs Albisser for teaching me a lot about the work with patients, László Demkó for taking over the responsibility for the software development, and Fabienne Hasler, Stefan Ortmann, and Mirella Rüttimann for their invaluable help in implementing the sensors into the daily clinical routine. A special thank goes to Werner Popp, who has been a tremendous help throughout all the stages of this thesis work. From spending hours solving the 'Kinderkrankheiten' of the ReSense sensor and answering my countless statistical questions, to revising my manuscripts and my thesis work and supporting me in any possible way during all the up-and-downs of my PhD life and beyond.

I want to thank the whole ZurichMOVE development team, especially Marco Hitz and Tobias Vögeli, for the development of the ReSense successor, for being open for any feedback and integrating all the little (and not so little) requests we had into the new JUMP sensors. Without this, we would not have been able to acquire the tons of data as we did.

Thank you also to all the members of the RELab 'assessment competence group' and all the

ZurichMOVE users for their valuable feedback during our many meetings.

A very big thank you goes to Iris Krüsi, who helped me with a lot of patience and kindness in all issues regarding ethics.

Another great thank you goes to all of my diligent students, Lara Arcari and Charlotte Werner, Seraina Aschwanden, Michelle Gwerder, Edwina Huber, Céline Jost, and Domenique Mai helping me acquiring this huge amount of data, and feeding me and the lab with cake.

Thank you also to the teams from Nottwil (Inge-Marie Velstra, Angela Frotzler, and Anne Brust), Basel (Isabelle Debecker, Kerstin Hug, and Margret Hund), and Bayreuth (Theresa Stöckert, Janina Burschka, and Rainer Abel) for their tremendous work in data collection.

A huge thank you also to all the subjects participating in my studies.

Another big thank you goes to my colleagues from the ParaLab and its orbit, who became very close friends over the years. Thanks Eve, Martina, Miriam, and Gergely for the (crashed) girls nights, exciting weekend escapes, and revitalizing '4-hours-hikes'. Thanks to Flickflaudr for keeping me busy with the telephone, and the VERY fun times inside and outside the Cämpus. Thanks to Anne, Fabian, Jere, and Lea for always bringing a smile to my face.

Thanks to all the ParaLabler and RELabies for the countless social events and creating such an amazing environment to work in.

Thank you also to all my friends and family back home, who always welcomed me with open arms, listened to my troubles, and celebrated my achievements.

The work was supported by the International Foundation for Research in Paraplegia (IRP), the Clinical Research Priority Program (CRPP) for Neuro-Rehab of the University of Zurich, the Swiss Paraplegic Foundation (SPS), Wings for Life, the ETH Zurich Foundation in collaboration with Hocoma AG, a HMZ seed project funded by the University of Zurich and the ETH Zurich Foundation, and the Swiss State Secretariat for Education, Research and Innovation (SERI, Horizon 2020). I am grateful for the financial support.

Zurich, May 2019 Sophie

Abstract

Spinal cord injury (SCI) is a neurological condition leading to severe sensorimotor impairments. The neurological recovery after an SCI is limited and in the acute phase mainly driven by activity-based rehabilitation. Furthermore, physical activity (PA) has been proven to have a beneficial effect on general health. However, levels of PA were reported to be low in SCI, mainly because of limited mobility in this population, and thus needs to be increased. Appropriate recommendations on the quantity of PA can help increasing PA in acute and chronic SCI individuals. Therefore, a framework is required to assess PA objectively and evaluate it specific to the level of impairment.

Wearable sensors have a high potential to assess PA not only in healthy adults, elderly, children and adolescents, but also in individuals with Multiple sclerosis, Parkinson's disease, and stroke. Recently, wearable sensors were also introduced to measure PA in SCI individuals. Within our research group, a framework has been developed to assess PA in SCI individuals comprising algorithms to quantify wheeling and distinguish between active and passive wheeling, to estimate the energy expenditure in wheelchair-dependent SCI individuals and to assess the laterality of upper limb usage. Our current framework was mainly focused on assessing PA in wheelchair-dependent SCI individuals. Extending it to the ambulatory population is required to comprehensively assess PA in the complete population of SCI. Furthermore, an extension to assess the quality of movement, additional to the quantity, can help clinicians and researchers to evaluate how well patients can transfer their acquired skills during therapies, e.g., walking, to daily life. To evaluate the quantitative measures of PA and give first recommendations, impairment-specific norm data about typical PA values in acute and chronic SCI individuals are required.

Therefore, the first aim of this work was to extend our existing framework to assess PA in individuals with an SCI. The second aim was to acquire norm data about PA to enable meaningful evaluation of the acquired PA levels. Ultimately, lesion-specific recommendations about PA levels should be given to increase motivation for PA and therefore increase PA in general. The first part of this thesis focuses on methods to assess PA in SCI individuals, while the second part of this thesis focuses on evaluating the PA levels in acute and chronic SCI individuals, revealing clinical insights and giving first recommendations about PA in SCI individuals.

In order to assess PA in SCI individuals, various algorithms to quantify and qualify PA were developed and validated. The algorithms were required to work on a minimal number of sensors to guarantee applicability in daily clinical routine and in clinical intervention studies.

First, a metric to quantify the posture (sitting and lying) of wheelchair-dependent individuals based on a chest sensor was developed and validated. This metric is especially useful in the very acute phases after an SCI, in which patients are rather inactive and need to be mobilized regularly to decrease the risk of pressure ulcers and to activate circulation.

Second, a metric to assess upper limb movement quality in tetraplegic SCI individuals was developed. This metric is based on a sensor attached to the wrist and enables an accurate distinction between compensatory and non-compensatory strategies while performing activities of daily living. Furthermore, it showed the potential to quantify upper limb compensation sensitively. This metric is particularly useful in clinical intervention studies aiming at increasing the functional recovery of the upper limbs and can help to distinguish true biological recovery from recovery driven by compensation.

Third, an analysis has been conducted to estimate the inter-day reliability of PA metrics. To get a reliable representation of the subjects' general PA, we presented guidelines on how many days researchers should aim to measure PA in inpatient rehabilitation and after discharge in the home-environment. We proposed to use at least 2 measurement days during the inpatient rehabilitation, and at least 3 measurement days after discharge.

Lastly, algorithms to estimate the energy expenditure and gait quality in ambulatory SCI and healthy individuals, and wheeling efficiency were developed within the scope of this thesis and are briefly discussed.

In order to evaluate PA, norm data were acquired and analyzed. PA was measured during acute SCI rehabilitation and related to clinical scores, e.g., to independence in terms of the Spinal Cord Independence Measure (SCIM) self-care subscores and mobility. We identified a strong relationship of the patients' independence and mobility to the PA levels, suggesting that these factors mainly drive the increase of PA in acute rehabilitation. We found increasing PA in both tetraplegic and paraplegic patients during rehabilitation, while the increase was stronger in tetraplegic patients. In terms of overall upper limb PA (i.e., activity counts) tetraplegic patients reached very similar levels compared to paraplegic patients towards the end of rehabilitation. However, we revealed that times spent in PA in higher intensity (i.e., moderate-vigorous PA) was significantly higher in paraplegic patients compared to tetraplegic patients. This implies the importance of assessing not only general PA in terms of activity counts but also PA intensity levels. Especially moderate-vigorous PA is a sensitive marker to detect changes of PA between patient groups and over time.
Furthermore, PA was assessed in therapy sessions and leisure time separately. We could show that PA in both, therapy sessions and leisure time, was susceptible to an increase. This suggests that interventional trials aiming at increasing PA during acute rehabilitation should focus on increasing motivation for PA during therapy sessions and leisure time.

Lastly, we identified four distinct PA clusters in chronic SCI individuals that showed significant differences in the PA levels, but also in clinical scores. These clusters comprised wheelchair-dependent SCI individuals with moderate independence, wheelchair-dependent SCI individuals with high independence, ambulatory SCI individuals with moderate walking capacity, and ambulatory SCI with high walking capacity, which is comparable to healthy controls. These findings revealed a relation of mobility and independence to PA not only in acute but also in chronic SCI individuals. Therefore, we suggest building PA recommendations which are specific to the mobility-mode and, eventually, to the independence of SCI individuals.

This work extends the existing framework to assess PA in individuals with an SCI by developing and validating new algorithms to assess movement quantity and quality. The main contribution lies in the extension of the framework to evaluate PA levels in acute and chronic SCI by acquiring and interpreting norm data of PA during acute rehabilitation and in chronic SCI together with the healthy population. Using our framework, researchers will be able to disentangle the causality between PA and functional recovery, investigate the effect of new therapeutic interventions and increase PA in acute and chronic SCI individuals in order to improve the functional recovery of SCI individuals and therefore their quality of life.

Zusammenfassung

Querschnittlähmung (QSL) ist eine neurologische Erkrankung, die zu schweren sensomotorischen Störungen führt. Die neurologische Erholung nach QSL ist begrenzt und wird in der akuten Phase hauptsächlich durch aktivitätsbasierte Rehabilitation bestimmt. Darüber hinaus konnte belegt werden, dass physische Aktivität (PA) einen positiven Einfluss auf den allgemeinen Gesundheitszustand hat. Jedoch wurde gezeigt, dass PA in Personen mit einer QSL gering ist und daher erhöht werden muss. Dies lässt sich hauptsächlich auf die eingeschränkte Mobilität in dieser Population zurückführen. Angemessene Empfehlungen zur Quantität von PA kann zu einer Erhöhung der PA sowohl in akuten als auch chronischen QSL Patienten beitragen. Daher ist ein Framework erforderlich, um die PA objektiv zu erfassen und sie unter Berücksichtigung des Grades der Beeinträchtigung zu bewerten.

Tragbare Sensoren bieten ein hohes Potenzial für die Messung der PA nicht nur in gesunden Erwachsenen, in älteren Menschen, Kindern und Jugendlichen, sondern auch in Personen mit Multipler Sklerose, Parkinson und Schlaganfall. Kürzlich wurde das Potenzial von tragbaren Sensoren gezeigt, um PA auch in Personen mit einer QSL zu erfassen.

In unserer Forschungsgruppe wurde ein Framework entwickelt, um PA in Personen mit einer QSL zu messen. Dieses Framework umfasst Algorithmen zur Quantifizierung des Rollstuhlfahrens und zur Unterscheidung zwischen aktivem und passivem Rollstuhlfahren, zur Abschätzung des Energieverbrauchs bei rollstuhlabhängigen Personen und zur Bewertung der Lateralität der oberen Extremitäten. Unser aktuelles Framework konzentriert sich hauptsächlich auf die Messung der PA bei rollstuhlabhängigen Personen mit einer QSL. Um eine Aussage über die PA in der gesamten QSL-Population zu machen, ist eine Ausweitung unseres Frameworks auf die ambulante Population erforderlich. Darüber hinaus kann das Messen der Qualität der Bewegungen, zusätzlich zur Quantität, Klinikern und Forschern helfen, zu bewerten, wie gut Patienten ihre erworbenen Fähigkeiten während der Therapie, z. B. das Gehen, auf das tägliche Leben übertragen können. Um die PA jedoch zu bewerten und erste Empfehlungen zu geben, fehlen Normdaten über die PA, die spezifisch für die jeweilige Beeinträchtigung bei akuten und chronischen QSL-Individuen sind.

Daher bestand das erste Ziel dieser Arbeit darin, unser bestehendes Framework zur Messung der PA bei QSL zu erweitern. Das zweite Ziel bestand darin, Normdaten über PA zu sammeln, um eine aussagekräftige Bewertung der erfassten PA zu ermöglichen. Damit sollten läsions-

spezifische Empfehlungen zu PA gegeben werden, um die Motivation für PA und damit die PA im Allgemeinen zu erhöhen. Der erste Teil dieser Arbeit befasst sich mit der Entwicklung von Methoden zum Erfassen der PA bei QSL, während der zweite Teil dieser Arbeit sich mit der Bewertung der PA bei akuten und chronischen Personen mit einer QSL, der Aufdeckung klinischer Erkenntnisse und ersten Empfehlungen zur PA bei Personen mit einer QSL befasst.

Um PA in Personen mit einer QSL zu erfassen, wurden verschiedene Algorithmen zur Quantifizierung und Qualifizierung von PA entwickelt und validiert. Die Algorithmen mussten auf einer minimalen Anzahl von Sensoren entwickelt werden, um die Anwendbarkeit im klinischen Alltag und in klinischen Interventionsstudien zu gewährleisten. Zunächst wurde ein Algorithmus zur Quantifizierung der Körperposition (Sitzen und Liegen) von rollstuhlabhängigen Personen entwickelt und validiert. Dieser Algorithmus basiert auf den Daten eines Sensors angebracht um den Burstkorb. Dieser Algorithmus ist besonders in den sehr akuten Phasen nach einer QSL nützlich, in denen die Patienten eher inaktiv sind und regelmäßig mobilisiert werden müssen, um das Risiko von Druckgeschwüren zu verringern und den Kreislauf zu aktivieren.

Zweitens wurde eine Messgröße zur Beurteilung der Bewegungsqualität der oberen Extremitäten bei Tetraplegikern entwickelt. Diese Messgröße basiert auf einem am Handgelenk angebrachten Sensor und ermöglicht eine genaue Unterscheidung zwischen kompensatorischen und nicht kompensatorischen Strategien bei der Durchführung von Aktivitäten des täglichen Lebens. Darüber hinaus konnten wir das Potenzial aufzeigen, die Kompensation der oberen Extremitäten sensitiv zu quantifizieren. Diese Messgröße ist besonders nützlich in klinischen Interventionsstudien mit dem Ziel die funktionelle Erholung der oberen Extremitäten zu verbessern. Sie kann dazu beitragen, echte biologische Erholung von einer Erholung aufgrund von Kompensationsstrategien zu unterscheiden.

Drittens wurde eine Analyse durchgeführt, um die Variabilität von PA an verschieden Messtagen abzuschätzen und die Reliabilität zu bestimmen. Um eine reliable Darstellung der allgemeinen PA der Probanden zu erhalten, haben wir Leitlinien erstellt, an wie vielen Tagen die PA in der stationären Rehabilitation und nach der Entlassung aus der Klinik im häuslichen Umfeld gemessen werden sollte. Wir konnten zeigen, dass PA an mindestens 2 Tagen während der stationären Rehabilitation und mindestens 3 Tagen nach der Entlassung gemessen werden sollte um eine reliable Darstellung der PA gewährleisten.

Schließlich wurden im Rahmen dieser Arbeit Algorithmen zur Schätzung des Energieverbrauchs und der Gangqualität bei ambulanten und gesunden Personen, sowie der Effizienz des Rollstuhlfahrens entwickelt. Diese werden in der Diskussion dieser Arbeit kurz erörtert.

Zur Auswertung und Beurteilung der PA wurden Normdaten erhoben und analysiert. PA wurde während der akuten Rehabilitation gemessen und es konnte ein Zusammenhang mit klinischen Scores aufgezeigt werden. Dazu zählte die Selbstständigkeit, gemessen durch die Unterpunkte Selbstversorgung und Mobilität des Spinal Cord Independence Measurement

(SCIM), sowie die Mobilität. Dies deutet darauf hin, dass diese Faktoren hauptsächlich die Zunahme der PA in der akuten Rehabilitation bestimmen. Während der Rehabilitation stellten wir sowohl bei Tetraplegikern als auch bei Paraplegikern einen Anstieg der PA fest. Jedoch war der Anstieg bei Tetraplegikern stärker. Bezogen auf die PA der oberen Extremitäten (gemessen durch 'activity counts'), erreichten tetraplegische Patienten gegen Ende der Rehabilitation sehr ähnliche Werte im Vergleich zu paraplegischen Patienten. In einer anschließenden Analyse haben wir jedoch gezeigt, dass Paraplegiker signifikant mehr Zeit in PA von höherer Intensität (moderate-bis-hoch-intensive PA) verbrachten als Tetraplegiker. Dies impliziert die Wichtigkeit, nicht nur die allgemeine PA in Bezug auf die activity counts, sondern auch die unterschiedlichen Intensitätsniveaus zu messen. Besonders moderate-bis-hoch-intensive PA ist ein sensitiver Marker um Veränderungen in der PA zwischen Patientengruppen und über die Zeit zu erkennen.

Darüber hinaus wurde die PA während Therapiesitzungen und Freizeit untersucht. Wir konnten aufzeigen, dass PA sowohl während der Therapiesitzungen als auch während der Freizeit das Potenzial zu einem Anstieg zeigte. Interventionsstudien zur Erhöhung der PA während der akuten Rehabilitation sollten daher nicht nur auf eine Erhöhung der PA während der Therapiesitzungen, sondern auch während der Freizeit abzielen.

Zuletzt identifizierten wir vier verschiedene PA-Cluster bei Personen mit einer chronischen QSL. Diese Cluster zeigten signifikante Unterschiede in der PA, aber auch in den klinischen Scores auf. Die Cluster umfassten rollstuhlabhängige Personen mit mäßiger Selbstständigkeit, rollstuhlabhängige Personen mit hoher Selbstständigkeit, ambulante Personen mit mäßiger Gehfähigkeit und Personen mit hoher Gehfähigkeit, die mit der von gesunden Kontrollen vergleichbar ist. Diese Ergebnisse zeigten, dass Mobilität und Selbstständigkeit nicht nur bei akuten Personen mit einer QSL, sondern auch bei chronischen Personen eine wichtige Rolle spielen. Daher schlagen wir vor, PA-Empfehlungen zu erstellen, die spezifisch auf die Mobilität und, ggf., auf die Selbstständigkeit von Personen mit einer QSL abgestimmt sind.

Diese Arbeit erweitert das bestehende Framework zur Erfassung von PA bei QSL durch die Entwicklung und Validierung neuer Algorithmen zur Erfassung der Bewegungsquantität und -qualität. Der Hauptbeitrag liegt in der Erweiterung des Frameworks um PA in Personen mit einer QSL bewerten zu können. Dies wurde durch das Sammeln und die Interpretation von Normdaten über PA in Personen mit einer QSL erreicht. Mithilfe unseres Frameworks können Forscher die Kausalität zwischen PA und funktioneller Genesung, sowie die Wirkung neuer therapeutischer Interventionen untersuchen. Weiterhin kann mit diesem Framework die PA bei Personen mit einer akuten und chronischen QSL erhöht werden, um die funktionelle Genesung von diesen Personen und damit deren Lebensqualität zu verbessern.

Contents

Acknowledgements **v**

Abstract (English/Deutsch) **vii**

List of figures **xix**

List of tables **xxvii**

1 General introduction **1**
1.1 Spinal cord injury . . . 2
1.2 Recovery after a spinal cord injury . . . 2
1.2.1 Activity-dependent plasticity . . . 3
1.2.2 Recent therapeutic advances . . . 3
1.2.3 Assessing the recovery after a spinal cord injury . . . 4
1.3 Physical activity in chronic spinal cord injury . . . 4
1.4 Assessing physical activity . . . 5
1.4.1 Physical activity questionnaires . . . 5
1.4.2 Wearable sensors . . . 6
1.5 Aims of the thesis . . . 7
1.6 Thesis outline . . . 8

I Methodological aspects **11**

2 Robust posture detection in spinal cord injured wheelchair users using a single inertial measurement unit **13**
2.1 Abstract . . . 14
2.2 Introduction . . . 14
2.3 Methods . . . 15
2.3.1 Subjects . . . 15
2.3.2 Sensor device . . . 16
2.3.3 Data collection . . . 16
2.3.4 Data analysis . . . 16
2.4 Results and Discussion . . . 17
2.5 Conclusion . . . 20

3 Predicting upper limb compensation during prehension tasks in tetraplegic spinal cord injured patients using a single wearable sensor 21

3.1 Abstract 22
3.2 Introduction 22
3.3 Methods 23
3.3.1 Subjects 23
3.3.2 Measurement protocol 23
3.3.3 Data processing 25
3.3.4 Statistics 26
3.4 Results 27
3.4.1 Subject characteristics 27
3.4.2 Standard clinical surrogate markers for UL compensation: Qualitative prehension score and task duration 27
3.4.3 Sensor-based marker for UL compensation: Spread of forearm pitch angles 29
3.5 Discussion 29
3.6 Conclusions 37

4 Reliability of wearable-sensor-derived measures of physical activity in wheelchair-dependent spinal cord injured patients 39

4.1 Abstract 40
4.2 Introduction 40
4.3 Methods 42
4.3.1 Patients 42
4.3.2 Measurement procedure 42
4.3.3 Data analysis and statistics 43
4.4 Results 48
4.4.1 Patient characteristics 48
4.4.2 Single-day reliabilities 48
4.4.3 Required number of days 49
4.4.4 Influence of weekday versus weekend 50
4.5 Discussion 54
4.5.1 Single-day reliabilities 54
4.5.2 Required number of days for reliable measures 55
4.5.3 Difference between weekdays and weekend 56
4.5.4 Comparison to literature 56
4.5.5 Choice of accelerometer cut-points 57
4.5.6 Study Limitations 57
4.6 Conclusion 58

II Clinical insights **59**

5 Monitoring Upper-Limb Recovery After Cervical Spinal Cord Injury: Insights Beyond Assessment Scores **61**
5.1 Abstract 62
5.2 Introduction 63
5.3 Methods 64
5.3.1 Subjects 64
5.3.2 Clinical Assessments 64
5.3.3 Data collection and measurement procedure 66
5.3.4 Data analysis 66
5.3.5 Sensor based outcome measures 67
5.3.6 UL activity categories 67
5.3.7 Statistical analysis 68
5.4 Results 70
5.4.1 Changes in sensor metrics 70
5.4.2 Changes in limb-use laterality 72
5.4.3 Group differences at six months 73
5.4.4 Centre differences at 6 months 75
5.5 Discussion 76
5.5.1 Limitations 80
5.6 Conclusion 80

6 Intensity of physical activity during therapy and leisure time in the rehabilitation of acute spinal cord injury **81**
6.1 Abstract 82
6.2 Introduction 83
6.3 Methods 83
6.3.1 Patients 83
6.3.2 Measurement device 84
6.3.3 Measurement protocol 84
6.3.4 Data analysis and statistics 85
6.4 Results 87
6.4.1 Patient characteristics 87
6.4.2 Longitudinal changes of PA levels 89
6.5 Discussion 89
6.5.1 Effect of therapy and group on changes of PA levels over time 94
6.5.2 Independence as an additional factor influencing the PA level 95
6.5.3 Additional factors influencing PA levels: Demographics 96
6.5.4 Limitations 97
6.6 Conclusion 97

7 Levels of physical activity in chronic spinal cord injury: adjustment to functional impairment **99**
7.1 Abstract 100
7.2 Introduction 100
7.3 Methods 101
7.3.1 Subjects 101
7.3.2 Measurement device 102
7.3.3 Measurement protocol 102
7.3.4 Data analysis and statistics 102
7.4 Results 104
7.4.1 Demographics 104
7.4.2 Differences in PA between chronic SCI subjects and healthy controls . . 104
7.4.3 Cluster analysis of PA metrics 107
7.4.4 Predicting PA clusters using clinical scores and age 108
7.5 Discussion 111
7.5.1 The influence of mobility on PA levels 111
7.5.2 Clustering of PA metrics into wheelchair-dependent and ambulatory SCI individuals 111
7.5.3 Comparison of PA levels to literature 112
7.5.4 Adherence to guidelines to literature 113
7.6 Limitations 114
7.7 Conclusion 114

8 General discussion **115**
8.1 Assessing physical activity 116
8.2 Evaluating physical activity 119
8.3 Towards physical activity recommendations 121
8.4 Thesis contributions 127
8.5 Conclusion and outlook 127

Bibliography **131**

A Supplementary material to Chapter 4 **155**

B Supplementary material to Chapter 6 **157**

C Supplementary material to Chapter 7 **165**

List of figures

2.1 Used sensor hardware and setup. A-B: Using an elastic strap, the sensor was mounted on the subject's chest in a way that the x-axis of the sensor was pointing towards the head of the subject. C: In optimal lying and sitting positions the pitch angle between the x-axis of the sensor and gravity is close to 90°and 180°, respectively. 15

2.2 Three representative time traces of the calculated chest pitch angles from the validation data set, indicating the phases identified as sitting using i) the clustering-based approach (first row, gray areas) and ii) the method based on a global threshold (second row, light red areas). The optimized global threshold used for the analysis in ii) is represented by the dashed red lines in D-F. 18

2.3 Posture detection accuracy as a function of the threshold value used with the classification method based on a global threshold. The vertical dashed black line represents the optimal threshold value of 112°resulting in an overall detection accuracy of 98.9%. The horizontal solid red line indicates the accuracy of the clustering-based approach (98.7%). 18

2.4 Time trace of the calculated chest pitch angle during a 24-hour recording, indicating the phases identified as sitting using A) the clustering-based approach (gray areas) and B) the method based on a global threshold (light red areas). The optimized global threshold assessed from the validation data set used in B) is represented by the dashed red line. 19

3.1 Schematic representation of the forearm pitch. The pitch angle is calculated relative to the earth referential frame using one inertial measurement unit (red box) attached to the wrist. No pitch, i.e., movement in the horizontal plane, results in a value of 0°. Pointing upwards results in positive values, pointing downwards in negative values. 24

3.2 Picture of the three investigated qualitative prehension grips. A. Cylindrical grip. B. Lateral grip. C. Pinch grip. 25

3.3 Picture of all six prehension tasks. A. Pouring water from a bottle. B. Opening a jar. C. Transferring nine pegs from board to board. D. Picking up and turning a key. E. Picking up four coins and placing them into slots. F. Screwing four nuts onto bolts. 25

3.4 Polar plots of the forearm pitch angle distribution of a representative SCI patient with compensation (red line) and a control subject (blue line) for each of the six prehension tasks. The outer solid circle denotes a histogram frequency of 100 datapoints (equals to 2sec), the inner dotted line a histogram frequency of 50 datapoints (equals to 1sec). The 95% central range of the forearm pitch is given for one representative tetraplegic and control subject. 30

3.5 Boxplots of the spread of the forearm pitch angles in tetraplegic subjects (filled red circles) and healthy controls subjects (empty blue triangles) without compensation and with compensation for all the six prehension tasks. 31

3.6 Predicted probabilities of compensation as functions of the spread of forearm pitch angles using logistic regression. Orange color denotes samples labeled as compensation, black denotes samples labeled as no compensation. Points denote correctly classified samples (true positives and true negatives), crosses incorrectly classified samples (false positive and false negatives). Confusion matrices for all tasks are given in percentages (Pred: predicted score, Ref: labeled score, NC: no compensation, C: compensation). 32

3.7 Correlation between the qualitative GRASSP prehension score (sum of scores for cylindrical, lateral, and pinch grip) and the spread of forearm pitch angles. Orange points denote subjects with labeled UL compensation, black points subjects without labeled UL compensation. Spearman correlation coefficients are shown. 33

3.8 Correlation between the quantitative GRASSP prehension score and the spread of forearm pitch angles for each task. Orange points denote subjects with labeled UL compensation, black points subjects without labeled UL compensation. Spearman correlation coefficients are shown. 34

3.9 Correlation between the task duration and the spread of forearm pitch angles for each task. Orange points denote subjects with UL compensation, black points subjects without UL compensation. Spearman correlation coefficients are shown. 35

4.1 Photograph of one examiner wearing the sensors. One sensor was attached to the right wheel of each wheelchair, one sensor was attached to each wrist. . . . 43

4.2 Measurement protocol. This study consists of two observational studies. In the 1st observational study, patients were measured at 5 time points during the rehabilitation process. In the 2nd observational study, a different patient cohort was measured only once, at least 1 year after injury. In stages VA, A I, A II, and partly A III of the 1st observational study, patients were in-patients (red). In the 2nd observational study, as well as partly in A III, and stage C of the 1st observational study, patients were out-patients (blue). At each time point (*), acceleration and angular velocity of the right and left wrists were recorded for 3 days, while the acceleration of the right wheel of the wheelchair was recorded for 7 days. Overall upper limb activity (AC) and PA based on energy expenditure (SED, LPA and MVPA) were calculated based on the 3 day recordings. All wheeling-related measures ($DIST_{TOT}$, $DIST_{ACT}$ and VEL) were calculated based on the 7 day recordings. 44

4.3 ICC values representing the single-day reliabilities for (A) activity counts (AC); (B) time spent in sedentary activity (SED), low physical activity (LPA), and moderate-to-vigorous activity (MVPA); (C) total distance travelled in a wheelchair ($DIST_{TOT}$) and distance travelled actively in a wheelchair ($DIST_{ACT}$); and (D) laterality (LAT) and mean velocity (VEL) for all in-patient rehabilitation stages (very acute (VA – 2 weeks after injury), acute I (A I – 4 weeks after injury), acute II (A II – 3 months after injury) , acute III (A III – 6 months after injury)), as well as for the out-patients (>6 months after injury). The horizontal dashed lines depict the ICC level of 0.8, which was chosen as a requirement for a reliable measurement. Solid and dotted lines indicate the confidence intervals. Indicated patient numbers n are the pooled numbers. 49

4.4 ICC values representing the single-day reliabilities for activity counts (AC), time spent in sedentary activity (SED), low physical activity (LPA), moderate-to-vigorous activity (MVPA), total distance traveled in a wheelchair ($DIST_{TOT}$), distance traveled actively in a wheelchair ($DIST_{ACT}$), laterality (LAT), and mean velocity during active wheeling (VEL) for wheelchair-dependent paraplegic patients (full circle, solid lines) compared to wheelchair-dependent tetraplegic patients (empty circle, dotted lines) for the in-patients (from 2 weeks after injury to 6 months after injury) and out-patients (>6 months after injury). The dashed horizontal lines depict the ICC level of 0.8, which was chosen as a requirement for a reliable measurement. Solid and dotted lines indicate the confidence intervals. Indicated patient numbers n are the pooled numbers. 50

4.5 The subfigures on the left side (A: in-patients, C: out-patients) represent the number of measurement days needed in order to achieve a reliability of 0.8 for different metrics of movement quantity (activity counts – AC, time spent in sedentary activity – SED, in low physical activity – LPA, in moderate-to-vigorous activity – MVPA, total distance wheeled – $DIST_{TOT}$, and distance wheeled actively – $DIST_{ACT}$) as well as metrics of movement quality (laterality – LAT and mean wheeling velocity – VEL). Additionally, the numbers of measurement days needed for a reliability of 0.5 and 0.75 are presented with magenta and blue vertical bars, respectively. The subfigures on the right side (B: in-patients, D: out-patients) show the reliabilities, which would be achieved when measuring 3 and 7 days, respectively. 51

4.6 Boxplots for total distance traveled in a wheelchair (A) and mean velocity during active wheeling (B) during weekdays vs. weekends in all single in-patient stages (VA, AI, AII, AIII), as well as out-patients. */+ denotes p-value of < 0.05, **/++ a p-value of < 0.01, ***/+++ a p-value of < 0.001, respectively. P-values were calculated using the TOST procedure for normally distributed data (*), respectively, the adapted equivalence test based on the Mann-Whitney-Wilcoxon Test for non-normally distributed data (+). 52

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. 68

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. 70

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 (Panel A) and three months (Panel 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 (Panel C) after injury (N = 27, P = 0.178, r = 0.273, Spearman correlation). MMT = manual muscle testing. 72

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. 74

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. 75

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. 76

6.1 Measurement protocol. Recruitment took place at stage VA (two weeks after injury) and A1 (one month after injury). Patients were measured during the subsequent stages, i.e., A2 (three months after injury) and A3 (six months after injury) during their stay in rehabilitation until discharge. 85

6.2 Longitudinal changes of activity counts (AC) and PA intensity levels during the rehabilitation. A-B: Mean AC with standard deviation at 2 weeks (VA), 1 month (A1), 3 months (A2), and 6 months (A3) after injury in thoracic/lumbar patients (light blue) and cervical patients (dark blue) (panel A) and in leisure time (light yellow) and active therapy (dark yellow) (panel B). Plotted is the mean value and the standard deviation (error bars). Significant differences based on the 'basic' linear mixed model were marked with asterisks (*** p < .001, ** p < .01, * p < .5). C-D: Mean minutes spent in resting intensity (REST), sedentary intensity (SED), low intensity (LPA), and moderate-vigorous intensity (MVPA) normalized to one hour in thoracic/lumbar and cervical patients (panel C), as well as in leisure time and active therapy (panel D), respectively. Higher PA intensities are represented by darker grey tones. 91

6.3 Partial residual plots based on the 'full' linear mixed model including all covariates and significant interactions for times spent in low physical activity (LPA, panel A-C), and time spent in moderate-to-vigorous intensity (MVPA, panel D-F). A: partial residuals for the interaction effect stage*group on LPA. B: partial residuals for the main effect therapy on LPA. C: partial residuals for the main effect mobility on LPA. D: partial residuals for the main effects stage and group on MVPA. E: partial residuals for the main effect therapy on MVPA. F: partial residuals for the main effect mobility on MVPA. 92

6.4 Partial residual plots based on 'full' linear mixed model including all covariates and significant interactions for the effect of SCIM self-care and group (panel A and C) and SCIM self-care and therapy (panel B and D) on times spent in low physical activity (LPA, panel A and B), and time spent in moderate-to-vigorous intensity (MVPA, panel C and D). A. partial residuals for the main effects SCIM self-care and group on LPA. B. partial residuals for the main effects SCIM self-care and therapy on LPA. C. partial residuals for the main effects SCIM self-care and group on MVPA. D. partial residuals plot for the interaction effect SCIM self-care*therapy on MVPA. Plotted lines are based on a linear fit of the data to indicate potential interaction effects. 93

7.1 Boxplots for average MET (panel A), time spent in sedentary PA (SED, panel B), time spent in low PA (LPA, panel C), and time spent in moderate-vigorous PA (MVPA, panel D) for the groups of wheelchair dependent SCI subjects, ambulatory SCI subjects, and healthy control subjects. *, **, ***, denote p-values of < 0.05, < 0.01, < 0.001, respectively. 105

7.2 Boxplots of PA metrics (Panel A-E), and clinical scores (panel F-H) in the four PA clusters 'wheelchair-dependent with moderate independence', 'wheelchair-dependent with high independence', 'ambulatory with moderate walking capacity', and 'ambulatory with high walking capacity' resulting from the hierarchical clustering. Red boxplots and points indicate the updated PA clusters after removing 'motivational outliers', which were wrongly predicted by the multinomial regression model and thus removed for the final PA clusters. *, **, ***, denote p-values of < 0.05, < 0.01, < 0.001, respectively and are given for the updated PA clusters only. 109

B.1 Longitudinal changes of activity counts (AC) during the rehabilitation from 2 weeks after injury (Stage VA) to 6 months after injury (Stage A3) during leisure time and active therapies for patients with a thoracic/lumbar lesion (light blue) and a cervical lesion (dark blue). Plotted is the mean value and the standard deviation (error bars). 158

C.1 Dendrogram resulting from hierarchical clustering of PA metrics. 'wheelSCI_xx' denote wheelchair-dependent SCI subjects, 'wheel_athleteSCI_xx' wheelchair-dependent SCI subjects participating in regular sports training and matches, 'ambuSCI_xx' ambulatory SCI subjects, and 'control_xx' healthy controls. . . . 166

List of tables

2.1 Performance analysis – absolute frequencies 19
2.2 Performance analysis – accuracy and sensitivity 19

3.1 Task duration and qualitative and quantitative grassp prehension scores in subjects showing compensatory strategies and not showing compensatory strategies in the single grassp tasks. median ± interquartile range is given. 28
3.2 Sensitivity, specificity, and accuracy of the logistic regression model for classifying UL compensation. 29

4.1 Patient demographics for all patients included as well as split up into patients included in the 1st and 2nd observational studies for 3-day as well as 7-day measurements. Detailed numbers are given for all single stages constituting the 1st observational study: 2 weeks after injury (VA), 4 weeks after injury (A I), 3 months after injury (A II), 6 months after injury (A III), and 1 year after injury (C). In stage A III, in- as well as out-patients are included. * For a combined analysis of all in-patients, data of stages VA, A I, A II, and A III (partly) were pooled. Data of stages A III (partly), stage C, as well as the 2nd observational study were pooled for a combined analysis of all out-patients. 'Tetraplegics' are defined by a lesion level from C1 to Th1. 45
4.2 Descriptive statistics for total distance travelled in a wheelchair ($DIST_{TOT}$), distance travelled actively in a wheelchair ($DIST_{ACT}$), and mean velocity during active wheeling (VEL) performed during weekdays and weekends (mean ± SD and median (IQR)) for pooled in-patients and out-patients, as well as all single stages, VA (very acute – 2 weeks after injury), A I (acute I – 4 weeks after injury), A II (acute II – 3 months after injury), A III (acute III – 6 months after injury). The last three columns contain the calculated limits of practical equivalence (LOPE) used for the equivalence tests, the confidence intervals, and the p-values resulting from the equivalence tests. a denotes p-values resulting from the Mann-Whitney-Wilcoxon Test of equivalence for non-normally distributed data, the remaining p-values were calculated using the TOST procedure for normally distributed data. 53

5.1 Demographic characteristics of the 31 spinal cord injured subjects included in the study. 65

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; t_1, one month; t_2, three months; t_3, six months. Results are displayed as estimates ± standard errors. * Bonferroni corrected. 71

6.1 Demographics and descriptive statistics. Descriptive statistics for activity counts (AC) were calculated based on the complete set of 42 patients (Stage VA: 13, Stage A1: 42, Stage A2: 42, Stage A3: 18 patients), and for time spent in resting (REST), sedentary (SED), low (LPA), and moderate-to-vigorous (MVPA) intensity based on the reduced set of 33 patients (Stage VA: 10, Stage A1: 33, Stage A2: 33, Stage A3: 16 patients). 88

6.2 Summary table of the linear mixed model statistics for the 'basic' models and the 'full' models. F and p values are given for all fixed effects and for significant interactions. Non-significant interactions were removed from the models ([a]). Note that the models for AC were built on all 42 subjects, the models for REST, SED, LPA, and MVPA were built on a reduced set of 33 subjects. 90

7.1 PA metrics of wheelchair-dependent SCI subjects, ambulatory SCI subjects, and control subjects. The χ^2 and p-values were calculated based on a Kruskal-Wallis Rank Sum Test. Significant differences (p-value < 0.05) are marked in bold. [a] denotes a significant post-hoc comparison (p-value < 0.05) between wheelchair-dependent SCI and healthy control subjects, [b] between wheelchair-dependent and ambulatory SCI subjects, and [c] between ambulatory SCI and healthy control subjects. 106

7.2 Sensitivity, specificity, and balanced accuracy for predicting PA clusters based on the clinical scores and age. 108

7.3 Demographics, clinical scores, and PA metrics of final PA clusters after removing 'motivational outliers'. a-f denote significant post-hoc comparisons (p-value < 0.05) between clusters: [a] 'wheelchair-dependent with moderate independence' vs. 'wheelchair-dependent with high independence' , [b] 'wheelchair-dependent with moderate independence' vs. 'ambulatory with moderate walking capacity', [c] 'wheelchair-dependent with moderate independence' vs. 'ambulatory with high walking capacity', [d] 'wheelchair-dependent with high independence' vs. 'ambulatory with moderate walking capacity', [e] 'wheelchair-dependent with high independence' vs. 'ambulatory with high walking capacity', and [f] 'ambulatory with moderate walking capacity'vs. 'ambulatory with high walking capacity'. . 110

8.1 PA level recommendations for the groups of wheelchair-dependent SCI individuals with moderate and full independence, and ambulatory SCI individuals with moderate and full walking capacity. The median (25^{th} - 75^{th} percentile) is given in minutes per 16h for the PA levels moderate-to-vigorous PA (MVPA), low-intense PA (LPA), sedentary PA (SED), resting (REST), and the sum of SED and REST. Median (25^{th} - 75^{th} percentile) is also given for the SCIM self-care, SCIM mobility indoors and outdoors and distance in 6-Minute Walk Test (6MWT) in meter for each group. Mean age and standard deviation (SD) is given in years. . 123
8.2 Comparison between PA levels from our study in ambulatory SCI and healthy controls with high walking capacity. [a] PA levels are standardized to a 16h-day of waking time. [b] Standardization of PA levels is not reported, but assessed during one complete day excluding sleep. 125

A.1 Sample size calculation for activity counts (AC), time spent in sedentary activity (SED), low physical activity (LPA), and moderate-to-vigorous activity (MVPA), total distance travelled in a wheelchair ($DIST_{TOT}$), distance travelled actively in a wheelchair ($DIST_{TOT}$), laterality (LAT) and mean velocity (VEL) for pooled in-and out-patients. The desired confidence interval width is set to 0.2. 156

B.1 Post-hoc comparisons for all significant effects in the 'basic' models. Post-hoc comparisons of main effects involved in a significant interaction were conducted for the interaction effect only. The Tukey multiple-comparison test was applied for pairwise comparisons, multivariate testing was used for comparing stages. Note that stages were compared consecutively only. Significant comparisons (α = 0.05) are highlighted in bold. a main effect involved in significant interaction. b non-significant effect. 159
B.2 Post-hoc comparisons for all significant effects in the 'full' models. Post-hoc comparisons of main effects involved in a significant interaction were conducted for the interaction effect only. The Tukey multiple-comparison test was applied for pairwise comparisons, multivariate testing was used for comparing stages. Note that stages were compared consecutively only. For the interaction effects SCIM self-care and therapy as well as age and therapy, the significance test was applied for the differences between slopes. Significant comparisons (α = 0.05) are highlighted in bold. a main effect involved in significant interaction. b non-significant effect. c significant main effect, but no post-hoc comparison possible, because of continuous scale of the variables.s 160
B.3 Estimated marginal means (EMM) and standard errors (SE) for all significant effects involving categorical variables in the 'basic' models. Please note that the EMM and SE were back-transformed from the square-root-scale to facilitate interpretation only. EMM were calculated for significant effects only. If a main effect was involved in a significant interaction, EMM were calculated for the interaction effect only. a main effect involved in significant interaction. b non-significant effect. 161

B.4 Estimated marginal means (EMM) and standard errors (SE) for all significant effects involving categorical variables in the 'full' models. Please note that the EMM and SE were back-transformed from the square-root-scale to facilitate interpretation. EMM were calculated for significant effects only. If a main effect was involved in a significant interaction, EMM were calculated for the interaction effect only. a main effect involved in significant interaction. b non-significant effect. 162
B.5 Estimated marginal (EM) trends and standard errors (SE) for all significant effects involving continuous variables in the 'full' models. Please note that the EM trends and SE were calculated after back-transforming from the square-root-scale to facilitate interpretation. EM trends were calculated for significant effects only. If a main effect was involved in a significant interaction, EM trends were calculated for the interaction effect only. a main effect involved in significant interaction. b non-significant effect. 163

C.1 Calculated PA metrics used for hierarchical clustering. * Metrics were not used in hierarchical clustering but only reported to compare between clusters and to literature. 167
C.2 Demographics, clinical scores, and PA metrics of PA clusters resulting from hierarchical clustering. a-f denote significant post-hoc comparisons (p-value < 0.05) between clusters: a 'wheelchair-dependent with moderate independence' vs. 'wheelchair-dependent with high independence' , b 'wheelchair-dependent with moderate independence' vs. 'ambulatory with moderate walking capacity', c 'wheelchair-dependent with moderate independence' vs. 'ambulatory with high walking capacity', d 'wheelchair-dependent with high independence' vs. 'ambulatory with moderate walking capacity', e 'wheelchair-dependent with high independence' vs. 'ambulatory with high walking capacity', and f 'ambulatory with moderate walking capacity'vs. 'ambulatory with high walking capacity'. . . 167
C.3 : Confusion matrix of the multinomial regression model. 167

1 General introduction

1.1 Spinal cord injury

Spinal cord injury (SCI) is a neurological condition that arises from damaged neurons in the spinal cord. The damage of the neurons can either have a traumatic (e.g., from road accidents, and falls) or a non-traumatic cause (e.g., cancer). The prevalence of SCI was estimated to be around 27 million in 2016 and is recognized as a global health priority (GBD 2016 Traumatic Brain Injury and Spinal Cord Injury Collaborators et al., 2019). The incidence of SCI was reported to be higher in men than in women (Chamberlain et al., 2017). In industrialized countries, an increasing proportion of SCI occurs in older patients (Jain et al., 2015).

SCI can lead to severe sensorimotor deficits, which strongly impact the quality of life. The degree of deficits depends on the number of damaged neurons and the location of the lesion. Lesions in the cervical cord (C1 – C8) result in impairments of all four limbs (tetraplegia), while lesions in the thoracic, lumbar and sacral cord (Th1 – S5) lead to impairments in the lower limbs (paraplegia). Around one-third of all lesions are cervical, with 50% being complete lesions (Wyndaele and Wyndaele, 2006). Additional to large sensorimotor deficits, SCI individuals suffer from difficulties in bladder and bowel management, sexual dysfunction, pain, and depression. Furthermore, secondary complications like pressure ulcers, autonomic dysreflexia, and pneumonia (McKinley et al., 1999) decrease the quality of life after an SCI drastically. The quality of life was reported to be mainly affected by age, employment status, motor level, completeness of the injury and the ambulatory mode of individuals with an SCI (Jain et al., 2007). Depending on the location and the completeness of the lesion, SCI individuals may be dependent on an electric or a manual wheelchair, or are able to walk with gait aids or unsupervised. Wheelchair-dependent mobility and walking with aids is often associated with limited participation in social life due to experienced barriers in the natural environment and transportation (Whiteneck et al., 2004), which explains the substantial impact of ambulation on the quality of life.

1.2 Recovery after a spinal cord injury

The recovery after an SCI is limited and mainly driven by compensatory strategies and functional adjustments rather than by biological repair mechanisms (Curt et al., 2008). The penetration or displacement of the spinal cord results in direct tissue damage (primary injury) which initiates a cascade of secondary injuries, including edema, death of neurons and activation of glial cells, expanding the injury site and thus preventing recovery (Hausmann, 2003). Nevertheless, spontaneous recovery after an SCI has been observed and there is likely a mechanism called neuroplasticity involved. Neuroplasticity is referred to various mechanisms in the brain and in the spinal cord including synaptic rearrangement, collateral sprouting of intact and lesioned axons, and altered properties of spared neuronal circuits (Onifer et al., 2011). This has the aim to optimize the functioning of neural networks, e.g. during learning (reviewed in Lillard and Erisir, 2011) or following brain injury (Chen et al., 2010). After an SCI, activity-dependent plasticity is assumed to play a significant role in recovery and (re)learning of motor skills (Wolpaw and Tennissen, 2002).

1.2.1 Activity-dependent plasticity

Activity-dependent plasticity can be induced through passive or active physical activity (PA) by increasing the expression of neurotrophins, a class of growth factors, which are responsible for neuronal survival, growth, and differentiation (Dunlop, 2008). Brain-derived neurotrophic factor (BDNF) is a protein in this class, to which a key role is attributed in spinal learning (reviewed in Dunlop, 2008). It has been shown that growth factors alone have the potential to promote recovery after an SCI (Fouad et al., 2011). Furthermore, PA is assumed to decrease the expression of growth inhibitory molecules. Animal studies showed that not only task-specific training can improve limb function (Starkey et al., 2011), but self-motivated unspecific training can promote functional recovery as well (Starkey et al., 2014). Therefore, activity-based rehabilitation is currently one of the most common and successful treatments after an SCI, which is likely enhancing the adaptive plasticity to improve recovery, while attenuating potential maladaptive changes inhibiting recovery (Fouad and Tetzlaff, 2012).

1.2.2 Recent therapeutic advances

Besides rehabilitative strategies, advances have been made in identifying drugs promoting the neural growth after an SCI. Two very promising compounds have been identified, the anti-Nogo-A antibody and chondroitinase ABC (ChABC). Anti-Nogo-A is an antibody which neutralizes the growth inhibitor Nogo-A (reviewed in Starkey and Schwab, 2012). It has been shown to induce regeneration of injured axons in the central nervous system of rats (Schnell and Schwab, 1990) and to induce axonal growth and functional recovery of manual dexterity in adult primates (Freund et al., 2006). A first-in-man study demonstrated the safety of intrathecal administration of the human anti-Nogo-A antibody ATI355 in acute patients with a complete SCI (Kucher et al., 2018). Further studies will follow to investigate its efficiency in humans. ChABC was identified to attenuate the inhibitory activity on neural growth of chondroitin sulphate proteoglycans (CSPG). CSPG have been shown to inhibit neuronal growth at the location at which the glial scar forms (Davies et al., 1999). Thus, by attenuating its activity through intrathecal administration of ChABC, the regeneration of ascending sensory projections and descending corticospinal tract axons can be promoted (Bradbury et al., 2002).

In past years, a combined treatment with anti-Nogo-A and ChABC has been proposed and shown to be more effective than the treatment with each compound individually (Zhao et al., 2013). Not only the combination of both compounds but also with rehabilitative training is an area of current research. Preclinical studies suggest that the combination of rehabilitative training and anti-Nogo-A lead to an improved recovery compared to training alone (Maier et al., 2009). Furthermore, the combination of ChABC with locomotor training has been shown to improve recovery in preclinical studies (Alluin et al., 2014). However, it is unclear which exact mechanisms underlie the effect of dose and timing on the recovery (Starkey and Schwab, 2012).

1.2.3 Assessing the recovery after a spinal cord injury

Besides electrophysiological measurements and imaging techniques, several clinical assessments exist to assess the level of impairment in SCI individuals, the resulting functional capacity and and how it recovers during rehabilitation.

The International Standards for the Neurological Classification of Spinal Cord Injury (ISNCSCI) (Kirshblum et al., 2011a) have been developed to classify SCI. While the neurological level of injury (NLI) indicates the location of the lesion (ranging from C1 to S2), the ASIA (American Spinal Injury Association) Impairment Scale (AIS) indicates the completeness of the lesion (A: complete lesion, B: sensory incomplete lesion, C and D: motor incomplete lesion, E: normal).
The independence of SCI individuals is commonly assessed using the Spinal Cord Independence Measure III (SCIM) (Catz et al., 1997), which includes questions about self-care, respiration and sphincter management, and mobility.
The functional impairment of the upper limb function in tetraplegic patients is commonly assessed using the Graded Assessment of Prehension (GRASSP, Kalsi-Ryan et al., 2012a) .
The walking capacity in ambulatory SCI individuals can be assessed with the 6 minute walk test (6MWT) focusing on the endurance, the 10 meter walk test (10MWT) focusing on a short duration speed and the timed up and go test (TUG) focusing on balance aspects (Van Hedel et al., 2005).

According to the International Classification of Functioning, Disability and Health (ICF, World Health Organisation, 2002), these assessments mainly measure the level of capacity of individuals, i.e., what a person can do in a standard environment. Although some items of the SCIM cover performance aspects, i.e., what a person does in their usual environment, comprehensive and objective measures of performance are missing to quantify how good patients translate new skills from the rehabilitation setting to their home environment.

1.3 Physical activity in chronic spinal cord injury

PA does not only play an essential role as a potential recovery-promoting factor but has been demonstrated with significant general health benefits preventing several chronic diseases like cardiovascular disease, cancer, diabetes, depression, and hypertension (Warburton et al., 2006). In SCI, it has been shown that increased PA was associated with lower levels of depressions, pain, and fatigue (Tawashy et al., 2009). Furthermore, PA was identified as a strong positive predictor of the overall quality of life (Stevens et al., 2008; Bize et al., 2007). SCI individuals themselves rated being physically active as very important (Carpenter et al., 2007). Nevertheless, PA was reported to be generally low in individuals with an SCI, especially in individuals depending on a wheelchair (Buchholz et al., 2003; Martin Ginis et al., 2010; Jörgensen et al., 2017).

1.4 Assessing physical activity

In the previous sections we have shown that clinicians should aim at increasing patients' PA due to its major role as a potential recovery-enhancing factor during acute SCI rehabilitation and as a beneficial factor to general health in chronic SCI individuals. Furthermore, PA can be used as a performance measure to track functional recovery and how patients translate their learned skills to daily life. Additionally, PA should be assessed in clinical intervention trials as it can act as a confounder modulating functional recovery in addition to plasticity-enhancing drugs. This demonstrates the need for a comprehensive assessment tool to measure PA.

There are several techniques to assess PA. Among the most reliable methods are direct observation using video cameras or indirect calorimetry (Vanhees et al., 2005). However, these methods have severe drawbacks being obtrusive and not applicable for long-term measurements of > 24h. The two most common methods which are also applied in the population of SCI are questionnaires/activity dairies and wearable sensors. Both methods will be briefly explained in the following two paragraphs.

1.4.1 Physical activity questionnaires

Questionnaires are inexpensive tools to assess PA in large study samples. For the population of SCI, the Physical Activity Recall (PARA-SCI) was developed (Martin Ginis et al., 2005). This questionnaire is a telephone-based interview, and its administration takes around 20-30 minutes. Therefore, it is time-demanding for the subjects and the investigators. It rates PA in mild, moderate, and heavy intensity. While moderate and heavy intensity show moderate to good correlation with indirect calorimetry, which can be defined as a gold standard, mild intensity only showed weak correlation, and thus its validity is limited.
The same authors developed the Leisure Time Physical Activity Questionnaire for People with Spinal Cord Injury (LTPAQ-SCI), which is the first self-reported measure for individuals with an SCI capturing leisure-time PA of different intensities (Martin Ginis and Latimer, 2007). However, only weak to moderate correlations were shown with the PARA-SCI, while not being validated against a gold standard.

Questionnaires can give investigators a general overview of overall PA intensity but might not be sensitive enough to detect smaller changes, e.g., during acute rehabilitation. Both, self-report and interview-based questionnaires are dependent on the subjects' memory, which might be impaired especially in older populations. The questions are answered based on a subjective interpretation of the questions, which may limit the validity of the questionnaires and impair their comparability on an individual level. Questionnaires for the healthy populations have been shown to underestimate moderate-to-vigorous PA and sedentary behavior (Cleland et al., 2018).

1.4.2 Wearable sensors

An objective measurement tool to assess PA is wearable sensors. Besides electromyographic (EMG) sensors to measure the amount and timing of muscle activation, global positioning satellite (GPS) sensors to measure the geographic location, and photoplethysmography sensors to measure the heart rate (reviewed in Dobkin and Dorsch, 2011), accelerometers and inertial measurement units (IMUs) showed a significant potential to measure PA in an unobstructive way over a long time duration (Mathie et al., 2004).

IMUs have been mainly applied to measure ambulation in the healthy population (Takeda et al., 2009), including elderly individuals (Kang et al., 2010; Wang et al., 2017; Lacroix et al., 2018), children, and adolescents (Riddoch et al., 2004; Tanaka and Tanaka, 2009; Cooper et al., 2015).
Research-grade IMUs such as the ActiGraph GT3X+ (Actigraph Inc., Pensacola, FL) and the SenseWear Armband (SWA) (BodyMedia Inc., Pittsburgh, PA) often come with in-built algorithms to evaluate the measured signals and translate them into measures of PA. However, these algorithms were most often developed for a healthy population and have limited validity in populations with altered movement patterns like stroke and SCI (Jayaraman et al., 2018).
Research has been conducted to develop dedicated algorithms to assess the altered movement patterns in neurological conditions such as Parkinson's Disease (Moore et al., 2007; Schlachetzki et al., 2017; Chang et al., 2016), Multiple Sclerosis (Storm et al., 2018), and stroke (Chang et al., 2016; Xu et al., 2012; Knorr et al., 2005; Leuenberger et al., 2017). Dedicated algorithms to assess PA in SCI individuals are rare and the development of algorithms have been mainly focused on quantifying the wheelchair-mobility (Sonenblum et al., 2012a; Coulter et al., 2011; Hiremath et al., 2013).

Therefore, our research group started developing a framework to assess PA in SCI individuals. Besides measuring the overall PA in the upper limb by commonly used activity counts (AC, for detailed explanation see Leuenberger, 2015), our framework comprises algorithms to not only quantify wheeling, but also distinguish between active and passive wheeling (Popp et al., 2016), estimate the energy expenditure in wheelchair-dependent SCI individuals (Popp et al., 2018) and assess the laterality of upper limb usage (Brogioli et al., 2016a).

Until now, the primary focus has been put on the development and validation of algorithms to quantify PA using IMUs. However, measures of movement quality would help clinicians to evaluate how well patients can transfer their acquired skills during therapies, e.g., walking, to daily life. Furthermore, measures of movement quality can help distinguishing functional recovery as a result of compensatory strategies from true biological recovery. Until now, algorithms to assess movement quality are rare. In Parkinson's disease, gyroscope data were used to assess bradykinesia (Summa et al., 2017), while in stroke, wearable sensors have been shown with the potential to predict clinical scores of the Functional Ability Scale, a subjective assessment tool for movement quality (Sapienza et al., 2017).
Dedicated algorithms to assess movement quality in the upper and lower limbs of SCI indi-

viduals are required and would extend our currently available framework to assess PA in SCI individuals. Furthermore, our current framework mainly comprises a quantification of the wheeling mobility and an extension to the walking mobility is necessary to apply it to the complete population of SCI. Once, algorithms exist to assess movement quality and quantity, our framework is missing an evaluation framework which comprises norm data about typical PA values in SCI individuals. Lesion-or impairment-specific norm data would help clinicians and researchers to set the measured PA values into context and help to set individualized rehabilitation goals.

1.5 Aims of the thesis

The first aim of this thesis was to extend our current framework to assess PA in SCI individuals. This tool should enable clinicians to track the PA during rehabilitation in order to learn more about the recovery of their patients. Especially, the transfer of functional capacity into performance in daily life can be assessed using our framework. Furthermore, the tool should be applicable to assess PA in clinical intervention studies to control for PA as a potential confounder affecting functional recovery, and to assess performance of patients in terms of PA as an additional marker for functional recovery. This additional marker could help researchers to differentiate true biological recovery from compensation and evaluate the effectiveness of pharmacological interventions, e.g., anti-Nogo-A or ChABC, in combination with PA. To achieve this aim, additional algorithms to estimate movement quantity and quality were required. These algorithms were required to work on a minimal number of wearable sensors to ensure applicability and compliance in daily clinical routine and in clinical intervention trials.

First, the posture of SCI individuals is an important aspect of daily PA especially in the acute care of patients, during which patients need to be mobilized regularly from the lying to an upright position (Consortium for Spinal Cord Medicine, 2008). Therefore, an algorithm to distinguish the seating from a lying position had to be developed and validated.

Second, a new algorithm to estimate energy expenditure in the population of ambulatory SCI individuals had to be developed to enable a monitoring of energy expenditure in the complete SCI population with different modes of mobility.

Third, tetraplegic patients often use compensatory strategies in their upper limbs to manage activities of daily living (ADLs). One aim was to develop a metric to assess and quantify this upper limb compensation in order to distinguish whether an improved function in the upper limbs is due to learned compensatory strategies or to biological recovery, which will be crucial in evaluating the effectiveness of clinical intervention trials.

Lastly, additional algorithms to assess wheeling efficiency and gait quality in SCI individuals would be required to complement our framework.

Furthermore, we discovered that many different measurement protocols to assess PA are proposed in the literature, suggesting a measurement period of 1 week for healthy adults (Aadland and Ylvisaker, 2015), one to 2 days for elderly individuals (Falck et al., 2017), up to 11 days for children (Barreira et al., 2015) and 4-7 days in multiple sclerosis (Klaren et al., 2016). In order to ensure reliability and comparability of the PA measurements in SCI individuals and to reduce the burden on patients by measuring for unnecessarily many days, a required number of measurement days needed to be defined.

The second aim of our thesis was to develop a tool to increase the PA in acute and chronic SCI individuals, because of its proven benefit for the functional recovery and general health. To achieve this goal, our current framework to assess PA, needed to be extended by a set of norm data about PA levels in SCI individuals. Ultimately, recommendations about PA were required in order to facilitate an evaluation of PA levels assessed by our framework. Therefore, PA during acute rehabilitation and after rehabilitation in the home-environment of SCI individuals needed to be acquired and related to clinical impairment levels. With this, insights should be gained about the typical recovery of PA during rehabilitation and levels in chronic SCI individuals. These insights will help clinicians to evaluate the recovery of their patients during acute rehabilitation and researchers to evaluate the effectiveness of therapeutic interventions. Furthermore, recommendations can help increasing the motivation for more PA in general.

1.6 Thesis outline

This thesis is divided into two main parts. The first part describes methodological aspects of assessing PA in subjects with an SCI. The second part describes clinical findings which were revealed by measuring PA in SCI and which will help evaluating PA in acute and chronic SCI individuals. In the first part, two new metrics to assess PA based on a minimal sensor setup have been proposed and validated. Chapter 2 describes an algorithm to detect the posture in wheelchair-dependent SCI individuals based on a single wearable sensor attached to the chest (Schneider et al., 2017, unpublished manuscript). Using the algorithm, lying posture against sitting posture can be discriminated. Chapter 3 proposes a metric to assess the upper limb compensation in tetraplegic SCI individuals using a single wearable sensor attached to the wrist and its validation to the GRASSP is shown (Schneider et al., 2019a). Chapter 4 addresses the issue of how many measurement days investigators need to assess to get a reliable representation of subjects' PA (Schneider et al., 2018). Furthermore, differences between weekdays and the weekend were assessed.

Within the second part of the thesis, clinical insights into PA of SCI individuals are presented. Chapter 5 and Chapter 6 present a longitudinal analysis of the PA of acute SCI individuals during the rehabilitation. While chapter 5 focuses on the change of overall PA metrics (wheeling and overall upper limb PA) in wheelchair-dependent SCI individuals from one month to 6 months after injury (Brogioli et al., 2016c), chapter 6 focused on the intensity of PA during the rehabilitation in ambulatory and wheelchair-dependent SCI individuals. Furthermore, it also looks at PA very early (i.e., two weeks) after injury and distinguishes the changes of PA intensity during active therapy sessions and leisure time and factors influencing this change (Schneider et al., 2019b). In chapter 7, we investigate the PA levels in chronic SCI individuals, revealing differences between ambulatory, wheelchair-dependent SCI and healthy controls and revealing clusters of PA patterns (Schneider et al., 2019c).

Methodological aspects Part I

2 Robust posture detection in spinal cord injured wheelchair users using a single inertial measurement unit

Sophie Schneider, Werner L. Popp, László Demkó, Roger Gassert and Armin Curt

Unpublished paper.

This work was supported by the Clinical Research Priority Program (CRPP) for Neuro-Rehab of the University of Zurich, by the International Foundation for Research in Paraplegia (IRP) and by the Swiss Paraplegic Foundation (SPS).

2.1 Abstract

This paper introduces a method to classify body postures of wheelchair users into lying and sitting, based on recordings of a single chest-mounted inertial measurement unit. The method is based on an orientation estimation using an established sensor fusion algorithm followed by a clustering approach, and was validated on 30 spinal cord injured subjects showing a classification accuracy of over 98%. The performance of the clustering approach was also compared to an optimized global threshold, and we found similar overall accuracy using the validation data of short (< 5 h) recordings. However, while the proposed clustering approach worked in all cases with similarly high accuracy, classification based on a global threshold failed for long-term recordings and also for some of the short validation data sets. The proposed method can be applied universally in different cohorts using adjusted sensor positions.

2.2 Introduction

Spinal cord injury (SCI) is a neurological disease leading, among others, to severe motor weakness and functional impairment. The clinical recovery of patients after a SCI is mainly driven by compensatory strategies and functional adjustments to accomplish tasks (Curt et al., 2008), rather than by repair mechanisms. Since neuronal plasticity can occur as a response to activity-based rehabilitative sessions (Lynskey et al., 2008), there is an urgent need to detect, classify and quantify physical activities in an objective and reliable way in order to tailor individualized therapies and control therapeutic interventions. This can be achieved by using inertial measurement units (IMUs). Current research focuses on widening the range of applications of IMUs to assess physical activity in various subpopulations with altered activity patterns like stroke survivors (Gebruers et al., 2010), SCI patients (Brogioli et al., 2016a), and elderly (Awais et al., 2016). One important aspect of assessing physical activity is, for example, to distinguish sedentary and non-sedentary behavior. SCI subjects are often wheelchair-dependent due to partial paralysis of the limbs, and thus, a classification into lying and sitting episodes is sufficient in this cohort. Here, especially in early stages of rehabilitation, it is important that patients are mobilized regularly and switch from a lying position to a seated one in order to reduce respiratory complications and decrease the risk of pressure ulcers, and also for the psychological reward of interacting with the environment in the upright position (Consortium for Spinal Cord Medicine, 2008).

Previous algorithms for detecting body postures relied on either a training data set (Cheng et al., 2016) or fixed inclination thresholds for the different postures (Najafi et al., 2003; Lockhart et al., 2013). Therefore, these methods show a high accuracy on average, but can not be applied to other applications without further training data. Furthermore, none of this algorithms has been validated for wheelchair users.

In this paper, we present a robust method to classify body postures of wheelchair users into lying and sitting, based on recordings of a single IMU.

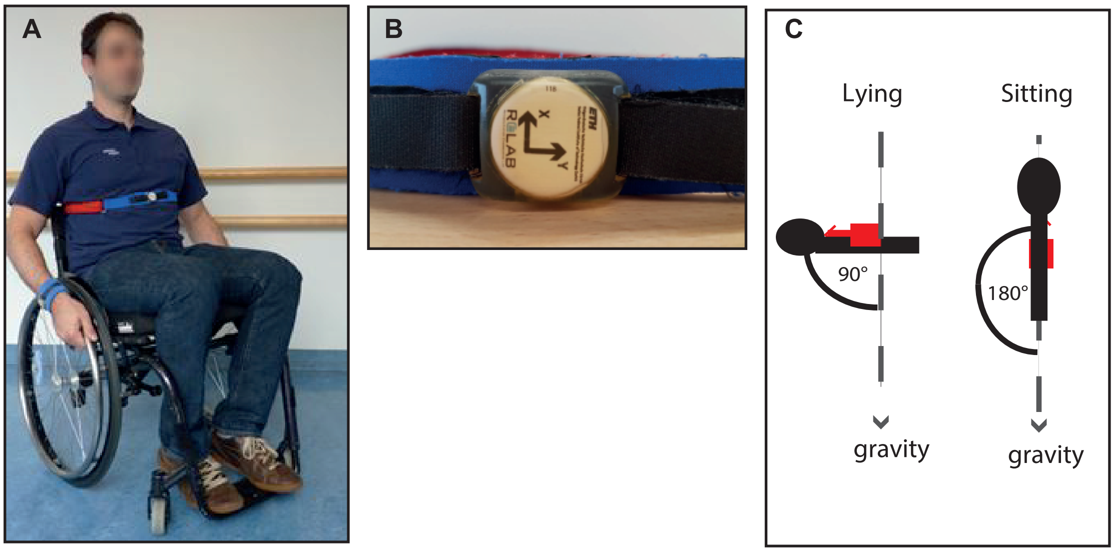

Figure 2.1 – Used sensor hardware and setup. A-B: Using an elastic strap, the sensor was mounted on the subject's chest in a way that the x-axis of the sensor was pointing towards the head of the subject. C: In optimal lying and sitting positions the pitch angle between the x-axis of the sensor and gravity is close to 90°and 180°, respectively.

2.3 Methods

2.3.1 Subjects

Our proposed method has been developed and validated on 30 chronic spinal cord injured wheelchair-dependent subjects (11 tetraplegics and 19 paraplegics, with altogether 3 female) in the chronic stage (at least 90 days after injury), with an age range of 27 to 74 years (with mean and standard deviation of 43 ± 12.7 years), and body height from 154 to 203 cm (176 ± 9 cm). This data set is further called validation data set. Furthermore, the algorithm has been also applied to one subject (male, 63 years) during the acute stage of injury (5 weeks after injury, C5 AIS D) measured for 24 h continuously. Here, no ground truth data about posture is available due to privacy reasons.

Subjects were recruited via the Balgrist University Hospital in Zurich, and lesion levels from C3 to L3 with any grade of AIS (AIS A – D) were included in this analysis. Exclusion criteria were any neurological (other than SCI), orthopaedic or rheumatologic disease affecting upper limb function and pre-morbid on-going major depressions or psychosis. Each subject provided written informed consent before joining the study, and the study was approved by the ethics committee of the canton of Zurich (KEK-ZH 2013-0202).

2.3.2 Sensor device

In this study, we used the ReSense module (Leuenberger and Gassert, 2011) to assess the body posture. The ReSense module is a miniature 10 degrees-of-freedom IMU designed for long-term monitoring of human physical activity, consisting 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). Data was recorded at a sampling frequency of 50 Hz, stored on an internal 2 GB microSD card, then transferred to a PC using a custom-made base station for post-processing.

2.3.3 Data collection

Using an elastic strap for the measurements, the ReSense module was fixed to the subjects' chest in a way that the x-axis of the device was pointing towards the head of the subjects (see Figure 2.1). Subjects were asked to perform a predefined set out of 24 different tasks, including lying down at rest and different activities while sitting in the wheelchair, for example reading, hanging out laundry, handbiking or wheeling a predefined track. Exact times of start and end of each activity have been recorded and used to validate and compare the performance of the different algorithms.

2.3.4 Data analysis

The proposed method is based on an orientation estimation of a chest-mounted IMU, and the resulting pitch angles were then classified for each subject individually using a clustering-based approach, or according to a global threshold optimized for the validation data set. Data analysis was conducted offline.

Orientation estimation

Orientation estimation was done based on a sensor fusion filter proposed by Madgwick et al. (Madgwick et al., 2011). This gradient descent algorithm fuses raw signals from the accelerometer, gyroscope, and optionally the magnetometer, into an optimal orientation estimate to compensate the drift of integrating the angular rate of the gyroscope. The filter outputs the orientation in a quaternion representation, which was then transformed into pitch angles of the sensor compared to gravity. See the work of Leuenberger (2015) for more details on this method.

Classification based on clustering

The estimated pitch angle of the chest was then classified into lying and sitting postures for each data point of the measurements, using a k-means clustering approach. K-means clustering is commonly used to partition data into k distinct classes based on minimizing the sum of squared Euclidean within-cluster distances. Due to the 1-dimensional nature of the present data, a k-means clustering optimized for 1 dimension has been applied (Wang and Song, 2011). The number of clusters were set to two, one corresponding to the sitting, and one to the lying posture, with the latter identified by its mean closer to 90°(see Figure 2.1C and gray/white areas in Figure 2.2). The result of the classification has been validated by the exact time information of the different tasks.

Performance analysis

Using the validation data set, the performance of our proposed method has been determined in terms of accuracy, sensitivity of lying detection (which is equal to the specificity of sitting detection) and sensitivity of sitting detection (which is equal to the specificity of lying detection), according to the following formulas:

$$\text{accuracy} = \frac{\text{TP} + \text{TN}}{\text{TP} + \text{TN} + \text{FP} + \text{FN}} \tag{2.1}$$

$$\text{sensitivity for lying detection} = \frac{\text{TP}}{\text{TP} + \text{FN}} \tag{2.2}$$

$$\text{sensitivity for sitting detection} = \frac{\text{TN}}{\text{FP} + \text{TN}} \tag{2.3}$$

where TP, TN, FP, and FN are the frequencies of true positive, true negative, false positive, and false negative within the validation data set, respectively. The validation data set used for the performance analysis was 56 h long in total, with 14 h (25%) spent in the lying posture.

Classification based on a global threshold

As a comparison, data points of orientation angles were also classified based on an optimized global threshold. According to Figure 2.3, this optimal threshold value has been determined by maximizing the overall accuracy of this method using the validation data set.

2.4 Results and Discussion

Using the clustering-based approach to classify the sitting and lying postures, the mean overall accuracy was found to be 98.7% with standard deviation of 4.6% (range: 75.6 —- 100.0%), with mean sensitivity for sitting detection 98.3% ± 5.9% (range: 69.6 —- 100.0%) and mean

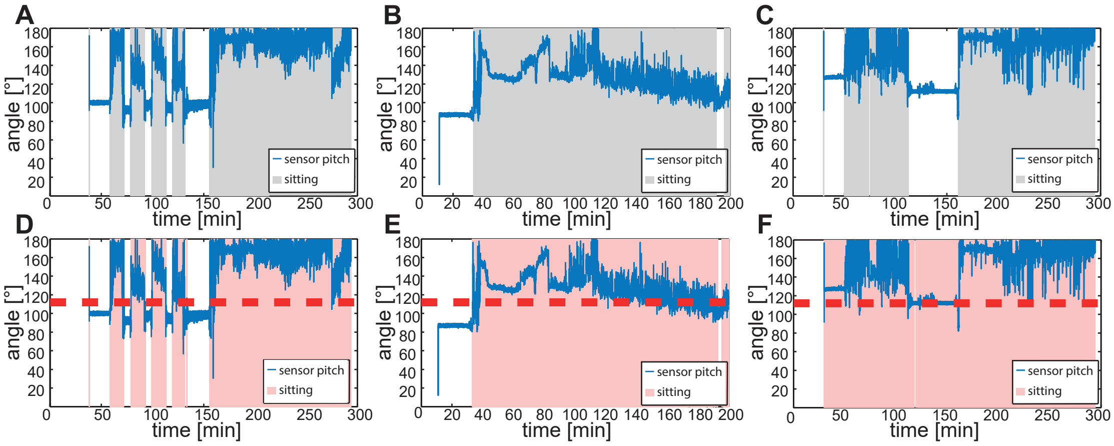

Figure 2.2 – Three representative time traces of the calculated chest pitch angles from the validation data set, indicating the phases identified as sitting using i) the clustering-based approach (first row, gray areas) and ii) the method based on a global threshold (second row, light red areas). The optimized global threshold used for the analysis in ii) is represented by the dashed red lines in D-F.

sensitivity for lying detection 100.0% ± 0.0% (range: 99.8 —- 100.0%). The frequencies of true positive, true negative, false positive, and false negative within the validation data set are presented in the first column of Table 2.1.

With the method based on a global threshold, the optimal threshold was found to be 112°as plotted in Figure 2.3, with a calculated accuracy of 98.9% ± 4.2% (78.8% – 100.0%) (see the second column of Table 2.1). The comparison of the different methods in terms of accuracy and sensitivity is presented in Table 2.2, including also the ranges of these values next to their mean and standard deviation. While the overall accuracy and posture detection sensitivity of the two methods were similarly high, the threshold-based method failed to correctly detect

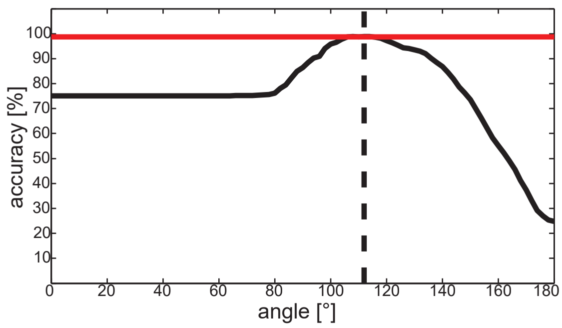

Figure 2.3 – Posture detection accuracy as a function of the threshold value used with the classification method based on a global threshold. The vertical dashed black line represents the optimal threshold value of 112°resulting in an overall detection accuracy of 98.9%. The horizontal solid red line indicates the accuracy of the clustering-based approach (98.7%).

	clustering-based	global threshold
true positive	0.735	0.744
true negative	0.253	0.245
false positive	0.012	0.003
false negative	0.000	0.008

Table 2.1 – Performance analysis – absolute frequencies

	clustering-based	global threshold
accuracy [%]	98.7 ± 4.6	98.9 ± 4.2
	(75.6 – 100.0)	(78.8 – 100.0)
sensitivity	98.3 ± 5.9	99.5 ± 2.3
– sitting [%]	(69.6 – 100.0)	(87.5 – 100.0)
sensitivity	100.0 ± 0.0	97.1 ± 15.3
– lying [%]	(99.8 – 100.0)	(16.2 – 100.0)

Table 2.2 – Performance analysis – accuracy and sensitivity

the lying phase of one subject as demonstrated in Figure 2.2F, resulting in a sensitivity of 16% for lying detection in this particular case. The clustering-based approach was found to be more robust and worked in all the cases.

Finally, both the methods have been applied to detect sitting and lying periods of a 24-hour recording. Visual inspection of the data plotted in Figure 2.4 suggests that the subject was lying during the whole night (approx. from 10 pm to 8 am), however, only the clustering-based approach classified this entire period as lying, also showing the robustness of this method. The global threshold-based approach using the previously determined optimal threshold classified more than half of this period as sitting, which is unlikely and can be rejected.

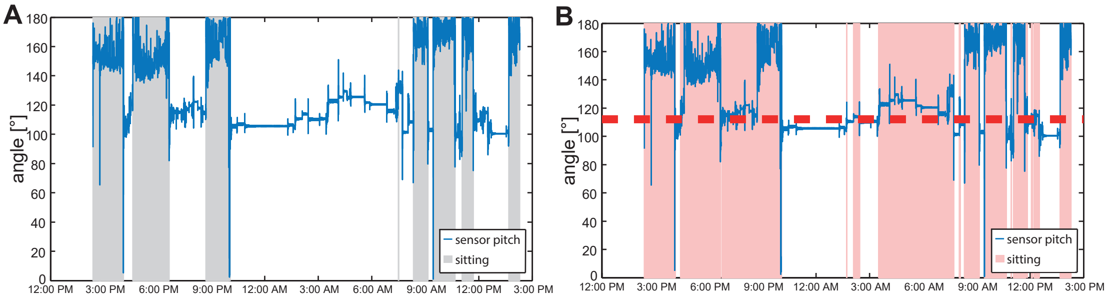

Figure 2.4 – Time trace of the calculated chest pitch angle during a 24-hour recording, indicating the phases identified as sitting using A) the clustering-based approach (gray areas) and B) the method based on a global threshold (light red areas). The optimized global threshold assessed from the validation data set used in B) is represented by the dashed red line.

2.5 Conclusion

To conclude, we propose a robust method to classify the posture of wheelchair-bound individuals into sitting and lying postures, using a single wearable inertial measurement unit placed at the chest, with excellent overall accuracy and sensitivity. The suggested clustering-based approach was found to be more reliable than using a fixed threshold, and does not require any training data set nor an adaptation for the individual patients, which is the main advantage of this method over other classification approaches as the algorithm can easily and readily be applied to existing or novel datasets. Furthermore, the algorithm was validated on a large dataset of 30 subjects with 56h of recordings in total and was found to be highly accurate (98.7%). We see three main limitations of our proposed method. Firstly, both postures, lying and sitting have to be prevalent in the acquired data set for the clustering approach to work. This is, however, guaranteed for recordings of complete days in case of subjects without sleep disorders which spend around one third of their day lying down (Holtermann et al., 2014) due to their natural sleep-wake cycle. Secondly, the strap holding the sensor can slip and change position during normal daily activity, changing also the pitch of the sensor relative to the upper body, and as such, the pitch values characteristic to sitting and lying (see e.g. Figs. 2.2B and E). A possible solution would be to fix the sensor using tape. Thirdly, some subjects may report discomfort wearing the strap especially while sleeping.

The cluster-based algorithm may oscillate, as evident in Figure 2.2B. A simple way of addressing this could be to set a time constraint, motivated by the fact that wheelchair-bound SCI patients will require some time to perform a transfer, and will likely not change posture very often.

The proposed method is powerful, as it can easily be applied in different cohorts if the sensor position is adjusted accordingly. In a follow-up study we are successfully applying the method to distinguish sedentary phases from non-sedentary intervals in children with neurological diseases based on a thigh-mounted sensor. This further confirms the universal applicability of our proposed method.

3 Predicting upper limb compensation during prehension tasks in tetraplegic spinal cord injured patients using a single wearable sensor

Sophie Schneider, Werner L. Popp, Michael Brogioli, Urs Albisser, Stefan Ortmann, Inge-Marie Velstra, László Demkó, Roger Gassert and Armin Curt

2019 International Conference on Rehabilitation Robotics (ICORR), in press

We would like to thank Larissa Angst, Karin Akermann, and Anne Brust for their help in recruiting subjects and performing the assessments and Anika Ballmer for her help in the manual labeling of the compensation.

This study has been funded by the International Foundation for Research in Paraplegia (IRP, project number: P 157), by the Clinical Research Priority Program (CRPP) Neuro-Rehab of the University of Zurich, by Wings for Life (project number: 143), by the Swiss Paraplegic Foundation (SPS), by the ETH Zurich Foundation in collaboration with Hocoma AG, by a HMZ seed project (project title: ZurichMOVE: Wearable sensors to monitor movement quality and mobility in health care) funded by the University of Zurich and the ETH Zurich Foundation, and by the Swiss State Secretariat for Education, Research and Innovation (SERI) under contract number 15.0255 (Horizon 2020, 681094).

3.1 Abstract

Upper limb (UL) compensation is a common strategy of patients with a high spinal cord injury (SCI), i.e., tetraplegic patients, to perform activities of daily living (ADLs) despite their sensorimotor deficits. Currently, an objective and sensitive tool to assess UL compensation, which is applicable in the clinical routine and in the daily life of patients, is missing. In this work, we propose a metric to quantify this compensation using a single inertial measurement unit (IMU). The spread of forearm pitch angles of an IMU attached to the wrist of 17 SCI patients and 18 healthy controls performing six prehension tasks of the graded redefined assessment of strength, sensibility and prehension (GRASSP) was extracted. Using the spread of the forearm pitch angles, a classification of UL compensation was possible with very good to excellent accuracies in all six different prehension tasks. Furthermore, the spread of forearm pitch angles correlated moderately to very strongly with qualitative and quantitative GRASSP prehension scores and the task duration. Therefore, we conclude that our proposed method has a high potential to classify compensation accurately and objectively and might be used to quantify the degree of UL compensation in ADLs. Thus, this method could be implemented in clinical trials investigating the effectiveness of interventions targeting UL functions.

3.2 Introduction

Individuals with a spinal cord injury (SCI) often suffer from sensorimotor deficits in the upper limbs (UL) leading to severe limitations in performing activities of daily living (ADLs) and thus decreasing patients' independence. In order to maintain a certain level of independence and to perform ADLs, patients learn compensatory strategies during the rehabilitation process to perform ADLs (Mateo et al., 2015). A common strategy is the use of a tenodesis grasp, in which SCI patients passively close their fingers by extending the wrist (Mateo et al., 2013). Furthermore, shoulder abduction is often used to compensate missing elbow extension (Mateo et al., 2015). Especially the latter can lead to increased shoulder pain and is thus desired to be reduced. Furthermore, compensation is different to biological recovery and thus it is crucial, especially in clinical intervention studies, to distinguish improved function due to compensation from biological recovery (Curt et al., 2008). There are clinical assessment tools to measure the upper limb function specific to tetraplegic patients, e.g., the graded redefined assessment of strength, sensibility and prehension (GRASSP) (Kalsi-Ryan et al., 2012a) and the Tetraplegia Hand Activity Questionnaire (THAQ) (Land et al., 2004). Although, in the GRASSP assessment the quality of the executed task is rated, this rating is subjective and only binary, i.e., either a patient is showing an altered grip or not. Kinematic analyses using optical marker systems were done to measure UL patterns during ADLs (De Los Reyes-Guzmán et al., 2010; Mateo et al., 2013; Laffont et al., 2000; Cacho et al., 2011), however this is not applicable in the standard clinical routine. Thus, an easy-to-use tool to objectively classify and quantify UL compensation is missing up to now. Therefore, we propose an objective and unobtrusive tool to assess UL compensation using a single inertial measurement unit (IMU), which is applicable in the standard clinical routine, but also in the daily life of the patients.

Furthermore, its potential to not only detect, but also to quantify UL compensation in SCI patients is evaluated, which would allow the application of this proposed method in clinical intervention studies aiming at improving UL function.

3.3 Methods

3.3.1 Subjects

In total, 17 tetraplegic SCI patients and 18 healthy controls were enrolled in this study. Inclusion criteria for the patients were a traumatic or non-traumatic SCI and a neurological level of impairment (NLI) at C7 or above, resulting in impairments in the UL. Patients with all levels of completeness of the lesion (AIS, A: complete and B-D: incomplete) were included in the study. Exclusion criteria were any neurological disease other than SCI, orthopaedic or rheumatic diseases affecting the UL, or an on-going major depression or psychosis. For the healthy controls, the inclusion criterion was an age above 18. Exclusion criteria were any neurological, orthopaedic or rheumatic disease affecting UL function, or an on-going major depression or psychosis.

SCI patients were recruited in the rehabilitation center of the Balgrist University Hospital in Zurich, Switzerland and the Swiss Paraplegic Centre in Nottwil, Switzerland. Healthy controls were recruited from the work environment of the university.

In accordance with the declaration of Helsinki, all subjects signed a written informed consent before participating in the study. This consents also contained the agreement to record videos of the assessments.

The study was approved by the ethical committees of the canton of Zurich (KEK-ZH No. 2013-0202), Lucerne (EK 13018), and the ethical committee of ETH Zurich (EK 2013-N-50).

3.3.2 Measurement protocol

All subjects were told to perform the GRASSP assessment version 1 and were instructed by a therapist or a trained movement scientist. SCI subjects executed each task once, whilst healthy controls performed ten repetitions of all tasks. Note, that not all SCI patients were able to perform all tasks due to their impairments. The execution of the tasks was measured with one IMU attached to each wrist. The x-axis of the sensor always pointed away from the body, i.e., distally (Figure 3.1).

GRASSP assessment

The GRASSP assessment version 1 is a clinical asssessment tool to assess sensorimotor and prehension function in tetraplegic SCI subjects (Velstra et al., 2015). It contains three main

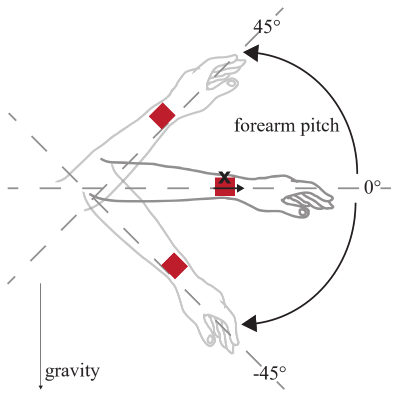

Figure 3.1 – Schematic representation of the forearm pitch. The pitch angle is calculated relative to the earth referential frame using one inertial measurement unit (red box) attached to the wrist. No pitch, i.e., movement in the horizontal plane, results in a value of 0°. Pointing upwards results in positive values, pointing downwards in negative values.

domains, strength, sensation and prehension. In this study, only the prehension domain was analyzed. The prehension domain consists of two parts, a qualitative and a quantitative assessment. In the qualitative part, three different finger grips (cylindrical, lateral, and pinch grip, Figure 3.2) are rated on a scale from 0 to 4. Thereby a score of 0 is equal to no voluntary control of the wrist and hand digits to perform the grip. A score of 4 is equal to a voluntary control of the wrist and hand digits to generate the grip with full force. Scores for all three grips are summed up for a total qualitative GRASSP prehension score.

In the quantitative part, six typical standardized ADLs are performed. The tasks are pouring water from a bottle ('Bottle' Figure 3.3A), opening jars ('Jar' Figure 3.3B), transferring nine pegs from board to board ('9 pegs' Figure 3.3C), picking up and turning a key ('Key', Figure 3.3D), picking up four coins and placing them into slots ('Coins', Figure 3.3E), and screwing four nuts onto bolts ('Nuts', Figure 3.3F). The duration of each task is measured and the quality of the execution is rated on a score from 0 to 5 (quantitative GRASSP prehension score). Scores < 3 are given for no (score 0) or a not completed (score 1 - less than 50%, score 2 - more than 50%) execution of the task, whereas scores ≥ 3 are given for a completed execution with varying quality (score 3 - altered grip, score 4 - appropriate grip with difficulties, score 5 - appropriate grip without difficulties).

IMU device

The ReSense sensor was used in this study (Leuenberger and Gassert, 2011). The sensor comprises 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). Data was stored in the internal memory and subsequently transferred to a PC using a custom-made docking station. The desired sampling frequency was set to 50 Hz. Due to varying sampling rates between 49 and 51Hz, raw data was resampled to 50Hz by

Figure 3.2 – Picture of the three investigated qualitative prehension grips. A. Cylindrical grip. B. Lateral grip. C. Pinch grip.

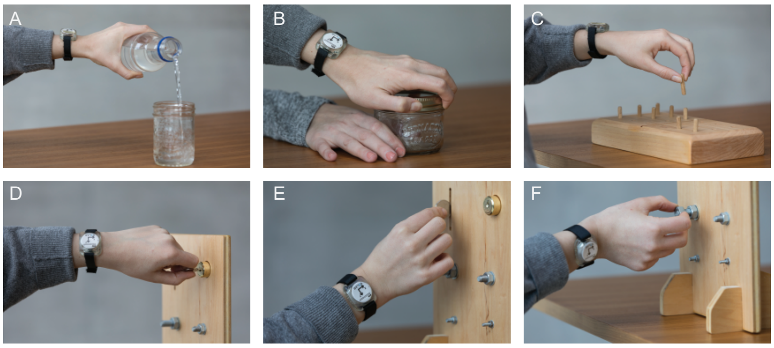

Figure 3.3 – Picture of all six prehension tasks. A. Pouring water from a bottle. B. Opening a jar. C. Transferring nine pegs from board to board. D. Picking up and turning a key. E. Picking up four coins and placing them into slots. F. Screwing four nuts onto bolts.

interpolation after transferring to the PC.

3.3.3 Data processing

Please note that each hand of each subject was analysed independently, because both hands could have different scores in the GRASSP assessment and in the labeling of UL compensation.

Calculation of forearm pitch

The forearm pitch was calculated relative to the referential earth frame (Figure 3.1) by using the acceleration signal and angular velocity rate. The gradient descent algorithm proposed by Madgwick et al. (Madgwick et al., 2011) was used to calculate an optimal orientation estimate by fusing the acceleration signal with the angular velocity rate to compensate for the drift resulting from integrating the angular rate. The calculated quaternion presentation was transformed into angles of the pitch relative to the earth referential frame. The approximate error of the calculated pitch angles is 0.6°. For more details about this method see the work of Leuenberger et al. (2017). For visualization purposes, histograms of pitch angles are plotted in polar representation from 90° to -90°with a bin-size of 1°.

Manual labeling of compensation

Trained movement scientists were asked to label all video recordings of the GRASSP assessments of both hands and of all subjects separately, while different kinds of compensation were labeled for each task. In this analysis a binarized value of 0 (no compensation) and 1 (any kind of compensation) was used. All further analyses of compensation and no compensation are based on this manual labeling of the tasks.

Measuring task duration

The duration of each of the six prehension tasks was extracted from the labeled video recordings to get more accurate measures compared to the manually assessed time during the GRASSP assessment. For this, each task was labeled in the video recordings by trained movement scientists and its duration was extracted. For the healthy controls, the average task duration of all tasks was taken. For the SCI patients, only task durations of tasks which could be executed completely, i.e., with a quantitative scores ≥ 3, were included in the analysis.

3.3.4 Statistics

To quantify the spread of the distribution of forearm pitch values, the 95% central range (95% CR) was calculated by:

$$95\%\ \text{CR} = 97.5^{th}\ \text{percentile} - 2.5^{th}\ \text{percentile}$$

Logistic regression was used to predict the compensation (0 - no compensation, 1 - compensation) based on the 95% CR of the forearm pitch as the only predictor. Due to the fact that logistic regression predicts probabilities rather than binary values, a cut-off needs to be specified for the classification problem. The standard cut-off threshold of 0.5 was used, where samples above 0.5 were classified as compensation. 5-fold cross-validation with 10 repetitions was used to validate the predictive model and its sensitivity, specificity, and accuracy calculated to evaluate the predictive power of the model. Within the cross-validation, a re-sampling technique called random over sampling examples (Menardi and Torelli, 2014) was applied to account for the class imbalance in the present data.

The Spearman correlation coefficient was calculated to assess the strength of the relationship between the spread of forearm pitch angles and the qualitative prehension scores as well as between the spread of forearm pitch angles and the task duration. Firstly, the correlation coefficient was calculated combining all subjects showing and not showing compensation, then, secondly, only for subjects showing compensation.

A Mann-Whitney U test was conducted to evaluate the differences of task duration, qualitative prehension score, and spread of forearm pitch angles in subjects with and without compensation.

The significance level was set to $\alpha = 0.05$. Correlation coefficients from 0.8 to 1 were defined as 'very strong', from 0.6 to 0.79 as 'strong' and from 0.4 to 0.59 as 'moderate'. (Evans, 1996). Accuracy values from 0.9 to 1 were defined as 'excellent', from 0.8 to 0.9 as 'very good' and from 0.7 to 0.8 as 'good'. (Šimundić, 2009). Statistics was performed in R Studio. Packages *caret* and *ROSE* were used for performing the logistic regression and cross-validation.

3.4 Results

3.4.1 Subject characteristics

The mean age of the included SCI patients was 44.5 ± 16.8 years, the mean age of the included healthy controls was 36.6 ± 15.6 years. One of the 17 included SCI patients was female, 5 of the 18 included healthy controls were female. The SCI patients were measured on average 12.5 ± 9 weeks after their injury. Lesion levels ranged from C3 to C7 (C3: 1, C4: 2, C5: 5, C6: 6, and C7: 3 patients) and AIS scores ranged from A to D (A: 7, B: 4, C: 2, and D: 4 patients).

3.4.2 Standard clinical surrogate markers for UL compensation: Qualitative prehension score and task duration

During the bottle task, 23 out of 32 hands showed compensatory strategies, during the jar task 26 out of 31 hands, during the 9 peg task 29 out of 34 hands, during the key 19 out of 25 hands, during the coins 18 out of 24 hands, and during the nuts 21 out of 25 hands. The qualitative GRASSP prehension score in all six prehension tasks was significantly lower in subjects showing compensatory strategies compared to subjects showing no compensatory strategies (Bottle: $U = 29$, $p < .001$; Jar: $U = 6$, $p < .001$; Pegs: $U = 7.5$, $p < .001$; Key: $U = 5$, $p < .001$; Coins: $U = 5$, $p < .001$; Nuts: $U = 0.5$, $p < .001$). Similarly, the quantitative GRASSP prehension score in all six prehension tasks was significantly lower in subjects showing compensatory strategies compared to subjects showing no compensatory strategies (Bottle: $U = 67.5$, $p < .001$; Jar: $U = 82$, $p < .001$; Pegs: $U = 0$, $p < .001$; Key: $U = 21$, $p < .001$; Coins: $U = 1$, $p < .001$; Nuts: $U = 0$, $p < .001$). Furthermore, the task duration of all completed tasks (prehension quantity score of ≥ 3) was significantly higher in subjects showing compensatory strategies compared to subjects showing no compensatory strategies in all six prehension tasks (Bottle: $U = 854$, $p < .001$; Jar: $U = 964$, $p < .001$; Pegs: $U = 963$, $p < .001$; Key: $U = 792$, $p < .001$; Coins: $U = 413$, $p < .001$; Nuts: $U = 232$, $p < .001$). Median and interquartile range of task durations and qualitative and quantitative GRASSP prehension scores can be found in Table 3.1.

		compensation	no compensation
Bottle			
	duration (s)	10.8 ± 7.1	5.0 ± 1.1
	qual. prehension score (-)	2 ± 3.5	12 ± 0
	quant. prehension score (-)	3 ± 0	5 ± 0
Jar			
	duration (s)	16.6 ± 19.1	3.2 ± 1.4
	qual. prehension score (-)	2 ± 3.8	12 ± 0
	quant. prehension score (-)	3 ± 0	5 ± 0
9 Pegs			
	duration (s)	26.7 ± 20.4	10.3 ± 1.7
	qual. prehension score (-)	2 ± 4	12 ± 0
	quant. prehension score (-)	3 ± 0	5 ± 0
Key			
	duration (s)	31.1 ± 32.1	3.6 ± 1.1
	qual. prehension score (-)	2 ± 3.5	12 ± 0
	quant. prehension score (-)	3 ± 0	5 ± 0
Coins			
	duration (s)	25.1 ± 25.2	8.2 ± 2.7
	qual. prehension score (-)	2.5 ± 3.8	12 ± 0
	quant. prehension score (-)	3 ± 1	5 ± 0
Nuts			
	duration (s)	55.6 ± 21.6	22.5± 9.1
	qual. prehension score (-)	2 ± 3	12 ± 0
	quant. prehension score (-)	2 ± 2	5 ± 0

Table 3.1 – Task duration and qualitative and quantitative grassp prehension scores in subjects showing compensatory strategies and not showing compensatory strategies in the single grassp tasks. median ± interquartile range is given.

	sensitivity	specificity	accuracy
Bottle	0.9	0.92	0.91
Jar	0.82	0.88	0.86
9 pegs	0.75	0.92	0.85
Key	0.9	0.93	0.92
Coins	0.89	0.92	0.91
Nuts	0.94	0.89	0.91

Table 3.2 – Sensitivity, specificity, and accuracy of the logistic regression model for classifying UL compensation.

3.4.3 Sensor-based marker for UL compensation: Spread of forearm pitch angles

Firstly, the spread of forearm pitch angles was significantly higher for subjects showing compensatory strategies compared to subjects showing no compensatory strategies in all six prehension tasks (Bottle: U = 47, p < .001; Jar: U = 80, p < .001; 9 pegs: U = 145 , p < .001; Key: U = 20, p < .001; Coins: U = 45, p < .001; Nuts: U = 9, p < .001; Figure 3.4 and 3.5).

Secondly, in all six prehension tasks, compensation could be predicted with a very good to excellent accuracy based on the spread of the forearm pitch angles. Sensitivities were very good to excellent, specificities were good to excellent in all six tasks (Table 3.2, Figure 3.6).

Furthermore, strong (-0.66) to very strong (-0.83) negative correlations between the qualitative GRASSP prehension score and the spread of forearm pitch angles were found in all six prehension tasks for all subjects (Figure 3.7) and strong negative correlations between the quantitative GRASSP prehension score and the spread of the forearm pitch angles (Figure 3.8).

Lastly, the spread of forearm pitch angles showed moderate (0.47) to strong (0.74) positive correlations with the task duration of completed tasks in all six prehension tasks (Figure 3.9).

3.5 Discussion

In this study, we investigated the potential to use a single wearable sensor to quantify UL compensation in SCI patients for six different ADL tasks. Therefore, we first investigated the applicability of three GRASSP assessment scores to quantify compensation, i.e., the total qualitative and quantitative GRASSP prehension scores and the task duration during the quantitative testing of the GRASSP to find surrogate markers of UL compensation. These surrogate markers could then serve as a validation score for the sensor-based metric we propose. We hypothesized that subjects with lower values of qualitative and quantitative GRASSP prehension scores were more likely to show compensatory strategies to handle ADLs. Additionally, it can be assumed that the usage of compensatory strategies would result in a longer movement duration as shown in (De Los Reyes-Guzmán et al., 2010), and thus act as a surrogate marker for compensation.

Subjects with UL compensation showed decreased values of qualitative and quantitative

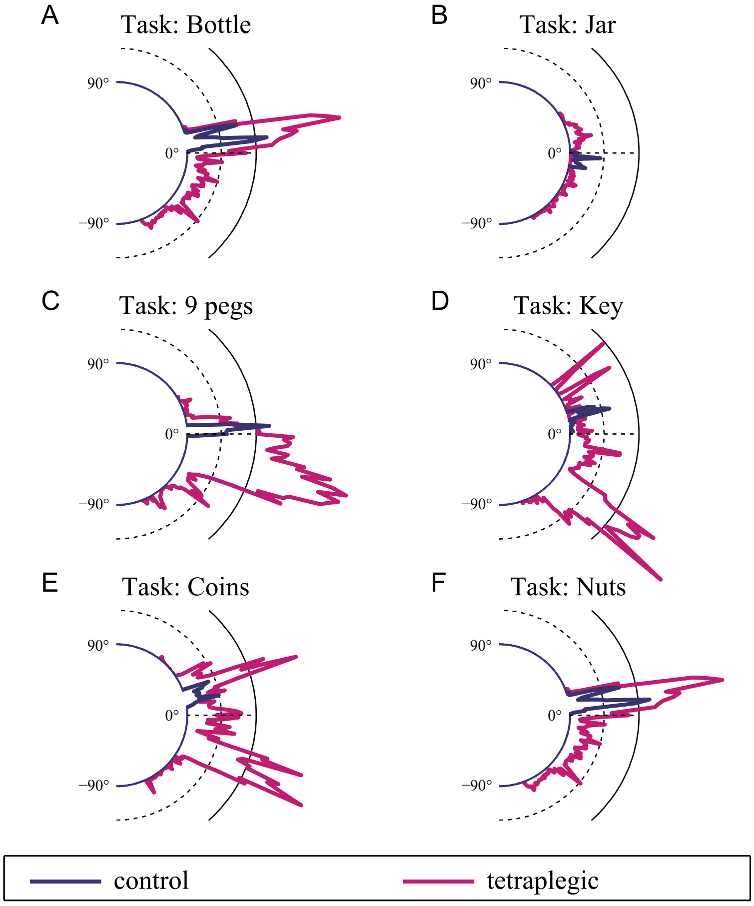

Figure 3.4 – Polar plots of the forearm pitch angle distribution of a representative SCI patient with compensation (red line) and a control subject (blue line) for each of the six prehension tasks. The outer solid circle denotes a histogram frequency of 100 datapoints (equals to 2sec), the inner dotted line a histogram frequency of 50 datapoints (equals to 1sec). The 95% central range of the forearm pitch is given for one representative tetraplegic and control subject.

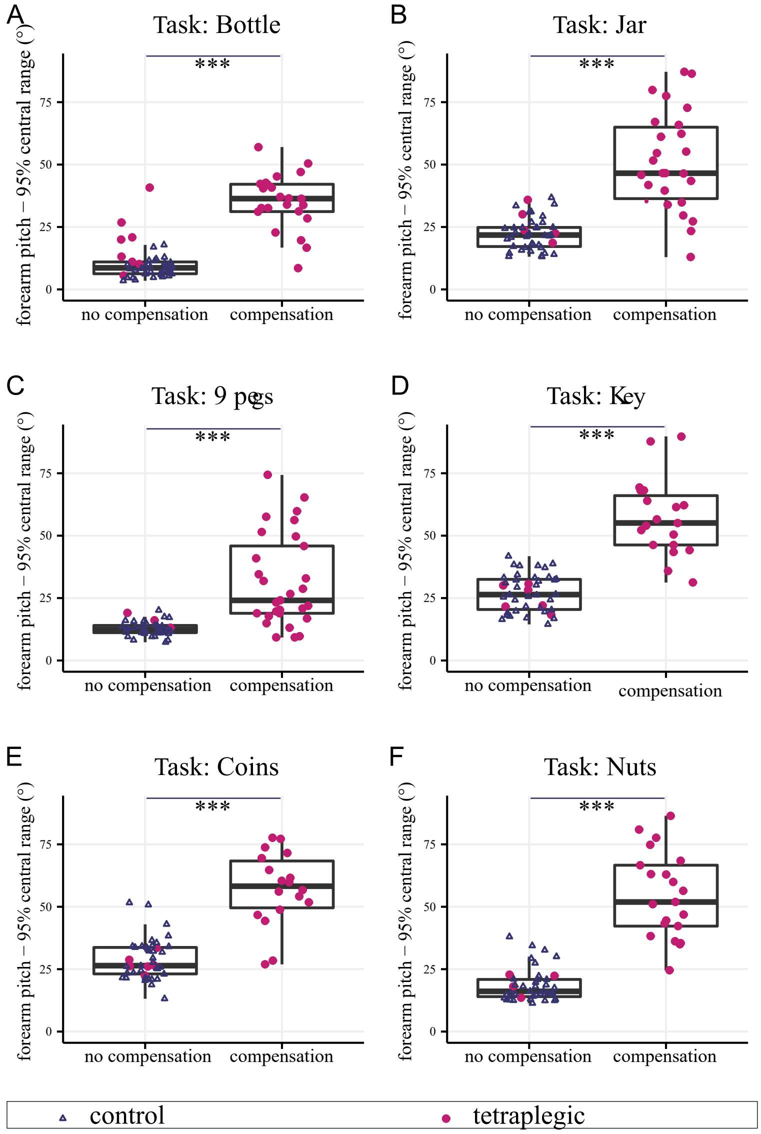

Figure 3.5 – Boxplots of the spread of the forearm pitch angles in tetraplegic subjects (filled red circles) and healthy controls subjects (empty blue triangles) without compensation and with compensation for all the six prehension tasks.

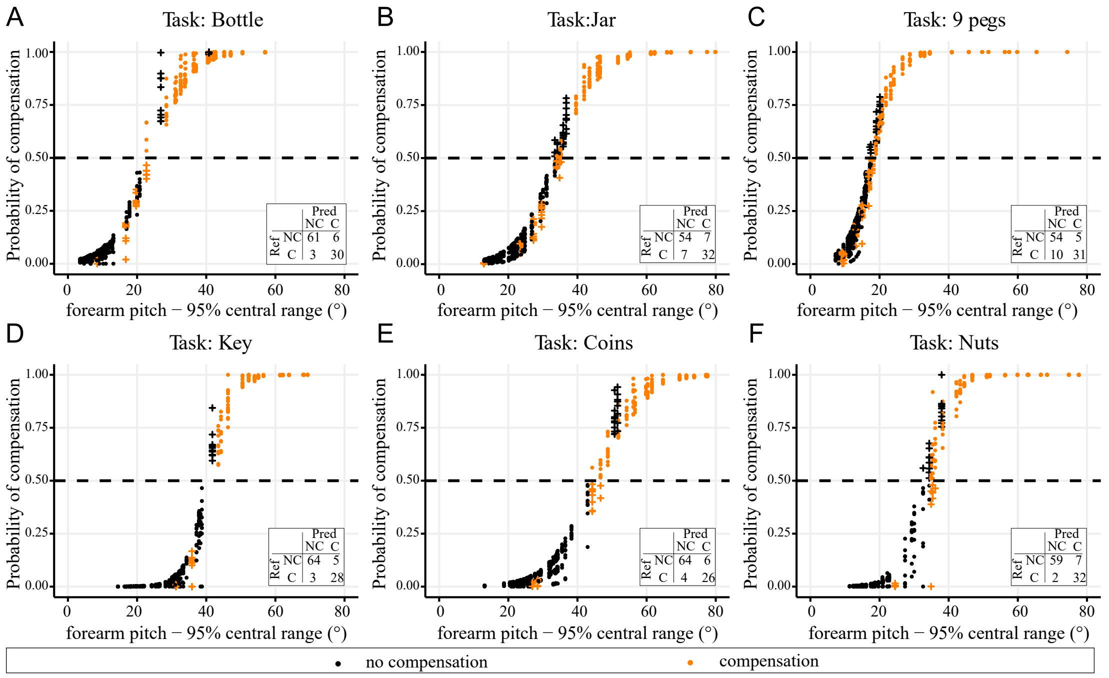

Figure 3.6 – Predicted probabilities of compensation as functions of the spread of forearm pitch angles using logistic regression. Orange color denotes samples labeled as compensation, black denotes samples labeled as no compensation. Points denote correctly classified samples (true positives and true negatives), crosses incorrectly classified samples (false positive and false negatives). Confusion matrices for all tasks are given in percentages (Pred: predicted score, Ref: labeled score, NC: no compensation, C: compensation).

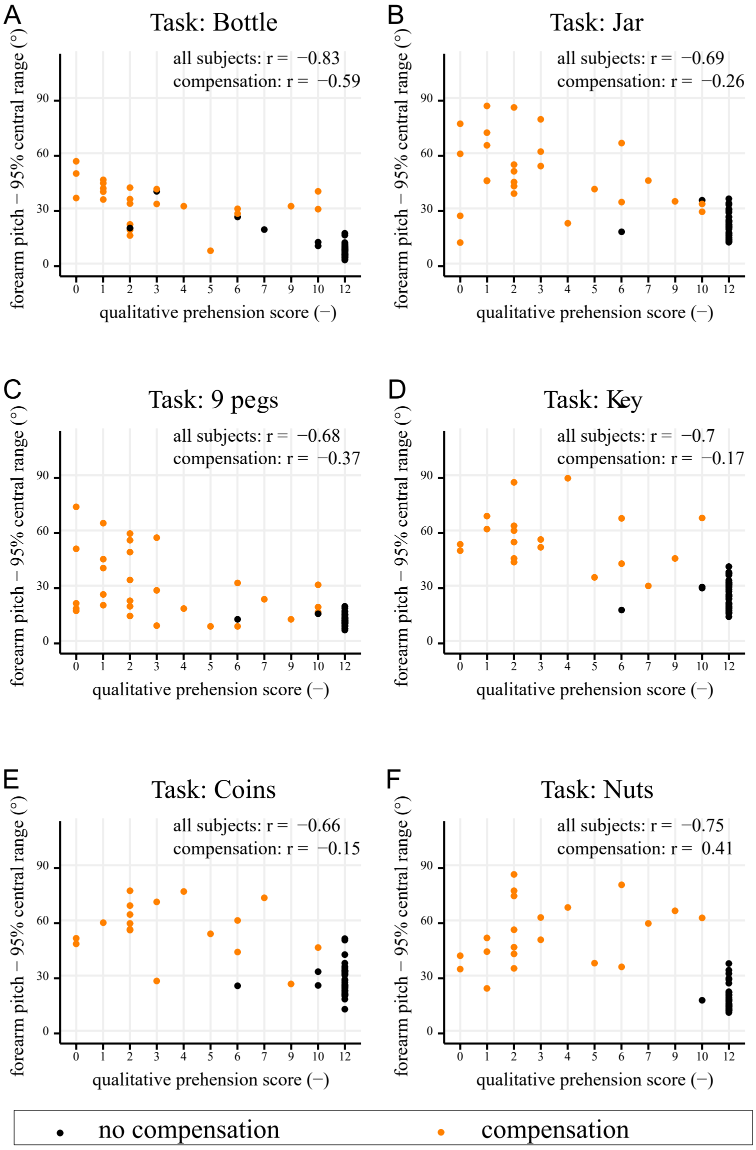

Figure 3.7 – Correlation between the qualitative GRASSP prehension score (sum of scores for cylindrical, lateral, and pinch grip) and the spread of forearm pitch angles. Orange points denote subjects with labeled UL compensation, black points subjects without labeled UL compensation. Spearman correlation coefficients are shown.

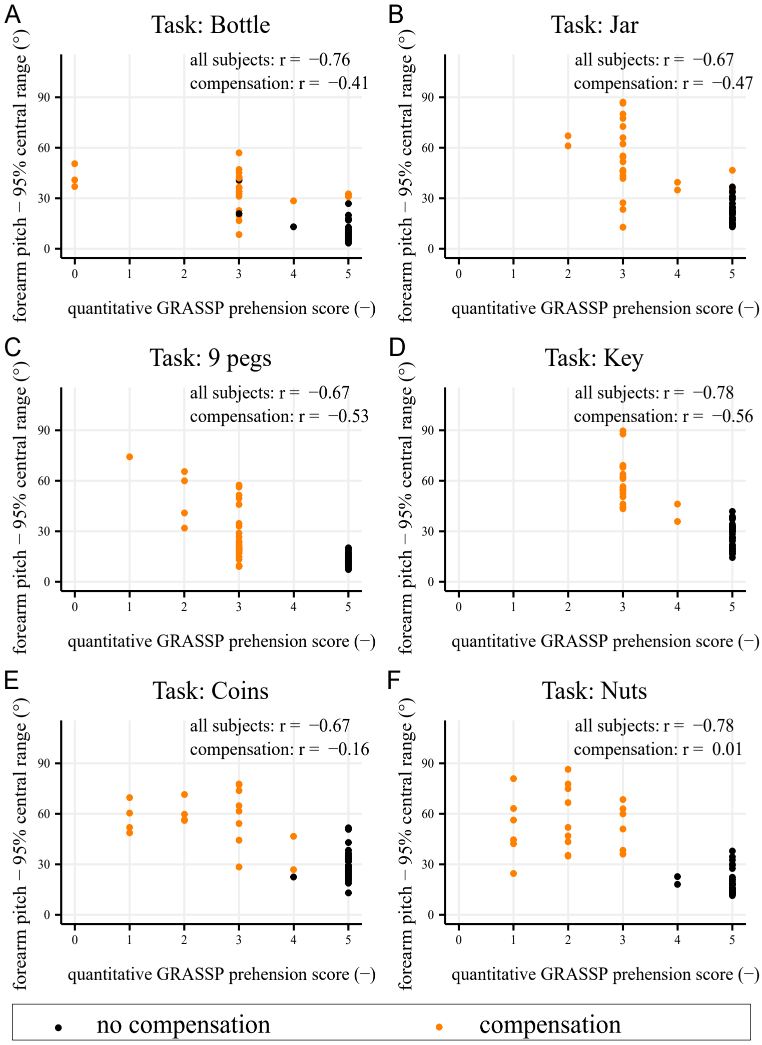

Figure 3.8 – Correlation between the quantitative GRASSP prehension score and the spread of forearm pitch angles for each task. Orange points denote subjects with labeled UL compensation, black points subjects without labeled UL compensation. Spearman correlation coefficients are shown.

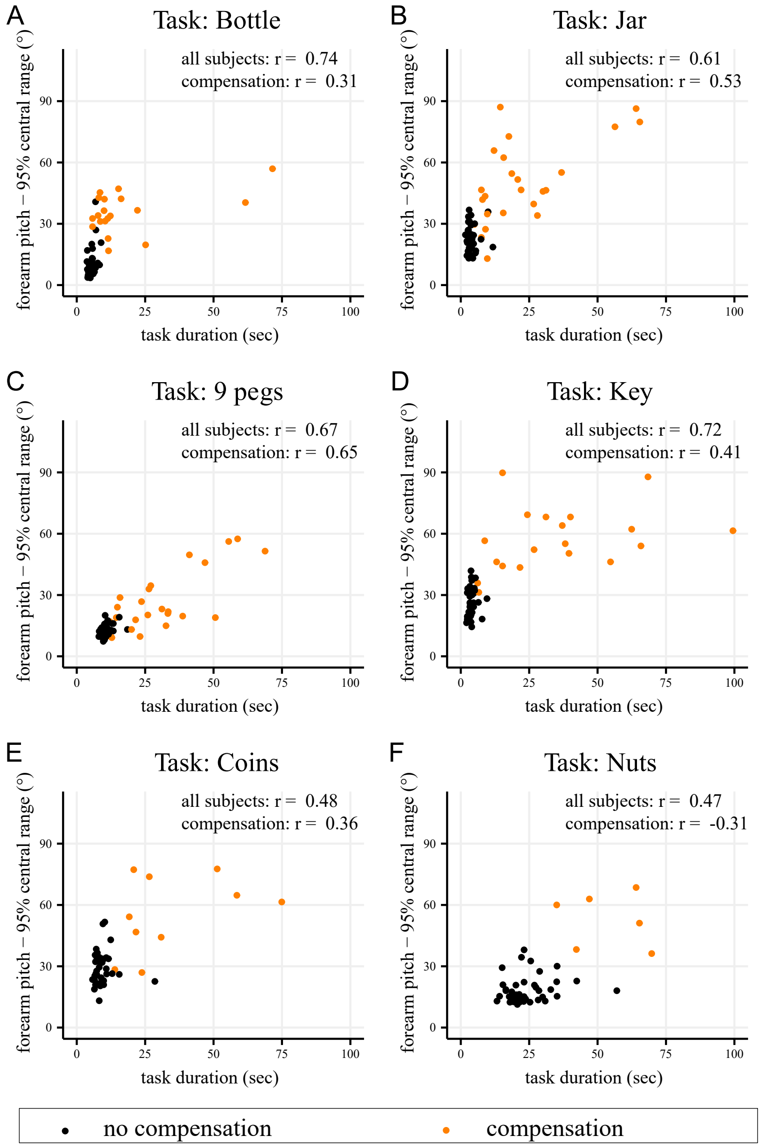

Figure 3.9 – Correlation between the task duration and the spread of forearm pitch angles for each task. Orange points denote subjects with UL compensation, black points subjects without UL compensation. Spearman correlation coefficients are shown.

GRASSP prehension scores compared to subjects without compensation, confirming our hypothesis. Furthermore, UL compensation was found to result in an increased movement duration. Subjects showing compensatory strategies had longer task durations in all six investigated prehension tasks. Therefore, our hypothesis that task duration can be interpreted as a surrogate marker for compensation was confirmed and thus, could be used as an additional marker to validate the proposed sensor-based metric.

The extracted spread of forearm elevation angles was found to be higher in subjects showing compensation than in subjects showing no compensation, suggesting a relationship between the spread of angles and the usage of compensatory strategies. Based on the spread of forearm pitch angles, we were able to classify UL compensation and no compensation with very good to excellent accuracies. This confirms the potential to use the spread of forearm elevation angles extracted from a single wearable sensor to detect compensatory strategies in subjects with an UL impairment. We hypothesize that our tool mainly detects compensatory strategies in which a shoulder abduction is involved. Thus, it performs less good in tasks like the 9 pegs task, in which compensation can only be done by altering the grip (e.g. using a lateral grip instead of a pinching grip), which does not involve compensation by a shoulder abduction. However, an increased contribution of the shoulder during reaching and pointing tasks has been shown previously (Laffont et al., 2000; Jacquier-Bret et al., 2009). Therefore, we hypothesize that our proposed metric is able to detect most of the UL compensatory strategies that occur in SCI patients.

Lastly, we investigated the relation between the spread of forearm pitch angles and the qualitative and quantitative GRASSP prehension scores as well as the task duration as a surrogate marker for compensation. We found moderate to very strong correlations in all six tasks, which might confirm the potential of the spread of forearm elevation not only as a binary classifier but also as an objective and sensitive metric to quantify the magnitude of compensation. However, correlations were less strong in some tasks, e.g., coins, when analyzing correlations within the group of subjects showing compensation. This suggests that not all tasks might be suited equally well to quantify the degree of compensation.

Nonetheless, a true ground truth for the magnitude of compensation is missing. Therefore, more research needs to be invested to confirm the potential of this metric to sensitively quantify the magnitude of compensation, e.g. by acquiring ground truth data by using a motion tracking system. Furthermore, the six standardized ADLs were investigated within a clinical environment. Although these tasks are representative, they do not cover the complete spectrum of prehension tasks occuring during daily life. The execution of ADLs during daily life may also be altered due to external circumstances like the usage of assistive devices and may thus show altered patterns.

3.6 Conclusions

We presented an objective and accurate metric to assess UL compensation in tetraplegic SCI patients using wearable sensors. This metric can be applied in clinical intervention studies to examine the presence of UL compensation as an outcome measure in an unobtrusive way and help to understand the true recovery of UL functions in SCI patients. Moreover, the reduction and thus detection, especially of shoulder compensation, is of high interest to prevent and minimize shoulder pain, which has a huge impact in terms of independence as well as of quality of life in SCI patients (Salisbury et al., 2003). Furthermore, we showed the potential of applying this tool not only as a binary classifier, but also as a sensitive marker to quantify the magnitude of compensation. However, this potential still needs to be validated in further studies. Compared to standard clinical assessments for UL function like the GRASSP, our metric can be applied during the daily life of patients and thus give insights into the performance of ADLs outside of the clinical environment. It could complement existing frameworks focusing on the quantity of physical activity (Zbogar et al., 2016; Brogioli et al., 2016c; Albert et al., 2017; Popp et al., 2018) by a qualitative component. However, more research needs to be invested to be able to detect ADLs in daily life. We believe that our metric for detecting compensatory movements in the ULs is not limited to the population of SCI, but could also be applied in other populations with neurological conditions, i.e., stroke.

4 Reliability of wearable-sensor-derived measures of physical activity in wheelchair-dependent spinal cord injured patients

Sophie Schneider, Werner L. Popp, Michael Brogioli, Urs Albisser, László Demkó, Isabelle Debecker, Inge-Marie Velstra, Roger Gassert, Armin Curt

Frontiers in Neurology, 2018

The authors would like to thank the following persons (in alphabetical order) for their valuable help in recruitment, data acquisition, and the interpretation of the results: Karin Akermann, Anne K. Brust, Dr. Angela Frotzler, Fabienne Hasler, Dr. Kerstin Hug, Dr. Margret Hund, Dr. Mike. D. Rinderknecht, and Dr. Michelle L. Starkey.

This work was supported by the International Foundation for Research in Paraplegia (IRP, project number: P 157), by the Clinical Research Priority Program (CRPP) Neuro-Rehab of the University of Zurich, by the Swiss Paraplegic Foundation (SPS), by Wings for Life (project number: 143), by the ETH Zurich Foundation in collaboration with Hocoma AG, by a HMZ seed project (project title: "ZurichMOVE: Wearable sensors to monitor movement quality and mobility in health care") funded by the University of Zurich and the ETH Zurich Foundation, and by the Swiss State Secretariat for Education, Research and Innovation (SERI) under contract number 15.0255 (Horizon 2020, 681094).

Final publication is available from `https://doi.org/10.3389/fneur.2018.01039`.

4.1 Abstract

Physical activity (PA) has been shown to have a positive influence on functional recovery in patients after a spinal cord injury (SCI). Hence, it can act as a confounder in clinical intervention studies. Wearable sensors are used to quantify PA in various neurological conditions. However, there is a lack of knowledge about the inter-day reliability of PA measures. The objective of this study was to investigate the single-day reliability of various PA measures in patients with a SCI and to propose recommendations on how many days of PA measurements are required to obtain reliable results. For this, PA of 63 wheelchair-dependent patients with a SCI were measured using wearable sensors. Patients of all age ranges (49.3 ± 16.6 years) and levels of injury (from C1 to L2, ASIA A-D) were included for this study and assessed at three to four different time periods during inpatient rehabilitation (2 weeks, 1 month, 3 months, and if applicable 6 months after injury) and after in-patient rehabilitation in their home-environment (at least 6 months after injury). The metrics of interest were total activity counts, PA intensity levels, metrics of wheeling quantity and metrics of movement quality. Activity counts showed consistently high single-day reliabilities, while measures of PA intensity levels considerably varied depending on the rehabilitation progress. Single-day reliabilities of metrics of movement quantity decreased with rehabilitation progress, while metrics of movement quality increased. To achieve a mean reliability of 0.8, we found that three continuous recording days are required for out-patients, and two days for in-patients. Furthermore, the results show similar weekday and weekend wheeling activity for in- and out-patients. To our knowledge, this is the first study to investigate the reliability of an extended set of sensor-based measures of PA in both acute and chronic wheelchair-dependent SCI patients. The results provide recommendations for sensor-based assessments of PA in clinical SCI studies.

4.2 Introduction

Neurological disorders such as Spinal Cord Injury (SCI) are characterized by the different degrees of impairment of motor and sensory function. Earlier studies have investigated the impact of physical activity (PA) on functional recovery and found a positive effect in various neurological diseases (Lynskey et al., 2008; Van Peppen et al., 2004; Damiano, 2007). Past intervention studies in SCI focused on the integration of activity-based therapies with various intensities, duration and type of PA, into rehabilitation programs to improve functional recovery. The outcome of these studies, however, are contradictory, with some of them showing improved strength or functional ability of the upper limbs (Beekhuizen and Field-Fote, 2008, 2005; Hodkin et al., 2018; Francisco et al., 2017) and performance in daily life (Hicks et al., 2003), whereas others could not show any significant effect on the functional recovery (Glinsky et al., 2009; Zariffa et al., 2012). One reason for such divergent results could be the subjective and non-comprehensive assessments of PA performed by the patient outside the controlled interventions. Thus, PA needs to be objectively assessed to better estimate the effects of interventions and the impact of PA on patient recovery in general. In the past 15 years, accelerometers and inertial measurement units (IMUs) have been introduced to quantify PA more objectively. The use of accelerometers is well established in health sciences, especially in quantifying PA in the able-bodied population (Godfrey et al., 2008), elderly (Najafi et al., 2003), children (Riddoch et al., 2004) and patients with various neurological conditions such as stroke (Uswatte et al., 2000; van der Pas et al., 2011), Parkinson's (Salarian et al., 2007), and multiple sclerosis (Motl et al., 2009). In SCI, studies have been conducted to develop metrics to capture PA in wheelchair-bound SCI patients (Popp et al., 2016; Brogioli et al., 2016a).

The levels of PA change throughout the rehabilitation process due to neurological recovery and compensation (Curt et al., 2008; Anderson, 2004), and can differ between individuals (Brogioli et al., 2016c). Furthermore, they may vary from day to day as well due to environmental factors, but also due to patient characteristics like motivation, or general health status and pain. Therefore, there is a need to quantify how much the PA varies between single days within one patient and how many days are required to account for this variability to obtain a reliable representation of the overall PA level of the subject. Guidelines on how many days the PA has to be monitored to obtain a reliable representation of the overall PA already exist for healthy adults and children. For healthy adults, a measurement period of one week has been suggested (Aadland and Ylvisaker, 2015), while a measurement period of up to 11 days has been suggest for children (Barreira et al., 2015). In older adults, a desired measurement duration of one to two days has been reported to achieve good reliabilities for sedentary, low and moderate-to-vigorous physical activity (Falck et al., 2017). In neurological diseases, e.g. in multiple sclerosis, guidelines suggest 4-6 days for sedentary behavior and 3-7 days for low and moderate-to-vigorous physical activity (Klaren et al., 2016). The existing guidelines, however, cannot easily be translated to the SCI population, and especially not to wheelchair-dependent patients because of the completely different PA patterns such as wheeling instead of walking. Because of the novelty of PA research in SCI, no comprehensive guidelines on measurement periods exist for this population. Sonenblum et al. (Sonenblum et al., 2012a) proposed a measurement period of one week to obtain reliable estimations of PA related solely to wheelchair usage, such as distance wheeled and duration of wheeling episodes. Yet, this conclusion is drawn from a limited number of patients with different neurological conditions, and only in their chronic stages. Since the variability between days might change between the stages and it might also be different for the different metrics of PA, we propose guidelines for the wheelchair-dependent patients on how many days of measurement are required for various measures of PA during the different stages of rehabilitation after the incidence of SCI. The primary aim of this study was to estimate the reliability of several sensor-based metrics of PA at different time points during the rehabilitation progress. The secondary aim was to compare the reliability of PA measures across days of active rehabilitation and on weekends.

4.3 Methods

4.3.1 Patients

In total, 63 patients with SCI were included in this analysis, participating in two observational studies (for information about the protocol see Measurement procedure). Patients suffering from a traumatic or non-traumatic acute SCI with all NLI and levels of lesion completeness were admitted to this study. Any neurological disease other than SCI, and any orthopedic or psychiatric disorders, were considered as exclusion criteria. Additionally, only wheelchair-dependent patients, defined by a value of < 3 in all the mobility domains (12, 13 and 14) of the Spinal Cord Independence Measure III (SCIM III) (Catz et al., 1997) were considered for the analysis.

The NLI and completeness of the lesion (AIS) was assessed following the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) (Kirshblum et al., 2011a). Patients with an NLI from C1 to Th1 were classified as tetraplegic, while patients with an NLI from Th2 to S2 were classified as paraplegic. Recruitment took place from 2014 until 2017, at the sites of the Swiss Paraplegic Centre in Nottwil, the Rehab Basel in Basel and the Balgrist University Hospital in Zurich, Switzerland. All patients signed a written consent before participating in the study in accordance with the Declaration of Helsinki. The study was approved by the ethical committees of the cantons of Zurich (KEK-ZH-Nr. 2013-0202), Lucerne (EK 13018), and Basel (EK 34313) and is registered on clinicaltrials.gov (Identifier: NCT02098122).

4.3.2 Measurement procedure

For this study, the ReSense modules (Leuenberger and Gassert, 2011) were used as a measurement device. The ReSense modules are compact IMUs recording 3D acceleration, 3D angular velocity, 3D magnetic field strength, and barometric pressure for more than 24 h continuously. By turning all sensors except the accelerometer off, the battery life can be extended to over 2 weeks. In this study, only the acceleration data were used. At all time points, patients were equipped with several ReSense modules (Figure 4.1). One sensor measuring acceleration was attached to each wrist with AlphaStrap Blue (North Coast) and Velcro Straps (Velcro) for a duration of three consecutive weekdays to capture upper limb movements. Patients were asked to wear the sensors continuously for about 72 hours during day- and nighttime and just take them off for showering or swimming activities. They were told that their amount of activity was being measured and that they should engage in their everyday life actives. Due to the limited battery lifetime, the sensors were exchanged once a day and recharged. Additionally, one module measuring acceleration was mounted on the right wheel of each wheelchair for the duration of seven consecutive days to capture wheeling metrics precisely (Sonenblum et al., 2008; Popp et al., 2016). Data collection was conducted in the context of two observational studies (Figure 4.2). In the first observational study, patients were measured at five different time points during rehabilitation, each time for 3 consecutive days wearing the wrist sensors, and 7 consecutive days using the wheelchair sensor, respectively. The first four time points were within the clinical rehabilitation facilities ('in-patient'), whereas the last time point took place after discharge ('out-patient'). The in-patient rehabilitation was divided into four distinct stages, which conform to the time windows of the European Multicenter Study about SCI (EMSCI[1]): very acute (VA), acute 1 (A I), acute 2 (A II), and acute 3 (A III), which are 2 weeks (0 – 15 days), 1 month (16 – 40 days), 3 months (70 – 98 days), and 6 months (150 – 186 days after injury), respectively. The last time point (out-patient) was defined to be 1 year after injury (chronic stage – C, 300 – 400 days). It is important to note that at stage A III, some

Figure 4.1 – Photograph of one examiner wearing the sensors. One sensor was attached to the right wheel of each wheelchair, one sensor was attached to each wrist.

4.3.3 Data analysis and statistics

The number of included patients varied depending on the specific analysis and time point (Table 4.1). For the analyses focusing on the whole in-patient group, data from stages VA, A I, A II, and partly A III of the 1st observational study were pooled. Similarly, data of the whole out-patient group were pooled from the 2nd observational study, and from stage A III (partly) and C of the 1st observational study.

[1] www.emsci.org

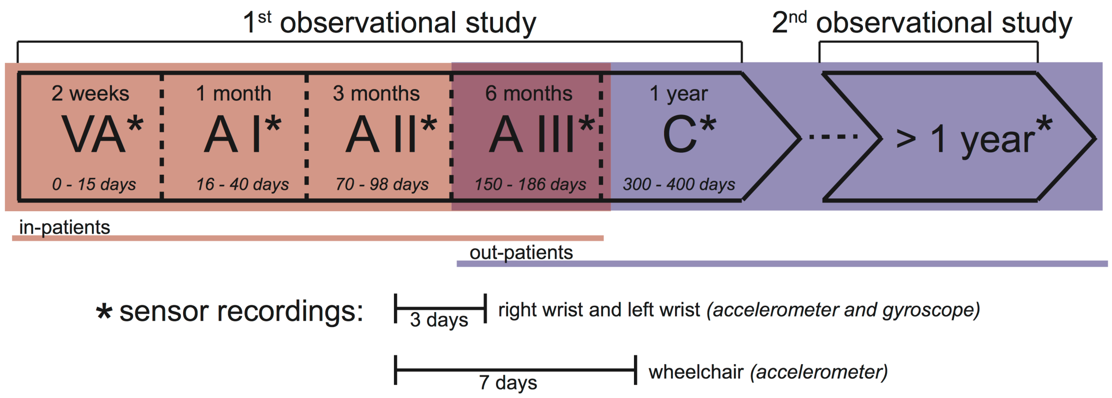

Figure 4.2 – Measurement protocol. This study consists of two observational studies. In the 1st observational study, patients were measured at 5 time points during the rehabilitation process. In the 2nd observational study, a different patient cohort was measured only once, at least 1 year after injury. In stages VA, A I, A II, and partly A III of the 1st observational study, patients were in-patients (red). In the 2nd observational study, as well as partly in A III, and stage C of the 1st observational study, patients were out-patients (blue). At each time point (*), acceleration and angular velocity of the right and left wrists were recorded for 3 days, while the acceleration of the right wheel of the wheelchair was recorded for 7 days. Overall upper limb activity (AC) and PA based on energy expenditure (SED, LPA and MVPA) were calculated based on the 3 day recordings. All wheeling-related measures ($DIST_{TOT}$, $DIST_{ACT}$ and VEL) were calculated based on the 7 day recordings.

		N		females N (%)		tetraplegics N (%)		Age [years] mean ± sd	
Total patients		**63**		**17 (27)**		**34 (54)**		**49.3 ± 16.6**	
		3-day	7-day	3-day	7-day	3-day	7-day	3-day	7-day
1st observational study		**41**	**42**	**12 (29)**	**12 (29)**	**26 (63)**	**27 (64)**	**49.4 ± 19.4**	**49.5 ± 19.2**
Very acute (VA)		10	10	2 (20)	2 (20)	7 (70)	7 (70)	43.0 ± 16.5	43.0 ±16.5
Acute 1 (A I)		36	36	11 (31)	11 (31)	22 (61)	23 (64)	48.0 ± 19.4	48.2 ± 19.0
Acute 2 (A II)		21	24	7 (33)	8 (33)	12 (57)	14 (58)	53.2 ± 18.0	52.1 ± 18.5
Acute 3 (A III)	total	17	20	6 (35)	7 (35)	10 (59)	11 (55)	49.1 ± 19.8	48.1 ± 19.4
	in	14	16	4 (29)	4 (25)	10 (71)	11 (69)	50.1 ± 18.3	48.8 ± 18.8
	out	3	4	2 (67)	3 (75)	0 (0)	0 (0)	44.0 ± 30.3	45.3 ± 24.9
Chronic (C)		5	4	1 (20)	0 (0)	3 (60)	3 (75)	42.6 ± 18.0	40.8 ± 20.3
2nd observational study		**22**	**19**	**5 (23)**	**5 (26)**	**8 (36)**	**8 (42)**	**49.5 ± 11.5**	**51 ± 11.3**
In-patient*		81	86	24 (30)	25 (29)	51 (63)	55 (64)	49.1 ± 18.5	48.8 ± 18.4
Out-patient*		30	27	8 (27)	8 (30)	11 (37)	11 (41)	47.8 ± 14.5	48.7 ± 14.9

Table 4.1 – Patient demographics for all patients included as well as split up into patients included in the 1st and 2nd observational studies for 3-day as well as 7-day measurements. Detailed numbers are given for all single stages constituting the 1st observational study: 2 weeks after injury (VA), 4 weeks after injury (A I), 3 months after injury (A II), 6 months after injury (A III), and 1 year after injury (C). In stage A III, in- as well as out-patients are included. * For a combined analysis of all in-patients, data of stages VA, A I, A II, and A III (partly) were pooled. Data of stages A III (partly), stage C, as well as the 2nd observational study were pooled for a combined analysis of all out-patients. 'Tetraplegics' are defined by a lesion level from C1 to Th1.

Preprocessing

The desired sampling rate of the sensor was 50 Hz. However, the exact sampling rate of the ReSense sensors can vary between 49-51 Hz. Therefore, the raw data was resampled to 50 Hz using a common set of time points for all the modules that were used together (Leuenberger, 2015). The periods of not wearing the sensors were removed from the data using a semi-automatic algorithm. The algorithm labels periods with 20 min of consecutive zero-counts as potential non-wear times (Mâsse et al., 2005). Thereafter, the labeled periods were visually inspected by an expert and manually adapted where necessary.

Sensor-based metrics

Sensor-based metrics were divided into 4 major categories: activity counts of overall upper limb movement, PA intensity levels (time spent in sedentary PA, low PA and moderate-to-vigorous PA), metrics of wheeling quantity (total and actively wheeled distance), and metrics of movement quality (upper limb movement laterality and mean wheeling velocity as a proximate of wheeling performance).

Overall upper limb activity

Activity counts (AC) were used to enumerate total forearm activity in a generalized way and were calculated by applying the discrete integral over the acceleration magnitude in epochs with the length of 1 min (Leuenberger et al., 2017) and subsequently averaging the AC values over all epochs. AC of the right and left wrist were summed up.

PA intensity levels

Different intensity levels of PA were defined by using AC cut-off values. These cut-off values were derived from previous energy expenditure measures in combination with IMU data (Popp et al., 2018) The intensity levels were defined by means of the metabolic equivalence of task (MET) adapted for SCI (Collins et al., 2010), where sedentary activities (SED) corresponded to a MET level below 1.5, low physical activity (LPA) to a MET value between 1.5 and 3, and moderate-to-vigorous activities (MVPA) corresponded to a MET level above 3. SED, LPA and MVPA are expressed in minutes spent in the respective intensity level per 24 h.

Metrics of wheeling quantity

To calculate wheeling-related metrics, a previously published algorithm (Popp et al., 2016) was used to i) detect the phases of wheeling activity by applying heuristic rules, and ii) to classify these phases into active and passive wheeling by using support vector machine classifiers. The total distance ($DIST_{TOT}$) and the distance wheeled actively ($DIST_{ACT}$) were extracted from the data and normalized to 24 h.

Metrics of movement quality

Whereas the three aforementioned categories described how often movements were performed, the following metrics describe how the movements were performed. Upper limb movement laterality (LAT) represents the symmetry of upper limb movements in general. LAT was calculated by computing the AC in epochs of 2 sec for the right and left hand, dividing AC of the right hand and left hand and log transforming this ratio. The median value of the absolute log transform was used for the analysis. Details about the calculation can be found in (Brogioli et al., 2016a). Scores for LAT range from minus to plus infinity quantifying the amount of LAT, with zero for no LAT. Mean velocity (VEL) can be interpreted as a proximate measure for the quality of wheeling. Patients with improved functional ability will be able to wheel on average faster than patients in earlier stages of rehabilitation, or with more severe impairments. VEL was defined as the mean absolute velocity of active propulsion, and was extracted using the aforementioned wheeling algorithm (Popp et al., 2016).

Statistics

First, the single-day reliabilities of all sensor-based metrics were calculated. Then the number of days needed for a reliable measurement was identified. Single-day reliabilities for AC, SED, LPA, MVPA, and LAT were calculated based on the 3-day measurements, because they require information of the wrist sensors. Single-day reliabilities for $DIST_{TOT}$, $DIST_{ACT}$, and VEL were calculated based on the 7-day measurements, because they require information of the wheel sensor only. Single-day reliability was defined as the Intraclass Correlation Coefficient (ICC), which was calculated using a variance portioning approach based on a one-way random effects model, with the random effect being on the subject level (Bland and Altman, 1986)

$$ICC = \frac{\sigma_s^2}{\sigma_s^2 + \sigma_{res}^2} \tag{4.1}$$

where σ_s^2 is the between-subject variance and σ_{res}^2 the residual variance. This approach is a well-established method especially in the field of PA research (Levin et al., 1999; Trost et al., 2000; Aadland and Ylvisaker, 2015). The confidence intervals for ICC were calculated based on the exact confidence limit equation (Searle, 1971). According to Koo and Li (Koo and Li, 2016), ICC values higher than 0.9 are considered as excellent, between 0.75 and 0.9 as good, between 0.5 and 0.75 as moderate, and lower than 0.5 as poor reliability. To calculate the number of days needed for a reliable measurement (N), the Spearman Brown prophecy formula was used (McGraw and Wong, 1996),

$$N = \frac{(ICC_t * (1 - ICC_s))}{(ICC^s * (1 - ICC_{t)})} \tag{4.2}$$

where ICC_t is the desired level of reliability and ICC_s is the single-day reliability. The desired reliability was set to 0.8, which is considered as an acceptable value according to literature (Trost et al., 2005). To assess the relation of the wheeling-related metrics during weekdays and the weekend, equivalence tests were used. For normally distributed data, the Two Sided T-test (TOST) approach was used (Berger and Hsu, 1996). In TOST, an epsilon (ϵ) has to be defined that corresponds to the level of practical equivalence (LOPE). We chose ϵ as the mean value of all the standard deviations of the respective metric:

$$\epsilon = (\sum_{(} i = 1)^n \sigma_i^{metric})/n \tag{4.3}$$

where n is the number of patients, and σ_i^{metric} is the standard deviation of the i-th subject for the metric of interest. For non-normally distributed data, the TOST procedure was adapted by using the non-parametric Mann-Whitney-Wilcoxon Test instead of the Student's t-test. A sample size calculation was performed according to the method presented in (Wolak et al., 2012). The results of this analysis can be found in Table A.1. Preprocessing and calculation of the output metrics was conducted using MATLAB R2017a (MathWorks, Natick, MA, USA). Statistics were computed using R (The R project for Statistical Computing, R Core Team).

4.4 Results

4.4.1 Patient characteristics

The mean age of all patients was 49.3 ± 16.6 years at the time of recruitment. 17 (27%) of the patients were female. ASIA impairment scale (AIS) levels ranged from A to D, (A: 27, B: 9, C: 16, and D: 11 patients at the time of recruitment) and the neurological level of injury (NLI) from C1 to L2 (C1 – C4: 17, C5 – C8: 17, T1 – T5: 6, T6 – T12: 19, and L1 – L2: 4 patients at the time of recruitment). More detailed information about patient numbers and demographics can be found in Table 4.1.

4.4.2 Single-day reliabilities

Single-day reliabilities of metrics of PA varied depending on the time after SCI (i.e. rehabilitation progress) ranging from excellent to poor reliability levels (Figure 4.3). ICC of metrics describing movement quantity (AC, SED, LPA, MVPA, $DIST_{TOT}$, and $DIST_{ACT}$) tended to decrease during the rehabilitation progress (Figure 4.3A-C) and decreased e.g., from excellent reliability levels (0.93) for LPA in stage VA to poor levels (0.44) for LPA in out-patients. In contrast, measures describing movement quality (LAT and VEL) tended to increase during rehabilitation (Figure 4.3D). Especially, reliability of VEL improved from a poor level of the ICC (0.19) at stage VA to a moderate level (0.66) for out-patients. Overall upper limb activity (AC) showed excellent ICC levels (ICC > 0.92) during the first three acute stages with a decrease at later stages of rehabilitation to a good level (0.79) and a moderate level (0.65) after discharge (out-patient).

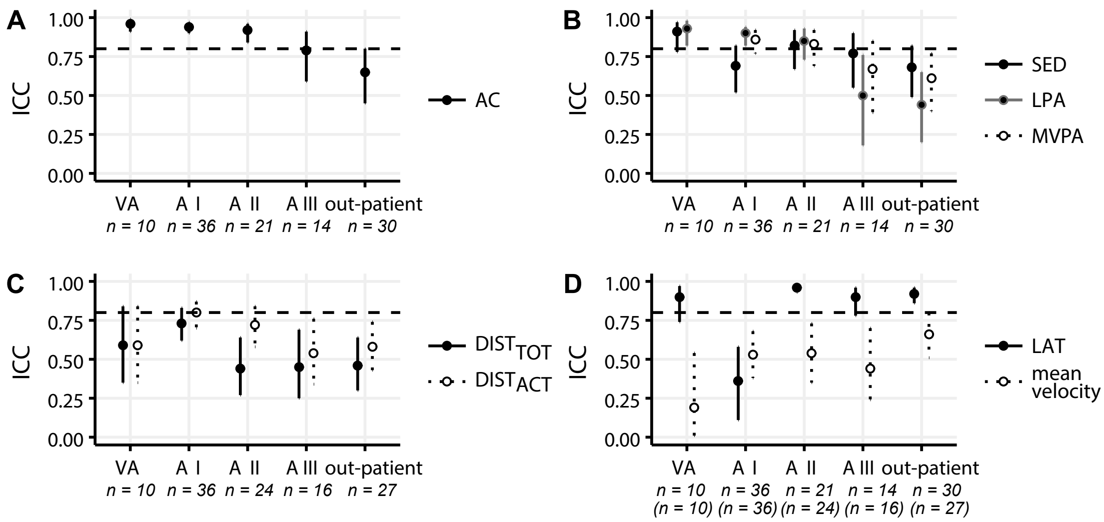

Figure 4.3 – ICC values representing the single-day reliabilities for (A) activity counts (AC); (B) time spent in sedentary activity (SED), low physical activity (LPA), and moderate-to-vigorous activity (MVPA); (C) total distance travelled in a wheelchair ($DIST_{TOT}$) and distance travelled actively in a wheelchair ($DIST_{ACT}$); and (D) laterality (LAT) and mean velocity (VEL) for all in-patient rehabilitation stages (very acute (VA – 2 weeks after injury), acute I (A I – 4 weeks after injury), acute II (A II – 3 months after injury) , acute III (A III – 6 months after injury)), as well as for the out-patients (>6 months after injury). The horizontal dashed lines depict the ICC level of 0.8, which was chosen as a requirement for a reliable measurement. Solid and dotted lines indicate the confidence intervals. Indicated patient numbers n are the pooled numbers.

Overall single-day reliabilities were higher in tetraplegic patients than in paraplegic patients for most metrics (Figure 4.4). One exception to this was found in the reliability of MVPA in the out-patients, were the single-day reliability for tetraplegic patients was poor (0.24) and thus lower than the moderate level (0.65) for the paraplegic patients. Furthermore, the single-day reliability of LPA is poor (0.03) in paraplegic out-patients.

4.4.3 Required number of days

A mean reliability of 0.8 is reached when monitoring in-patients for 2 days and out-patients for 3 days for all metrics (Figure 4.5A and Figure 4.5C). A 7-day measurement is estimated to reach excellent reliabilities for all metrics in both in- and out-patients (Figure 4.5B and Figure 4.5D).

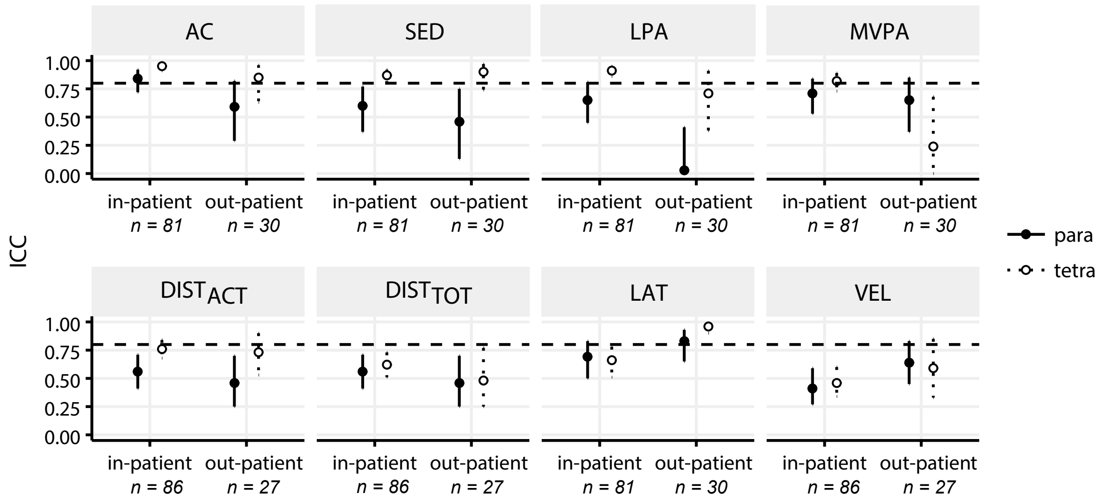

Figure 4.4 – ICC values representing the single-day reliabilities for activity counts (AC), time spent in sedentary activity (SED), low physical activity (LPA), moderate-to-vigorous activity (MVPA), total distance traveled in a wheelchair ($DIST_{TOT}$), distance traveled actively in a wheelchair ($DIST_{ACT}$), laterality (LAT), and mean velocity during active wheeling (VEL) for wheelchair-dependent paraplegic patients (full circle, solid lines) compared to wheelchair-dependent tetraplegic patients (empty circle, dotted lines) for the in-patients (from 2 weeks after injury to 6 months after injury) and out-patients (>6 months after injury). The dashed horizontal lines depict the ICC level of 0.8, which was chosen as a requirement for a reliable measurement. Solid and dotted lines indicate the confidence intervals. Indicated patient numbers n are the pooled numbers.

4.4.4 Influence of weekday versus weekend

With the chosen LOPEs and a significance level of 0.05, equivalence could be established for $DIST_{TOT}$ as well as $DIST_{ACT}$ between weekdays and the weekend in all in-patients and out-patients, as well as single stages VA and A I (Table 4.2, Figure 4.6A). At stages A II and A III, no equivalence could be shown (Figure 4.6A) for $DIST_{TOT}$ and $DIST_{ACT}$. Results for active distance are very similar to total distance for all stages, and thus not presented. For VEL, equivalence could be shown in all in-patients and out-patients, as well as at single stages A I, A II, whereas in stage VA and A III no equivalence could be established (Table 4.2 and Figure 4.6B).

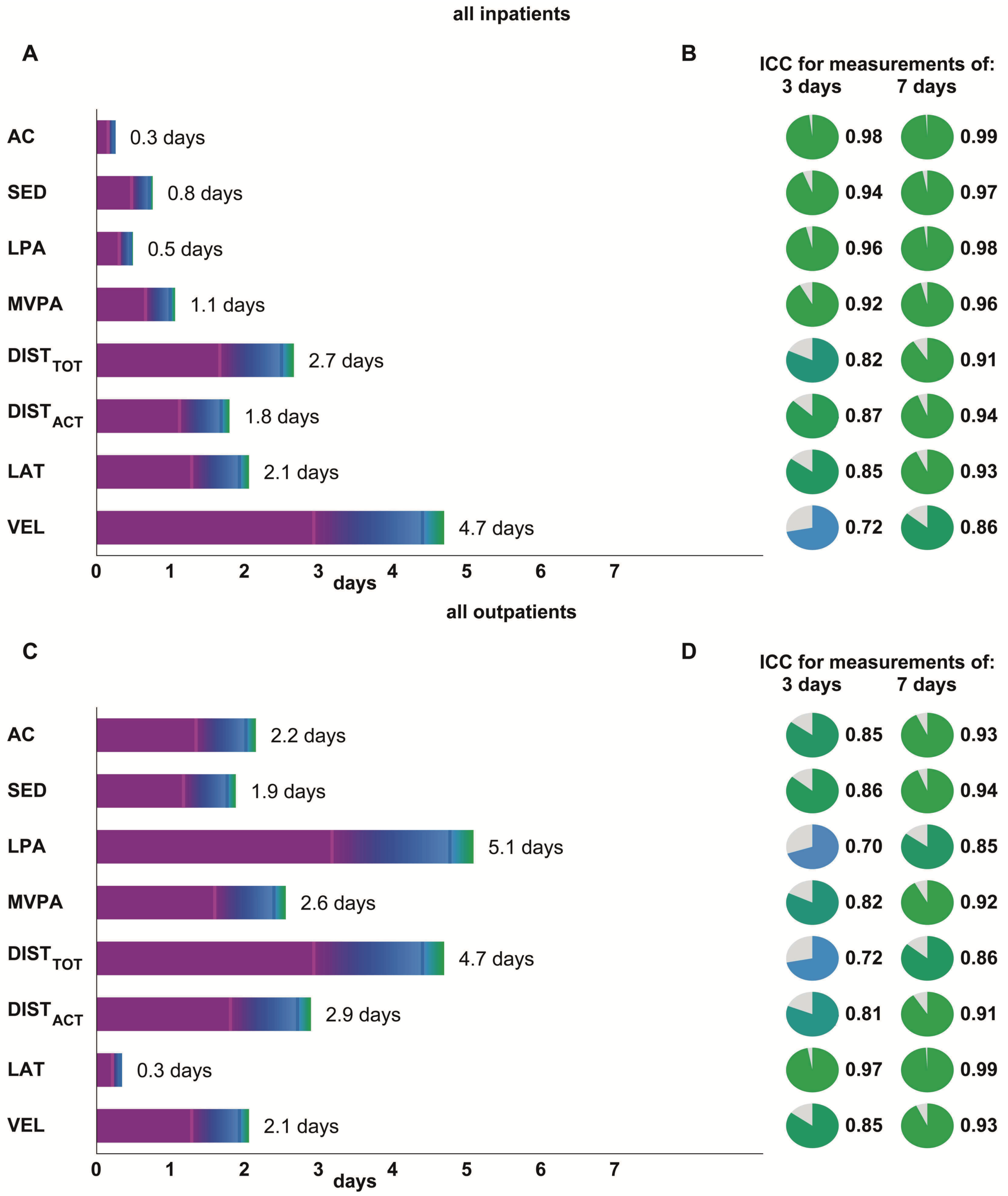

Figure 4.5 – The subfigures on the left side (A: in-patients, C: out-patients) represent the number of measurement days needed in order to achieve a reliability of 0.8 for different metrics of movement quantity (activity counts – AC, time spent in sedentary activity – SED, in low physical activity – LPA, in moderate-to-vigorous activity – MVPA, total distance wheeled – $DIST_{TOT}$, and distance wheeled actively – $DIST_{ACT}$) as well as metrics of movement quality (laterality – LAT and mean wheeling velocity – VEL). Additionally, the numbers of measurement days needed for a reliability of 0.5 and 0.75 are presented with magenta and blue vertical bars, respectively. The subfigures on the right side (B: in-patients, D: out-patients) show the reliabilities, which would be achieved when measuring 3 and 7 days, respectively.

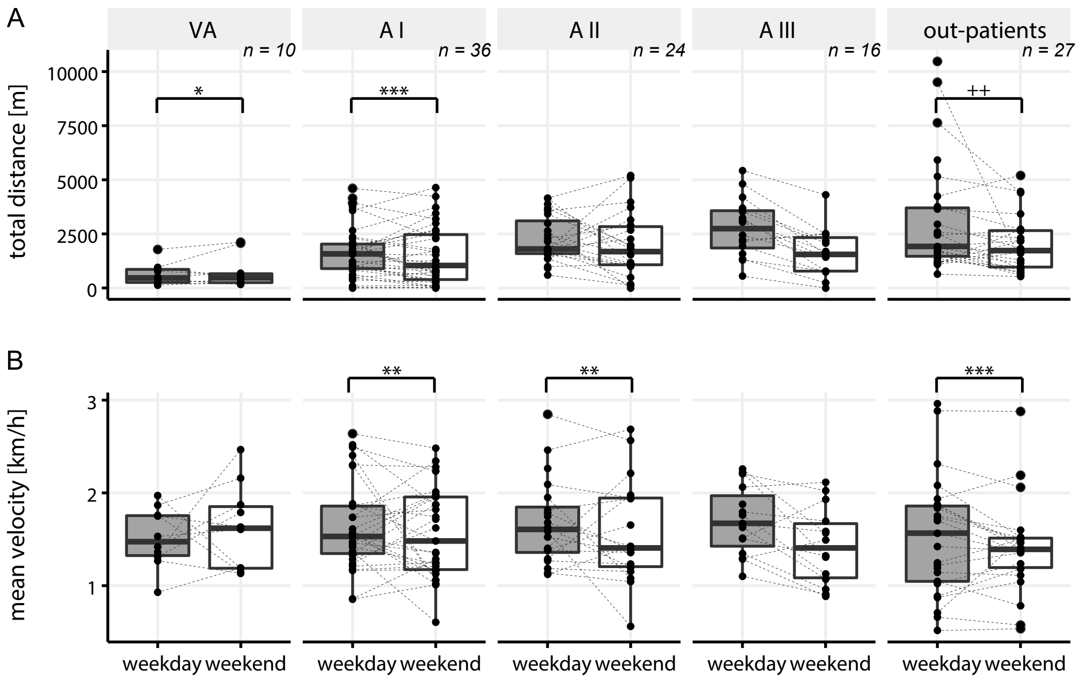

Figure 4.6 – Boxplots for total distance traveled in a wheelchair (A) and mean velocity during active wheeling (B) during weekdays vs. weekends in all single in-patient stages (VA, AI, AII, AIII), as well as out-patients. */+ denotes p-value of < 0.05, **/++ a p-value of < 0.01, ***/+++ a p-value of < 0.001, respectively. P-values were calculated using the TOST procedure for normally distributed data (*), respectively, the adapted equivalence test based on the Mann-Whitney-Wilcoxon Test for non-normally distributed data (+).

	workday mean (± SD)	weekend mean (± SD)	workday median (IQR)	weekend median (IQR)	Limit of practical equivalence (± LOPE)	confidence Interval	Equivalence p-value
				$DIST_{TOT}$ [m]			
in-patients	1910.9 ± 1271.6	1562.3 ± 1312.9	1722.1 (1631.64)	1184.1 (1828.9)	± 750.1	127.8, 538.7	0.001
VA	625.7 ± 499.8	723.2 ± 740.7	467.1 (605.3)	467.3 (409.1)	± 368.6	-338.9, 143.8	0.035
A I	1644.3 ± 1170	1501.1 ± 1321	1576.2 (1133.9)	1040.3 (2078.3)	± 615.1	-148.3, 315.1	<0.001
A II	2264.5 ± 1059.6	1980.9 ± 1502.9	1803.3 (1512.3)	1681.3 (1763.7)	± 744.6	-251.9, 875.6	0.1
A III	2783.7 ± 1346.8	1646.5 ± 1095.4	2742.5 (1724.1)	1551.9 (1550.7)	± 1277.5	817.2, 1618.6	0.399
out-patients	3365.2 ± 2698.3	2139.9 ± 1367	2462.9 (1367)	1812.4 (621.9)	± 1092.3	31.5, 772.9	0.003
				$DIST_{ACT}$ [m]			
in-patients	1686.4 ± 1396	1379 ± 1270.9	1446.8 (1927.7)	1100.2 (1841.7)	± 661.2	130.6, 464.7	<0.001
VA	625.3 ± 499.5	722.9 ± 740.6	467.1 (604.9)	466.8 (408.9)	± 368.6	-338.9, 143.7	0.035
A II	1494.9 ± 1268.1	1370.2 ± 1370.7	1225.8 (1495)	819.8 (2202.4)	± 537.4	-151.8, 264.2	<0.001
A II	1836.8 ± 1427.7	1508.9 ± 1375.6	1690.6 (2562.7)	1160.2 (1466)	± 610.2	-77.6, 712.2	0.108
A III	2555.2 ± 1528.4	1645.7 ± 1094.9	2329.7 (2250)	1551.5 (1546.9)	± 1147	700.9, 1458.9	0.38
out-patients	2738.7 ± 2605.2	1871.1 ± 1561.7	2443 (2565.7)	1727.8 (1946)	± 672.2	-16.6, 550.3	0.012
				VEL [km/h]			
in-patients	1.64 ± 0.43	1.54 ± 0.48	1.54 (0.52)	1.43 (0.77)	± 0.36	0, 0.19	<0.001
VA	1.52 ± 0.32	1.62 ± 0.46	1.47 (0.43)	1.62 (0.66)	± 0.41	-0.42, 0.22	0.055
A I	1.63 ± 0.47	1.56 ± 0.48	1.53 (0.51)	1.48 (0.78)	± 0.35	-0.06, 0.25	0.004
A II	1.68 ± 0.46	1.57 ± 0.55	1.61 (0.49)	1.41 (0.74)	± 0.36	-0.11, 0.26	0.009
A III	1.7 ± 0.37	1.43 ± 0.41	1.67 (0.54)	1.41 (0.58)	± 0.36	0.09, 0.43	0.161
out-patients	1.53 ± 0.64	1.41 ± 0.51	1.57 (0.81)	1.39 (0.32)	± 0.32	-0.06, 0.17	<0.001

Table 4.2 – Descriptive statistics for total distance travelled in a wheelchair ($DIST_{TOT}$), distance travelled actively in a wheelchair ($DIST_{ACT}$), and mean velocity during active wheeling (VEL) performed during weekdays and weekends (mean ± SD and median (IQR)) for pooled in-patients and out-patients, as well as all single stages, VA (very acute – 2 weeks after injury), A I (acute I – 4 weeks after injury), A II (acute II – 3 months after injury), A III (acute III – 6 months after injury). The last three columns contain the calculated limits of practical equivalence (LOPE) used for the equivalence tests, the confidence intervals, and the p-values resulting from the equivalence tests. a denotes p-values resulting from the Mann-Whitney-Wilcoxon Test of equivalence for non-normally distributed data, the remaining p-values were calculated using the TOST procedure for normally distributed data.

4.5 Discussion

To our knowledge, this study is the first to investigate the reliabilities of a comprehensive set of sensor-based measures of PA in both acute and chronic wheelchair-dependent SCI patients. These findings provide recommendations for the application of sensor-based assessments of PA that enable non-obstructive long term recordings throughout clinical studies in in- and out patients.

4.5.1 Single-day reliabilities

Single-day reliabilities of PA metrics depend highly on the clinical condition, i.e. the stage of rehabilitation and the extent of functional impairment. The reliability of measures of movement quantity such as activity counts of upper limb activity, PA intensity levels and wheeling-related metrics decreased during in-patient rehabilitation and in the out-patient setting, while in general was found to be higher for tetraplegic patients. One reason for this might be that in-patients have a more regular daily schedule due to preplanned therapy sessions as observed by therapists at the different rehabilitation centers, resulting in lower variability of daily activities. Reliabilities of metrics of movement quantity are higher in patients with a higher impairment like in tetraplegia and in the early stages of rehabilitation, as the use of the upper limbs for these patients is mostly limited to the very structured therapy sessions, lowering the variability between single days. Additionally, these patients might also reach their upper limits of PA during their daily schedules, resulting in a very low variability between single days. High reliability levels of upper limb activity in terms of AC compared to the other quantitative metrics suggest that this measure, although widely used in PA-research, may provide a rather rough approximation of PA levels in SCI patients, lacking the detailed information about PA intensity patterns and specific movements like wheeling. Metrics based on PA intensity levels show lower single-day reliability levels than AC, suggesting that these metrics capture more detailed information about PA levels which likely vary between single days. Another possible explanation could be that the AC thresholding for this analysis introduces noise into the estimates. Future studies are needed to investigate this in more detail. The reliability of LPA in paraplegic out-patients was considerably lower compared to the remaining metrics based on PA intensity levels. Since the reliability is calculated by dividing the between-subject variance by the total variance (eq.1), for LPA in paraplegic out-patients, the poor reliability can be explained by a very low variance between the individual patients compared to the variance between the single days. While tetraplegic patients show a much higher between-subject variance, this might be a hint that LPA could be influenced by the level of impairment of the upper limbs. LPA is likely to represent activities of daily living, as demonstrated earlier (Popp et al., 2018). Assuming that a large amount of activities of daily living (not involving mobility), e.g., feeding, showering, and dressing are equally presented in each patient, LPA should not vary strongly between single patients. This hypothesis is valid for patients that are not impaired in the upper-limbs, i.e., paraplegics, as can be seen in the low variability of LPA between the patients (LPA: SD: 1.1h, Min: 9h, Max: 13h). In contrast, the level of impairment of the upper limbs varies strongly in the tetraplegic group, which might be the reason for a higher variability of LPA between the patients (LPA: SD: 2.8h, Min: 6h, Max: 15 h). In contrast to the increased reliability in LPA for tetraplegic outpatients, MVPA shows a decreased single-day reliability in these patients. A possible reason is that these patients are challenged to even reach moderate-to-vigorous intensities (Zbogar et al., 2016; Jörgensen et al., 2017) and thus show it only occasionally and not in everyday PA. In contrast to metrics of movement quantity, single-day reliabilities of metrics of movement quality like LAT and VEL increased during the rehabilitation and stayed on a higher level after discharge. During in-patient rehabilitation, patients learn various skills to handle their impairment, e.g. wheeling techniques or compensatory strategies for activities of daily living, which may result in higher variability between single days at the earlier stages of rehabilitation. Moreover, at the beginning of the rehabilitation process arm rehabilitative training is often unilateral (e.g. with ArmeoPower training Keller et al., 2015), leading to a high discrepancy of LAT between specific therapy sessions and leisure time and thus increasing the variability of LAT between different days. Furthermore, the therapy schedules may vary strongly between different days at these stages, which can result in more variable measures of movement quality on different days due to dedicated rehabilitation sessions with specific training aims such as improving the function of the more impaired side in tetraplegics leading to a higher variability in measures of movement quality as can be seen for LAT in the AI stage. After the patients learn certain strategies, they may apply them more consistently during their daily activities, resulting in higher single-day reliabilities at the later stages of rehabilitation. The high reliability of LAT in the stage VA might be due to the fact that patients are mainly bound to the bed, and not showing much PA in general, which may lead to a higher reliability.

4.5.2 Required number of days for reliable measures

Based on our data, metrics of movement quality should optimally be measured for 4 days to achieve a mean reliability of 0.8, which is commonly used in the field of PA research (Tudor-Locke et al., 2005; Aadland and Ylvisaker, 2015; Barreira et al., 2015; Klaren et al., 2016). In the in-patient setting, we suggest measuring metrics of movement quantity for 2 days to achieve a mean reliability of 0.8, while in the out-patient setting measuring on average for 3 days is required to achieve the same reliability. The findings of high reliability of 2-days recordings increase the applicability of sensor measurements in the clinical routine where, especially in acute patients, wearing sensors for too long may be an additional burden. However, we suggest 4 days to capture all analyzed metrics of movement quantity reliably, and one to two days for the measures of movement quality in the out-patient setting. Measuring for 7 days would yield excellent reliabilities for all metrics in all patients, which might be relevant in research and clinical studies where even the detection of small changes in PA patterns may have an impact on outcomes. However, measurement duration is always in tradeoff with clinical applicability and patient compliance.

4.5.3 Difference between weekdays and weekend

We investigated whether it makes a difference to measure PA on weekends or during the week. For this, only wheeling-related metrics ($DIST_{TOT}$, $DIST_{ACT}$, and VEL) were analyzed, as 7-day recordings were only available from the wheel-mounted sensor. In in-patients as well as in out-patients we could show equivalence of $DIST_{TOT}$ and $DIST_{ACT}$ between weekdays and weekends. This suggests that measurements can be taken on any day of the week, keeping in mind that single days might represent unexpected outliers due to an event not occurring regularly. Nevertheless, the results for the in-patients have to be taken with precautions. Splitting up the in-patients into the single stages, equivalence between weekdays and weekends of $DIST_{TOT}$ and $DIST_{ACT}$ could only be shown at the very early stages of rehabilitation (VA and AI), suggesting that for the stages of A II and A III both weekdays and weekends should be measured in order to obtain a comprehensive picture of the patients' overall PA. During early phases of rehabilitation, patients typically receive individual therapy instead of group therapies and their therapy schedules are less tight as observed by therapist at the different centers. We hypothesize that this could explain the observation of similar amounts of activity on the weekends and during the week. At later stages, however, the therapy schedule of the patients gets tighter during the week, which is why they might use the weekends for recovery. The fact that some patients can leave the rehabilitation facility over the weekend at later stages of rehabilitation might have an additional impact on their different behaviors during weekdays and weekends. One could hypothesize that in out-patients the wheeling distances differ during weekdays and weekends mainly due to the fact that patients might work during the week and thus show different activity patterns than on the weekends. However, in out-patients, equal wheeling distances ($DIST_{ACT}$ and $DIST_{TOT}$) were found during the week and on the weekends, which might indicate that the patients we measured were not yet, or if then only partially back to work (Lidal et al., 2007) or worked rather from home instead of having a working space away from home. Equivalence of VEL could be shown in all in- and out-patients, suggesting that measurements can be taken on any day of the week to reliably capture VEL. However, when examining individual stages of the in-patient rehabilitation, at stage VA as well as at A III, no equivalence could be shown. In the latter stage, patients showed a higher VEL during the week than on the weekends, which might be due to the integration of sports activities into their therapy schedule, as already shown for ambulatory SCI patients (Franz et al., 2018). The result found for the stage VA is based on only a limited number of observations as most of these patients do not wheel actively, and thus has to be taken with care.

4.5.4 Comparison to literature

Our results for the reliabilities of wheeling-related metrics in the out-patients are in line with literature, proposing up to one week of measuring wheeling-related PA in wheelchair-dependent chronic SCI patients (Sonenblum et al., 2012b). For AC as well as PA intensity times (SED, LPA, and MVPA), we can only compare our results to those of the able-bodied population. Single-day reliability for AC was found to be moderate in able-bodied individuals (Aadland and

Ylvisaker, 2015), which is consistent with our results in the out-patients. Similarly, single-day reliabilities for SED and MVPA are moderate and comparable to our results (Aadland and Ylvisaker, 2015; Falck et al., 2017). In contrast to a low single-day reliability found in our study, a good single-day reliability for LPA has been reported in the able-bodied population (Aadland and Ylvisaker, 2015). This low single-day reliability happens to be distinctive to the wheelchair-dependent SCI population, and thus should not be compared to the able-bodied population. To the best of our knowledge, this is the first work to analyze the reliability of physical activity metrics in the in-patient setting and thus no comparable data is available.

4.5.5 Choice of accelerometer cut-points

Cut-off points are commonly used to define intensity levels and were established in previous studies for the healthy population (Gorman et al., 2014; Kim et al., 2012) and for stroke survivors (Mattlage et al., 2015). However, appropriate cut-off values depend on populations and type of wearable sensors used (Lee and Shiroma, 2014). Furthermore, changes in those cut-off values directly influence the metrics of intensity levels (Loprinzi et al., 2012). Therefore, we defined cut-off values specific for our population of interest and for the wearable sensor used in this study. We calculated our cut-off points based on indirect calorimetry values as commonly done in the field (Gorman et al., 2014; Kim et al., 2012; Mattlage et al., 2015; Lee and Shiroma, 2014; Loprinzi et al., 2012). Transferring our results to methodologies using different accelerometer cut-off points has to be done carefully, as the influence of the cut-off points on the reliability is unknown, and reliability values might change.

4.5.6 Study Limitations

We would like to emphasize three main limitations of our study. The first one is the moderate sample size particularly in the very acute stage. Sample size is often a problem in SCI research. Especially in very acute stages recruitment of the patients and measuring these is challenging. In reliability studies, low sample size results in larger confidence intervals, making the interpretation of the results more difficult. Nevertheless, our sample size is reasonable if compared to other studies in the SCI population. A further limitation is recording for only three days with the sensors attached to the wrists. Especially in tetraplegic patients, there is a risk of pressure sores caused by wearing the sensor straps for too long. Thus, a longer measurement time would expose the patients to an increased risk of damage to the skin. Furthermore, compliance decreases with increased number of measurement days. This limitation might result in larger confidence intervals. A sample size calculation was conducted. Assuming an acceptable confidence interval width of 0.2, our sample sizes in the inpatient-setting are sufficient. In the outpatient setting, higher sample sizes would be required to make more precise statements. The problem of large confidence intervals in reliability studies has been addressed previously (Wolak et al., 2012). This issue can be resolved by either increasing the number of subjects or the number of measurement days, and should be considered for further studies. One limitation in studies using wearable sensors in general are possible behavioral reactions, i.e., subjects could alter their behavior because of the knowledge of being measured. Conflicting statements about the amount of reactivity have been made in literature (Vanhelst et al., 2017; Baumann et al., 2018). However, the accuracy of PA measures based on wearable sensors is higher than the accuracy of the conventional questionnaires (Bandmann, 2008; Giggins et al., 2017) and thus better suitable to estimate PA levels. Lastly, PA intensity levels were estimated from activity counts based on a previous study. Dedicated algorithms for the direct estimation of energy expenditure (Popp et al., 2018; Nightingale et al., 2017) or direct measurements of energy expenditure might lead to slightly altered results, but the latter is very challenging to perform especially with acute patients due to the required equipment and the extensive protocol including standardized food intake and calibration phases.

4.6 Conclusion

We conclude that single-day reliabilities of metrics to capture PA in acute and chronic wheelchair-dependent SCI patients vary considerably depending on the clinical setting. With increasing functional recovery of the patients, metrics of movement quantity tend to become less reliable, whereas metrics of movement quality become more reliable. Depending on the specific metrics, 2 days are required on average to capture PA reliably in in-patients, whereas 3 days are required for out-patients. Furthermore, we suggest using AC only as a rather general measure for assessing the overall PA level of patients, and only in combination with more detailed metrics, e.g. PA intensity levels and wheeling-related metrics. This avoids a possible loss of information about the variability of PA during a whole day. Our results are based on a reasonable sample size for this population and thus provide robust recommendations on how to design clinical studies investigating PA as a primary outcome, or as a confounder in intervention studies in order to better evaluate the actual intervention effect.

Clinical insights Part II

5 Monitoring Upper-Limb Recovery After Cervical Spinal Cord Injury: Insights Beyond Assessment Scores

Michael Brogioli*, Sophie Schneider*, Werner L. Popp, Urs Albisser, Anne K. Brust, Inge-Marie Velstra, Roger Gassert, Armin Curt, Michelle L. Starkey

Frontiers in Neurology, 2016

The authors would like to thank the following persons (in alphabetical order): Karin Akermann, Annika Ballmer, Deborah Bergman, Isabelle Debecker, Dr. Angela Frotzler, Dr. med. Margret Hund, Dr. med. Kerstin Hug, Dr. Kaspar Leuenberger, and Nils Reiner.

This work was supported by the Clinical Research Priority Program (CRPP) for Neuro-Rehab of the University of Zurich, by the International Foundation for Research in Paraplegia (IRP), by the Swiss Paraplegic Foundation (SPS), and by the ETH Zurich Foundation.

* These authors contributed equally to the work.

Final publication is available from `https://doi.org/10.3389/fneur.2016.00142`.

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 novel measurement tools that are 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 for 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 the 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 those for 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 due to functional compensation and/or 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 have been shown to improve forelimb function and enhance plastic sprouting of undamaged corticospinal tract fibres in adult rats (Brus-Ramer et al., 2007; Maier et al., 2008; Carmel et al., 2010; Starkey et al., 2011; Song et al., 2016).

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 (Spooren et al., 2009; Lu et al., 2015). 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 both training characteristics (e.g. frequency, duration or intensity) and 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 associated exclusively 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 a feasible solution for measuring total UL activity. Wearable sensors provide objective and continuous measures so that 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, 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, 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 Tab. 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 at 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.

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

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.

Assessment of Strength, Sensibility and Prehension (GRASSP) (Kalsi-Ryan et al., 2012b; 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.

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 extremitiy 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 5.1). 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.

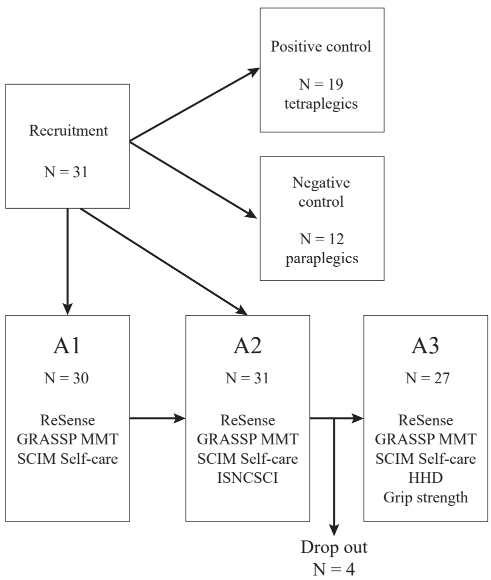

Figure 5.1 – Flow diagram depicting the study groups and the measurement performed in each time frame. Stage A1: 1 month after injury; Stage A2: 3 months after injury; Stage A3: 6 months after injury; GRASSP: Graded and Redefined Assessment of Strength, Sensibility and Prehension; SCIM: Spinal Cord Independence Measure; HHD: hand-held dynamometer.

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 (Asghar and Saleh, 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 over the three time frames for paraplegic and tetraplegic patients are summarized in Table 5.2.

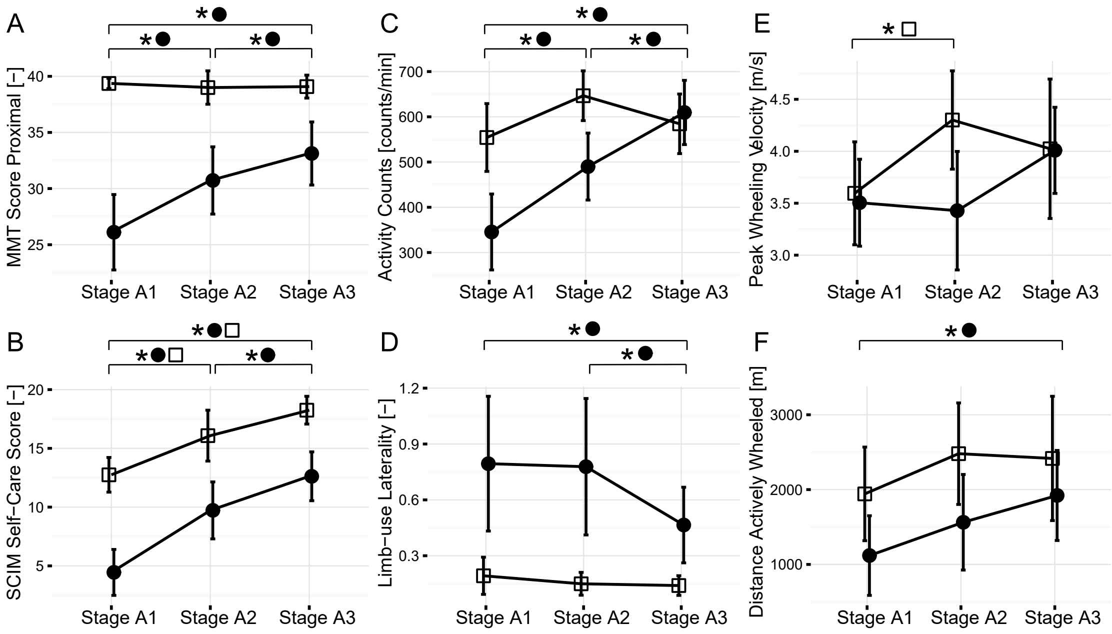

Figure 5.2 – Changes in sensor-based and clinical measures over time among a group of paraplegic and tetraplegic patients. Lines represent the means, error bars represent the 95% confidence interval. Paraplegic patients are displayed with empty squares whereas tetraplegic patients are displayed with 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	Group	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)	Non-lateralized	0.159 (0.122)
	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)		0.226 (0.138)
	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)		0.203 (0.093)
	Significant pairwise comparisons (p <.05*)	ns	t_1 - t_2, t_1 - t_3	ns	ns	t_1 - t_2	ns		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)	Lateralized	1.344 (0.173)
	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)		0.890 (0.194)
	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)		0.453 (0.130)
	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		t_1 - t_2, 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; t_1, one month; t_2, three months; t_3, six months. Results are displayed as estimates ± standard errors. * Bonferroni corrected.

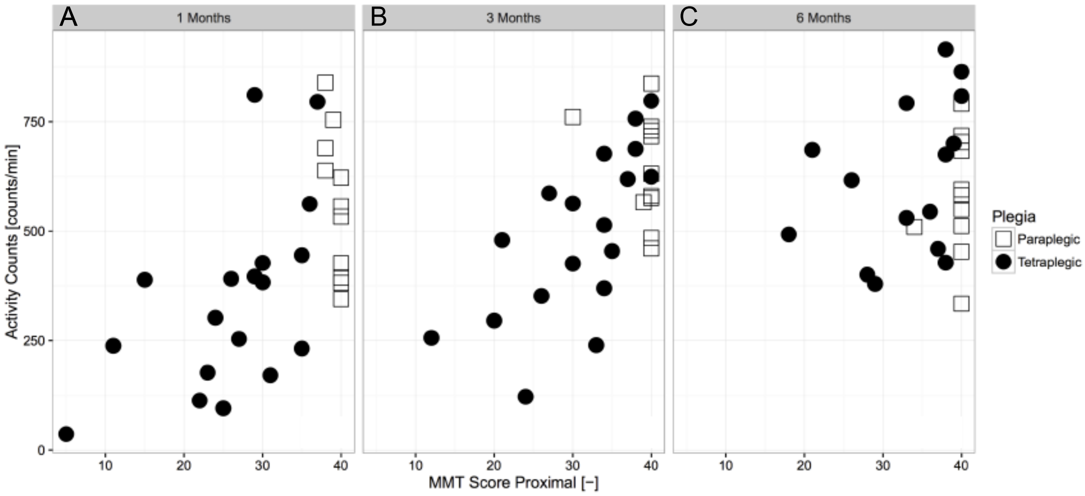

Figure 5.3 – Cross-sectional relationship between proximal muscle function and overall upper-limb activity across time. Paraplegic patients are displayed with empty squares whereas tetraplegic patients are displayed with full circles. The relationship at one (Panel A) and three months (Panel B) after 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 (Panel C) after injury (N = 27, P = 0.178, r = 0.273, Spearman correlation). MMT = manual muscle testing.

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 the relationship was not significant at six months after injury (P = 0.178, r = 0.273, Spearman correlation).

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 remained unchanged 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 seemed 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 was 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 cohort of lateralized subjects. In this case lateralized subjects were defined as those subjects whose laterality values at one month were more than two standard deviations of 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 counterparts 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) compared to leisure time (536.02 ± 122.16 and 514.47 ± 180.92 counts/min). The increase in counts 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, $t(10) = 2.261$, $p < 0.05$).

Next, to determine if the similarity in UL activity between groups was due to similar motor impairments, comparisons between the 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 and tetraplegic subjects revealed that the HHD scores of antigravity muscles were equal between paraplegic (mean rank elbow flexors = 17.45, mean rank shoulder flexors = 17.00) and 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 =

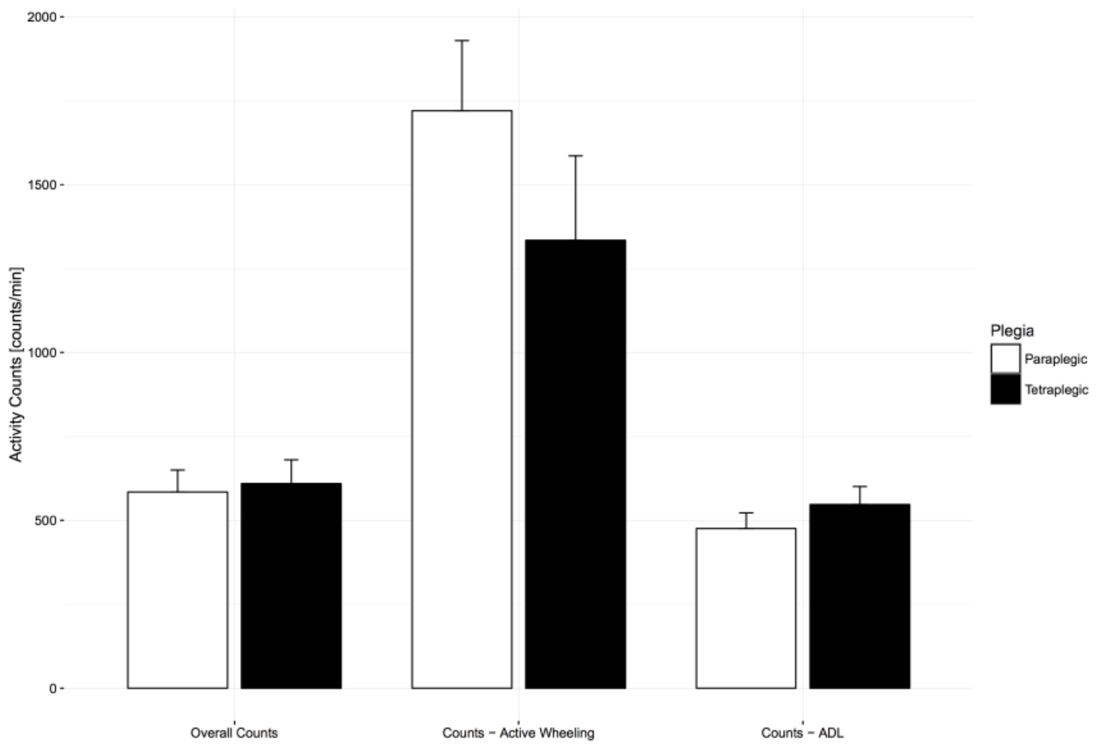

Figure 5.4 – Comparison of activity count (AC) categories between paraplegic and tetraplegic patients six months after injury. Bars represent the means, error bars represent the 95% confidence interval. Paraplegic patients are displayed in white whereas tetraplegic patients are displayed black. Differences are not statistically significant. ADL – activities of daily living.

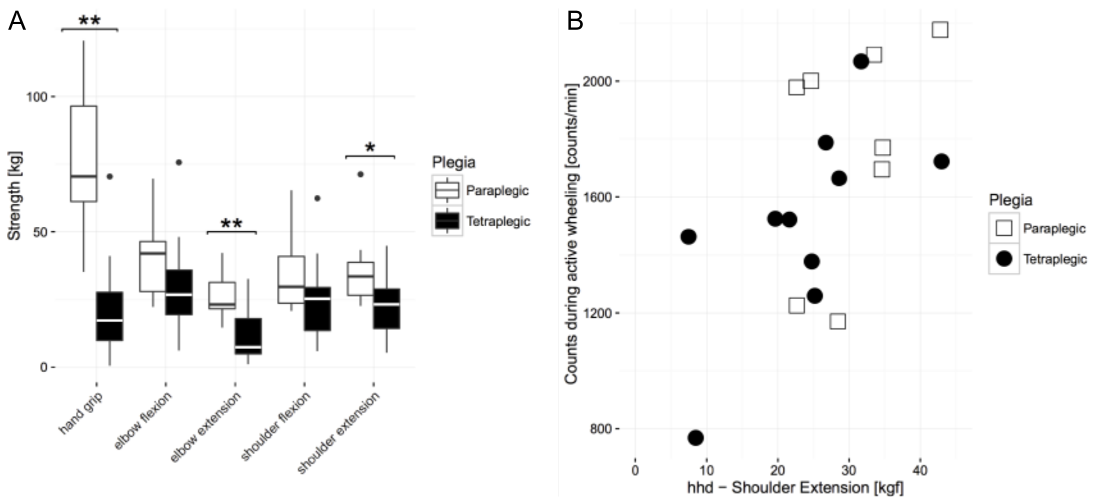

Figure 5.5 – Comparison of strength values between paraplegic and tetraplegic patients six months after injury. Panel A. The boxplot shows the median of each strength measurement. The bottom represents the first quartile whereas the top represents the third quartile. The whisker is 1.5 times the interquartile 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.

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 lower 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).

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 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 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 and revealed 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).

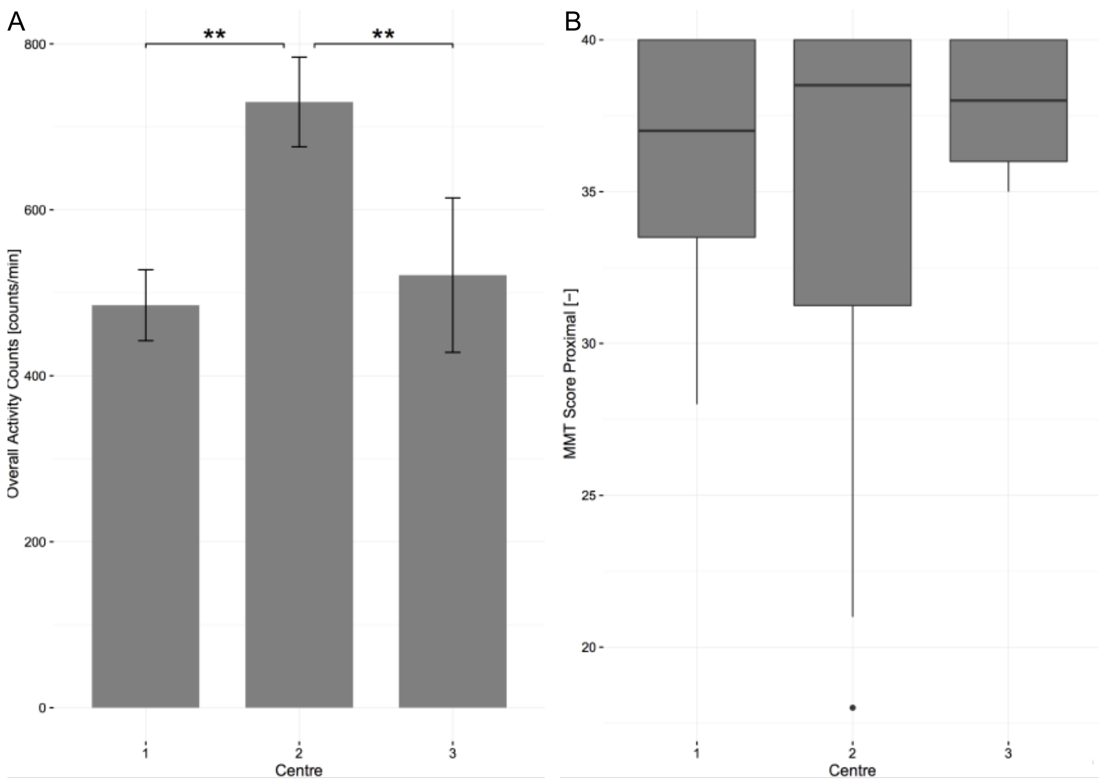

Figure 5.6 – Centre differences in overall activity counts and in scores of proximal muscle strength at 6 months after injury for all patients. Panel A. The bars represent the means of overall activity counts, error bars represent the 95% confidence interval. Significant differences are represented with 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 show that subjects with cervical SCI significantly increase the overall amount of UL activity compared to their thoracic injured counterparts that did not experience significant changes. Moreover, six months after injury, subjects 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 kinematic 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.; submitted manuscript) 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 have shown that proximal muscle function was strongly related to overall AC during acute inpatient rehabilitation (Brogioli et. al.; submitted manuscript). 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 (21), 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 differences 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 cofounders, 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 Intensity of physical activity during therapy and leisure time in the rehabilitation of acute spinal cord injury

Sophie Schneider, Werner L. Popp, László Demkó, Michael Brogioli, Urs Albisser, Isabelle Debecker, Inge-Marie Velstra, Rainer Abel, Roger Gassert, and Armin Curt

submitted to *Neurorehabilitation and Neural Repair*.

The authors would like to thank the following persons for their help with the study setup, recruitment, data acquisition, and interpretation of the results in alphabetical order: Karin Akermann, Anne K. Brust, Janina Burschka, Dr. Angela Frotzler, Fabiene Hasler, Dr. Kerstin Hug, Dr. Margret Hund, Dr. Michelle Starkey, and Theresa Stöckert.

This work was funded by the International Foundation for Research in Paraplegia (IRP, project number: P 157), the Clinical Research Priority Program (CRPP) for Neuro-Rehab of the University of Zurich, the Swiss Paraplegic Foundation (SPS), Wings for Life (project number: 143), the ETH Zurich Foundation in collaboration with Hocoma AG, a HMZ seed project (project title: ZurichMOVE: Wearable sensors to monitor movement quality and mobility in health care) funded by the University of Zurich and the ETH Zurich Foundation, and the Swiss State Secretariat for Education, Research and Innovation (SERI) under contract number 15.0255 (Horizon 2020, 681094).

6.1 Abstract

Background. Duration, intensity, task-specificity and timing of physical activity (PA) are assumed to affect the extent of functional recovery after acute spinal cord injury (SCI). Also, levels of PA during leisure time in addition to structured therapy sessions are considered to influence recovery and therefore require an objective assessment of PA during both, leisure time and therapy sessions.

Objective. To objectively and unobtrusively quantify levels of PA during therapy sessions and leisure time across patients with different levels of cervical and thoracic/lumbar SCI, and to relate PA to the level of physical independence.

Methods. In total, PA was monitored in 42 acute SCI patients with wearable sensors fitted to both wrists, the wheelchair and/or both ankles for three consecutive days for up to four time points (2 weeks, 1 months, 3 months, and 6 months after injury) during inpatient rehabilitation. Activity counts and time spent in different levels of PA intensity (i.e., resting, sedentary, low, and moderate-vigorous) were assessed.

Results. Levels of PA were higher in therapy sessions compared to leisure times and increased during the course of rehabilitation. The level of independence (SCIM self-care score) was strongly related to the metrics of overall physical activity.

Conclusion. The increase of PA over time is strongly related to a gain of independence achieved during the rehabilitation. Future studies are needed to investigate the causality between PA and independence. Moderate-vigorous intensity is crucial to be assessed in future studies investigating PA as a sensitive marker for changes in PA.

6.2 Introduction

Functional recovery after a spinal cord injury (SCI) is limited, and assumed to be mainly driven by mechanisms of compensation and adjustments rather than repair mechanisms (Curt et al., 2008). However, there is evidence that physical activity (PA) can modulate spinal cord and brain plasticity, improving functional outcomes (Jones et al., 2012; Behrman et al., 2017; Quel de Oliveira et al., 2017; Lynskey et al., 2008). A study investigating the longitudinal changes of PA during rehabilitation after SCI showed increasing PA with progressing rehabilitation (van den Berg-Emons et al., 2008). While the results of this study can help to increase the understanding of the interdependence between functional recovery and the amount of PA, the latter was only described in terms of duration. However, there is evidence from preclinical and human SCI studies that not only the duration of PA, but also the intensity, task-specificity, and the timing of the PA intervention (Basso and Lang, 2017) shapes the amount of functional recovery (Onifer et al., 2011) While past research mainly focused on the effect of specific controlled interventions, (Foy et al., 2011; Franz et al., 2018) the potential effect of 'self-training' outside of the structured rehabilitative therapy sessions has been neglected. In fact, preclinical studies showed a positive effect of "self-training" during daily life in rats (Starkey et al., 2014), which can be assumed to have important implications for human spinal cord injury as well. To assess leisure time PA, questionnaires like the Physical Activity Recall Assessment for People with Spinal Cord Injury (PARA-SCI Latimer et al., 2006) are commonly used in the field. So far, only one study by Zbogar et al. (Zbogar et al., 2016) assessed leisure time PA, but only at admission and discharge from inpatient rehabilitation by administering the PARA-SCI. They also conducted accelerometer measurements, but only calculated activity counts (AC) to quantify changes of PA. Therefore, detailed insights by increasing the temporal resolution to better evaluate PA changes during rehabilitation progress and by distinguishing both leisure time and therapy sessions have been missing. Additionally, more refined analyses beyond AC will be essential to better reveal the impact of PA as a potential confounder in clinical interventional studies, and to identify points of action, i.e. leisure time or therapy sessions, to increase PA during rehabilitation in general. The aim of this study was a) to quantify and study changes in PA based on AC and intensity levels related to energy expenditure across the continuum of inpatient rehabilitation (i.e. from two weeks after injury to six months after injury), and b) to reveal the relationship between PA changes and levels of impairments as reflected by the level of lesion (i.e. cervical compared to thoracic/lumbar) and the degree of independence.

6.3 Methods

6.3.1 Patients

In total, 42 patients were enrolled in this study. Recruitment and measurements took place in the rehabilitation facilities of the Swiss Paraplegic Centre in Nottwil, Switzerland, the REHAB Basel in Basel, Switzerland, the Clinic Hohe Warte in Bayreuth, Germany, and the Balgrist

University Hospital in Zurich, Switzerland from 2014 until 2018. Inclusion criteria were an acute traumatic or non-traumatic SCI and admission within 4 weeks after incidence. All levels of neurological level of injury (NLI) and completeness of the lesion (ASIA Impairment Scale, AIS) were admitted to the study. Exclusion criteria were any neurological disease other than SCI, and comorbidities (like psychiatric or metabolic disorders) affecting rehabilitation and outcome measures. Patients signed a written consent before participating in the study in accordance with the Declaration of Helsinki. The study was approved by the ethical committees of the cantons of Zurich (KEK-ZH118 no. 2013-0202), Lucerne (EK 13018), Basel (EK 34313) in Switzerland, and the state of Bavaria (EK 16018) in Germany, and is registered on clinicaltrials.gov (Identifier: NCT02098122).

6.3.2 Measurement device

To measure PA, inertial measurement units were used. The ReSense sensor (Leuenberger and Gassert, 2011) was used from 2014 until 2017. It comprises a 3D accelerometer, a 3D gyroscope, a 3D magnetometer and an altimeter. Due to limited battery capacity, the sensors had to be exchanged once a day. From 2018, a successor of the ReSense was used (www.zurichmove.com), which allowed to continuously monitor patients for three days without exchanging the sensor. Note, that the successor has the same sensing capabilities as the ReSense sensor (e.g., difference in measured acceleration < 1%).

6.3.3 Measurement protocol

Patients were recruited either 2 weeks or 4 weeks after injury and measured for up to 4 time points during inpatient rehabilitation according to the standardized protocol of the European Multicenter Study about SCI (EMSCI). Measurement time points were: very acute (VA, 0-15 days after injury), acute 1 (A1, 16 – 40 days after injury), acute 2 (A2, 70 – 98 days after injury), and acute 3 (A3, 150 – 186 days after injury) (Figure 6.1). For all patients, at least measurement stages A1 and A2 were available. Due to later recruitment and/or early discharge from the inpatient rehabilitation, not all patients could be included in the analysis of stages VA and A3. At each time point measured, patients were equipped with a set of sensors and measured for 3 consecutive days. Sensors were attached to the right wheel of the wheelchair, both wrists, and both ankles for subjects with some voluntary lower-limb control. Patients were instructed to wear the sensors for 72 hours and remove them for showering or swimming activities only. Additionally, the NLI and the AIS grade using the International Standard for Neurological Classification of Spinal Cord Injury (ISNCSCI), the level of independence using the Spinal Cord Independence Measure III (SCIM, Catz et al., 1997), demographics (i.e., age and gender) were assessed, and the therapy schedules of each patient were collected.

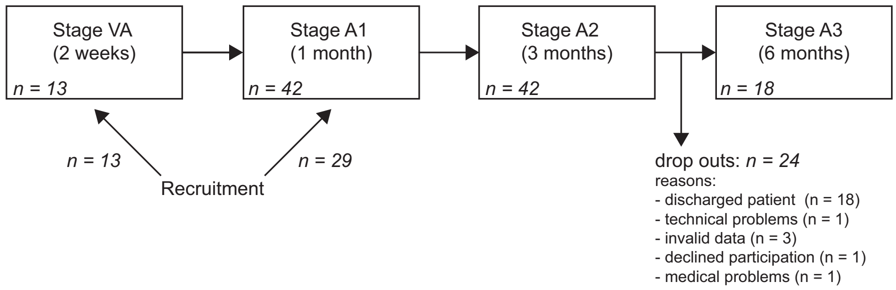

Figure 6.1 – Measurement protocol. Recruitment took place at stage VA (two weeks after injury) and A1 (one month after injury). Patients were measured during the subsequent stages, i.e., A2 (three months after injury) and A3 (six months after injury) during their stay in rehabilitation until discharge.

6.3.4 Data analysis and statistics

Pre-Processing

The raw sensor data were resampled to assure a constant sampling rate of 50Hz and were temporally aligned. Sensor data were then labeled for non-wear time using a semi-automatic algorithm described elsewhere (Schneider et al., 2018). In addition, the therapy sessions overlapping with the sensor measurements were digitalized, and the sensor data were labeled with 'active therapy' and 'leisure time', accordingly. Outcome metrics described below were calculated for both, therapy sessions and leisure time.

Outcome metrics

Outcome metrics were calculated for days with at least 13 hours of wear-time and for time points with at least one valid day according to previous work (Schneider et al., 2018; Herrmann et al., 2014). Only the awake-time of patients was considered, defining 'awake' as the time interval between 7am and 11pm. The metrics of interest were activity counts (AC) and time spent in resting (REST), sedentary (SED), low (LPA), and moderate-to-vigorous (MVPA) intensity. Overall PA was estimated from the AC of the upper limbs only. AC of the lower limbs were excluded from the calculation of AC to include all 42 subjects and permit comparisons to previous results (Brogioli et al., 2016c). AC were calculated by integrating the acceleration magnitude in epochs of 1 min and were then averaged over the measured days. Time spent in REST, SED, LPA, and MVPA were calculated in 15s epochs using cut-off values of AC to avoid underestimation, especially of MVPA, (Gabriel et al., 2010; Logan et al., 2016) and are presented in minutes per hour. These cut-off values were defined in a previous study using the estimated energy expenditure in SCI patients (Popp et al., 2018). Different thresholds were defined for wheelchair users based on the wrist sensors only, and ambulatory patients based on the wrist and ankle sensors. REST corresponds to metabolic equivalent of task values <1.1, SED between 1.1 and 1.5, LPA between 1.5 and 3 and MVPA > 3 (Pate et al., 2008; Ainsworth et al., 2011). Time spent in REST, SED, LPA, and MVPA were summed up over the valid days per measurement and normalized to 1h units of therapy session or leisure time. For these metrics, ambulatory patients without ankle sensors had to be excluded, which resulted in a reduced set of 33 patients.

Postprocessing of the sensor data and calculation of the outcome metrics was performed in MATLAB 2017b (The MathWorks, Natick, USA).

Independent variables and covariates

The three main independent variables used for the analysis were the time point in terms of rehabilitation stage ('VA', 'A1', 'A2', and 'A3') as a categorical factor, the group in terms of NLI ('thoracic/lumbar' for lesion levels from Th2 to S2 and 'cervical' for lesion levels from C1 to Th1) as a categorical factor, and therapy ('leisure time' and 'active therapy') as a categorical factor. 'Active therapy' is comprised of occupational therapy, physical therapy, medical training therapy, sports therapy, individual training, MOTOmed®(RECK-Technik GmbH & Co. KG, Germany) movement therapy, robot-assisted therapy for upper and lower limbs (e.g., Armeo®Spring (Hocoma AG, Switzerland), Free Levitation for Overground Active Training (Vallery et al., 2013), and Lokomat®training (Hocoma AG, Switzerland)), Feldenkrais training, and group trainings.

The patients' age at the time of measurement in years as a continuous covariate, the gender ('female' and 'male') as a categorical factor, the rehabilitation center ('1', '2', '3', and '4') as a categorical factor, and the subscale 'self-care' of the SCIM III (question 1 to 8) as a continuous covariate (maximal score of 20) served as additional covariates. The subscale 'mobility' (questions 12 to 17) of the SCIM III was binarized into a categorical factor defined by the ability to walk, i.e. by an 'ambulatory' class and a 'wheelchair-dependent' class to avoid collinearity in the conducted linear mixed models, and to simplify interpretation.

Statistical analysis

Mean and standard deviation were used for a descriptive summary of the continuous variables, and frequency was used for the categorical variables, respectively. A square-root transform was applied to all outcome metrics to ensure normality of the error residuals and to remove their heteroscedasticity. In the first analysis, linear mixed effect models were used to assess the effect of therapy (leisure time and active therapy), stage ('VA', 'A1', 'A2', and 'A3'), and group (cervical and thoracic/lumbar) on AC and on different intensity levels (REST, SED, LPA, and MVPA) by constructing individual models for each outcome metric separately. Random intercepts for individual patients and random slopes for the therapy were defined to account for individual differences. A restricted maximum likelihood (REML) estimator was used to fit the models. These models are referred to as 'basic' models. In the subsequent analysis, we additionally controlled for the fixed effects of the SCIM self-care score, mobility, gender, age, and center. These models are referred to as 'full' models. The constructed 'basic' models aimed to describe the observed changes in PA intensity levels over the course of inpatient rehabilitation, between patients with a thoracic/lumbar and a cervical lesion, and between leisure time and active therapy sessions. The constructed 'full' models aimed at explaining these changes by identifying additional factors modulating them. Significance of effects was investigated using ANOVA with the Satterthwaite approximation for p-values (Luke, 2017). Significance of a possible stage and group-interaction was tested for each outcome metric and remained in the model if statistically significant. Furthermore, interaction effects between therapy and all covariates were explored and remained in the model if statistically significant. In the case of significant effects, post-hoc analysis based on the estimated marginal means was used for the final models including all covariates and significant interactions. Tukey multiple-comparison correction was applied for pairwise comparisons, while multivariate testing for the consecutive comparisons. The reported estimated marginal means were back-transformed after all analyses, and data on the original scale were used for plotting to facilitate interpretation. Significance levels were set to $\alpha < 0.05$. Statistical analysis was performed in RStudio(RStudio Team 2015), utilizing the packages lme4 and emmeans.

6.4 Results

6.4.1 Patient characteristics

In total, 29 of the enrolled 42 patients were tetraplegic and showed a mean age of 49.3 ± 17.8 years. NLI ranged from C1 to L2 (C1-C4: 11, C5-C8: 18, Th1-Th5: 2, Th6-Th12: 7, L1-L2: 4 patients) and AIS levels from A to D (A: 10, B: 7, C: 10, D: 15 patients) at the time of enrollment (descriptive summary in Table 6.1). Patients received active therapy for an average of 1.45 h (standard deviation (SD): 0.53h) in stage VA, 2.18 h (SD: 0.74 h) in stage A1, 2.65 h (SD: 0.85 h) in stage A2, and 2.74 h (SD:1.01 h) in stage A3 per day. Patients had leisure time on average for 12.69 h (SD: 1.17h) in stage VA, 12.33 h (SD: 1.21 h) in stage A1, 11.54 h (SD:1.14 h) in stage A2, and 11.46 h (SD: 1.07 h) in stage A3 per day while being awake (i.e., 16h). Patients had a mean of 2.2 valid days of recordings (SD: 0.76 days) and wore the sensors for an average of 14.8 h (SD: 0.74h) per day.

		Stage VA				Stage A1				Stage A2				Stage A3			
		thoracic/lumbar		cervical		thoracic/lumbar		cervical		thoracic/lumbar		cervical		thoracic/lumbar		cervical	
		all	red	all	red	all	red	all	red	all	red	all	red	all	red	all	red
		n = 5	n = 4	n = 8	n = 6	n = 13	n = 10	n = 29	n = 23	n = 14	n = 11	n = 28	n = 22	n = 4	n = 4	n = 14	n = 12
Demographics																	
age	mean (sd)	42.2 (12.4)	45 (10.9)	42.5 (18.2)	40.2 (17.6)	47.1 (17.1)	51.3 (16.6)	50.2 (18.5)	49 (19.5)	47.6 (16.4)	51.5 (15.6)	50.3 (18.9)	49 (19.9)	50.5 (5.2)	50.5 (4.6)	48.1 (18.7)	46.3 (18.9)
female	n (%)	2 (40)	2 (50)	1 (12.5)	0 (0)	5 (38.5)	5 (50)	8 (27.6)	5 (21.7)	6 (42.8)	6 (54.5)	7 (25)	4 (18.2)	3 (75)	3 (75)	3 (21.4)	2 (16.7)
Clinical scores																	
ambulatory	n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3.4)	0 (0)	3 (21.4)	0 (0)	11 (39.3)	5 (22.7)	0 (0)	0 (0)	2 (14.2)	0 (0)
SCIM score	mean (sd)	8.8 (3.6)	8.8 (3.7)	1.13 (1.89)	1.5 (1.9)	12.8 (3.1)	12.3 (2.8)	4.3 (4.1)	4.2 (4.1)	16.5 (4.2)	15.5 (4.2)	9.3 (6.7)	8.1 (6.2)	18.5 (1.9)	18.5 (1.7)	9 (5.2)	7.8 (4.3)
SCIM score	median (iqr)	9 (4)	8 (5.3)	0 (1.5)	0.5 (3)	13 (5)	12 (5)	4 (5)	4 (5)	18 (5)	18 (8)	9.5 (10.25)	7.5 (12)	19 (2.5)	19 (2.5)	8 (6)	8.0 (3.5)
Center																	
Center1	n (%)	3 (60)	2 (50)	6 (75)	5 (83.3)	7 (53.8)	4 (40)	14 (48.3)	12 (52.2)	7 (50.0)	4 (36.3)	14 (50)	12 (54.5)	1 (25)	1 (25)	8 (57.1)	6 (50)
Center2	n (%)	0 (0)	0 (0)	0 (0)	0 (0)	1 (7.7)	1 (10)	9 (31.0)	7 (30.4)	2 (14.3)	2 (18.2)	8 (28.6)	6 (27.3)	2 (50)	2 (50)	5 (35.7)	5 (41.7)
Center3	n (%)	0 (0)	0 (0)	1 (12.5)	0 (0)	3 (23.1)	3 (30)	2 (6.9)	0 (0)	3 (21.4)	3 (27.3)	2 (7.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Center4	n (%)	2 (40)	2 (50)	1 (12.5)	1 (16.7)	2 (15.4)	2 (20)	4 (13.8)	4 (17.4)	2 (14.3)	2 (18.2)	4 (14.3)	4 (18.2)	1 (25)	1 (25)	1 (7.2)	1 (8.3)
PA LEVELS																	
active therapy																	
AC	mean (sd)	462.6 (416.2)		176.1 (85.7)		788.5 (321.7)		386.5 (194.8)		954. (238.9)		616.3 (288.3)		830.3 (227.6)		773.1 (368.8)	
REST	mean (sd)	21.8 (12.5)		26.9 (10.8)		13.5 (10)		18.3 (11.1)		10.5 (3.3)		9 (5.5)		11 (2.6)		8.5 (6.5)	
SED	mean (sd)	9.9 (3.1)		15.9 (5.5)		10.4 (3.3)		14.3 (3.6)		10.1 (2.4)		17.8 (8.0)		11.0 (4.2)		11.8 (5.7)	
LPA	mean (sd)	25.9 (10.9)		17.1 (7.4)		32.4 (9.5)		26.5 (10.2)		35.0 (3.1)		30.6 (10.3)		33.0 (2.5)		36.6 (10.5)	
MVPA	mean (sd)	2.4 (4.0)		0.1 (0.2)		3.7 (3.2)		0.8 (1.3)		4.4 (2.8)		2.6 (3.1)		5.0 (2.6)		3.0 (3.2)	
leisure time																	
AC	mean (sd)	350.7 (158.6)		112.9 (57.3)		450.1 (164)		248.6 (201)		530.4 (138.7)		359.7 (181.7)		646.8 (209.3)		423.6 (189.8)	
REST	mean (sd)	27.7 (9.4)		37.7 (9.5)		23.9 (7.8)		33.4 (11.9)		20.2 (5.9)		25.6 (11.0)		20.7 (7.4)		23.2 (7.3)	
SED	mean (sd)	9.7 (2.1)		10.2 (5.0)		10.1 (2.8)		9.6 (2.8)		10.7 (2.0)		14.6 (7.5)		9.5 (1.4)		9.7 (3.0)	
LPA	mean (sd)	21.6 (7.9)		12.1 (5.4)		24.9 (9.5)		16.7 (9.5)		27.1 (4.6)		19.1 (9.7)		25.8 (4.8)		26.3 (7.9)	
MVPA	mean (sd)	1.0 (1.2)		0 (0)		1.1 (1.0)		0.3 (0.7)		2.0 (1.5)		0.7 (0.8)		4.0 (2.5)		0.9 (1.0)	

Table 6.1 – Demographics and descriptive statistics. Descriptive statistics for activity counts (AC) were calculated based on the complete set of 42 patients (Stage VA: 13, Stage A1: 42, Stage A2: 42, Stage A3: 18 patients), and for time spent in resting (REST), sedentary (SED), low (LPA), and moderate-to-vigorous (MVPA) intensity based on the reduced set of 33 patients (Stage VA: 10, Stage A1: 33, Stage A2: 33, Stage A3: 16 patients).

6.4.2 Longitudinal changes of PA levels

In the analysis of the 'basic' models we investigated the effects of therapy, stage, and group on all outcome metrics (Figure 6.2). Statistics of the linear mixed models are reported in Table 6.2. Post-hoc comparisons and estimated marginal means and trends are reported in Supplementary tables B.1 to B.5. Analyses revealed a significant main effect of stage on SED and MVPA, with increasing values for SED from Stage A1 and A2 and decreasing values from Stage A2 to A3, and increasing values for MVPA over all stages. Furthermore, there were significant interactions between stage and group for AC (Figure 6.2A), REST, and LPA. AC differed significantly between groups at stages VA, A1, and A2, but reached similar levels at stage A3. Therapy was identified as a significant main effect on LPA and MVPA, with higher values of LPA and MVPA during active therapy compared to leisure time (Figure 6.2D). Additionally, significant interactions with therapy were found for AC (therapy*stage, Figure 6.2B), REST (therapy*stage and therapy*group), and SED (therapy*group). A significant main effect of group was found on MVPA, with higher values for patients with a thoracic/lumbar lesion compared to a cervical lesion at all rehabilitation stages (Figure 6.2C).

Next, we investigated which additional factors had an influence on the PA levels (Figure 6.3 and Figure 6.4). We found a significant main effect of the SCIM self-care score on AC and LPA (Figure 6.4A and 6.4B) with increasing AC and LPA for increasing values of SCIM self-care. Furthermore, the SCIM self-care score was included in a significant interaction with therapy for SED and MVPA (Figure 6.4D) with increasing SED in leisure time and decreasing SED in active therapies and increasing MVPA for both leisure time and active therapies for increasing SCIM self-care scores. Moreover, mobility had a significant influence on SED, LPA (Figure 6.3C), and MVPA (Figure 6.3F), with higher SED, lower LPA, and higher MVPA in ambulatory patients compared to wheelchair-dependent patients. Age had a significant main effect on AC, REST, and MVPA, with decreasing AC, increasing REST and decreasing MVPA with increasing age, and was included in a significant interaction with therapy on SED, with higher SED for both leisure time and active therapy with increasing age. A significant main effect of center was found on AC, REST, and MVPA. Lastly, a significant main effect of gender on MVPA, with higher levels in female than in male, and a significant interaction between gender and therapy on AC was revealed, with higher values for female in leisure time, but lower values during active therapies. Figure 6.3A and 6.3D illustrate the residual effect of stage and group on LPA and MVPA after correcting for the effects of SCIM self-care, mobility, age, gender, therapy, and center. Figure 6.3B and 6.3E illustrate the residual effect of therapy on LPA and MVPA after correcting for the effects of SCIM self-care, mobility, age, gender, group, stage, and center.

6.5 Discussion

This study focused on investigating the changes in PA intensity levels longitudinally over the time course of inpatient rehabilitation in patients suffering from acute spinal cord injury. Emphasis was put on the time course and extent of PA levels between therapy sessions and

			AC		REST		SED		LPA		MVPA	
			F value	p value	F value	p value	F value	p value	F value	p value	F value	p value
'basic' models	Fixed effects											
		Stage	55.59	< 0.001	33.72	< 0.001	6.27	0.001	15.88	< 0.001	27.89	< 0.001
		Group	8.37	0.005	0.18	0.674	7.82	0.008	0.38	0.540	14.38	< 0.001
		Therapy	106.61	< 0.001	176.59	< 0.001	6.36	0.017	116.70	< 0.001	36.44	< 0.001
		Stage*Group	3.03	0.031	5.86	0.001	a		3.65	0.014	a	
		Stage*Therapy	3.32	0.021	3.51	0.017	a		a		a	
		Group* Therapy	a		8.12	0.005	6.87	0.013	a		a	
	Random effects											
	variance	subject (intercept)	18.63		0.58		0.09		0.82		0.14	
	variance	subject(active therapy)	0.28		0.00		0.07		0.02		0.05	
	variance	residual	10.11		0.35		0.23		0.34		0.24	
	Diagnostics											
		marginal R2	0.43		0.52		0.21		0.29		0.35	
		conditional R2	0.81		0.83		0.42		0.77		0.68	
'full' models	Fixed effects											
		Stage	10.34	<0.001	6.62	<0.001	1.88	0.137	7.34	<0.001	3.21	0.025
		Group	0.70	0.404	2.39	0.126	0.06	0.804	1.08	0.301	3.49	0.067
		Therapy	74.11	<0.001	167.13	<0.001	0.07	0.798	153.83	<0.001	2.15	0.147
		SCIM selfcare	44.71	<0.001	17.35	<0.001	5.28	0.024	9.48	0.002	43.13	<0.001
		Mobility	3.76	0.054	0.02	0.886	78.90	<0.001	46.15	<0.001	4.78	0.030
		Sex	1.00	0.325	0.59	0.451	0.95	0.339	0.17	0.684	5.01	0.032
		Age	10.37	0.003	4.81	0.038	0.90	0.352	3.58	0.071	7.14	0.012
		Center	3.98	0.015	3.27	0.037	0.90	0.453	1.54	0.230	3.76	0.019
		Stage*Group	3.29	0.022	5.30	0.002	*a*	*a*	8.29	<0.001	*a*	*a*
		Stage*Therapy	4.38	0.005	4.27	0.006	*a*	*a*	*a*	*a*	*a*	*a*
		Group* Therapy	*a*	*a*	7.77	0.007	*a*	*a*	*a*	*a*	*a*	*a*
		SCIM selfcare*Therapy	a	*a*	*a*	*a*	29.45	<0.001	a	*a*	12.34	<0.001
		Sex*Therapy	8.54	0.004	*a*	*a*	*a*	*a*	*a*	*a*	*a*	*a*
		Age*Therapy	*a*	*a*	*a*	*a*	18.75	<0.001	*a*	*a*	*a*	*a*
	Random effects											
	variance	subject (intercept)	4.17		0.25		0.06		0.51		0.01	
	variance	subject(active therapy)	1.01		0.04		0.01		0.01		0.05	
	variance	residual	9.09		0.33		0.20		0.27		0.18	
	Diagnostics											
		marginal R2	0.70		0.66		0.54		0.53		0.68	
		conditional R2	0.83		0.84		0.63		0.83		0.77	

Table 6.2 – Summary table of the linear mixed model statistics for the 'basic' models and the 'full' models. F and p values are given for all fixed effects and for significant interactions. Non-significant interactions were removed from the models (^{a}). Note that the models for AC were built on all 42 subjects, the models for REST, SED, LPA, and MVPA were built on a reduced set of 33 subjects.

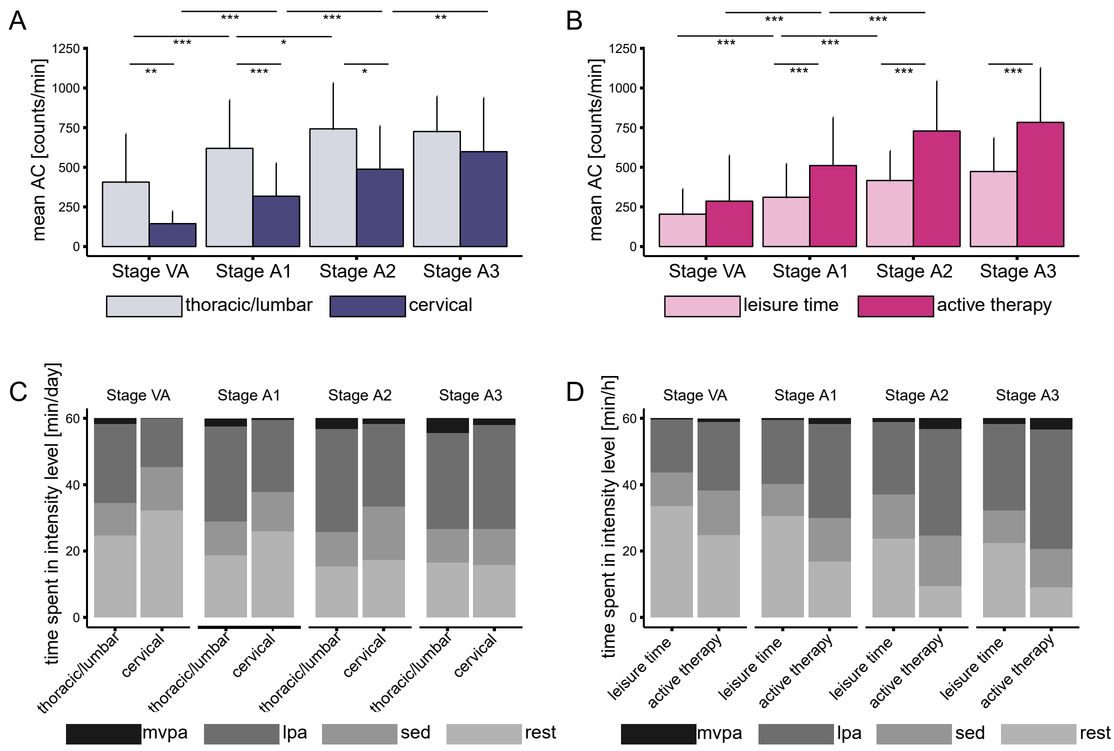

Figure 6.2 – Longitudinal changes of activity counts (AC) and PA intensity levels during the rehabilitation. A-B: Mean AC with standard deviation at 2 weeks (VA), 1 month (A1), 3 months (A2), and 6 months (A3) after injury in thoracic/lumbar patients (light blue) and cervical patients (dark blue) (panel A) and in leisure time (light yellow) and active therapy (dark yellow) (panel B). Plotted is the mean value and the standard deviation (error bars). Significant differences based on the 'basic' linear mixed model were marked with asterisks (*** $p < .001$, ** $p < .01$, * $p < .5$). C-D: Mean minutes spent in resting intensity (REST), sedentary intensity (SED), low intensity (LPA), and moderate-vigorous intensity (MVPA) normalized to one hour in thoracic/lumbar and cervical patients (panel C), as well as in leisure time and active therapy (panel D), respectively. Higher PA intensities are represented by darker grey tones.

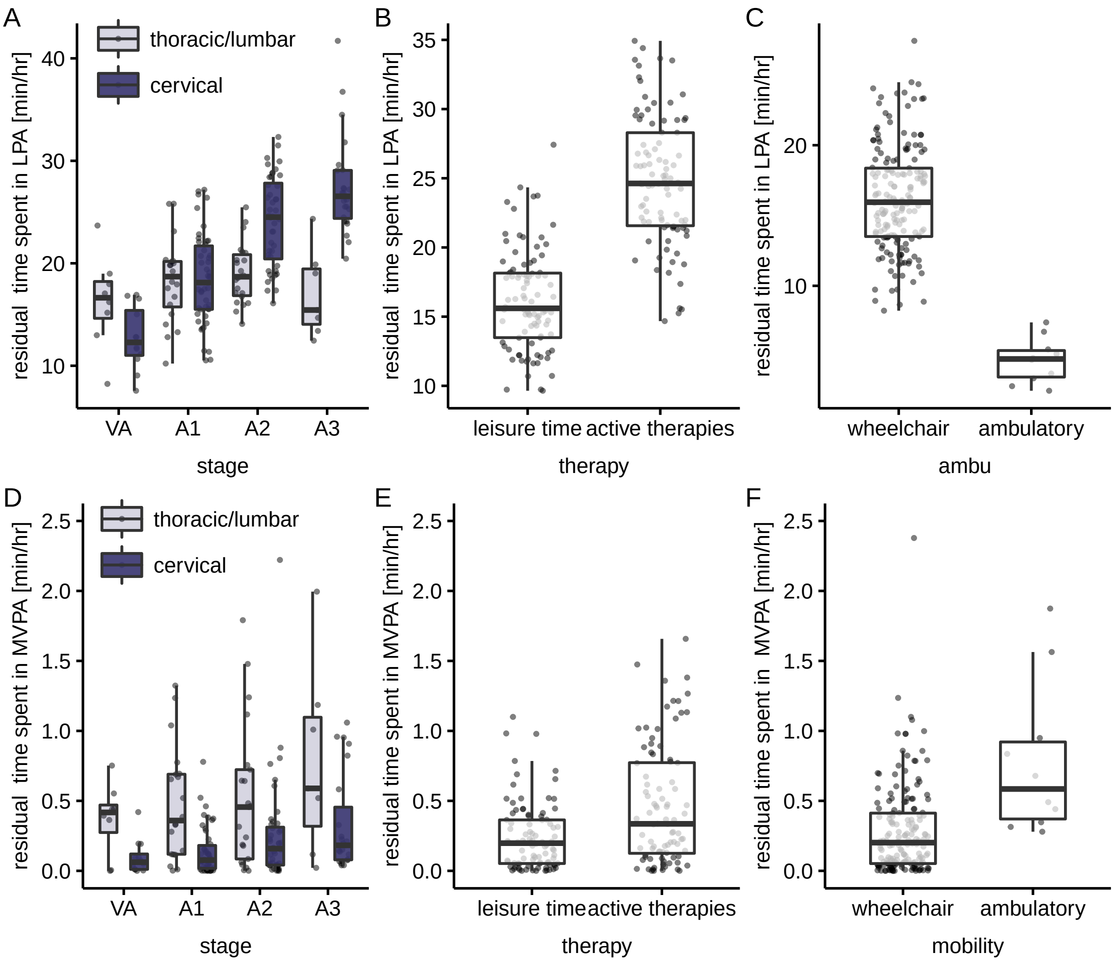

Figure 6.3 – Partial residual plots based on the 'full' linear mixed model including all covariates and significant interactions for times spent in low physical activity (LPA, panel A-C), and time spent in moderate-to-vigorous intensity (MVPA, panel D-F). A: partial residuals for the interaction effect stage*group on LPA. B: partial residuals for the main effect therapy on LPA. C: partial residuals for the main effect mobility on LPA. D: partial residuals for the main effects stage and group on MVPA. E: partial residuals for the main effect therapy on MVPA. F: partial residuals for the main effect mobility on MVPA.

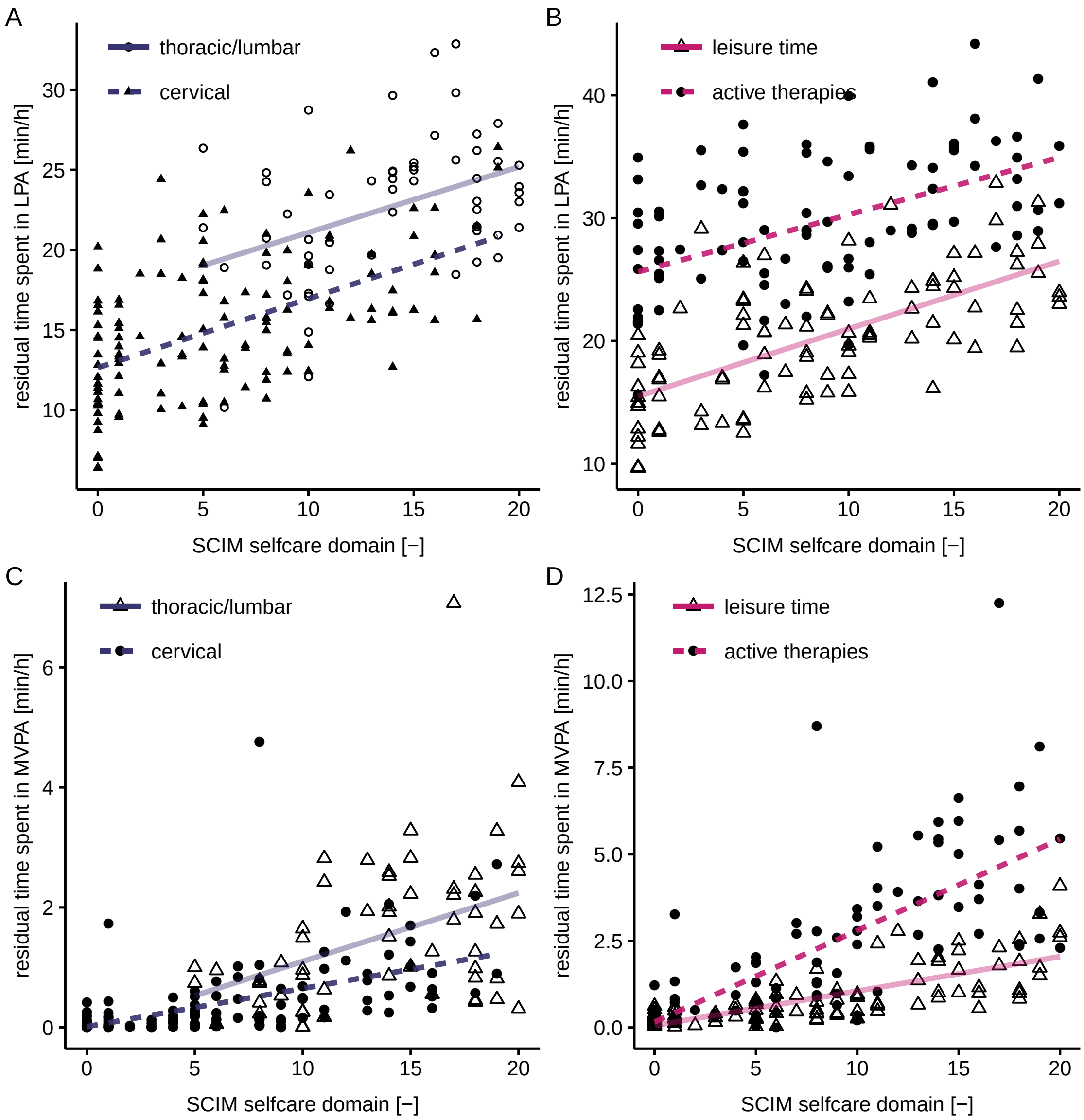

Figure 6.4 – Partial residual plots based on 'full' linear mixed model including all covariates and significant interactions for the effect of SCIM self-care and group (panel A and C) and SCIM self-care and therapy (panel B and D) on times spent in low physical activity (LPA, panel A and B), and time spent in moderate-to-vigorous intensity (MVPA, panel C and D). A. partial residuals for the main effects SCIM self-care and group on LPA. B. partial residuals for the main effects SCIM self-care and therapy on LPA. C. partial residuals for the main effects SCIM self-care and group on MVPA. D. partial residuals plot for the interaction effect SCIM self-care*therapy on MVPA. Plotted lines are based on a linear fit of the data to indicate potential interaction effects.

leisure time, as well as between different levels of lesion (i.e. thoracic/lumbar compared to cervical lesion). The overall aim was to develop a framework to integrate wearable sensors for PA monitoring during rehabilitation with the potential to become applicable to better target and account for PA in clinical trials.

6.5.1 Effect of therapy and group on changes of PA levels over time

AC increased over the rehabilitation period in both leisure time and therapy sessions independent of the lesion level, confirming the results of a previous study reporting significant changes in AC during inpatient rehabilitation (Zbogar et al., 2016). In general, therapy sessions showed higher values of AC than leisure time from one month after injury on, which is in line with previous results (Brogioli et al., 2016c). However, in the VA stage, i.e. two weeks after injury, no significant difference in AC between leisure time and therapy was found. This is likely due to the fact that patients in this stage were often bound to the bed and some patients were in an intensive care unit. Therapies in this early stage of rehabilitation mainly focus on correct positioning of the patients in bed, mobilization and verticalization, and preventing complications like pressure ulcers (Kessler et al., 2018), limiting the PA in general. We found increasing levels of AC over time for both groups, patients with a cervical lesion and a thoracic/lumbar lesion. As expected, AC increased more strongly in patients with a cervical lesion, which is in line with the results of previous studies (Brogioli et al., 2016c; van den Berg-Emons et al., 2008) and can be explained by an improving upper-limb function in tetraplegic patients (Petersen et al., 2017). We also found increasing AC over time in patients with a thoracic/lumbar lesion, although the increase from one month (A1) to three months (A2) was rather small. The latter was only revealed as a trend in a previous study, probably due to a smaller sample size (Brogioli et al., 2016c) Overall higher levels of AC could be observed in thoracic/lumbar patients compared to cervical patients, which was significant at all stages except at six months after injury (A3). Similarly to previous findings (Brogioli et al., 2016c), both groups reached similar AC values at six months after injury, albeit the presence of upper limb impairment and reduced SCIM values in tetraplegia. This suggests indicates that measures of AC are of limited sensitivity to evaluate changes in PA levels. Therefore, we subdivided PA into intensity levels commonly used in the literature, namely REST, SED, LPA, and MVPA, to improve the sensitivity of PA evaluations. At all rehabilitation stages, measures of MVPA showed a significant difference between thoracic/lumbar and cervical patients with MVPA increasing significantly at every stage in both groups. Thus, MVPA can be used as a marker of high intensity activities allowing to detect changes in PA more sensitively than commonly used measures of overall PA like AC. Time spent in higher intensity levels were longer in therapy sessions than in leisure time. As expected, patients showed more time spent in REST during leisure time than during therapy sessions at all rehabilitation stages. Moreover, patients showed more time in LPA and in MVPA in therapy sessions than in leisure time at all rehabilitation stages. Time spent in SED was higher in cervical patients compared to thoracic/lumbar patients during active therapy sessions, but similar during leisure time. Assuming that SED corresponds to daily activities like watching TV or reading a book, as shown by Ainsworth et al. (Ainsworth et al.,

2011) these activities likely don't differ in leisure time between cervical and thoracic/lumbar patients. However, during active therapy sessions the time spent in SED was higher in cervical patients than in thoracic/lumbar patients, because their therapy might have a stronger focus on consulting and educating patients on how to optimally adapt their environment to compensate for their impairments.

6.5.2 Independence as an additional factor influencing the PA level

We identified a strong effect of the level of independence in terms of SCIM self-care and mobility scores on the changes in AC and the intensity times during rehabilitation. When including SCIM self-care and mobility scores in the model, post-hoc comparisons for MVPA between rehabilitation stages were not significantly different. Similarly, post-hoc comparisons for AC between rehabilitation stages revealed no significant difference but for the very early stage. Thus, the gain of independence mainly accounted for the longitudinal change of PA during leisure time, suggesting that the increased PA levels (i.e. AC and MVPA) during leisure time can mostly be explained by a gain of independence. In contrast, AC during therapy sessions increased more strongly than it would be predicted solely by the increase in independence, and this increase can thus be attributed to factors not directly related to independence. Indeed, the SCIM self-care assessment aims at capture the performance of the patients in daily life, (Rudhe and Van Hedel, 2009), i.e., what they actually do in their environment. However, in therapy sessions, patients are likely pushed to their functional limits and thus better approach their full capacity, i.e., show their maximal ability to perform a task. Especially at later stages of the rehabilitation, capacity and performance might not match. Although patients would be able to perform a certain activity, it might require too much of an effort to translate into their daily life, or there is actually no need to perform such activities to master their daily life, e.g., due to an adapted environment facilitating the activities of daily living. The increased independence was related to the increase of AC during the rehabilitation in both groups, patients with a cervical and a thoracic/lumbar lesion. This effect was stronger in thoracic/lumbar patients than in cervical patients, suggesting that AC in cervical patients increased more than it would be expected by the increase of their independence. This could be explained by an increasing endurance of the cervical patients. Another possible explanation could be that cervical patients need to invest more effort in terms of PA to reach similar levels of independence compared to thoracic/lumbar patients, and this increase might not be linear. The hypothesis of an increased effort in cervical patients to handle activities of daily living is in line with the finding that cervical patients show significantly higher levels of LPA and lower values of REST compared to thoracic patients at later stages of rehabilitation when controlling for demographics and assessment scores, i.e., under the hypothetical assumption that demographics and assessment scores are equal in both patient groups. However, in fact, e.g. SCIM self-care values of cervical patients are lower than those of thoracic/lumbar patients, which balanced the levels of LPA and REST for both groups. This suggest that cervical patients show more time in LPA compared to thoracic/lumbar patients with similar levels of independence most likely due to their impairment in the upper-limbs. Although patients learn strategies to compensate for their impairment, the impairment still manifests, especially in activities of daily living, which is assumed to be represented by LPA. Thereby, the increased LPA in cervical patients is associated with longer movement durations (Mateo et al., 2015). SED decreased with increasing SCIM self-care score for active therapies, however, did not change in leisure time. Assuming that SED corresponds to passive daily activities like watching TV or reading a book, the frequency of these activities likely does not change with increasing independence. Although MVPA increased in both leisure time and therapy time with a gain of independence, i.e. SCIM self-care score and mobility, the effect in therapy sessions was stronger than in leisure time. MVPA is mostly present in walking activities, which are likely to increase more strongly in supervised therapy sessions, and their translation to the leisure time might be limited.

6.5.3 Additional factors influencing PA levels: Demographics

Demographic factors also affect the different metrics of PA. Firstly, elderly patients engaged in less AC and less MVPA, while spending more time in REST. This effect is not specific to patients with SCI, but can also be observed in the healthy population (Colley et al., 2011; Ramirez et al., 2018). Secondly, we saw that female patients showed significantly higher levels of MVPA than male patients. This is in contrast to research in the healthy population, in which studies reported higher levels of MVPA for males than females (Hansen et al., 2012), or no gender effect on the overall PA (Ramirez et al., 2018). However, it has been shown that the recovery after SCI is higher for women than for men (Sipski et al., 2004; Furlan et al., 2005). Thus, a possible explanation for the increase in PA in women compared to men is that the women in our dataset did indeed recover more in aspects not assessed and controlled for in our model. We saw a significant increase of AC in women compared to men, especially in their leisure time. Literature states that women report less limitations in societal participation (Forchheimer et al., 2004), suggesting that they engage in more PA, especially during their leisure time, and therefore show a better recovery. However, we cannot make any statements about the direction of the causality between increased PA and increased independence. Until now, it is not known whether an increased independence enables higher levels of PA, or a higher engagement in PA increases the independence of patients. Further research needs to be done to reveal the direction of the causality between increased independence and PA levels. AC, REST, and MVPA were also affected by the rehabilitation center patients were admitted to. One center showed consistently higher values of PA, which might suggest that it offers more possibilities to the patients to engage in PA not only during therapy sessions, but also during their leisure time. Lastly, it is likely that other factors like social integration, family support, and the season of the year influenced the changes in PA and should be assessed in future studies to investigate these effects as well (Perrier et al., 2012; Borisoff et al., 2018).

6.5.4 Limitations

One limitation of the study is the sample size. Especially in the very acute stage, recruitment of patients was challenging due to the health conditions of patients affecting the timing of admissions and consenting to the study. Furthermore, at the last recording stage, about 6 months after injury, especially thoracic/lumbar patients are often discharged already from the rehabilitation facility (Kessler et al., 2018), which explains higher dropouts at this stage. Additionally, on average only two days of valid measurements per patient could be retained for the analysis due to the strict quality criteria for data inclusion. Although this is rather low compared to studies in other populations, in a recently published study we could show that two days of measurements are sufficient in the in-patient setting to provide reliable outcomes (Schneider et al., 2018). A general draw-back of PA assessments using inertial measurement units is the underestimation of PA intensity during weight-loading activities. Previous studies showed that energy expenditure estimation is less accurate during these activities (Popp et al., 2018). Eventually, additional sensing capabilities, e.g., a heart-rate monitor, could be included in future studies to account for this limitation. Lastly, intensity times are calculated based on AC thresholds. A calculation based on a more sophisticated approach, e.g., by using a dedicated energy expenditure estimation model (Popp et al., 2018) would be favorable to achieve more precise estimates. The estimation of the energy expenditure, however, relies on anthropometric information like body height and body weight, which was not available for all included patients.

6.6 Conclusion

In this study, we investigated the changes in PA intensity levels over the rehabilitation process for patients both with a cervical lesion and a thoracic/lumbar lesion. Compared to previous studies focusing on the general PA level in terms of AC, PA intensity levels appear to be more sensitive to detect differences between both patient groups, which are not detectable using AC only, especially at later stages of the rehabilitation process. Thus, PA intensity levels should be measured and reported when assessing PA as a confounder in clinical studies, or when designing interventional studies, aiming at increased PA in general. Furthermore, we could show that PA intensity during both leisure time and active therapies are susceptible to changes during the rehabilitation, and both should be targeted in interventional studies aiming at increasing PA level. The applied sensor technology will be applicable also in patients following discharge from the inpatient rehabilitation and may present means to further foster and expand achievements as achieved during rehabilitation.

7 Levels of physical activity in chronic spinal cord injury: adjustment to functional impairment

Sophie Schneider, Werner L. Popp, László Demkó, Roger Gassert and Armin Curt

Manuscript in preparation. *

*List of authors may be subject to change

7.1 Abstract

Despite the well-known health benefits of an active lifestyle, the level of physical activity (PA) is reported to be low in individuals with chronic spinal cord injury (SCI). The aim was to reveal the impact and relation of impairment and demographic factors in chronic SCI individuals to levels of PA performed after discharge from rehabilitation. By using wearable sensors, PA was measured in 52 chronic SCI subjects (24 ambulatory, and 28 wheelchair-dependent SCI subjects) and 17 healthy controls. We compared the PA intensity levels between SCI subjects and healthy controls and performed a cluster analysis based on PA metrics. Multinomial logistic regression was applied to predict the PA clusters by the clinical scores and age. We identified 4 distinct clusters of PA patterns with mobility and independence being the most discriminating factors between the PA clusters. The accuracy to predict subjects into their classified cluster was 70%. We suggest that this high misprediction is because of other factors than the clinical scores and demographics influencing the PA levels. We suggest that these factors might be motivational-driven and adapted the PA clusters my removing 'motivational outliers'. Our study provides first reference values of PA levels, which are specific to the mobility-mode and independence of individuals with an SCI. Using these reference values, existing guidelines for PA can be adapted and rehabilitation goals during acute rehabilitation set.

7.2 Introduction

Physical activity (PA) has been proven to provide a wide range of health benefits not only to neurological intact adults (Warburton et al., 2006; Bize et al., 2007), but also to individuals suffering from a spinal cord injury (SCI) (Jörgensen et al., 2019). Besides its positive effect on the cardiovascular system, PA has been shown to decrease pain, fatigue, and depressive symptoms and has an overall benefit on the quality of life of SCI individuals (Stevens et al., 2008; Buchholz et al., 2009; Tawashy et al., 2009). During rehabilitation in acute SCI, an increased PA is furthermore assumed to improve clinical recovery (Jones et al., 2012; Lynskey et al., 2008; Quel de Oliveira et al., 2017). So far, PA levels in the chronic SCI population are rather less well studied and has been reported as being low (Buchholz et al., 2003; Martin Ginis et al., 2010; Jörgensen et al., 2017). Some recommendations on how much PA is needed to gain a health benefit have been developed specifically for SCI patients (Martin Ginis et al., 2011; Totosy de Zepetnek et al., 2015; Nightingale et al., 2017). However, they are unspecific regarding the impact of impairment onto achievable PAs. Studies grossly related the influence of the lesion level on the PA of SCI individuals during daily life but with profound variations ranging from a strong (Martin Ginis et al., 2010) to even no relation to the lesion level (Tawashy et al., 2009). These variations in the findings might be due to the application of mainly questionnaires to assess PA although specific questionnaires had been developed and validated for the population of SCI, e.g., the Physical Activity Recall Assessment (Martin Ginis et al., 2005). Nevertheless questionnaires are limited by the recall ability and thus suffer from subjectivity, an indeed several studies showed a mismatch between PA questionnaires and objective measures of PA, i.e., wearable sensors (Zbogar et al., 2016; Ma et al., 2018; Cleland et al., 2018). Wearable sensors have already been successfully applied to assess PA objectively during the inpatient rehabilitation of acute SCI patients (Brogioli et al., 2016c). Besides being an objective measure of PA, the main advantage of wearable sensors is its easy translation from the inpatient rehabilitation to the home environment. van den Berg-Emons et al. (2008) measured SCI individuals one year after discharge using accelerometers and reported an decreased PA in SCI subjects compared to able-bodied individuals in terms of the duration of dynamic activities and body motility. This study demonstrated the feasibility to measure PA in SCI subjects compared to healthy controls and found lower levels in SCI individuals at 1 year after discharge compared to healthy controls. In this study, we aimed to gain insights into PA levels in chronic SCI individuals applying measures of energy expenditure estimated by wearable sensors and being related to activities of mobility (Popp et al., 2018, 2019a). We intended to investigate PA levels in ambulatory and wheelchair-dependent SCI, and how they relate to the level of impairment and demographic factors. The comparison to healthy controls aimed for revealing the overall impact of mobility on PA measures. Using these measures, recommendations of PA levels in chronic SCI individuals should become based on specific levels of impairment and mobility. The latter may guide clinicians to set realistic PA goals for their patients following discharge from rehabilitation and to improve existing PA guidelines.

7.3 Methods

7.3.1 Subjects

In total, 69 subjects were included in this analysis. Of these subjects, 52 subjects were chronic SCI subjects and 17 healthy controls without any neurological impairment. Out of the 52 subjects with SCI, 24 subjects showed some ambulatory mobility during daily life, while 28 subjects were wheelchair-dependent during daily life activities. Inclusion criteria for the SCI subjects were traumatic or non-traumatic chronic SCI (> one year after injury). All neurological level of injury (NLI) and completeness of the lesion according to the ASIA impairment scale (AIS) were admitted to the study. Ambulatory SCI subjects had to be able to walk at least 100 m without supervision, and all included subjects were community-walkers. Wheelchair-dependent SCI subjects had to use a manual or an electric wheelchair as their primary mode of mobility. Ten of the included wheelchair-dependent SCI subjects were enrolled to a wheelchair-sports club (mainly basketball and rugby) and regularly participated in training and games. Exclusion criteria were any neurological impairments other than SCI, orthopedic or rheumatic diseases or an on-going major depression or psychosis. Healthy controls were age-and-gender-matched to the ambulatory SCI subjects. Recruitment took place from 2016 to 2018. SCI subjects were recruited from the Spinal Cord Injury Center of the Balgrist University Hospital and local wheelchair-sports clubs. Healthy control subjects were recruited from the work environment of the university. All subjects signed a written consent before participating in the study following the Declaration of Helsinki. The study was approved by the ethical committee of the canton of Zurich, Switzerland (KEK-ZH No. 2013-0202).

7.3.2 Measurement device

An inertial measurement unit (IMU) was used to assess PA during daily life. From 2016 to 2017 the ReSense sensor (Leuenberger and Gassert, 2011) was used. The sensor comprises a 3D accelerometer, a 3D gyroscope, a 3D magnetometer, and an altimeter. The battery capacity was limited to a maximum of 1.5 days and had to be exchanged once a day. In 2018, the successor of the ReSense was used (www.zurichmove.com) which has the same sensing capabilities as the ReSense. This sensor allowed for continuous monitoring of 3 days without exchanging the sensors.

7.3.3 Measurement protocol

Subjects were asked to come to the Balgrist University Hospital for the initial assessments. For SCI subjects, the SCIM scores and the upper limb motor score was assessed. All ambulatory subjects (SCI subjects and control subjects) had to perform the 6-Minute Walk Test (6MWT), the 10-Meter Walk Test (10MWT), and the Timed Up and Go Test (TUG). In all three tests, subjects were asked to perform them in the fastest speed possible, while still feeling safe and comfortable. Furthermore, a questionnaire about general life circumstances and demographics has been filled out by all subjects. After these initial assessments, subjects got the wearable sensors attached, one to each wrist, one to each ankle in ambulatory subjects, and one to the right wheel of each wheelchair in wheelchair-dependent subjects. Subjects were instructed to wear the sensors for 3 consecutive days and only remove them for water activities (showering or swimming). Additionally, all subjects were instructed to fill out an activity log by entering times sleeping, working and doing sports. After the three measurement days, subjects sent the sensors and the activity log back to the hospital.

7.3.4 Data analysis and statistics

Pre-processing

In order to assure a constant sampling rate of 50 Hz, the raw sensor data were resampled and temporally aligned using a spline interpolation function. Data were then labeled for non-wear time using a semi-automatic algorithm (Schneider et al., 2018). The awake time of each subject was labeled visually, considering the information provided in the activity logs.

PA features

PA features were extracted for days with at least 13h of sensor data (sleep not included) (Hermann et al., 2014). PA features were based on the estimated energy expenditure as described previously (Popp et al., 2018). The algorithm was adapted to ambulatory SCI subjects (Popp et al., 2019a) and healthy control subjects (unpublished data from our group). The energy expenditure was expressed in terms of the metabolic equivalent of task (MET) by dividing the estimated energy expenditure by the resting energy expenditure. All extracted features are based on the MET values. Time spent in sedentary (SED), time spent in low (LPA), and time spent in moderate-vigorous (MVPA) intensities were calculated based on $1 \leq \text{MET} \leq 1.5$, $1.5 < \text{MET} < 3$, and $\text{MET} \geq 3$, respectively (Ainsworth et al., 2011). Additional to the time spent in the respective intensity, the MET-minutes were calculated for each intensity by summing the MET values of each minute spent in the respective intensity. Furthermore, the time spent in bouts ≥ 2min (sporadic bouts), ≥ 5min (short bouts), and ≥ 10min (medium-to long bouts) and the number of bouts of continuous movement in all four intensities were calculated, because longer bout durations have been associated with a reduced risk of overweight and obesity (Willis et al., 2015). Lastly, activity counts (AC) were calculated by integrating the acceleration magnitude in epochs of 1 min. AC were reported to facilitate comparison with previous results stated in the literature. AC of both wrists were summed up for wheelchair-users, and both wrists and ankles for ambulatory subjects. All features were normalized to 24 h. A list of all calculated features can be found in Table C.1.

Clinical scores and demographics

The time after injury, the SCIM subdomains self-care (max. score 20), room and toilet mobility (max. score 10), indoors and outdoors mobility (max. score 30), and the manual muscle testing (MMT) score of the upper limb (max. score 100, 50 per side) were used to characterize the wheelchair-dependent and ambulatory SCI subjects. The distance in the 6MWT (in meter), time in 10MWT (in seconds), and time in TUG (in seconds) were used to characterize the ambulatory SCI subjects and healthy controls. Age and gender of all subjects were further included in the analysis.

Statistics

For the comparison of PA metrics between the three included subject groups, wheelchair-dependent SCI, ambulatory SCI, and control subjects, an analysis of variance was conducted. Due to non-normality of the data, median and interquartile range (IQR) were reported for descriptive statistics, and the Kruskal-Wallis Rank Sum test for continuous variables and the Fisher's Exact Test applied for inferential statistics. The Dunn test was applied as a post-hoc test. To identify subjects with similar patterns in terms of PA levels, a hierarchical clustering method was applied. To reduce dimensionality and noise in the PA data, a principal component analysis was applied to the scaled and centered data. The first 3 components explaining the most variance were retained and used in further analyses. Then, hierarchical clustering was applied to the principal components to find groups of subjects with similar patterns in terms of PA levels. Euclidean distance was used as a distance measure and Ward's method as merging criterion. Ward's method is an agglomerative clustering method that aims to minimize the total within-cluster variance (Murtagh and Legendre, 2014). The number of final clusters was determined by evaluating the silhouette coefficient together with the meaningfulness of the clusters. To interpret the groups, comparisons between clusters were made using the Kruskal-Wallis Rank Sum Test for continuous variables and the Fisher's Exact Test for categorical variables. Multinomial logistic regression was conducted to predict the PA clusters based on the clinical scores and demographics. Ten-fold cross-validation was conducted to evaluate the final model. The sensitivity, specificity, and balanced accuracy of the regression model was calculated by the following formulas.

Statistical analysis was performed in RStudio (RStudio Team, 2015).

7.4 Results

7.4.1 Demographics

The mean age of all included subjects was 51.6 ± 12.0 years (wheelchair-dependent SCI: 48.5 ± 11.8 years, ambulatory SCI: 53.9 ± 11.9 years, healthy controls: 51.6 ± 12.2 years), with 13 female and 56 male subjects (wheelchair-dependent SCI: 23 male, 5 female, ambulatory SCI: 19 male, 5 female, healthy controls: 14 male, 3 female). The NLI ranged from C3 to T11 (tetraplegic: 9, paraplegic: 19 subjects) in the wheelchair-dependent SCI subjects and from C5 to S3 (tetraplegic: 8, paraplegic: 16 subjects) in the ambulatory SCI subjects. The completeness of the lesion ranged from A to D in the wheelchair-dependent subjects (A: 18, B: 4, C: 4, D: 2 subjects) and from B to D (A: 0, B: 3, C: 1, D: 20 subjects) in the ambulatory SCI subjects. Subjects wore the sensors for 18.6 ±10.9 hours while being awake. On average 2.5 ± 0.8 valid days could be extracted for the analysis.

7.4.2 Differences in PA between chronic SCI subjects and healthy controls

All investigated PA metrics were significantly different across the three groups (Figure 7.1, Table 7.1). Average MET, total AC, time spent in MVPA, and MET-minutes of MVPA were significantly lower in wheelchair-dependent SCI subjects than in healthy controls and ambulatory SCI subjects. Time spent in LPA and MET-minutes of LPA were significantly higher in wheelchair-dependent SCI subjects than in healthy controls. Additionally, MET-minutes of LPA was significantly higher in wheelchair-dependent SCI subjects compared to ambulatory SCI subjects. Time spent in SED was significantly lower in ambulatory SCI than in wheelchair-dependent SCI subjects and healthy controls.

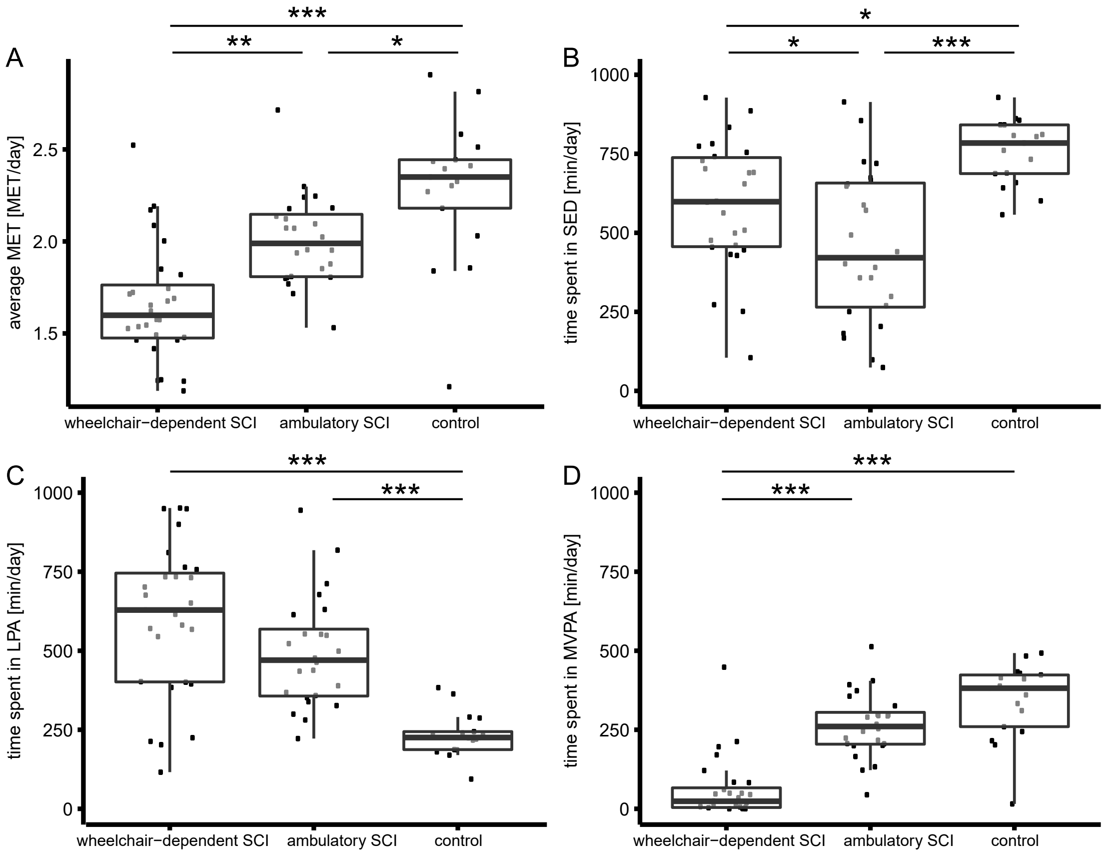

Figure 7.1 – Boxplots for average MET (panel A), time spent in sedentary PA (SED, panel B), time spent in low PA (LPA, panel C), and time spent in moderate-vigorous PA (MVPA, panel D) for the groups of wheelchair dependent SCI subjects, ambulatory SCI subjects, and healthy control subjects. *, **, ***, denote p-values of < 0.05, < 0.01, < 0.001, respectively.

	wheelchair-dependent SCI	ambulatory SCI	control	χ^2	p-value
average MET [MET/day]	1.6 (0.29)^{a,b}	1.99 (0.34)^{b,c}	2.35 (0.26)^{a,c}	29.28	< 0.001
time spent in SED [min/day]	627.43 (300.18)^{a,b}	421.19 (392.69)^{b,c}	784.05 (154.14)^{a,c}	17.06	< 0.001
MET-minutes in SED [MET-min/day]	824.6 (381.19)^{b}	355.41 (324.87)^{b,c}	639.85 (112.92)^{c}	28.28	< 0.001
time spent in LPA [min/day]	639.96 (356.83)^{a}	470.2 (211.67)^{c}	225.49 (56.96)^{a,c}	28.58	< 0.001
MET-minutes in LPA [MET-min/day]	1194.44 (784.27)^{a,b}	652.29 (321.32)^{b,c}	319 (86.12)^{a,c}	36.1	< 0.001
time spent in MVPA [min/day]	23.9 (62.3)^{a,b}	260.44 (100.74)^{b}	381.51 (163.61)^{a}	38.93	< 0.001
MET-minutes in MVPA [MET-min/day]	96 (221.82)^{a,b}	657.38 (319.09)^{b,c}	1249.04 (427.56)^{a,c}	35.16	< 0.001
time spent in bouts ≥ 10min of MVPA [min/day]	0 (27.25)^{a,b}	18.18 (34.34)^{b,c}	85.43 (72.28)^{a,c}	6.47	0.039
average activity counts [counts/min]	786.17 (338.01)^{a,b}	1147.21 (418.21)^{b}	1493.98 (344.45)^{a}	20.3	< 0.001

Table 7.1 – PA metrics of wheelchair-dependent SCI subjects, ambulatory SCI subjects, and control subjects. The χ^2 and p-values were calculated based on a Kruskal-Wallis Rank Sum Test. Significant differences (p-value < 0.05) are marked in bold. ^{a} denotes a significant post-hoc comparison (p-value < 0.05) between wheelchair-dependent SCI and healthy control subjects, ^{b} between wheelchair-dependent and ambulatory SCI subjects, and ^{c} between ambulatory SCI and healthy control subjects.

7.4.3 Cluster analysis of PA metrics

To find clusters of subjects with similar PA patterns, hierarchical clustering was conducted. To reduce noise in the data, a principal component analysis was applied before the clustering. The first three components of the principal component analysis explained 77% of the total variance in the data (Component 1: 35%, Component 2: 28%, Component 3: 14%). The PA features time spent in MVPA (7.6%) and MET-minutes of MVPA (8.2%) contributed most to the first principal component, time spent in SED (10.9%) and MET-minutes of SED (10.6%) contributed most to the second principal component, and time spent in bouts of MVPA (≥ 5min: 15.8%, ≥ 10min: 15.7%, ≥ 2min: 15.7%) contributed most to the third principal component. Time spent in LPA (first component: 5.2%, second component: 5.1%) and MET-minutes of LPA (first component: 4.0%, second component: 6.7%) contributed almost equally to the first and second principal component. A hierarchical clustering method was then applied to the first three principal components. According to the silhouette coefficient, merging the branches of the hierarchical tree at height 12.0 was recommended, resulting in 6 clusters. However, this led to one cluster of only 2 subjects making statistical analysis impossible. Therefore, we had to merge the branches at height 23.3, resulting in a final number of 4 clusters (Figure C.1). A comparison of the clinical scores and PA metrics between all 4 clusters (Figure 7.2, Table C.2) revealed that two PA clusters mainly contained wheelchair-users and were separated in terms of PA metrics by a significantly lower time spent in SED and significantly higher time spent in LPA in the second cluster. These clusters are referred to as wheelchair-dependent with moderate independence and wheelchair-dependent with full independence. The remaining two PA clusters mainly contained pedestrian, with a significantly higher time spent in SED, and lower time spent in LPA in the second cluster. These two clusters are referred to as ambulatory with moderate walking capacity and ambulatory with high walking capacity. The naming of the clusters will be explained in the following section.

Whereas the time spent in MVPA did not differ between the two ambulatory clusters, MET-minutes in MVPA were significantly higher in the ambulatory cluster with full walking capacity compared to the ambulatory cluster with moderate walking capacity. The time spent in MVPA and average MET was significantly higher in both ambulatory clusters compared to the wheelchair-dependent clusters, while not differing significantly within both wheelchair-dependent and ambulatory clusters. The wheelchair-dependent cluster with moderate independence and ambulatory cluster with full walking capacity showed similar time spent in SED.

The SCIM mobility indoors and outdoors score was significantly higher in both ambulatory clusters than in the wheelchair-dependent clusters, while the SCIM self-care score was significantly higher in both ambulatory clusters compared to the wheelchair-dependent with moderate independence only. Although the wheelchair-dependent clusters mainly contained wheelchair-dependent subjects, three ambulatory SCI subjects were also classified into these groups. Furthermore, three wheelchair-dependent SCI subjects were classified to the ambulatory clusters.

	Class 1	Class 2	Class 3	Class 4
Sensitivity	0.63	0.83	0.33	0.95
Specificity	0.94	0.89	0.96	0.76
Balanced Accuracy	0.78	0.86	0.65	0.85

Table 7.2 – Sensitivity, specificity, and balanced accuracy for predicting PA clusters based on the clinical scores and age.

7.4.4 Predicting PA clusters using clinical scores and age

The prediction of the PA clusters based on the clinical scores and age resulted in an accuracy of 0.67 (95% CI: 0.54, 0.78), with 46 out of 69 subjects being correctly classified (Table C.3, Figure 7.2). The prediction accuracy, sensitivity, and specificity for each PA cluster is presented in Table 7.2. After removing all wrongly classified subjects and retraining the model, the accuracy improved to 1.0 (95% CI: 0.92, 1) with all subjects being correctly classified. The demographics, clinical scores, and PA metrics of the updated PA clusters can be found in Table 7.3. SCIM self-care, SCIM mobility room and toilet, SCIM mobility indoors and outdoors, upper limb motor score, 6MWT, 10MWT, TUG and work time differed significantly between the clusters. In contrast to the PA clusters before removing 'motivational outliers' (as reported in Table C.2), in the updated PA clusters the SCIM self-care scores were significantly lower in the wheelchair-dependent cluster with moderate independence compared to all other clusters, explaining the naming of this cluster. The distance walked in the 6MWT was significantly lower in the ambulatory cluster with moderate walking capacity compared to the ambulatory cluster with high walking capacity, the time needed in the 10MWT, and the TUG significantly higher in the ambulatory cluster with moderate walking capacity compared to the ambulatory cluster with high walking capacity. The naming of the clusters thus arises from the difference in independence between the wheelchair-dependent clusters, and the difference in walking capacity in the ambulatory clusters.

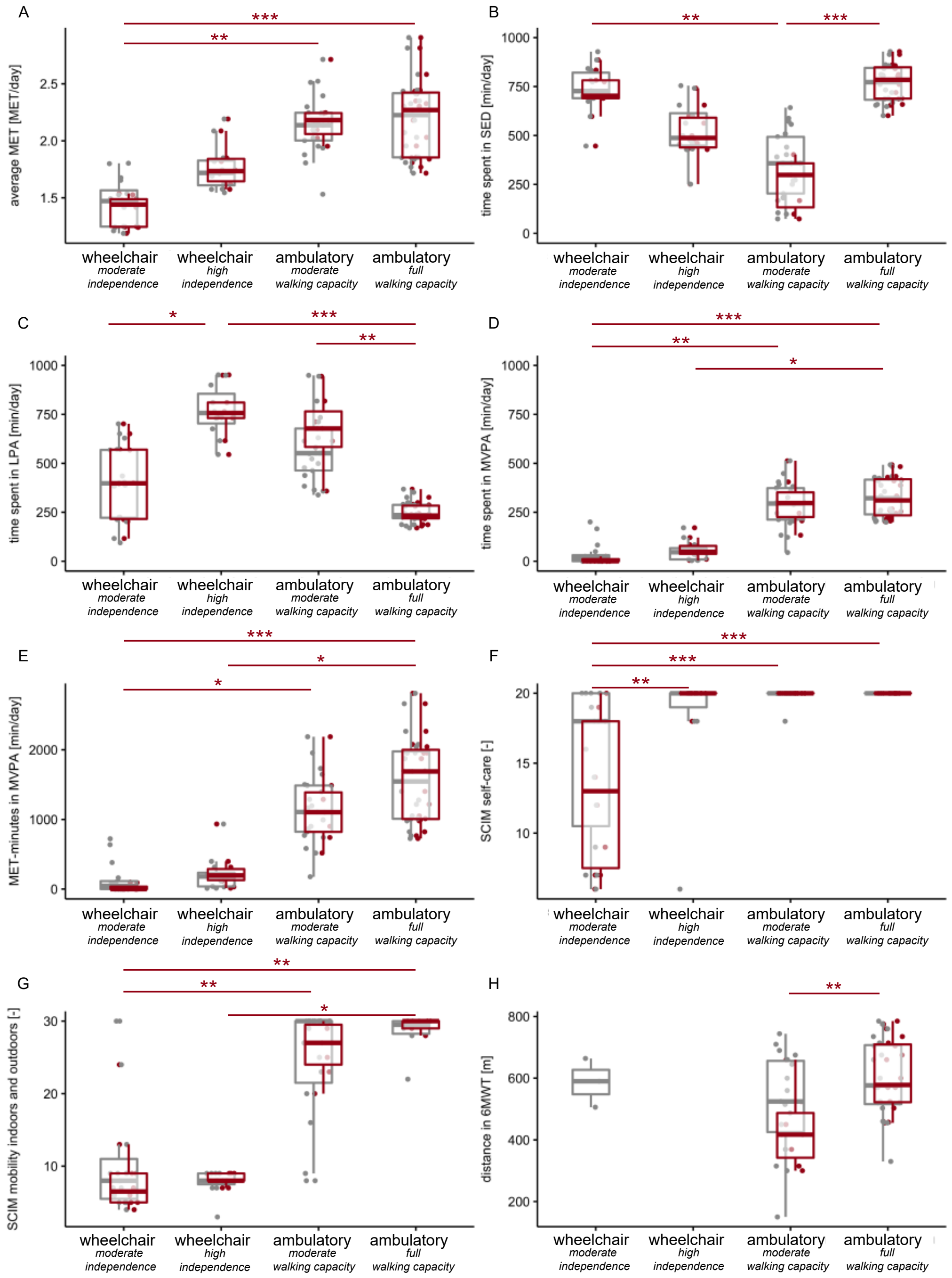

Figure 7.2 – Boxplots of PA metrics (Panel A-E), and clinical scores (panel F-H) in the four PA clusters 'wheelchair-dependent with moderate independence', 'wheelchair-dependent with high independence', 'ambulatory with moderate walking capacity', and 'ambulatory with high walking capacity' resulting from the hierarchical clustering. Red boxplots and points indicate the updated PA clusters after removing 'motivational outliers', which were wrongly predicted by the multinomial regression model and thus removed for the final PA clusters. *, **, ***, denote p-values of < 0.05, < 0.01, < 0.001, respectively and are given for the updated PA clusters only.

	wheelchair-dependent	wheelchair-dependent	ambulatory	ambulatory		
	moderate independence n = 10	high independence n = 10	moderate walking capacity n = 7	high walking capacity n = 19	χ^2	p-value
Age [years]	46.5 (16.8)	47.5 (15.2)	65 (11.5)	56 (14.5)	6.6	0.086
Body mass index [kg/m^2]	24.2 (7.9)	23 (2.6)	28.1 (2.8)	23.2 (4.7)	5.62	0.132
Gender						1
female	2	2	1	4		
male	8	8	6	15		
Plegia						0.012
paraplegic	4	9	3	4		
tetraplegic	6	1	4	1		
control	0	0		14		
Main mobility type						< 0.001
wheelchair-user	10	10	0	0		
pedestrian	0	0	7	19		
Time after injury [years]	6.5 (9.7)	14.7 (16.9)	9.4 (7.4)	9.6 (13.3)	3.52	0.319
SCIM self-care score [-]	13 (10.5)^{a,b,c}	20 (0)^{a}	20 (0)^{b}	20 (0)^{c}	22.14	< 0.001
SCIM mobility room and toilet score [-]	7 (6)^{a,b,c}	10 (0)^{a}	10 (0)^{b}	10 (0)^{c}	14.9	0.002
SCIM mobility indoors and outdoors score [-]	6.5 (4)^{b,c}	8 (1)^{d,e}	27 (5.5)^{b,d}	30 (1)^{c,e}	21.55	< 0.001
upper limb motor score [-]	87.5 (41.2)	100 (0)	95 (18.5)	100 (0)	8.53	0.036
reported time exercising [h/day]	1.3 (1.7)	1.1 (1.4)	0.8 (0.8)	1.9 (2.7)	3.3	0.347
reported time working [h/day]	0 (3.4)^{b,c}	2.5 (7.3)^{e}	7.5 (3.5)^{b}	11.3 (6.1)^{c,e}	15.66	0.001
distance in 6MWT [m]	-	-	417 (145)^{f}	578 (187.5)^{f}	8.2	0.004
time in 10MWT [sec]	-	-	8.7 (2.8)^{f}	5.9 (2.7)^{f}	5.21	0.022
time in TUG [sec]	-	-	10.1 (4.4)^{f}	6.6 (3.2)^{f}	4.21	0.04
average MET [MET/day]	1.44 (0.24)^{b,c}	1.73 (0.2)^{e}	2.18 (0.18)^{b}	2.27 (0.57)^{c,e}	30.36	< 0.001
time spent in SED [min/day]	738.34 (130.76)^{a,b}	487.66 (151.88)^{a,e}	298.72 (224.86)^{b,f}	784.05 (159.83)^{e,f}	28.08	< 0.001
MET-minutes in SED [MET-min/day]	950.02 (192.54)^{a,b}	644.69 (188.61)^{a,e}	403.83 (290.88)^{b,f}	959.78 (188.43)^{e,f}	27.03	< 0.001
time spent in LPA [min/day]	397.7 (353.73)^{a}	760.55 (182.83)^{a,e}	677.72 (181.52)^{f}	232.83 (65.16)^{e,f}	29.03	< 0.001
MET-minutes in LPA [MET-min/day]	750.96 (628.34)^{a,b}	1549.9 (337.84)^{a,e}	1481.71 (457.1)^{b,f}	485.93 (130.4)^{e,f}	29.67	< 0.001
time spent in MVPA [min/day]	0.27 (10.83)^{b,c}	48.08 (40.97)^{d,e}	296.97 (125.84)^{b,d}	310.66 (184.96)^{c,e}	35.17	< 0.001
MET-minutes in MVPA [MET-min/day]	0.84 (35.51)^{b,c}	196.37 (159.73)^{e}	1104.23 (566.55)^{b}	1689.12 (994.34)^{c,e}	34.69	< 0.001
time spent in bouts > 10min of MVPA [min/day]	0 (0)^{b,c}	11.78 (30.55)^{e}	26.35 (57.6)^{b}	65.95 (71.17)^{c,e}	25.87	< 0.001
average activity counts [counts/min]	637.68 (205.09)^{b,c}	946.26 (219.14)	1415.81 (461.75)^{b}	1469.47 (566.35)^{c}	25.87	< 0.001

Table 7.3 – Demographics, clinical scores, and PA metrics of final PA clusters after removing 'motivational outliers'. a-f denote significant post-hoc comparisons (p-value < 0.05) between clusters: ^{a} 'wheelchair-dependent with moderate independence' vs. 'wheelchair-dependent with high independence' , ^{b} 'wheelchair-dependent with moderate independence' vs. 'ambulatory with moderate walking capacity', ^{c} 'wheelchair-dependent with moderate independence' vs. 'ambulatory with high walking capacity', ^{d} 'wheelchair-dependent with high independence' vs. 'ambulatory with moderate walking capacity', ^{e} 'wheelchair-dependent with high independence' vs. 'ambulatory with high walking capacity', and ^{f} 'ambulatory with moderate walking capacity'vs. 'ambulatory with high walking capacity'.

7.5 Discussion

In this study, we investigated the difference in PA levels between wheelchair-dependent SCI, ambulatory SCI, and healthy control subjects. We found four distinct clusters of PA patterns which were related to differences in the impairment.

7.5.1 The influence of mobility on PA levels

PA metrics differed significantly between the three cohorts of wheelchair-dependent SCI, ambulatory SCI, and healthy controls suggesting that the mode of mobility largely influences the level of PA. Wheelchair-dependent SCI subjects showed less time spent in MVPA than ambulatory SCI subjects and healthy controls, which can be explained by the fact that the activity of wheeling is less intense than the activity of walking (Popp et al., 2018, 2019a). In previous studies from our group, we have seen that wheeling at 2 and 5km/h (MET: 2.5 and 3.7) is less intense than walking at 2 and 5km/h (MET: 2.8 and 4.4). The time spent in MVPA was not significantly different between ambulatory SCI subjects and healthy controls. However, the MET-minutes of MPVA were significantly higher in healthy controls suggesting that they might be walking the same amount but with higher intensity, e.g., a faster speed. Furthermore, the time spent in LPA was higher in ambulatory SCI subjects than in healthy controls, which undermines this hypothesis further. Although walking at a comfortable speed is mainly in the MVPA level (MET: 4.0), slow walking (< 2km/h) is classified as LPA (Popp et al., 2019a). A further distinction into mobility-related PA intensity would be required to answer whether SCI subjects and healthy controls walk the same amount but in a different intensity level or whether the quantity differs as well. The time spent in LPA was higher in wheelchair-dependent SCI subjects compared to healthy controls, which can be explained by the fact that wheeling is less intense than walking, since only two limbs are involved and mobility-related activity is a large part of the total daily PA (Jörgensen et al., 2017). The time spent in SED was highest in healthy controls, which is counterintuitive. However, mobility-impaired individuals, i.e., wheelchair-dependent and ambulatory SCI subjects, might need a longer time to cover daily distances which can be assumed to be equal in all cohorts and therefore have less time to do sedentary activities. Furthermore, SCI subjects might be more occupied with therapies and therefore show less sedentary activities.

7.5.2 Clustering of PA metrics into wheelchair-dependent and ambulatory SCI individuals

The clustering of PA metrics revealed four distinct PA clusters, two wheelchair-dependent clusters and two ambulatory classes. The wheelchair-dependent clusters were further separated into two distinct PA clusters. Although both clusters mainly consisted of wheelchair users, one very inactive healthy control and two ambulatory SCI subjects were classified in the less active cluster. The two wheelchair-dependent clusters differed significantly in time spent in SED and LPA while showing similar, very low, levels of MVPA. This is likely because the amount of active wheeling is higher in the second wheelchair-dependent cluster. The very low level of MVPA can be explained by the fact that the activity of wheeling is mainly within a low-intensity range as shown previously (Popp et al., 2018). The ambulatory clusters were further divided into two clusters. The first ambulatory cluster contained mainly ambulatory SCI subjects and only two healthy controls. Additional, three wheelchair-dependent SCI subjects, who regularly participated in sports training and matches were classified into this pedestrian cluster. In contrast, the second ambulatory cluster contained a mix of ambulatory SCI subjects and healthy controls. This suggests that not only mobility influences the PA levels, but motivation might play an important role as well. Therefore, we built a multinomial regression model aiming at predicting the subjects solely based on their clinical scores and age into the PA clusters. About 70% of the subjects were predicted into the correct PA cluster, suggesting that clinical scores and age does indeed drive the PA levels. However, 30% of mispredicted subjects confirms the hypothesis that additional factors, e.g., motivational factors, drives the PA levels confirming results of previous studies (Jörgensen et al., 2017). We removed these mispredicted subjects, i.e., 'motivational outliers', from the four PA clusters in order to get truly impairment-driven PA levels. After removing the 'motivational outliers', the first wheelchair-dependent cluster showed significantly lower SCIM self-care and mobility room and toilet scores than all the other clusters. Furthermore, it contained more tetraplegic patients than the second wheelchair-dependent cluster. Thus, we can state that this cluster represents typical PA levels of chronic wheelchair-dependent SCI subjects with low to moderate independence in daily life and a higher impairment. In contrast, subjects in the second wheelchair-dependent cluster showed high levels of independence and thus represent typical PA levels of independent and less impaired wheelchair-dependent SCI subjects. The first ambulatory cluster contained no healthy controls after removing 'motivational outliers' and showed significantly lower distances in the 6MWT and longer times needed for the TUG and 10MWT than the second ambulatory cluster. Thus, it represents the typical PA levels of ambulatory SCI subjects with limited or moderate walking capacity, compared to the second ambulatory cluster containing ambulatory SCI subjects and healthy controls with high walking capacity. As discussed previously, we see counterintuitively higher times spent in SED in the ambulatory cluster with full walking capacity than in the cluster with moderate walking. This might be due to a slower walking speed in the limited pedestrian cluster and therefore longer times needed to cover daily distances which might be equal in both groups. However, more research needs to be invested whether the quantity of walking is comparable in both groups or quantity differs additional to the intensity.

7.5.3 Comparison of PA levels to literature

Jörgensen et al. (2017) investigated the amount of leisure-time PA in elderly chronic SCI subjects by using the Physical Activity Recall Assessment questionnaire. They found that the wheelchair-usage was strongly associated with lower levels of leisure-time PA confirming our results. Furthermore, they reported a median of 5 minutes per day of MVPA leisure-time PA in their cohort, which is much lower than our observations. Although the wheelchair users with moderate independence in our study did not show any time in MVPA, the majority of SCI subjects was clearly above this value. However, Jörgensen et al. (2017) only investigated self-reported leisure-time PA compared to our study in which we considered the PA during a complete day. Furthermore, the age of their sample size is higher, which might explain the discrepancy to our results further. Mesquita et al. (2017) investigated clusters of PA levels using a similar approach like ours, although on patients with a chronic obstructive pulmonary disease. They identified five distinct clusters of patients. The two pedestrian clusters in our study were comparable in terms of time spent in MVPA and MET-minutes of MVPA to the two second most active clusters ('sedentary exercisers' and 'busy bees'), suggesting that our cohort is rather active. The two 'wheelchair-users' clusters of our study lied in the range of their three most inactive clusters. However, Mesquita et al. (2017) did only look at ambulatory subjects.

7.5.4 Adherence to guidelines to literature

World Health Organisation (2011) suggests 150 min of MVPA intensity per week for healthy adults, which translates to a time spent on MVPA of > 30min on five days per week. These guidelines would be reached by all found PA clusters, but the wheelchair-dependent cluster with moderate independence which might not be able to reach it due to their impairment in the upper limbs and fewer possibilities to engage in high-intense PA. However, World Health Organisation (2011) further recommends that an activity in MVPA should last at least 10min. This is on average only reached by the ambulatory cluster with full walking capacity. Although this group spent more time in SED, this is the group in which most of the subjects adhered to the WHO guidelines, which were established for the healthy population. In the ambulatory cluster with moderate walking capacity half of the subjects, in the wheelchair-dependent cluster with high independence one-third of the subjects, and in the wheelchair-dependent cluster with moderate independence no subject did reach this guideline. This suggests that the guideline might be too challenging for people with impaired mobility. Martin Ginis et al. (2018) proposed a fitness guideline specific to the SCI population, which should aim at 2 0min of MVPA of aerobic exercise 2 times per week. Assuming that an activity should last at least 10 min in order to be treated as an 'exercise', both 'pedestrian' clusters reached this goal. The wheelchair-dependent cluster with high independence had a median of 11 minutes of MVPA per day over two to three days suggesting that they would reach this goal of 20 minutes on two days a week as well. Only the wheelchair-dependent cluster with moderate independence could not reach this goal with a median of 0 minutes of MVPA per day. Within the latter cluster many subjects were using an electric wheelchair during daily life and only occasionally using a manual wheelchair, which is not enough to reach the suggested minutes of MVPA. Eventually, the guideline by Martin Ginis et al. (2018) is too challenging for more severely impaired SCI subjects and needs to be updated to address the impairments of this SCI cohort. Neither the World Health Organisation (2011) guidelines, nor the guidelines from Martin Ginis et al. (2018) included LPA into their recommendations on PA. However, it has been shown that LPA can elicit an increase in brain volume (Spartano et al., 2019) and reduce the risk of cardiovascular diseases (Hamer et al., 2014). Therefore, we suggest including LPA in future guidelines as well.

With this work, we provide first observational-based norm values about PA in chronic SCI individuals which are specific to the mobility mode and independence and include several PA intensities. In a next step, these norm values have to be validated in order to reveal their suitability to serve as recommendations for the population of SCI.

7.6 Limitations

One main limitation of the study is our recruitment bias. SCI subjects agreeing to participate in our study were on general higher motivated patients who were mainly living independently. Especially, the ambulatory SCI subjects were good to very good walkers and the difference compared to the healthy controls was rather low. Therefore, subsequent studies should aim at a higher stratification of grades of impairment. Furthermore, the sample size appears to be a limitation as well. Although a set of 52 SCI subjects is a considerable large sample size, the heterogeneity in this population is very high. Larger sample size would be required to consolidate the found PA clusters further and eventually detect new clusters which might be present. A limitation of wearable sensors, in general, is that weight-loading activities are underestimated. Combining these sensors with heart-rate monitors may solve this. Lastly, the leisure time PA cannot be distinguished from the occupational time just by the use of sensors. A combination of the wearable sensor technology with well-established questionnaires like the Physical Activity Recall Assessment might be the next step towards a more comprehensive picture of subjects PA.

7.7 Conclusion

With this study we showed that there is an unknown variable, assumingly motivational-related, influencing the level of PA in subjects with a chronic SCI. Therefore, extracting lesion-specific guidelines becomes challenging. Although there is a relation between the mode of mobility and PA levels, this does not fully explain differences in observed PA levels. Our PA clusters give first hints about typical PA levels in chronic SCI subjects and can be used as rough guidelines of expected PA levels in subjects with a SCI. Especially during acute rehabilitation, these guidelines might be more appropriate to use as rehabilitation goals than commonly reported WHO guidelines. However, we did not investigate any health benefit of the suggested PA levels, and thus these are purely observational-driven. This research is a critical contribution to adapt existing guidelines of PA for individuals with an SCI and identifies clusters of PA, which can serve as a comparison to PA levels during acute rehabilitation and in interventional trials in which PA is assumed to drive a significant role.

8 General discussion

This thesis had two main aims. First, we targeted an extension of the current framework to assess physical activity (PA) in individuals with a spinal cord injury (SCI) developed within our research group by adding quantitative and qualitative measures of PA. This framework should enable clinicians during the clinical routine and investigators in clinical trials to track the progress of SCI individuals in terms of how they translate their functional capacity to performance in daily life. This also included the generation of a guideline on how many days clinicians and researchers need to measure PA to get reliable representations of the individuals overall PA level.

The second aim of the thesis was to provide a tool to evaluate the measured PA in acute SCI rehabilitation and chronic SCI subjects living in the home environment. To achieve this aim, representative data were acquired and analyzed. These led to first observational-based recommendations on PA that can help clinicians and researchers to evaluate the level of PA for the given impairment of the SCI individual and increase motivation for PA in general.

In the following chapter, the results of both aims will be discussed and a conclusion including an outlook to future work will be given.

8.1 Assessing physical activity

Within the scope of this work, new metrics were developed and validated to assess movement quantity and quality in individuals with an SCI.

An algorithm to distinguish accurately between sitting and lying posture in wheelchair-dependent individuals based on a single inertial measurement unit (IMU) attached to the chest was developed (Chapter 2). The algorithm is especially suitable in early rehabilitation of SCI patients, in which it is of great importance to track the mobilization of patients and ensure that they are mobilized regularly to reduce the risk of pressure ulcers and to activate circulation (Consortium for Spinal Cord Medicine, 2008). However, we observed that the fixation of the chest sensor using an elastic strap was challenging. Especially when patients started being more active, a frequent slipping of the sensor strap led to a change in the position of the sensor which could not guarantee a reliable detection of posture during daily life in all patients. However a better fixation of the sensor will appropriately address this issue.
The algorithm was not only applied to distinguish lying from sitting posture in wheelchair-dependent SCI individuals but also to separate sedentary and non-sedentary behavior in children and adolescents in a collaborative project together with the Rehabilitation Center Affoltern am Albis, University Children's Hospital Zurich. In this study, sensors at the thigh and ankle were used to distinguish lying position from sitting or standing (ankle sensor) and standing position from sitting and lying (thigh sensor). This application demonstrated the generalizability of the developed algorithm not only to other populations but also to other sensor locations (von Büren, 2017).

Furthermore, algorithms were developed to assess the energy expenditure of ambulatory SCI subjects (Popp et al., 2019a) and healthy controls (unpublished work) similar to the one that was developed for wheelchair-dependent SCI subjects (Popp et al., 2018). These algorithms were developed for a setup of 8 sensors (2 forefeet, 2 ankles, 2 wrists, hip, and chest). To guarantee the applicability and compliance during clinical routine and in intervention trials, we adapted the algorithms to a reduced set of 4 sensors, i.e., 2 ankles and 2 wrists (Popp et al., 2019b). Reducing the number of sensors decreased the accuracy only slightly ($\tilde{1}$%).

Based on these algorithms to estimate the energy expenditure, we calculated the metabolic equivalent of task (MET) and were thus able to extract PA intensity levels, which enabled us to investigate not only total PA in terms of activity counts and wheeling-specific PA but PA intensity and duration. Resting (REST), sedentary (SED), low-intense (LPA), and moderate-to-vigorous (MVPA) PA was defined by a MET < 1, $1 \leq$ MET ≤ 1.5, $1.5 <$ MET < 3, and MET ≥ 3, respectively (Ainsworth et al., 2011). The developed algorithm relied on the height and weight information of the individuals. In the longitudinal study with acute SCI patients, this information was not easily available. Therefore, we developed SCI-specific cut-offs values to approximate the energy expenditure by activity counts (AC). This approach is commonly applied in other studies (Schmitz et al., 2005; Innerd et al., 2018; Spartano et al., 2019). However, approximating energy expenditure based on the AC has been shown to be less accurate than estimating the energy expenditure by dedicated algorithms (Altini et al., 2015). This is why we only applied the AC cut-off approach in the longitudinal study and acquired height and weight information for the subsequent cross-sectional studies to increase the accuracy. In literature, both approaches are used commonly. However, the AC cut-offs strongly depend on the measurement device used and the specific population investigated (Hills et al., 2014). Therefore, we calibrated these AC cut-offs for the population of wheelchair-dependent and ambulatory SCI individually.

Besides these additional measures of movement quantity, we developed measures of movement quality.

Based on previous work (Leuenberger et al., 2017), a metric to quantify the forearm elevation was adapted to the population of tetraplegic SCI individuals (Chapter 3). By estimating the distribution of forearm elevation angles, we were able to predict whether SCI individuals showed compensatory strategies while performing activities of daily living (ADLs) (Schneider et al., 2019a). We also showed the potential of quantifying the amount of upper limb compensation. The algorithm is dependent on a single wearable sensor attached to the wrist, which makes it easily applicable in daily clinical routine and intervention trials.
So far, this metric is only applicable to previously classified ADLs. For extracting the upper limb compensation out of 24h-measurements, a classification into ADLs is required but has not been developed so far. However, during inpatient rehabilitation, this algorithm can be applied to detect and quantify upper limb compensation from sensor-enriched assessments such as the Graded Assessment of Prehension (GRASSP, Kalsi-Ryan et al., 2012a) in SCI.
With this algorithm, we present the first tool to objectively assess compensatory movement in

the upper limbs of tetraplegic patients, which is easily applicable in clinical routine and clinical intervention studies. In combination with the GRASSP, this metric will enable researchers to distinguish functional recovery driven by biological repair and compensatory strategies in an easy and objective way.

Within the scope of this thesis work, a master thesis was conducted to quantify the efficiency during manual wheelchair propulsion (Arcari, 2017). Algorithms were developed to identify single strokes, to distinguish between different rim patterns (under-rim and over-rim), and to estimate the wheeling efficiency based on IMUs attached to both wrists and the right wheel of the wheelchair. The accuracy of distinguishing the over-rim from the under-rim stroke pattern was 100% and outperformed algorithms stated in the literature with reported accuracies from 90 to 96% (French et al., 2008; Ramirez Herrera et al., 2018). It could be shown that the under-rim pattern was more efficient than the over-rim pattern. This is in line with findings in literature stating a higher efficiency and reduced risk of upper limb trauma for under-rim patterns (Boninger et al., 2002; Kwarciak et al., 2009). While algorithms to detect propulsion patterns based on wearable sensors have been proposed previously (French et al., 2008; Ramirez Herrera et al., 2018), we presented the first tool to estimate the wheeling efficiency using wearable sensors as well. With the help of these algorithms, therapists can monitor the wheeling performance of SCI individuals, analyze their patterns, and adapt the strategies to optimize the efficiency and reduce upper limb pain, which has been shown to be a limiting complication in wheelchair-dependent SCI individuals (Curtis et al., 1999).

A second master thesis was conducted, which focused on the development of the first algorithm to assess gait quality in SCI individuals using wearable sensors (Werner, 2018). An algorithm was developed to detect gait events from previously classified periods of walking and to estimate temporal and spatial gait parameters based on wearable sensors attached to both ankles. The gait event detection had an excellent sensitivity of 99.6%. The mean absolute error in estimating the heel strike and toe off was below the frame rate of the video recording, which was used as a validation method. The error in estimating the step length was with 3.75 $\pm$ 3.56% highly comparable to the results stated in the literature (3%) for hemiparetic gait (Trojaniello et al., 2014). Features like the step length and step duration strongly correlated with the distance in the 6 minute walk test (6MWT). This demonstrates the validity of the developed algorithms. Other features, e.g., gait symmetry, did not correlate with the distance in the 6MWT, which confirms results from previous studies (Tang et al., 2006). This suggests that we were able to capture features, which yield additional information about gait quality like symmetry, smoothness, and risk of falling.

Lastly, an analysis was conducted to identify how many days of measurement are needed to obtain a reliable representation of the PA levels in acute and chronic SCI individuals (Chapter 4). We showed that during acute rehabilitation, at least 2 days of measurement were required to get reliable measures of PA, while at least 3 days were required in chronic individuals. For chronic SCI individuals, Sonenblum et al. (2012b) proposed a measurement duration of 3 days to reliably capture wheeling distance which is in line with our results. Our study was the first to investigate the reliability of PA intensity times in acute and chronic SCI individuals and of the wheeling distance in acute SCI individuals.

8.2 Evaluating physical activity

The second aim of this thesis was to acquire and interpret reference data about PA in SCI individuals. Therefore, a longitudinal study to measure PA during acute rehabilitation and cross-sectional studies to measure PA in chronic wheelchair-dependent and ambulatory SCI individuals and healthy controls was conducted.

The longitudinal study revealed that PA was increasing during acute rehabilitation from 2 weeks after injury until 6 months after injury in paraplegic and tetraplegic patients. However, there was a slight mismatch about the increase of PA in paraplegic patients in both longitudinal analyses we conducted (Chapter 5 and Chapter 6). In the first analysis (Chapter 5), the increase of PA in paraplegic SCI individuals was not significant, whereas we observed a significant increase in the second analysis (Chapter 6). However, in the first analysis, we investigated the change in paraplegic SCI individuals from 1 months until 6 months after injury, including already discharged patients. In contrast, we focused on inpatient rehabilitation in the second analysis. Furthermore, we included a measurement at 2 weeks after injury. The increase from 2 weeks to 1 month after injury was highly significant (p-value <0.001), whereas the increase from 1 month to 3 months was significant with a p-value of 0.045. This increase could only be detected as a trend in the previous study, probably due to a smaller sample size.

The independence of patients, assessed in terms of the SCIM self-care subscore, was a significant contributor modulating the increase of PA in SCI individuals. The increase of PA was stronger related to the increase in independence in paraplegic than in tetraplegic patients. In tetraplegic patients, additional factors, like an increased upper limb strength and an increased effort to perform ADLs, contributed to the increased PA during rehabilitation. Nevertheless, at later stages, the relationship between upper limb strength and PA was less strong, which can be explained by learned compensatory strategies in the upper limbs. This could also explain the comparable upper limb PA levels (in terms of AC) of tetraplegic and paraplegic patients towards the end of inpatient rehabilitation. Zbogar et al. (2016) also investigated the change of upper limb AC in para- and tetraplegic patients from admission to discharge. Comparable to our study, they found a significant increase in upper limb AC in tetraplegic patients. They observed an increase of upper limb AC in paraplegic patients as well, however this increase was not significant. In contrast to our study, Zbogar et al. (2016) did not measure the PA at fixed time windows, but at admission and at discharge. This led to varying time periods between the two measurements, which could explain the discrepancy compared to our results. Compared to our study in which we should similar upper limb PA at 6 months after injury in para-and tetraplegic patients, Zbogar et al. (2016) found upper limb AC twice as high in paraplegic SCI individuals than in tetraplegic individuals at discharge. According to the reported grip strength of the tetraplegic patients in the study of Zbogar et al. (2016), they included tetraplegic patients with more severe impairments than we could include in our study. This could have led to much lower levels of PA in tetraplegic patients compared to the paraplegic patients.

Despite this eventually too low stratification in impairment levels in our study, we observed a significant difference in terms of MVPA between paraplegic and tetraplegic patients at 6 months after injury. We were the first to show that assessing the PA intensity levels gives a more sensitive measure to estimate differences between patient groups and individual improvements than AC.
Besides lower levels of MVPA, we observed higher levels of LPA in tetraplegic patients compared to paraplegic patients when controlling for the differences in independence. It has been shown that ADLs are mainly low intense activities (Popp et al., 2018, 2019a; Ainsworth et al., 2011), which suggests that tetraplegic patients need to spend more time for handling ADLs than paraplegic patients. A prolonged movement duration can explain these higher levels of LPA in tetraplegics due to their impairment in the upper limbs (Mateo et al., 2015) and the resultant use of compensatory strategies. Assessing movement quality, i.e., with our presented algorithm to detect upper limb compensation (Chapter 3), would be required to confirm this hypothesis.

Additional to the independence, mobility affected the level of PA. SCI individuals using a wheelchair showed higher levels in LPA, but lower levels of MVPA than ambulatory SCI individuals. Mobility constitutes a significant part of PA during daily life (Jörgensen et al., 2017). Furthermore, wheeling at 2 and 5km/h has been shown to be less intense (MET: 2.5 and 3.7) than walking at 2 and 5km/h (MET: 2.8 and 4.4) (Popp et al., 2018, 2019a). This explains the lower levels of MVPA and higher levels of LPA in wheelchair-dependent SCI individuals.

Based on the cross-sectional studies, we could reveal the importance of independence and mobility on PA levels in chronic SCI individuals as well. PA levels of chronic SCI and healthy controls clustered into 4 distinct classes, with 2 wheelchair-dependent and two ambulatory clusters. This confirms the strong influence of the mobility on the PA levels. The two wheelchair-dependent classes were further separated into a highly independent group (i.e., high SCIM self-care scores) and a group with limited independence, also demonstrating the significant influence of the independence.
However, we hypothesized that other factors than demographical and injury-related factors additionally influenced the amount of PA. This was already hypothesized in a previous study investigating leisure-time PA in chronic SCI-individuals using questionnaires (Jörgensen et al., 2017). We hypothesized these additional factors to be associated with motivation, since intrinsic and extrinsic motivation have been shown to be crucial determinants for engaging in PA (Allender et al., 2006; Hagger and Chatzisarantis, 2008; Teixeira et al., 2012; Parish and Treasure, 2013) . Future studies need to investigate this further by using dedicated questionnaires to

assess intrinsic and extrinsic motivational factors and disentangle them from lesion-specific limitations in engaging in PA.

We can assume that motivation does not only play a significant role in PA levels in chronic SCI individuals but might also influence PA levels during acute rehabilitation and is thus to be maximized. The potential of wearable sensors to increase PA has been shown in several studies (Wang et al., 2015; Coughlin and Stewart, 2016; Cooper et al., 2018). To increase the motivation for PA and give appropriate goals, we build first lesion-specific recommendations which are based on observational data about typical PA patterns in chronic SCI individuals and healthy controls.

8.3 Towards physical activity recommendations

In order to guide PA in acute and chronic SCI individuals, appropriate recommendations about PA levels are required. The World Health Organization (WHO) set guidelines to engage in 150 min of MVPA per week (World Health Organisation, 2011). This activity should be performed in bouts of at least 10min of continuous PA. However, these guidelines were established for the healthy population. Therefore, Martin Ginis et al. (2018) proposed a fitness guideline specific to the SCI population, aiming at 20 min of MVPA of aerobic exercise 2 times per week. Yet, this guideline does not distinguish between different modes of mobility. Furthermore, like the WHO guidelines, it only focuses on MVPA, whereas it has been shown in previous studies that engaging in LPA was associated with a lower risk of cardiovascular diseases (Hamer et al., 2014), and an increased brain volume (Spartano et al., 2019) and thus should not be neglected.

With this work, we aimed at providing first observational-based PA recommendations which are lesion-specific and cover not only MVPA but also different levels of intensities. Initially, we aimed at providing lesion-level-specific guidelines, e.g., for tetraplegic and paraplegic patients. Novel insight from our studies required an alternative approach to set these guidelines.
In our longitudinal study and in the cross-sectional studies, we observed that the PA levels are mainly dependent on mobility and independence and not necessarily on the lesion-level solely. Therefore, we were the first to propose building recommendations specific for the mode of mobility, i.e., for wheelchair-dependent and ambulatory SCI individuals and, eventually, to include the level of independence into these recommendations.
However, we have to state that adapting PA recommendations to the level of independence, as assessed using the SCIM self-care domain, might be controversial. The SCIM self-care asks for the independence in performing ADLs, such as dressing. In the early stages of SCI rehabilitation, we can assume that the performance of patients in accomplishing ADLs might be very similar to their capacity. In other words, in early rehabilitation, the SCIM self-care score can be interpreted as a measure of capacity.
However, in chronic SCI individuals, the performance of the patients is less than the capacity. Therefore, the SCIM self-care score has to be interpreted as a performance measure, which is influenced by motivational factors and not solely by the level of impairment.

As a consequence, building PA recommendations based on this performance measure, which includes motivational factors already, might give misleading recommendations. We would preferably need a measure of the capacity of independence (i.e., is the patient able to perform a particular task) to give truly impairment driven recommendations. This could be easily achieved by asking the SCIM self-care differently. Instead of asking whether the patient regularly performs a particular task independently, we would be interested in whether the patient is be able to perform a particular task independently. Future studies need investigate the relation between SCIM self-care as a performance and capacity assessment of independence, motivation, and PA levels further.

Nevertheless, for the first recommendations, we obtained representative PA levels, which were based on the previously presented clustering approach, for the following four groups: wheelchair-dependent SCI individuals with moderate level of independence, wheelchair-dependent SCI individuals with high level of independence, ambulatory SCI subjects with moderate walking capacity, and ambulatory SCI subjects with high walking capacity. As mentioned earlier, we did not include many patients with severe impairments (i.e., low independence and low walking capacity) due to a bias in the recruitment. In future studies, PA of these subpopulations need to be acquired as well.
In Table 8.1 we give the 25^{th}, 50^{th}, and 75^{th} percentile of all PA intensity levels for these 4 groups normalized to a 16h day (excluding sleep). We suggest using the 75^{th} percentile for LPA and MVPA and 25^{th} percentile for REST and SED as a goal to increase the motivation for the patients. Furthermore, the SCIM mobility indoors and outdoors subscores, SCIM self-care subscores, and the 6MWT distances are given for each group to facilitate the choice of the right class for which the recommendations should be given. These values can serve as the first evidence for typical PA levels and can be given as goals during acute rehabilitation and potentially after discharge.

	wheelchair-dependent SCI moderate independence	wheelchair-dependent SCI high independence	ambulatory SCI moderate walking capacity	ambulatory SCI/control high walking capacity
# subjects [-]	10	10	7	19
female (%)	20	20	14	21
age [years] (mean (SD))	46.5 (16.8)	47.5 (15.2)	65 (11.5)	56 (14.5)
SCIM self-care [-]	13 (7 - 18)	20 (20-20)	20 (20-20)	20 (20-20)
SCIM mobility in-outdoors [-]	6 (5 - 9)	8 (8-9)	27 (24 - 29)	30 (29 - 20)
distance 6MWT [m]	-	-	417 (342 - 487)	578 (522 - 709)
MVPA [min/16h]	0.2 (0 - 7.2)	32.1 (24.0 - 52.2)	198.0 (150.5 - 234.4)	207.1 (156.1 - 279.3)
MVPA in bouts > 10min [min/16h]	0 (0 - 0)	7.9 (0- 19.0)	17.8 (5.8 - 45.4)	44.9 (23.4- 73.4)
LPA [min/16h]	265.1 (144.0 - 379.8)	507.0 (487.9 - 609.8)	451.8 (389.0 - 510.1)	155.2 (146.0 - 189.4)
SED [min/16h]	492.2 (460.1 - 547.3)	325.1 (292.5 - 393.8)	199.1 (88.6 - 238.5)	522.7 (458.9 - 565.5)
REST [min/16h]	107.6 (51.6 - 280.3)	24.5 (9.5 - 39.0)	82.3 (62.9 - 202.5)	52.5 (23.6 - 97.4)
REST + SED [min/16h]	678.9 (572.65 - 815.9)	405.4 (327.4 - 439.6)	320.8 (248.4 - 335.6)	575.2 (541.4 - 613.7)

Table 8.1 – PA level recommendations for the groups of wheelchair-dependent SCI individuals with moderate and full independence, and ambulatory SCI individuals with moderate and full walking capacity. The median (25^{th} - 75^{th} percentile) is given in minutes per 16h for the PA levels moderate-to-vigorous PA (MVPA), low-intense PA (LPA), sedentary PA (SED), resting (REST), and the sum of SED and REST. Median (25^{th} - 75^{th} percentile) is also given for the SCIM self-care, SCIM mobility indoors and outdoors and distance in 6-Minute Walk Test (6MWT) in meter for each group. Mean age and standard deviation (SD) is given in years.

To evaluate the validity of the given recommendations, we compared them with results from the longitudinal study at the latest stage of inpatient rehabilitation, i.e., 6 months after injury, and to values based on wearable sensor-based PA measurements of the healthy population stated in the literature.
At 6 months after injury, only wheelchair-dependent patients were in the inpatient rehabilitation. We observed median SCIM self-care scores of 8.5 (7.8 – 15.3) and mobility indoors and outdoors scores of 6 (4.8 – 7), which matches the scores of the chronic wheelchair-dependent SCI group with moderate independence (Table 8.1). In the inpatient rehabilitation, the time spent in MVPA was with 21.2 (11.8 – 51.4) min higher than in the chronic group with moderate independence and almost reached values of the highly independent group. Also, the time spent in LPA was higher than in the moderate independence group but lower than in the highly independent group. This implies that chronic PA levels are lower than at the end of inpatient rehabilitation. This is expected since patients are pushed during inpatient rehabilitation to be as active as possible (i.e., high extrinsic motivation) to promote recovery. After discharge, this extrinsic motivation is likely disappearing, and SCI individuals have to follow their intrinsic motivation. One promising approach to keep this extrinsic motivation is the usage of wearable sensors as discussed earlier in this thesis.
However, this also suggests that the recommendations for the moderate independence group are set too low and recommendations of the highly independent group could be given even to patients with lower levels of independence. This also reflects the controversy about the SCIM self-care score being a mixture between performance and capacity measure. Further research need to investigate this in more detail.

Next, we compared the acquired values for the chronic ambulatory group with high walking capacity to values reported in the literature. However, this turned out to be challenging due to different reporting guidelines and different methodologies used. Table 8.2 gives an overview of PA levels acquired in three different studies. In all of the investigated studies, SED did also include REST without distinguishing these two intensities. Therefore, we compare the reported SED to our combined SED and REST. Unfortunately, not all studies reported the exact MET cut-points used.
Furthermore, normalization to the wear time of the sensor was only reported in one study (Spartano et al., 2019). Nevertheless, all studies only included hours of waking time in their analysis. Therefore, we compared the reported results from the literature to our results standardized to an average awake day, i.e., 16h.

	Schneider2019 - chronic full walking capacity	Laeremans2017	Innerd2019	Spartano2019
Population	ambu SCI / healthy	healthy	healthy	healthy, diabetes, etc
Sensor location	wrists + ankles	triceps	waist	hip
Device	ReSense/ZurichMOVE	SenseWear	Actigraph GT3X+	Actical
SED (MET)	< 1.5	< 1.5	n.r.	n.r.
LPA MET)	1.5 - 3	-	n.r.	n.r.
MVPA (MET)	> 3	> 3	n.r.	n.r.
norm to wear time	yes	n.r.	n.r.	partly
Age [yrs] (mean (SD))	56 (14.5)	35 (10)	~ 44 (9)	53 (13)
Gender (%female)	21	54	49	54.2
MVPA [min]				
median (25% - 75%)/day	190.7 (172.2 - 290.5)[a]	-	-	19.9 (9.8 - 34.9)[b]
mean (SD)/day	217.2 (68.8)[a]	-	158 (17)[b]	-
MVPA in bouts > 10min [min]				
median (25% - 75%)/day	44.9 (23.4- 73.4)[a]	71 (49-111)[b]	-	-
LPA [min]				
mean (SD)/day	162.8 (34.9)[a]	-	-	142.2 (49.8)[a]
REST + SED [min]				
median (25% - 75%)/day	575.2 (541.4 - 613.7)[a]	550 (481-635)[b]	-	-
mean (SD)/day	580.0 (63.2)[a]	-	560 (60)[b]	789.0 (61.2)[a]

Table 8.2 – Comparison between PA levels from our study in ambulatory SCI and healthy controls with high walking capacity.
[a] PA levels are standardized to a 16h-day of waking time. [b] Standardization of PA levels is not reported, but assessed during one complete day excluding sleep.

The study by Laeremans et al. (2017) investigated SED and MVPA of 122 healthy control subjects with an average age of 35 ± 10 yrs. MVPA performed in bouts of ≥ 10min was summed up. In this study, the SenseWear device was used attached to the triceps. The time spent in SED was very similar to what we observed in our population, while MVPA was slightly higher (approx. 25min) in their study population than in our cohort. However, their study population was 20 yrs younger than our study cohort. Since age has been reported to correlate negatively with PA (Colley et al., 2011; Ramirez et al., 2018), this difference in age distribution can explain the lower values of MVPA in our study population.

The study by Innerd et al. (2018) investigated MVPA, SED, and walking in a healthy population of 120 subjects with a mean age of 44 ± 9 yrs. They assessed the relationship between PA measured by an accelerometer (Actigraph GT3X+) attached to the waist in normal, overweight and obese subjects. To compare this study to our results, we only investigated the reported MVPA and SED measured by the accelerometer in the normal weight population. Innerd et al. (2018) reported a mean time spent in MVPA of 158 ± 18 min. This is lower than our observed values (217.2 ± 68.8 min). However, considering our relatively high standard deviations, the values between our studies lie in a comparable range. Lower levels of MVPA in the study population of Innerd et al. (2018) might be due to higher percentage of included women (49% compared to 21% in our study population), as it has been shown that MVPA is decreased in women compared to men (Hansen et al., 2012). The time spent in SED is highly similar in our full walking capacity class compared to the study population of Innerd et al. (2018), which can prove the validity of our chosen method.

The study by Spartano et al. (2019) investigated SED, LPA, and MVPA in 2354 participants including healthy subjects, subjects with diabetes, stage 2 hypertension, and cardiovascular disease using an Actical sensor attached the hip. The time spent in LPA was very similar in our study compared to the study of Spartano et al. (2019). However, we found a high discrepancy of MVPA and SED. Spartano et al. (2019) reported much higher SED than we observed, with times spent in MVPA being 10 times smaller than in our cohort. One possible explanation for this is that Spartano et al. (2019) did not only include healthy subjects leading to reduced PA in their cohort. Furthermore, Spartano et al. (2019) estimated the PA intensity levels by using AC cut-off values which were validated in the younger population and thus might be too high for the population they were looking at (Barnett et al., 2016). Furthermore, it has been shown that AC cut-offs can result in a decreased accuracy of up to 88% compared to dedicated algorithms (Altini et al., 2015) and significantly underestimate MVPA (Ellis et al., 2016). Furthermore, our study population was recruited in Switzerland, Spartano et al. (2019) recruited in the US. Possibly, the population in Switzerland is indeed more active than the population in the US. A study by Althoff et al. (2017) analyzed the number of steps taken in 717'527 people in 111 countries based on smartphone measurements. This study confirmed the hypothesis that people in Switzerland take more steps (5512) than people in the US (4774). However, Spartano et al. (2019) reported the estimated number of steps of 7519 which is even higher than what Althoff et al. (2017) observed in Switzerland. To fully reveal this discrepancy, a study would need to be performed estimating the PA in both countries using the same accurate device and algorithms to estimate the energy expenditure.

To conclude, evaluating the validity of our proposed PA recommendations poses challenges due to different methodologies used in the literature. Not only different wearable sensors are used but also different algorithms to extract metrics of PA and different reporting guidelines make the comparison between different studies almost impossible. Therefore, we appeal to researchers working on PA to clearly report, which methods were used, e.g., to extract PA intensity levels (by clearly stating chosen cut-off values) and whether/ how PA was normalized to the wear time of the sensors. More research is required to validate and improve our built recommendations by collecting data from a larger cohort of subjects including acute SCI individuals using a uniform methodology. Furthermore, we did not (and did not aim to) investigate the health benefits of our first proposed observational-based PA recommendations but aimed at reporting typical PA values specific for the mobility mode and level of independence. We propose to adapt health recommendations as given by Martin Ginis et al. (2018) specific to mobility modes and levels of independence in order to set realistic goals, which can be used to motivate for more PA in acute and chronic SCI individuals.

8.4 Thesis contributions

The two major aims to extend the current existing framework to assess PA in SCI individuals by additional quantitative and qualitative measures (Part I of this thesis) and to evaluate the acquired PA metrics (Part II of this thesis) and give first observational-based PA recommendations have been achieved. In addition to the main achievements, several additional contributions were made within this thesis. First, this thesis contributed to the validation of our framework to assess PA in individuals with a spinal cord injury (Brogioli et al., 2016b). Second, contributions were made towards the analysis pipeline which automatically creates reports for patients and clinicians as soon as data is uploaded to a central server. This automated report generation helped to establish the framework in the clinical routine and made it possible to integrate it into an upcoming multicenter clinical trial (Nogo Inhibition in Spinal Cord Injury, NISCI, NCT03935321). Third, our framework to assess PA has been applied in clinical studies like the INSTrUCT-SCI (NCT03069404) and a Body Weight Supported Training Study (NCT03534518). Last, the sensor framework together with the automated reports have also been applied in outreaching events like the Scientifica 2017 (Scientifica 2017) and the Jeux Intercentres 2018 (Universitätsklinik Balgrist Blog 2018).

8.5 Conclusion and outlook

This thesis constitutes a major contribution towards the goal to have the first comprehensive framework to assess and to evaluate PA in individuals with an SCI. This was achieved by delivering tools to assess the quantity and quality of PA and to give recommendations about typical PA levels in SCI individuals in order to evaluate measured PA levels in the clinical setting or the home environment. Due to the rather low and adjustable number of sensors needed, the framework is applicable in the clinical routine and in clinical intervention trials.

To assess PA in SCI individuals, our currently available framework comprises algorithms to quantify upper limb PA using AC, wheeling activities (Popp et al., 2016), posture of wheelchair-dependent individuals (Schneider et al., 2017), and energy expenditure in wheeling (Popp et al., 2018) and walking SCI individuals (Popp et al., 2019a). This includes the estimation of PA intensity times based on the energy expenditure algorithm and based on AC cut-offs. An algorithm to quantify gait in SCI individuals is currently under development by László Demkó from our group and needs to be validated in the next step.
Furthermore, an algorithm to quantify ADLs during long-term measurements is required. However, this will be challenging due to the high variability in ADLs where no regular movement patterns, like in walking and wheeling, are existent. Eventually, labeled norm data of various ADLs would need to be acquired in order to apply supervised machine learning techniques aiming at classifying these activities. To assess movement quality, our framework comprises algorithms to assess the upper limb laterality (Brogioli et al., 2016a), upper limb compensation (Schneider et al., 2019a), wheeling efficiency (Arcari, 2017), and gait quality (Werner, 2018). To apply the measures of upper limb compensation and gait quality to long-term measurements, algorithms to classify walking activities (as developed by László Demkó) and activities of daily living will be required.

An additional metric which could nicely complement our framework would be the assessment of balance of SCI individuals while standing, as an improved balanced has been shown to improve static stability and gait in SCI individuals (Tamburella et al., 2013). Balanced training is often performed in acute rehabilitation during the transition from wheelchair to ambulatory mobility (Nas, 2015) and it thus would be helpful to quantify it additional to the wheeling and walking activities. Furthermore, a robust sleep detection algorithm would facilitate the exclusion of sleep time during long-term measurements. So far, the sleep time was excluded by visual inspection of the IMU data with the help of daily activity logs filled by the subjects. However, this method requires much effort due to the manual work required and is not accurate especially in very acute stages after the injury. In these stages patients lie almost a whole day in bed and have trouble sleeping at all. Currently, a sleep detection algorithm is developed by Franziska Ryser for our used sensor device and would need adaption and validation in the population of SCI once the development is finished. Lastly, an assessment tool to measure spasticity would round off our framework. Spasticity is reported in up to 78% of individuals with an SCI and drastically decrease quality of life limiting ADLs in general (reviewed in Adams and Hicks, 2005). At the moment spasticity is not detected in IMU-measurements and could be treated as PA falsely. Therefore, we suggest developing an algorithm to detect and assess spasticity to reduce this potential overestimation of PA elicited by spasticity. Furthermore, a detection of spasticity could track the efficiency of antispastic medications and physical therapy. However, this detection might be challenging and may be only achievable by using additional sensing modalities like EMG sensors (Arami et al., 2017; Lonini et al., 2017).

To evaluate PA in SCI individuals, this thesis added norm values of PA in chronic SCI individuals and insights about factors influencing PA levels in acute and chronic SCI to our existing framework on assessing PA in SCI. We were the first to show that the PA is increasing during the rehabilitation and independence and mobility of SCI individuals are main factors influencing the PA and it is not necessarily the lesion-level alone which influences PA. Thus, our initial goal to build lesion-level specific recommendations became challenging. This is why we chose to give recommendations specific for mobility modes and independence, which is novel to the field. We revealed another important role driving PA levels, which we hypothesized to be motivation as has been proven for the healthy population already (Allender et al., 2006; Hagger and Chatzisarantis, 2008; Teixeira et al., 2012; Parish and Treasure, 2013). Thus, we suggest to include motivational questionnaires like the Physical Activity and Leisure Motivation Scale (Molanorouzi et al., 2014) into future studies to account for it and investigate this effect further.

Furthermore, still unclear is the causality between PA and functional recovery. Does an increased PA indeed elicit functional recovery? Or is an increased PA just resulting from an increased functional recovery? Although there is strong evidence that PA increases functional recovery, future research needs to confirm the hypothesis and reveal the exact influence of task-specificity, intensity, duration, and timing of PA on functional recovery. To answer these questions, a huge amount of measurements in a high temporal resolution would be required to reveal the timing of changes in PA and recovery and eventually reveal the effect of PA on recovery. Our framework gives a tool to researchers to tackle these challenging questions.

The effect of plasticity-enhancing medications on the functional recovery in SCI will be investigated in future clinical intervention studies like the NISCI trial. In these studies, PA acts as a confounder with the potential to modulate neuronal plasticity and thus recover independently from or in interaction with the medication. Therefore, researchers need to control for this confounder, which can be done using our framework to assess PA. Furthermore, biological recovery would need to be disentangled from compensation to investigate the effectiveness of clinical interventions. Applying algorithms to assess gait quality and upper limb compensation developed within our framework will help to understand whether functional recovery was driven by true biological recovery or by learned compensatory strategies.

To summarize, we now have a framework which can be and is currently implemented into the clinical routine of acute SCI rehabilitation and clinical intervention trials. This framework enables clinicians and researchers to assess movement quantity and quality and to evaluate and understand measured PA levels using our acquired norm data. We delivered the first comprehensive framework with which researchers will be able to entangle the causality between PA and functional recovery, investigate the effect of new therapeutic interventions and increase the PA in acute and chronic SCI individuals in order to improve the effect of rehabilitation and the quality of life of individuals with an SCI.

Bibliography

Aadland, E. and Ylvisaker, E. (2015). Reliability of objectively measured sedentary time and physical activity in adults. *PLoS ONE* 10, e0133296. doi:10.1371/journal.pone.0133296

Adams, M. M. and Hicks, A. L. (2005). Spasticity after spinal cord injury. *Spinal Cord* 43, 577–586. doi:10.1038/sj.sc.3101757

Ainsworth, B. E., Haskell, W. L., Herrmann, S. D., Meckes, N., Bassett, D. R., Tudor-Locke, C., et al. (2011). 2011 compendium of physical activities: A second update of codes and MET values. *Medicine and Science in Sports and Exercise* 43, 1575–1581. doi:10.1249/MSS.0b013e31821ece12

Albert, M. V., Azeze, Y., Courtois, M., and Jayaraman, A. (2017). In-lab versus at-home activity recognition in ambulatory subjects with incomplete spinal cord injury. *Journal of NeuroEngineering and Rehabilitation* doi:10.1186/s12984-017-0222-5

Alexander, M. S., Anderson, K. D., Biering-Sorensen, F., Blight, A. R., Brannon, R., Bryce, T. N., et al. (2009). Outcome measures in spinal cord injury: Recent assessments and recommendations for future directions. *Spinal Cord* 47, 582–591. doi:10.1038/sc.2009.18

Allender, S., Cowburn, G., and Foster, C. (2006). Understanding participation in sport and physical activity among children and adults: A review of qualitative studies. *Health Education Research* 21, 826–835. doi:10.1093/her/cyl063

Alluin, O., Delivet-Mongrain, H., Gauthier, M. K., Fehlings, M. G., Rossignol, S., and Karimi-Abdolrezaee, S. (2014). Examination of the combined effects of chondroitinase ABC, growth factors and locomotor training following compressive spinal cord injury on neuroanatomical plasticity and kinematics. *PLoS ONE* 9, e111072. doi:10.1371/journal.pone.0111072

Althoff, T., Sosič, R., Hicks, J. L., King, A. C., Delp, S. L., and Leskovec, J. (2017). Large-scale physical activity data reveal worldwide activity inequality. *Nature* 547, 336–339. doi:10.1038/nature23018

Altini, M., Penders, J., Vullers, R., and Amft, O. (2015). Estimating energy expenditure using body-worn accelerometers: A comparison of methods, sensors number and positioning. *IEEE Journal of Biomedical and Health Informatics* 19, 219–226. doi:10.1109/JBHI.2014.2313039

Anderson, K. D. (2004). Targeting Recovery: Priorities of the Spinal Cord-Injured Population. *Journal of Neurotrauma* 21, 1371–1383. doi:10.1089/neu.2004.21.1371

Arami, A., Tagliamonte, N. L., Tamburella, F., Huang, H. Y., Molinari, M., and Burdet, E. (2017). A simple tool to measure spasticity in spinal cord injury subjects. In *IEEE International Conference on Rehabilitation Robotics* (IEEE), 1590–1596. doi:10.1109/ICORR.2017.8009475

Arcari, L. (2017). *Assessing the efficiency of wheelchair propulsion in chronic spinal cord injured wheelchair-bound individuals.* Master thesis, ETH Zurich

Asghar, G. and Saleh, Z. (2012). Normality Tests for Statistical Analysis A Guide for Non-Statisticians. *International Journal of Endocrinology and Metabolism* 10, 486–489.

Awai, L. and Curt, A. (2014). Intralimb coordination as a sensitive indicator of motor-control impairment after spinal cord injury. *Frontiers in Human Neuroscience* 8. doi:10.3389/fnhum.2014.00148

Awais, M., Palmerini, L., Bourke, A., Ihlen, E., Helbostad, J., and Chiari, L. (2016). Performance Evaluation of State of the Art Systems for Physical Activity Classification of Older Subjects Using Inertial Sensors in a Real Life Scenario: A Benchmark Study. *Sensors* 16, 2105. doi:10.3390/s16122105

Bailey, R. R., Klaesner, J. W., and Lang, C. E. (2014). An accelerometry-based methodology for assessment of real-world bilateral upper extremity activity. *PLoS ONE* 9, e103135. doi:10.1371/journal.pone.0103135

Bailey, R. R., Klaesner, J. W., and Lang, C. E. (2015). Quantifying Real-World Upper-Limb Activity in Nondisabled Adults and Adults with Chronic Stroke. *Neurorehabilitation and Neural Repair* 29, 969–978. doi:10.1177/1545968315583720

Bandmann, E. (2008). Physical activity questionnaires - A critical review of methods used in validity and reproducibility studies. *Health (San Francisco)* 17, 2005–2008. doi:10.1016/S0140-6736(11)60393-0

Barnett, A., Van Den Hoek, D., Barnett, D., and Cerin, E. (2016). Measuring moderate-intensity walking in older adults using the ActiGraph accelerometer. *BMC Geriatrics* 16, 211. doi:10.1186/s12877-016-0380-5

Barreira, T. V., Schuna, J. M., Tudor-Locke, C., Chaput, J.-P., Church, T. S., Fogelholm, M., et al. (2015). Reliability of accelerometer-determined physical activity and sedentary behavior in school-aged children: a 12-country study. *International Journal of Obesity Supplements* 5, S29–S35. doi:10.1038/ijosup.2015.16

Basso, D. M. and Lang, C. E. (2017). Consideration of Dose and Timing When Applying Interventions after Stroke and Spinal Cord Injury. *Journal of Neurologic Physical Therapy* 41, S24–S31. doi:10.1097/NPT.0000000000000165

Baumann, S., Groß, S., Voigt, L., Ullrich, A., Weymar, F., Schwaneberg, T., et al. (2018). Pitfalls in accelerometer-based measurement of physical activity: The presence of reactivity in an adult population. *Scandinavian Journal of Medicine and Science in Sports* 28, 1056–1063. doi:10.1111/sms.12977

Beekhuizen, K. S. and Field-Fote, E. C. (2005). Massed practice versus massed practice with stimulation: Effects on upper extremity function and cortical plasticity in individuals with incomplete cervical spinal cord injury. *Neurorehabilitation and Neural Repair* 19, 33–45. doi:10.1177/1545968305274517

Beekhuizen, K. S. and Field-Fote, E. C. (2008). Sensory Stimulation Augments the Effects of Massed Practice Training in Persons With Tetraplegia. *Archives of Physical Medicine and Rehabilitation* 89, 602–608. doi:10.1016/j.apmr.2007.11.021

Behrman, A. L., Ardolino, E. M., and Harkema, S. J. (2017). Activity-Based Therapy: From Basic Science to Clinical Application for Recovery after Spinal Cord Injury. *Journal of Neurologic Physical Therapy* 41, S39–S45. doi:10.1097/NPT.0000000000000184

Berger, R. L. and Hsu, J. C. (1996). Bioequivalence Trials, Intersection–Union Tests and Equivalence Confidence Set. *Statistical Science* 11, 283–319

Bize, R., Johnson, J. A., and Plotnikoff, R. C. (2007). Physical activity level and health-related quality of life in the general adult population: A systematic review. *Preventive Medicine* 45, 401–415. doi:10.1016/j.ypmed.2007.07.017

Bland, J. and Altman, D. G. (1986). Statistical methods for assessing agreement between two methods of clinical measurement. *The Lancet* 327, 307–310. doi:10.1016/S0140-6736(86)90837-8

Blesch, A. and Tuszynski, M. H. (2009). Spinal cord injury: plasticity, regeneration and the challenge of translational drug development. *Trends in Neurosciences* 32, 41–47. doi:10.1016/j.tins.2008.09.008

Boninger, M. L., Souza, A. L., Cooper, R. A., Fitzgerald, S. G., Koontz, A. M., and Fay, B. T. (2002). Propulsion patterns and pushrim biomechanics in manual wheelchair propulsion. *Archives of Physical Medicine and Rehabilitation* 83, 718–723. doi:10.1053/apmr.2002.32455

Borisoff, J. F., Ripat, J., and Chan, F. (2018). Seasonal Patterns of Community Participation and Mobility of Wheelchair Users Over an Entire Year. *Archives of Physical Medicine and Rehabilitation* 99, 1553–1560. doi:10.1016/j.apmr.2018.02.011

Bradbury, E. J., Moon, L. D., Popat, R. J., King, V. R., Bennett, G. S., Patel, P. N., et al. (2002). Chondroitinase ABC promotes functional recovery after spinal cord injury. *Nature* 416, 636–640. doi:10.1038/416636a

Brogioli, M., Popp, W. L., Albisser, U., Brust, A. K., Frotzler, A., Gassert, R., et al. (2016a). Novel sensor technology to assess independence and limb-use laterality in cervical spinal cord injury. *Journal of Neurotrauma* 33, 1950–1957. doi:10.1089/neu.2015.4362

Brogioli, M., Popp, W. L., Schneider, S., Albisser, U., Brust, A. K., Frotzler, A., et al. (2016b). Multi-Day Recordings of Wearable Sensors Are Valid and Sensitive Measures of Function and Independence in Human Spinal Cord Injury. *Journal of Neurotrauma* , ahead of printdoi: 10.1089/neu.2016.4583

Brogioli, M., Schneider, S., Popp, W. L., Albisser, U., Brust, A. K., Velstra, I.-M., et al. (2016c). Monitoring Upper Limb Recovery after Cervical Spinal Cord Injury: Insights beyond Assessment Scores. *Frontiers in Neurology* 7, 142. doi:10.3389/fneur.2016.00142

Brus-Ramer, M., Carmel, J. B., Chakrabarty, S., and Martin, J. H. (2007). Electrical Stimulation of Spared Corticospinal Axons Augments Connections with Ipsilateral Spinal Motor Circuits after Injury. *Journal of Neuroscience* 27, 13793–13801. doi:10.1523/jneurosci.3489-07.2007

Buchholz, A. C., Martin Ginis, K. A., Bray, S. R., Craven, B. C., Hicks, A. L., Hayes, K. C., et al. (2009). Greater daily leisure time physical activity is associated with lower chronic disease risk in adults with spinal cord injury. *Applied Physiology, Nutrition, and Metabolism* 34, 640–647. doi:10.1139/H09-050

Buchholz, A. C., McGillivray, C. F., and Pencharz, P. B. (2003). Physical activity levels are low in free-living adults with chronic paraplegia. *Obesity Research* 11, 563–570. doi:10.1038/oby.2003.79

Cacho, E. W. A., De Oliveira, R., Ortolan, R. L., Varoto, R., and Cliquet, A. (2011). Upper limb assessment in tetraplegia: Clinical, functional and kinematic correlations. *International Journal of Rehabilitation Research* 34, 65–72. doi:10.1097/MRR.0b013e32833d6cf3

Carmel, J. B., Berrol, L. J., Brus-Ramer, M., and Martin, J. H. (2010). Chronic Electrical Stimulation of the Intact Corticospinal System after Unilateral Injury Restores Skilled Locomotor Control and Promotes Spinal Axon Outgrowth. *Journal of Neuroscience* 30, 10918–10926. doi:10.1523/jneurosci.1435-10.2010

Carpenter, C., Forwell, S. J., Jongbloed, L. E., and Backman, C. L. (2007). Community Participation After Spinal Cord Injury. *Archives of Physical Medicine and Rehabilitation* 88, 427–433. doi:10.1016/j.apmr.2006.12.043

Casha, S., Zygun, D., McGowan, M. D., Bains, I., Yong, V. W., and John Hurlbert, R. (2012). Results of a phase II placebo-controlled randomized trial of minocycline in acute spinal cord injury. *Brain* 135, 1224–1236. doi:10.1093/brain/aws072

Catz, A., Itzkovich, M., Agranov, E., Ring, H., and Tamir, A. (1997). SCIM–spinal cord independence measure: a new disability scale for patients with spinal cord lesions. *Spinal cord* 35, 850–6

Chamberlain, J. D., Ronca, E., and Brinkhof, M. W. (2017). Estimating the incidence of traumatic spinal cord injuries in Switzerland: Use of administrative data to identify potential coverage error in a cohort study. *Swiss Medical Weekly* 147. doi:10.4414/smw.2017.14430

Chang, H. C., Hsu, Y. L., Yang, S. C., Lin, J. C., and Wu, Z. H. (2016). A wearable inertial measurement system with complementary filter for gait analysis of patients with stroke or Parkinson's disease. *IEEE Access* 4, 8442–8453. doi:10.1109/ACCESS.2016.2633304

Chen, H., Epstein, J., and Stern, E. (2010). Neural plasticity after acquired brain injury: Evidence from functional neuroimaging. *PM and R* 2, S306–S312. doi:10.1016/j.pmrj.2010.10.006

Chen, K. Y. and Bassett, D. R. (2005). The technology of accelerometry-based activity monitors: Current and future. In *Medicine and Science in Sports and Exercise*. vol. 37, 490–500. doi:10.1249/01.mss.0000185571.49104.82

Cheng, Y. W., Chen, P. Y., Yang, C. Y., and Samani, H. (2016). IMU based activity detection for post mini-stroke healthcare. In *2016 IEEE International Conference on System Science and Engineering, ICSSE 2016* (IEEE), 1–4. doi:10.1109/ICSSE.2016.7551611

Chubb, H. and Simpson, J. M. (2012). The use of Z-scores in paediatric cardiology. *Annals of Pediatric Cardiology* 5, 179. doi:10.4103/0974-2069.99622

Cleland, C., Ferguson, S., Ellis, G., and Hunter, R. F. (2018). Validity of the International Physical Activity Questionnaire (IPAQ) for assessing moderate-to-vigorous physical activity and sedentary behaviour of older adults in the United Kingdom. *BMC Medical Research Methodology* 18, 176. doi:10.1186/s12874-018-0642-3

Colley, R. C., Garriguet, D., Janssen, I., Craig, C. L., Clark, J., and Tremblay, M. S. (2011). Physical activity of Canadian Adults: Accelerometer results from 2007 to 2009 Canadian Health Measures Survey. *Health Rep* 22

Collins, E. G., Gater, D., Kiratli, J., Butler, J., Hanson, K., and Langbein, W. E. (2010). Energy cost of physical activities in persons with spinal cord injury. *Medicine and Science in Sports and Exercise* 42, 691–700. doi:10.1249/MSS.0b013e3181bb902f

Consortium for Spinal Cord Medicine (2008). *Early Acute Management in Adults with Spinal Cord Injury*, vol. 31 (Taylor & Francis). doi:10.1043/1079-0268-31.4.408

Cooper, A. R., Goodman, A., Page, A. S., Sherar, L. B., Esliger, D. W., van Sluijs, E. M., et al. (2015). Objectively measured physical activity and sedentary time in youth: The International children's accelerometry database (ICAD). *International Journal of Behavioral Nutrition and Physical Activity* 12, 113. doi:10.1186/s12966-015-0274-5

Cooper, C., Gross, A., Brinkman, C., Pope, R., Allen, K., Hastings, S., et al. (2018). The impact of wearable motion sensing technology on physical activity in older adults. *Experimental Gerontology* 112, 9–19. doi:10.1016/J.EXGER.2018.08.002

Coughlin, S. S. and Stewart, J. (2016). Use of Consumer Wearable Devices to Promote Physical Activity: A Review of Health Intervention Studies. *Journal of environment and health sciences* 2. doi:10.15436/2378-6841.16.1123

Coulter, E. H., Dall, P. M., Rochester, L., Hasler, J. P., and Granat, M. H. (2011). Development and validation of a physical activity monitor for use on a wheelchair. *Spinal cord : the official journal of the International Medical Society of Paraplegia* 49, 445–450. doi:10.1038/sc.2010.126

Curt, A., Van Hedel, H. J. A., Klaus, D., and Dietz, V. (2008). Recovery from a spinal cord injury: significance of compensation, neural plasticity, and repair. *Journal of Neurotrauma* 25, 677–685. doi:10.1089/neu.2007.0468

Curtis, K. A., Drysdale, G. A., Lanza, R. D., Kolber, M., Vitolo, R. S., and West, R. (1999). Shoulder pain in wheelchair users with tetraplegia and paraplegia. *Archives of Physical Medicine and Rehabilitation* 80, 453–457. doi:10.1016/S0003-9993(99)90285-X

Damiano, D. L. (2007). Activity, Activity, Activity: Rethinking Our Physical Therapy Approach to Cerebral Palsy. *Physical Therapy* 86, 1534–1540. doi:10.2522/ptj.20050397

Davies, S. J. A., Goucher, D. R., Doller, C., and Silver, J. (1999). Robust Regeneration of Adult Sensory Axons in Degenerating White Matter of the Adult Rat Spinal Cord. *The Journal of Neuroscience* 19, 5810–5822. doi:10.1523/jneurosci.19-14-05810.1999

De Los Reyes-Guzmán, A., Gil-Agudo, A., Peñasco-Martín, B., Solís-Mozos, M., Del Ama-Espinosa, A., and Pérez-Rizo, E. (2010). Kinematic analysis of the daily activity of drinking from a glass in a population with cervical spinal cord injury. *Journal of NeuroEngineering and Rehabilitation* 7. doi:10.1186/1743-0003-7-41

Dobkin, B. H. and Dorsch, A. (2011). The promise of mHealth: Daily activity monitoring and outcome assessments by wearable sensors. *Neurorehabilitation and Neural Repair* 25, 788–798. doi:10.1177/1545968311425908

Dunlop, S. A. (2008). Activity-dependent plasticity: implications for recovery after spinal cord injury. *Trends in Neurosciences* 31, 410–418. doi:10.1016/j.tins.2008.05.004

Ellis, K., Kerr, J., Godbole, S., Staudenmayer, J., and Lanckriet, G. (2016). Hip and wrist accelerometer algorithms for free-living behavior classification. *Medicine and Science in Sports and Exercise* 48, 933–940. doi:10.1249/MSS.0000000000000840

Evans, J. D. (1996). *Straightforward Statistics for the Behavioral Sciences.* (Brooks/Cole Pub. Co). doi:10.2307/2291607

Falck, R. S., Landry, G. J., Brazendale, K., and Liu-Ambrose, T. (2017). Measuring physical activity in older adults using motion watch 8 actigraphy: How many days are needed? *Journal of Aging and Physical Activity* 25, 51–57. doi:10.1123/japa.2015-0256

Forchheimer, M., Kalpakjian, C., and Tate, D. (2004). Gender Differences in Community Integration After Spinal Cord Injury. *Topics in Spinal Cord Injury Rehabilitation* 10, 163–174. doi:10.1310/KG8C-TJCP-95A5-N949

Fouad, K., Krajacic, A., and Tetzlaff, W. (2011). Spinal cord injury and plasticity: Opportunities and challenges. *Brain Research Bulletin* 84, 337–342. doi:10.1016/j.brainresbull.2010.04.017

Fouad, K. and Tetzlaff, W. (2012). Rehabilitative training and plasticity following spinal cord injury. *Experimental Neurology* 235, 91–99. doi:10.1016/j.expneurol.2011.02.009

Foy, T., Perritt, G., Thimmaiah, D., Heisler, L., Offutt, J. L., Cantoni, K., et al. (2011). The SCIRehab project: treatment time spent in SCI rehabilitation. Occupational therapy treatment time during inpatient spinal cord injury rehabilitation. *The journal of spinal cord medicine* 34, 162–75. doi:10.1179/107902611X12971826988093

Francisco, G. E., Yozbatiran, N., Berliner, J., OMalley, M. K., Pehlivan, A. U., Kadivar, Z., et al. (2017). Robot-Assisted Training of Arm and Hand Movement Shows Functional Improvements for Incomplete Cervical Spinal Cord Injury. *American Journal of Physical Medicine & Rehabilitation* 96, S171–S177. doi:10.1097/PHM.0000000000000815

Franz, M., Richner, L., Wirz, M., Von Reumont, A., Bergner, U., Herzog, T., et al. (2018). Physical therapy is targeted and adjusted over time for the rehabilitation of locomotor function in acute spinal cord injury interventions in physical and sports therapy article. *Spinal Cord* 56, 158–167. doi:10.1038/s41393-017-0007-5

French, B., Smailagic, A., Siewiorek, D., Ambur, V., and Tyamagundlu, D. (2008). Classifying Wheelchair Propulsion Patterns with a Wrist Mounted Accelerometer. In *Proceedings of the ICST 3rd international conference on Body area networks* (ICST (Institute for Computer Sciences, Social-Informatics and Telecommunications Engineering)), 20. doi:10.4108/icst.bodynets2008.2963

Freund, P., Schmidlin, E., Wannier, T., Bloch, J., Mir, A., Schwab, M. E., et al. (2006). Nogo-A-specific antibody treatment enhances sprouting and functional recovery after cervical lesion in adult primates. *Nature Medicine* 12, 790–792. doi:10.1038/nm1436

Furlan, J. C., Krassioukov, A. V., and Fehlings, M. G. (2005). The Effects of Gender on Clinical and Neurological Outcomes after Acute Cervical Spinal Cord Injury. *Journal of Neurotrauma* 22, 368–381. doi:10.1089/neu.2005.22.368

Gabriel, K. P., McClain, J. J., Schmid, K. K., Storti, K. L., High, R. R., Underwood, D. A., et al. (2010). Issues in accelerometer methodology: the role of epoch length on estimates of physical activity and relationships with health outcomes in overweight, post-menopausal women. *Int J Behav Nutr Phys Act* 7, 53. doi:10.1186/1479-5868-7-53

GBD 2016 Traumatic Brain Injury and Spinal Cord Injury Collaborators, S. L., Theadom, A., Ellenbogen, R. G., Bannick, M. S., Montjoy-Venning, W., Lucchesi, L. R., et al. (2019). Global, regional, and national burden of traumatic brain injury and spinal cord injury, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet. Neurology* 18, 56–87. doi:10.1016/S1474-4422(18)30415-0

Gebruers, N., Vanroy, C., Truijen, S., Engelborghs, S., and De Deyn, P. P. (2010). Monitoring of Physical Activity After Stroke: A Systematic Review of Accelerometry-Based Measures. *Archives of Physical Medicine and Rehabilitation* 91, 288–297. doi:10.1016/j.apmr.2009.10.025

Gefen, J., Gelmann, A., Herbison, G., Cohen, M., and Schmidt, R. (1997). Use of shoulder flexors to achieve isometric elbow extension in C6 tetraplegic patients during weight shift. *Spinal Cord* 35, 308–313

Giggins, O. M., Clay, I., and Walsh, L. (2017). Physical Activity Monitoring in Patients with Neurological Disorders: A Review of Novel Body-Worn Devices. *Digital Biomarkers* 1, 14–42. doi:10.1159/000477384

Glinsky, J., Harvey, L., van Es, P., Chee, S., and Gandevia, S. C. (2009). The addition of electrical stimulation to progressive resistance training does not enhance the wrist strength of people with tetraplegia: a randomized controlled trial. *Clinical Rehabilitation* 23, 696–704. doi:10.1177/0269215509104171

Godfrey, A., Conway, R., Meagher, D., and G, O. L. (2008). Direct measurement of human movement by accelerometry. *Med Eng Phys* 30, 1364–1386. doi:10.1016/j.medengphy.2008.09.005

Gorman, E., Hanson, H. M., Yang, P. H., Khan, K. M., Liu-Ambrose, T., and Ashe, M. C. (2014). Accelerometry analysis of physical activity and sedentary behavior in older adults: A systematic review and data analysis. *European Review of Aging and Physical Activity* 11, 35–49. doi:10.1007/s11556-013-0132-x

Hagger, M. and Chatzisarantis, N. (2008). Self-determination Theory and the psychology of exercise. *International Review of Sport and Exercise Psychology* 1, 79–103. doi:10.1080/17509840701827437

Hamer, M., de Oliveira, C., and Demakakos, P. (2014). Non-Exercise Physical Activity and Survival. *American Journal of Preventive Medicine* 47, 452–460. doi:10.1016/j.amepre.2014.05.044

Hansen, B. H., Kolle, E., Dyrstad, S. M., Holme, I., and Anderssen, S. A. (2012). Accelerometer-determined physical activity in adults and older people. *Medicine and Science in Sports and Exercise* 44, 266–272. doi:10.1249/MSS.0b013e31822cb354

Hausmann, O. N. (2003). Post-traumatic inflammation following spinal cord injury. *Spinal Cord* 41, 369–378. doi:10.1038/sj.sc.3101483

Herrmann, S. D., Barreira, T. V., Kang, M., and Ainsworth, B. E. (2014). Impact of accelerometer wear time on physical activity data: A NHANES semisimulation data approach. *British Journal of Sports Medicine* 48, 278–282. doi:10.1136/bjsports-2012-091410

Hicks, A. L., Martin, K. A., Ditor, D. S., Latimer, A. E., Craven, C., Bugaresti, J., et al. (2003). Long-term exercise training in persons with spinal cord injury: Effects on strength, arm ergometry performance and psychological well-being. *Spinal Cord* 41, 34–43. doi:10.1038/sj.sc.3101389

Hills, A. P., Mokhtar, N., and Byrne, N. M. (2014). Assessment of Physical Activity and Energy Expenditure: An Overview of Objective Measures. *Frontiers in Nutrition* 1, 5. doi:10.3389/fnut.2014.00005

Hiremath, S. V., Ding, D., Farringdon, J., Vyas, N., and Cooper, R. a. (2013). Physical activity classification utilizing SenseWear activity monitor in manual wheelchair users with spinal cord injury. *Spinal cord* 51, 705–9. doi:10.1038/sc.2013.39

Hodkin, E. F., Lei, Y., Humby, J., Glover, I. S., Choudhury, S., Kumar, H., et al. (2018). Automated FES for upper limb rehabilitation following stroke and spinal cord injury. *IEEE Transactions on Neural Systems and Rehabilitation Engineering* 26, 1067–1074. doi:10.1109/TNSRE.2018.2816238

Holtermann, A., Mork, P. J., and Nilsen, T. I. L. (2014). Hours lying down per day and mortality from all-causes and cardiovascular disease: The HUNT Study, Norway. *European Journal of Epidemiology* 29, 559–565. doi:10.1007/s10654-014-9939-7

Howard, I. S., Ingram, J. N., Körding, K. P., and Wolpert, D. M. (2009). Statistics of Natural Movements Are Reflected in Motor Errors. *Journal of Neurophysiology* 102, 1902–1910. doi:10.1152/jn.00013.2009

Innerd, P., Harrison, R., and Coulson, M. (2018). Using open source accelerometer analysis to assess physical activity and sedentary behaviour in overweight and obese adults. *BMC Public Health* 18, 543. doi:10.1186/s12889-018-5215-1

Itzkovich, M., Gelernter, I., Biering-Sorensen, F., Weeks, C., Laramee, M. T., Craven, B. C., et al. (2007). The Spinal Cord Independence Measure (SCIM) version III: Reliability and validity in a multi-center international study. *Disability and Rehabilitation* 29, 1926–1933. doi:10.1080/09638280601046302

Jacquier-Bret, J., Rezzoug, N., Vallier, J. M., Tournebise, H., and Gorce, P. (2009). Reach to grasp kinematics and EMG analysis of C6 quadriplegic subjects. In *Proceedings of the 31st Annual International Conference of the IEEE Engineering in Medicine and Biology Society: Engineering the Future of Biomedicine, EMBC 2009* (IEEE), 5934–5937. doi:10.1109/IEMBS.2009.5334747

Jain, N. B., Ayers, G. D., Peterson, E. N., Harris, M. B., Morse, L., O'Connor, K. C., et al. (2015). Traumatic spinal cord injury in the United States, 1993-2012. *JAMA - Journal of the American Medical Association* 313, 2236–2243. doi:10.1001/jama.2015.6250

Jain, N. B., Sullivan, M., Kazis, L. E., Tun, C. G., and Garshick, E. (2007). Factors associated with health-related quality of life in chronic spinal cord injury. *American Journal of Physical Medicine and Rehabilitation* 86, 387–396. doi:10.1097/PHM.0b013e31804a7d00

Jayaraman, C., Mummidisetty, C. K., Mannix-Slobig, A., McGee Koch, L., and Jayaraman, A. (2018). Variables influencing wearable sensor outcome estimates in individuals with stroke and incomplete spinal cord injury: a pilot investigation validating two research grade sensors. *Journal of NeuroEngineering and Rehabilitation* 15, 19. doi:10.1186/s12984-018-0358-y

Jones, M. L., Harness, E., Denison, P., Tefertiller, C., Evans, N., and Larson, C. a. (2012). Activity-based Therapies in Spinal Cord Injury: Clinical Focus and Empirical Evidence in Three Independent Programs. *Topics in Spinal Cord Injury Rehabilitation* 18, 34–42. doi:10.1310/sci1801-34

Jörgensen, S., Martin Ginis, K. A., and Lexell, J. (2017). Leisure time physical activity among older adults with long-term spinal cord injury. *Spinal Cord* 55, 848–856. doi:10.1038/sc.2017.26

Jörgensen, S., Svedevall, S., Magnusson, L., Martin Ginis, K. A., and Lexell, J. (2019). Associations between leisure time physical activity and cardiovascular risk factors among older adults with long-term spinal cord injury. doi:10.1038/s41393-018-0233-5

Kalsi-Ryan, S., Beaton, D., Curt, A., Duff, S., Popovic, M. R., Rudhe, C., et al. (2012a). The Graded Redefined Assessment of Strength Sensibility and Prehension: Reliability and Validity. *Journal of Neurotrauma* 29, 905–914. doi:10.1089/neu.2010.1504

Kalsi-Ryan, S., Curt, A., Verrier, M. C., and Fehlings, M. G. (2012b). Development of the Graded Redefined Assessment of Strength, Sensibility and Prehension (GRASSP): reviewing measurement specific to the upper limb in tetraplegia. *Journal of Neurosurgery: Spine* 17, 65–76. doi:10.3171/2012.6.aospine1258

Kang, D. W., Choi, J. S., Lee, J. W., Chung, S. C., Park, S. J., and Tack, G. R. (2010). Real-time elderly activity monitoring system based on a tri-axial accelerometer. *Disability and Rehabilitation: Assistive Technology* 5, 247–253. doi:10.3109/17483101003718112

Keller, U., Schölch, S., Albisser, U., Rudhe, C., Curt, A., Riener, R., et al. (2015). Robot-assisted arm assessments in spinal cord injured patients: A consideration of concept study. *PLoS ONE* 10, e0126948. doi:10.1371/journal.pone.0126948

Kessler, T. M., Traini, L. R., Welk, B., Schneider, M. P., Thavaseelan, J., and Curt, A. (2018). Early neurological care of patients with spinal cord injury. *World Journal of Urology* 36, 1529–1536. doi:10.1007/s00345-018-2343-2

Kim, Y., Beets, M. W., and Welk, G. J. (2012). Everything you wanted to know about selecting the " right" Actigraph accelerometer cut-points for youth, but...: A systematic review. *Journal of Science and Medicine in Sport* 15, 311–321. doi:10.1016/j.jsams.2011.12.001

Kirshblum, S. C., Burns, S. P., Biering-Sorensen, F., Donovan, W., Graves, D. E., Jha, A., et al. (2011a). International standards for neurological classification of spinal cord injury (Revised 2011) The authors are the members of the International Standards Committee of ASIA. *The journal of spinal cord medicine* 34, 535–46. doi:10.1179/204577211X13207446293695

Kirshblum, S. C., Waring, W., Biering-Sorensen, F., Burns, S. P., Johansen, M., Schmidt-Read, M., et al. (2011b). Reference for the 2011 revision of the international standards for neurological classification of spinal cord injury. *The Journal of Spinal Cord Medicine* 34, 547–554. doi: 10.1179/107902611x13186000420242

Klaren, R. E., Hubbard, E. A., Zhu, W., and Motl, R. W. (2016). Reliability of accelerometer scores for measuring sedentary and physical activity behaviors in persons with multiple sclerosis. *Adapted Physical Activity Quarterly* 33, 195–204. doi:10.1123/APAQ.2015-0007

Kloosterman, M., Snoek, G., and Jannink, M. (2009). Systematic review of the effects of exercise therapy on the upper extremity of patients with spinal-cord injury. *Spinal Cord* 47, 196–203

Kloosterman, M. G. . M., Snoek, G. J., Kouwenhoven, M., Nene, A. V., and Jannink, M. J. A. (2010). Influence of gravity compensation on kinematics and muscle activation patterns during reach and retrieval in subjects with cervical spinal cord injury: An explorative study. *The Journal of Rehabilitation Research and Development* 47, 617. doi:10.1682/JRRD.2010.02.0014

Knorr, B., Hughes, R., Sherrill, D., Stein, J., Akay, M., and Bonato, P. (2005). Quantitative measures of functional upper limb movement in persons after stroke. In *2nd International IEEE EMBS Conference on Neural Engineering* (IEEE), vol. 2005, 252–255. doi:10.1109/CNE.2005.1419604

Koo, T. K. and Li, M. Y. (2016). Cracking the Code: Providing Insight Into the Fundamentals of Research and Evidence-Based Practice A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. *Journal of Chiropractic Medicine* 15, 155–163. doi:10.1016/j.jcm.2016.02.012

Kucher, K., Johns, D., Maier, D., Abel, R., Badke, A., Baron, H., et al. (2018). First-in-Man Intrathecal Application of Neurite Growth-Promoting Anti-Nogo-A Antibodies in Acute Spinal Cord Injury. *Neurorehabilitation and Neural Repair* 32, 578–589. doi:10.1177/1545968318776371

Kwarciak, A. M., Sisto, S. A., Yarossi, M., Price, R., Komaroff, E., and Boninger, M. L. (2009). Redefining the Manual Wheelchair Stroke Cycle: Identification and Impact of Nonpropulsive Pushrim Contact. *Archives of Physical Medicine and Rehabilitation* 90, 20–26. doi:10.1016/J.APMR.2008.07.013

Lacroix, J., Compagnat, M., Ferry, B., Daviet, J., and Mandigout, S. (2018). Estimation of the energy expenditure by the actigraph accelerometer in elderly on different physical activities. *Annals of Physical and Rehabilitation Medicine* 61, e73. doi:10.1016/J.REHAB.2018.05.157

Laeremans, M., Dons, E., Avila-Palencia, I., Carrasco-Turigas, G., Orjuela, J. P., Anaya, E., et al. (2017). Physical activity and sedentary behaviour in daily life: A comparative analysis of the Global Physical Activity Questionnaire (GPAQ) and the SenseWear armband. *PLoS ONE* 12, e0177765. doi:10.1371/journal.pone.0177765

Laffont, I., Briand, E., Dizien, O., Combeaud, M., Bussel, B., Revol, M., et al. (2000). Kinematics of prehension and pointing movements in C6 quadriplegic patients. *Spinal Cord* 38, 354–362. doi:10.1038/sj.sc.3100999

Lammertse, D., Jones, L., Charlifue, S., Kirshblum, S., Apple, D., Ragnarsson, K., et al. (2012). Autologous incubated macrophage therapy in acute, complete spinal cord injury: Results of the phase 2 randomized controlled multicenter trial. *Spinal Cord* 50, 661–671. doi:10.1038/sc.2012.39

Land, N. E., Odding, E., Duivenvoorden, H. J., Bergen, M. P., and Stam, H. J. (2004). Tetraplegia Hand Activity Questionnaire (THAQ): The development, assessment of arm-hand function-related activities in tetraplegic patients with a spinal cord injury. *Spinal Cord* 42, 294–301. doi:10.1038/sj.sc.3101588

Latimer, A. E., Ginis, K. A., Craven, B. C., and Hicks, A. L. (2006). The physical activity recall assessment for people with spinal cord injury: Validity. *Medicine and Science in Sports and Exercise* 38, 208–216. doi:10.1249/01.mss.0000183851.94261.d2

Lee, I. M. and Shiroma, E. J. (2014). Using accelerometers to measure physical activity in large-scale epidemiological studies: Issues and challenges. *British Journal of Sports Medicine* 48, 197–201. doi:10.1136/bjsports-2013-093154

Leuenberger, K. and Gassert, R. (2011). Low-power sensor module for long-term activity monitoring. *Conf Proc IEEE Eng Med Biol Soc* 2011, 2237–2241. doi:10.1109/IEMBS.2011.6090424

Leuenberger, K., Gonzenbach, R., Wachter, S., Luft, A., and Gassert, R. (2017). A method to qualitatively assess arm use in stroke survivors in the home environment. *Medical and Biological Engineering and Computing* 55, 141–150. doi:10.1007/s11517-016-1496-7

Leuenberger, K., Gonzenbach, R., Wiedmer, E., Luft, A., and Gassert, R. (2014). Classification of stair ascent and descent in stroke patients. *Proceedings - 11th International Conference on Wearable and Implantable Body Sensor Networks Workshops, BSN Workshops 2014* , 11–16doi:10.1109/BSN.Workshops.2014.10

Leuenberger, K. D. (2015). *Long-term activity and movement monitoring in neurological patients*. Ph.D. thesis, ETH Zurich. doi:10.3929/ETHZ-A-010594517

Levin, S., Jacobs, D. R., Ainsworth, B. E., Richardson, M. T., and Leon, A. S. (1999). Intra-individual variation and estimates of usual physical activity. *Annals of Epidemiology* 9, 481–488. doi:10.1016/S1047-2797(99)00022-8

Lidal, I. B., Huynh, T. K., and Biering-Sørensen, F. (2007). Return to work following spinal cord injury: a review. *Disability and Rehabilitation* 29, 1341–1375. doi:10.1080/09638280701320839

Lillard, A. S. and Erisir, A. (2011). Old dogs learning new tricks: Neuroplasticity beyond the juvenile period. *Developmental Review* 31, 207–239. doi:10.1016/J.DR.2011.07.008

Lockhart, T. E., Soangra, R., Zhang, J., and Wu, X. (2013). Wavelet based automated postural event detection and activity classification with single IMU. *Biomedical sciences instrumentation* 49, 224

Logan, G. R. M., Duncan, S., Harris, N. K., Hinckson, E. A., and Schofield, G. (2016). Adolescent physical activity levels: discrepancies with accelerometer data analysis. *Journal of sports sciences* 34, 2047–53. doi:10.1080/02640414.2016.1150599

Lonini, L., Shawen, N., Ghaffari, R., Rogers, J., and Jayarman, A. (2017). Automatic detection of spasticity from flexible wearable sensors. In *UBICOMP/ISWC*. 133–136. doi:10.1145/3123024.3123098

Loprinzi, P. D., Lee, H., Cardinal, B. J., Crespo, C. J., Andersen, R. E., Smit, E., et al. (2012). The relationship of actigraph accelerometer cut-points for estimating physical activity with selected health outcomes: Results from NHANES 2003–06. *Research Quarterly for Exercise and Sport* 83, 422–430. doi:10.1080/02701367.2012.10599877

Lu, X., Battistuzzo, C. R., Zoghi, M., and Galea, M. P. (2015). Effects of training on upper limb function after cervical spinal cord injury: A systematic review. *Clinical Rehabilitation* 29, 3–13. doi:10.1177/0269215514536411

Luke, S. G. (2017). Evaluating significance in linear mixed-effects models in R. *Behavior Research Methods* 49, 1494–1502. doi:10.3758/s13428-016-0809-y

Lynskey, J. V., Belanger, A., and Jung, R. (2008). Activity-dependent plasticity in spinal cord injury. *Journal of rehabilitation research and development* 45, 229–240. doi:10.1682/JRRD.2007.03.0047

Ma, J. K., McCracken, L. A., Voss, C., Chan, F. H. N., West, C. R., and Martin Ginis, K. A. (2018). Physical activity measurement in people with spinal cord injury: comparison of accelerometry and self-report (the Physical Activity Recall Assessment for People with Spinal Cord Injury). *Disability and Rehabilitation* , 1–7doi:10.1080/09638288.2018.1494213

Madgwick, S. O. H., Harrison, A. J. L., and Vaidyanathan, R. (2011). Estimation of IMU and MARG orientation using a gradient descent algorithm. *IEEE International Conference on Rehabilitation Robotics* doi:10.1109/ICORR.2011.5975346

Maier, I. C., Baumann, K., Thallmair, M., Weinmann, O., Scholl, J., and Schwab, M. E. (2008). Constraint-Induced Movement Therapy in the Adult Rat after Unilateral Corticospinal Tract Injury. *Journal of Neuroscience* 28, 9386–9403. doi:10.1523/jneurosci.1697-08.2008

Maier, I. C., Ichiyama, R. M., Courtine, G., Schnell, L., Lavrov, I., Edgerton, V. R., et al. (2009). Differential effects of anti-Nogo-A antibody treatment and treadmill training in rats with incomplete spinal cord injury. *Brain* 132, 1426–1440. doi:10.1093/brain/awp085

Martin Ginis, K., Hicks, A., Latimer, A., Warburton, D., Bourne, C., Ditor, D., et al. (2011). The development of evidence-informed physical activity guidelines for adults with spinal cord injury. *Spinal Cord* 49, 1088–1096. doi:10.1038/sc.2011.63

Martin Ginis, K. A. and Latimer, A. (2007). *Leisure Time Physical Activity Questionnaire for People with Spinal Cord Injury*. Tech. rep.

Martin Ginis, K. A., Latimer, A. E., Arbour-Nicitopoulos, K. P., Buchholz, A. C., Bray, S. R., Craven, B. C., et al. (2010). Leisure Time Physical Activity in a Population-Based Sample of People With Spinal Cord Injury Part I: Demographic and Injury-Related Correlates. *Archives of Physical Medicine and Rehabilitation* 91, 722–728. doi:10.1016/J.APMR.2009.12.027

Martin Ginis, K. A., Latimer, A. E., Hicks, A. L., and Craven, B. C. (2005). Development and evaluation of an activity measure for people with spinal cord injury. *Medicine and Science in Sports and Exercise* 37, 1099–1111. doi:10.1249/01.mss.0000170127.54394.eb

Martin Ginis, K. A., Van Der Scheer, J. W., Latimer-Cheung, A. E., Barrow, A., Bourne, C., Carruthers, P., et al. (2018). Evidence-based scientific exercise guidelines for adults with spinal cord injury: An update and a new guideline. *Spinal Cord* 56, 308–321. doi:10.1038/s41393-017-0017-3

Mâsse, L. C., Fuemmeler, B. F., Anderson, C. B., Matthews, C. E., Trost, S. G., Catellier, D. J., et al. (2005). Accelerometer data reduction: a comparison of four reduction algorithms on select outcome variables. *Medicine and science in sports and exercise* 37, S544–54

Mateo, S., Revol, P., Fourtassi, M., Rossetti, Y., Collet, C., and Rode, G. (2013). Kinematic characteristics of tenodesis grasp in C6 quadriplegia. *Spinal Cord* 51, 144–149. doi:10.1038/sc.2012.101

Mateo, S., Roby-Brami, A., Reilly, K. T., Rossetti, Y., Collet, C., and Rode, G. (2015). Upper limb kinematics after cervical spinal cord injury: A review. *Journal of NeuroEngineering and Rehabilitation* 12, 9. doi:10.1186/1743-0003-12-9

Mathie, M. J., Coster, A. C., Lovell, N. H., and Celler, B. G. (2004). Accelerometry: Providing an integrated, practical method for long-term, ambulatory monitoring of human movement. *Physiological Measurement* 25, R1–R20. doi:10.1088/0967-3334/25/2/R01

Mattlage, A. E., Redlin, S. A., Rippee, M. A., Abraham, M. G., Rymer, M. M., and Billinger, S. A. (2015). Use of Accelerometers to Examine Sedentary Time on an Acute Stroke Unit. *Journal of Neurologic Physical Therapy* 39, 166–171. doi:10.1097/NPT.0000000000000092

McGraw, K. O. and Wong, S. P. (1996). Forming Inferences about Some Intraclass Correlation Coefficients. *Psychological Methods* 1, 30–46. doi:10.1037/1082-989X.1.1.30

McKinley, W. O., Jackson, A. B., Cardenas, D. D., and DeVivo, M. J. (1999). Long-term medical complications after traumatic spinal cord injury: A Regional Model Systems Analysis. *Archives of Physical Medicine and Rehabilitation* 80, 1402–1410. doi:10.1016/S0003-9993(99)90251-4

Menardi, G. and Torelli, N. (2014). Training and assessing classification rules with imbalanced data. *Data Mining and Knowledge Discovery* 28, 92–122. doi:10.1007/s10618-012-0295-5

Mesquita, R., Spina, G., Pitta, F., Donaire-Gonzalez, D., Deering, B. M., Patel, M. S., et al. (2017). Physical activity patterns and clusters in 1001 patients with COPD. *Chronic Respiratory Disease* 14, 256–269. doi:10.1177/1479972316687207

Molanorouzi, K., Khoo, S., and Morris, T. (2014). Validating the physical activity and leisure motivation scale (PALMS). *BMC Public Health* 14. doi:10.1186/1471-2458-14-909

Moncada-Torres, A., Leuenberger, K., Gonzenbach, R., Luft, A., and Gassert, R. (2014). Activity classification based on inertial and barometric pressure sensors at different anatomical locations. *Physiological Measurement* 35, 1245–1263. doi:10.1088/0967-3334/35/7/1245

Moore, S. T., MacDougall, H. G., Gracies, J. M., Cohen, H. S., and Ondo, W. G. (2007). Long-term monitoring of gait in Parkinson's disease. *Gait and Posture* 26, 200–207. doi:10.1016/j.gaitpost.2006.09.011

Motl, R. W., McAuley, E., Snook, E. M., and Gliottoni, R. C. (2009). Physical activity and quality of life in multiple sclerosis: Intermediary roles of disability, fatigue, mood, pain, self-efficacy and social support. *Psychology, Health and Medicine* 14, 111–124. doi:10.1080/13548500802241902

Murtagh, F. and Legendre, P. (2014). Ward's Hierarchical Agglomerative Clustering Method: Which Algorithms Implement Ward's Criterion? *Journal of Classification* 31, 274–295. doi:10.1007/s00357-014-9161-z

Najafi, B., Aminian, K., Paraschiv-Ionescu, A., Loew, F., Büla, C. J., and Robert, P. (2003). Ambulatory system for human motion analysis using a kinematic sensor: Monitoring of daily physical activity in the elderly. *IEEE Transactions on Biomedical Engineering* 50, 711–723. doi:10.1109/TBME.2003.812189

Nas, K. (2015). Rehabilitation of spinal cord injuries. *World Journal of Orthopedics* 6, 8. doi:10.5312/wjo.v6.i1.8

Nightingale, T. E., Rouse, P. C., Thompson, D., and Bilzon, J. L. J. (2017). Measurement of Physical Activity and Energy Expenditure in Wheelchair Users: Methods, Considerations and Future Directions. *Sports Medicine - Open* 3, 10. doi:10.1186/s40798-017-0077-0

Nooijen, C., Stam, H., Bergen, M., Bongers-Janssen, H., Valent, L., van Langeveld, S., et al. (2016). A behavioural intervention increases physical activity in people with subacute spinal cord injury: a randomised trial. *Journal of physiotherapy* 62, 35–41. doi:10.1016/j.jphys.2015.11.003

Nooijen, C. F. J., de Groot, S., Postma, K., Bergen, M. P., Stam, H. J., Bussmann, J. B. J., et al. (2012). A more active lifestyle in persons with a recent spinal cord injury benefits physical fitness and health. *Spinal cord* 50, 320–3. doi:10.1038/sc.2011.152

Noreau, L. and Vachon, J. (1998). Comparison of three methods to assess muscular strength in individuals with spinal cord injury. *Spinal Cord* 36, 716–723

Onifer, S. M., Smith, G. M., and Fouad, K. (2011). Plasticity After Spinal Cord Injury: Relevance to Recovery and Approaches to Facilitate It. *Neurotherapeutics* 8, 283–293. doi:10.1007/s13311-011-0034-4

Parish, L. E. and Treasure, D. C. (2013). Physical activity and situational motivation in physical education: Influence of the motivational climate and perceived ability. *Research Quarterly for Exercise and Sport* 74, 173–182. doi:10.1080/02701367.2003.10609079

Pate, R. R., O'Neill, J. R., and Lobelo, F. (2008). The evolving definition of "sedentary". *Exercise and Sport Sciences Reviews* 36, 173–178. doi:10.1097/JES.0b013e3181877d1a

Perrier, M. J., Latimer-Cheung, A. E., and Ginis, K. A. (2012). An investigation of seasonal variation in leisure-time physical activity in persons with spinal cord injury. *Spinal Cord* 50, 507–511. doi:10.1038/sc.2012.11

Petersen, J. A., Spiess, M., Curt, A., Weidner, N., Rupp, R., Abel, R., et al. (2017). Upper Limb Recovery in Spinal Cord Injury: Involvement of Central and Peripheral Motor Pathways. *Neurorehabilitation and Neural Repair* 31, 432–441. doi:10.1177/1545968316688796

Popp, W. L., Brogioli, M., Leuenberger, K., Albisser, U., Frotzler, A., Curt, A., et al. (2016). A novel algorithm for detecting active propulsion in wheelchair users following spinal cord injury. *Med Eng Phys* 38, 267–274. doi:10.1016/j.medengphy.2015.12.011

Popp, W. L., Richner, L., Brogioli, M., Wilms, B., Spengler, Christina M. Curt, A. E., Starkey, M. L., et al. (2018). Estimation of energy expenditure in wheelchair-bound spinal cord injured individuals using inertial measurement units. *Frontiers in Neurology* 9, 478. doi:10.3389/FNEUR.2018.00478

Popp, W. L., Schneider, S., Bär, J., Bösch, P., Spengler, C. M., Gassert, R., et al. (2019a). Wearable sensors in pedestrians with a spinal cord injury: from energy expenditure estimation to activity recommendations. *submitted to Frontiers in Neurology*

Popp, W. L., Schneider, S., Demkó, L., Spengler, C. M., Gassert, R., and Curt, A. (2019b). Comparison of wearable sensor setups for energy expenditure estimation in pathological gait. *manuscript in preparation*

Prajapati, S. K., Gage, W. H., Brooks, D., Black, S. E., and McIlroy, W. E. (2011). A novel approach to ambulatory monitoring: Investigation into the quantity and control of everyday walking in patients with subacute stroke. *Neurorehabilitation and Neural Repair* 25, 6–14. doi:10.1177/1545968310374189

Quel de Oliveira, C., Refshauge, K., Middleton, J., de Jong, L., and Davis, G. M. (2017). Effects of Activity-Based Therapy Interventions on Mobility, Independence, and Quality of Life for People with Spinal Cord Injuries: A Systematic Review and Meta-Analysis. *Journal of Neurotrauma* 34, 1726–1743. doi:10.1089/neu.2016.4558

Ramirez, V., Shokri-Kojori, E., Cabrera, E. A., Wiers, C. E., Merikangas, K., Tomasi, D., et al. (2018). Physical activity measured with wrist and ankle accelerometers: Age, gender, and BMI effects. *PLoS ONE* 13, e0195996. doi:10.1371/journal.pone.0195996

Ramirez Herrera, R., Heravi, B. M., Barbareschi, G., Carlson, T., and Holloway, C. (2018). Towards a Wearbale Wheelchair Monitor: Classification of Push Style Based on Inertial Sensors at Multiple Upper Limb Locations. In *IEEE International Conference on Systems, Man, and Cybernetics*

Rankin, J., Richter, W., and Neptune, R. (2011). Individual muscle contributions to push and recovery subtasks during wheelchair propulsion. *Journal of Biomechanics* 44, 1246–1252

Riddoch, C. J., Andersen, L. B., Wedderkopp, N., Harro, M., Klasson-Heggebø, L., Sardinha, L. B., et al. (2004). Physical Activity Levels and Patterns of 9- and 15-yr-Old European Children. *Medicine and Science in Sports and Exercise* 36, 86–92. doi:10.1249/01.MSS.0000106174.43932.92

RStudio Team (2015). RStudio: Integrated Development Environment for R

Rudhe, C. and Van Hedel, H. J. A. (2009). Upper extremity function in persons with tetraplegia: Relationships between strength, capacity, and the spinal cord independence measure. *Neurorehabilitation and Neural Repair* 23, 413–421. doi:10.1177/1545968308331143

Sadowsky, C. L. and McDonald, J. W. (2009). Activity-based restorative therapies: Concepts and applications in spinal cord injury-related neurorehabilitation. *Developmental Disabilities Research Reviews* 15, 112–116. doi:10.1002/ddrr.61

Salarian, A., Russmann, H., Vingerhoets, F. J. G., Burkhard, P. R., and Aminian, K. (2007). Ambulatory monitoring of physical activities in patients with Parkinson's disease. *IEEE Trans Biomed Eng* 54, 2296–2299. doi:10.1109/tbme.2007.896591

Salisbury, S. K., Choy, N. L., and Nitz, J. (2003). Shoulder pain, range of motion, and functional motor skills after acute tetraplegia. *Archives of Physical Medicine and Rehabilitation* 84, 1480–1485. doi:10.1016/S0003-9993(03)00371-X

Sapienza, S., Adans-Dester, C., Obrien, A., Vergara-Diaz, G., Lee, S., Patel, S., et al. (2017). Using a Minimum Set of Wearable Sensors to Assess Quality of Movement in Stroke Survivors. In *Proceedings - 2017 IEEE 2nd International Conference on Connected Health: Applications, Systems and Engineering Technologies, CHASE 2017* (IEEE), 284–285. doi:10.1109/CHASE.2017.104

Schlachetzki, J. C., Barth, J., Marxreiter, F., Gossler, J., Kohl, Z., Reinfelder, S., et al. (2017). Wearable sensors objectively measure gait parameters in Parkinson's disease. *PLoS ONE* 12, e0183989. doi:10.1371/journal.pone.0183989

Schmitz, K. H., Treuth, M., Hannan, P., McMurray, R., Ring, K. B., Catellier, D., et al. (2005). Predicting energy expenditure from accelerometry counts in adolescent girls. *Medicine and science in sports and exercise* 37, 155–61

Schneider, S., Popp, W. L., Brogioli, M., Albisser, U., Demkó, L., Debecker, I., et al. (2018). Reliability of wearable-sensor-derived measures of physical activity in wheelchair-dependent spinal cord injured patients. *Frontiers in Neurology* 9, 1039. doi:10.3389/FNEUR.2018.01039

Schneider, S., Popp, W. L., Brogioli, M., Albisser, U., Ortmann, S., Velstra, I.-M., et al. (2019a). Predicting upper limb compensation during prehension tasks in tetraplegic spinal cord injured patients using a single wearable sensor. In *2019 International Conference on Rehabilitation Robotics (ICORR), in press*

Schneider, S., Popp, W. L., Demkó, L., Brogioli, M., Albisser, U., Debecker, I., et al. (2019b). Intensity of physical activity during therapy and leisure time in the rehabilitation of acute spinal cord injury. *submitted to Neurorehabilitation and neural repair*

Schneider, S., Popp, W. L., Demkó, L., Gassert, R., and Curt, A. (2017). *Robust posture detection in spinal cord injured wheelchair users using a single inertial measurement unit.* Tech. rep., ETH Zürich, Zürich

Schneider, S., Popp, W. L., Demkó, L., Gassert, R., and Curt, A. (2019c). Levels of physical activity in chronic spinal cord injury: adjustment to clinical impairment. *manuscript in preparation*

Schnell, L. and Schwab, M. E. (1990). Axonal regeneration in the rat spinal cord produced by an antibody against myelin-associated neurite growth inhibitors. *Nature* 343, 269–272. doi:10.1038/343269a0

Searle, S. (1971). *Linear Models* (John Wiley & Sons, Inc.)

Šimundić, A.-M. (2009). Measures of Diagnostic Accuracy: Basic Definitions. *EJIFCC* 19, 203–11. doi:10.1017/S0142716412000069

Sipski, M. L., Jackson, A. B., Gómez-Marín, O., Estores, I., and Stein, A. (2004). Effects of gender on neurologic and functional recovery after spinal cord injury. *Archives of Physical Medicine and Rehabilitation* 85, 1826–1836. doi:10.1016/j.apmr.2004.04.031

Snoek, G. J., IJzerman, M. J., Hermens, H. J., Maxwell, D., and Biering-Sorensen, F. (2004). Survey of the needs of patients with spinal cord injury: impact and priority for improvement in hand function in tetraplegics. *Spinal Cord* 42, 526–532. doi:10.1038/sj.sc.3101638

Sonenblum, S. E., Sprigle, S., Caspall, J., and Lopez, R. (2012a). Validation of an accelerometer-based method to measure the use of manual wheelchairs. *Medical Engineering and Physics* 34, 781–786. doi:10.1016/j.medengphy.2012.05.009

Sonenblum, S. E., Sprigle, S., Harris, F. H., and Maurer, C. L. (2008). Characterization of Power Wheelchair Use in the Home and Community. *Archives of Physical Medicine and Rehabilitation* 89, 486–491. doi:10.1016/j.apmr.2007.09.029

Sonenblum, S. E., Sprigle, S., and Lopez, R. A. (2012b). Manual Wheelchair Use: Bouts of Mobility in Everyday Life. *Rehabilitation Research and Practice* 2012, 1–7. doi:10.1155/2012/753165

Song, W., Amer, A., Ryan, D., and Martin, J. H. (2016). Combined motor cortex and spinal cord neuromodulation promotes corticospinal system functional and structural plasticity and motor function after injury. *Experimental Neurology* 277, 46–57. doi:10.1016/j.expneurol.2015.12.008

Spartano, N. L., Davis-Plourde, K. L., Himali, J. J., Andersson, C., Pase, M. P., Maillard, P., et al. (2019). Association of Accelerometer-Measured Light-Intensity Physical Activity With Brain Volume. *JAMA Network Open* 2, e192745. doi:10.1001/jamanetworkopen.2019.2745

Spooren, A., Janssen-Potten, Y., Kerckhofs, E., and Seelen, H. (2009). Outcome of motor training programmes on arm and hand functioning in patients with cervical spinal cord injury according to different levels of the ICF: A systematic review. *Journal of Rehabilitation Medicine* 41, 497–505

Starkey, M. L., Bleul, C., Kasper, H., Mosberger, A. C., Zörner, B., Giger, S., et al. (2014). High-impact, self-motivated training within an enriched environment with single animal tracking dose-dependently promotes motor skill acquisition and functional recovery. *Neurorehabilitation and Neural Repair* 28, 594–605. doi:10.1177/1545968314520721

Starkey, M. L., Bleul, C., Maier, I. C., and Schwab, M. E. (2011). Rehabilitative training following unilateral pyramidotomy in adult rats improves forelimb function in a non-task-specific way. *Experimental Neurology* 232, 81–89. doi:10.1016/j.expneurol.2011.08.006

Starkey, M. L. and Schwab, M. E. (2012). Anti-Nogo-A and training: Can one plus one equal three? *Experimental Neurology* 235, 53–61. doi:10.1016/j.expneurol.2011.04.008

Stevens, S. L., Caputo, J. L., Fuller, D. K., and Morgan, D. W. (2008). Physical activity and quality of life in adults with spinal cord injury. *Journal of Spinal Cord Medicine* 31, 373–378. doi:10.1080/10790268.2008.11760739

Stoll, T., Huber, E., Seifert, B., Michel, B. A., and Stucki, G. (2000). Maximal isometric muscle strength. Normative values and gender-specific relation to age. *Clinical Rheumatology* 19, 105–113. doi:10.1007/s100670050026

Storm, F. A., Nair, K. P., Clarke, A. J., Van der Meulen, J. M., and Mazzà, C. (2018). Free-living and laboratory gait characteristics in patients with multiple sclerosis. *PLoS ONE* 13, e0196463. doi:10.1371/journal.pone.0196463

Summa, S., Tosi, J., Taffoni, F., Di Biase, L., Marano, M., Rizzo, A. C., et al. (2017). Assessing bradykinesia in Parkinson's disease using gyroscope signals. In *IEEE International Conference on Rehabilitation Robotics* (IEEE), 1556–1561. doi:10.1109/ICORR.2017.8009469

Takeda, R., Tadano, S., Todoh, M., and Yoshinari, S. (2009). Human Gait Analysis using Wearable Sensors of Acceleration and Angular Velocity. In *IFMBE Proceedings* (Berlin, Heidelberg: Springer Berlin Heidelberg), vol. 23, 1069–1072. doi:10.1007/978-3-540-92841-6_263

Tamburella, F., Scivoletto, G., and Molinari, M. (2013). Balance training improves static stability and gait in chronic incomplete spinal cord injury subjects: a pilot study. *EUR J PHYS REHABIL MED*

Tanaka, C. and Tanaka, S. (2009). Daily physical activity in japanese preschool children evaluated by triaxial accelerometry: the relationship between period of engagement in moderate-to-vigorous physical activity and daily step counts. *J Physiol Anthropol* 28, 283–288

Tang, A., Sibley, K. M., Bayley, M. T., McIlroy, W. E., and Brooks, D. (2006). Do functional walk tests reflect cardiorespiratory fitness in sub-acute stroke? *Journal of NeuroEngineering and Rehabilitation* 3, 23. doi:10.1186/1743-0003-3-23

Tawashy, A. E., Eng, J. J., Lin, K. H., Tang, P. F., and Hung, C. (2009). Physical activity is related to lower levels of pain, fatigue and depression in individuals with spinal-cord injury: a correlational study. *Spinal Cord* 47, 301–306. doi:10.1038/sc.2008.120

Taylor-Schroeder, S., LaBarbera, J., McDowell, S., Zanca, J. M., Natale, A., Mumma, S., et al. (2011). The SCIRehab project: treatment time spent in SCI rehabilitation. Physical therapy treatment time during inpatient spinal cord injury rehabilitation. *The journal of spinal cord medicine* 34, 149–61. doi:10.1179/107902611X12971826988057

Teixeira, P. J., Carraça, E. V., Markland, D., Silva, M. N., and Ryan, R. M. (2012). Exercise, physical activity, and self-determination theory: A systematic review. *International Journal of Behavioral Nutrition and Physical Activity* 9, 78. doi:10.1186/1479-5868-9-78

Totosy de Zepetnek, J. O., Pelletier, C. A., Hicks, A. L., and MacDonald, M. J. (2015). Following the Physical Activity Guidelines for Adults With Spinal Cord Injury for 16 Weeks Does Not Improve Vascular Health: A Randomized Controlled Trial. *Archives of Physical Medicine and Rehabilitation* 96, 1566–1575. doi:10.1016/J.APMR.2015.05.019

Trojaniello, D., Cereatti, A., and Della Croce, U. (2014). Accuracy, sensitivity and robustness of five different methods for the estimation of gait temporal parameters using a single inertial sensor mounted on the lower trunk. *Gait & posture* 40, 487–492

Trost, S. G., McIver, K. L., and Pate, R. R. (2005). Conducting accelerometer-based activity assessments in field-based research. *Medicine and Science in Sports and Exercise* 37, S531

Trost, S. G., Pate, R. R., Freedson, P. S., Sallis, J. F., and Taylor, W. C. (2000). Using objective physical activity measures with youth: How many days of monitoring are needed? *Medicine and Science in Sports and Exercise* 32, 426–431. doi:10.1097/00005768-200002000-00025

Tudor-Locke, C., Burkett, L., Reis, J. P., Ainsworth, B. E., Macera, C. A., and Wilson, D. K. (2005). How many days of pedometer monitoring predict weekly physical activity in adults? *Preventive Medicine* 40, 293–298. doi:10.1016/j.ypmed.2004.06.003

Uswatte, G., Miltner, W. H., Foo, B., Varma, M., Moran, S., and Taub, E. (2000). Objective measurement of functional upper-extremity movement using accelerometer recordings transformed with a threshold filter. *Stroke* 31, 662–7. doi:10.1161/01.STR.31.3.662

Vallery, H., Lutz, P., Von Zitzewitz, J., Rauter, G., Fritschi, M., Everarts, C., et al. (2013). Multidirectional transparent support for overground gait training. In *IEEE International Conference on Rehabilitation Robotics* (IEEE), 1–7. doi:10.1109/ICORR.2013.6650512

van den Berg-Emons, R. J., Bussmann, J. B., Haisma, J. A., Sluis, T. A., van der Woude, L. H., Bergen, M. P., et al. (2008). A Prospective Study on Physical Activity Levels After Spinal Cord Injury During Inpatient Rehabilitation and the Year After Discharge. *Archives of Physical Medicine and Rehabilitation* 89, 2094–2101. doi:10.1016/J.APMR.2008.04.024

Van Den Berg-Emons, R. J., L'Ortye, A. A., Buffart, L. M., Nieuwenhuijsen, C., Nooijen, C. F., Bergen, M. P., et al. (2011). Validation of the physical activity scale for individuals with physical disabilities. *Archives of Physical Medicine and Rehabilitation* 92, 923–928. doi:10.1016/j.apmr.2010.12.006

van der Pas, S. C., Verbunt, J. A., Breukelaar, D. E., van Woerden, R., and Seelen, H. A. (2011). Assessment of Arm Activity Using Triaxial Accelerometry in Patients With a Stroke. *Archives of Physical Medicine and Rehabilitation* 92, 1437–1442. doi:10.1016/J.APMR.2011.02.021

Van Hedel, H. J., Wirz, M., and Dietz, V. (2005). Assessing walking ability in subjects with spinal cord injury: Validity and reliability of 3 walking tests. *Archives of Physical Medicine and Rehabilitation* 86, 190–196. doi:10.1016/j.apmr.2004.02.010

Van Peppen, R. P., Kwakkel, G., Wood-Dauphinee, S., Hendriks, H. J., Van der Wees, P. J., and Dekker, J. (2004). The impact of physical therapy on functional outcomes after stroke: What's the evidence? *Clinical Rehabilitation* 18, 833–862. doi:10.1191/0269215504cr843oa

van Tuijl, J., Janssen-Potten, Y., and Seelen, H. (2002). Evaluation of upper extremity motor function tests in tetraplegics. *Spinal Cord* 40, 51–64

Vanhees, L., Lefevre, J., Philippaerts, R., Martens, M., Huygens, W., Troosters, T., et al. (2005). How to assess physical activity? How to assess physical fitness? *European Journal of Preventive Cardiology* 12, 102–114. doi:10.1097/01.hjr.0000161551.73095.9c

Vanhelst, J., Béghin, L., Drumez, E., Coopman, S., and Gottrand, F. (2017). Awareness of wearing an accelerometer does not affect physical activity in youth. *BMC Medical Research Methodology* 17. doi:10.1186/s12874-017-0378-5

Vega-Gonzalez, A., Bain, B. J., Dall, P. M., and Granat, M. H. (2007). Continuous monitoring of upper-limb activity in a free-living environment: A validation study. *Medical and Biological Engineering and Computing* 45, 947–956. doi:10.1007/s11517-007-0233-7

Velstra, I.-M., Curt, A., Frotzler, A., Abel, R., Kalsi-Ryan, S., Rietman, J. S., et al. (2015). Changes in Strength, Sensation, and Prehension in Acute Cervical Spinal Cord Injury: European Multicenter Responsiveness Study of the GRASSP. *Neurorehabilitation and neural repair* 29, 755–766. doi:10.1177/1545968314565466

von Büren, M. (2017). *A new method to assess activity profiles of children and adolescents with neuromotor disorders in their everyday life.* Master thesis, ETH Zurich

Wang, H. and Song, M. (2011). Ckmeans.1d.dp: Optimal k-means Clustering in One Dimension by Dynamic Programming. *The R journal* 3, 29–33

Wang, J. B., Cadmus-Bertram, L. A., Natarajan, L., White, M. M., Madanat, H., Nichols, J. F., et al. (2015). Wearable Sensor/Device (Fitbit One) and SMS Text-Messaging Prompts to Increase Physical Activity in Overweight and Obese Adults: A Randomized Controlled Trial. *Telemedicine and e-Health* 21, 782–792. doi:10.1089/tmj.2014.0176

Wang, Z., Yang, Z., Dong, T., Wang, Z., Yang, Z., and Dong, T. (2017). A Review of Wearable Technologies for Elderly Care that Can Accurately Track Indoor Position, Recognize Physical Activities and Monitor Vital Signs in Real Time. In *Sensors* (Multidisciplinary Digital Publishing Institute), vol. 17, 341. doi:10.3390/s17020341

Warburton, D. E. R., Nicol, C. W., and Bredin, S. S. D. (2006). Health benefits of physical activity: The evidence. *CMAJ* 174, 801–809. doi:10.1503/cmaj.051351

Welch, R. D., Lobley, S. J., O'Sullivan, S. B., and Freed, M. M. (1986). Functional independence in quadriplegia: critical levels. *Archives of physical medicine and rehabilitation* 67, 235–240

Werner, C. (2018). *Assessing gait quality in spinal cord injured individuals using wearable sensors.* Master thesis, ETH Zurich

Whiteneck, G., Gassaway, J., Dijkers, M., Backus, D., Charlifue, S., Chen, D., et al. (2011). Inpatient treatment time across disciplines in spinal cord injury rehabilitation. *The Journal of Spinal Cord Medicine* 34, 133–148. doi:10.1016/j.eursup.2009.01.001

Whiteneck, G., Meade, M. A., Dijkers, M., Tate, D. G., Bushnik, T., and Forchheimer, M. B. (2004). Environmental factors and their role in participation and life satisfaction after spinal cord injury. *Archives of Physical Medicine and Rehabilitation* 85, 1793–1803. doi:10.1016/j.apmr.2004.04.024

Willis, E. A., Ptomey, L. T., Szabo-Reed, A. N., Honas, J. J., Lee, J., Washburn, R. A., et al. (2015). Length of moderate-to-vigorous physical activity bouts and cardio-metabolic risk factors in elementary school children. *Preventive Medicine* 73, 76–80. doi:10.1016/j.ypmed.2015.01.022

Wolak, M. E., Fairbairn, D. J., and Paulsen, Y. R. (2012). Guidelines for estimating repeatability. *Methods in Ecology and Evolution* 3, 129–137. doi:10.1111/j.2041-210X.2011.00125.x

Wolpaw, J. R. and Tennissen, A. M. (2002). Activity-Dependent Spinal Cord Plasticity in Health and Disease. *Annual Review of Neuroscience* 24, 807–843. doi:10.1146/annurev.neuro.24.1.807

World Health Organisation (2002). *Towards a Common Language for Functioning, Disability and Health ICF Towards a Common Language for Functioning, Disability and Health: ICF The International Classification of Functioning, Disability and Health*. Tech. rep.

World Health Organisation (2011). *Global Recommendations on Physical Activity for Health*. Tech. rep.

Wyndaele, M. and Wyndaele, J. J. (2006). Incidence, prevalence and epidemiology of spinal cord injury: What learns a worldwide literature survey? *Spinal Cord* 44, 523–529. doi:10.1038/sj.sc.3101893

Xu, X., Batalin, M., Wang, Y., and Kaiser, W. (2012). Gait quality evaluation method for post-stroke patients. In *ICASSP, IEEE International Conference on Acoustics, Speech and Signal Processing - Proceedings* (IEEE), 613–616. doi:10.1109/ICASSP.2012.6287958

Zariffa, J., Kapadia, N., Kramer, J. L., Taylor, P., Alizadeh-Meghrazi, M., Zivanovic, V., et al. (2012). Feasibility and efficacy of upper limb robotic rehabilitation in a subacute cervical spinal cord injury population. *Spinal Cord* 50, 220–226. doi:10.1038/sc.2011.104

Zbogar, D., Eng, J. J., Miller, W. C., Krassioukov, A. V., and Verrier, M. C. (2016). Physical activity outside of structured therapy during inpatient spinal cord injury rehabilitation. *Journal of NeuroEngineering and Rehabilitation* 4, 2050312116666941. doi:10.1177/2050312116666941

Zhao, R.-R., Andrews, M. R., Wang, D., Warren, P., Gullo, M., Schnell, L., et al. (2013). Combination treatment with anti-Nogo-A and chondroitinase ABC is more effective than single treatments at enhancing functional recovery after spinal cord injury. *European Journal of Neuroscience* 38. doi:10.1111/ejn.12276

A Supplementary material to Chapter 4

	in-patients	out-patients
AC	6	91
SED	28	80
LPA	15	158
MVPA	42	105
$DIST_{TOT}$	66	81
$DIST_{TOT}$	49	69
LAT	89	9
VEL	82	56

Table A.1 – Sample size calculation for activity counts (AC), time spent in sedentary activity (SED), low physical activity (LPA), and moderate-to-vigorous activity (MVPA), total distance travelled in a wheelchair ($DIST_{TOT}$), distance travelled actively in a wheelchair ($DIST_{TOT}$), laterality (LAT) and mean velocity (VEL) for pooled in-and out-patients. The desired confidence interval width is set to 0.2.

B Supplementary material to Chapter 6

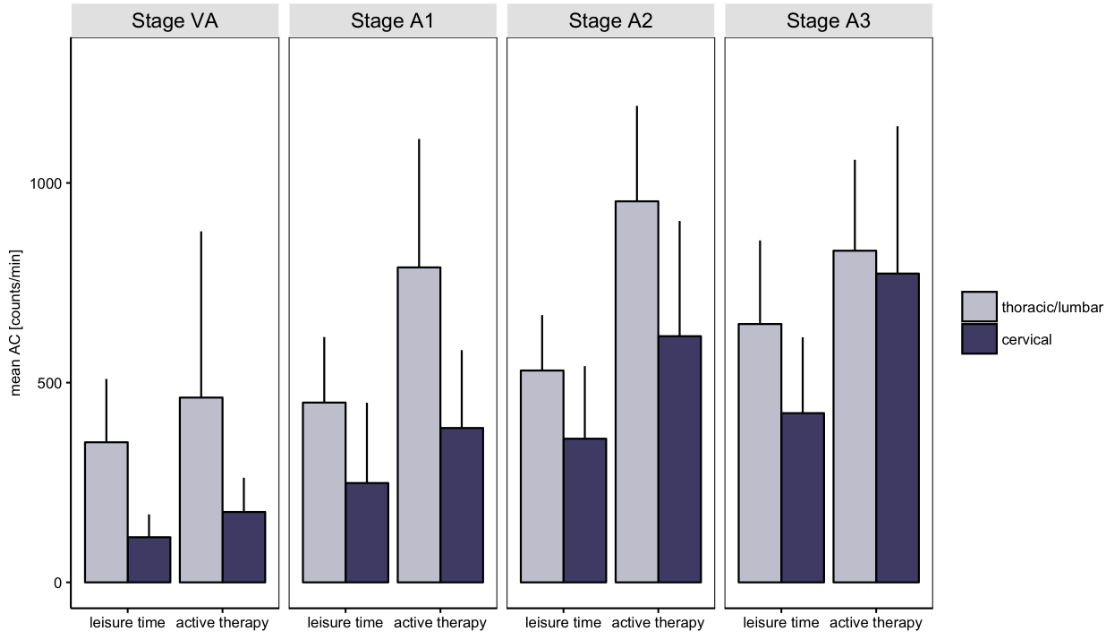

Figure B.1 – Longitudinal changes of activity counts (AC) during the rehabilitation from 2 weeks after injury (Stage VA) to 6 months after injury (Stage A3) during leisure time and active therapies for patients with a thoracic/lumbar lesion (light blue) and a cervical lesion (dark blue). Plotted is the mean value and the standard deviation (error bars).

		AC		REST		SED		LPA		MVPA	
		t-ratio	p-value	t-ratio	p-value	t-ratio	p-value	t-ratio	p-value	t-ratio	p-value
		MAIN EFFECTS									
Stage	A1 - VA					-0.12	0.999			3.09	0.007
	A2 - A1	a		a		3.61	0.001	a		5.21	<0.001
	A3 - A2					-3.45	0.002			2.60	0.031
Group	thoracic -cervical	a		a		a		a		3.65	<0.001
Therapy	leisure - active therapy	a		a		a		-10.74	<0.001	-6.01	<0.001
		INTERACTION EFFECTS									
cervical											
Stage	A1 - VA	5.36	<0.001	-3.93	<0.001			3.46	0.005		
	A2 - A1	7.64	<0.001	-8.17	<0.001	b		3.41	0.005	b	
	A3 - A2	3.75	0.002	-1.83	0.333			4.33	<0.001		
Therapy	leisure - active therapy	-10.20	<0.001	14.24	<0.001	-4.57	<0.001			b	
thoracic											
Stage	A1 - VA	4.49	<0.001	-2.75	0.039			1.90	0.297		
	A2 - A1	0.70	0.045	-1.52	0.544	b		1.37	0.657	b	
	A3 - A2	0.43	0.998	-0.21	1.000			-0.40	0.999		
Therapy	leisure - active therapy	-10.20	<0.001	6.76	<0.001	0.05	0.959			b	
leisure											
Stage	A1 - VA	3.82	0.001	-2.13	0.183						
	A2 - A1	3.81	0.001	-3.24	0.009	b		b		b	
	A3 - A2	1.81	0.347	-0.95	0.906						
Group	thoracic -cervical	2.81	0.006	-1.34	0.185	-0.81	0.425	b		b	
active therapy											
Stage	A1 - VA	6.38	<0.001	-4.71	<0.001						
	A2 - A1	5.80	<0.001	-5.37	<0.001	b		b		b	
	A3 - A2	1.57	0.496	-0.74	0.968						
Group	thoracic -cervical	2.81	0.006	0.51	0.612	-3.57	0.001	b		b	
Stage VA											
Group	thoracic -cervical	2.71	0.007	-1.54	0.126	b		1.53	0.129	b	
Therapy	leisure - active therapy	-1.74	0.083	2.96	0.004	b		b		b	
Stage A1											
Group	thoracic -cervical	3.79	<0.001	-1.72	0.090	b		1.28	0.205	b	
Therapy	leisure - active therapy	-7.24	<0.001	9.31	<0.001	b		b		b	
Stage A2											
Group	thoracic -cervical	2.38	0.020	0.74	0.464	b		0.74	0.463	b	
Therapy	leisure - active therapy	-9.30	<0.001	11.56	<0.001	b		b		b	
Stage A3											
Group	thoracic -cervical	0.69	0.491	1.23	0.220	b		-1.50	0.136	b	
Therapy	leisure - active therapy	-5.76	<0.001	7.54	<0.001	b		b		b	

Table B.1 – Post-hoc comparisons for all significant effects in the 'basic' models. Post-hoc comparisons of main effects involved in a significant interaction were conducted for the interaction effect only. The Tukey multiple-comparison test was applied for pairwise comparisons, multivariate testing was used for comparing stages. Note that stages were compared consecutively only. Significant comparisons ($\alpha = 0.05$) are highlighted in bold. a main effect involved in significant interaction. b non-significant effect.

		AC		REST		SED		LPA		MVPA	
		t-ratio	p-value	t-ratio	p-value	t-ratio	p-value	t-ratio	p-value	t-ratio	p-value
		MAIN EFFECTS									
Stage	A1 - VA									0.91	0.731
	A2 - A1	a		a		b		a		1.39	0.412
	A3 - A2									1.93	0.156
Group	thoracic -cervical	a		a		b		a		b	
Therapy	leisure - active therapy	a		a		a		-12.34	<0.001	a	
Mobility	wheelchair - ambulatory	b		b		-8.70	<0.001	6.75	<0.001	-2.14	0.034
Gender	male - female	a		b		b		b		-2.15	0.040
Center	Center 1 - Center 2	-3.20	0.014	1.93	0.242					-2.75	0.049
	Center 1 - Center 3	-0.02	1.000	1.59	0.401					0.71	0.894
	Center 1 - Center 4	-0.09	1.000	-1.10	0.695	b		b		-1.69	0.349
	Center 2 - Center 3	2.16	0.151	0.36	0.984					2.24	0.134
	Center 2 - Center 4	2.40	0.095	-2.54	0.076					0.74	0.879
	Center 3 - Center 4	-0.05	1.000	-2.14	0.163					-1.69	0.346
Age		c		c		b		b		c	
SCIM selfcare		c		c		c		c		c	
		INTERACTION EFFECTS									
cervical											
Stage	A1 - VA	3.52	0.003	-2.48	0.081			3.70	0.002		
	A2 - A1	3.80	0.001	-5.17	<0.001	b		4.86	<0.001	b	
	A3 - A2	2.34	0.115	-0.94	0.913			2.21	0.158		
Therapy	leisure - active therapy	b		13.88	<0.001	b		b		b	
thoracic											
Stage	A1 - VA	2.73	0.041	-1.33	0.689			1.02	0.878		
	A2 - A1	1.07	0.857	-0.36	0.999	b		0.56	0.993	b	
	A3 - A2	-0.90	0.931	0.46	0.998			-0.99	0.896		
Therapy	leisure - active therapy	b		6.59	<0.001	b		b		b	
leisure											
Stage	A1 - VA	1.73	0.397	-0.54	0.994						
	A2 - A1	1.38	0.652	-1.51	0.554	b		b		b	
	A3 - A2	0.21	1.000	0.01	1.000						
Group	thoracic -cervical	b		0.60	0.551	b		b		b	
Gender	male - female	-2.35	0.024	b		b		b		b	
active therapy											
Stage	A1 - VA	4.64	<.001	-3.27	0.008						
	A2 - A1	3.29	0.007	-3.57	0.003	b		b		b	
	A3 - A2	0.30	1.000	-0.14	1.000						
Group	thoracic -cervical	b		2.17	0.033	b		b		b	
Gender	male - female	0.24	0.809	b		b		b		b	
Stage VA											
Group	thoracic -cervical	1.49	0.138	-0.19	0.846	b		1.18	0.243	b	
Therapy	leisure - active therapy	-1.07	0.284	2.83	0.005	b		b		b	
Stage A1											
Group	thoracic -cervical	1.94	0.055	0.28	0.782	b		-0.04	0.972	b	
Therapy	leisure - active therapy	-6.49	<0.001	9.32	<0.001	b		b		b	
Stage A2											
Group	thoracic -cervical	0.72	0.476	2.28	0.025	b		-1.65	0.102	b	
Therapy	leisure - active therapy	-8.54	<0.001	11.58	<0.001	b		b		b	
Stage A3											
Group	thoracic -cervical	-1.23	0.222	2.71	0.008	b		-3.02	0.003	b	
Therapy	leisure - active therapy	-5.66	<0.001	7.96	<0.001	b		b		b	
Age											
	leisure - active therapy	b		b		-4.31	<0.001	b		b	
SCIM selfcare											
	leisure - active therapy	b		b		5.28	<0.001	b		-3.42	0.001
female											
	leisure - active therapy	-3.77	<0.001	b		b		b		b	
male											
	leisure - active therapy	-10.47	<0.001	b		b		b		b	

Table B.2 – Post-hoc comparisons for all significant effects in the 'full' models. Post-hoc comparisons of main effects involved in a significant interaction were conducted for the interaction effect only. The Tukey multiple-comparison test was applied for pairwise comparisons, multivariate testing was used for comparing stages. Note that stages were compared consecutively only. For the interaction effects SCIM self-care and therapy as well as age and therapy, the significance test was applied for the differences between slopes. Significant comparisons (α = 0.05) are highlighted in bold. a main effect involved in significant interaction. b non-significant effect. c significant main effect, but no post-hoc comparison possible, because of continuous scale of the variables.s

			AC		REST		SED		LPA		MVPA	
			EMM	SE	EMM	SE	EMM	SE	EMM	SE	EMM	SE
Stage	VA		a		a		10.74	0.98	a		0.19	0.13
	A1						10.62	0.60			0.74	0.19
	A2						13.05	0.66			1.70	0.28
	A3						10.03	0.79			2.55	0.42
Plegia	cervical		a		a		a		a		0.54	0.16
	thoracic										1.85	0.41
Therapy	leisure time		a		a		a		19.20	1.57	0.64	0.14
	active therapy								28.51	1.71	1.69	0.32
Interaction stage*plegia	cervical	VA	140.80	29.16	32.07	2.86	b		14.86	1.97	b	
		A1	295.57	31.69	23.30	1.74			20.95	1.72		
		A2	473.59	40.85	14.46	1.41			24.95	1.92		
		A3	610.35	52.67	12.33	1.47			32.16	2.44		
	thoracic	VA	297.97	55.89	25.44	3.27			20.03	2.95		
		A1	531.56	61.19	18.53	2.26			24.76	2.71		
		A2	645.47	65.54	16.19	2.04			27.28	2.74		
		A3	678.19	88.98	15.72	2.56			26.14	3.34		
Interaction stage*therapy	leisure time	VA	180.99	31.98	33.14	2.84	b		b		b	
		A1	309.53	30.90	27.74	1.89						
		A2	413.58	35.21	22.81	1.68						
		A3	493.04	50.37	21.01	2.03						
	active therapy	VA	245.67	39.07	24.51	2.51						
		A1	513.21	42.67	14.93	1.44						
		A2	719.94	49.92	9.31	1.12						
		A3	814.70	69.99	8.37	1.37						
Interaction therapy*plegia	leisure time	cervical	267.88	29.10	27.98	1.89	10.68	0.65	b		b	
		thoracic	417.26	50.36	24.03	2.42	9.81	0.89				
	active therapy	cervical	457.78	40.91	13.05	1.36	14.39	0.83				
		thoracic	648.00	65.23	14.19	1.97	9.75	0.99				

Table B.3 – Estimated marginal means (EMM) and standard errors (SE) for all significant effects involving categorical variables in the 'basic' models. Please note that the EMM and SE were back-transformed from the square-root-scale to facilitate interpretation only. EMM were calculated for significant effects only. If a main effect was involved in a significant interaction, EMM were calculated for the interaction effect only. a main effect involved in significant interaction. b non-significant effect.

			AC EMM	AC SE	REST EMM	REST SE	SED EMM	SED SE	LPA EMM	LPA SE	MVPA EMM	MVPA SE
Stage	VA		a		a		b		a		1.13	1.13
	A1										1.39	0.30
	A2										1.67	0.32
	A3										2.21	0.48
Group	cervical		a		a		b		a		a	
	thoracic											
Therapy	leisure		a		a		b		13.03	1.59	a	
	active therapy								20.90	1.95		
Mobility	wheelchair		b		b		10.80	0.46	25.21	1.60	1.09	0.14
	ambulatory						25.99	2.26	9.99	2.03	2.15	0.61
Gender	female		a		b		b		b		1.91	0.39
	male										1.27	1.27
Center	1		365.39	31.00	20.87	2.13	b		b		1.31	0.29
	2		519.54	52.22	16.16	2.41					2.24	0.48
	3		366.33	51.39	14.79	3.28					1.00	0.42
	4		370.02	50.42	24.10	3.09					1.90	0.43
Interaction Stage*Group	cervical	VA	233.82	37.03	24.13	3.03	b		10.93	2.01	b	
		A1	349.78	30.40	19.20	2.04			16.22	1.93		
		A2	452.77	31.24	13.33	1.57			21.66	2.12		
		A3	532.47	43.12	12.23	1.82			24.84	2.65		
	thoracic	VA	317.11	48.34	23.38	3.13			14.15	2.37		
		A1	452.92	50.49	19.99	2.66			16.13	2.36		
		A2	492.86	53.21	19.40	2.83			16.90	2.58		
		A3	438.13	72.76	20.53	3.66			14.93	2.99		
Interaction Stage*Therapy	leisure time	VA	252.14	35.23	27.58	2.86	b		b		b	
		A1	314.07	28.44	26.29	2.22						
		A2	351.64	29.64	23.91	2.17						
		A3	359.68	44.05	23.94	2.87						
	active therapy	VA	296.53	41.23	20.21	2.59						
		A1	495.61	39.45	13.88	1.75						
		A2	611.41	43.24	10.02	1.51						
		A3	627.07	63.22	9.83	1.95						
Interaction Therapy*Group	leisure time	cervical	b		24.53	2.19	b		b		b	
		thoracic			26.30	2.94						
	active therapy	cervical			10.69	1.57						
		thoracic			15.94	2.54						
Interaction Gender*Therapy	leisure time	female	362.52	36.40	b		b		b		b	
		male	276.19	26.65								
	active therapy	female	490.92	51.10								
		male	504.84	40.50								

Table B.4 – Estimated marginal means (EMM) and standard errors (SE) for all significant effects involving categorical variables in the 'full' models. Please note that the EMM and SE were back-transformed from the square-root-scale to facilitate interpretation. EMM were calculated for significant effects only. If a main effect was involved in a significant interaction, EMM were calculated for the interaction effect only. a main effect involved in significant interaction. b non-significant effect.

		AC		REST		SED		LPA		MVPA	
		EM trends	SE	EM trends	SE	EM trends	SE	EM trends	SE	EM trends	SE
SCIM self-care		21.22	3.25	-0.69	0.17	a		0.44	0.15	a	
Age		-3.39	1.08	0.12	0.06	a		b		-0.02	0.01
Interaction	leisure time	b		b		0.03	0.11	b		0.10	0.02
SCIM self-care*Therapy	active therapy					-0.49	0.11			0.27	0.04
Interaction	leisure time	b		b		0.04	0.03	b		b	
Age*Therapy	active therapy					0.10	0.03				

Table B.5 – Estimated marginal (EM) trends and standard errors (SE) for all significant effects involving continuous variables in the 'full' models. Please note that the EM trends and SE were calculated after back-transforming from the square-root-scale to facilitate interpretation. EM trends were calculated for significant effects only. If a main effect was involved in a significant interaction, EM trends were calculated for the interaction effect only. a main effect involved in significant interaction. b non-significant effect.

C Supplementary material to Chapter 7

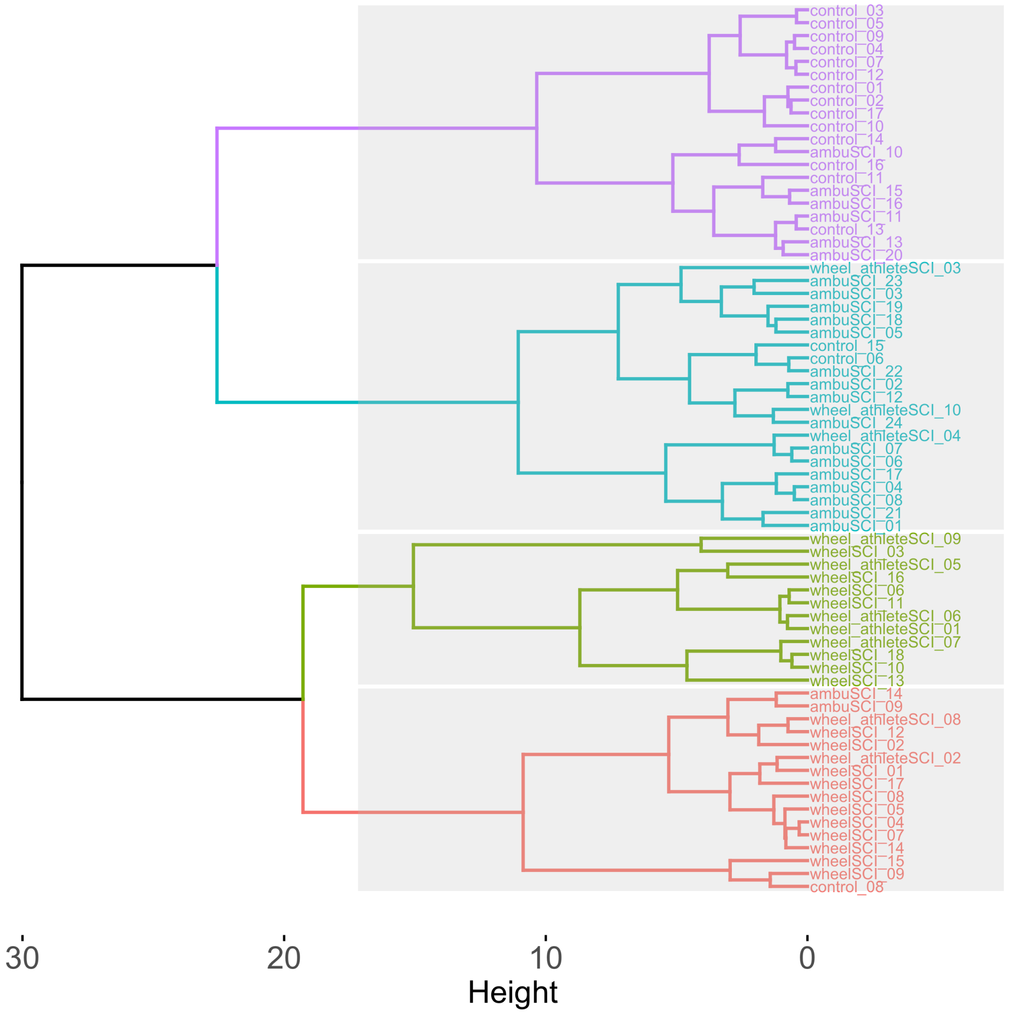

Figure C.1 – Dendrogram resulting from hierarchical clustering of PA metrics. 'wheelSCI_xx' denote wheelchair-dependent SCI subjects, 'wheel_athleteSCI_xx' wheelchair-dependent SCI subjects participating in regular sports training and matches, 'ambuSCI_xx' ambulatory SCI subjects, and 'control_xx' healthy controls.

MET general	SED/LPA/MVPA	
mean MET	time spent in SED/LPA/MVPA (minutes/24h)	Activity counts (AC) *
standard deviation MET	MET-minutes of SED/LPA/MVPA (MET-minutes/24h)	total time spent in bouts > 10min of MVPA (minutes/24h)*
maximal MET	mean bout length > 2min in SED/LPA/MVPA (minutes)	
	mean bout length > 5min in SED/LPA/MVPA (minutes)	
	mean bout length > 10min in SED/LPA/MVPA (minutes)	
	number of bouts > 2min in SED/LPA/MVPA (minutes)	
	number of bouts > 5min in SED/LPA/MVPA (minutes)	
	number of bouts > 10min in SED/LPA/MVPA (minutes)	

Table C.1 – Calculated PA metrics used for hierarchical clustering. * Metrics were not used in hierarchical clustering but only reported to compare between clusters and to literature.

	wheelchair-dependent moderate independence n = 16	wheelchair-dependent high independence n = 12	ambulatory moderate walking capacity n = 21	ambulatory high walking capacity n = 20	χ^2	p-value
Age [years]	50 (16.5)	47.5 (12.8)	53 (20)	55.5 (15)	2.34	0.506
Body mass index [kg/m2]	24.2 (9.6)	22.5 (2.2)	24.7 (6)	23.3 (4.6)	3.57	0.312
Gender					-	1
female	3	2	4	4		
male	13	10	17	16		
Plegia					-	< 0.001
paraplegic	7	10	13	5		
tetraplegic	8	2	6	1		
control	1		2	14		
Main mobility type						< 0.001
wheelchair-user	13	12	3	0		
pedestrian	3	0	18	20		
Time after injury [years]	8.6 (11.6)	19 (13)	14.1 (13)	12.8 (11.5)	2.68	0.443
SCIM self-care score [-]	18 (9.5)b,c	20 (1)	20 (0)b	20 (0)c	18.58	< 0.001
SCIM mobility room and toilet score [-]	10 (5)b	10 (0)	10 (0)b	10 (0)	12.58	0.006
SCIM mobility indoors and outdoors score [-]	8 (5.5)b,c	8 (1.5)d,e	30 (8.5)b,d	29.5 (1.8)c,e	24.37	< 0.001
upper limb motor score [-]	99 (31.5)	100 (0.8)	100 (2.5)	100 (0)	6.71	0.082
reported time exercising [h/day]	1 (1.8)	1 (2)	0.8 (1.4)	1.9 (2.7)	3.83	0.281
reported time working [h/day]	0 (7.8)c	3.7 (7.6)d	9.5 (5.3)d	11.3 (6.1)c	12.78	0.005
distance in 6MWT [m]	590 (79)	-	524.5 (231)	576.5 (191.5)	2.27	0.321
time in 10MWT [sec]	5.2 (1.2)	-	6.3 (3)	5.9 (3)	2.06	0.357
time in TUG [sec]	5.7 (0.6)	-	6.9 (4.5)	6.6 (3.5)	1.49	0.474
average MET [MET/day]	1.47 (0.32)b,c	1.72 (0.22)d,e	2.14 (0.24)b,d	2.23 (0.56)c,e	41.75	< 0.001
time spent in SED [min/day]	751.25 (161.93)a,b	487.66 (164.74)a,e	357.68 (289.26)b,f	772.51 (162.61)e,f	45.16	< 0.001
MET-minutes in SED [MET-min/day]	962.99 (192.63)a,b	644.69 (212.71)a,e	463.24 (356.31)b,f	955.88 (198.11)e,f	43.84	< 0.001
time spent in LPA [min/day]	397.7 (346.64)a	760.55 (194.88)a,d,e	551.93 (214.25)d,f	235.5 (68.33)e,f	43.27	< 0.001
MET-minutes in LPA [MET-min/day]	779.7 (571.37)a,b	1549.9 (408.6)a,e	1159.61 (512.63)b,f	486.99 (149.47)e,f	43.93	< 0.001
time spent in MVPA [min/day]	13.97 (30.75)b,c	46 (57.33)d,e	294.89 (160.74)b,d	321.83 (177.62)c,e	47	< 0.001
MET-minutes in MVPA [MET-min/day]	46.28 (114.44)b,c	180.41 (196.98)d,e	1106.73 (664.33)b,d	1546.02 (969.08)c.e	47.71	< 0.001
time spent in bouts >10 min of MVPA [min/day]	0 (0)b,c	3.92 (28.23)e	26.35 (54.94)b	65.43 (70.62)c,e	33.38	< 0.001
average activity counts [counts/min]	667.36 (249.69)b,c	881.87 (219.34)d,e	1328.76 (406)b,d	1411.64 (540.57)c,e	37.99	< 0.001

Table C.2 – Demographics, clinical scores, and PA metrics of PA clusters resulting from hierarchical clustering. a-f denote significant post-hoc comparisons (p-value < 0.05) between clusters: a 'wheelchair-dependent with moderate independence' vs. 'wheelchair-dependent with high independence' , b 'wheelchair-dependent with moderate independence' vs. 'ambulatory with moderate walking capacity', c 'wheelchair-dependent with moderate independence' vs. 'ambulatory with high walking capacity', d 'wheelchair-dependent with high independence' vs. 'ambulatory with moderate walking capacity', e 'wheelchair-dependent with high independence' vs. 'ambulatory with high walking capacity', and f 'ambulatory with moderate walking capacity'vs. 'ambulatory with high walking capacity'.

Reference					
		PA class 1	PA class 2	PA class 3	PA class 4
Prediction	PA class 1	10	2	1	0
	PA class 2	3	10	3	0
	PA class 3	1	0	7	1
	PA class 4	2	0	10	19

Table C.3 – : Confusion matrix of the multinomial regression model.