Quantifizierung motorischer Fatigue durch Bewegungsanalyse – Entwicklung und Evaluation eines neuen Diagnostikverfahrens bei Patienten mit Multipler Sklerose

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Summary

Motor fatigue is one of the most common and disabling symptom in patients with multiple sclerosis. Despite the high incidence of this symptom and its serious consequences for the patients, no instruments or methods that could detect the motor fatigue objectively have been developed. The present work concentrates on the development and testing of a method for objective measurement of motor fatigue among patients with multiple sclerosis and after stroke. This dissertation is a cumulative work consisting of three empirical studies.

The first study develops and tests a new method to quantify changes in gait patterns among healthy volunteers. The properties of the limit cycle attractor were used in this study. This method identifies changes in movement patterns, that is, changes in gait characteristic and gait variability, in individuals both at the group and at the individual level.

In the second study, the newly developed method was used to quantify motor fatigue among patients with multiple sclerosis. More specifically, in this context, the Fatigue index Kliniken Schmieder was developed for an objective detection of motor fatigue. Using this index, for the first time, changes in gait patterns due to the acute motor fatigue could be detected in patients with multiple sclerosis. In addition, the limits which allowed a clear diagnosis of motor fatigue were calibrated. Furthermore, it was demonstrated that motor fatigue is not related to muscle fatigue.

In the third study, the Fatigue index Kliniken Schmieder was successfully used to measure motor fatigue among stroke patients. This allowed for a unique comparison of motor fatigue between stroke patients and patients with multiple sclerosis on the basis of empirical data. Our results show that stroke patients display similar degrees of motor fatigue as patients with multiple sclerosis. The Fatigue index Kliniken Schmieder proved to be robust with respect to chronic walking impairments.

Zusammenfassung

Motorische Fatigue ist eines der häufigsten und belastendsten Symptome bei Patienten mit Multipler Sklerose. Trotz des häufigen Auftretens dieses Symptoms und seiner teilweise schwerwiegenden Folgen für die Betroffenen existierten bisher keine Messinstrumente und -verfahren, welche motorische Fatigue objektiv erfassen können. Die vorliegende Arbeit beschäftigt sich mit der Entwicklung und Testung eines Verfahrens zur objektiven Messung von motorischer Fatigue bei Patienten mit Multipler Sklerose und nach einem Schlaganfall. Das vorliegende Dissertationsvorhaben ist eine kumulative Arbeit aus drei empirischen Untersuchungen.

In der ersten Studie wurde das neue Verfahren zur Quantifizierung von Veränderungen im Gangmuster entwickelt und erfolgreich an gesunden Probanden getestet. Hierbei wurden die Eigenschaften des Grenzzyklus-Attraktors herangezogen. Diese Methode ermöglicht die Identifizierung von Veränderungen im Bewegungsmuster bei Personen sowohl auf der Gruppen- als auch auf der Individualebene, indem die Veränderungen in der Gangcharakteristik und in der Gangvariabilität erfasst werden.

In der zweiten Studie wurde das neu entwickelte Verfahren zur Quantifizierung von motorischer Fatigue bei Patienten mit Multipler Sklerose herangezogen. In diesem Zusammenhang wurde auch der Fatigue Index Kliniken Schmieder zur objektiven Erfassung von motorischer Fatigue entwickelt. Mit Hilfe des Fatigue Index Kliniken Schmieder konnten zum ersten Mal Veränderungen im Gangmuster auf Grund von akut auftretender motorischer Fatigue bei Patienten mit Multipler Sklerose erfasst werden. Zudem konnten verlässliche Grenzwerte, die eine klare Diagnose von motorischer Fatigue ermöglichten, bestimmt werden. Weiterhin konnte demonstriert werden, dass motorische Fatigue keinen Zusammenhang mit der muskulären Fatigue aufweist.

In der dritten Studie wurde der Fatigue Index Kliniken Schmieder zur Messung von motorischer Fatigue bei Patienten nach einem Schlaganfall erfolgreich eingesetzt. Dies ermöglichte erstmalig einen Vergleich der motorischen Fatigue anhand der empirischen Daten zwischen den Schlaganfall-Patienten und Patienten mit Multipler Sklerose. Die Schlaganfall-Patienten zeigten ein ähnliches

Ausmaß an motorischer Fatigue wie die Patienten mit Multipler Sklerose. Der Fatigue Index Kliniken Schmieder erwies sich als robust gegenüber bereits bestehenden chronischen Gangbeeinträchtigungen.

Abkürzungsverzeichnis

a	Right or left
ACA	Anterior cerebral artery
ANOVA	Analysis of variance
B	Begin
BDI-II	Beck-Depressions-Inventar II / Beck Depression-Inventory II
bpm	beats per minute
C	Beginning or end
cm	Centimeter
CNS	Central nervous system
δD	Maß für die Änderung in der Bewegungsvariabilität
E	End
EDSS	Expanded Disability Status Scale
δF	Index der Bewegungsänderung
FAI	Fatigue Assessment Instrument
FAS	Fatigue Assessment Scale
FIS	Fatigue Impact Scale
FKS	Fatigue Index Kliniken Schmieder / Fatigue index Kliniken Schmieder
FSMC	Fatigue Skala für Motorik und Kognition / Fatigue Scale for Motor and Cognitive Functions
FSS	Fatigue Severity Scale
h	Hour

H^+	Hydron
Hz	Hertz
ICC	Intraclass Correlation Coefficient
K^+	Potassium
kg	Kilogram
km	Kilometer
km/h	Kilometer per hour
L	Left
M	Walking with an additional mental task
m	Meter
δM	Maß für die Änderung in der Bewegungscharakteristik
MCA	Middle cerebral artery
MFIS	Modified Fatigue Impact Scale
MFSI	Multidimensional Fatigue Symptom Inventory
6MGT	6-Minuten-Gehtest
min	Minute
MMG	Mechanomyography
mmol/L	Millimoles per Liter
MS	Multiple Sklerose / Multiple Sclerosis
MS-F	Group: patients with multiple sclerosis and fatigue symptom
MS-NF	Group: patients with multiple sclerosis and without fatigue symptom
MVC	Maximal voluntary contraction
6MWT	6-minute walk test

N	Walking without any load
n	Number of subjects
Non-MS	Group: healthy persons
Nr.	Nummer
n.s.	Not statistically significant
p	Probability value
PF-10	Physical functioning 10 subscale
Pi	Inorganic phosphate
PP	Primary progressive
r	Correlation coefficient or right
R^2	Coefficient of determination
RR	Relapsing-remitting
SF-36	Short-Form 36
s	Second
sEMG	Surface electromyography
SP	Secondary progressive
stroke-F	Group: stroke patients with fatigue symptom
stroke-NF	Group: stroke patients without fatigue symptom
t	T-statistic
t_1	Recording of data at the beginning of the test
t_2	Recording of data at the end of the test
TMS	Transkranielle Magnetstimulation / Transcranial magnetic stimulation
TNF-α	Tumor necrosis factor alpha

χ^2-test	Chi-square test
v	Velocity
W	Walking with a two kilogram weight on each ankle
WEIMuS	Würzburg Fatigue Inventory in Multiple Sclerosis

1 Allgemeine Einleitung

In der Neurologie ist Fatigue eines der häufigsten Symptome (Kluger, Krupp, & Enoka, 2013). Fatigue beeinflusst die Lebensqualität der Patienten negativ und wird oft bei Patienten mit Multipler Sklerose (MS), nach einem Schlaganfall oder nach einem Schädelhirntrauma sowie bei Patienten mit Morbus Parkinson, Post-Polio-Syndrom, Myasthenia gravis und Amyotrophe Lateralsklerose berichtet (Braley, Chervin, & Segal, 2012; Chaudhuri & Behan, 2004; Kluger et al., 2013). Die vorliegende Arbeit beschäftigt sich mit Fatigue bei Patienten mit MS und nach einem Schlaganfall. Insbesondere bei MS gilt Fatigue als größte Beeinträchtigung im alltäglichen Leben und ist einer der Hauptgründe für Erwerbsunfähigkeit, was zu einer hohen wirtschaftlichen Belastung führt (Andersen, Christensen, Kirkevold, & Johnsen, 2012; Chaudhuri & Behan, 2004; Simmons, Tribe, & McDonald, 2010). Trotz weltweit intensiver Forschung auf diesem Gebiet gibt es derzeit noch viele ungeklärte Fragestellungen. Dazu gehören unter anderem das Fehlen einer allgemein anerkannten Definition, objektiver Diagnoseverfahren sowie des ausreichenden Wissens über die Pathophysiologie der Fatigue.

Trotz der fehlenden allgemein anerkannten Definition für Fatigue (Kluger et al., 2013) ist man sich in der Literatur einig, dass dieses Symptom ein multidimensionales Phänomen darstellt (Acciarresi, Bogousslavsky, & Paciaroni, 2014; Chaudhuri & Behan, 2004; Kos, Kerckhofs, Nagels, D'Hooghe M, & Ilsbroukx, 2008). Allerdings gibt es noch keinen Konsens über die verschiedenen Dimensionen der Fatigue (Kos et al., 2008). Es herrscht jedoch Einigkeit in Bezug auf die klare Trennung zwischen der kognitiven und der motorischen Dimension der Fatigue (Kluger et al., 2013; Penner et al., 2009).

Dabei besteht das entscheidende Problem darin, dass derzeit keine standardisierten Messinstrumente und -verfahren existieren, die Fatigue objektiv erfassen können (Kluger et al., 2013). Hierbei gestaltet sich gerade durch die verschiedenen Dimensionen der Fatigue die Messung dieses Symptoms als schwierig. Auch die Tatsache, dass die Pathophysiologie der Fatigue bis heute nicht vollständig geklärt ist (Acciarresi et al., 2014; Chaudhuri & Behan, 2004; Kluger et al., 2013; Kos et al., 2008), erschwert ihre objektive Beurteilung. Die-

se Vermutung wird bestätigt durch die große Anzahl von generischen und krankheitsspezifischen Fragebögen, die derzeit zur ein- oder mehrdimensionalen Messung von Fatigue zur Verfügung stehen (Acciarresi et al., 2014; Elbers et al., 2012; Penner et al., 2009). Insbesondere bei MS-Patienten sind solche Befragungsinstrumente zum Goldstandard für die Erfassung von Fatigue geworden (Penner et al., 2009). Der Hauptnachteil dieser Methode liegt in ihrer Subjektivität und der damit verbundenen Problematik bei der Bewertung der Ergebnisse.

Bisherige Versuche, das Fatigue-Symptom objektiv zu erfassen, brachten keine zufriedenstellenden Ergebnisse (Hu, Tong, & Hung, 2006; Iriarte & de Castro, 1998; Knorr, Ivanova, Doherty, Campbell, & Garland, 2011; Schwid et al., 1999; Sehle et al., 2011; Severijns, Lamers, Kerkhofs, & Feys, 2014; Surakka et al., 2004; Svantesson, Sunnerhagen, Carlsson, & Grimby, 1999). Der Beitrag vorheriger Untersuchungen besteht darin, dass die Aussagen hinsichtlich Fatigue auf der Gruppenebene getroffen werden konnten. Für Ärzte, Therapeuten sowie betroffene Patienten ist es jedoch notwendig, Aussagen über das Vorliegen von Fatigue individuell treffen zu können.

Das vorliegende Dissertationsvorhaben zielt auf die empirische Untersuchung der motorischen Fatigue und auf die Entwicklung eines geeigneten Verfahrens für eine möglichst objektive Diagnose dieses Symptoms sowohl auf der Individual- als auch auf der Gruppenebene ab. Im Rahmen dieser Arbeit wurde zunächst eine neue Methode zur Quantifizierung von Unterschieden im Gangmuster mit Hilfe des Grenzzyklus-Attraktors entwickelt. Diese Methode verfolgt das Ziel, motorische Fatigue bei Patienten mit MS und nach einem Schlaganfall objektiv zu erfassen. Zuerst wurde das neue Verfahren an gesunden Personen in verschiedenen dynamischen Situationen getestet. Danach wurde angenommen, dass den Gangmusterunterschieden die Änderungen neurologischer Natur zugeordnet werden können, z.B. bei Auftreten der motorischen Fatigue. Deshalb wurde diese Methode an den gewonnenen Daten von weiteren gesunden Personen, Patienten mit MS und nach einem Schlaganfall zur Quantifizierung von motorischer Fatigue eingesetzt und getestet. Hierfür wurde ein Index entwickelt, der als Fatigue Index Kliniken Schmieder (FKS) bezeichnet wird. Mit Hilfe des FKS sollten die Veränderungen im Gangmuster (in der Gangcharakteristik und in der Gangvariabilität) berechnet werden, die durch den Wechsel

vom körperlich erholten Zustand in den Zustand nach körperlicher Belastung beziehungsweise in den erschöpften Zustand entstehen. Der FKS soll die Erfassung der motorischen Fatigue für einzelne Patienten sowie für aggregierte Daten ermöglichen.

Die Erkenntnisse der vorgelegten Arbeit sollten eine schnelle, objektive und zuverlässige Beurteilung der Betroffenheit von Patienten durch motorische Fatigue erlauben. Eine auf diese Weise erreichte zuverlässige und frühzeitige Diagnose der motorischen Fatigue ist sowohl für die Patienten als auch für die behandelnden Ärzte von besonderer Relevanz. Die Betroffenen könnten somit eine rechtzeitige und bestmögliche Behandlung bekommen und ihre Alltagsgestaltung entsprechend dem Befund anpassen. Weiterhin könnten durch das neue Verfahren langjährige sozialmedizinische Untersuchungen, z.B. im Rahmen von Rentenverfahren, vermieden werden. Nicht zuletzt kann eine objektive Erfassung der motorischen Fatigue zu einem besseren Verständnis und zur Akzeptanz dieses Symptoms seitens der Angehörigen und der Gesellschaft führen.

1.1 Neuer Ansatz zur Quantifizierung von Gangmuster-Unterschieden mit Hilfe von Attraktoreigenschaften zur Erfassung der motorischen Fatigue

Wie bereits in der vorangehenden Einleitung beschrieben wurde, besteht das Ziel der vorliegenden Arbeit in der empirischen Untersuchung der motorischen Fatigue und in der Entwicklung eines Verfahrens für eine objektive Diagnose dieses Symptoms. Im klinischen Alltag kann häufig beobachtet werden, dass sich die Bewegungsmuster bei Patienten mit motorischer Fatigue nach körperlicher Belastung verändern. Dabei zeigen Patienten mit motorischer Fatigue anfangs fast unauffällige Gangmuster. Mit zunehmender körperlicher Beanspruchung werden die Veränderungen immer deutlicher. In unserer Pilot-Studie konnten solche Veränderungen im Gangmuster bei Patienten mit MS auf der Gruppenebene erfasst und analysiert werden (Sehle et al., 2011). Allerdings konnten keine Aussagen für einzelne Patienten getroffen werden. Bisher existierende Methoden, z.B. die konventionelle kinematische Bewegungsanalyse oder eine nicht-lineare Zeitreihenanalyse, ließen keine präzisen Aussagen über die Veränderungen im Bewegungsmuster der Probanden auf der individuellen

Ebene zu (Schablowski-Trautmann & Gerner, 2006; van Schooten, Rispens, Pijnappels, Daffertshofer, & van Dieën, 2013). Insbesondere für die klinische Forschung und im klinischen Alltag sind jedoch die auf die individuelle Patientensituation bezogenen Aussagen von großer Bedeutung, unabhängig davon, ob es um Diagnose, Auswahl der Behandlung oder Evaluation des Krankheitsverlaufes geht.

Deshalb wurde im Rahmen dieser Arbeit eine neue Methode zur Quantifizierung von Veränderungen im Gangmuster mit einem zugrunde liegenden Grenzzyklus-Attraktor entwickelt. Sie zielt darauf ab, die Gangmusterveränderungen auf Individual- sowie Gruppenebene zu identifizieren und zu klassifizieren. Bei dieser Methode werden die Bewegungsdaten – Beschleunigung der Füße – in verschiedenen Situationen aufgenommen. Danach erfolgt die Approximation des Grenzzyklus-Attraktors für jede Untersuchungseinheit. Nachfolgend werden die Differenz zwischen zweie Attraktoren (ein Maß für die Abweichung von zwei Bewegungen beziehungsweise die Änderung in der Bewegungscharakteristik, δM) und die Bewegungsvariation um die zugehörigen Attraktoren (ein Maß für die Änderungen in der Bewegungsvariation beziehungsweise die Änderung in der Bewegungsvariabilität, δD) berechnet. Anschließend wurde δF aus den Parametern δM und δD berechnet. δF ist ein repräsentativer Index der Bewegungsänderung.

Das neu entwickelte Verfahren wurde zunächst an gesunden Probanden beim Gehen auf dem Laufband in drei unterschiedlichen Situationen und an jeweils zwei verschiedenen Tagen getestet. Die drei unterschiedlichen Situationen beinhalteten: 1. das Gehen auf dem Laufband mit einer für die Probanden angenehmen Geschwindigkeit ohne Zusatzaufgaben; 2. das Gehen auf dem Laufband mit einer zusätzlichen kognitiven Aufgabe; 3. das Gehen auf dem Laufband mit zusätzlichen Gewichten an den Füßen. Die Gehgeschwindigkeit blieb unabhängig von den unterschiedlichen Aufgaben und an den verschiedenen Tagen konstant. Die Grundannahme bestand darin, dass sich die Bewegungsmuster zwischen diesen drei unterschiedlichen Gangsituationen verändern werden. Des Weiteren wurde angenommen, dass die erhobenen Daten reproduzierbar sind.

In einem weiteren Schritt wurde die im Rahmen dieser Arbeit entwickelte Methode an Patienten mit MS und an Schlaganfall-Patienten sowie an einer Kontrollgruppe in einem Erschöpfungsexperiment getestet. Es wurde angenommen, dass beim Einsetzen der motorischen Fatigue während des Gehens auf dem Laufband Veränderungen im Bewegungsmuster entstehen und diese mit Hilfe des neuen Verfahrens erfasst werden können. Der Einfluss anderer Ursachen wurde durch einen über die Untersuchungszeit unveränderten und standardisierten Testablauf sowie durch die Messung der Laktatkonzentration im Blut und der Herzfrequenz kontrolliert und ausgeschlossen. Die Veränderungen in der Gangcharakteristik und in der Gangvariabilität wurden im FKS zusammengefasst. Weiterhin wurde angenommen, dass für den FKS empirische Grenzwerte kalibriert werden können, die eine klare Klassifizierung in Gruppen mit und ohne motorische Fatigue erlauben. Das neue Verfahren sollte die erstmalige Quantifizierung der motorischen Fatigue auf der Individual- und auf der Gruppenebene ermöglichen (Dippel, Mäurer, Schinzel, Müller-Bohn, & Larisch, 2015).

1.2 Multiple Sklerose und motorische Fatigue

Es existieren zahlreiche Erkrankungen, die bisher nicht heilbar sind und zu einer deutlichen und unter Umständen progredienten Behinderung der Patienten führen. Ein Beispiel hierfür ist die Multiple Sklerose. MS ist eine Autoimmunerkrankung des zentralen Nervensystems, welche die Zerstörung des Myelins und axonale Schäden im Gehirn und Rückenmark verursacht (Braley et al., 2012). MS stellt die häufigste nicht-traumatische neurologische Erkrankung bei jungen Erwachsenen dar (Braley et al., 2012). Dabei erkranken Frauen nahezu doppelt so häufig an MS wie Männer (Maida, 2005). Schätzungen zufolge wurde die Prävalenz der MS in Deutschland bisher mit etwa 120 000 bis 140 000 angegeben (Flachenecker et al., 2008). Entsprechend neuesten Datenbanken der Kostenträger wird die Prävalenz mit etwa 200 000 fast doppelt so hoch eingeschätzt.

Bei MS existieren drei verschiedene Verlaufsformen: schubförmiger Verlauf, primär chronisch-progredienter Verlauf und sekundär chronisch-progredienter Verlauf (Maida, 2005). Bei rund 70% der Fälle verläuft die MS zu Beginn der Erkrankung schubförmig, gekennzeichnet durch klar definierte Episoden mit

neurologischen Funktionsstörungen, die als Schübe bezeichnet werden (Maida, 2005). Bei solchen Funktionsstörungen treten Seh-, Empfindungs-, Gleichgewichts-, Bewegungs- und Koordinationsstörungen sowie vegetative Symptome auf (Maida, 2005). Nach den Schüben kommt es zur Besserung von neurologischen Beschwerden, der Remission (Braley & Chervin, 2010; Maida, 2005), wobei sich die Ausfälle anfangs noch vollständig zurückbilden können (Maida, 2005). Mit der ansteigenden Anzahl der Schübe wird die Rückbildung der Ausfälle unvollständiger, was im Laufe der Erkrankung zu einer zunehmenden Behinderung führt (Maida, 2005). In der Mehrzahl der unbehandelten Fälle geht die schubförmige Verlaufsform der Erkrankung in einen sekundär chronisch-progredienten Verlauf über (Braley & Chervin, 2010). Bei dieser Verlaufsform erfahren die Patienten eine allmähliche, schleichende Verschlechterung, häufig in Form von Paraparese, Halbseitenlähmung, Ataxie, Blasenstörungen oder kognitiven Störungen (Braley & Chervin, 2010). Ein primär chronisch-progredienter Verlauf tritt bereits ab Beginn der Erkrankung bei einem relativ kleineren Prozentsatz der Patienten auf (etwa 10% bis 15%), gekennzeichnet durch eine langsame Verschlechterung der neurologischen Funktionen ohne deutliche Schübe (Braley & Chervin, 2010).

Die MS ist mit einer Vielzahl von neurologischen Symptomen assoziiert. Dazu zählen unter anderem Symptome wie Paresen, Ataxie, Spastik, Empfindungsstörungen, Blasenstörungen, Sprechveränderungen und kognitive sowie akute psychische Störungen (Maida, 2005). Vor allem jedoch gehört eine stark ausgeprägte körperliche sowie kognitive Erschöpfung, die in der Medizin als Fatigue bezeichnet wird, zu den bei MS-Betroffenen am häufigsten auftretenden Symptomen (Guidelines, 1998).

Zwischen 38% und 83% der MS-Betroffenen leiden unter Fatigue, und bei etwa 50% bis 60% dieser Patienten steht Fatigue im Vordergrund der Beschwerden (Comi, Leocani, Rossi, & Colombo, 2001; Fisk, Pontefract, Ritvo, Archibald, & Murray, 1994; Freal, Kraft, & Coryell, 1984; Kluger et al., 2013). Es gibt zahlreiche Definitionen für Fatigue. Eine davon stammt vom Multiple Sclerosis Council for Clinical Practice Guidelines und findet breite Anwendung. Das Fatigue-Symptom wird demnach als “a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities” definiert (Guidelines, 1998). Diese Definition verdeutlicht, dass

Fatigue als eine subjektive Wahrnehmung betrachtet wird, unabhängig davon, ob es sich um einen physischen oder einen mentalen Prozess handelt.

Wie bereits oben in der Einleitung zu diesem Kapitel erwähnt, werden im klinischen Alltag und in der klinischen Forschung häufig subjektive Messinstrumente in Form von Fragebögen für die Erfassung von Fatigue eingesetzt. Der Einsatz von Fragebögen ermöglicht den Ärzten und Forschern die Erstellung von Datenbanken über Prozesse, die nicht direkt beobachtbar sind (Penner et al., 2009). Zudem sind solche Methoden schnell und kostengünstig. Allerdings sind die Ergebnisse der Befragungen rein subjektiv, und ihr Hauptnachteil liegt in der vollständigen Abhängigkeit von der Versuchsperson (Penner et al., 2009). Gerade die Subjektivität stellt ein großes Problem sowohl für die Diagnostik als auch für die Evaluation des Krankheitsverlaufs dar. Dabei spielen Einwilligung (Compliance), Selbstbeobachtung, Selbstbewusstsein, Aufmerksamkeit und die Bereitschaft, die Fragen offen zu beantworten, eine große Rolle (Penner et al., 2009). Auf Grund der Subjektivität können die Ergebnisse der Fragebögen in manchen Fällen erschwert oder gar nicht interpretiert werden. Deshalb sind solche Befragungsdaten, z.B. bei sozialmedizinischen Fragestellungen im Rahmen von Rentenverfahren, nur eingeschränkt brauchbar. Eine zuverlässige Entscheidung, ob ein Patient von Fatigue betroffen ist oder nicht, sollte auf der Basis eines objektiven Messinstruments getroffen werden.

Der objektiven Erfassung von Fatigue wurden zahlreiche Arbeiten gewidmet. Manche Untersuchungen konzentrierten sich vorrangig auf die kognitive Dimension (Claros-Salinas et al., 2010; Morrow, Rosehart, & Johnson, 2015), während andere Studien die motorische Dimension der Fatigue in den Fokus rückten (Schwid et al., 1999; Severijns et al., 2014; Surakka et al., 2004). Das Hauptaugenmerk der vorliegenden Arbeit liegt auf der motorischen Dimension der Fatigue. Dementsprechend wurde das Gehen auf dem Laufband als Belastungstest gewählt. In diesem Test gingen alle Teilnehmer mit einer für sie komfortablen Geschwindigkeit plus 10% auf dem Laufband entweder bis zur subjektiven körperlichen Erschöpfung (Wert 17 auf der Borg-Skala (Borg, 1982)) oder maximal 60 Minuten. Dabei wurden die kinematischen Daten und Videoaufnahmen von Patientenbewegungsabläufen jeweils am Anfang und am Ende des Belastungstests aufgezeichnet. Zudem wurden die Laktatkonzentration im Blut, die Herzfrequenz und der Anstrengungsgrad auf der Borg-Skala erfasst.

Es wurde vermutet, dass alle Probanden während des Erschöpfungsexperiments im aeroben Bereich bleiben und somit die muskuläre Fatigue als Ursache für motorische Fatigue ausgeschlossen werden kann. Die zurückgelegte Gehstrecke und die Gehgeschwindigkeit während des Belastungsexperiments wurden ebenso protokolliert. Das eingesetzte Testdesign hat den entscheidenden Vorteil, dass die großen Muskelgruppen und viele Freiheitsgrade in die Bewegung integriert sind. Außerdem stellt das Gehen eine alltagsrelevante Bewegung dar, die gerade bei Patienten mit motorischer Fatigue wesentlich beeinträchtigt sein kann.

Im Gegensatz dazu untersuchten bisherige Studien die motorische Fatigue in dynamischen und statischen Kontraktionstests der unteren oder oberen Extremitäten mit Hilfe eines Dynamometers (Greim, Benecke, & Zettl, 2007; Iriarte & de Castro, 1998; Schwid et al., 1999; Severijns et al., 2014; Surakka et al., 2004). Somit wurde die motorische Fatigue oft in isolierten Bewegungen gemessen, was den Alltag der Patienten nicht korrekt widerspiegeln konnte. Weiterhin konnten frühere Untersuchungen keine klare Einteilung der MS-Patienten in Gruppen mit und ohne motorische Fatigue vornehmen (Greim et al., 2007; Iriarte & de Castro, 1998; Schwid et al., 1999; Severijns et al., 2014; Surakka et al., 2004). Mit Hilfe des hier entwickelten FKS sollte eine objektive und präzise Einteilung der MS-Patienten erreicht werden.

In den vorherigen Studien wurden die Daten von MS-Betroffenen ausschließlich auf der Gruppenebene analysiert und interpretiert (Greim et al., 2007; Iriarte & de Castro, 1998; Schwid et al., 1999; Severijns et al., 2014; Surakka et al., 2004). Für Ärzte, Therapeuten und Patienten sind Aussagen auf der individuellen Ebene jedoch von größerer Bedeutung. Auch dieses Ziel sollte durch den Einsatz des FKS erreicht werden.

Außerdem wurden die persönlichen Daten aller Teilnehmer sowie der Krankheitsverlauf und die Expanded Disability Status Scale (EDSS) (Kurtzke, 1983) der MS-Patienten protokolliert. An einem anderen Tag absolvierten alle Untersuchungsteilnehmer einen 6-Minuten-Gehtest (6MGT) (Laboratories, 2002). Dieser Test wird oft in der klinischen Praxis eingesetzt und liefert Informationen über die körperliche Beeinträchtigung der Probanden (Paul & Enright, 2003). Es wurde bei allen Teilnehmern anhand des Beck-Depressions-Inventars II (BDI-

II) das Ausmaß der subklinischen Depression erfasst (Hautzinger, Keller, & Kühner, 2008; Kühner, Bürger, Keller, & Hautzinger, 2007). Zudem wurden alle MS-Patienten gebeten, die Fatigue Skala für Motorik und Kognition (FSMC) auszufüllen (Penner et al., 2009). Mit Hilfe der FSMC können die subjektive motorische, kognitive und gesamte Dimension der Fatigue erfasst werden (Penner et al., 2009).

Alle zusätzlich zum FKS erfassten Parameter sollten wichtige Informationen über die Teilnehmer und ihren momentanen körperlichen sowie psychischen Zustand liefern. Die erhobenen Messgrößen erlauben einen Zwischengruppenvergleich und eine Analyse des Zusammenhangs zwischen dem FKS und den Ergebnissen der FSMC sowie der EDSS.

1.3 Schlaganfall und motorische Fatigue

Der Schlaganfall ist ein Krankheitsbild, bei dem klinische Zeichen einer fokalen oder globalen Störung zerebraler Funktionen plötzlich auftreten, mindestens 24 Stunden anhalten oder zum Tode führen und offensichtlich nicht auf andere als vaskuläre Ursachen zurückzuführen sind (WHO, 1989). In dieser Definition sind die meisten Fälle von ischämischen Schlaganfällen, nicht traumatischen Hirnblutungen und Subarachnoidalblutungen eingeschlossen und gleichzeitig die transienten ischämischen Attacken sowie subdurale Blutungen ausgeschlossen (Mäurer & Diener, 1996). Etwa 80% bis 83% der Schlaganfälle sind Ischämien, 10% bis 12% sind intrazerebrale Blutungen, und 7% bis 8% sind Subarachnoidalblutungen (Mattle & Mumenthaler, 2012). Dabei sind Männer öfter davon betroffen als Frauen (Mattle & Mumenthaler, 2012).

Den epidemiologischen Daten zufolge ereignen sich in Deutschland jährlich circa 196 000 erstmalige und 66 000 wiederholte Schlaganfälle (Heuschmann et al., 2010). Mit circa 63 000 Todesfällen pro Jahr ist der Schlaganfall die dritthäufigste Todesursache in Deutschland (Heuschmann et al., 2010). In den meisten Industrienationen ist der Schlaganfall eine der Hauptursachen für Langzeitbehinderungen und Pflegebedürftigkeit; die Prognosen gehen von einer konstanten Entwicklung aus (Mehrholz, 2011). In Abhängigkeit von der Lokalisation der vaskulären Schäden sind Funktionen, Aktivitäten und die Teilnahme am gesellschaftlichen Leben eingeschränkt beziehungsweise zwischenzeitlich oder dauerhaft beeinträchtigt (Mehrholz, 2011; WHO, 1989). Die Überlebenden

haben in vielen Fällen mit bleibenden körperlichen, psychischen und sozialen Folgen der Erkrankung zu kämpfen (Mäurer & Diener, 1996). Eine davon ist das Fatigue-Symptom.

Fatigue ist bei Schlaganfall-Patienten ein häufiges Symptom, das jedoch erst im letzten Jahrzehnt zunehmende Beachtung erfahren hat (Staub & Bogousslavsky, 2001a; van der Werf, van den Broek, Anten, & Bleijenberg, 2001). Aktuell wird von einer Prävalenz zwischen 36% und 77% ausgegangen (Kluger et al., 2013). Trotzdem ist nur wenig über die Entstehung von Fatigue nach einem Schlaganfall, ihre Entwicklung über die Zeit sowie ihren Zusammenhang mit anderen klinischen Faktoren bekannt (Lerdal, Lee, Bakken, Finset, & Kim, 2012). Lerdal et al. (2012) konnten den Zusammenhang zwischen dem Verlauf von Fatigue nach einem Schlaganfall und den bereits bestehenden Vorerfahrungen mit der Fatigue sowie körperlicher Leistungsfähigkeit in der Akutphase nachweisen (Lerdal et al., 2012).

Im Gegensatz zur MS-Forschung ist die Erforschung der Fatigue bei Schlaganfallpatienten ein relativ junger Forschungszweig (Staub & Bogousslavsky, 2001b). Allerdings konnte man in den letzten Jahren wachsendes Interesse an diesem Forschungsgebiet beobachten (Lerdal et al., 2009; Naess, Lunde, & Brogger, 2012). Fatigue bei Schlaganfallpatienten kann als “a feeling of lack of energy, weariness, and aversion to effort” definiert werden (Mead et al., 2007). Analog zur Fatigue bei MS-Patienten basiert auch diese Definition vorrangig auf subjektiven Empfindungen. Deshalb werden auch hier verschiedene Fragebögen zur Messung von Fatigue eingesetzt, was die objektive Erfassung erschwert. Eine objektive Messung von Fatigue wäre bei Patienten nach einem Schlaganfall daher ebenso von großer Bedeutung wie bei Patienten mit MS.

Aus diesem Grund wird in der vorliegenden Arbeit auch die objektive Messung und Untersuchung von motorischer Fatigue bei Patienten nach einem Schlaganfall angestrebt. Dafür wurde mit allen Schlaganfall-Patienten ein identischer Belastungstest mit denselben Messinstrumenten wie bei den MS-Patienten durchgeführt. Somit konnte zunächst überprüft werden, ob der FKS für eine objektive und präzise Erfassung von motorischer Fatigue auch bei Patienten nach einem Schlaganfall eingesetzt werden kann. Darüber hinaus konnte das Ausmaß von motorischer Fatigue zwischen den beiden Patientengruppen (MS und

Schlaganfall) verglichen werden. Für Forscher, Ärzte und Therapeuten wäre es von großem Interesse zu wissen, ob Patienten mit MS und nach einem Schlaganfall im gleichen Ausmaß von motorischer Fatigue betroffen sind. Diese Information kann bei der Entscheidung über den Behandlungsansatz sehr hilfreich sein.

In vorangegangenen Studien wurde die motorische Fatigue mit Hilfe der Transkraniellen Magnetstimulation (TMS), des Dynamometers sowie der Elektromyografie an den unteren und oberen Extremitäten untersucht (Hu et al., 2006; Knorr et al., 2011; Svantesson et al., 1999). Bisherige Untersuchungen weisen dieselben Probleme auf wie bei der MS-Forschung. Auch bei diesen Patienten erfolgte die Erfassung der motorischen Fatigue oft in isolierten Bewegungen. Es Schlaganfall in Gruppen mit und ohne motorische Fatigue vornehmen konnte, und dazu wurden alle erhobenen Daten ausschließlich auf der Gruppenebene analysiert. Diese Probleme sollten mit dem gewählten Belastungstest auf dem Laufband und dem Einsatz des FKS gelöst werden.

Weiterhin sollte überprüft werden, ob chronische Gangbeeinträchtigungen (in Form von Paresen) bei Patienten nach einem Schlaganfall den FKS beeinflussen können. Somit sollte die Unabhängigkeit des neuen Index von bereits bestehenden chronischen Gangbeeinträchtigungen bestätigt werden. Dies ist insbesondere deswegen wichtig, da viele Schlaganfallpatienten diverse Störungen des Gangbildes aufweisen, was die Erfassung von motorischer Fatigue mit traditionellen Messinstrumenten wesentlich erschwert.

Zusätzlich wurde bei allen Patienten die Wahrnehmung des allgemeinen Gesundheitszustandes (PF-10) und der Vitalität (Fatigue) mit Hilfe von Short-Form 36 (SF-36) erfasst und mit den Daten von MS-Patienten verglichen (Bullinger et al., 2003; Mead et al., 2011). Dadurch sollte kontrolliert werden, wie die verschiedenen Gruppen ihren allgemeinen Gesundheitszustand und die Fatigue einschätzen beziehungsweise ob MS- und Schlaganfall-Patienten ähnlich stark beeinträchtigt sind.

1.4 Fragestellungen und Hypothesen

Das Hauptziel der vorliegenden Arbeit ist die Entwicklung eines neuen Verfahrens, das eine objektive Erfassung der motorischen Fatigue bei Patienten mit

MS und nach einem Schlaganfall ermöglicht. Dafür wurden insgesamt drei empirische Studien durchgeführt.

In der ersten Studie wurde eine neuartige Methode zur Berechnung und Interpretation von Veränderungen im Gangmuster mit Hilfe von Attraktoreigenschaften entwickelt und anhand der erhobenen Daten überprüft. Es wurde angenommen, dass sich das Gangmuster in verschiedenen dynamischen Situationen verändert. Diese Veränderungen sind mittels der neu entwickelten Methode quantifizierbar. Das neue Verfahren soll die Erfassung von Veränderungen sowohl in der Gangcharakteristik als auch in der Gangvariabilität in zwei verschiedenen Situationen ermöglichen. Der Index, der anhand dieser Messgröße gebildet wird, soll zur Quantifizierung von Veränderungen im Gangmuster auf Gruppen- und auf Individualebene einsetzbar sein. Zudem wurde für die neue Methode eine hohe Reliabilität angestrebt.

Im Testdesign der ersten Studie wurden alle gesunden Probanden drei unterschiedlichen Gang-Situationen an jeweils zwei verschiedenen Tagen ausgesetzt: 1. Gehen auf dem Laufband ohne Zusatzaufgaben, 2. Gehen auf dem Laufband mit zusätzlichen kognitiven Aufgaben (dual task), 3. Gehen auf dem Laufband mit zusätzlichen Gewichten an den Füßen. Tabelle 1 fasst die zentralen Fragestellungen und Hypothesen für diese Studie zusammen.

Tabelle 1 Zentrale Fragestellungen und Hypothesen der Studie Nr. 1.

Fragestellungen	Hypothesen
F1: Kann das neue Verfahren die Veränderungen des Gangmusters von gesunden Personen beim Gehen auf dem Laufband in verschiedenen dynamischen Situationen erfassen?	**H1:** Die Veränderungen im Gangmuster auf Grund von veränderten Situationen können mit Hilfe des neuen Verfahrens erfasst werden.
F2: Erlaubt die neue Methode Datenanalysen sowohl auf der Individual- als auch auf der Gruppenebene?	**H2:** Die neu entwickelte Methode erlaubt Datenanalysen sowohl auf der Individual- als auch auf der Gruppenebene.
F3: Ist das neue Verfahren reliabel?	**H3:** Das neue Verfahren ist reliabel.

In der zweiten Studie wurde das neue Messverfahren in einem Erschöpfungsexperiment auf dem Laufband an MS-Patienten sowie gesunden Probanden getestet. In Rahmen dieser Untersuchung gingen alle Teilnehmer auf dem Laufband bei einer für sie angenehmen Gehgeschwindigkeit plus 10% entweder bis zur subjektiven körperlichen Erschöpfung oder maximal 60 Minuten. Das Ziel dieser Studie war es, motorische Fatigue bei MS-Patienten objektiv zu erfassen. Ein Zustand, der sich über eine bestimmte Zeit nicht verändert, wird als stabile Situation bezeichnet und ist durch unveränderte Gangcharakteristik und -variabilität gekennzeichnet. In dieser Studie wurde angenommen, dass die gesunden Probanden und MS-Patienten ohne motorische Fatigue ein solches stabiles System darstellen sollten, d. h. keine Veränderungen im Gangmuster während des Erschöpfungsexperimentes aufweisen werden. Bei MS-Patienten mit motorischer Fatigue sollte es dagegen während des Belastungstest zu Veränderungen im Gangmuster kommen, welche mit Hilfe des FKS objektiv erfasst werden können. Der FKS wurde anschließend hinsichtlich seiner Spezifität und Sensitivität überprüft. Darüber hinaus wurde untersucht, ob motorische Fatigue einen Zusammenhang mit muskulärer Fatigue aufweist. Hierfür wurden die Laktatkonzentration im Blut und die Herzfrequenz am Anfang sowie am Ende des Erschöpfungsexperimentes bei allen Studienteilnehmern kontrolliert. Tabelle 2 fasst die zentralen Fragestellungen und Hypothesen dieser Studie zusammen.

Tabelle 2 Zentrale Fragestellungen und Hypothesen der Studie Nr. 2.

Fragestellungen	Hypothesen
F4: Wie hoch ist die Spezifität und Sensitivität des FKS?	**H4:** Der FKS weist eine hohe Spezifität und Sensitivität auf.
F5: Gibt es einen Zusammenhang zwischen der motorischen und muskulären Fatigue?	**H5:** Motorische Fatigue steht in keinem Zusammenhang mit der muskulären Fatigue.

Basierend auf den Erkenntnissen der vorherigen Studien, die unter anderem gezeigt haben, dass eine Quantifizierung der motorischen Fatigue mit Hilfe des FKS möglich ist, wurde in der dritten Studie ermittelt, ob der FKS auch bei Pati-

enten nach einem Schlaganfall erfolgreich angewendet werden kann. Weiterhin sollte überprüft werden, ob sich das Ausmaß der motorischen Fatigue bei Patienten nach einem Schlaganfall und MS-Patienten unterscheidet. Dafür wurde mit Schlaganfall-Patienten dasselbe Erschöpfungsexperiment auf dem Laufband durchgeführt wie bei den MS-Patienten. Letztlich war zu überprüfen, ob der FKS durch die bereits bestehenden chronischen Gangbeeinträchtigungen beeinflusst werden kann. Tabelle 3 stellt die zentralen Fragestellungen und Hypothesen der dritten Studie dar.

Tabelle 3 Zentrale Fragestellungen und Hypothesen der Studie Nr. 3.

Fragestellungen	Hypothesen
F6: Ist der FKS bei Patienten nach Schlaganfall für die objektive Messung von motorischer Fatigue anwendbar?	**H6:** Der FKS eignet sich für die objektive Messung von motorischer Fatigue bei Patienten nach einem Schlaganfall.
F7: Unterscheidet sich das Ausmaß der motorischen Fatigue zwischen den beiden Patientengruppen?	**H7:** Das Ausmaß der motorischen Fatigue unterscheidet sich nicht zwischen den beiden Patientengruppen.
F8: Lässt sich das Erschöpfungsexperiment bei Patienten nach einem Schlaganfall gut durchführen?	**H8:** Das Erschöpfungsexperiment ist bei Patienten nach einem Schlaganfall gut durchführbar.
F9: Beeinflussen chronische Gangbeeinträchtigungen den FKS negativ?	**H9:** Die bereits bestehenden chronischen Gangbeeinträchtigungen haben keinen Einfluss auf die Validität des FKS.

2 STUDIE 1: A novel approach to quantify time series differences of gait data using attractor attributes

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2.1 Abstract

In this paper we introduce a new method to expressly use live/corporeal data in quantifying differences of time series data with an underlying limit cycle attractor; and apply it using an example of gait data. Our intention is to identify gait pattern differences between diverse situations and classify them on group and individual subject levels. First we approximated the limit cycle attractors, from which three measures were calculated: *δM* amounts to the difference between two attractors (a measure for the differences of two movements), *δD* computes the difference between the two associated deviations of the state vector away from the attractor (a measure for the change in movement variation), and *δF*, a combination of the previous two, is an index of the change. As an application we quantified these measures for walking on a treadmill under three different conditions: normal walking, dual task walking, and walking with additional weights at the ankle. The new method was able to successfully differentiate between the three walking conditions. Day to day repeatability, studied with repeated trials approximately one week apart, indicated excellent reliability for *δM* (ICC_{ave}>0.73 with no differences across days; p>0.05) and good reliability for *δD* (ICC_{ave}=0.414 to 0.610 with no differences across days; p>0.05). Based on the ability to detect differences in varying gait conditions and the good repeatability of the measures across days, the new method is recommended as an alternative to expensive and time consuming techniques of gait classification assessment. In particular, the new method is an easy to use diagnostic tool to quantify clinical changes in neurological patients.

2.2 Introduction

Typically, conventional kinematic analysis of human gait derives a characteristic pattern for an individual from a few single stride cycles (Harris & Smith, 1996; Schablowski-Trautmann & Gerner, 2006). These approaches are very common in clinical trials and in clinical practice; however, a major disadvantage of this method is the neglect of essential information that may be included in the dynamical sequences of multiple strides during continuous locomotion (Schablowski-Trautmann & Gerner, 2006). Hence, some researchers have used other methods to analyze gait data, e.g. methods of non-linear time series (Kantz & Schreiber, 2004). Especially common is an approach using a non-linear time series analysis where Taken's (Takens, 1981) embedding theorem enables the reconstruction of the phase state and the calculation and analysis of the maximal Lyapunov exponent (Kantz, 1994; Rosenstein, Collins, & De Luca, 1993) is performed. The estimation of local dynamic stability can then be estimated though the largest Lyapunov exponent (Bruijn, Meijer, Beek, & van Dieën, 2010; Buzzi, Stergiou, Kurz, Hageman, & Heidel, 2003; Dingwell & Cusumano, 2000; Dingwell, Cusumano, Cavanagh, & Sternad, 2001; Dingwell, Cusumano, Sternad, & Cavanagh, 2000; Dingwell & Marin, 2006). Perc (Perc, 2005) has built on these techniques in his study of human gait.

Non-linear time series approaches seem to have an advantage over conventional ones. However, while results are significant at the group level; a rating for an individual does not seem possible. van Schooten et al. (van Schooten et al., 2013) confirmed that depending on the state space reconstruction, local dynamic stability can be detected reliably enough to assess differences on the group level. However, on the individual level, they concluded that local dynamic stability only measures substantial changes, "which might not be realistic". Looking at the theory behind this type of analysis, it seems understandable where problems might arise. The Lyapunov exponent as a measure for stable or unstable attractors was developed to examine deterministic chaos, i.e. describing (mathematical) systems without random elements involved. Time series, and gait data specifically, do contain random elements, which make the calculation of the Lyapunov exponent a tricky endeavor. A straight forward calculation of the Lyapunov exponent (Williams, 1997) as in the case of classical deterministic chaos

is not possible; instead, estimation procedures must be applied. Two popular algorithms are those of Wolf et al. (Wolf, Swift, Swinney, & Vastano, 1985) and Rosenstein et al. (Rosenstein et al., 1993). However, these algorithms also have shortcomings (Bruijn, Bregman, Meijer, Beek, & van Dieën, 2012; Cignetti, Decker, & Stergiou, 2012), which lead to the discussed problems of stability estimates for individuals. Floquet theory (Klausmeier, 2008) is advocated for "… the study of the stability of linear periodic systems in continuous time." In this case as well, theory works best when applying it to classical deterministic systems.

Our original task was to find a diagnostic tool that allows quantification of changing conditions in neurological patients, namely quantifying fatigue in the Multiple Sclerosis (MS) patient. The rationale is that movement patterns of gait show changes, when fatigue sets in. Ensuring that fatigue is the only possible reason for a pattern change in combination with a change in local variability would make it possible for the first time to quantify fatigue. The problem is that walking quality/stability of MS patients is very diverse. Consequently, the stability of the gait does not tell anything about fatigue, but its change would. Unfortunately, to the best of our knowledge, there is no method available allowing quantification of the changes in the movement pattern that are precise enough to rate the severity of fatigue on an individual level. Our new approach seeks to fill this gap and present a way to measure and document changes within the responses of an individual subject, as well as between subjects.

A dynamic system can be described by its state vector (Liu, 2001), and its undisturbed movement characterized by its attractor. Attractors represent equilibrium regions in the geometric space that are formed by the relevant variables describing the undisturbed movement dynamics (Newell, Van Emmerik, Lee, & Sprague, 1993). Attractors can differ greatly in complexity. They can be as simple as a fixed point attractor, manifest as a limit cycle attractor, quasi-periodic, or be a chaotic attractor (Newell et al., 1993). An example of a fixed point attractor in 3D coordinate space is the lowest point of a half-sphere shaped bowl at which a rolling marble will eventually stop moving. More complicated systems, such as humans walking, do not settle towards a point, but rather towards a track, which can be multi-dimensional and e.g. in the case of treadmill walking, is a closed loop, or limit cycle (Perc, 2005). The problem with real world sys-

tems is their complexity. Building a model from first principles could mean the state space dimension could be very large (Alligood, Sauer, & Yorke, 1997). In such a case, writing the full state vector seems impossible. We were looking for an approach, which would be sensitive enough to judge the differences of movement on an individual level. This requires a practical approach for such a task; one which need not include the complete state vector and therefore, is not overly demanding in terms of measurement and analysis. A part of the state vector and the respective attractor should characterize the walking movement sufficiently without being too complex, yet without the lack of essential information. Any vector coordinate of a point on the human body can serve as part of the state vector, which can be compared to the respective parts of its attractor. Points at each ankle can establish a good option, since from the supporting leg to the swinging leg we have a long kinematic chain with a high degree of freedom. Hence the possible movement variability is very large and can be used to express substantial parts of the walking characteristics. For a further description of our method and its use, it will not be necessary to decipher the actual walking characteristics; it is sufficient to simply calculate the attractor in different situations and quantify its change.

In this work, we describe a novel method for calculating and interpreting attractor variations and the differences between the attractor and state vector when comparing two time series, with underlying limit cycle attractors. As an example we analyzed data from a treadmill study examining the influence a dual task (mental assignment) or an additional physical load has in causing changes in normal walking. It was hypothesized that the changes in gait pattern due to the dual task and/or the additional load can be captured using the changes in the attractor and the change of the attractor/state vector’s standard deviations, which are each calculated from the distance between the attractor and the state vector. While the purpose of the current study was not to directly examine gait, the index formed from these two variables can be used to detect the changes in gait pattern both at the individual level and at the group level. Finally, we tested the reliability of our new method.

2.3 Methods

A time series is a sequence of data points, which can contain almost any kind of time sequenced data. When dealing with gait, coordinate positions, velocity, and acceleration data constitute meaningful choices. An effective description of the attractor can be given e.g. in coordinate, velocity or acceleration space (Alligood et al., 1997; Sekine et al., 2000), which are connected via $\frac{d^2\vec{x}(t)}{dt^2} = \frac{d\vec{v}(t)}{dt} = \vec{a}(t)$. For reasons that will become clear later, we have used the acceleration space.

The following method is valid for movements with an underlying limit cycle attractor. The time series data are treated according to the following simple model of the actual movement parameter: after transient oscillations have stabilized, the acceleration $\vec{a}(t)$ is governed by the attractor value $\vec{A}(\tau)$ plus a fluctuating contribution $\vec{b}(t)$ that varies around the attractor; this value "b(t)" is normally distributed with a zero mean.

$$\vec{a}(t = i \cdot \tau) = \vec{A}(\tau) + \vec{b}(t = i \cdot \tau) \quad \text{i refers to the cycle} \tag{1}$$

We measured two such parameters, the 3D acceleration ($\vec{a}_r(t), \vec{a}_l(t)$) of the right and left ankles to allow detection of asymmetries in gait. The attractors' $\vec{A}_r(\tau), \vec{A}_l(\tau)$ are approximated as the acceleration at time τ (ordering parameter of a complete cycle) averaged over all loops. $\vec{D}_r(\tau), \vec{D}_l(\tau)$ are the standard deviations describing the irregularities from the actual acceleration attractor. The start and the end of a loop are defined as the passing of $\vec{a}_r(t), \vec{a}_l(t)$ through a well-defined area A, as shown in Figure 1.

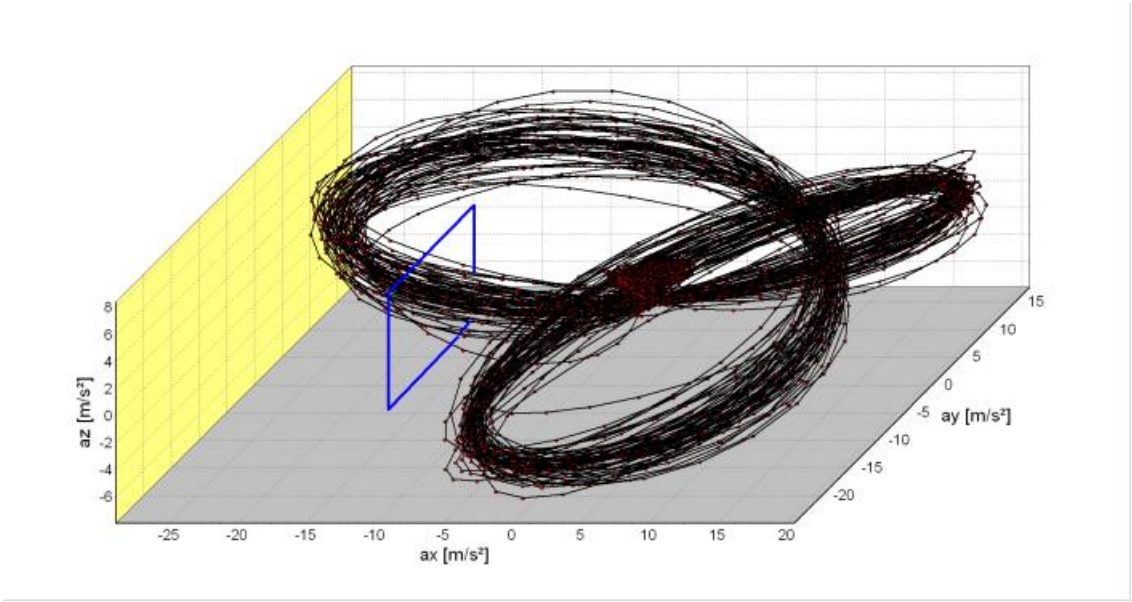

Figure 1 Three dimensional view of the acceleration data in m•s^{-2} illustrating the path of the state vector and cutting point to determine the start and end of a loop. Depicted is the side view of the area A (in blue) defining the start and the end of a cycle. All traces of the state vector must pass through and be perpendicular to the rectangle.

With n being the number of measured cycles, the two expressions have the following form:

$$\vec{A}_{\mathrm{a,C}}\left(\tau_j\right)=\frac{1}{n}\sum_{i=1}^{n}\vec{a}_{\mathrm{a,C}}\left(i\cdot\tau_j\right)+\frac{1}{n}\sum_{i=1}^{n}\vec{b}_{\mathrm{a,C}}\left(t=i\cdot\tau_j\right)\approx\frac{1}{n}\sum_{i=1}^{n}\vec{a}_{\mathrm{a,C}}\left(i\cdot\tau_j\right)\quad\text{with}\quad\lim_{n\to\infty}\frac{1}{n}\sum_{i=1}^{n}\vec{b}\left(i\cdot\tau_j\right)=0 \tag{2}$$

$$D_{\mathrm{a,C}}\left(\tau_j\right)=\sqrt{\frac{1}{n-1}\sum_{i=1}^{n}\left[\vec{A}_{\mathrm{a,C}}\left(\tau_j\right)-\vec{a}_{\mathrm{a,C}}\left(i\cdot\tau_j\right)\right]^2}\qquad\text{a=r or l and C=B or E} \tag{3}$$

For the actual calculation of the attractors (equation (2)), the number of data points in cycles varies slightly. We term a data point of an attractor as valid, if the number of elements $\vec{a}_{a,C}$ is at least 20% the number of elements of the first attractor point. This procedure is carried out via the software StatFree Version 7.0.3.1 (VietenDynamics, University of Konstanz, Germany; freely available on the Internet). Now the gait data can be compared at two different time intervals – index B: = begin, E: = end (e.g. one minute measuring at the beginning and

at the end of treadmill walking). We define three parameters, wherein $m = \min(m_{r,B}, m_{r,E}, m_{l,B}, m_{l,E})$ denotes the number of data points within the attractor with the fewest data points, v the walking speed and $\langle \dots \rangle$ denotes average of the included expression:

$$\delta M = \sqrt{\frac{1}{m \cdot v^2} \sum_{j=1}^{m} \left[\left(\vec{A}_{r,B}(\tau_j) - \vec{A}_{r,E}(\tau_j) \right)^2 + \left(\vec{A}_{l,B}(\tau_j) - \vec{A}_{l,E}(\tau_j) \right)^2 \right]} = \frac{1}{v} \sqrt{\sum_{i=1}^{3} \left[\left\langle \left(A_{r,B,x_i} - A_{r,E,x_i} \right)^2 \right\rangle + \left\langle \left(A_{l,B,x_i} - A_{l,E,x_i} \right)^2 \right\rangle \right]} \tag{4}$$

$$\delta D = \sqrt{\frac{1}{m} \sum_{j=1}^{m} \left[\left(D_{r,B}(\tau_j) - D_{r,E}(\tau_j) \right)^2 + \left(D_{l,B}(\tau_j) - D_{l,E}(\tau_j) \right)^2 \right]} = \sqrt{\left\langle \left(D_{r,B} - D_{r,E} \right)^2 \right\rangle + \left\langle \left(D_{l,B} - D_{l,E} \right)^2 \right\rangle} \tag{5}$$

$$\delta F = \delta M \cdot \delta D \tag{6}$$

δM is the velocity normalized (see explanation below) square root of the squared average distance between two attractors, which can account for the change in the movement pattern of a person walking. *δD* identifies the fluctuation change of the state vectors around the two attractors, which quantifies a change in movement precision. The third definition (*δF*) is the product of the first two, which is an index being of interest in the event the changes affect the movement style and the movement quality simultaneously. *δM*, *δD*, and *δF* are invariant under rotation which easily can be shown. Let *δM'* be calculated in terms of a rotated coordinate system Σ'. Any term of the form

$$\begin{aligned} &\left(\vec{A}'_{r,B}(\tau_j) - \vec{A}'_{r,E}(\tau_j) \right)^2 \\ &= \left(\vec{A}_{r,B}(\tau_j) - \vec{A}_{r,E}(\tau_j) \right)^T \Re^T(\alpha,\beta,\gamma) \Re(\alpha,\beta,\gamma) \left(\vec{A}_{r,B}(\tau_j) - \vec{A}_{r,E}(\tau_j) \right) \\ &= \left(\vec{A}_{r,B}(\tau_j) - \vec{A}_{r,E}(\tau_j) \right)^T \left(\vec{A}_{r,B}(\tau_j) - \vec{A}_{r,E}(\tau_j) \right) \\ &= \left(\vec{A}_{r,B}(\tau_j) - \vec{A}_{r,E}(\tau_j) \right)^2 \end{aligned} \tag{7}$$

is invariant under rotation. Here the rotation matrix $\Re(\alpha,\beta,\gamma)$ represents an arbitrary rotation and $\Re^T(\alpha,\beta,\gamma) = \Re^{-1}(\alpha,\beta,\gamma)$ the transposed inverse matrix re-

spectively. Both matrices can be functions of τ_j as well. All three expressions are combinations of those kinds of terms and therefore, are rotationally invariant.

Measurements can be done with a digitizing system giving the coordinates of a track, which permits approximating the attractor in coordinate space. However, using a kinematic tracking system requires a large degree of experimental effort and expense. A cheaper, simpler, and less work intensive system is an accelerometer. Mounted onto the human body, without using a gyroscope, it will not give acceleration data in the well-defined laboratory coordinate system, but since our three parameters are rotationally invariant this is not a hindrance. Furthermore, an additional argument for choosing acceleration over coordinate data is that the position on the treadmill results in some ambiguity; e.g. the subject's position could be at the front of the treadmill throughout the first measurement and at the rear during the second measurement. This automatically would result in a huge *δM* even without being caused by a change in the walking style. This difference in measurement may be of interest if coordinate position is relevant in a study. Otherwise this variation can be removed by using the velocity instead of coordinate data as shown in the following equation.

$$\vec{v}' = \frac{d\vec{x}'}{dt} = \frac{d\left(\vec{x} + \vec{x}_0\right)}{dt} = \frac{d\vec{x}}{dt} = \vec{v} \tag{8}$$

(no difference if walking at the front or rear; $\vec{x}_0$ constant)

By taking the acceleration data instead of the velocity data, one is not even restricted to constant speed treadmill walking (see equation (9)).

$$\vec{a}' = \frac{d\vec{v}'}{dt} = \frac{d\left(\vec{v} + \vec{v}_0\right)}{dt} = \frac{d\vec{v}}{dt} = \vec{a} \tag{9}$$

(independent of the choice of the inertia system; $\vec{v}_0$ constant)

To differentiate coordinate data twice causes a substantial ratio of high frequency noise in the signal (Freal et al., 1984). Therefore, a low pass filter must be applied when using data from a digitizing system. Temporary accelerometers are not free of such noise problems either and thus a low pass filter is required

here as well. From these statements it is clear that the described method analyzes the low frequency information of our example time series. However, this is not a principal feature of our method. If data with a low noise ratio is available the full information content, with the high frequency part included, can be accessed.

A few remarks on normalization: *δM* as well as *δD* contains a factor $1/\sqrt{m}$, which accounts for the different time intervals and sampling frequencies of different measuring situations, equipment, and subjects. The factor $1/v$ within *δM* is included to make results from measuring subjects at different walking speeds comparable. This can be understood in the following way:

The subject is walking at a speed v. While a foot is on the ground/treadmill it has the relative velocity of zero. The foot in a swing phase must accelerate to make up for the time during stance. Hence, the average walking speed of one cycle is equal to the average velocity of the foot.

$$\vec{v} = \int_{\text{full cycle}} \vec{a}(t)\,dt \tag{10}$$

To compensate for different walking velocities we normalize to the walking/treadmill speed.

$$\hat{v} = \int_{\text{full cycle}} \frac{\vec{a}(t)}{v}\,dt \tag{11}$$

For a normalized walking speed the parameter $\vec{A}$ must be substituted by $\vec{A}/v$. As a last step the average velocity v is moved to the front of the equation. Thus it might be possible to use our method in the case of a non-constant walking speed, making the measuring situation once again simpler. If possible, v can be substituted by v_i the average velocity of a cycle and the velocity would still be under the summation sign. However, we did not test this even more general procedure within the current study. In any case, *δM* and *δD* are abstract expressions and the dimensions are not of particular importance since they are not used for further calculations. However, we have used SI units to make sure

the numbers can be compared; *δM* is given in s^{-1} while *δD* has the dimension $m \bullet s^{-2}$.

Adaptation to a specific measuring situation and calibration

δM, *δD* and *δF* represent relative results, which means a first measurement sets a baseline and the deviation between the base and the second measurement is calculated. This is a major difference compared with the calculation of the Lyapunov exponent that gives a kind of stability measure, an absolute quantity (Bruijn et al., 2010; Buzzi et al., 2003; Dingwell & Cusumano, 2000; Dingwell et al., 2001; Dingwell et al., 2000; Dingwell & Marin, 2006; England & Granata, 2007). However, for practical use the outcome still must be interpreted for both cases. For our method an interpretation schema can be established in two ways. If no known or appropriate classification is available, a given spectrum can be divided into subsections with increasing numbers denoting more crucial changes. If groups are definable, using well-known conventional methods (Harris & Smith, 1996; Schablowski-Trautmann & Gerner, 2006), medians of *δM*, *δD*, or *δF* are calculated for each group. While conventional methods are not sensitive enough to judge individuals, they do produce adequate group results. Also, by calculating the median, not the mean, we avoid the substantial influence of outliers. The group intervals are obtained by calculating the upper α-quantile of the group with the smaller median and the lower α-quantile of the group with the bigger median as consecutive non-overlapping areas. For the next two consecutive groups we calculate upper β-quantile and lower β-quantile connected with the next set of medians and so on for all adjacent groups (see Figure 2).

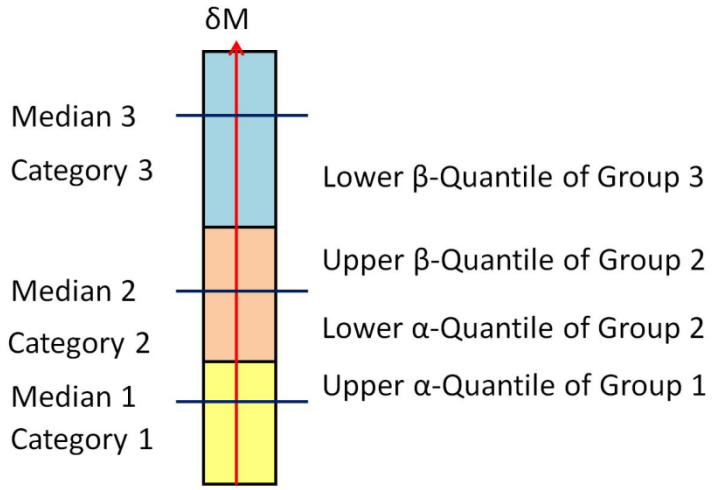

Figure 2 Illustration of example categories used to allow the creation of Quantiles from the medians of different groups.

These resultant numbers – e.g. $\delta M_{\text{Group Median}} \pm {}^{\text{upper } \beta\text{-quantile}}_{\text{lower } \alpha\text{-quantile}}$ - serve as a calibration for our method. Once this procedure is done, individuals can be sorted into categories by calculating the appropriate *δM*, *δD* or *δF*.

Method inherent aberration

As with all measurements, the outcome depends on the sensitivity and accuracy of the measuring equipment. In addition the method can cause extra deviations. This method's inherent deviations from an exact numerical value are extremely small. However, there are two reasons for errors: 1) The first data point within a cycle is defined as the first measurement after passing the area A (Figure 1). These can be located within a volume $\mathrm{A} \cdot \left[0, \frac{da_i}{dt} \cdot \frac{1}{f_s}\right]$, not directly on the area A. For this reason we do have a subtle dependence of the outcome on the definition of the cycle's start, which can be decreased by raising the sampling frequency f_s. 2) The attractor's standard errors along the attractor path are dependent on the number of cycles analyzed. For each data point on the attractor path we have the real attractor $\vec{A}_\infty\left(\tau_j\right) = \lim_{n\to\infty} \frac{1}{n} \sum_{i=1}^{n} \vec{a}\left(i \cdot \tau_j\right)$ located (one sigma probability) within an interval defined by $\vec{A}\left(\tau_j\right) \pm \vec{s}_A\left(\tau_j\right)$ with $\vec{s}_A\left(\tau_j\right)$ being the standard error. This induces the error margins for *δM*, which we calculate using the error propagation of independent variables.

$$s_{\delta M} = \sqrt{\sum_{j=1}^{m}\left\{\left(\frac{\partial(\delta M)}{\partial A_{r,B,x}(\tau_j)}\right)^2 \cdot s^2_{A_{r,B,x}}(\tau_j) + \ldots + \left(\frac{\partial(\delta M)}{\partial A_{l,E,z}(\tau_j)}\right)^2 \cdot s^2_{A_{l,E,z}}(\tau_j)\right\}} \tag{12}$$

$$= \frac{1}{m v^2 \delta M}\left(\begin{array}{l}\left[\sum_{i=1}^{m}\left(A_{r,B,x}(\tau_i) - A_{r,E,x}(\tau_i)\right)\right]^2 \cdot \sum_{j=1}^{m}\left[s^2_{A_{r,B,x}}(\tau_j) + s^2_{A_{r,E,x}}(\tau_j)\right] + \ldots \\ \ldots + \left[\sum_{i=1}^{m}\left(A_{l,B,z}(\tau_i) - A_{l,E,z}(\tau_i)\right)\right]^2 \cdot \sum_{j=1}^{m}\left[s^2_{A_{l,B,z}}(\tau_j) + s^2_{A_{l,E,y}}(\tau_j)\right]\end{array}\right)^{\frac{1}{2}}$$

$$= \frac{\sqrt{m}}{v^2 \delta M}\left(\begin{array}{l}\left\langle A_{r,B,x} - A_{r,E,x}\right\rangle^2 \cdot \left[\left\langle s^2_{A_{r,B,x}}\right\rangle + \left\langle s^2_{A_{r,E,x}}\right\rangle\right] + \ldots \\ \ldots + \left\langle A_{l,B,z} - A_{l,E,z}\right\rangle^2 \cdot \left[\left\langle s^2_{A_{l,B,z}}\right\rangle + \left\langle s^2_{A_{l,E,y}}\right\rangle\right]\end{array}\right)^{\frac{1}{2}}$$

The complete expression consists of 6 terms (right and left side with three components each). The deviation of δD appears to depend via $D(\tau_j)$ on the standard error $\vec{s}_A(\tau_j)$ as well, but it does not. Formally the deviation is

$$s_{\delta D} = \sqrt{\sum_{j=1}^{m}\left\{\left(\frac{\partial(\delta D)}{\partial D_{r,B}(\tau_j)}\right)^2 \cdot s^2_{D_{r,B}}(\tau_j) + \ldots + \left(\frac{\partial(\delta D)}{\partial D_{l,E}(\tau_j)}\right)^2 \cdot s^2_{D_{l,E}}(\tau_j)\right\}} \tag{13}$$

with

$$s_{D_{a,C}} = \sqrt{\sum_{j=1}^{m}\sum_{i=1}^{3}\left(\frac{\partial D}{\partial A_{a,C,x_i}(\tau_j)}\right)^2 \cdot s^2_{A_{a,C,x_i}}(\tau_j)} \tag{14}$$

and a=r or l and C=B or E.

First we calculate the derivative of $D(\tau_j)$ in regard to one component of $\vec{A}_{a,C}(\tau_j)$

$$\frac{\partial D(\tau_j)}{\partial A_{a,C,x}(\tau_j)} = \frac{\partial}{\partial A_{a,C,x}(\tau_j)}\sqrt{\frac{1}{n-1}\sum_{i=1}^{n}\left[\vec{A}_{a,C}(\tau_j) - \vec{a}_{a,C}(i\cdot\tau_j)\right]^2} \tag{15}$$

$$= \frac{n A_{a,C,x}(\tau_j) - \sum_{i=1}^{n} a_{a,C,x}(i\cdot\tau_j)}{(n-1)D(\tau_j)} = 0$$

As a consequence $s_{\delta D}$ is identically zero

$$s_{\delta D} \equiv 0 \tag{16}$$

since all derivatives have the same result. This might look strange, but it is a consequence of the definition of *D*, in which attractor inaccuracies cancel each other. *δF'*s deviation is simply

$$s_{\delta F} = \frac{\partial(\delta F)}{\partial(\delta M)} \cdot s_{\delta M} = \delta D \cdot s_{\delta M} \tag{17}$$

Experimental procedures

Thirty healthy subjects (11 female, age: 31±11 years, height: 1.70±0.07 m, mass: 60±9 kg; 19 male, age: 29±11 years, height: 1.82±0.05 m, mass: 82±12 kg) participated in the study. The study protocol and informed consent process were approved by the local ethics committee of the University of Konstanz, Germany and was conducted in accordance with the Declaration of Helsinki. All subjects gave written informed consent according to this approval.

The participants performed a walking test on a treadmill under three different conditions: 1) five minutes walking without any load (N); 2) five minutes walking with an additional mental task (M); and 3) five minutes walking with a two kilogram weight on each ankle (W). Each of the combinations NM, NW and MW were done using equations (4) and (5) with B and E equal to N, M or W respectively. The treadmill speed was set to 1.39 $m \cdot s^{-1}$ and kept constant throughout the test. Thus one minute of walking was equivalent to about 60 cycles. Gait data were recorded while walking on the treadmill for one minute, for each subject, after each of the five minute conditions. This test was performed on two different days to check the repeatability.

Data were recorded using the RehaWatch 4.1.9.0 (HASOMED GmbH, Magdeburg, Germany). The equipment includes two inertial sensors, which were mounted on the lateral aspect of each ankle, and a data logger. Output data were internally corrected for data shift. The inertial sensors contain tri-axial accelerometers for measuring acceleration and tri-axial gyroscopes for measuring the angular velocity; the data of the latter were not used in this study.

Data analysis

Analyses were limited to the acceleration data of the two foot sensors which were taken at a sampling rate of 500 Hz. We filtered the data with a 4.5 Hz low-pass filter (Vieten, 2004) after performing a residual analysis (Winter, 2009) to find the optimal cutoff frequency. All statistical tests and numerical calculations were performed using StatFree, SPSS v19.0 (IBM, Armonk, NY, USA), and Microsoft Excel 2010 (Microsoft Office Professional Plus 2010). All group parameters were tested for normal distribution. Reliability estimates for δM and δD for each of the three conditions were performed by determining the day to day Intraclass Correlation Coefficient (ICC; 3, k) and differences between days via a paired t-test. Differences in normally distributed parameters between N and M, between N and W, as well as between M and W, were detected using a one-way Repeated Measures ANOVA. Bonferroni adjustment was applied to account for multiple comparisons, and the significance level for all statistical tests was set a priori to $\alpha=0.005$.

2.4 Results

The numerical values of all measurements of δM were between 0 and 7.1 s^{-1}, while the variation of δD was between 0 and 2.5 $m \cdot s^{-2}$ (Figure 3). This graph shows the clustering of the data for each of the three conditions.

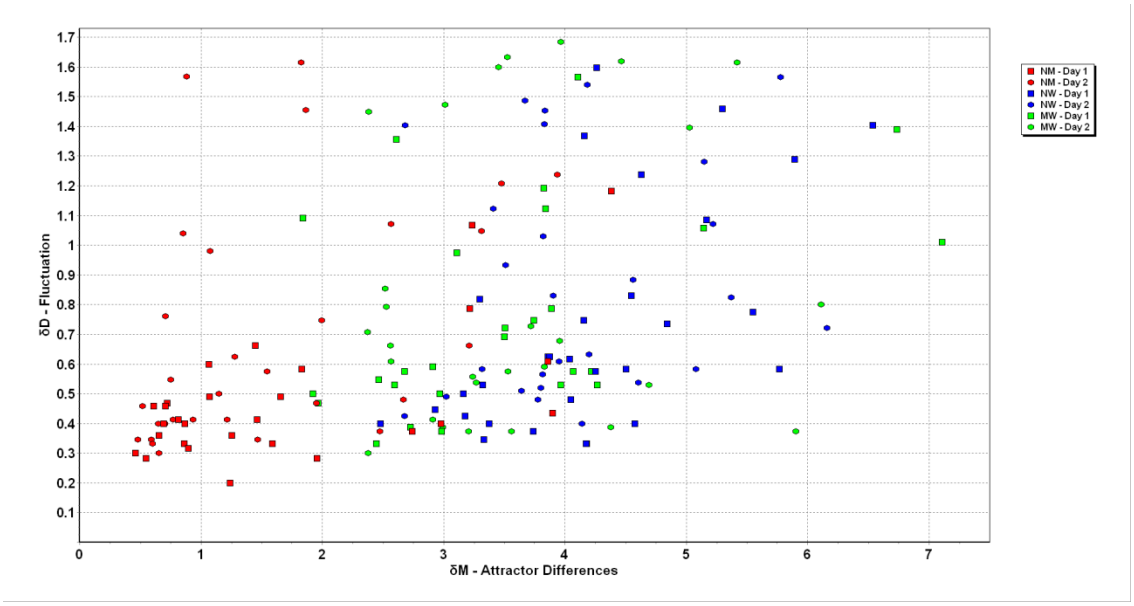

Figure 3 Scatterplot of *δM* and *δD* for the attractors in the three conditions. Note the clustering of data for each of the three conditions.

Figures 4 and 5 illustrate the individuals' data points for *δM* and *δD* for all three conditions on both days.

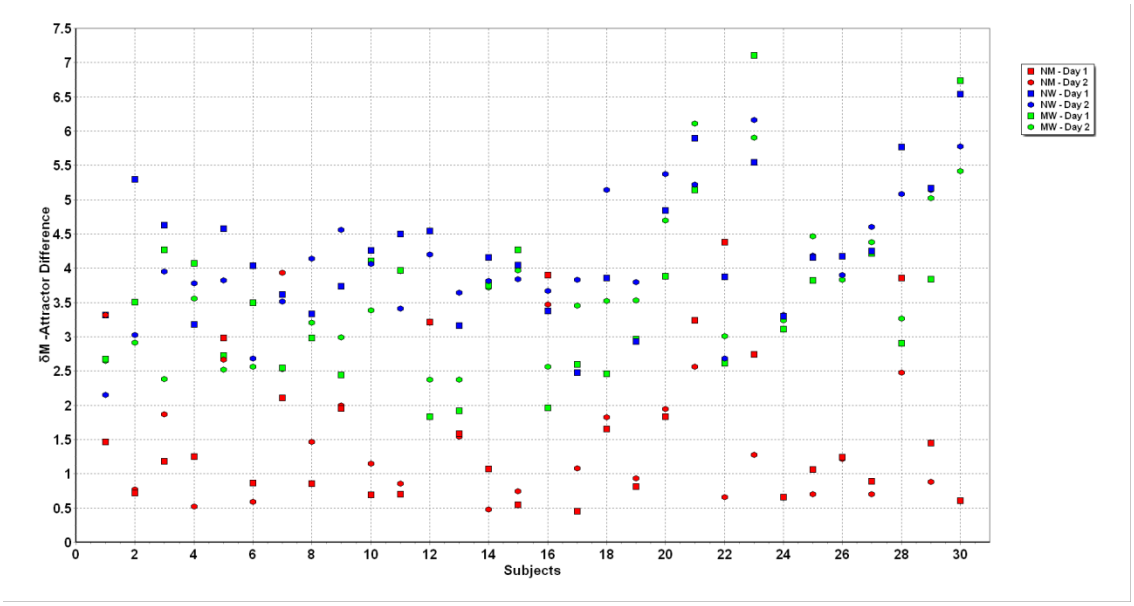

Figure 4 Individual subject values of *δM* for normal-mental, normal-weighted and mental-weighted walking on days 1 and 2.

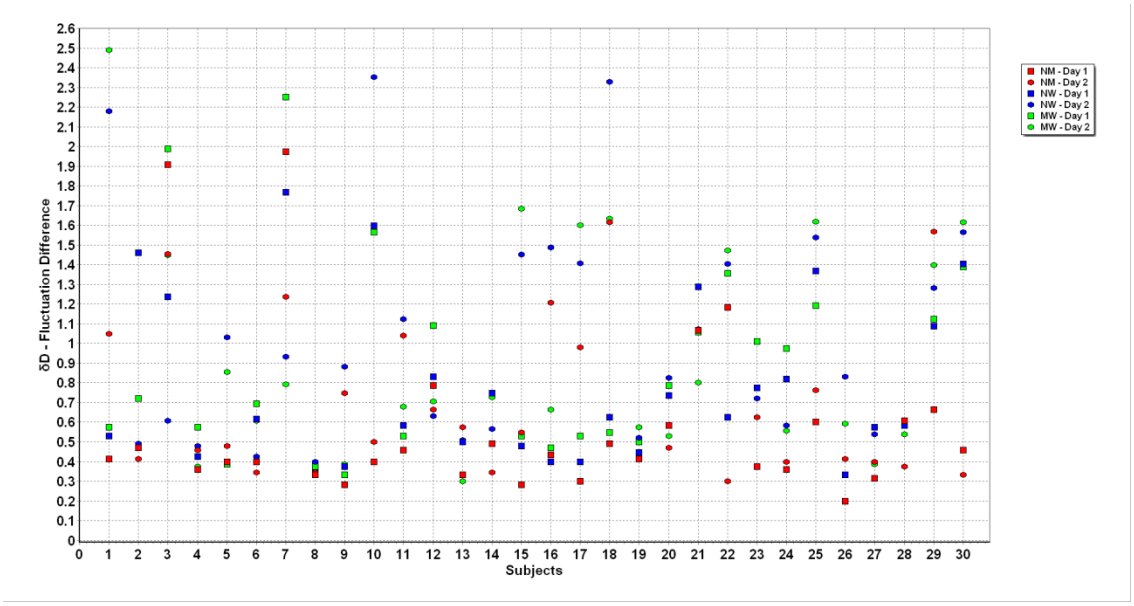

Figure 5 Individual subject values of *δD* for normal-mental, normal-weighted and mental-weighted walking on days 1 and 2.

The comparison of all three situations normal to mental, normal to weight, and mental to weight walking show significant differences (see Figure 6).

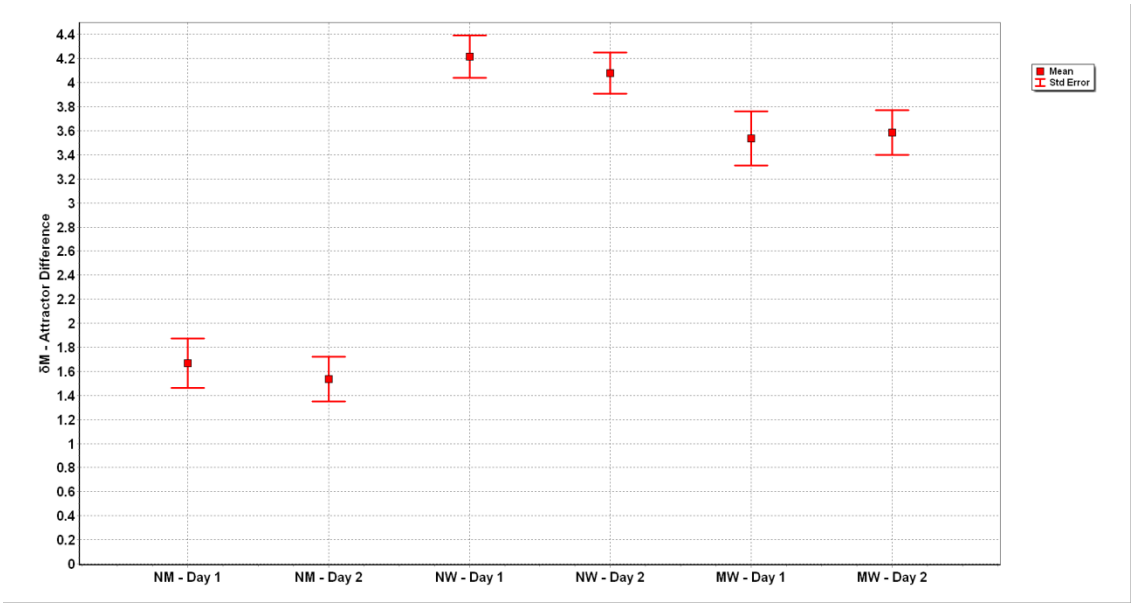

Figure 6 Means and Standard Error of *δM* for the three conditions across the two days. Significant differences occurred between all three tasks ($p<0.001$), but not within conditions.

The ANOVA revealed a significant main ($p<0.001$) effect for *δM*; with post hoc analyses showing that *δM* differed between all three tasks ($p<0.001$). Compari-

son of *δD* revealed a significant difference (p<0.001) between the three conditions. Post hoc analysis indicated that the fluctuation around the differences of normal to mental walking was less than either condition that included walking with weights on the ankles, i.e. normal to weighted and mental to weighted walking (see Figure 7).

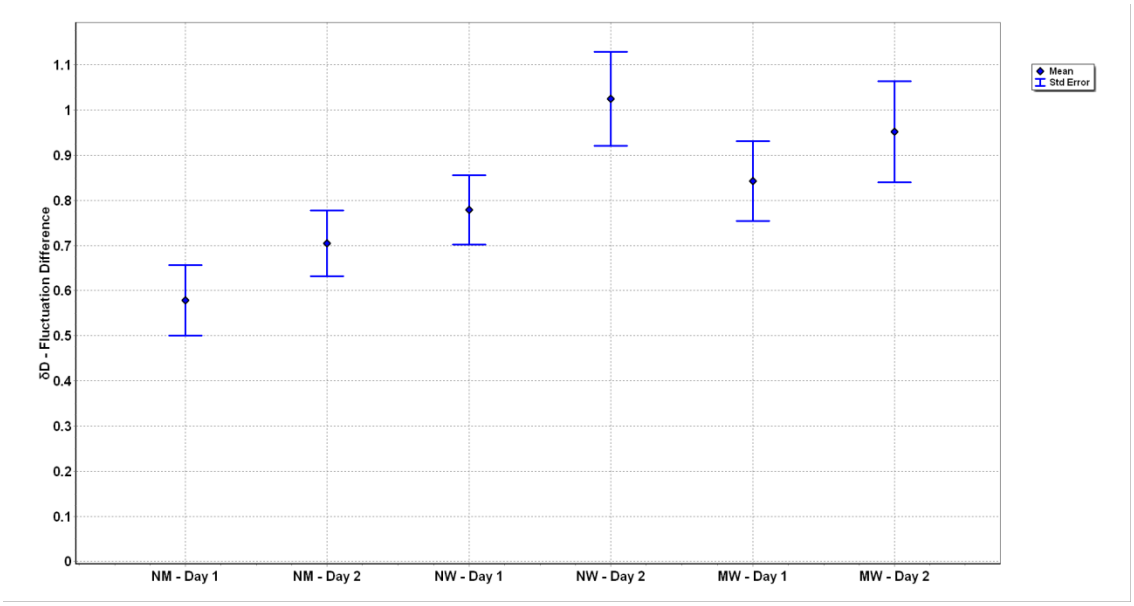

Figure 7 Illustration of the Means and Standard Error of *δD* for the three conditions across the two days. Significant differences occurred between all three tasks (p<0.001), but not within conditions.

Reliability estimates revealed that *δM* displayed excellent day to day reliability as indicated by the ICC and lack of differences (p>0.05) between days (Table 1 and Figure 6). Day to day reliability of *δD* expressed via ICC was moderate to good and not different between days (p>0.05) (Table 1 and Figure 7).

Table 1 Intraclass Correlation Coefficient (ICC) and the probability of a difference across days for *δM* and *δD* of normal walking without any load (N), walking with an additional mental task (M), and walking with two kilogram weights on each foot (W).

Measurements	ICC_{ave}	Probability of Difference
δM N vs. M	0.732	p = 0.47
δM N vs. W	0.752	p = 0.38
δM M vs. W	0.881	p = 0.74
δD N vs. M	0.610	p = 0.13
δD N vs. W	0.414	p = 0.06
δD M vs. W	0.502	p = 0.36

The impact of different cutting conditions, defining the cycle's start, were found to be smaller than 5% of the value of each parameter. We also calculated the error (equation (12)) caused by the attractor's standard error and found $s_{\delta M} < 0.05\ \delta M$.

2.5 Discussion

The purpose of this new method is to allow the easy quantification of differences between dynamic situations on the group and on the individual level. In the case of our example, differences between gait patterns under different constraints were determined. The constraints included normal walking, walking while performing a mental task (counting backwards by threes), and walking with weights added to the ankles. In the current study the gait pattern differed in all three conditions, i.e normal walking was different from mental and weighted walking, which also differed from each other. Previous studies have shown changes in gait patterns as a response to a cognitive or motor task while walking (Baetens et al., 2013; Camicioli, Howieson, Lehman, & Kaye, 1997; Hollman, Kovash, Kubik, & Linbo, 2007; O'Shea, Morris, & Iansek, 2002; Yogev-Seligmann, Giladi, Gruendlinger, & Hausdorff, 2013).

The estimation of reliability for the proposed methodology indicated that *δM* and *δD* are reliable and the results of one day can be replicated on a second day occurring approximately a week later. This is in agreement with the results of other studies. In a study with acceleration-based gait tests Senden et al. (Senden, Grimm, Heyligers, Savelberg, & Meijer, 2009) found high repeatability in basic gait parameters such as step length, cadence, speed, and step time. Henriksen and coworkers (Henriksen, Lund, Moe-Nilssen, Bliddal, & Danneskiod-Samsøe, 2004) established the test–retest reliability of a trunk accelerometric gait test in healthy subjects. Gait parameters of step length, stride length, cadence and the mean acceleration were found to be stable. Kadaba et al. (Kadaba et al., 1989) investigated repeatability of gait data in normal adults at three times on three different days. They showed the gait parameters “are quite repeatable”; with good repeatability within a test day, but less so for measurements on different days. Recently, van Schooten et al. (van Schooten et al., 2013) also found reliability of local dynamic stability within a day was good, but was only moderate to poor between days.

While, *δD* displayed lower repeatability, the ICC_{ave} was still moderate to good ranging from 0.414 to 0.610, with no differences across days ($p>0.05$). This is in agreement with Senden and colleagues (Senden et al., 2009) who also found less repeatability in the irregularity and asymmetry of gait measures.

An interesting point to note from the current study was the ability of the method to identify outlying values from one of the subjects who had different experiences between days. Subject 22 performed the mental task in a non-native language and commented afterwards that, “I was more nervous about getting the answers correct on the first day than the second day”. This subject displayed a much larger *δM* for the normal to mental walking on day 1 than on day 2 (see Figure 4). This instance, while anecdotal, suggests that when an individual displays characteristics that differ from the group, he/she will be classified into a different group by their *δM* and *δD*. Thus the sensitivity of *δM* and *δD* appears to allow the sorting of individuals into the various categories as explained in the methods section.

The described new method relies on thousands of data points for each subject and measurement. This makes for a strong statistical outcome. The attractor

change *δM* and the fluctuation change *δD* for two different time intervals can then be reliably quantified at a high degree of accuracy. In our example study the error margins of *δM* and *δD* are in the range of 5%. Therefore, individuals can be rated precisely and categorization on a personal level is possible. The method is easy to apply, simple to use in the case of gait data acquisition, the analysis is uncomplicated, and results are sensitive and stable. Thus it appears that the new method could be useful in many situations, but may be most helpful in clinical settings where the low cost of accelerometers and minimal amount of data processing required would be desired.

A comparison between the well-established non-linear methods calculating the Lyapunov exponent or the Floquet multiplier shows big differences compared to our method. Lyapunov exponent and the Floquet multiplier were developed for the analysis of classical deterministic systems. Those methods allow deep insight into the mathematical working of dynamical systems, an ability that our method lacks completely. The application of established non-linear methods to data obtained from experiments is not without problems. To be able to handle more or less noisy data, algorithms have been developed (for a comprehensive overview see (Williams, 1997)), but the liability of these algorithms is still not completely assured (Bruijn et al., 2012). On the other hand our method is developed to handle real live data of processes with an underlying limit cycle attractor only. The two main parameters in our method calculate the velocity normalized mean distance between limit cycle attractors (*δM*) and the change of the variation, which is the deviation of actual movement compared to the attractor (*δD*). The simplicity of our method and its stability allows quantification of factors responsible for changing movement pattern and movement variation as in the clinical example mentioned above.

In a clinical setting a central object is to diagnose functional problems which are reflected as walking abnormalities or changes in gait patterns between two different conditions. For example, fatigue is a common and frequently disabling symptom of Multiple Sclerosis with negative effects on normal activities of daily life (Thickbroom, Sacco, Faulkner, Kermode, & Mastaglia, 2008). Despite the high incidence of fatigue, there are no objective measures for assessing motor fatigue in Multiple Sclerosis. With our new method we can quantify the changes in gait patterns between two conditions: at the beginning and at the end (under

full exertion) of the treadmill walking for each individual. If the change in a patient exceeds the threshold value – which we can define using the results of a control group – then the individual can be classified as a patient with fatigue symptom. In addition it could be used in other neurological conditions, such as Parkinson's Disease, stroke, trauma, etc. Thus, the proposed method does not judge the quality of the movement, but allows quantification of the changes in gait pattern between two different conditions and hence gauges the acuteness of a neurological detraction. We therefore recommend this novel method as a tool to use in clinical studies and in the clinical practice.

Acknowledgments

We thank all subjects who participated in the study. The study was approved by the local Ethical Committee of the University of Konstanz, Germany.

Author Contributions

Conceived and designed the experiments: MMV AS RLJ. Performed the experiments: AS. Analyzed the data: MMV AS RLJ. Contributed reagents/materials/analysis tools: MMV. Wrote the paper: MMV AS RLJ. Developed the mathematical procedure: MMV. Designed the software used in analysis: MMV.

3 STUDIE 2: Objective assessment of motor fatigue in multiple sclerosis: The Fatigue index Kliniken Schmieder (FKS)

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3.1 Abstract

Fatigue is a common and frequently disabling symptom of multiple sclerosis (MS). The aim of this study was to develop the Fatigue index Kliniken Schmieder (FKS) for detecting motor fatigue in patients with MS using kinematic gait analysis. The FKS relies on the chaos theoretical term “attractor”, which, if unchanged, is a necessary and sufficient indicator of a stable dynamical system. We measured the acceleration of the feet at the beginning of and shortly before stopping a treadmill walking task in 20 healthy subjects and 40 patients with multiple sclerosis. The attractor and movement variability were calculated. In the absence of muscular exhaustion a significant difference in the attractor and movement variability between the two time points demonstrates altered motor control indicating fatigue. Subjects were classified using the FKS. All healthy subjects had normal FKS and thus no fatigue. 29 patients with MS were classified into a fatigue group and 11 patients into a non-fatigue group. This classifi-

cation agreed with the physician's observation and video analyses in up to 97% of cases. The FKS did not correlate significantly with the overall and motor dimensions of the fatigue questionnaire scores in patients with MS and motor fatigue. The common concept of fatigue as overall subjective sensation of exhaustion can be affected by conditions including depression, sleep disorder and others. FKS constitutes a robust and objective measure of changes in motor performance. Therefore, the FKS allows correct identification of motor fatigue even in cases where common comorbidities mask motor fatigue.

3.2 Introduction

Fatigue is a common and frequently disabling symptom of Multiple Sclerosis (MS) with profound negative effects on normal activities of daily life and substantially reduces quality of life (Thickbroom et al., 2008). Fatigue is associated with a subjective feeling of weakness, lack of energy and lethargy (Romani et al., 2004). Between 38% and 83% of patients with MS suffer from fatigue (Kluger et al., 2013), and many patients report fatigue to be their most debilitating symptom (Romani et al., 2004). However, despite the high incidence of fatigue, its pathophysiology is still poorly understood. Many factors have been proposed to play a role in the development of fatigue in MS (Liepert, Mingers, Heesen, Bäumer, & Weiller, 2005). Two distinct types of fatigue in MS – mental and motor fatigue – can occur in isolation or in combination. Psychological and/or physical condition might be compromised by factors such as depression, sleep disorder and deconditioning, which may influence the symptoms of fatigue (Romani et al., 2004). Further, fatigue may be caused by a failure of the neuromuscular system to generate force (Bigland-Ritchie, Rice, Garland, & Walsh, 1995). Patients with MS show significantly prolonged central motor conduction times and lower motor evoked potential amplitudes following fatiguing exercise (Petajan & White, 2000). Fatigue may be caused by an intermittent central use-dependent conduction block (McDonald et al., 2001), and metabolic abnormalities in the frontal cortex und basal ganglia have been observed via positron emission tomography in MS patients with fatigue (Roelcke et al., 1997).

In the current study, we focused on the motor dimension of fatigue. Presently, there is no "gold standard" for detecting motor fatigue. Commonly, fatigue is assessed by several questionnaires including the Fatigue Severity Scale (FSS)

(Krupp, LaRocca, Muir-Nash, & Steinberg, 1989), the Fatigue Assessment Instrument (FAI) (J. E. Schwartz, Jandorf, & Krupp, 1993), the Fatigue Impact Scale (FIS) (Fisk et al., 1994), the Modified Fatigue Impact Scale (MFIS) (Guidelines, 1998) and, in Germany, the Fatigue Scale for Motor and Cognitive Functions (FSMC) (Penner et al., 2009) and the Würzburg Fatigue Inventory in Multiple Sclerosis (WEIMuS) (Flachenecker et al., 2006). These standardized questionnaires are based on patients' self-assessments and capture their general condition during a particular time course. However, because these questionnaires are based on the patients' subjective feelings, they may be distorted (overestimation or underestimation) due to an inaccurate self-perception. In some patients with MS, deciding whether motor fatigue is present or whether other factors cause similar symptoms can be very difficult. Hence, an objective tool for assessing motor fatigue in MS is crucial for a more precise diagnosis of fatigue and for the design and evaluation of treatment and rehabilitation programs.

Recently, we have introduced an unbiased instrument for assessing motor fatigue (Sehle et al., 2011). Specific gait parameters including step length, width and height, bilateral leg circumduction, bilateral knee flexion angle and mediolateral trunk sway changed during a walking test. The step cycle was more irregular at the end compared with the beginning of the test. These changes in gait patterns were found to be symptomatic for MS patients with motor fatigue. Such traditional kinematic analyses of human gait captures the characteristic pattern for an individual based on a few single gait cycles (Harris & Smith, 1996; Schablowski-Trautmann & Gerner, 2006) but neglect essential information of the dynamics of continuous locomotion (Schablowski-Trautmann & Gerner, 2006). Non-linear methods use gait data in a time series format to calculate and interpret the Lyapunov exponent as an estimator for dynamic stability (Kantz, 1994; Rosenstein et al., 1993). Although this method may have its advantages, the results can be well presented only at the group level and not at the individual patient level (van Schooten et al., 2013). This must be considered in clinical trials and for decision-making in clinical practice.

We have recently presented a new method for quantifying differences in time series of gait data using attractor attributes with an underlying limit cycle attractor (Vieten, Sehle, & Jensen, 2013). Using this method, we were able to identify

subtle gait pattern differences between different situations and classify these on group and subject levels. A stable situation is characterized by an unchanged attractor and unchanged movement variability. Thus, changes of these two parameters indicate an alteration of the gait mechanism, which, by ruling out other reasons, we identify as acute motor fatigue.

To the best of our knowledge, an objective method for classifying fatigue in patients with MS is lacking. Therefore, the purpose of this study was to establish the “Fatigue index Kliniken Schmieder (FKS)” as an objective numerical indicator for assessing motor fatigue using kinematic gait analysis and to test its sensitivity and specificity. We hypothesized that the FKS allows precise identification of subjects with motor fatigue and that motor fatigue in MS is not related to muscle fatigue.

3.3 Materials and methods

Subjects

Twenty healthy subjects and forty patients with definite MS according to the McDonald criteria (McDonald et al., 2001) participated in this study (Table 1).

Table 1 Mean (1 standard deviation) subject characteristics.

Parameters	Patients with MS	Healthy subjects	*P* value
Sex (female/male)	27/13	11/9	n.s.
Age (years)	45.9 (7.0)	43.1 (8.6)	n.s.
Height (cm)	171.3 (10.7)	173.4 (8.4)	n.s.
Mass (kg)	74.1 (15.6)	80.4 (21.3)	n.s.
Disease course (n)			
RR	30	Not applicable	
PP	3	Not applicable	
SP	7	Not applicable	
EDSS	3.4 (1.3)	Not applicable	
BDI-II>8 (*n* with depression)	26	3	0.001

MS multiple sclerosis, *RR* relapsing-remitting, *PP* primary progressive, *SP* secondary progressive, *EDSS* Expanded Disability Status Scale, *BDI-II* Beck Depression-Inventory, *n* number of subjects, *P value* probability value*, n.s.* not statistically significant.

Patients and controls were all between 18 and 65 years old and recruited between October 2011 and July 2012. All patients were admitted to the inpatient rehabilitation clinic specializing in MS; and had to be able to walk on a treadmill without aids or assistance. There were no limitations of disease course and disability levels. Patients were in a stable condition and those with relapses within the past three months were excluded. Subjects were also excluded from the study if they received the drug Fampyra® (Fampridin; Biogen Idec Inc., 225 Binney Street, Cambridge, MA 02142). Participants were consecutively enrolled upon their willingness to partake in this study. Control subjects were recruited from the local population and from clinic staff. The healthy subjects were included in the study by volunteering and if they had no neurological or orthopedic disorders.

Exercise task

All participants completed a walking test on a treadmill: they walked either until they experienced complete exhaustion (17, very hard on the Borg scale (Borg, 1982)) or for a maximum of 60 minutes. Based on our previous results (Sehle et al., 2011), we expected that the MS patients with fatigue will be exhausted within substantially less than 60 minutes. All subjects wore a harness during the walking test to prevent falling. The treadmill speed was set to 10% above a subject-specific comfortable walking speed or to a maximum of 5 km/h and kept constant throughout the test. During the test, participants were repeatedly asked to rate their exhaustion on a Borg scale from 6 (absolutely no effort) to 20 (maximum effort). The test was stopped one minute after the patient reached 17 on the Borg scale ("very hard") or after 60-minutes walking.

Gait data were recorded for 1 minute at the beginning (t_1) and for 1 minute at the end of the test (t_2) using the motion analysis device AS200 (LUKOtronic, Lutz Mechatronic Technology e.U., Innsbruck, Austria; sampling rate 80 Hz). Markers were placed bilaterally on the heel counter of the shoes; bilaterally with a rod on the distal portion of the Achilles tendon at the level of the ankle; bilaterally on the posterior aspect of the knee; bilaterally on the belt at the highest point of the iliac crest; and bilaterally centered on the margo medialis. Accelerations of the markers were computed as the second derivatives of the position traces after filtering with an F^3-filter at 4.5 Hz cutoff (Vieten, 2004).

Blood samples were taken prior to t_1 and immediately after t_2. Blood lactate levels were measured using a lactate analyzer and lactate strips with a precision of 3% coefficient of variation (Arkray Lactate Pro LT-17810, Kyoto, Japan). Heart rate was measured prior to t_1 and at t_2 using a chest strap and a heart rate monitor (Garmin Forerunner 305, Garmin Ltd., Kansas City, Kansas, U.S.A.).

Diagnostic criteria

Theoretical background

Human walking in the absence of disturbances is characterized by a stable movement pattern and consistent movement control. Because we kept the walking situation unchanged and muscular exhaustion was excluded (lactate assessment), pattern and variability changes during the walking test were

deemed to have been caused by fatigue. We applied a new method (Vieten et al., 2013) for quantifying movement pattern changes and changes of movement variability using attractor attributes of the acceleration of the feet. The limit cycle attractors were approximated and three measures were calculated: *δM* is a measure of the difference between two attractors quantifying the differences between two movement patterns; *δD* is the difference between the two associated deviations of the state vector away from the attractor representing the change in movement variation; and *δF* is the product of *δM* and *δD* and represents an index of the change which we termed the Fatigue index Kliniken Schmieder (FKS).

$$\delta F = \delta M \cdot \delta D \tag{1}$$

Three-dimensional acceleration measurements $(\vec{a}_r(t), \vec{a}_l(t))$ of two markers (l - left foot; r - right foot) were used. The start and the end of a loop were defined as the passing of $\vec{a}_r(t)$ respectively $\vec{a}_l(t)$ through a well-defined 2D area (Figures 1a,b, 2a,b).

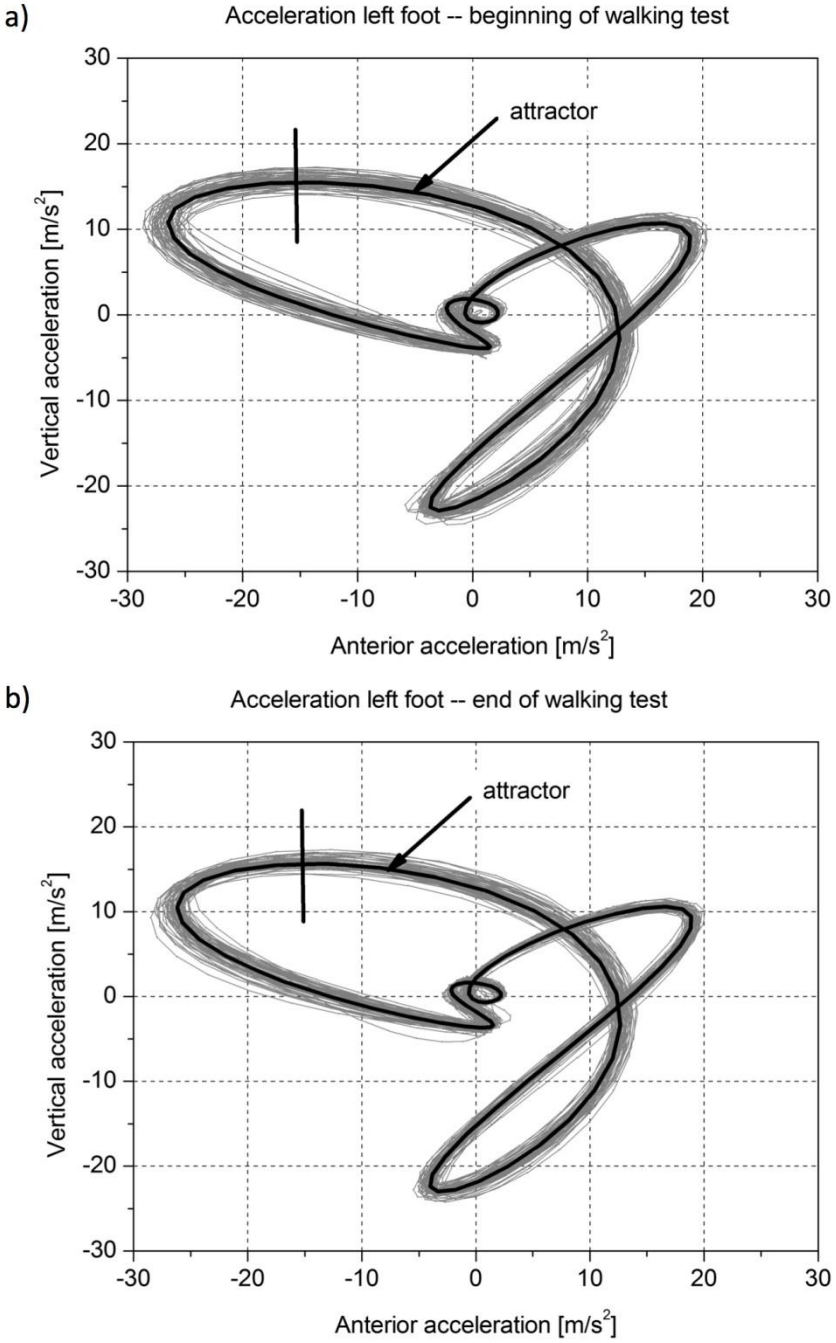

Figure 1 Two-dimensional graph of the acceleration data of a subject's left foot for 1 minute **a** at the beginning and **b** at the end of the walking task for one healthy subject. The vertical black line indicates the plane that was used to define the beginning and end of each gait cycle.

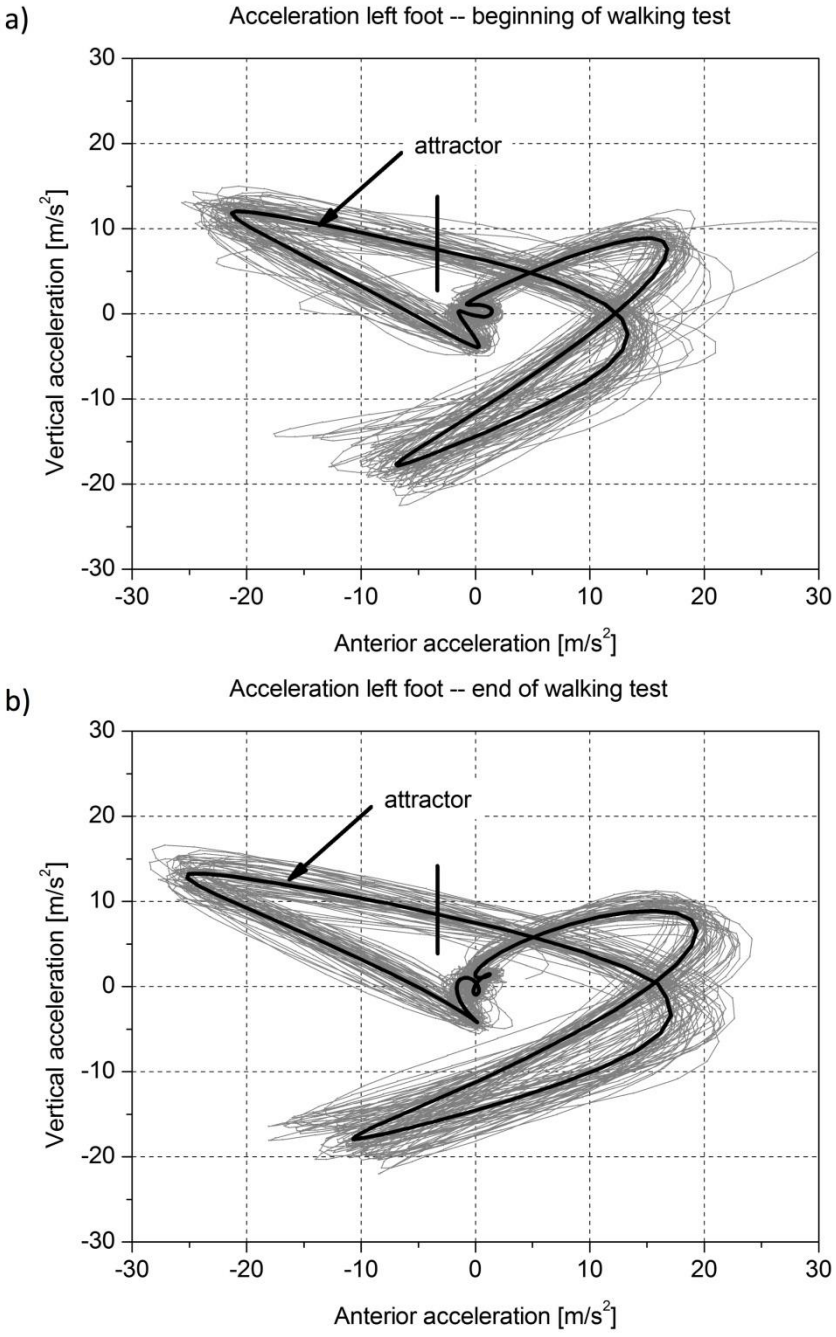

Figure 2 Two-dimensional graph of the acceleration data of a subject's left foot for one minute **a** at the beginning and **b** at the end of the walking task for one MS patient with fatigue. The vertical black line indicates the plane that was used to define the beginning and end of each gait cycle.

The attractor parameters $\vec{A}_r(\tau), \vec{A}_l(\tau)$ were approximated as the acceleration at time *τ* (ordering parameter of a complete cycle) averaged over n loops.

$$\vec{A}_{\mathrm{a,C}}\left(\tau_j\right)=\frac{1}{n}\sum_{i=1}^{n}\vec{a}_{\mathrm{a,C}}\left(i\cdot\tau_j\right)+\frac{1}{n}\sum_{i=1}^{n}\vec{b}_{\mathrm{a,C}}\left(t=i\cdot\tau_j\right) \approx \frac{1}{n}\sum_{i=1}^{n}\vec{a}_{\mathrm{a,C}}\left(i\cdot\tau_j\right) \tag{2}$$

with

$$\lim_{n\to\infty}\frac{1}{n}\sum_{i=1}^{n}\vec{b}\left(i\cdot\tau_j\right)=0$$

and a = right or left and C = beginning or end.

$\vec{D}_r\left(\tau\right),\vec{D}_l\left(\tau\right)$ are the standard deviations describing differences of the actual acceleration and the attractor.

$$D_{\mathrm{a,C}}\left(\tau_j\right)=\sqrt{\frac{1}{n-1}\sum_{i=1}^{n}\left[\vec{A}_{\mathrm{a,C}}\left(\tau_j\right)-\vec{a}_{\mathrm{a,C}}\left(i\cdot\tau_j\right)\right]^2} \tag{3}$$

Differences in gait parameters between the beginning (B) and the end (E) of the walking test were calculated as

$$\delta M=\frac{1}{v}\sqrt{\sum_{i=1}^{3}\left[\left\langle\left(A_{r,B,x_i}-A_{r,E,x_i}\right)^2\right\rangle+\left\langle\left(A_{l,B,x_i}-A_{l,E,x_i}\right)^2\right\rangle\right]} \tag{4}$$

The change in the standard deviation of attractor and acceleration measurements was defined as

$$\delta D=\sqrt{\left\langle\left(D_{r,B}-D_{r,E}\right)^2\right\rangle+\left\langle\left(D_{l,B}-D_{l,E}\right)^2\right\rangle} \tag{5}$$

where $\langle\ldots\rangle$ is the average of the included expression.

Deriving the Fatigue index Kliniken Schmieder (FKS)

The FKS is based on the two attractors calculated from the 3-dimensional acceleration data of the feet of a walking person. Non-changing attractors define a stable system. The FKS allows for capturing altered movement patterns and variability on an individual level representing fatigability. To calibrate the FKS, we used the method described in (Vieten et al., 2013) requiring data of two groups of subjects as selected by a conventional method. Central to this method is the median of the two groups, which are not significantly influenced by out-

liers. Conventional methods allow clear identification of the most typical group members; e.g. when looking for fatiguing MS patients it is easy to identify heavily fatigued subjects. Those individuals with mild symptoms might be wrongly classified as not fatiguing. Similarly non-fatiguing persons with walking constraints have a high probability of wrongly being included into the fatigue group. As long as a group does not contain more than 25% wrongly sorted subjects and both groups have about the same ratio of wrong members, it would not substantially influence the FKS-medians of the groups. The next step in the calibration process is to calculate the lower α-quantile of the fatigue group and the upper α-quantile of the non-fatigue group. We increased the α until the maximal non-overlapping quantiles were identified (Figure 3) (Vieten et al., 2013).

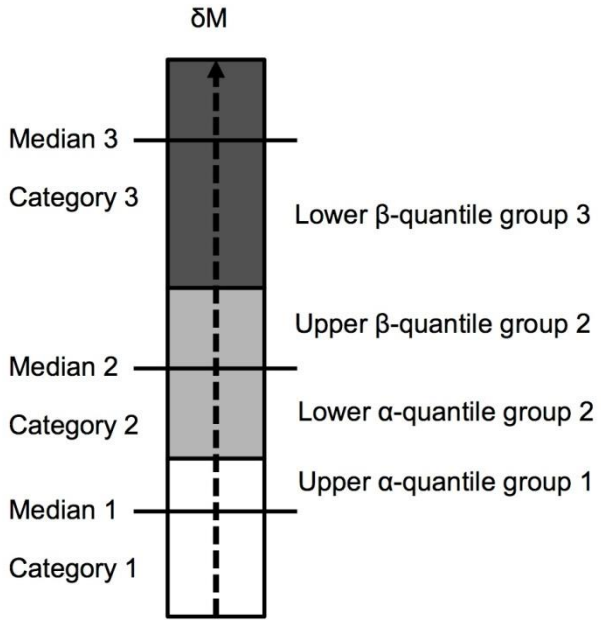

Figure 3 "Illustration of example categories used to allow the creation of Quantiles from the medians of different groups" (Vieten et al., 2013).

The nearest integer within the interval defined by the smallest FKS-value in the lower α-quantile (fatigue group) and the largest FKS-value in the upper α-quantile (non-fatigue group) established the limit between fatigue and non-fatigue.

Next, the FKS of healthy individuals was used as a benchmark test; and following, all subjects were classified according to the FKS values into the fatigue and

the non-fatigue groups. All further analyses were performed for three groups: patients with fatigue symptom (MS-F), patients without fatigue symptom (MS-NF) and healthy persons (Non-MS). The results of a “conventional” instrument (physician`s judgment, physiotherapists’ rating, fatigue questionnaire) were compared to those of the new instrument (FKS). Also, the effect of disease course or Expanded Disability Status Scale (EDSS) scores (Kurtzke, 1983) on FKS was investigated. Finally, we detected the differences between groups’ movement patterns as well as in their physical performance.

Assessment by the neurologist

The objective measure of motor fatigue was calibrated using a neurologist’s judgment of fatigue presence. As explained above the calibration is based on the most obvious fatiguing subjects being classified into the fatigue group and the clearly non-fatiguing members in the non-fatigue group. The judgment of the “critical cases”, those which are not clearly classifiable, cannot uniquely be rated by experts; FKS, however, gives definite results.

The neurologist sorted MS patients into two groups: patients with fatigue symptom and patients without fatigue symptom. Motor fatigue was assumed if the patient reported an abnormal rapid physical exhaustion in daily living and if a severe reduction in maximum gait distance could not be explained by the degree of paresis, spasticity or ataxia. The neurologist (C.D.) was not aware of the results of the walking test, which was used to establish the numerical base of the FKS calculation. The researcher (A.S.) performing the walking test did not have any knowledge of the neurologist’s assessment.

Video recordings

Videos of the subjects while walking were recorded and shown to experienced physiotherapists. The physiotherapists were given simultaneously recorded side and back views of the subjects. Two raters (employees of the rehabilitation clinic) who were unaware of the FKS analysis and the neurologist’s assessment rated the video recordings of the subjects while walking on the treadmill. For each participant, videos of the beginning and the end of the test were shown to the raters in random sequence. Raters were asked to assign the videos of each subject to the beginning or the end of the walking test.

Questionnaires

All patients completed questionnaires for assessing dimensions of subjective cognitive, motor and total fatigue (FSMC: the Fatigue Scale for Motor and Cognitive Functions (Penner et al., 2009)) and for measuring the degree of subclinical depression according to the Beck Depression Inventory II (BDI-II) (Hautzinger et al., 2008; Kühner et al., 2007). The healthy volunteers only completed the BDI-II.

Conventional gait analysis

Spatial parameters were calculated for each gait parameter and time interval for each subject using the three-dimensional coordinates of the infrared markers. The following gait parameters were assessed and compared between groups: step length, step width, step height, maximum circumduction with the right and left leg, maximum knee flexion angle of the right and left leg, and medio-lateral sway of the upper body.

Functional tests

Walking distance, walking velocity, lactate level, and heart rate as well as the degree of exertion on the Borg scale during the walking test were recorded. All subjects completed a 6-minute walk test (6MWT) (Laboratories, 2002). The 6MWT is safe, easy to administer, well-tolerated, and reflects the ability to perform activities of daily living (Paul & Enright, 2003). A reduced distance during the 6MWT indicates impairment and is often used in clinical practice (Paul & Enright, 2003).

Statistical methods

All statistical tests were performed using StatFree Version 7.0.2.3 (VietenDynamics, University of Konstanz, Germany) and Stata Version 11.0 (StatCorp LP, College Station, Texas, USA). The null hypothesis for each analysis was rejected at $p<0.05$. Differences in parameters between groups and between time points were detected using analysis of variance (ANOVA). Bonferroni post hoc tests were used to detect significant differences between groups. Differences in FKS values between the three groups were identified using Student's t-tests for independent samples. Variations in non-normally distributed parameters between groups were detected using Kruskal-Wallis test with Mann-Whitney *U* test

as post hoc tests. For binary variables, we used the Cohen's Kappa test to measure agreement between raters. For categorical variables we used the χ^2-test. Pearson correlation coefficients were used to detect significant associations between the components of the FKS, the dimensions of fatigue questionnaires and the EDSS. Multiple regression analysis was used to detect the effect of disease course and EDSS scores on the FKS.

3.4 Results

Calibrating of the FKS

With the conventional method (neurologist rating) eleven patients with MS were categorized as not having fatigue. They together with the healthy subjects displayed an FKS-median of 0.9. The fatigue group, as identified conventionally, consisted of 29 MS patients having an FKS-median of 9.5. The largest non-overlapping quantiles were 46%, where the largest FKS value of the upper quantile (non-fatigue group) was 3.9 and the smallest value of the lower quantile (fatigue group) was 4.2. The nearest integer "4" was established as the boundary between non-fatigue and fatigue (Table 2).

Table 2 Classification of subjects into groups.

FKS	Classification	MS-F (*n*)	MS-NF (*n*)	Non-MS (*n*)
≤4	No fatigue		11	20
>4	Fatigue	29		

FKS the Fatigue index Kliniken Schmieder, *MS-F* patients with multiple sclerosis and fatigue symptom, *MS-NF* patients with multiple sclerosis and without fatigue symptom, *Non-MS* healthy persons, *n* number of subjects.

The FKS between 0 and 4 points represented the "normal range". Quantiles of 50% would have meant identical selections by the traditional method and by using FKS. Quantiles of 46% indicate wrong allocations, two cases as we found out. However, as detailed in the methodology, the boundary "4" between the non-fatigue and the fatigue group is not substantially influenced by up to 25% wrongly sorted subjects (mildly fatiguing subjects within the non-fatigue group and persons with walking constraints within the fatigue group). To test this we

deliberately shifted the four subjects with the highest FKS from the non-fatigue group into to fatigue group and four with the lowest FKS from the fatigue into the non-fatigue group. By using the same calculation procedure we obtained medians 0.9 and 8.8 respectively. Here the maximal non-overlapping quantiles were found at 35% with 3.9 as the largest FKS value in the non-fatigue selection and the smallest value of the lower quantile (fatigue group) as 4.2. This is the same result as before with exactly the same “nearest integer” as the boundary value between non-fatigue and fatigue in spite of the bigger number of wrongly sequenced subjects.

Benchmark test

All healthy subjects’ FKS were below the threshold of “4”, which discriminates between subjects without and with fatigue. The median FKS in healthy subjects was 0.7 (range, 0.3 to 3.9), *δM* ranged from 0.6 to 4.3 and *δD* from 0.3 to 1.5. All healthy subjects walked for 60 minutes and had maximum scores below 17 on the Borg scale.

Rearranging the MS patients using the FKS results

The MS-F group had a FKS range from 4.2 to 125, *δM* between 2.8 and 30.4, and *δD* between 0.9 and 4.1. The MS-NF group had a range of FKS from 0.5 to 3.4, *δM* between 1 and 3.6, and *δD* between 0.4 and 1.0. The FKS differed significantly between the MS-F and the MS-NF and Non-MS groups ($p<0.001$) as expected based on the definition of fatigue, but not between the MS-NF group and the Non-MS group ($p=0.69$). Patients with fatigue showed greater changes in movement pattern and variability during the test than patients without fatigue and healthy subjects (Figure 4).

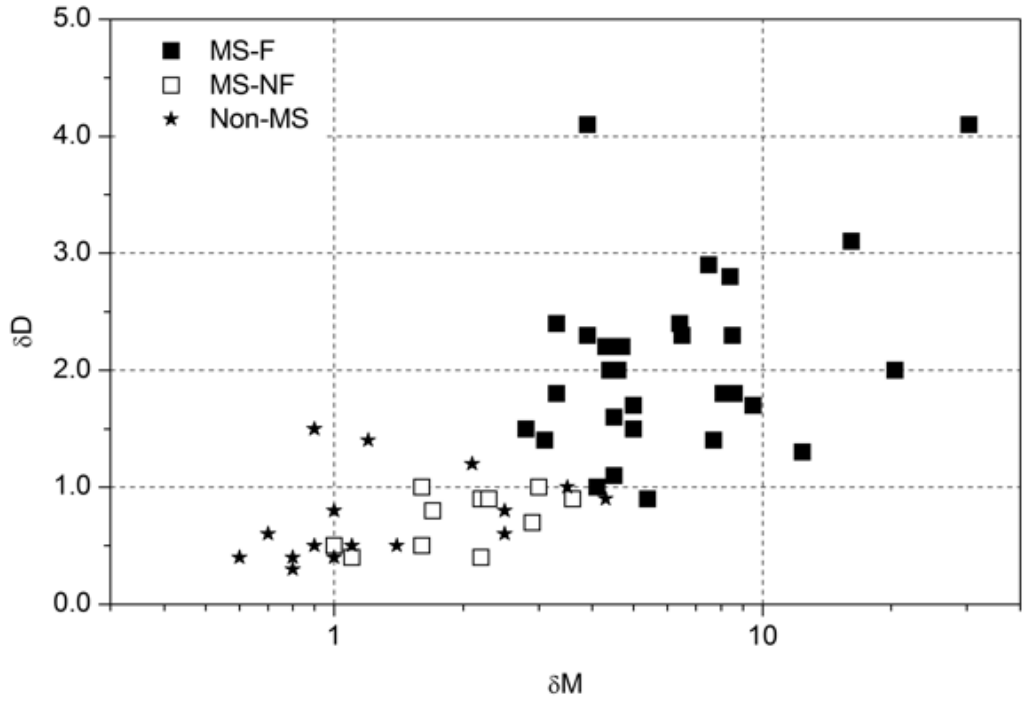

Figure 4 *δM* versus *δD* for all subjects. MS patients with fatigue, MS patients without fatigue and healthy subjects are clearly separated. A logarithmic scale was used for the *δM*-axis to account for the large differences in *δM* between and within groups.

Age, gender distribution, body height and weight did not differ between the MS-F and the MS-NF groups ($p>0.51$) (Table 3).

Table 3 Mean (1 standard deviation) characteristics of MS patients with fatigue (MS-F) and MS patients without fatigue (MS-NF).

Parameters	MS-F	MS-NF	*P* value
Sex (female/male)	19/10	8/3	n.s.
Age (years)	45.3 (7.0)	46.6 (7.6)	n.s.
Height (cm)	170.6 (10.3)	173.3 (11.9)	n.s.
Mass (kg)	72.5 (13.9)	78.0 (19.6)	n.s.
Disease duration (years)	12.3 (7.3)	6.7 (5.4)	0.03
EDSS	3.8 (1.2)	2.4 (1.1)	0.004
Disease course (n)			n.s.
RR	20	10	
PP	2	1	
SP	7	0	
FSMC motor dimension score	38.6 (8.1)	27.4 (10.0)	0.002
BDI-II (% of depression)	65.5	63.4	n.s.

MS multiple sclerosis, *EDSS* Expanded Disability Status Scale, *n* number of subjects, *RR* relapsing-remitting, *PP* primary progressive, *SP* secondary progressive, *FSMC* Fatigue Scale for Motor and Cognitive Functions, *BDI-II* Beck Depression-Inventory, *P value* probability value, *n.s.* not statistically significant.

Moreover, patients in both groups were similarly affected by depression and there was no significant difference in the course of the disease ($p>0.51$). However, the MS-F group had significantly longer disease duration and greater EDSS and FSMC scores than the MS-NF group ($p<0.03$).

Comparison of FKS results, assessment by the physician, and video analysis through physiotherapists

Classification of fatigue using the FKS and the neurologist's assessment was consistent for 97% (false positive of 3%) for the fatigue group; and 91% (false negative of 9%) for non-fatigue. One patient was classified into the fatigue

group by the neurologist but did have a FKS of 2.1, a clear indication of no fatigue. Another patient had a FKS of 11 – massively fatiguing – but was classified into the no fatigue group by the neurologist.

Both physiotherapists correctly classified 56 of 58 (97%) videos in the MS-F group. After the test, they reported that they could not see any difference in the two misclassified videos. For the non-fatiguing and healthy subjects the video-classification would simply show random results – having a 50% chance for correct classification. One physiotherapist classified 12 of 22 videos and the other physiotherapist 8 of 22 videos correctly for the MS-NF group. In the group of healthy subjects the physiotherapists correctly classified 26 of 40 and 34 of 40 videos, respectively.

We compared the results of the subjective assessment by physician and physiotherapists to the results of the objective measure FKS and found overall good agreement but faulty classifications as well. The accordance between the physician's assessment and FKS were good (Cohen's Kappa: k=0.88), between physiotherapists' assessment and FKS (Cohen's Kappa: k from 0.32 to 0.49) fair to moderate agreement.

FKS, EDSS and questionnaires

In the MS-F group, the FKS and *δM* did not correlate significantly with any dimensions of the FSMC or EDSS (range r, -0.05 to 0.20; p>0.13). *δD* correlated negatively with all dimensions of the FSMC (range r, -0.39 to -0.28; p<0.03) and positively with the EDSS (r=0.28; p<0.03). In the MS-NF group, the FKS and *δM* correlated negatively with all dimensions of the FSMC (range r, -0.67 to -0.57, p<0.006). *δD* correlated with the overall and motor dimensions of the FSMC (r=0.42; p<0.04) but not with the cognitive score of the FSMC (r=-0.39; p>0.07). None of the components of the FKS correlated with the EDSS (range r, -0.35 to 0.31; p>0.11).

Multiple linear regression analysis did not reveal significant relationships between disease course (p=0.40) and EDSS scores (p=0.11) and FKS (model: adjusted R^2=0.03, p=0.25). Correlations between EDSS and FKS for each disease group revealed an interaction effect: while there is a small correlation between the two measures in the group with relapsing-remitting disease course (r=0.33;

p<0.01), the correlation in the group with secondary progressive disease course is nearly zero (r=0.05; p=0.86).

Gait analysis

The MS-F group proved to be significantly different from the MS-NF and healthy groups in all gait parameters including step length, width and height, bilateral leg circumduction, bilateral knee flexion angle and medio-lateral trunk sway at t_1 and t_2 (p<0.001). Patients in the MS-F group had smaller step length, step height and maximum knee flexion angle on the right and left side and greater step width, circumduction with the right and left leg and sway than patients in the MS-NF group and healthy subjects.

Physical performance

The MS-NF and healthy subject groups walked significantly faster (p<0.001) and a longer distance (p<0.001) than the MS-F group (Table 4).

Table 4 Mean (1 standard deviation) gait and physiological parameters of the treadmill walking test for MS patients with fatigue (MS-F), MS patients without fatigue (MS-NF) and healthy subjects (Non-MS).

Parameters	MS-F	MS-NF	Non-MS	*P* value Kruskal-Wallis test	*P* value Post hoc test
Walking distance (km)	1.8 (1.2)	4.4 (1.2)	5.3 (0.3)	0.001	0.001* 0.001† 0.012‡
Walking speed (km/h)	0.81 (0.36)	4.7 (0.5)	5.0 (0.0)	0.001	0.001* 0.001† 0.001‡
6MWT (km)	0.49 (0.09)	0.56 (0.12)	0.68 (0.10)	0.001	0.008* 0.001† 0.011‡
Lactate (mmol/l)					
t_1	1.2 (0.5)	0.9 (0.6)	0.8 (0.6)	n.s.	
t_2	0.7 (0.5)	0.4 (0.5)	0.6 (0.6)	n.s.	
Heart rate (bpm)					
t_1	80.0 (11.3)	77.0 (10.4)	79.4 (20.7)	n.s.	
t_2	103.7 (18.2)	107.5 (12.8)	108.8 (20.8)	n.s.	
Borg scale	16.9 (0.4)	13.5 (4.0)	10.0 (2.5)	0.001	0.001* 0.001† 0.007‡

6MWT 6-minute walk test, *n.s.* not statistically significant, * significantly different between MS-F and MS-NF, † significantly different between MS-F and Non-MS, ‡ significantly different between MS-NF and Non-MS, *P-value* probability value.

The 6MWT differed significantly between the MS-F and the other groups ($p<0.008$). All participants used aerobic energy production during the walking test, and the lactate level decreased during the walking test in most cases. The heart rate remained well below age predicted maximal heart rate.

3.5 Discussion

We introduced the objective measure FKS for assessing motor fatigue in patients with MS. Healthy subjects typically do not display symptoms of fatigue during limited submaximal walking. Their walking pattern is stable and hence the attractor of the movement and its variability do not change substantially. We first calibrated our new method by taking the “medians” of the classically selected fatigue and non-fatigue groups and established the threshold value for discriminating fatigue from non-fatigue patients. Next we checked the results of our healthy subjects finding nobody classified wrongly. Finally, FKS was applied to establish fatigue and non-fatigue groups. There were moderate differences between the classification of fatigue using the FKS and the classification by the neurologist and two physiotherapists. We found FKS to be a more sensitive and reliable measure for motor fatigue in patients with MS compared to traditional methods. FKS is firmly based on the definition of “system stability”. For calibration it uses the “medians” of classically defined subject groups, a parameter largely insensitive to incorrect subject selection. Lactate levels below the lactate threshold in all patients and subjects suggest that motor fatigue is not related to muscle fatigue.

The classification into fatigue and non-fatigue groups using the FKS versus the classification by the neurologist disagreed for two patients. In one patient, the diagnosis of MS was very recent (primary progressive course of disease). She complained of paraesthesia in her right leg, reported that she got tired more easily than previously and described her walking distance as reduced. In the neurological exam, she had difficulty jumping on her right leg and a tendency to pronate her left arm during arm holding. In addition her motor FSMC was 27

(moderate motor fatigue). The treadmill test clearly showed that she had no motor fatigue (4.4 km in 60 minutes). Hence, this patient was likely misclassified by the traditional classification system suggesting FKS was superior to traditional assessment.

Another patient classified as not having fatigue by the neurologist showed a high FKS. This patient suffered from severe depression with apathy and sleep disorder making the additional clinical diagnosis of motor fatigue difficult. The pathological FKS, however, clearly demonstrated increased variability while walking indicating motor fatigue.

A recent study (Braley et al., 2012) has shown that reduced sleep efficiency on nocturnal polysomnographic findings correlate with fatigue, tiredness, and lack of energy in patients with MS. Labuz-Roszak et al. (Labuz-Roszak, Kubicka-Baczyk, Pierzchala, Machowska-Majchrzak, & Skrzypek, 2012) observed an association between fatigue and sleep disorders and between fatigue and either depression or anxiety, and stated that the treatable causes of fatigue in MS such as sleep and mood disturbances should be identified and treated. The results of our study clearly indicate the presence of additional motor fatigue besides the presence of sleep disorder and depression, which cannot be identified with certainty on clinical grounds without an objective measure of fatigue. These observations further confirm the importance of an objective measure for assessing motor fatigue in patients with MS.

None of the patients in our study reported absence of motor fatigue and were tested positive on the FKS. We would consider such cases rather rare. Nonetheless, we believe that a patient without subjective complaints of motor fatigue should not be treated for motor fatigue.

The results of the FKS largely agreed with the results of the video analysis. Both physiotherapists assigned videos of the beginning and end correctly for 97% of patients with fatigue. Such classification was almost impossible for healthy subjects or patients without fatigue. Even if this evaluation was very successful for these cases, this analysis is subjective and depends on many factors and in particular on the therapists' experience. These results further emphasize the value and the effectiveness of an objective measure of motor fatigue using FKS.

We consider the FKS superior compared to traditional methods because of its unambiguous approach and objectivity. Overall, the diagnosis of fatigue conducted by physicians or physiotherapists may be faster, but also more likely to give false results. Practical experience demonstrates that a precise diagnosis of fatigue and non-fatigue depends on the experience of the therapist and physician. It is possible that experienced neurologists and physiotherapists may be correct in their classification in most MS patients. However, some neurologists with no or little experience with MS patients may doubt the existence of fatigue and its organic cause; and thus may argue that fatigue just reflects the difficulty of the patient to cope with MS. In some cases, identifying motor fatigue may be very difficult even for an expert; especially if depression, sleep disturbances, adiposity and lack of exercise and endurance are also prevalent. In these cases, identifying different components of the patients' symptoms is very helpful for the therapist, neurologist and patient and is important for the "therapeutic alliance" or "therapeutic contract" between patient and therapist.

Our observations of differences in conventional gait patterns in the MS-F group compared to the MS-NF and healthy group are in agreement with literature. Previous studies (Kelleher, Spence, Solomonidis, & Apatsidis, 2010; Morris, Cantwell, Vowels, & Dodd, 2002; Remelius et al., 2012; Sosnoff, Sandroff, & Motl, 2012; Spain et al., 2012) have reported reduced gait speed, reduced stride length, step width and maximum knee extension as well as greater trunk angle range of motion in patients with MS compared with healthy subjects. However, the authors of these studies did not distinguish between patients with fatigue and those without fatigue, and there is no previous data on changes in gait patterns dependent on fatigue. In comparison, our novel classification method can attribute changes in gait patterns to the presence or absence of fatigue.

The overall and motor dimensions of self-rated fatigue questionnaires did not correlate with the FKS in the MS-F group. These findings are in agreement with earlier reports of no relation between changes in walking patterns and self-assessed fatigue (Morris et al., 2002). Morris et al. (Morris et al., 2002) suggested that mechanisms controlling locomotion differ from those regulating perceived fatigue. Perceived fatigue may not be associated with performance in conventional neuropsychological tests or motor function tasks (Geisler et al.,

1996; Krupp, 2003; C. E. Schwartz, Coulthard-Morris, & Zeng, 1996). Kluger et al. (Kluger et al., 2013) emphasized the importance of distinguishing between subjective sensation and objective changes of performance representing fatigability. In this context, the scientists used the term "fatigability" rather than “fatigue syndrome”. This is also in line with the current concept that fatigue has a state and trait component (Genova et al., 2013). Genova et al. (Genova et al., 2013) defined “state fatigue” as a transient condition that can fluctuate based on both external and internal factors and ”trait fatigue” as a more stable condition in an individual. According to this definition, the FSMC and other questionnaires might capture the trait component of fatigue; while the FKS represents the state component of fatigue after physical exertion. Our parameters allow statements regarding the changes in movement pattern and changes in movement variability after exhausting or prolonged walking. Hence, these values measure a patient’s current state of fatigue in contrast to the FSMC questionnaire, which presumably captures a patient’s general physical and mental condition. This indicates that the fatigue questionnaire and the FKS record two different features of fatigue.

We found no evidence of an effect of disease course or EDSS scores on FKS. The overall model fit was very low, indicating that FKS measures fatigue differently than other existing measures.

All participants in our study remained below the anaerobic threshold throughout the walking test and had only slight changes in heart rate between t_1 and t_2 suggesting that motor fatigue in MS is not related to muscle fatigue. In contrast, Sharma et al. (Sharma, Kent-Braun, Mynhier, Weiner, & Miller, 1995) reported that during exercise phosphocreatine and intracellular pH was greater in patients with MS than in controls. Simultaneously, during the exercise inorganic phosphate and monovalent inorganic phosphate increased more in patients with MS than in healthy persons. They suggested that metabolism plays a role in abnormal muscle fatigue in MS. The discrepancy between our results and those reported by Sharma et al. may be related to differences in EDSS scores in both cohorts (Sharma et al.: 5.1 (range, 2-8), 20 of 28 patients walked with a cane, walker or were wheelchair-bound; our study: 3.4 (range, 1-6.5), no walking aids) and to the use of intermittent tetanic stimulation of the peroneal nerve versus

walking exercise. The walking test in our study may better resemble daily activities while being standardized and reproducible.

In summary, we have developed an objective method for assessing motor fatigue on an individual basis using kinematic gait analysis – the FKS. It correctly classified patients with MS into fatigue and non-fatigue groups. This method represents a quick, cost-effective, and efficient method for objectively assessing motor fatigue. The FKS did not correlate with the results of the fatigue questionnaire and was not related to muscle fatigue. Perceived fatigue assessed using questionnaires and changes in performance, measured using gait analysis, appear to capture two different features of fatigue in multiple sclerosis. In most patients, neurologists can detect the obvious fatigue syndrome in patients with MS using “classic” instruments. However, in some patients, the diagnosis of the fatigue syndrome is less definite, requiring a more comprehensive analysis. The FKS may be particularly useful for diagnosing fatigue in MS patients with comorbidity such as depression, sleep disturbances, low cardiovascular fitness, and for evaluating intervention programs.

3.6 Study Limitations

The main limiting factor in this study was that only one neurologist performed the classical fatigue assessment. Future studies should consider simultaneous assessments by many specialists. The physiotherapists should be given a slightly different task. Instead of rating the sequence in which the walking tests were performed, they should answer the question: “In which subject do you spot motor fatigue and in which do you not”. In our study, we focused on patients with an EDSS between 1 and 6.5 (3 indicating the border between light and moderate disability) who were able to walk on a treadmill. Hence, the applicability and validity of our method using the FKS in other groups of MS patients is unknown, particularly for those with a more severely compromised walking distance. For instance, we did not assess the quality of sleep using the Epworth Sleepiness Scale, which might be relevant for assessing fatigue in patients with MS.

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Conflict of interest

The authors declare no conflicts of interest with respect to the authorship and/or publication of this article.

Ethical standards

The study was approved by the local ethics committee and conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent prior to their participation.

4 STUDIE 3: Difference in motor fatigue between patients with stroke and patients with multiple sclerosis: a pilot study

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4.1 Abstract

Fatigue is often reported in stroke patients. However, it is still unclear if fatigue in stroke patients is more prominent, more frequent or more “typical” than in patients with multiple sclerosis (MS) and if the pathophysiology differs between these two populations. The purpose of this study was to compare motor fatigue and fatigue-induced changes in kinematic gait parameters between stroke patients, MS patients, and healthy persons. Gait parameters at the beginning and end of a treadmill walking test were assessed in 10 stroke patients, 40 MS patients, and 20 healthy subjects. The recently developed Fatigue index Kliniken Schmieder (FKS) based on change of the movement’s attractor and its variability was used to measure motor fatigue. Six stroke patients had a pathological FKS. The FKS (indicating the level of motor fatigue) in stroke patients was similar compared to MS patients. Stroke patients had smaller step length, step height and greater step width, circumduction with the right and left leg, and greater sway compared to the other groups at the beginning and at the end of test. A severe walking impairment in stroke patients does not necessarily cause a pathological FKS indicating motor fatigue. Moreover, the FKS can be used as

a measure of motor fatigue in stroke and MS and may also be applicable to other diseases.

4.2 Introduction

Fatigue is a frequent symptom in many neurologic diseases (Kluger et al., 2013) and especially common and disabling in patients with multiple sclerosis (MS) (Fisk et al., 1994; Romani et al., 2004). Moreover, fatigue is often the reason for early retirement and hence represents a high economic burden (Simmons et al., 2010). Despite the high prevalence of fatigue in MS of up to 83% (Kluger et al., 2013), its pathophysiology is largely unknown (Kos et al., 2008; Mills & Young, 2008). Nonetheless, several pathophysiological pathways have been proposed: demyelinisation and axonal injury may cause “electric failure” (Bakshi, 2003); immunological and inflammatory factors such as cytokines may hamper neuronal processing (Heesen et al., 2006); hormonal dysregulation may be caused by failed cortico-hypothalamic loops (Téllez et al., 2008); and reorganization and compensation might add to the ineffectiveness of cerebral control and cause fatigue (Liepert et al., 2005). Moreover, fatigue may be secondary to conditions including depression, sleep disorders, physical deconditioning, anemia, or side effects of medication (Braley et al., 2012; Labuz-Roszak et al., 2012; Romani et al., 2004).

In the last decade, reports of fatigue in neurological conditions other than MS, such as for instance stroke, have become more frequent (Lerdal et al., 2009; Naess et al., 2012), and the prevalence of fatigue in patients after stroke ranges from 36 to 77% (Kluger et al., 2013). Fatigue is a common and debilitating symptom even in patients with good recovery after stroke (Zedlitz, van Eijk, Kessels, Geurts, & Fasotti, 2012). Patients’ level of fatigue does not change over time (Lerdal et al., 2012) and baseline fatigue immediately after a stroke predicts fatigue outcome (Snaphaan, van der Werf, & de Leeuw, 2011). Staub and Bogousslavsky (Staub & Bogousslavsky, 2001b) suspected that primary poststroke fatigue may be caused by minor attentional deficits due to the interruption of neural networks, such as the reticular activating system. Patients use different strategies and coping styles to deal with poststroke fatigue (Kirkevold, Christensen, Andersen, Johansen, & Harder, 2012). In addition, poststroke fa-

tigue appears to be an independent determinant of not being able to resume paid work following stroke (Andersen et al., 2012).

Currently, there are no widely accepted standard definitions or accepted standardized methods and instruments for assessing fatigue (Kluger et al., 2013). Moreover, fatigue is understood as a multidimensional phenomenon with different aspects including a complex interplay between the underlying disease process, peripheral, and central control systems, as well as environmental factors (Chaudhuri & Behan, 2004). Its multidimensionality complicates the assessment of fatigue in neurological disorders. Kluger et al. (Kluger et al., 2013) proposed a new taxonomy for fatigue in neurologic diseases and suggested differentiating between fatigue as subjective sensation and fatigability as an objective change in performances. Here, we distinguish between cognitive and motor components, which can occur in isolation or in combination. Commonly, the subjective perception of fatigue is assessed using questionnaires (Braley & Chervin, 2010), and the measurement properties of fatigue questionnaires in MS have previously been evaluated (Elbers et al., 2012). The most frequently used instruments for measuring fatigue in MS patients are the Fatigue Severity Scale (FSS) (Krupp et al., 1989), the Fatigue Assessment Instrument (FAI) (J. E. Schwartz et al., 1993), the Fatigue Impact Scale (FIS) (Fisk et al., 1994), the Modified Fatigue Impact Scale (MFIS) (Guidelines, 1998), the Fatigue Scale for Motor and Cognitive Functions (FSMC) (Penner et al., 2009), and the Würzburg Fatigue Inventory in Multiple Sclerosis (WEIMuS) (Flachenecker et al., 2006). Despite the reported prevalence of fatigue in MS and stroke, few studies used the same tools for assessing fatigue in these two conditions (compare also Lukoschek et al., in this special issue) (Elbers et al., 2012). Moreover, in contrast to MS, there are no fatigue questionnaires that have been developed specifically for measuring fatigue after stroke (Acciarresi et al., 2014). Often, the following instruments are used: the FSS (Krupp et al., 1989), the Short-form 36/12 vitality questions (Fink et al., 2010), the Fatigue Assessment Scale (FAS) (Michielsen, De Vries, & Van Heck, 2003), and the Multidimensional Fatigue Symptom Inventory (MFSI) (Lerdal et al., 2009; Smets, Garssen, Bonke, & De Haes, 1995). Overall, fatigue may be assessed quickly using fatigue questionnaires. However, these questionnaires are based on patients' self-assessments and may be distorted (overestimation or underestimation) due to an inaccurate self-

perception (Sehle, Vieten, Sailer, Mundermann, & Dettmers, 2014). Moreover, fatigue questionnaires capture patients' general condition during a particular time period (Sehle et al., 2014) and fatigue may also be quickly clinically assessed by physicians or physiotherapists. However, clinical experience suggests that an accurate identification of fatigue and non-fatigue depends on the experience of the therapists and physicians, and in some cases a clear diagnosis of fatigue is difficult. Especially, comorbidities (depression, sleep disorders, physical deconditioning, anemia, or side effects of medication) may cause similar symptoms (Sehle et al., 2014). In these cases, the objective instrument can be extremely helpful for measuring fatigue. A correct diagnosis of fatigue is not only important to define optimal treatment but also when it is used as criterion for early retirement.

In the current study, we focused on the motor dimension of fatigability (here, we used the term motor fatigue as a synonym) in stroke and MS patients. The motor dimension of fatigability has previously been assessed in lower limbs using dynamometry in isometric contractions, sustained maximal contractions, repetitive maximal contractions, and walking as far as 500 m (Schwid et al., 1999; Surakka et al., 2004) and in upper limbs using static and dynamic contraction tests (Greim et al., 2007; Iriarte & de Castro, 1998; Severijns et al., 2014) in MS patients. Hence, overall maximal force appeared to decrease either during repeated maximal contraction or during sustained contraction in MS patients. Furthermore, Severijns et al. (Severijns et al., 2014) observed differences in sustained maximal hand grip contraction but not in dynamic contraction between healthy subjects and MS patients with high EDSS (≥6) (Severijns et al., 2014). Schwid et al. (Schwid et al., 1999) proposed that motor fatigue can be measured as a decline in strength during sustained muscle contractions (Schwid et al., 1999). Similarly, Greim et al. (Greim et al., 2007) proposed that decreases in strength of maximal repetitive muscle contraction and/or decrease of walking speed can be used to measure motor fatigue objectively (Greim et al., 2007). Poststroke motor fatigue has previously been assessed in a few studies in upper and lower limbs using transcranial magnetic stimulation, dynamometry, and/or electromyography during the maximal voluntary contraction (MVC), sustained isometric contraction, submaximal contraction, and repetitive eccentric–concentric contraction (Hu et al., 2006; Knorr et al., 2011; Svantesson et al.,

1999). Knorr et al. (Knorr et al., 2011) showed that during fatigue the silent period duration increased significantly in both upper limbs, whereas the motor evoked potential amplitude significantly increased only in the non-paretic limb (Knorr et al., 2011). After fatigue, the reductions in the M wave, twitch peak torque, and MVC peak torque were observed in both limbs. Furthermore, the reduction in voluntary activation was greater in the paretic than in the non-paretic limb (Knorr et al., 2011). Another study concluded that a reduction in work in high-intensity dynamic muscle activity may not be associated with a reduction in mean power frequency (Svantesson et al., 1999). Hu et al. (Hu et al., 2006) suggested that for identifying fatigue associated with neuromuscular transmission failure, the motor unit firing parameters firing rate, minimum interpulse interval, and maximum oscillation were more sensitive than the mean power frequency (Hu et al., 2006).

We recently developed the Fatigue index Kliniken Schmieder (FKS) as an objective tool for assessing motor fatigue in MS based on gait changes in a walking test on the treadmill (Sehle et al., 2014). In this study, the subjects walked on a treadmill under different conditions: in a normal rested state and in an exhausted state or after 60-min walking. We measured the changes in acceleration patterns and acceleration variability of the feet during the walking test at the beginning and at the end of the walking test in MS patients and healthy subjects. Furthermore, in this study, we developed the FKS that is composed of these two components and which makes the distinction between fatigue and non-fatigue. The FKS described the changes in acceleration patterns and acceleration variability during the walking test on the individual level. The advantage of a walking test is that the entire musculature, especially the major muscle groups are required. This task is daily task-oriented and represents a complex movement with many degrees of freedom. In contrast to fatigue questionnaires, this test captures the current state of motor fatigue.

To date, it is still unclear if fatigue is specific to MS or at least to inflammatory disease or if it is an unspecific reaction of the brain after any kind of brain injury (Kluger et al., 2013). The inflammatory etiology is supported by the fact that other inflammatory diseases such as sarcoidosis or cerebral vasculitis can be accompanied by serious fatigue. In stroke, fatigue may be related to reorganization or inefficient/suboptimal fiber tract connections or compensatory effort. Alt-

hough we were not able to investigate different pathophysiological mechanisms directly by surrogate markers such as cytokines or tumor necrosis factor alpha or by different cerebral activation patterns, the intention of our study was to compare motor fatigue in patients with stroke and MS. This should facilitate better understanding limitations and needs of patients and more accurately define their goals for instance in rehabilitation. Therefore, the aim of our study was to investigate if the amount of change of the gait pattern during an exhausting physical task differs between stroke and MS patients. After propagating the test for identifying motor fatigue in MS (Sehle et al., 2014), this investigation also should clarify if this test and the FKS are feasible for stroke patients and that a severe walking impairment in stroke patients does not necessarily cause a pathological FKS. Data of patients after stroke were collected and compared with previously published data (Sehle et al., 2014) on 40 patients with MS and 20 healthy subjects.

4.3 Materials and methods

Subjects

Ten patients who were admitted to a neurological rehabilitation clinic after stroke, met the inclusion criteria, and volunteered to participate between March and October 2012 were included in this study. Inclusion criteria were central hemiparesis affecting the leg, reduced walking capacity, and the ability to walk on a treadmill without aids or assistance. All stroke patients were chronic (time since the onset of stroke > 12 months). Hemiparesis was left sided in four patients and right sided in six patients. Eight patients had a proportional hemiparesis affecting arm and leg, and two patients were more affected in their legs. Three patients had a haemorrhagic infarction and seven patients an ischemic infarction. One infarct was located in the brainstem, one in the anterior cerebral artery (ACA), and eight in the middle cerebral artery (MCA). Two MCA infarcts showed additional involvement of the ACA.

Data from our previous study (Sehle et al., 2014) involving 20 healthy subjects and 40 patients with definite MS according to the McDonald criteria (McDonald et al., 2001) were used in this study. MS patients and control subjects were recruited between October 2011 and July 2012. The MS patients were admitted to a neurological rehabilitation clinic. Inclusion criterion for MS patients was the

ability to walk on a treadmill without aids or assistance. There were no limitations regarding the disease course and disability levels. Subjects were excluded from the study if they had relapses within the preceding three months or received Fampyra® (Fampridin; Biogen Idec Inc., 225 Binney Street, Cambridge, MA 02142). Healthy subjects were recruited from the local population and from clinic staff. Healthy subjects were excluded if they had any neurological or orthopedic disorders. In the previous study, the MS patients were classified into two groups based on the FKS: patients with a FKS > 4 were categorized as having motor fatigue (MS-F), and patients with a FKS ≤ 4 were categorized as having no motor fatigue (MS-NF). According to these criteria, 29 MS patients were in the fatigue group and 11 MS patients in the non-fatigue group.

All participants provided informed written consent prior to participation. The study protocol was approved by the University Ethics Committee and conducted in accordance with the Declaration of Helsinki.

Questionnaires

At admission to the study, all subjects answered the Beck Depression Inventory II (BDI-II) to assess the level of subclinical depression (Kühner et al., 2007). Self-reported physical function was assessed by patients using the physical functioning 10 subscale of the Short-form 36 (PF-10; SF-36) and four vitality questions of the SF-36 (Bullinger et al., 2003; Mead et al., 2011). Vitality questions from the SF-36 have previously been suggested as measures of fatigue (Fennessy et al., 2010). These two assessments allowed for comparison of physical impairments and complaints about fatigue between groups.

Experimental procedure

An exercise task and a functional test were carried out on two different days for each stroke patient. The exercise task included a walking test on a treadmill: patients walked either until they felt physically exhausted [17 – very hard, on the Borg scale (Borg, 1982)]; or for up to 60 min at 10% above their preferred speed or a maximum speed of 5 km/h on a level treadmill. The preferred walking speed was determined at an initial exam where each subject walked on the treadmill to familiarize them with the set-up. An important criterion was that the subjects were able to walk on a treadmill without aids or assistance. The walk-

ing speed was limited to a maximum of 5 km/h so that subjects stayed within a comfortable walking speed (Bohannon, 1997). The treadmill speed was kept constant throughout the test. The participants were repeatedly asked to rate their exhaustion on a Borg scale. The walking test was stopped 1 min after the patient reached 17 on the Borg scale or after 60-min walking on the treadmill. Kinematic gait data were measured for 1 min at the beginning of the walking test (t_1) and for 1 min after reaching 17 on the Borg scale or for the final minute of 60 min (t_2).

The functional test consisted of a 6-min walk test (6MWT) (Laboratories, 2002). The 6MWT is often used in clinical practice and has been frequently used for measuring the response to therapeutic interventions in various diseases. Heart rate was measured prior to and at the end of the walking test, and lactate concentration was measured prior to and immediately after walking. We used the 4 mmol/L lactate threshold originally described by Mader et al. (Mader et al., 1976).

Technical equipment

The AS200 system (80 Hz; LUKOtronic, Lutz Mechatronic Technology e.U., Innsbruck, Austria) was used to record the gait data. This system consists of a three line-scanning camera system and 10 active markers attached bilaterally to the subjects' body: centered on the margo medialis; the highest point of the ilium; the posterior aspect of the knee; on the shoes on top of the calcaneus and on the rod attached at the level of the ankle.

Videos were recorded with a HD digital camera synchronized with the motion analysis system (Exilim EX-F1, digital camera, Casio Computer Co. Ltd., Tokyo, Japan). Heart rate was captured using a chest strap and a gage (Garmin Forerunner 305, Garmin Ltd., KS, USA). Lactate levels in the blood were detected using a lactate analyzer and lactate strips (Arkray Lactate Pro LT-17810, Kyoto, Japan).

Calculation of the Fatigue index Kliniken Schmieder

For each stroke patient, the change in the movement pattern described by the attractor (δM) and change in movement variability (δD) of the acceleration of the feet between t_1 and t_2 were calculated (Figures 1 and 2A,B).

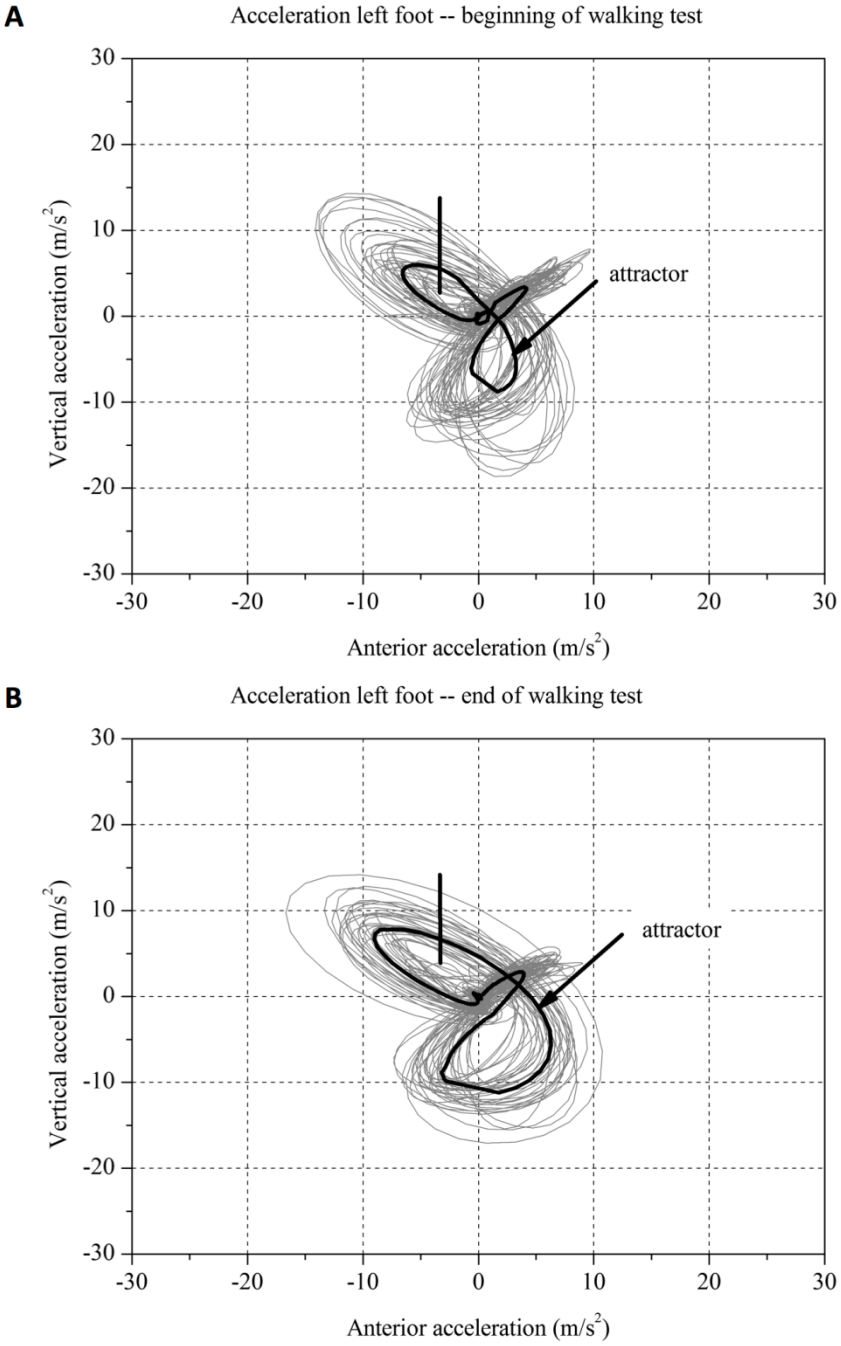

Figure 1 Two-dimensional graph of the acceleration data of a subject's left foot for one minute (A) at the beginning and (B) at the end of the walking test for one stroke patient with fatigue.

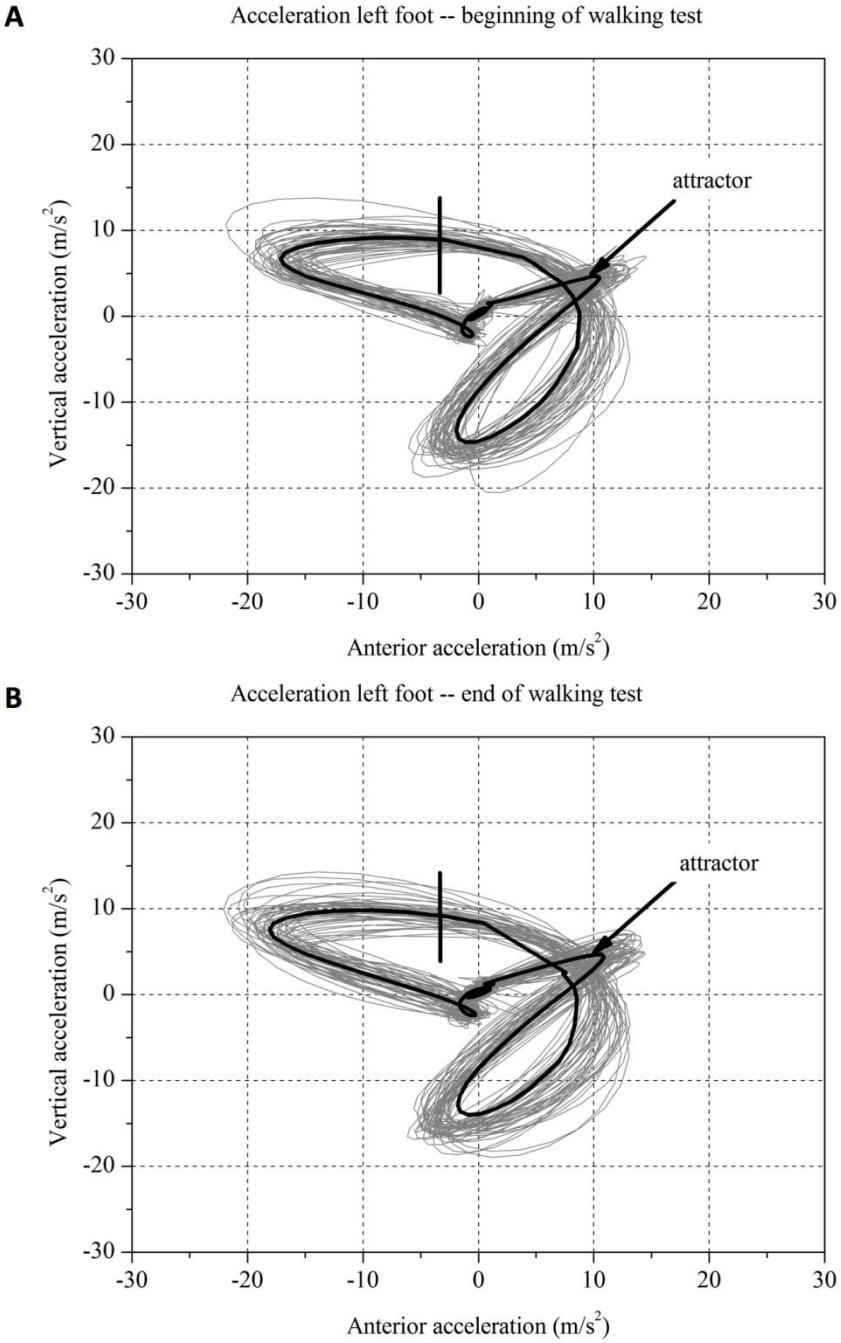

Figure 2 Two-dimensional graph of the acceleration data of a subject's left foot for one minute (A) at the beginning and (B) at the end of the walking test for one stroke patient without fatigue.

This new method has recently been described in detail by Vieten et al. (Vieten et al., 2013) and used to detect motor fatigue in patients with MS (Sehle et al., 2014). The changes in movement acceleration patterns and variability were used as indicators of motor fatigue. It is well known that human walking in the

absence of disturbances is characterized by a stable movement pattern and consistent movement control. We kept the walking situation unchanged throughout the walking test, and hence changes in attractor and movement variability indicated an alteration of the gait mechanism, which by ruling out other reasons, we identified as acute motor fatigue. The calculation of FKS was based on both feet. The FKS was defined as the changes in *δM* and *δD* between the beginning and the end of walking (Vieten et al., 2013) and represented as

$$\delta F = \delta M \cdot \delta D \quad (1)$$

The FKS was calculated for each stroke patient. These patients were then classified according to the FKS in a fatigue and non-fatigue group. This method allows analyzing fatigue on the individual patient level and on the group level. Based on FKS, stroke patients with FKS ≤ 4 were identified as having no motor fatigue (stroke-NF) and stroke patients with FKS > 4 were identified as having motor fatigue (stroke-F). The FKS cut-off of 4 was calculated in our previous study in the following order: first, using the group medians calculated using traditional methods (neurologist rating) to find the threshold between normal and fatigue (Sehle et al., 2014). Second, the FKS of healthy individuals was used as a benchmark test. Third, all subjects were classified according to the FKS values into the fatigue and the non-fatigue groups.

Conventional gait analysis

Spatial parameters were calculated: step length, step width, step height, maximum circumduction of the right and left leg, and medio-lateral sway of the upper body were calculated using three-dimensional co-ordinates of the active markers. This analysis allowed comparisons between different groups on the group level.

Evaluation of the video recordings

The subjects' movement patterns were recorded on videos captured during t_1 and t_2 from the side and from the back. Videos were evaluated by two experienced physiotherapists from the rehabilitation clinic. The order of the videos was randomized, and thus the physiotherapists did not know which video had been captured at the beginning and which at the end of walking test when at-

tempting to correctly assign the videos to the corresponding time period. The physiotherapists did not evaluate the details regarding the modality of movement.

Statistical analysis

Data of stroke patients were compared to those of MS patients and healthy control subjects (Sehle et al., 2014). All statistical tests were performed using StatFree Version 8.0.0.9 (VietenDynamics, University of Konstanz, Germany) and Stata Version 11.0 (StatCorp LP, College Station, TX, USA). Differences in non-normally distributed parameters between groups were detected using Kruskal–Wallis test with Mann–Whitney U test as post hoc tests. For categorical variables, we used the χ^2-test. Pearson correlation coefficients were used to detect significant associations between the changes in the movement pattern and changes in movement variability as well as between FKS and the results of BDI-II. The significance level for all statistical tests was set a priori to .05.

4.4 Results

Differences between stroke patients, MS patients, and healthy subjects

Table 1 presents descriptive characteristics for stroke patients, MS, and healthy subjects.

Table 1 Mean (1 standard deviation) characteristics of participants.

Characteristic	Stroke	MS	Healthy subjects	*p*-value
Sex male/female	7/3	13/27	9/11	0.03[a]
Age	51.6 (8.3)	45.9 (7.0)	43.1 (8.6)	0.03[a]
				0.01[b]
Height (cm)	177.2 (7.7)	171.4 (10.7)	173.4 (8.4)	0.04[a]
Mass (kg)	84.5 (16.5)	74.1 (15.6)	80.4 (21.3)	0.04[a]
SF-36, PF-10	16.3 (4.8)	21.0 (4.3)	Not collected	0.04[a]
SF-36, vitality	15.8 (2.2)	11.1 (3.5)	Not collected	0.02[a]
BDI-II (% of patients with depression)	20.0	65	15.0	0.02[a]
EDSS	Not applicable	3.4 (1.3)	Not applicable	
Disease duration (years)	8.3 (7.9)	10.8 (7.2)	not applicable	

MS, MS patients; SF-36, PF-10, ten items of the physical functioning (ranging from 10 to 30, where low values indicate strong impairment, high values low impairment); SF-36, vitality scale, four items each ranging from 1 (low vitality/high fatigue) and to six (high vitality/low fatigue); BDI-II, Beck Depression Inventory II; EDSS, Extended Disability Status Scale ranging from 0 (no symptoms) to 10 (death through MS).

[a]significantly different between stroke and MS.

[b]significantly different between stroke and healthy subjects. Only the significant differences are indicated.

Significant differences between stroke and MS patients were found for sex, age, height, and mass. Furthermore, the PF-10 and vitality score of the SF-36 differed significantly between the stroke and MS groups with a higher physical im-

pairment and higher vitality level in stroke patients ($p<0.04$ and $p<0.02$, respectively). In contrast, no significant differences were detected between stroke patients and healthy subjects with the exception of age.

Based on the BDI-II questionnaire, one patient was affected by minimal depression and one patient was affected by slight depression in the stroke group. All other patients with stroke were not affected by depression. Moreover, 65% of MS patients and 15% of healthy subjects were affected by depression.

Physical performance in stroke patients compared with MS patients and healthy subjects

Table 2 shows the physical performance in three groups.

Table 2 Mean (1 standard deviation) gait and physiological parameters of the walking test**.**

Parameters	Stroke	MS	Healthy subjects	*p*-value Kruskal-Wallis test	*p*-value Post hoc test
Walking distance (km)	1.9 (0.9)	2.5 (1.6)	5.3 (0.3)	.001	.001[b]
Walking speed (km/h)	2.2 (0.8)	3.4 (1.4)	5.0 (0.0)	.001	.01[a] .001[b]
6MWT (km)	0.30 (0.11)	0.51 (0.10)	0.68 (0.10)	.001	.001[a] .001[b]
Lactate (mmol/L)					
t_1	0.7 (0.6)	1.1 (0.6)	0.8 (0.6)	.04	.02[a]
t_2	0.2 (0.4)	0.6 (0.5)	0.6 (0.6)		
Heart rate (bpm)					
t_1	70.0 (10.8)	79.2 (11.0)	79.4 (20.7)		
t_2	99.9 (13.2)	104.8 (16.8)	108.8 (20.8)		
Borg scale	14.0 (1.7)	16.0 (2.6)	10.0 (2.5)	.001	.001[a] .001[b]

Stroke, stroke patients; MS, MS patients; 6MWT, 6-minute walk test
[a]significantly different between stroke and MS, [b]significantly different between stroke and healthy subjects.

The stroke patients walked significantly slower than the healthy subjects ($p<0.001$) and a shorter distance than MS patients and healthy persons ($p<0.01$) in the walking test on the treadmill. Walking distance ranged from 1.0 to 3.4 km and walking speed ranged from 1.0 to 3.3 km/h in stroke patients. In MS patients, walking distance ranged from 0.2 to 5.6 km and walking speed ranged from 0.9 to 5.0 km/h. In healthy subjects, walking distance ranged from

5.0 to 6.0 km and walking speed was 5 km/h. The stated speed refers to the speed with which subjects walked on the treadmill after the familiarization phase and in which all data were collected. Some subjects walked slower in the familiarization phase and then they increased their speed. The important criterion was that the subjects do not walk over 60 min in the test. In the 6MWT, stroke patients walked a significantly shorter distance than the other groups ($p<0.001$).

All subjects remained below the aerobic-anaerobic threshold (lactate concentration below 4 mmol/L) during the walking test and had a heart rate below the maximal heart rate. At the end of the test, the level of exertion on the Borg scale was significantly lower in stroke patients than in MS patients ($p<0.001$). In contrast, stroke patients had greater levels of exertion than healthy subjects ($p<0.001$).

Conventional gait analysis in stroke patients compared with MS patients and healthy subjects

Significant group differences in gait parameters were observed at t_1 and at t_2 ($p<0.001$). The results of the post hoc tests revealed that stroke patients had shorter step lengths and greater step widths than the other groups both at t_1 and t_2 ($p<0.001$). Furthermore, the stroke patients had lower step height than the MS patients and healthy persons at t_1 and t_2 ($p<0.001$). Circumduction with the right and left legs as well as the sway were significantly greater in the stroke group than in the other groups at t_1 and t_2 ($p<0.009$).

Video analysis

One physiotherapist correctly classified 6 of 20 (30%) and the other physiotherapist 8 of 20 (40%) videos of stroke patients indicating that they were correct just by chance and did not recognize increasing gait abnormality at the end compared to the beginning of the walking test. In contrast, the physiotherapists classified most of the videos correctly in the MS group 68 of 80 (85%) and 64 of 80 (80%), respectively. In healthy subjects, the physiotherapists properly classified 26 of 40 (65%) and 34 of 40 (85%) videos, respectively.

Fatigue index Kliniken Schmieder comparison between groups

Based on the FKS scores, six stroke patients were classified into the fatigue group (stroke-F) and four patients into the non-fatigue group (stroke-NF). The FKS in the stroke-F group ranged from 5.3 to 15.3 (*δM*: 4.1–9.3; *δD*: 1.1–1.9) and in the stroke-NF group from 2.2 to 3.2 (*δM*: 1.8–3.6; *δD*: 0.6–1.4). The FKS in the MS-F group ranged from 4.2 to 125 (*δM*: 2.8–30.4; *δD*: 0.9–4.1) and in the MS-NF group from 0.5 to 3.4 (*δM*: 1.0–3.6; *δD*: 0.4–1.0). The FKS in the healthy subjects ranged from 0.3 to 3.9 (*δM*: 0.6–4.3; *δD*: 0.3–1.5) (Figure 3).

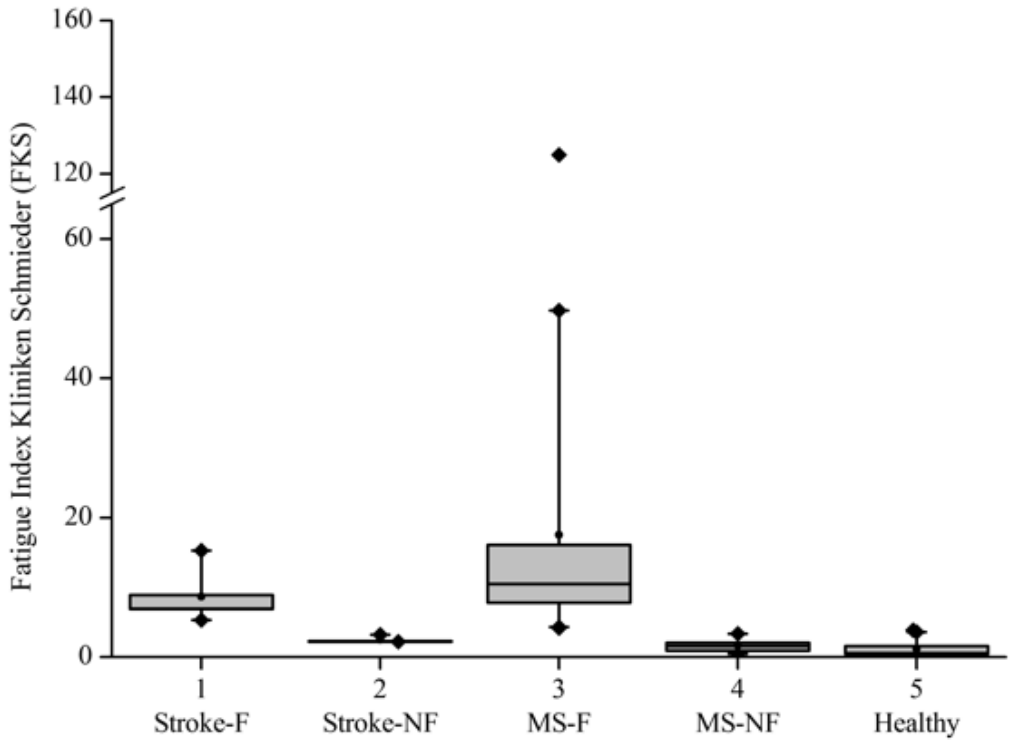

Figure 3 Boxplot for FKS values in all groups.

The FKS differed significantly between stroke patients and healthy persons ($p<0.001$) but not between stroke and MS patients ($p=0.44$). In the subgroups, the FKS differed significantly between the stroke-F and the stroke-NF, MS-NF, and healthy groups ($p<0.01$). Mean FKS in the stroke-F group was smaller than that in the MS-F group, but this difference did not reach statistical significance (8.7 versus 17.5;$p=0.18$). In all groups, subjects with greater changes in move-

ment patterns also showed greater changes in movement variability (r=0.66, p<0.001) (Figure 4).

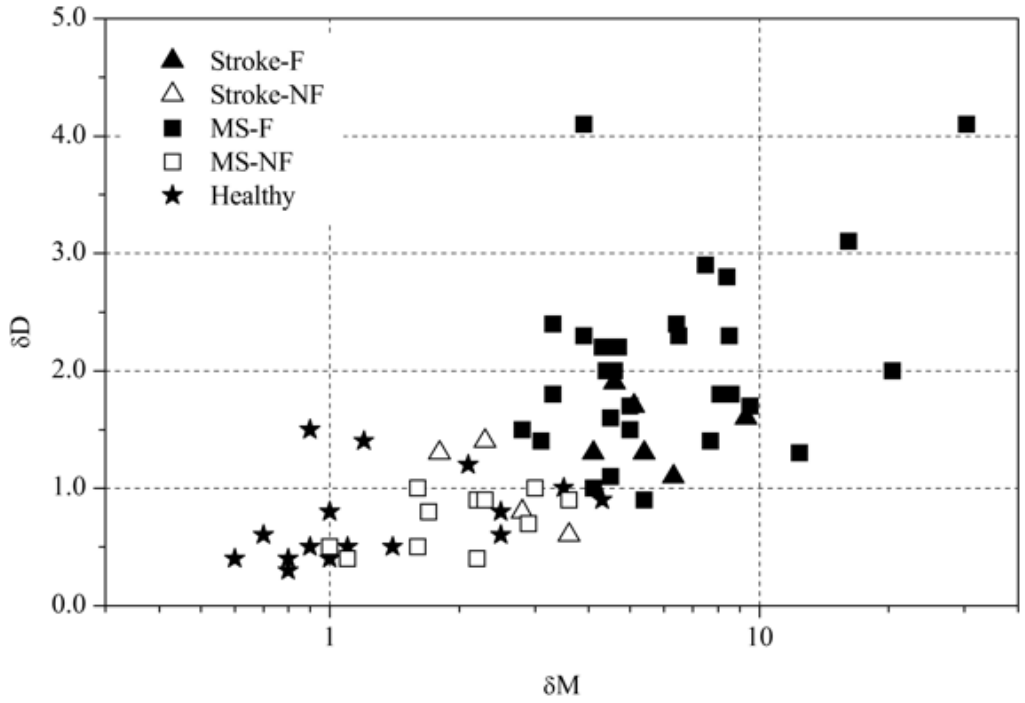

Figure 4 Scatterplot between changes in movement pattern and movement variability**.**

The differences in changes in movement patterns and changes in movement variability between groups corresponded to the differences in FKS between groups. Furthermore, FKS did not correlate significantly with the results of BDI-II (r=0.27, p<0.09).

4.5 Discussion

The purpose of this study was to compare motor fatigue in stroke and MS patients by analyzing changes in movement patterns and their variability. In this pilot study, we observed no significant difference in FKS values between stroke and MS patients as well as in their subgroups: between stroke patients with fatigue symptom and MS patients with fatigue symptom. Hence, fatigue induced similar changes in the movement patterns and variability in both patient groups.

Furthermore, the results of our study showed that the FKS can also be used in stroke patients for objectively measuring motor fatigue.

We intended to verify that severe walking impairment in stroke patients does not cause a pathological FKS. During the walking test on the treadmill, stroke patients rated their fatigue on the Borg scale significantly lower than the MS patients. Interestingly, despite lower perception of fatigue on the Borg scale, the stroke patients had greater physical impairment. All stroke patients had a hemiparesis affecting the leg. A higher level of impairment was observed using kinematic gait analysis, PF-10 of SF-36, and physical performance. Using conventional kinematic gait analysis of a few single stride cycles, we observed very clear differences in all gait parameters between the stroke patients and the other groups at t_1 and t_2. Generally, the stroke patients showed smaller step length, step height and greater step width, circumduction with the right and left leg, and greater sway compared to MS patients and healthy subjects. These results are in agreement with other studies (Chen, Patten, Kothari, & Zajac, 2005; Olney & Richards, 1996). The reduced step length and greater step width in stroke patients indicate an unsteady gait and the attempt to improve their stability to avoid falling while walking. The altered gait pattern already present at the beginning of the walking test on the treadmill, compared to the other groups, is presumably caused by the hemiparesis in this patient group. The reduction of walking speed and walking distance in stroke patients compared to the other groups as measured in our study are well established (Olney & Richards, 1996; Sosnoff et al., 2012).

Although stroke patients had higher physical impairment on PF-10 of SF-36 than MS patients, they showed greater vitality scores on the SF-36 than MS patients. These results point toward a conceptual and pathophysiological difference between impairment and fatigue. While it can be disputed whether or not fatigue should be rated as impairment, the neurological exam or the PF-10 of SF-36 do not assess fatigue.

The origin of peripheral or muscle fatigue is outside the central nervous system (CNS). For example, the peripheral fatigue can be caused by an increased blood lactate accumulation and hydrogen ions, accumulation of ammonia, loss of water, an accumulation of Pi (inorganic phosphate), and an accumulation of

H+ ions in the sarcoplasm (Ament & Verkerke, 2009). There are several objective methods for measuring peripheral fatigue. Among others, muscle fatigue can be detected using surface electromyography (sEMG) and mechanomyography (MMG) (Xie, Zheng, & Jing-Yi, 2009). Previous studies investigated manifestations of fatigue in prolonged activities involving repetitive low force work tasks. In contrast to our study, they used task duration of more than 1 h with an intensity of 20% maximum voluntary contraction in an isolated movement with few active muscles (de Looze, Bosch, & van Dieën, 2009). For example, they measured fatigue using electromyography of a descending part of the trapezius muscle. In our study, walking is a complex movement with involvement of many muscle groups and several degrees of freedom. Based on the results of our previous studies, we expected that patients with fatigue would be exhausted in less than 60 min (Sehle et al., 2011; Sehle et al., 2014). One of the most popular cost-efficient and quick measurement of muscle fatigue is the analysis of blood lactate during exhaustive exercises. We used this method in our study. All subjects walked on the treadmill without reaching their lactate threshold, which reflects the rate at which a person can work aerobically without accumulation of acid substances associated with muscular fatigue (Pariser, Madras, & Weiss, 2006). However, some patients have reached exhaustion as these patients reported 17 (very hard) on the Borg scale and/or the FKS was >4. None of the healthy persons reached exhaustion in the walking test determined using the Borg scale and the FKS. Hence, it seems unlikely that motor fatigue was associated with muscular fatigue.

A strong relationship between depression and fatigue has been described in both patient groups (Naess et al., 2012; Staub & Bogousslavsky, 2001b). Moreover, depression is considered one of the most confounding factors associated with fatigue; it can be hard to disentangle depression and fatigue in a patient. In the present study, the depression was more common in MS groups than in the stroke or healthy subjects. Epidemiological studies reported that depression is common in MS with annual prevalence rates as high as 20% and a lifetime prevalence of up to 50% (Patten et al., 2003; Patten, Williams, Lavorato, Koch, & Metz, 2013; Siegert & Abernethy, 2005), which is approximately three times higher than in healthy people (Patten et al., 2013). Approximately one-third of all patients with stroke experience depression symptoms and the prevalence only

slightly decreases within the first 2 years after stroke (Egeto, Fischer, Ismail, Smith, & Schweizer, 2014; House, 1987). In our study, the FKS did not correlate with BDI-II. The FKS is an important tool for detecting motor fatigue objectively and independent of the presence or absence of depression.

It may be speculative and beyond the scope of the present investigation, but the motor fatigue in stroke and MS patients probably suggests different underlying pathophysiological mechanisms. Ischemic lesions occur according to the all-or-nothing principle: if oligemia causes an ischemic lesion, it results in a complete lesion of the tissue finally ending up in the chronic stage as a substantial cyst (simply speaking as a hole in the brain). Fatigue in this case may be related to compensation or use of alternative, less efficient, or reorganized pathways. Inflammation in MS might cause demyelination or partial impairment of neural pathways. Neuronal function may be partially preserved, but under high demand or long or highly repetitive requirements function might slowly decline. Further or additional compensation does not seem to be possible, and it is unclear if this is due to loss of K^+ as suggested in the literature explaining the function of 4-aminopyridine (Sherratt, Bostock, & Sears, 1980). Completely different pathomechanisms may be related to inflammatory substances such as cytokines or tumor necrosis factor alpha (TNF-α) (Hacken et al., this special issue) (Heesen et al., 2006). Increased cytokines, however, are not a prominent finding in the liquor of chronic stroke patients, and hence fatigue is expected to have a different pathomechnism in stroke. Different pathomechanisms of fatigue would require different treatment options (Flachenecker et al., 2004; Heesen et al., 2006). For instance, compensation in stroke patients may be enhanced by training, and electric failure in MS lesions may be ameliorated by substances such as 4-aminopyridine or inhibitors of TNF-α (Goodman et al., 2007; Goodman & Stone, 2013).

Most standardized fatigue questionnaires are based on patients' self-assessments and often used for rating fatigue symptoms. However, because these questionnaires are based on the patients' subjective impressions, they may be distorted because of an inaccurate self-perception. Currently, most of the fatigue questionnaires are disease specific and have been specifically developed to assess fatigue in MS (Acciarresi et al., 2014). Elbers et al. (Elbers et al., 2012) recommended the FSMC for the multidimensional assessment of fa-

tigue in MS patients (Elbers et al., 2012). In contrast, the FSS is the most commonly used instrument to measure fatigue in stroke patients (Lerdal & Gay, 2013), which was also recommended by Elbers et al. (Elbers et al., 2012). Since most of the motor scores are disease specific, it is not easy to compare the degree of impairment in stroke and MS patients. For instance, the Motricity Index (Demeurisse, Demol, & Robaye, 1980), the Fugl-Meyer test (Sanford, Moreland, Swanson, Stratford, & Gowland, 1993), or Rivermead Motor Assessment (Lincoln & Leadbitter, 1979) are evaluated for stroke, whereas the application of the Expanded Disability Status Scale (Kurtzke, 1983) is restricted to MS, and there is no common measure for both entities. To overcome this difficulty, we used the Physical Functioning Scale of the SF-36 to assess daily life motor activities and their restrictions. This allowed for some rough comparison of motor impairment and disabilities in daily life. Currently, there is a validated scale for fatigue in both MS and stroke patients (Mills et al., 2012), which was not available at the time of data collection.

The estimation error may occur in the clinical assessment of the patient by physicians and physiotherapists. Some patients are hard to classify into fatigue and non-fatigue groups based on patient's survey and traditional clinical tests carried out by physicians and therapists. The results of the FKS largely agreed with the results of the video analysis in MS patients. The physiotherapists assigned videos of the beginning and end correctly in 80–85% of MS patients. Such classification was difficult for stroke patients and healthy subjects. In general, the MS patients have almost an unremarkable gait pattern at the beginning of walking. In the state of fatigue, the gait changed greatly. Thus, it can be clearly seen in most cases. However, it depends on the experience of the physiotherapist. In contrast to MS, the stroke patients had an impaired gait pattern at the beginning of walking test. All stroke patients had a hemiparesis and hence an abnormal gait pattern at both time points. It is possible that the raters cannot be distinguishing between the abnormal gait characteristics caused by the hemiparesis and those caused by motor fatigue. This could lead to difficulties to assess the changes in gait pattern. Even if this evaluation was very successful for these cases, the analysis is subjective and depends on many factors and particularly on the therapists' experience. These results emphasize the importance of an

objective measure of motor fatigue that is independent of the subjective assessment of a rater.

The FKS is an objective measure. As acknowledged above in many cases, a neurologist can detect the presence of fatigue in patients with MS using “classic” instruments. However, in some cases, a physician cannot be sure of the diagnosis of the fatigue syndrome, and in these cases, the FKS can be extremely helpful for objectively measuring motor fatigue. The correct diagnosis of fatigue is especially important when it is used as criterion for early retirement emphasizing the relevance of this test. For example, the most important differential diagnosis may be depression. In some instances, it may not be easy to disentangle both phenomena. Treatment may be similar involving antidepressive agents, increasing regular physical activity, acceptance of limitations, energy conservation programs, etc. However, the patient will feel more accepted and understood, if the therapist and neurologist are able to discriminate, explain, and treat different components of his complex symptom. Moreover, the FKS can be used both for diagnosis and for the evaluation of the course of treatment.

4.6 Conclusion

Using FKS, a new and objective tool for identifying and quantifying motor fatigue, we found that fatigue was similarly pronounced in both patient groups. We observed that a more severe walking impairment in stroke patients at baseline is not associated with a pathologically higher FKS. The objective assessment of motor fatigue via the FKS allows the comparison of motor fatigue between stroke patients, MS patients, and healthy persons.

Acknowledgments

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5 Allgemeine Diskussion der Ergebnisse

Das Hauptergebnis der vorliegenden Arbeit ist die erfolgreiche Entwicklung und Testung einer neuen Methode zur Quantifizierung von motorischer Fatigue bei Patienten mit MS und nach einem Schlaganfall. In diesem Zusammenhang wurden die Unterschiede im Gangmuster in zwei verschiedenen dynamischen Situationen genauer untersucht und der FKS entwickelt. Das neue Verfahren ermöglicht eine objektive, präzise, kostengünstige und schnelle Diagnostik motorischer Fatigue.

In der ersten Studie wurde eine neue Methode entwickelt, die mit Hilfe von Attraktoreigenschaften eine Quantifizierung von Unterschieden im Bewegungsmuster in verschiedenen dynamischen Situationen erlaubt. Hierfür wurden die Daten von gesunden Probanden beim Gehen auf dem Laufband in verschiedenen Situationen und an jeweils zwei verschiedenen Tagen erhoben. Mit Hilfe des neuen Verfahrens konnten in dieser Studie eindeutige Unterschiede im Gangmuster der Probanden zwischen drei verschiedenen Bedingungen gezeigt werden. Dabei konnte eine sehr gute Reliabilität für die Veränderungen in der Gangcharakteristik nachgewiesen werden. Die Reliabilität für die Veränderungen in der Gangvariabilität lag zwischen moderat und gut. Bereits in der ersten Studie konnte die Möglichkeit von Analysen sowohl auf der Individual- als auch auf der Gruppenebene präsentiert werden. Dank dieser Eigenschaft ist die neue Methode insbesondere für die klinische Forschung und Diagnostik von sehr großer Bedeutung.

In der zweiten Studie wurden das neu entwickelte und an gesunden Probanden erprobte Verfahren sowie der darauf basierende FKS zur objektiven Messung der motorischen Fatigue bei Patienten mit MS und gesunden Personen angewandt. Hierfür wurden die Daten von MS-Patienten und gesunden Probanden beim Gehen auf dem Laufband am Anfang und am Ende des Tests erhoben. Dabei wurde eine Kalibrierung der neuen Methode durchgeführt, so dass exakte Grenzwerte zwischen dem stabilen Zustand und pathologischer Erschöpfung festgelegt werden konnten. Der FKS zeigte sich den klassischen Diagnostikmethoden in Bezug auf die Spezifität und Sensitivität überlegen. So erfolgte mit Hilfe des FKS eine präzise Diagnostik der motorischen Fatigue bei MS-

Patienten: alle Patienten mit MS, die während der Untersuchung keine motorische Fatigue angegeben hatten, wurden anhand des FKS korrekt in die nicht Fatigue-Gruppe eingeteilt. Ferner hatte kein gesunder Proband laut dem FKS motorische Fatigue. In dieser Studie gab es die ersten Hinweise darauf, dass der FKS bei Patienten mit Begleiterkrankungen erfolgreich zur Differenzierung z.B. gegenüber Depressionen und Schlafstörungen angewendet werden kann. Es konnte beobachtet werden, dass die motorische Fatigue unabhängig von den Begleiterkrankungen diagnostiziert werden kann.

In der dritten Studie wurde die Einsatzmöglichkeit des FKS zur objektiven Erfassung der motorischen Fatigue bei Patienten nach einem Schlaganfall eruiert. Mit dieser Pilotstudie konnte gezeigt werden, dass der FKS auch bei diesen Patienten als Diagnostikinstrument zur Erfassung von motorischer Fatigue eingesetzt werden kann. Der FKS erfasste die motorische Fatigue gleich gut sowohl bei MS-Patienten als auch bei Patienten nach einem Schlaganfall und zeigte, dass in beiden Patientengruppen ähnliche Veränderungen sowohl in der Gangcharakteristik als auch in der Gangvariabilität infolge motorischer Fatigue entstehen. Der Belastungstest im Rahmen der Datenerhebung erwies sich für die Schlaganfall-Patienten als sehr gut durchführbar. Ein weiteres wichtiges Ergebnis der Untersuchung ist, dass der FKS auch bei dieser Patientengruppe in hohem Maße sensitiv ist und nicht durch vorhandene Hemiparese beeinflusst wird.

5.1 Einsatz der neuartigen Methode zur Quantifizierung von Unterschieden im Gangmuster auf der Individual- und Gruppenebene

Die hier entwickelte Methode mit dem darauf basierenden FKS konnte, unserem Wissen nach, zum ersten Mal die Unterschiede im Gangmuster in verschiedenen dynamischen Situationen sowohl auf der Individual- als auch auf der Gruppenebene präzise erfassen. Dabei spielte es keine Rolle, ob es sich um kranke Personen oder um gesunde Probanden handelte. Bisher wurden in klinischen Studien und in den Studien zur menschlichen Bewegungsanalyse andere Analyseverfahren, wie z.B. die konventionelle kinematische Bewegungsanalyse oder nichtlineare Zeitreihenanalysen, verwendet (Kantz & Schreiber, 2004; Schablowski-Trautmann & Gerner, 2006). Insbesondere in den

klinischen Studien findet die konventionelle kinematische Bewegungsanalyse verbreitete Anwendung (Huisinga, Schmid, Filipi, & Stergiou, 2012; Kaipust, Huisinga, Filipi, & Stergiou, 2012; Kelleher et al., 2010; Sosnoff et al., 2012).

Ein wesentlicher Nachteil bisheriger Studien bestand drin, dass die Daten häufig auf der Gruppenebene analysiert wurden, unabhängig davon, ob ein konventionelles oder nichtlineares Verfahren zur Analyse von Bewegungsdaten herangezogen wurde. Für Ärzte und Therapeuten ist jedoch die Individualebene von größerer Bedeutung, da im klinischen Alltag die Entscheidungen für jeden einzelnen Patienten individuell getroffen werden müssen, so z.B. in Bezug auf die Therapieart sowie die Therapiemenge. Außerdem werden bei der konventionellen Gangbildanalyse wenige einzelne Schrittzyklen analysiert (Harris & Smith, 1996; Schablowski-Trautmann & Gerner, 2006). Somit liegt der Hauptnachteil der traditionellen Methoden in der Vernachlässigung der wesentlichen Informationen, die in den dynamischen Sequenzen mehrerer Schritte während der kontinuierlichen Fortbewegung enthalten sein könnten (Schablowski-Trautmann & Gerner, 2006). Weiterhin hat ein nichtlineares Verfahren, wie z.B. die Berechnung des Lyapunov-Exponenten, den Nachteil, dass er für ein rauschfreies System entwickelt wurde. Diese Bedingung können die empirischen Daten von Bewegungsabläufen der Probanden nicht erfüllen (Vieten et al., 2013; Williams, 1997).

Die aufgezeigten Kritikpunkte wurden bei der Entwicklung der neuen Methode berücksichtigt. Die neue Methode besitzt eine hohe externe Validität und bezieht somit die empirisch erhobenen Daten umfassend ein. Das hier entwickelte Verfahren erlaubt Bewegungsanalysen sowohl auf der Individual- als auch auf der Gruppenebene. Weiterhin ermöglicht diese Methode die Analyse der realen Daten, die ein gewisses Rauschen beinhalten. Das unterscheidet das neue Verfahren von herkömmlichen Methoden und verleiht ihm für verschiedene Gebiete, wie z.B. für die Forschung und Medizin, Bedeutung.

5.2 Einsatz des FKS zur Erfassung motorischer Fatigue

Die bisherigen Versuche, motorische Fatigue bei Patienten mit MS oder nach einem Schlaganfall objektiv zu erfassen, lieferten keine zufriedenstellenden Ergebnisse. Zum einen analysierten die vorangegangenen Studien die Daten ausschließlich auf der Gruppenebene, und zum anderen konnten sie keine prä-

zise Feststellung der motorischen Fatigue vornehmen (Greim et al., 2007; Hu et al., 2006; Iriarte & de Castro, 1998; Knorr et al., 2011; Schwid et al., 1999; Severijns et al., 2014; Surakka et al., 2004; Svantesson et al., 1999). Diese Lücken konnten mit der vorliegenden Arbeit geschlossen werden. Mit Hilfe des FKS konnte motorische Fatigue bei Patienten mit MS und nach einem Schlaganfall erfasst und analysiert werden. Der FKS erlaubte eine präzise Einteilung aller Teilnehmer in Gruppen mit und ohne motorische Fatigue. Die Vorteile des FKS gegenüber den anderen Methoden liegen in seiner hohen Reliabilität, Spezifität sowie Sensitivität.

5.3 Der FKS und subjektive Bewertungen durch Arzt und Physiotherapeuten

Bei den Untersuchungen konnte eine zum Teil hohe Übereinstimmung (bis zu 97%) zwischen dem FKS und der ärztlichen sowie physiotherapeutischen Einschätzung beobachtet werden. Tatsächlich liegen die Experten auf diesem Gebiet mit ihrer Beurteilung, ob bei einem Patienten eine motorische Fatigue vorliegt, in den meisten Fällen richtig. Vor allem bei Patienten, die von einer moderaten bis schweren motorischen Fatigue betroffen sind, scheint die Diagnostik mit Hilfe von klinischen Assessments gut zu funktionieren. Schwierigkeiten können dagegen dann entstehen, wenn die Patienten entweder von einer leichten motorischen Fatigue betroffen sind oder wenn die Begleiterkrankungen ähnliche Symptome verursachen. In solchen Fällen erweist sich die Identifizierung von motorischer Fatigue sogar für Experten als sehr schwierig. Dies gilt besonders dann, wenn solche Begleiterkrankungen – wie Depression und Schlafstörungen – diagnostiziert werden, die einen direkten Zusammenhang mit Fatigue aufweisen (Braley et al., 2012; Labuz-Roszak et al., 2012). Bei Patienten mit einer leichten motorischen Fatigue ist eine frühzeitige Diagnose jedoch von großer Bedeutung für eine bestmögliche Behandlung. Weiterhin kann die Alltagsgestaltung der Patienten rechtzeitig angepasst und somit die Lebensqualität der Patienten erheblich verbessert werden. Die Patienten können lernen, ihren körperlichen Zustand besser einzuschätzen, körperlich schwere Arbeit zu vermeiden sowie rechtzeitig Ruhepausen einzulegen. Darüber hinaus kann eine korrekte Diagnose von motorischer Fatigue die Akzeptanz seitens der Angehörigen und der Gesellschaft steigern und bei damit verbundenen Schwierigkeiten Abhilfe

schaffen. Wenn umgekehrt keine motorische Fatigue nachweisbar ist, sondern die Begleiterkrankung (z.B. Depression, Schlafstörungen, Adipositas) Ursache der verminderten Gehstrecke ist, so muss die Begleiterkrankung oder -ursache vorrangig behandelt werden. Auch ist es für die sozialmedizinische Leistungseinschätzung im Rahmen der Rehabilitation oder im Rahmen von Gutachten vorteilhaft, wenn sich die Einschätzung nicht auf die subjektive Beobachtung eines Physiotherapeuten stützt, sondern auf objektive und evaluierte Messparameter. Nicht zuletzt spricht für den Einsatz des FKS die Tatsache, dass nicht alle Ärzte und Physiotherapeuten über genügend Erfahrungen mit motorischer Fatigue bei Patienten mit MS und nach Schlaganfall verfügen.

5.4 Der FKS und subjektive Befragungsinstrumente

In den beiden patientenbezogenen Studien (Studie 2 und 3) wurden verschiedene Befragungsinstrumente in Form von Selbsteinschätzungsfragebögen zur Erfassung von Fatigue, Depression sowie des allgemeinen Gesundheitszustandes und der Vitalität der Patienten eingesetzt. Die Analysen der Ergebnisse dieser Fragebögen und deren Zusammenhang mit dem FKS lieferten wichtige zusätzliche Informationen.

In der zweiten Studie wurde zur subjektiven Erfassung von Fatigue bei Patienten mit MS der FSMC-Fragebogen verwendet. Die Korrelationsanalyse ergab keinen Zusammenhang zwischen dem FKS und der FSMC. Dieses Ergebnis stimmt überein mit den Resultaten der vorherigen Studien, die ebenso keinen Zusammenhang zwischen einer subjektiv wahrgenommenen Müdigkeit und der Leistung in konventionellen neuropsychologischen oder motorischen Tests beobachteten (Geisler et al., 1996; Krupp, 2003; C. E. Schwartz et al., 1996). Kluger et al. (2013) betonten deshalb die Wichtigkeit der Unterscheidung zwischen dem subjektiven Empfinden und der objektiven Veränderung in der Leistungsfähigkeit infolge von Fatigue (Kluger et al., 2013). Somit handelt es sich dabei um zwei verschiedene Dimensionen von Fatigue, die auf unterschiedliche Weise zu erfassen sind. Die Korrelationsanalyse bestätigte, dass mit Hilfe des FKS die objektive Veränderung in der Leistungsfähigkeit erfasst werden kann.

In der dritten Studie wurden die Wahrnehmung der körperlichen Beeinträchtigung (PF-10) und die Vitalität von Patienten mit MS und nach Schlaganfall mit Hilfe von SF-36 erfasst. Die Vitalitätssubskala wurde, wie in der Literatur vorge-

schlagen, zur Messung der subjektiven motorischen Fatigue eingesetzt (Fennessy et al., 2010). Dieser Befragung zufolge wiesen die Patienten nach Schlaganfall bessere Vitalitätswerte (weniger Fatigue) bei gleichzeitiger höherer körperlicher Beeinträchtigung auf als die Patienten mit MS. Somit scheint eine höhere körperliche Beeinträchtigung nicht zwangsläufig zur höheren Beeinträchtigung durch motorische Fatigue zu führen (Lukoschek, Sterr, Claros-Salinas, Gütler, & Dettmers, 2015).

In der zweiten und dritten Studie wurde ein Fragebogen zur Messung des Niveaus der subklinischen Depression (BDI-II) verwendet. Aus früheren Studien ist ein starker Zusammenhang zwischen Depression und Fatigue bekannt (Labuz-Roszak et al., 2012; Romani et al., 2004; Staub & Bogousslavsky, 2001b). Das Vorhandensein einer Depression kann die Identifizierung von motorischer Fatigue sogar für Experten sehr schwierig gestalten. Eine Korrelationsanalyse konnte keinen Zusammenhang zwischen dem FKS und dem BDI-II feststellen. Das deutet darauf hin, dass der FKS ein von der Depression unabhängiges Diagnostikinstrument darstellt. Dies ist eine wesentliche Eigenschaft des FKS. Gerade bei Patienten mit Depressionen und eingeschränkter Gehstrecke bietet der FKS eine wichtige Möglichkeit, motorische Fatigue und Depressionen zu differenzieren.

5.5 Der FKS und funktionelle Tests sowie konventionelle Gangbildanalyse

Die Erfassung weiterer Parameter, wie z.B. der Gehstrecke, der Gehgeschwindigkeit, der maximalen Gehstrecke während eines 6-Minuten-Gehtests (6MGT) sowie der Gangparameter mit Hilfe einer konventionellen Gangbildanalyse, erlaubte es, wichtige Aussagen zum Zusammenhang zwischen diesen Parametern und dem FKS zu treffen. Laut diesen Parametern zeigten die Patienten nach einem Schlaganfall im Gegensatz zu MS-Patienten und gesunden Personen größere körperliche Beeinträchtigungen. Bereits vorliegende chronische körperliche Beeinträchtigungen hatten jedoch keinen Einfluss auf den FKS. Somit zeigte sich der FKS als ein von diesen Parametern unabhängiges Messinstrument. Der Grund dafür besteht darin, dass der FKS quantitative Veränderungen des Gangmusters zwischen zwei Messzeitpunkten analysiert und keine Aussagen über die Gangqualität oder das Gangmuster per se bietet. Deshalb

hat ein Patient mit einer spastischen Halbseitenlähmung und einer Zirkumduktion des spastisch-paretischen Beines (ein sogenanntes Gangbild „Wernicke-Mann-Typ“) nicht automatisch einen pathologischen FKS, sondern nur dann, wenn sich dieses Gangbild im Laufe der Belastung verändert. Das unterscheidet das neue Verfahren von den herkömmlichen Methoden und eröffnet neue wissenschaftliche Analysemöglichkeiten.

5.6 Motorische Fatigue versus muskuläre Fatigue

Während des Erschöpfungsexperiments auf dem Laufband wurde bei jedem Studienteilnehmer die Laktatkonzentration im Blut analysiert. Somit wurde eine kostengünstige und schnelle Methode zur Erfassung der peripheren muskulären Fatigue eingesetzt. Die Analysen der Laktatkonzentration im Blut und der Herzfrequenz während des Erschöpfungsexperiments lieferten eindeutige Ergebnisse. Bei allen Untersuchungsteilnehmern blieben die Laktatkonzentration im Blut deutlich unter der Laktatschwelle von 4 mmol/L und die Herzfrequenz unter der auf das Alter bezogenen maximalen Herzfrequenz. Daher befanden sich alle Probanden während des gesamten Experiments im aeroben Bereich. Diese Ergebnisse bestätigten unsere Vermutung, dass die motorische Fatigue bei Patienten mit MS und nach einem Schlaganfall keinen Zusammenhang mit der muskulären Fatigue, die mit der erhöhten Laktatkonzentration im Blut assoziiert ist, aufweist (Pariser et al., 2006).

Andere Methoden zur Messung der muskulären Fatigue sind z.B. die Untersuchung weiterer Energiestoffwechselprodukte (unter anderem Phosphokreatin, anorganisches Phosphat, monovalentes anorganisches Phosphat, intrazellulärer pH-Wert), Oberflächen-Elektromyografie oder Mechanomyografie (de Looze et al., 2009; Sharma et al., 1995; Xie et al., 2009). Im Gegensatz zu bisherigen Untersuchungen, die sich auf die Vorgänge entweder in einem Muskel oder in einem Anteil eines Muskels konzentriert hatten, wurde in unserem Experiment die muskuläre Fatigue während einer komplexen Bewegung mit Beteiligung vieler Muskelgruppen und mehreren Freiheitsgraden untersucht. Außerdem stellt das Gehen eine alltagsrelevante Bewegung dar.

6 Fazit

In der vorliegenden Arbeit wurden insgesamt drei empirische Studien, die methodisch und inhaltlich aufeinander aufbauen, dargestellt.

In der ersten Studie wurde erfolgreich ein neues Verfahren zur Quantifizierung von Veränderungen im Gangmuster der Probanden in verschiedenen dynamischen Situationen mit Hilfe von Attraktoreigenschaften entwickelt und getestet. Diese Studie zeigte, dass die neue Methode eine Reihe von vorteilhaften Eigenschaften besitzt. Eine davon ist die Möglichkeit, die Veränderungen im Bewegungsmuster zwischen zwei Messzeitpunkten unabhängig von der Bewegungsqualität zu quantifizieren. Weiterhin ermöglicht das neue Verfahren neben den herkömmlichen Gruppenanalysen auch Analysen von Bewegungsdaten auf der Individualebene. Dabei können empirische Daten vollständig analysiert werden. Wir konnten bestätigen, dass Veränderungen im Gangmuster auf Grund von veränderten Situationen durch Veränderungen des Attraktors (Gangcharakteristik) und seiner Standardabweichung (Gangvariabilität) sowohl auf der Individual- als auch auf der Gruppenebene erfasst werden können. Die neue Methode zeigte moderate bis sehr gute Reliabilität.

Basierend auf den Ergebnissen der ersten Studie konnte in der zweiten Studie das neuartige Verfahren an MS-Patienten und gesunden Personen während eines Belastungstests erprobt werden. Im Fokus standen dabei der Einsatz des FKS zur objektiven Messung der motorischen Fatigue und die Berechnung und Einführung von Grenzwerten, die eine präzise Einteilung der Teilnehmer in Gruppen mit und ohne motorische Fatigue ermöglichen. Der FKS ermöglichte eine präzise Identifikation von MS-Patienten mit und ohne motorische Fatigue. Zudem wurden alle gesunden Probanden richtig als nicht von motorischer Fatigue betroffen identifiziert. Dies bestätigt die hohe Spezifität und Sensitivität dieser Methode. Ferner wurde festgestellt, dass die motorische Fatigue in keinem Zusammenhang mit der muskulären Fatigue steht. Das deutet darauf hin, dass die Ursache der motorischen Fatigue bei MS-Patienten auf die Vorgänge im Zentralnervensystem zurückzuführen ist.

In der letzten Studie wurde die motorische Fatigue bei Patienten nach einem Schlaganfall untersucht. Dabei zeigten diese Patienten ein ähnliches Ausmaß an motorischer Fatigue während des Belastungstests wie die MS-Patienten. Mit dieser Studie konnte bestätigt werden, dass der FKS auch bei dieser Patientengruppe zur Erfassung der motorischen Fatigue eingesetzt werden kann. Der Belastungstest auf dem Laufband zeigte eine gute Durchführbarkeit bei Patienten nach einem Schlaganfall. Zuletzt konnte verifiziert werden, dass der FKS nicht von chronischen Gangbeeinträchtigungen beeinflusst werden kann.

7 Ausblick

Die in der vorliegenden Arbeit entwickelte neuartige Methode ermöglicht die Quantifizierung von Veränderungen im Gangmuster. Dabei nutzt diese Methode die Eigenschaften eines Grenzzyklus-Attraktors. Der auf dieser Methode basierende FKS stellt ein neues Diagnostik-Instrument dar, das akute objektive Veränderungen im Gangmuster infolge motorischer Fatigue erfassen kann. Erstmalig können Aussagen bezüglich des Fatigue-Symptoms auf der Individualebene getroffen werden. Im Vergleich zu herkömmlichen Verfahren kann der FKS auf Grund seiner Objektivität sowie hohen Spezifität und Sensitivität für die Erfassung von motorischer Fatigue als überlegen betrachtet werden. Der FKS kann über die Diagnose motorischer Fatigue hinaus zur Evaluation der Krankheitsverläufe und Therapieerfolge bei Patienten mit motorischer Fatigue eingesetzt werden.

Das neue Verfahren erfasst quantitative Veränderungen des Gangmusters und kann daher keine Aussagen über die Gangqualität per se treffen. Daher kann diese Methode bei allen Forschungsfragen angewandt werden, bei denen nicht die Qualität des Gehens bewertet wird, sondern die quantitativen Veränderungen des Gangmusters infolge einer Situationsänderung im Fokus stehen.

In weiteren Studien könnten folgende Forschungspunkte überprüft werden:

- Es könnte eine Präzisierung angestrebt werden, sodass Grenzwerte für die Einteilung der Fatigue nach Betroffenheitsgrad in leichte, moderate oder schwere motorische Fatigue bestimmt werden könnten.
- Der FKS sollte an weiteren neurologischen Krankheitsbildern, die ebenso von motorischer Fatigue betroffen sind, getestet werden.
- Es wäre zu überprüfen, ob ein bewusstes Vortäuschen von motorischer Fatigue möglich ist.
- Potentiell vielversprechend wäre auch eine Kombination des neuen Verfahrens während des Belastungstests mit elektrophysiologischen Messungen, wie z.B. mit der Oberflächen-Elektromyografie oder der Transkraniellen Magnetstimulation. So könnten die pathophysiologischen Me-

chanismen der Entstehung und Entwicklung der motorischen Fatigue genauer untersucht werden.

Von den Erkenntnissen der vorliegenden Arbeit können nicht nur betroffene Patienten, sondern auch ihre Angehörigen und das medizinische Personal profitieren. Wie bereits erwähnt, ist die Differenzierung von Schlafstörungen, Depression und Adipositas wichtig und ermöglicht eine rechtzeitige Diagnose und eine bestmögliche Behandlung. Weiterhin könnte die Alltagsgestaltung der Patienten dementsprechend angepasst und somit ihre Lebensqualität erheblich verbessert werden. Nicht zu vernachlässigen ist die Akzeptanz dieses Symptoms durch Angehörige der Patienten und die Gesellschaft, die durch eine definitive Diagnose positiv beeinflusst werden kann. Außerdem erlaubt diese Arbeit schnelle, kostengünstige und zuverlässige Analysen im Bereich der sozialmedizinischen Leistungsbeurteilung.

8 Abgrenzung der eigenen Arbeitsleistung

Bei der vorliegenden Arbeit handelt es sich um eine kumulative Dissertation, in deren Rahmen insgesamt drei wissenschaftliche empirische Studien durchgeführt wurden. Aus diesen drei Studien wurden drei Artikel in wissenschaftlichen Zeitschriften mit Peer-Review-Verfahren publiziert.

STUDIE 1:

A novel approach to quantify time series differences of gait data using attractor attributes.

PLOS ONE, 2013; 8(8):e71824. doi: 10.1371/journal.pone.0071824.

Erst-Autorenschaft	Manfred M. Vieten
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Konzeption der Studie	ja	Manfred M. Vieten Randall L. Jensen
Durchführung der Experimente	ja	
Datenanalyse	ja	Manfred M. Vieten Randall L. Jensen
Interpretation der Ergebnisse	ja	Manfred M. Vieten Randall L. Jensen
Anfertigung der Abbildungen		Manfred M. Vieten
Überarbeitung der Publikation	ja	Manfred M. Vieten Randall L. Jensen

STUDIE 2:

Objective assessment of motor fatigue in multiple sclerosis: the Fatigue index Kliniken Schmieder (FKS).

Journal of Neurology, 2014; 261(9):1752-62. doi: 10.1007/s00415-014-7415-7.

Erst-Autorenschaft	Aida Sehle
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STUDIE 3:

Difference in motor fatigue between patients with stroke and patients with multiple sclerosis: a pilot study.

Frontiers in Neurology, 2014; 5:279. doi: 10.3389/fneur.2014.00279.

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