

**Erfassung und Trainierbarkeit der posturalen
Kontrolle und Modulation des Gangbildes bei
Patienten mit Morbus Parkinson**

Dissertation zur Erlangung des Doktorgrades der Philosophischen Fakultät der
Christian-Albrechts-Universität zu Kiel

vorgelegt von

Christian Schlenstedt

Kiel

2014

Erstgutachter: Prof. Dr. Burkhard Weisser

Zweitgutachter: Prof. Dr. Karsten Witt

Tag der mündlichen Prüfung: 14.01.2015

Durch den Prodekan Prof. Dr. John Peterson

zum Druck genehmigt am: 19.01.2015

Shaking Palsy (Paralysis Agitans)

„Involuntary tremulous motion, with lessened muscular power,
in parts not in action and even when supported;
with a propensity to bend the trunk forwards,
and to pass from a walking to a running pace:
the senses and intellects being uninjured.”

JAMES PARKINSON, 1817

Publikationen im Zusammenhang mit dieser Dissertation

Studie 1:

Schlenstedt, C., Brombacher, S., Hartwigsen, G., Weisser, B., Möller, B. & Deuschl, G. (2014). Comparing the Fullerton Advanced Balance scale with the Mini-BESTest and Berg Balance Scale to assess postural control in patients with Parkinson's Disease. *Arch Phys Med Rehabil*, 10.1016/j.apmr.2014.09.002.

Studie 2:

Schlenstedt, C., Paschen, S., Kruse, A., Raethjen, J., Weisser, B. & Deuschl, G. (under review). Resistance Training versus Balance Training to improve postural control in patients with Parkinson's Disease – a randomized controlled rater blinded trial. *Neurorehabil Neural Repair*.

Studie 3:

Fasano, A.*, Schlenstedt, C.*, Herzog, J., Plotnik, M., Rose, F., Volkmann, J. & Deuschl, G. (under review). Split-belt Locomotion in Parkinson's Disease links Asymmetry, Dyscoordination and Sequence Effect. *Parkinsonism & related disorders*.
**beide Autoren haben zu gleichen Teilen zu der Arbeit beigetragen*

Danksagung

Ich möchte mich ganz besonders bei Prof. Dr. Günther Deuschl für seine Betreuung bedanken. Für den Freiraum, eigene Ideen zu entwickeln und umzusetzen, für die fachliche Unterstützung, wann immer diese notwendig war, und für das Gefühl, in den zahlreichen Diskussionen immer wertgeschätzt zu sein, bin ich sehr dankbar.

Mein Dank geht an Prof. Dr. Burkhard Weisser für seine freundliche Unterstützung bei allen sportmedizinischen Fragen und seine Promotionsbetreuung.

Prof. Dr. Karsten Witt danke ich für seine Hilfe und seine Bereitschaft, diese Arbeit zu begutachten. Mein Dank geht auch an Prof. Dr. Jan Raethjen für sein offenes Ohr bei allen Fragen.

Ohne die finanzielle Unterstützung der Coppenrath-Stiftung und der Krumme-Stiftung wären diese Arbeit und die Teilnahme an zahlreichen Kongressen nicht möglich gewesen. Dafür möchte ich mich herzlich bedanken.

Die Studien wären nicht ohne die Bereitschaft der Parkinsonpatienten möglich gewesen. Die Probanden haben die zum Teil langen Messungen geduldig durchlaufen und ich freue mich über die gemeinsam verbrachten Trainingsstunden.

Dr. Steffen Paschen, Dr. Alfonso Fasano und Dr. Meir Plotnik danke ich für den wissenschaftlichen Austausch und die interessanten Diskussionen.

Bei allen Mitarbeitern der Arbeitsgruppe für Bewegungsstörungen der Klinik für Neurologie möchte ich mich für die Hilfe der Patientenrekrutierung und für jede weitere Unterstützung bedanken. Die Umsetzung dieser Projekte war nur auf Grund dieser guten Zusammenarbeit möglich.

Allen Menschen, die mir im Privaten nahestehen danke ich ganz besonders. Dieser gute Rückhalt ist essentiell für das Gelingen meiner wissenschaftlichen Arbeit.

Inhaltsverzeichnis

Publikationen im Zusammenhang mit dieser Dissertation.....	IV
Danksagung.....	V
Inhaltsverzeichnis.....	VI
Abkürzungsverzeichnis	VIII
1 Einleitung.....	1
2 Posturale Kontrolle bei Patienten mit Morbus Parkinson.....	5
2.1 Posturale Kontrolle: Allgemeine Begriffsbestimmung.....	5
2.2 Posturale Kontrolle bei ruhigem Stand	6
2.3 Posturale Kontrolle bei Perturbation der Standfläche.....	8
3 Exkurs: Kraftfähigkeiten bei Morbus Parkinson	9
4 Messbarkeit der posturalen Kontrolle: Studie 1	11
4.1 Fragestellung zur Studie 1	11
4.2 Studie 1: „Comparing the Fullerton Advanced Balance scale with the Mini-BESTest and Berg Balance Scale to assess postural control in patients with Parkinson’s Disease“	12
5 Trainierbarkeit der posturalen Kontrolle bei Patienten mit Morbus Parkinson: Studie 2	14
5.1 Allgemeine Begriffsbestimmung	14
5.2 Stand der Forschung und Fragestellung: Trainingsinterventionen zur Verbesserung der posturalen Kontrolle	15
5.3 Studie 2: „Resistance Training versus Balance Training to improve postural control in patients with Parkinson’s Disease – a randomized controlled rater blinded trial“.....	17
6 Modulation des Gangbildes durch asymmetrisches Laufbandtraining: Studie 3	19
6.1 Fragestellung zur Studie 3	19
6.2 Studie 3: „Split-Belt Locomotion in Parkinson’s Disease Links Asymmetry, Dyscoordination and Sequence Effect“	21

7	Zusammenfassung und Ausblick.....	23
	Literaturverzeichnis.....	25
	Anhang	33
	A	Studie 1: „Comparing the Fullerton Advanced Balance scale with the Mini-BESTest and Berg Balance Scale to assess postural control in patients with Parkinson’s Disease”
	B	Studie 2: „Resistance Training versus Balance Training to improve postural control in patients with Parkinson’s Disease – a randomized controlled rater blinded trial”
	C	Studie 3: „Split-Belt Locomotion in Parkinson’s Disease Links Asymmetry, Dyscoordination and Sequence Effect”

Abkürzungsverzeichnis

BESTest	Balance Evaluation System Test
BSR	Split-Belt-Laufbandbedingung, bei der die Geschwindigkeit der Bandseite des Beines mit der größeren Schrittlänge reduziert wird (<i>Best Side Reduction</i>)
COG	Gravitationszentrum (<i>center of gravity</i>)
COM	Körperschwerpunkt (<i>center of mass</i>)
COP	Druckmittelpunkt (<i>center of pressure</i>)
FAB	Fullerton Advanced Balance
FOG	Gangblockaden (<i>Freezing of gait</i>)
H&Y	Hoehn & Yahr
ICC	Intraklassen-Korrelationskoeffizient
LOS	Stabilitätslimit (<i>limits of stability</i>)
OFF	ohne Einnahme von Medikamenten
ON	unter Einnahme von Medikamenten
PDQ-39	Parkinson's Disease Questionnaire
TB	Split-Belt-Laufbandbedingung, bei der beide Bandseiten mit der gleichen Geschwindigkeit laufen (<i>Tied-Belt</i>)
TUG	Timed-up-and-go-test
UPDRS	Unified Parkinson's Disease Rating Scale
WSR	Split-Belt-Laufbandbedingung, bei der die Geschwindigkeit der Bandseite des Beines mit der kürzeren Schrittlänge reduziert wird (<i>Worst Side Reduction</i>)

1 Einleitung

Die Parkinson-Krankheit wurde nach dem englischen Arzt und Naturforscher James Parkinson benannt, welcher 1817 in seiner Monographie „An essay on the Shaking Palsy“ (PARKINSON 2002 (Original veröffentlicht 1817)) die Symptome der Krankheit anhand von sechs Patientenfällen beschrieb und als Schüttellähmung bezeichnete. Als motorische Kardinalsymptome des Morbus Parkinson gelten Tremor, Rigor, Bradykinese/Akinese und posturale Instabilität. Während James Parkinson vorrangig die motorischen Symptome beschrieb, werden heutzutage zusätzlich die nicht-motorischen Symptome berücksichtigt. Hierzu zählen neuropsychiatrische Symptome (Depression, Apathie, kognitive Dysfunktion, Psychosen, Impulskontrollstörungen), autonome Dysfunktion (orthostatische Hypotension, Obstipation, Inkontinenz), Störung der Schlaf-Wach-Regulation, sensorische Störungen (Hyposmie) und Schmerzen (OERTEL et al. 2011). Auf Grund dieser Vielzahl an Symptomen, welche die Lebensqualität der Patienten zunehmend einschränken, beschreibt James Parkinson den Zustand der Patienten wie folgt:

„The disease, respecting which the present inquiry is made, is of a nature highly afflictive [...] [and] the unhappy sufferer has considered it as an evil, from the domination of which he had no prospect of escape” (PARKINSON 2002 (Original veröffentlicht 1817), S.223).

Die Aussichtslosigkeit hat sich seitdem insofern für die Patienten nicht geändert, als dass bisher keine Therapieformen existieren, die einen Progress der Erkrankung sicher verhindern. So kommt es nach Braak et al. (2003) zu einer fortschreitenden Degeneration vorrangig dopaminergischer Nervenzellen, ausgehend von der Substantia nigra. Die Therapie des Morbus Parkinson konzentriert sich daher auf eine symptombezogene Behandlung, mit dem Ziel der Verbesserung der Lebensqualität. Die Prävalenz der Parkinson-Krankheit liegt in Deutschland bei 1-2% der Bevölkerung über 65 Jahren (OERTEL et al. 2011). Trotz gleichbleibender Inzidenz (BOWER et al. 1999) geht man auf Grund der demographischen Entwicklung weltweit von einer Verdoppelung der Anzahl der Patienten bis 2030 aus (DORSEY et al. 2007). Dadurch steigt die Bedeutung, eine evidenzbasierte, optimale Therapie zu gewährleisten.

Die drei Haupttherapie Säulen der symptomatischen Parkinsontherapie werden aktuell gebildet durch Bewegungstherapie, medikamentöse Behandlung und operative Verfahren (wie z.B. die Tiefe Hirnstimulation). Diese Behandlungsfelder wirken ergänzend und müssen auf den

Patienten individuell abgestimmt sein. Bewegungstherapie bietet den Vorteil, dass im Vergleich zur medikamentösen Behandlung keine Wirkfluktuationen sowie keine Nebenwirkungen (wie z.B. Halluzinationen oder Impulskontrollstörungen) auftreten. Bewegungstherapeutische Maßnahmen werden medikamentös-bedingte Effekte nicht ersetzen, sollten aber bei der Behandlung ergänzend berücksichtigt werden. Die Bedeutung und die positiven Effekte von Bewegungstherapie bei Patienten mit Morbus Parkinson wurden in verschiedenen Übersichtsarbeiten beschrieben (ALLEN et al. 2012; DIBBLE et al. 2009; GOODWIN et al. 2008; KEUS et al. 2009; SHERRINGTON et al. 2008). Obwohl besonders in den letzten 10 Jahren die Anzahl an randomisiert-kontrollierten Studien zunahm (KEUS et al. 2009) (siehe Abbildung 1), existieren dennoch angewendete Trainingsformen, für die keine ausreichende Evidenz vorliegt.

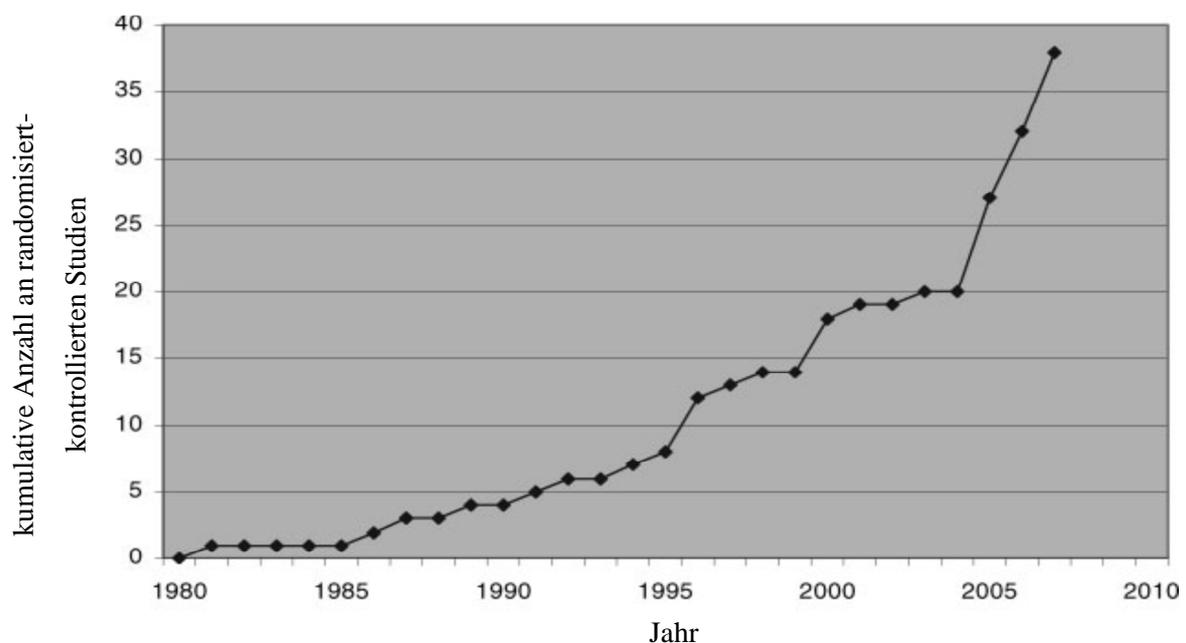


Abbildung 1. Kumulative Anzahl an randomisiert-kontrollierten Studien zu physiotherapeutischen Interventionen bei Patienten mit Morbus Parkinson (modifiziert nach KEUS et al. 2009, S.4).

Um eine bestmögliche Trainingsform zur gezielten Behandlung bestimmter Symptome zu identifizieren, ist es wichtig, verschiedene Therapieformen miteinander zu vergleichen. Eine kürzlich publizierte Übersichtsarbeit zeigt, dass ein Vergleich verschiedener Trainingskonzepte auf Grund der heterogenen Durchführung der Untersuchungen durch den Vergleich verschiedener Arbeiten bisher nicht möglich war (TOMLINSON et al. 2014). Die Übungsformen müssen daher durch Studien direkt miteinander verglichen werden. Des Weiteren bemängeln Dibble et al. (2009), dass die zu Grunde liegenden Mechanismen der

Trainingseffekte auf Grund multidimensionaler Trainingsprogramme nicht bestimmt werden können. Durch die vielseitig gestalteten Übungen ist es nicht möglich zu entscheiden, auf welche Komponente des Trainings Effekte zurückzuführen sind. Eine gezielte Reduzierung des Trainingsinhalts ist daher zum besseren Verständnis der Effekte notwendig. Es bedarf somit weiterer Studien, die neue Trainingsformen untersuchen oder bereits etablierte Übungen vergleichen und Aufschluss über zu Grunde liegende Mechanismen geben.

Eine besondere Bedeutung hat Bewegungstherapie bei der Behandlung von Störungen der posturalen Kontrolle. Posturale Instabilität zählt zu den Kardinalsymptomen bei Morbus Parkinson (OERTEL et al. 2011), ist ein unabhängiger Risikofaktor von Stürzen (KERR et al. 2010; LATT et al. 2009; ROBINSON et al. 2005) und verschlechtert sich im Krankheitsverlauf (BLASZCZYK et al. 2007; MANCINI et al. 2012). Posturale Instabilität lässt sich durch Medikamente kaum verbessern (BLOEM et al. 1996; NANTEL et al. 2012). Auch operative Verfahren, wie die Tiefe Hirnstimulation, liefern keine zufriedenstellenden Effekte zur Verbesserung dieses Symptoms (POTTER-NERGER & VOLKMANN 2013; VISSER et al. 2008). Die positiven Effekte von Bewegungstherapie hingegen konnten durch mehrere Studien gezeigt werden (DIBBLE et al. 2009; LI et al. 2012). Bewegungstherapie nimmt hinsichtlich der Behandlung der Gleichgewichtsfähigkeit¹ der Patienten eine entscheidende Rolle ein.

Die Gangstörung von Patienten mit Morbus Parkinson ist eine häufige Ursache von Stürzen (HAUSDORFF et al. 2001; SCHAAFSMA et al. 2003). Die Häufigkeit von sturzgefährdeten Patienten liegt zwischen 39% (ASHBURN et al. 2001) und 68% (WOOD et al. 2002) und ist damit doppelt so hoch im Vergleich zu gesunden, älteren Menschen (BLOEM et al. 2004). Bei Patienten mit Morbus Parkinson ist das Risiko einer Hüftgelenksfraktur auf Grund eines Sturzes bei Frauen 2,8-fach und bei Männern 5,3-fach höher als bei Gesunden (MELTON et al. 2006). Gangstörungen und die damit verbundene Einschränkung, sich unabhängig und sicher zu bewegen, haben einen entscheidenden Einfluss auf die Lebensqualität (SOH et al. 2011). Die Verbesserung des Gangbildes durch bewegungstherapeutische Maßnahmen ist ein wichtiger Aspekt, um Stürze zu verhindern.

Ziel dieser Arbeit ist es, die Bewegungstherapie zur Verbesserung der posturalen Kontrolle und der Gangstörung bei Patienten mit Morbus Parkinson zu optimieren. Die Arbeit gliedert

¹ Im Folgenden werden die Begriffe posturale Kontrolle und Gleichgewichtsfähigkeit synonym verwendet (siehe Definition Kapitel 2).

sich in drei Abschnitte und es werden drei Studien zur Beantwortung folgender Fragestellungen vorgestellt: Im ersten Schritt geht es um die Messbarkeit von posturaler Kontrolle. Es wird in diesem Teil ein klinischer Gleichgewichtstest evaluiert und mit anderen Testverfahren verglichen. Dies geschieht vor dem Hintergrund der Notwendigkeit, Therapieeffekte mittels geeigneter Tests möglichst präzise zu erfassen, um einen genauen Vergleich mit anderen Trainingsformen zu gewährleisten. Im zweiten Schritt wird die Effektivität von zwei konkurrierenden Trainingsformen zur Verbesserung der Standstabilität verglichen. Hierbei findet der validierte Gleichgewichtstest Anwendung. Der dritte Teil befasst sich mit der Möglichkeit, das Gangbild der Patienten durch ein asymmetrisches Gangtraining auf einem speziellen Laufband zu verbessern.

2 Posturale Kontrolle bei Patienten mit Morbus Parkinson

2.1 Posturale Kontrolle: Allgemeine Begriffsbestimmung

Der Begriff *posturale Kontrolle* ist definiert als Fähigkeit, sowohl unter statischen als auch unter dynamischen Bedingungen seine Körpersegmente gegen die Schwerkraft kontrolliert auszurichten (SHUMWAY-COOK & WOOLLACOTT 2012). Die posturale Kontrolle soll im Folgenden aus biomechanischer Betrachtungsweise erklärt werden. Der Körperschwerpunkt eines Körpers (*center of mass*, COM)² ist ein fiktiver Punkt und Angriffspunkt der Schwerkraft (siehe Abbildung 2 A). Die vertikale Projektion des COM auf die Unterstützungsfläche wird als Gravitationszentrum (*center of gravity*, COG) bezeichnet (SHUMWAY-COOK & WOOLLACOTT 2012). Durch die Gewichtskraft und durch Muskelaktivität wirken Kräfte auf die Unterstützungsfläche. Das Zentrum dieser Kräfte ist der Druckmittelpunkt (*center of pressure*, COP), welcher sich auf Grund des Einflusses der Muskelaktivität vom COG unterscheidet. Im stabilen Stand wandert der COP um den COG. Je höher die Schwankungsgeschwindigkeit des COM, desto größer die Differenz zwischen COP und COG (HOF 2008). Ein Körper ist im Stand oder im Sitzen postural stabil, solange der COG innerhalb der Grenzen der Unterstützungsfläche bleibt, d.h. die Unterstützungsfläche nicht vergrößert oder anders positioniert werden muss, um einen Sturz zu vermeiden. Dabei spielen die Geschwindigkeit und die Bewegungsrichtung des COG eine entscheidende Rolle. Die Grenzen der Unterstützungsfläche sind nicht statisch, sondern stehen in ständiger Abhängigkeit von der Bewegungsgeschwindigkeit und der Bewegungsrichtung des COG. Bei der Ganginitiierung wird der COG nach vorne verlagert und über die Grenze der Unterstützungsfläche gebracht (siehe Abbildung 2 B). Dabei muss ein Schritt erfolgen, um einen Sturz zu vermeiden, wodurch die Unterstützungsfläche verändert wird.

² Im Folgenden werden einige Ausdrücke mit der in der englisch-sprachigen Fachliteratur üblichen englischen Bezeichnung benannt. Dies entspricht der Notation des englischen Artikels (Studie 2, siehe Anhang) und soll zu einem leichteren Verständnis führen.

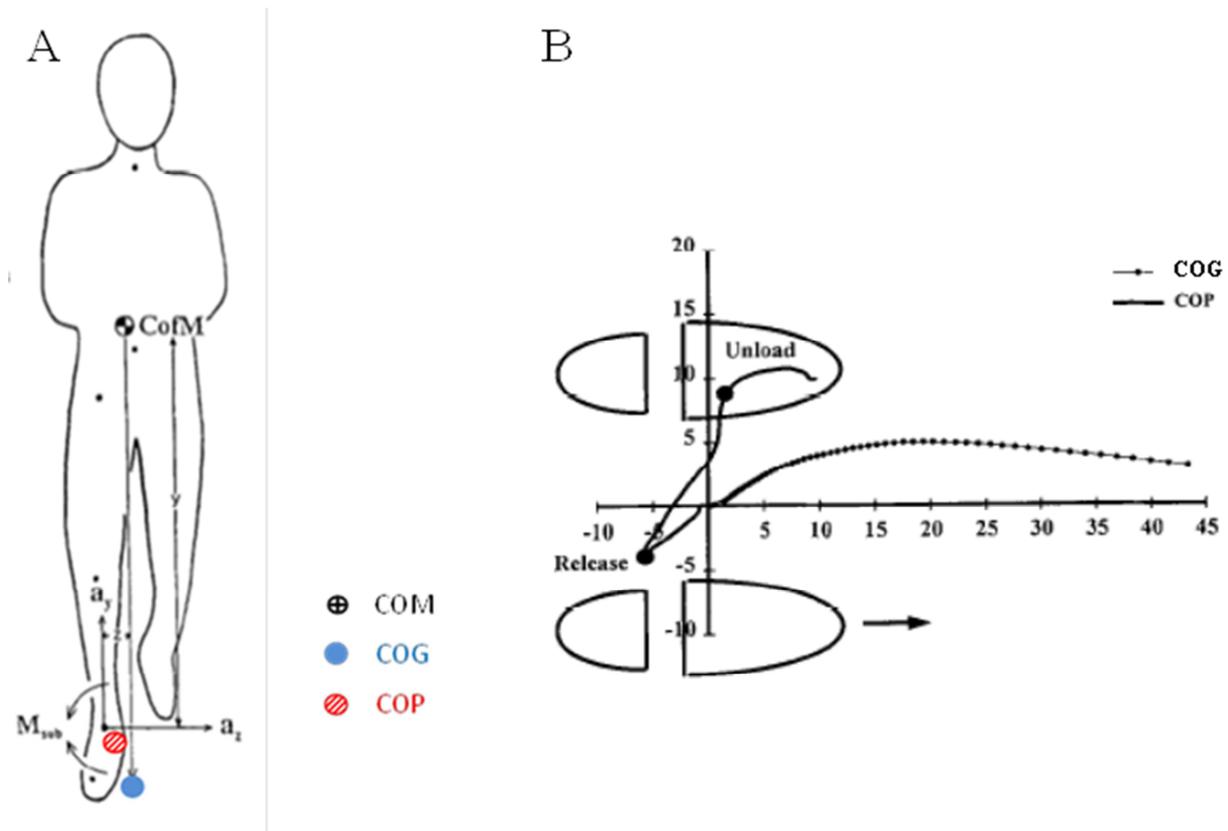


Abbildung 2. **A** Center of mass (COM), center of gravity (COG) und center of pressure (COP) (modifiziert nach WINTER 1995, S. 211). **B** COG- und COP-Verlauf bei der Ganginitiierung (modifiziert nach WINTER 1995, S. 204).

2.2 Posturale Kontrolle bei ruhigem Stand

Die posturale Kontrolle beim Stand kann als statische posturale Kontrolle bezeichnet werden. Allerdings sollte beachtet werden, dass dynamische Prozesse hierbei zu Grunde liegen (SHUMWAY-COOK & WOOLLACOTT 2012). Hinsichtlich der Analyse der Körperschwankung beim bipedalen Stand wurden bei der Literaturrecherche ausschließlich Studien mit einer Fallzahl von mindestens 10 Parkinsonpatienten³ berücksichtigt. Die Methodik zur Bestimmung des COM sowie die Wahl der Messparameter (Gesamtschwankungsweg, durchschnittliche Schwankungsgeschwindigkeit, Schwankungsfläche (95%-Vertrauensellipse), max. Schwankungsamplitude, Schwankungsintensität (quadratisches Mittel der Beschleunigung des COP) etc.) sind dabei sehr vielfältig, wodurch ein Vergleich der Studienergebnisse nur bedingt möglich ist.

³ Der Begriff *Parkinsonpatient* wird in dieser Arbeit synonym für Patienten mit einem idiopathischen Parkinsonsyndrom verwendet.

Patienten mit Morbus Parkinson weisen eine erhöhte COP-Schwankung in mediolateraler Richtung im Vergleich zu gesunden älteren Menschen auf (BLASZCZYK & ORAWIEC 2011; BLASZCZYK et al. 2007; STYLIANOU et al. 2011). Diese erhöhte Schwankung kann genauer beschrieben werden durch einen signifikant erhöhten Gesamtschwankungsweg (BLASZCZYK & ORAWIEC 2011; STYLIANOU et al. 2011; VIITASALO et al. 2002), eine signifikant erhöhte durchschnittliche Schwankungsgeschwindigkeit (VIITASALO et al. 2002), eine signifikant größere Schwankungsfläche (BLASZCZYK et al. 2007; VIITASALO et al. 2002) sowie eine signifikant erhöhte maximale Amplitude (ADKIN et al. 2005; MATINOLLI et al. 2007). Hinsichtlich der Körperschwankung in anterior-posteriorer Richtung herrscht keine Einigkeit, ob Parkinsonpatienten ein verändertes Standverhalten aufweisen. Einige Autoren konnten eine erhöhte Schwankung feststellen (ADKIN et al. 2005; BLASZCZYK & ORAWIEC 2011; MENANT et al. 2011). Dieses Ergebnis kann von anderen Untersuchungen jedoch nicht bestätigt werden (STYLIANOU et al. 2011; VIITASALO et al. 2002). Das Schwankungsausmaß in mediolateraler Richtung korreliert mit der Krankheitsdauer (VIITASALO et al. 2002), dem Krankheitszustand (gemessen am Unified Parkinson's Disease Rating Scale (UPDRS)) (BLASZCZYK & ORAWIEC 2011; FRENKLACH et al. 2009; MATINOLLI et al. 2007; VIITASALO et al. 2002) und gilt als sensitiver Parameter zur Dokumentation des Krankheitsverlaufs (MANCINI et al. 2012). Schieppati und Nardone (1991) konnten eine Verlagerung des COP in Abhängigkeit vom Krankheitszustand feststellen. Dabei verlagern Patienten im frühen Krankheitsstadium den COP nach posterior und stärker betroffene Patienten nach anterior. In einer weiteren Studie, bei der nicht nach Krankheitszustand differenziert wurde, konnte eine Verlagerung des COP nach anterior bei moderat betroffenen Parkinsonpatienten (Hoehn & Yahr (H&Y) 1-3) festgestellt werden (BLASZCZYK et al. 2007). Ähnlich wie bei Gesunden ist die statische posturale Kontrolle mit der Durchführung einer kognitiven Zusatzaufgabe verringert (MORRIS et al. 2000), wobei Bloem et al. (2006) vermuten, dass Parkinsonpatienten bei Zusatzaufgaben mit einer *posture second strategy* reagieren, bei der der kognitiven Aufgabe Priorität geschenkt wird.

Das Stabilitätslimit (*limits of stability*, LOS; gewolltes maximales Heranführen des *center of pressure* an den Rand der Unterstützungsfläche) ist bei Parkinsonpatienten im Vergleich zu Gesunden vor allem in anteriorer Richtung reduziert (ADKIN et al. 2005; BARTOLIC et al. 2005; MANCINI et al. 2008; MENANT et al. 2011; SCHIEPPATI et al. 1994; VAN WEGEN et al. 2001) und wird vor allem in posteriorer Richtung langsamer als beim Gesunden erreicht (MANCINI et al. 2008).

2.3 Posturale Kontrolle bei Perturbation der Standfläche

Durch rotatorische und translatorische Perturbationen der Standfläche kann die posturale Antwort zum Erhalt des Gleichgewichts untersucht werden. Parkinsonpatienten haben im Vergleich zu gesunden älteren Menschen eine erhöhte Koaktivierung der Antagonisten bei translatorischen und rotatorischen Störreizen der Standfläche (CARPENTER et al. 2004; HORAK et al. 1992). Die Patienten sind außerdem nicht in der Lage, auf veränderte Störreize oder unterschiedliche Standpositionen flexibel und adäquat zu reagieren (BLOEM et al. 1996; DIMITROVA et al. 2004; DIMITROVA et al. 2004; HORAK et al. 2005; HORAK et al. 1992; SCHIEPPATI & NARDONE 1991).

Kompensatorische Schritte zum Erhalt des Gleichgewichts bei translatorischen Perturbationen in anterior-posteriorer Richtung wurden durch mehrere Studien untersucht und können wie folgt beschrieben werden: Parkinsonpatienten führen im Vergleich zu gesunden älteren Menschen viele kleine langsame Schritte durch, dabei erfolgt die Initiierung verspätet (KING et al. 2010; LEE et al. 2013; MCVEY et al. 2013). Bei lateralen Perturbationen werden wie bei Gesunden überwiegend *side-steps* und keine Kreuzschritte durchgeführt. Während Gesunde überwiegend mit einem großen Ausfallschritt reagieren, führen Parkinsonpatienten mehrere kleine, langsame Schritte durch, die zudem verspätet eingeleitet werden, was zu einer höheren Sturzrate führt (KING & HORAK 2008).

3 Exkurs: Kraftfähigkeiten bei Morbus Parkinson

Zum besseren Verständnis der Fragestellung der Studie 2 soll im Folgenden ein Exkurs stattfinden, bei dem die Kraftfähigkeiten von Patienten mit Morbus Parkinson beschrieben werden. In der Literatur lassen sich Untersuchungen mit isokinetischen und isometrischen Kraftmessungen finden. Dabei können die Unterschiede im Vergleich zu gesunden älteren Menschen folgendermaßen beschrieben werden: Es herrscht Einigkeit darüber, dass Parkinsonpatienten bei isokinetischen Messungen signifikant reduzierte durchschnittliche Kraftwerte aufbauen (INKSTER et al. 2003; KOLLER & KASE 1986; PEDERSEN et al. 1997). Bei konzentrischer Muskularbeit sind diese Differenzen umso größer, je höher die Winkelgeschwindigkeit der Bewegungsdurchführung ist (NOGAKI et al. 1999; PANG & MAK 2012). Bei exzentrischer Muskularbeit hingegen weisen Parkinsonpatienten vergleichbare Kraftwerte wie Gesunde auf (NOGAKI et al. 1999). Beim Vergleich der Körperseiten von Parkinsonpatienten wurde festgestellt, dass bei hohen Winkelgeschwindigkeiten bei Flexion und Extension die stärker betroffene Körperseite signifikant schlechtere maximale Kraftwerte als die weniger betroffene Seite aufweist (KAKINUMA et al. 1998; NOGAKI et al. 1995; NOGAKI et al. 1999; NOGAKI et al. 2001). Dieser Unterschied verringert sich allerdings bei geringen Winkelgeschwindigkeiten und andere Studien konnten bei langsamen Geschwindigkeiten sogar keinen Unterschied feststellen (INKSTER et al. 2003; KOLLER & KASE 1986; PEDERSEN et al. 1997).

Bei isometrischen Kraftmessungen herrscht Uneinigkeit, ob Patienten mit Morbus Parkinson reduzierte maximale Kraftwerte im Vergleich zu Gesunden aufbauen. Einige Studien konnten im Vergleich zu gesunden Probanden signifikant verringerte maximale Werte bei Parkinsonpatienten feststellen (ALLEN et al. 2009; OLIVEIRA et al. 2008; PAASUKE et al. 2004; PAASUKE et al. 2002; PEDERSEN et al. 1997; ROBICHAUD et al. 2004; YANAGAWA et al. 1990). Bei anderen Untersuchungen konnte dieser Unterschied nicht registriert werden (JORDAN et al. 1992; KOLLER & KASE 1986; STELMACH & WORRINGHAM 1988). Gesichert ist, dass die Patienten bei isometrischen Kraftmessungen signifikant länger brauchen, um die Kraft zu initiieren (STELMACH et al. 1989), eine geringere Explosivkraft aufweisen (PAASUKE et al. 2004; PAASUKE et al. 2002; STELMACH & WORRINGHAM 1988), unregelmäßigere Kraft-Zeit-Verläufe aufzeigen (KUNESCH et al. 1995; STELMACH & WORRINGHAM 1988) und länger brauchen, die Kontraktion wieder abzubauen (KUNESCH et al. 1995; ROBICHAUD et al. 2005).

Im Gegensatz zur posturalen Kontrolle lässt sich die Kraftfähigkeit von Parkinsonpatienten durch Medikation verbessern. Es konnte gezeigt werden, dass Patienten ohne Medikamente (OFF) signifikant reduzierte maximale Kraftwerte aufbauen im Vergleich zum Zustand unter Medikation (ON) (CORCOS et al. 1996; FOLLAND et al. 2011; PEDERSEN & OBERG 1993; VAILLANCOURT et al. 2006). Corcos et al. (1996) konnten dabei einen Unterschied zwischen Flexoren und Extensoren der Ellenbogenmuskulatur bei isometrischer Kraftmessung finden (10% Steigerung der maximalen Kraftwerte der Flexoren und 34% Steigerung der maximalen Kraftwerte der Extensoren im ON) und vermuten, dass der stärkere Abbau der Muskelkraft der Extensoren bei Fortschreiten der Erkrankung ein Grund für die generell gebeugte Haltung der Patienten sein könnte. Corcos et al. (1996) untersuchten außerdem den Einfluss der Medikation auf die Fähigkeit, die Muskulatur schnellstmöglich zu entspannen. Die Patienten sollten dabei 50% ihrer Maximalkraft halten und nach einem Signal schnellstmöglich die Kontraktion lösen. Dabei war die Zeitspanne des Lösens der Kontraktion im OFF signifikant erhöht im Vergleich zur ON-Bedingung. Den stärkeren Einfluss der Medikation auf die Extensoren konnte durch Folland et al. (2011) an der Kniegelenkmuskulatur bei isometrischer Kraftmessung nicht bestätigt werden (10,8% Kraftanstieg der Flexoren; 6,9% Kraftanstieg der Extensoren im ON). Eine isokinetische Kraftmessung wurde von Pederson und Oberg (1993) bei den Dorsalflexoren des Sprunggelenkes unter verschiedenen Winkelgeschwindigkeiten durchgeführt. Eine signifikante Reduzierung der Kraftwerte fand dort bei fast allen Geschwindigkeiten im OFF statt.

Es lässt sich zusammenfassen, dass das Kraftdefizit der Maximalkraft bei Parkinsonpatienten im Vergleich zu Gesunden sowie bei der stärker betroffenen Körperseite der Patienten im Vergleich zur weniger stark betroffenen Körperseite besonders bei Bewegungen mit hoher Bewegungsgeschwindigkeit zum Vorschein kommt. Parkinsonpatienten initiieren ihre Kraft verspätet, weisen eine reduzierte Explosivkraft sowie unregelmäßige Kraft-Zeit-Verläufe und erhöhte Relaxationszeiten im Vergleich zu Gesunden auf. Durch Medikamente können die Maximalkraft und die Relaxationszeit verbessert werden.

4 Messbarkeit der posturalen Kontrolle: Studie 1

In Kapitel 2 wurde die posturale Kontrolle von Patienten mit Morbus Parkinson beschrieben und mit der Gleichgewichtsfähigkeit von gesunden älteren Menschen verglichen. Dies erfolgte über Untersuchungen, die apparative Verfahren zur Messung der posturalen Instabilität einsetzten. Apparative Verfahren sind häufig sensitiver als klinische Tests und können die zu Grunde liegenden Mechanismen exakter beschreiben. Klinische Tests hingegen sind einfacher und schneller durchführbar. Die Gleichgewichtsfähigkeit kann dabei durch den Einschluss mehrerer Einzelübungen multidimensional erfasst werden (YELNIK & BONAN 2008). So kann zum Beispiel die Erfassung von *feedback*- und *feedforward*-Prozessen sowie statischem und dynamischem Gleichgewicht über einen Test erfolgen. Alltagsrelevante Situationen können durch klinische Tests häufig besser erfasst werden (YELNIK & BONAN 2008). Klinische Gleichgewichtstests sind bei Therapiestudien relevant, wenn ein Gesamtbild der posturalen Kontrolle erfasst werden soll.

4.1 Fragestellung zur Studie 1

Die Berg Balance Scale (BERG 1989) ist ein klinischer Gleichgewichtstest zur Erfassung der posturalen Kontrolle von älteren Menschen und wurde 2005 für Patienten mit Morbus Parkinson validiert (QUTUBUDDIN et al.). Die Skala besteht aus 14 Übungen (0-4 Punkte/Übung), hat einen maximalen Summenwert von 56 Punkten (höhere Werte beschreiben eine bessere posturale Kontrolle) und kann in ca. 20 Minuten durchgeführt werden (BERG 1989; SCHOTT 2011). Obwohl der Test selbst bei neurologischen Patienten mit erhöhter Instabilität einen Deckeneffekt aufweist (GODI et al. 2013; KING et al. 2012) und obwohl Berg (1989) bei dem Test das Fehlen einer Übung zur Messung der posturalen Antwort auf einen Störreiz als Limitierung kritisierte, wurde die Skala lange Zeit als Gold-Standard verwendet.

Zur Vermeidung eines Deckeneffekts und zur differenzierten Erfassung von posturalen Kontrollmechanismen entwarfen Horak et al. (2009) den Balance Evaluation System Test (BESTest), welcher zu einer kürzeren Version (Mini-BESTest) modifiziert wurde (FRANCHIGNONI et al. 2010). Der Mini-BESTest besteht aus 14 ordinalskalierten Übungen mit 0-2 Punkten pro Übung. Die Durchführung nimmt 10 – 15 Minuten in Anspruch

(FRANCHIGNONI & VELOZO 2005; GODI et al. 2013; LEDDY et al. 2011). Der Test wurde für Patienten mit Morbus Parkinson validiert (LEDDY et al. 2011) und weist keinen Deckeneffekt auf (GODI et al. 2013; KING et al. 2012). Allerdings ist die 3-Punkt Ordinalskala der einzelnen Übungen nicht sehr differenziert abgestuft und es bleibt fraglich, ob geringe Unterschiede beziehungsweise geringe Therapieeffekte durch die Skala abgebildet werden.

Die Fullerton Advanced Balance (FAB) Scale ist ein klinischer Gleichgewichtstest und wurde für gesunde, unabhängig lebende ältere Menschen mit leichten Gleichgewichtsproblemen konzipiert (ROSE et al. 2006) und validiert (SCHOTT 2011). Aus folgenden Gründen ist die FAB Scale ein vielversprechender Test zur Bestimmung der posturalen Kontrolle bei Patienten mit Morbus Parkinson: Die Elemente der Skala sind anspruchsvoller als bei der Berg Balance Scale und Deckeneffekte könnten dadurch vermieden werden. Außerdem sind die Aufgaben der Skala (im Gegensatz zum Mini-BESTest) 5-Punkt skaliert, wodurch sich die Gleichgewichtsfähigkeit vermutlich differenzierter erfassen lässt. Des Weiteren besteht die FAB Scale aus nur 10 Übungen und lässt sich in kürzerer Zeit durchführen als der Mini-BESTest und die Berg Balance Scale (HERNANDEZ & ROSE 2008; ROSE et al. 2006).

Ob die FAB Scale ein adäquates Testverfahren zur Erfassung der posturalen Kontrolle bei Patienten mit Morbus Parkinson ist, wurde in der folgenden Studie analysiert. Dabei wurde die Hypothese gestellt, dass die FAB Scale ein valides und trotz der differenzierten Skala reliables Messinstrument zur Bestimmung der posturalen Kontrolle bei Parkinsonpatienten ist. Weiter wurden die Verteilungen der FAB Scale, des Mini-BESTest und der Berg Balance Scale verglichen und auf Deckeneffekte untersucht.

4.2 Studie 1: „Comparing the Fullerton Advanced Balance scale with the Mini-BESTest and Berg Balance Scale to assess postural control in patients with Parkinson’s Disease“

Zusammenfassung (vollständiger Artikel siehe Anhang)

Ziel der Studie war es, die FAB Scale für Patienten mit Morbus Parkinson zu validieren und mit dem Mini-BESTest und der Berg Balance Scale zu vergleichen. Hierfür wurden 85 Patienten mit Morbus Parkinson (H&Y: 1-4) eingeschlossen und mit den folgenden Tests

untersucht: FAB Scale, Mini-BESTest, Berg Balance Scale, Timed-up-and-go-test (TUG) (PODSIADLO & RICHARDSON 1991), UPDRS (FAHN & ELTON 1987) und visuelle Analogskala (zur Erfassung der subjektiven Selbstwahrnehmung der Gleichgewichtsfähigkeit).

Zur Bestimmung der Übereinstimmungsvalidität wurde die FAB Scale mit dem Mini-BESTest und dem TUG korreliert (Spearman). Interrater-Reliabilität wurde mit einer Teilgruppe (n=15) und mit drei Beobachtern erfasst. Retest-Reliabilität wurde mit einer Untergruppe (n=17) und über einem Zeitintervall von 3 (+/- 1) Tagen untersucht. Zur Bestimmung der Interrater- und Retest-Reliabilität wurden Intraklassen-Korrelationskoeffizienten (ICC) berechnet. Cronbachs Alpha wurde zur Erfassung der internen Konsistenz ermittelt. Die Verteilungen der FAB Scale, des Mini-BESTest und der Berg Balance Scale wurden deskriptiv und graphisch über Histogramme und Bland-Altman-Diagramme untersucht.

Die FAB Scale korrelierte signifikant mit dem Mini-BESTest (Spearman's Rho: 0,87) und dem TUG (Spearman's Rho: 0,83). Interrater-Reliabilität und Retest-Reliabilität waren für alle drei Skalen hoch (ICCs \geq 0,95). Cronbachs Alpha betrug 0,90 für die FAB Scale. Im Gegensatz zur Berg Balance Scale wies die FAB Scale keinen Deckeneffekt auf. Im Vergleich zum Mini-BESTest und zur Berg Balance Scale war die Verteilung der FAB Scale am symmetrischsten (Schiefe: FAB Scale: -0,54; Mini-BESTest: -1,07; Berg Balance Scale: -2,14).

Die FAB Scale ist ein valides und hoch reliables Testinstrument zur Erfassung der posturalen Kontrolle bei Patienten mit Morbus Parkinson. Der Test ist schneller durchführbar als der Mini-BESTest und die Berg Balance Scale. Deckeneffekte wie bei der Berg Balance Scale können durch die FAB Scale vermieden werden. Trotz der differenzierten Skala ist die FAB Scale genauso reliabel wie der Mini-BESTest und die Berg Balance Scale.

5 Trainierbarkeit der posturalen Kontrolle bei Patienten mit Morbus Parkinson: Studie 2

Durch die erste Studie konnte gezeigt werden, dass die FAB Scale ein geeigneter klinischer Gleichgewichtstest zur Erfassung der posturalen Kontrolle bei Patienten mit Morbus Parkinson ist. In diesem Kapitel wird die Verbesserung der posturalen Stabilität durch Training diskutiert. Es wird dabei die zweite Studie vorgestellt, bei der zwei konkurrierende Trainingsformen zur Steigerung der Gleichgewichtsfähigkeit verglichen werden und bei der die FAB Scale verwendet wird.

5.1 Allgemeine Begriffsbestimmung

In der Literatur wird keine einheitliche Terminologie für die Beschreibung von Trainingsformen mit dem primären Ziel der Verbesserung der posturalen Kontrolle verwendet. Sensomotorisches Training (BRUHN et al. 2004; GRANACHER et al. 2009; GRANACHER et al. 2007; GRUBER & GOLLHOFER 2004; GRUBER et al. 2007), neuromuskuläres Training (FILIPA et al. 2010; HOLM et al. 2004), propriozeptives Training (SILVA et al. 2010; STOLZENBERG et al. 2013) und Gleichgewichts- beziehungsweise Balancetraining (HIRSCH et al. 2003; SMANIA et al. 2010) sind häufig verwendete Bezeichnungen. Sensomotorisches- und neuromuskuläres Training sind sehr weitläufige Begriffe, die auch andere Trainingsformen, die nicht der Schulung der Standstabilität dienen, beinhalten können. Die Bezeichnung propriozeptives Training beinhaltet nur die sensorische Informationsaufnahme. Dabei wird die Weiterverarbeitung als motorische Antwort nicht berücksichtigt. Die Begriffe Gleichgewichts- beziehungsweise Balancetraining geben zwar keine Auskunft über die zu Grunde liegenden neuromuskulären Mechanismen, bringen aber die Zielsetzung des Trainings am besten zum Ausdruck und werden deshalb in dieser Arbeit verwendet. Die Trainingsinhalte können dabei stark variieren. Zudem gibt es derzeit noch keine wissenschaftlich fundierten Richtlinien für die Durchführung dieser Trainingsform. In Anlehnung an Froböse et al. (2010) wird in dieser Arbeit Gleichgewichtstraining als Trainingsintervention verstanden, bei der durch Veränderung der Rahmenbedingungen die sensorische Informationsaufnahme reduziert, beziehungsweise verändert wird und dadurch die Wahrnehmung, die Verarbeitung und die Umsetzung in eine adäquate Bewegung geschult

werden. Die Standstabilität kann dabei durch Standaufgaben auf instabilen Unterlagen, durch eine veränderte Blickrichtung des Trainierenden, durch das vollständige Schließen der Augen etc. trainiert werden.

5.2 Stand der Forschung und Fragestellung:

Trainingsinterventionen zur Verbesserung der posturalen Kontrolle

In den letzten Jahren wurde eine Vielzahl an Studien durchgeführt, die die Effekte von Bewegungstherapie auf die posturale Kontrolle bei Patienten mit Morbus Parkinson untersucht haben. Die durchgeführten Trainingsprogramme sind sehr vielseitig und beinhalten Gleichgewichtstraining (HIRSCH et al. 2003; PICELLI et al. 2014; SMANIA et al. 2010), Tai Chi (HACKNEY & EARHART 2008; LI et al. 2012), Tanzinterventionen (EARHART 2009; HACKNEY & EARHART 2010), Ganzkörpervibrationstraining (EBERSBACH et al. 2008; SHARIFIFAR et al. 2014), Laufbandtraining (CAKIT et al. 2007; GANESAN et al. 2014; HARRO et al. 2014; HERMAN et al. 2009) und weitere Trainingsformen. Da sich die Studien bezüglich Trainingsbelastung, Messverfahren und Patientenkollektiv unterscheiden, ist ein Vergleich der Effektivität von unterschiedlichen Trainingsprogrammen durch verschiedene Studien nicht möglich. Es bedarf weiterer Studien, die die Effekte von zwei oder mehr Interventionen direkt vergleichen.

Gleichgewichtstraining ist eines der am häufigsten angewendeten Trainingsprogramme bei der Therapie von posturaler Instabilität. Trotz der häufigen Anwendung wurden kaum Studien durchgeführt, die die Effekte von Gleichgewichtstraining auf die posturale Kontrolle bei Patienten mit Morbus Parkinson untersuchen. Die Literatur wurde diesbezüglich durchsucht und es wurden Studien mit einer Fallzahl von mindestens 10 Patienten pro Übungsgruppe berücksichtigt. Außerdem wurden nur Studien mit isoliertem Balancetraining eingeschlossen, da die Effekte von multidimensionalen Trainingsprogrammen nur schwer interpretierbar sind. Bezüglich dieser Suchkriterien sind derzeit lediglich zwei Studien bekannt, die den Einfluss von Gleichgewichtstraining bei Patienten mit Morbus Parkinson untersucht haben: Smania et al. (2010) untersuchten die Effekte eines 7-wöchigen Gleichgewichtstrainings bei 64 Patienten mit Morbus Parkinson. Es wurde dabei dreimal pro Woche 50 Minuten trainiert. Die Interventionsgruppe führte Balancetraining auf instabilen Unterlagen durch, wobei die

Kontrollgruppe Beweglichkeits- und verschiedene Koordinationsübungen durchführte. Vor und nach der Intervention sowie vier Wochen im *Follow-up* wurden als primäre Testverfahren die Berg Balance Scale, die Activities-Specific Balance Confidence Scale, ein posturaler Transfertest (vom Liegen zum Sitzen, vom Sitzen zum Stehen), Posturographie (Probanden sollten ihren COP zu vorgegebenen Punkten verlagern) und ein Sturzkalender (Anzahl der Stürze im jeweiligen Monat vor der Messung) durchgeführt. Die Interventionsgruppe verbesserte sich bei allen primären Testverfahren signifikant und die Effekte waren signifikant stärker als bei der Kontrollgruppe. Eine erst kürzlich veröffentlichte Studie untersuchte die Effekte von Gleichgewichtstraining im Vergleich zu einem roboterunterstützten Gangtraining bei 66 Patienten mit Morbus Parkinson (PICELLI et al. 2014). Trainiert wurde über 4 Wochen dreimal wöchentlich 45 Minuten. Vor und nach der Intervention sowie 4 Wochen im *Follow-up* wurde die Berg Balance Scale als Hauptparameter erhoben. Es konnte hierbei kein signifikanter Unterschied zwischen den Trainingsformen gefunden werden.

Das Kraftdefizit der Patienten wurde in Kapitel 3 detailliert beschrieben. Verringerte Kraftfähigkeiten zählen neben posturaler Instabilität zu den unabhängigen Risikofaktoren von Stürzen (LATT et al. 2009). Außerdem konnte ein Zusammenhang zwischen Kraftfähigkeit und posturaler Stabilität gezeigt werden (NALLEGOWDA et al. 2004; NOCERA et al. 2010). Es stellt sich die Frage, ob sich die Standstabilität durch eine Verbesserung der Kraftfähigkeit steigern lässt. Es gibt derzeit nur wenige Studien, die die Auswirkungen von Krafttraining bei Patienten mit Morbus Parkinson untersucht haben. Geringe Probandenzahlen und ein Mangel an randomisiert-kontrollierten Studien wurden in mehreren Übersichtsarbeiten kritisiert (BRIENESSE & EMERSON 2013; DAVID et al. 2012; LIMA et al. 2013). Die Effekte von Krafttraining auf die posturale Kontrolle der Patienten wurden bei zwei Studien analysiert (SCHILLING et al. 2010; SHEN & MAK 2014). Bei der Studie von Schilling et al. (2010) trainierten die Probanden der Trainingsgruppe (n=8) über 8 Wochen zweimal wöchentlich die Beinmuskulatur mit dem Ziel der Maximalkraftsteigerung. Die Kontrollgruppe (n=7) bekam keine Intervention. Bezüglich der posturalen Kontrolle konnten keine signifikanten Veränderungen ermittelt werden (Testverfahren: Activities-Specific Balance Confidence Scale, Timed-Up-and-Go-Test). Allerdings ist die Aussagekraft der Studie auf Grund der geringen Probandenzahl, der inaktiven Kontrollgruppe sowie der zur Erhebung der posturalen Stabilität eingesetzten Messverfahren begrenzt. Bei der erst kürzlich veröffentlichten Studie von Shen und Mak (2014) wurde ein Schritt- und Gangtraining mit Krafttraining der

Beinmuskulatur verglichen. Bei dem Schritt- und Gangtraining kamen ein computergesteuertes Tanzschrittsystem sowie Perturbationen beim Gehen auf einem Laufband zum Einsatz. 51 Patienten nahmen an der Studie teil und trainierten über 12 Wochen. Das primäre Ziel der Studie war die Erhebung der sturzassoziierten Selbstwirksamkeit, wofür die Activities-Specific Balance Confidence Scale eingesetzt wurde. Posturale Kontrolle wurde als sekundäres Ziel über einen LOS-Test erhoben. Krafttraining führte hierbei zu einer signifikanten Verbesserung der Stabilitätslimits. Ein multidimensionaler klinischer Test zur Erhebung der posturalen Kontrolle wurde bei dieser Studie nicht eingesetzt.

Die Effekte von Krafttraining – insbesondere auf die posturale Kontrolle – und die zu Grunde liegenden Mechanismen sind noch nicht ausreichend geklärt. Die Verbesserung der Standstabilität auf Grund von verbesserten Krafteigenschaften könnte als Kompensationsstrategie angesehen werden. Eine kürzlich veröffentlichte Studie, bei der Krafttraining mit Gleichgewichtstraining bei gesunden älteren Menschen verglichen wurde, bestätigt diesen Ansatz (JOSHUA et al. 2014). Die Autoren berichten von einer erhöhten Verbesserung der Standstabilität durch Krafttraining im Vergleich zu Balancetraining.

Ziel der im folgenden Kapitel beschriebenen Studie war es, die Effektivität von Krafttraining mit der Effektivität von Gleichgewichtstraining zur Steigerung der posturalen Kontrolle bei Patienten mit Morbus Parkinson zu vergleichen. Zu Grunde liegende Mechanismen wurden dabei untersucht, um das Verständnis möglicher Trainingseffekte zu vertiefen.

5.3 Studie 2: „Resistance Training versus Balance Training to improve postural control in patients with Parkinson’s Disease – a randomized controlled rater blinded trial“

Zusammenfassung (vollständiger Artikel siehe Anhang)

Ziel der Studie war es, die Effektivität von Krafttraining im Vergleich zu Gleichgewichtstraining zur Verbesserung der posturalen Kontrolle bei Patienten mit Morbus Parkinson zu untersuchen. Hierfür wurden 40 Patienten mit idiopathischem Parkinsonsyndrom und erhöhter posturaler Instabilität (FAB Scale \leq 25 Punkte)

eingeschlossen. Die Patienten wurden randomisiert in eine Krafttrainings- und eine Gleichgewichtstrainingsgruppe. Beide Gruppen trainierten 7 Wochen zweimal wöchentlich über 60 Minuten. Das Krafttraining beinhaltete das Training der Beinmuskulatur mit dem Ziel der Maximalkraftsteigerung. Übungen wurden mit dem eigenen Körpergewicht, mit Therabändern und mit Gewichtsmanschetten als Widerstand durchgeführt. Beim Gleichgewichtstraining wurde die Standstabilität durch ein- oder beidbeiniges Balancieren auf festem oder instabilem Untergrund mit verschiedenen Variationen trainiert. Die Probanden wurden vor, nach der Trainingsphase und 4 Wochen im *Follow-up* untersucht. Hauptoutcome Parameter zur Bestimmung der posturalen Kontrolle war die FAB Scale. Die folgenden Tests wurden als sekundäre Verfahren durchgeführt: Analyse der COM-Schwankung bei translatorischen Perturbationsreizen der Standfläche, TUG, Clinical-Global-Improvement (GUY 1976), UPDRS, Parkinson's Disease Questionnaire (PDQ-39) (JENKINSON et al. 1997), Beck-Depressions-Inventar (BECK et al. 1961), Ganganalyse und Erhebung der Maximal- und Explosivkraft mittels Beinpresse. Die klinischen Tests wurden verblindet erhoben und gefilmt. Die Videos wurden durch einen weiteren verblindeten Untersucher bewertet.

Im Gegensatz zur Gleichgewichtsgruppe verbesserte sich die Krafttrainingsgruppe signifikant bei der FAB Scale (+2,4 Punkte) und beim TUG (-1,7 Sekunden) ($p < 0,05$). Es gab keine signifikanten Unterschiede zwischen den Therapieeffekten der beiden Gruppen. Innerhalb der Krafttrainingsgruppe korrelierten die Verbesserungen bei der FAB Scale signifikant mit den Verbesserungen der Explosivkraft und der Gangvariabilität.

Die posturale Kontrolle konnte durch Krafttraining verbessert werden. Die Studie zeigt Tendenzen, dass Krafttraining effektiver sein könnte als Gleichgewichtstraining zur Verbesserung der Standstabilität bei Patienten mit Morbus Parkinson. Studien mit größeren Probandenzahlen sind notwendig, um insbesondere den Zusammenhang zwischen der Verbesserung der posturalen Kontrolle und der Steigerung der Explosivkraft zu untersuchen.

6 Modulation des Gangbildes durch asymmetrisches Laufbandtraining: Studie 3

6.1 Fragestellung zur Studie 3

Dieser Teil der Arbeit befasst sich mit der Gangstörung von Patienten mit Morbus Parkinson. Giladi et al. (2013) unterscheiden zwischen einer kontinuierlichen Beeinträchtigung des Gangbildes und einer episodischen Gangstörung. Die kontinuierliche Einschränkung ist bei Parkinsonpatienten durch eine verlangsamte Gehgeschwindigkeit, eine reduzierte Schrittlänge und eine erhöhte Doppelstandphase gekennzeichnet (EBERSBACH et al. 1999; SOFUWA et al. 2005) (siehe Übersichtsarbeit (FASANO & BLOEM 2013)). Zudem haben Patienten mit Morbus Parkinson eine erhöhte Schrittzeitvariabilität, was ein Marker eines erhöhten Sturzrisikos ist (HAUSDORFF 2005; HAUSDORFF et al. 2001; SCHAAFSMA et al. 2003). Zwei weitere Merkmale der kontinuierlichen Beeinträchtigung sind Symmetrie und bilaterale Koordination. Die Gangsymmetrie gibt Auskunft über die Bewegungsdurchführung von einem Bein im Vergleich zur Bewegungsdurchführung des anderen Beins und kann durch eine zeitliche oder örtliche Dimension gekennzeichnet werden (PLOTNIK et al. 2005). Bilaterale Koordination beschreibt die Schrittkoordination zwischen dem rechten und linken Bein. Die bilaterale Koordination beinhaltet zum einen den durchschnittlichen Fersenkontakt eines Beines in Relation zum Schrittzklus sowie die Variabilität der Fersenkontakte in Relation zum Durchschnittswert (PLOTNIK et al. 2007).

Zu den episodischen Gangstörungen zählt *Freezing of gait*⁴ (FOG). FOG ist eine Gangblockade, die definiert ist als „brief, episodic absence or marked reduction of forward progression of the feet despite having the intention to walk“ (NUTT et al. 2011, S. 734). Patienten empfinden FOG häufig als Festkleben der Füße am Boden (GILADI et al. 2001). FOG zählt zu den episodischen Gangstörungen, da es plötzlich, unerwartet und kurzzeitig auftritt (GILADI et al. 2013). Im frühen Krankheitsstadium leiden 21 – 27 % der

⁴ Im Folgenden werden einige Ausdrücke mit der in der englisch-sprachigen Fachliteratur üblichen englischen Bezeichnung genannt. Dies entspricht der Notation des englischen Artikels (Studie 3, siehe Anhang) und soll zu einem leichteren Verständnis führen.

Parkinsonpatienten an FOG (GILADI et al. 2001; TAN et al. 2011). Im späten Stadium sind bis zu 80% der Patienten betroffen (HELY et al. 2008; TAN et al. 2011). FOG gilt als einer der unabhängigen Risikofaktoren von Stürzen (LATT et al. 2009) und schränkt die Patienten hinsichtlich ihrer Mobilität und ihrer Lebensqualität ein (KERR et al. 2010; MOORE et al. 2007). Die Pathophysiologie und die zu Grunde liegenden Mechanismen von FOG sind derzeit ungeklärt. In einer kürzlich veröffentlichten Übersichtsarbeit wurden verschiedene Erklärungsmodelle vorgestellt (NIEUWBOER & GILADI 2013). Ein Erklärungsansatz von FOG beruht auf der Annahme, dass FOG ein Resultat einer eingeschränkten, kontinuierlichen Gangstörung in Kombination mit einer kognitiven, motorischen oder emotionalen Zusatzbelastung sein könnte. Dabei wird vermutet, dass die durch kontinuierliche Gangstörungen eingeschränkte Gangqualität durch eine Zusatzbelastung eine Reizschwelle erreicht, bei der die Gangleistung einbricht und der Gang vollständig einfriert (NIEUWBOER & GILADI 2013; PLOTNIK et al. 2012; VERCRUYSSSE et al. 2014).

Es ist derzeit nicht geklärt, welche kontinuierlichen Gangparameter den Haupteinfluss auf FOG haben. Eine Arbeitsgruppe vermutet, dass bilaterale Koordination, Asymmetrie und Schrittzeitvariabilität die Haupteinflussfaktoren sind, da diese Komponenten besonders bei Patienten mit FOG im Vergleich zu Patienten ohne FOG eingeschränkt sind (PETERSON et al. 2012; PLOTNIK et al. 2005; PLOTNIK et al. 2008; PLOTNIK & HAUSDORFF 2008). Andere Autoren sehen eine schrittweise Verkürzung der Schrittlänge (*sequence effect*) in Kombination mit einer generell verkürzten Schrittlänge als Hauptursache von FOG (CHEE et al. 2009; IANSEK et al. 2006).

Gelingt es, die kontinuierliche Gangstörung, insbesondere die Parameter Asymmetrie, bilaterale Koordination und *sequence effect* zu verbessern, so könnte dadurch die Reizschwelle, an der FOG auftritt, erhöht werden. Somit könnte die FOG-Häufigkeit reduziert werden, wodurch Stürze vermieden werden könnten. Eine geeignete Therapie zur Verbesserung der genannten Gangparameter existiert derzeit nicht.

Die im Folgenden beschriebene Studie beruht auf dem Ansatz durch das Gehen auf einem Split-Belt Laufband die Parameter Symmetrie, bilaterale Koordination und *sequence effect* positiv zu verändern. Bei einem Split-Belt Laufband kann die Gehgeschwindigkeit von jedem Bein separat gesteuert werden. Dadurch kann ein asymmetrischer Gang erzeugt werden. Ein Split-Belt Laufband bietet somit eine einzigartige Möglichkeit das Gangbild zu modulieren.

6.2 Studie 3: „Split-Belt Locomotion in Parkinson’s Disease Links Asymmetry, Dyscoordination and Sequence Effect”

Zusammenfassung (vollständiger Artikel siehe Anhang)

Ziel der Studie war es, die Kurzzeiteffekte von unterschiedlichen Split-Belt Laufbandbedingungen bei Patienten mit Morbus Parkinson zu untersuchen. 20 Patienten mit idiopathischem Parkinsonsyndrom wurden hierfür eingeschlossen. Die Patienten liefen zunächst 5 Minuten auf einem Split-Belt Laufband mit beiden Laufbandseiten in der gleichen Geschwindigkeit (*Tied-Belt*⁵ (TB); TB1). Dann folgten 10 Minuten Split-Belt Bedingung: entweder 25-prozentige Reduzierung der Bandgeschwindigkeit des Beines mit der kürzeren Schrittlänge (*Worst Side Reduction* (WSR)) oder des Beines mit der längeren Schrittlänge (*Best Side Reduction* (BSR)). Schließlich folgten 5 Minuten TB2. Räumliche und zeitliche Gangparameter wurden am Ende von TB1, am Anfang und am Ende von WSR/BSR und am Anfang von TB2 erhoben. Patienten wurden im OFF untersucht.

In der Bedingung TB2 nach der Split-Belt Bedingung BSR waren die bilaterale Koordination, die Gangsymmetrie und die Anzahl der *sequences* signifikant verbessert im Vergleich zu der Bedingung TB1 ($p < 0,01$). Die Gangasymmetrie reduzierte sich auf Grund einer signifikanten Steigerung der Schrittlänge des Beines mit der kürzeren Schrittlänge ($p < 0,01$). Unter der TB2-Bedingung nach der WSR hatten die Patienten signifikant schlechtere Werte der bilateralen Koordination ($p < 0,01$), wohingegen die Gangsymmetrie und die Anzahl der *sequences* unverändert blieben.

Patienten mit Morbus Parkinson sind in der Lage, sich an unterschiedliche Split-Belt-Bedingungen anzupassen und Kurzzeiteffekte bleiben erhalten, wenn Patienten danach unter Laufbandbedingungen mit gleichen Bandgeschwindigkeiten gehen. Interessanterweise wird der Gang unterschiedlich moduliert, je nachdem ob die Geschwindigkeit des Beines mit der kürzeren oder längeren Schrittlänge reduziert wird. Bilaterale Koordination, Asymmetrie und Anzahl der *sequences* waren signifikant verbessert nach einer 10-minütigen Split-Belt Phase mit Reduzierung der Geschwindigkeit des Beines mit der längeren Schrittweite. Da

⁵ Zum leichteren Verständnis werden im Folgenden die englischen Bezeichnungen aus dem Artikel (siehe Anhang) verwendet.

verschlechterte bilaterale Koordination, Asymmetrie und der *sequence effect* in Zusammenhang mit FOG stehen, könnte Split-Belt Laufbandtraining eine wichtige Therapieform zur Verbesserung des Gangbildes und zur Reduzierung der FOG-Häufigkeit sein. Ob Langzeiteffekte umsetzbar sind, muss in weiteren Studien untersucht werden.

7 Zusammenfassung und Ausblick

Posturale Instabilität und Gangstörungen führen zu einem erhöhten Sturzrisiko bei Patienten mit Morbus Parkinson. Eingeschränkte Mobilität und Angst vor weiteren Stürzen schränken die Lebensqualität der Patienten ein. Im Rahmen dieser Arbeit wurde ein Beitrag zur Optimierung der Therapie von Gleichgewichts- und Gangstörungen geleistet.

Die Validierung des Gleichgewichtstests FAB Scale und der Vergleich mit anderen Messverfahren brachte hervor, dass bisher verwendete Verfahren optimierbar sind. Es konnte gezeigt werden, dass die FAB Scale ein valides und ein reliables Messinstrument zur Erhebung der posturalen Kontrolle bei Parkinsonpatienten ist. Im Gegensatz zu anderen Verfahren können Deckeneffekte durch den Einsatz der FAB Scale vermieden werden. Eine schnelle und einfache Durchführbarkeit des Tests sind weitere Vorteile. Durch die differenzierte Skalierung des Tests könnten geringe Veränderungen der posturalen Kontrolle messbar sein. Die Messbarkeit von Therapieeffekten und die klinische Relevanz sollten durch zukünftige Studien untersucht werden. Ob sich das Sturzrisiko von Patienten mit Morbus Parkinson durch die FAB Scale erheben lässt, ist eine weitere Fragestellung, die derzeit ungeklärt ist.

Im zweiten Teil dieser Arbeit wurde Krafttraining mit Gleichgewichtstraining unter dem Ziel der Verbesserung der posturalen Kontrolle bei Patienten mit Morbus Parkinson verglichen. Dabei konnte kein signifikanter Unterschied zwischen den Therapieeffekten beider Trainingsformen gefunden werden. Dennoch konnte durch die Studie eine signifikante Steigerung der Standstabilität durch Krafttraining nachgewiesen werden. Die Untersuchung zeigt Tendenzen, dass Krafttraining effektiver als Gleichgewichtstraining zur Verbesserung der posturalen Kontrolle bei Parkinsonpatienten sein könnte. Außerdem wurde ein Zusammenhang zwischen der Verbesserung der Gleichgewichtsfähigkeit und der Steigerung der Explosivkraft sichtbar. Es existieren kaum Studien, die den Einfluss von Krafttraining bei Morbus Parkinson untersucht haben. Es besteht weiter Bedarf an randomisiert kontrollierten Studien mit hohen Fallzahlen, welche die Effekte von Krafttraining und insbesondere die zu Grunde liegenden Mechanismen untersuchen.

Die Verbesserung der Gangstörung war Thema des dritten Teils dieser Arbeit. Dabei wurde untersucht, inwiefern das Gangbild durch das Gehen auf einem Split-Belt Laufband

modulierbar ist. Der Einsatz eines Split-Belt Laufbands ist eine einzigartige Option, den schlecht koordinierten und asymmetrischen Gang von Parkinsonpatienten und anderen Patientengruppen zu beeinflussen. Das Split-belt Laufband bietet die Möglichkeit, die kontinuierliche Gangstörung der Patienten zu verbessern. Die durchgeführte Studie zeigt, dass das Gangbild durch ein kurzzeitiges Gehen auf einem Split-Belt Laufband mit Reduzierung der Geschwindigkeit des Beines mit der längeren Schrittlänge positiv verändert wird. Dabei werden insbesondere die Gangparameter verbessert, welche im Zusammenhang mit FOG gesehen werden. Es bleibt zu klären, ob Langzeiteffekte durch ein Split-Belt Laufbandtraining möglich sind und ob dadurch die FOG-Häufigkeit verringert werden kann. Des Weiteren ist nicht geklärt, welche Einstellung des Laufbandes die bestmöglichen Erfolge liefert. Vermutlich wird die Geschwindigkeitsdifferenz der beiden Bänder einen Einfluss auf die Effekte haben. Derzeit werden Split-Belt Laufbänder in der Forschung eingesetzt. Sollten sich die positiven Effekte durch längerfristige Trainingsinterventionen bestätigen, wäre der Einsatz von Split-Belt Laufbändern in der bewegungstherapeutischen Behandlung denkbar.

Zusammenfassend konnte durch diese Arbeit gezeigt werden, dass die Erhebung und Bewegungstherapie der posturalen Kontrolle optimierbar ist, und dass eine Modulation des Gangbildes der Patienten möglich ist.

Literaturverzeichnis

- ADKIN, A. L., BLOEM, B. R. & ALLUM, J. H. (2005). Trunk sway measurements during stance and gait tasks in Parkinson's disease. *Gait Posture*, 22(3), 240-249.
- ALLEN, N. E., CANNING, C. G., SHERRINGTON, C. & FUNG, V. S. (2009). Bradykinesia, muscle weakness and reduced muscle power in Parkinson's disease. *Movement Disorders*, 24(9), 1344-1351.
- ALLEN, N. E., SHERRINGTON, C., SURIYARACHCHI, G. D., PAUL, S. S., SONG, J. & CANNING, C. G. (2012). Exercise and motor training in people with Parkinson's disease: a systematic review of participant characteristics, intervention delivery, retention rates, adherence, and adverse events in clinical trials. *Parkinson's disease*, 2012, 854-869.
- ASHBURN, A., STACK, E., PICKERING, R. M. & WARD, C. D. (2001). Predicting fallers in a community-based sample of people with Parkinson's disease. *Gerontology*, 47(5), 277-281.
- BARTOLIC, A., PIRTOSEK, Z., ROZMAN, J. & RIBARIC, S. (2005). Postural stability of Parkinson's disease patients is improved by decreasing rigidity. *Eur J Neurol*, 12(2), 156-159.
- BECK, A. T., WARD, C. H., MENDELSON, M., MOCK, J. & ERBAUGH, J. (1961). An inventory for measuring depression. *Archives of general psychiatry*, 4, 561-571.
- BERG, K. (1989). Measuring balance in the elderly: preliminary development of an instrument. *Physiotherapy Canada*, 41(6), 304-311.
- BLASZCZYK, J. W. & ORAWIEC, R. (2011). Assessment of postural control in patients with Parkinson's disease: sway ratio analysis. *Hum Mov Sci*, 30(2), 396-404.
- BLASZCZYK, J. W., ORAWIEC, R., DUDA-KLADOWSKA, D. & OPALA, G. (2007). Assessment of postural instability in patients with Parkinson's disease. *Exp Brain Res*, 183(1), 107-114.
- BLOEM, B. R., BECKLEY, D. J., VAN DIJK, J. G., ZWINDERMAN, A. H., REMLER, M. P. & ROOS, R. A. (1996). Influence of dopaminergic medication on automatic postural responses and balance impairment in Parkinson's disease. *Movement Disorders*, 11(5), 509-521.
- BLOEM, B. R., GRIMBERGEN, Y. A., VAN DIJK, J. G. & MUNNEKE, M. (2006). The "posture second" strategy: a review of wrong priorities in Parkinson's disease. *J Neurol Sci*, 248(1-2), 196-204.
- BLOEM, B. R., HAUSDORFF, J. M., VISSER, J. E. & GILADI, N. (2004). Falls and freezing of gait in Parkinson's disease: a review of two interconnected, episodic phenomena. *Movement Disorders*, 19(8), 871-884.
- BOWER, J. H., MARAGANORE, D. M., MCDONNELL, S. K. & ROCCA, W. A. (1999). Incidence and distribution of parkinsonism in Olmsted County, Minnesota, 1976-1990. *Neurology*, 52(6), 1214-1220.
- BRAAK, H., DEL TREDICI, K., RUB, U., DE VOS, R. A., JANSEN STEUR, E. N. & BRAAK, E. (2003). Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiology of aging*, 24(2), 197-211.
- BRIENESSE, L. A. & EMERSON, M. N. (2013). Effects of resistance training for people with Parkinson's disease: a systematic review. *J Am Med Dir Assoc*, 14(4), 236-241.
- BRUHN, S., KULLMANN, N. & GOLLHOFER, A. (2004). The effects of a sensorimotor training and a strength training on postural stabilisation, maximum isometric contraction and jump performance. *Int J Sports Med*, 25(1), 56-60.
- CAKIT, B. D., SARACOGLU, M., GENÇ, H., ERDEM, H. R. & INAN, L. (2007). The effects of incremental speed-dependent treadmill training on postural instability and fear of falling in Parkinson's disease. *Clin Rehabil*, 21(8), 698-705.
- CARPENTER, M. G., ALLUM, J. H., HONEGGER, F., ADKIN, A. L. & BLOEM, B. R. (2004). Postural abnormalities to multidirectional stance perturbations in Parkinson's disease. *J Neurol Neurosurg Psychiatry*, 75(9), 1245-1254.
- CHEE, R., MURPHY, A., DANOUDIS, M., GEORGIU-KARISTIANIS, N. & IANSEK, R. (2009). Gait freezing in Parkinson's disease and the stride length sequence effect interaction. *Brain*, 132(Pt 8), 2151-2160.

- CORCOS, D. M., CHEN, C. M., QUINN, N. P., MCAULEY, J. & ROTHWELL, J. C. (1996). Strength in Parkinson's disease: relationship to rate of force generation and clinical status. *Ann Neurol*, 39(1), 79-88.
- DAVID, F. J., RAFFERTY, M. R., ROBICHAUD, J. A., PRODOEHL, J., KOHRT, W. M., VAILLANCOURT, D. E., et al. (2012). Progressive resistance exercise and Parkinson's disease: a review of potential mechanisms. *Parkinson's disease*, 2012, 124527.
- DIBBLE, L. E., ADDISON, O. & PAPA, E. (2009). The effects of exercise on balance in persons with Parkinson's disease: a systematic review across the disability spectrum. *J Neurol Phys Ther*, 33(1), 14-26.
- DIMITROVA, D., HORAK, F. B. & NUTT, J. G. (2004). Postural muscle responses to multidirectional translations in patients with Parkinson's disease. *J Neurophysiol*, 91(1), 489-501.
- DIMITROVA, D., NUTT, J. & HORAK, F. B. (2004). Abnormal force patterns for multidirectional postural responses in patients with Parkinson's disease. *Exp Brain Res*, 156(2), 183-195.
- DORSEY, E. R., CONSTANTINESCU, R., THOMPSON, J. P., BIGLAN, K. M., HOLLOWAY, R. G., KIEBURTZ, K., et al. (2007). Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. *Neurology*, 68(5), 384-386.
- EARHART, G. M. (2009). Dance as therapy for individuals with Parkinson disease. *European journal of physical and rehabilitation medicine*, 45(2), 231-238.
- EBERSBACH, G., EDLER, D., KAUFHOLD, O. & WISSEL, J. (2008). Whole body vibration versus conventional physiotherapy to improve balance and gait in Parkinson's disease. *Archives of physical medicine and rehabilitation*, 89(3), 399-403.
- EBERSBACH, G., SOJER, M., VALLDEORIOLA, F., WISSEL, J., MULLER, J., TOLOSA, E., et al. (1999). Comparative analysis of gait in Parkinson's disease, cerebellar ataxia and subcortical arteriosclerotic encephalopathy. *Brain*, 122 (Pt 7), 1349-1355.
- FAHN, S. & ELTON, R. L. (1987). Unified Parkinson's Disease Rating Scale. In S. FAHN, C. D. MARSDEN, D. CALNE & M. GOLDSTEIN (Hrsg.), *Recent developments in Parkinson's disease* (S. 153-163). Florham Park (NJ): MacMillan Health Care Information.
- FASANO, A. & BLOEM, B. R. (2013). Gait disorders. *Continuum (Minneap Minn)*, 19(5), 1344-1382.
- FILIPA, A., BYRNES, R., PATERNO, M. V., MYER, G. D. & HEWETT, T. E. (2010). Neuromuscular training improves performance on the star excursion balance test in young female athletes. *The Journal of orthopaedic and sports physical therapy*, 40(9), 551-558.
- FOLLAND, J. P., HAAS, B. & CASTLE, P. C. (2011). Strength and activation of the knee musculature in Parkinson's disease: effect of medication. *NeuroRehabilitation*, 29(4), 405-411.
- FRANCHIGNONI, F., HORAK, F., GODI, M., NARDONE, A. & GIORDANO, A. (2010). Using psychometric techniques to improve the Balance Evaluation Systems Test: the mini-BESTest. *Journal of rehabilitation medicine*, 42(4), 323-331.
- FRANCHIGNONI, F. & VELOZO, C. A. (2005). Use of the Berg Balance Scale in rehabilitation evaluation of patients with Parkinson's disease. *Arch Phys Med Rehabil*, 86(11), 2225-2226.
- FRENKLACH, A., LOUIE, S., KOOP, M. M. & BRONTE-STEWART, H. (2009). Excessive postural sway and the risk of falls at different stages of Parkinson's disease. *Movement Disorders*, 24(3), 377-385.
- FROBÖSE, I., NELLESSEN-MARTENS, G. & WILKE, C. (2010). *Training in der Therapie: Grundlagen und Praxis* (3. überarbeitete Aufl.). München: Urban & Fischer.
- GANESAN, M., SATHYAPRABHA, T. N., GUPTA, A. & PAL, P. K. (2014). Effect of partial weight-supported treadmill gait training on balance in patients with Parkinson disease. *PM & R : the journal of injury, function, and rehabilitation*, 6(1), 22-33.
- GILADI, N., HORAK, F. B. & HAUSDORFF, J. M. (2013). Classification of gait disturbances: distinguishing between continuous and episodic changes. *Movement disorders*, 28(11), 1469-1473.
- GILADI, N., MCDERMOTT, M. P., FAHN, S., PRZEDBORSKI, S., JANKOVIC, J., STERN, M., et al. (2001). Freezing of gait in PD: prospective assessment in the DATATOP cohort. *Neurology*, 56(12), 1712-1721.
- GILADI, N., TREVES, T. A., SIMON, E. S., SHABTAI, H., ORLOV, Y., KANDINOV, B., et al. (2001). Freezing of gait in patients with advanced Parkinson's disease. *J Neural Transm*, 108(1), 53-61.

- GODI, M., FRANCHIGNONI, F., CALIGARI, M., GIORDANO, A., TURCATO, A. M. & NARDONE, A. (2013). Comparison of reliability, validity, and responsiveness of the mini-BESTest and Berg Balance Scale in patients with balance disorders. *Physical therapy*, 93(2), 158-167.
- GOODWIN, V. A., RICHARDS, S. H., TAYLOR, R. S., TAYLOR, A. H. & CAMPBELL, J. L. (2008). The effectiveness of exercise interventions for people with Parkinson's disease: a systematic review and meta-analysis. *Movement Disorders*, 23(5), 631-640.
- GRANACHER, U., GRUBER, M. & GOLLHOFER, A. (2009). Auswirkungen von sensomotorischem Training auf die posturale Kontrolle älterer Männer. *Deutsche Zeitschrift für Sportmedizin*, 60(12), 387-392.
- GRANACHER, U., GRUBER, M., STRASS, D. & GOLLHOFER, A. (2007). Auswirkungen von sensomotorischem Training im Alter auf die Maximal- und Explosivkraft. *Deutsche Zeitschrift für Sportmedizin*, 58(12), 446-451.
- GRUBER, M. & GOLLHOFER, A. (2004). Impact of sensorimotor training on the rate of force development and neural activation. *Eur J Appl Physiol*, 92(1-2), 98-105.
- GRUBER, M., GRUBER, S. B., TAUBE, W., SCHUBERT, M., BECK, S. C. & GOLLHOFER, A. (2007). Differential effects of ballistic versus sensorimotor training on rate of force development and neural activation in humans. *Journal of strength and conditioning research*, 21(1), 274-282.
- GUY, W. (1976). *ECDEU assessment manual for psychopharmacology*. Rockville, Md: U.S. Dept. of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute of Mental Health, Psychopharmacology Research Branch, Division of Extramural Research Programs.
- HACKNEY, M. E. & EARHART, G. M. (2008). Tai Chi improves balance and mobility in people with Parkinson disease. *Gait Posture*, 28(3), 456-460.
- HACKNEY, M. E. & EARHART, G. M. (2010). Effects of dance on gait and balance in Parkinson's disease: a comparison of partnered and nonpartnered dance movement. *Neurorehabilitation and neural repair*, 24(4), 384-392.
- HARRO, C. C., SHOEMAKER, M. J., FREY, O., GAMBLE, A. C., HARRING, K. B., KARL, K. L., et al. (2014). The effects of speed-dependent treadmill training and rhythmic auditory-cued overground walking on balance function, fall incidence, and quality of life in individuals with idiopathic Parkinson's disease: a randomized controlled trial. *NeuroRehabilitation*, 34(3), 541-556.
- HAUSDORFF, J. M. (2005). Gait variability: methods, modeling and meaning. *Journal of neuroengineering and rehabilitation*, 2, 19.
- HAUSDORFF, J. M., RIOS, D. A. & EDELBERG, H. K. (2001). Gait variability and fall risk in community-living older adults: a 1-year prospective study. *Archives of physical medicine and rehabilitation*, 82(8), 1050-1056.
- HELY, M. A., REID, W. G., ADENA, M. A., HALLIDAY, G. M. & MORRIS, J. G. (2008). The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years. *Movement disorders*, 23(6), 837-844.
- HERMAN, T., GILADI, N. & HAUSDORFF, J. M. (2009). Treadmill training for the treatment of gait disturbances in people with Parkinson's disease: a mini-review. *Journal of neural transmission*, 116(3), 307-318.
- HERNANDEZ, D. & ROSE, D. J. (2008). Predicting which older adults will or will not fall using the Fullerton Advanced Balance scale. *Arch Phys Med Rehabil*, 89(12), 2309-2315.
- HIRSCH, M. A., TOOLE, T., MAITLAND, C. G. & RIDER, R. A. (2003). The effects of balance training and high-intensity resistance training on persons with idiopathic Parkinson's disease. *Arch Phys Med Rehabil*, 84(8), 1109-1117.
- HOF, A. L. (2008). The 'extrapolated center of mass' concept suggests a simple control of balance in walking. *Hum Mov Sci*, 27(1), 112-125.
- HOLM, I., FOSDAHL, M. A., FRIIS, A., RISBERG, M. A., MYKLEBUST, G. & STEEN, H. (2004). Effect of neuromuscular training on proprioception, balance, muscle strength, and lower limb function in female team handball players. *Clinical journal of sport medicine : official journal of the Canadian Academy of Sport Medicine*, 14(2), 88-94.
- HORAK, F. B., DIMITROVA, D. & NUTT, J. G. (2005). Direction-specific postural instability in subjects with Parkinson's disease. *Exp Neurol*, 193(2), 504-521.

- HORAK, F. B., NUTT, J. G. & NASHNER, L. M. (1992). Postural inflexibility in parkinsonian subjects. *J Neurol Sci*, 111(1), 46-58.
- HORAK, F. B., WRISLEY, D. M. & FRANK, J. (2009). The Balance Evaluation Systems Test (BESTest) to differentiate balance deficits. *Physical therapy*, 89(5), 484-498.
- IANSEK, R., HUXHAM, F. & MCGINLEY, J. (2006). The sequence effect and gait festination in Parkinson disease: contributors to freezing of gait? *Movement Disorders*, 21(9), 1419-1424.
- INKSTER, L. M., ENG, J. J., MACINTYRE, D. L. & STOESSL, A. J. (2003). Leg muscle strength is reduced in Parkinson's disease and relates to the ability to rise from a chair. *Movement Disorders*, 18(2), 157-162.
- JENKINSON, C., FITZPATRICK, R., PETO, V., GREENHALL, R. & HYMAN, N. (1997). The Parkinson's Disease Questionnaire (PDQ-39): development and validation of a Parkinson's disease summary index score. *Age Ageing*, 26(5), 353-357.
- JORDAN, N., SAGAR, H. J. & COOPER, J. A. (1992). A component analysis of the generation and release of isometric force in Parkinson's disease. *J Neurol Neurosurg Psychiatry*, 55(7), 572-576.
- JOSHUA, A. M., D'SOUZA, V., UNNIKRISHNAN, B., MITHRA, P., KAMATH, A., ACHARYA, V., et al. (2014). Effectiveness of progressive resistance strength training versus traditional balance exercise in improving balance among the elderly - a randomised controlled trial. *Journal of clinical and diagnostic research*, 8(3), 98-102.
- KAKINUMA, S., NOGAKI, H., PRAMANIK, B. & MORIMATSU, M. (1998). Muscle weakness in Parkinson's disease: isokinetic study of the lower limbs. *European neurology*, 39(4), 218-222.
- KERR, G. K., WORRINGHAM, C. J., COLE, M. H., LACHEREZ, P. F., WOOD, J. M. & SILBURN, P. A. (2010). Predictors of future falls in Parkinson disease. *Neurology*, 75(2), 116-124.
- KEUS, S. H., MUNNEKE, M., NIJKRAKE, M. J., KWAKKEL, G. & BLOEM, B. R. (2009). Physical therapy in Parkinson's disease: evolution and future challenges. *Movement Disorders*, 24(1), 1-14.
- KING, L. A. & HORAK, F. B. (2008). Lateral stepping for postural correction in Parkinson's disease. *Archives of physical medicine and rehabilitation*, 89(3), 492-499.
- KING, L. A., PRIEST, K. C., SALARIAN, A., PIERCE, D. & HORAK, F. B. (2012). Comparing the Mini-BESTest with the Berg Balance Scale to Evaluate Balance Disorders in Parkinson's Disease. *Parkinson's disease*, 2012, 375419.
- KING, L. A., ST GEORGE, R. J., CARLSON-KUHTA, P., NUTT, J. G. & HORAK, F. B. (2010). Preparation for compensatory forward stepping in Parkinson's disease. *Archives of physical medicine and rehabilitation*, 91(9), 1332-1338.
- KOLLER, W. & KASE, S. (1986). Muscle strength testing in Parkinson's disease. *European neurology*, 25(2), 130-133.
- KUNESCH, E., SCHNITZLER, A., TYERCHA, C., KNECHT, S. & STELMACH, G. (1995). Altered force release control in Parkinson's disease. *Behav Brain Res*, 67(1), 43-49.
- LATT, M. D., LORD, S. R., MORRIS, J. G. & FUNG, V. S. (2009). Clinical and physiological assessments for elucidating falls risk in Parkinson's disease. *Movement Disorders*, 24(9), 1280-1289.
- LEDDY, A. L., CROWNER, B. E. & EARHART, G. M. (2011). Utility of the Mini-BESTest, BESTest, and BESTest sections for balance assessments in individuals with Parkinson disease. *J Neurol Phys Ther*, 35(2), 90-97.
- LEE, P. Y., GADAREH, K., NAUSHAHI, M. J., GREY, M. & BRONSTEIN, A. M. (2013). Protective stepping response in Parkinsonian patients and the effect of vibrotactile feedback. *Movement disorders*, 28(4), 482-489.
- LI, F., HARMER, P., FITZGERALD, K., ECKSTROM, E., STOCK, R., GALVER, J., et al. (2012). Tai chi and postural stability in patients with Parkinson's disease. *N Engl J Med*, 366(6), 511-519.
- LIMA, L. O., SCIANNI, A. & RODRIGUES-DE-PAULA, F. (2013). Progressive resistance exercise improves strength and physical performance in people with mild to moderate Parkinson's disease: a systematic review. *J Physiother*, 59(1), 7-13.
- MANCINI, M., CARLSON-KUHTA, P., ZAMPIERI, C., NUTT, J. G., CHIARI, L. & HORAK, F. B. (2012). Postural sway as a marker of progression in Parkinson's disease: a pilot longitudinal study. *Gait Posture*, 36(3), 471-476.

- MANCINI, M., ROCCHI, L., HORAK, F. B. & CHIARI, L. (2008). Effects of Parkinson's disease and levodopa on functional limits of stability. *Clin Biomech* 23(4), 450-458.
- MATINOLLI, M., KORPELAINEN, J. T., KORPELAINEN, R., SOTANIEMI, K. A., VIRRANNIEMI, M. & MYLLYLÄ, V. V. (2007). Postural sway and falls in Parkinson's disease: a regression approach. *Movement Disorders*, 22(13), 1927-1935.
- MCVEY, M. A., AMUNDSEN, S., BARNDI, A., LYONS, K. E., PAHWA, R., MAHNKEN, J. D., et al. (2013). The effect of moderate Parkinson's disease on compensatory backwards stepping. *Gait & Posture*, 38(4), 800-805.
- MELTON, L. J., 3RD, LEIBSON, C. L., ACHENBACH, S. J., BOWER, J. H., MARAGANORE, D. M., OBERG, A. L., et al. (2006). Fracture risk after the diagnosis of Parkinson's disease: Influence of concomitant dementia. *Movement Disorders*, 21(9), 1361-1367.
- MENANT, J. C., LATT, M. D., MENZ, H. B., FUNG, V. S. & LORD, S. R. (2011). Postural sway approaches center of mass stability limits in Parkinson's disease. *Movement Disorders*, 26(4), 637-643.
- MENANT, J. C., LATT, M. D., MENZ, H. B., FUNG, V. S. & LORD, S. R. (2011). Postural sway approaches center of mass stability limits in Parkinson's disease. *Mov Disord*, 26(4), 637-643.
- MOORE, O., PERETZ, C. & GILADI, N. (2007). Freezing of gait affects quality of life of peoples with Parkinson's disease beyond its relationships with mobility and gait. *Movement disorders*, 22(15), 2192-2195.
- MORRIS, M., IANSEK, R., SMITHSON, F. & HUXHAM, F. (2000). Postural instability in Parkinson's disease: a comparison with and without a concurrent task. *Gait Posture*, 12(3), 205-216.
- NALLEGOWDA, M., SINGH, U., HANDA, G., KHANNA, M., WADHWA, S., YADAV, S. L., et al. (2004). Role of sensory input and muscle strength in maintenance of balance, gait, and posture in Parkinson's disease: a pilot study. *American journal of physical medicine & rehabilitation*, 83(12), 898-908.
- NANTEL, J., MCDONALD, J. C. & BRONTE-STEWART, H. (2012). Effect of medication and STN-DBS on postural control in subjects with Parkinson's disease. *Parkinsonism & related disorders*, 18(3), 285-289.
- NIEUWBOER, A. & GILADI, N. (2013). Characterizing freezing of gait in Parkinson's disease: Models of an episodic phenomenon. *Movement Disorders*, 28(11), 1509-1519.
- NOCERA, J. R., BUCKLEY, T., WADDELL, D., OKUN, M. S. & HASS, C. J. (2010). Knee extensor strength, dynamic stability, and functional ambulation: are they related in Parkinson's disease? *Arch Phys Med Rehabil*, 91(4), 589-595.
- NOGAKI, H., FUKUSAKO, T., SASABE, F., NEGORO, K. & MORIMATSU, M. (1995). Muscle strength in early Parkinson's disease. *Movement Disorders*, 10(2), 225-226.
- NOGAKI, H., KAKINUMA, S. & MORIMATSU, M. (1999). Movement velocity dependent muscle strength in Parkinson's disease. *Acta Neurol Scand*, 99(3), 152-157.
- NOGAKI, H., KAKINUMA, S. & MORIMATSU, M. (2001). Muscle weakness in Parkinson's disease: a follow-up study. *Parkinsonism Relat Disord*, 8(1), 57-62.
- NUTT, J. G., BLOEM, B. R., GILADI, N., HALLETT, M., HORAK, F. B. & NIEUWBOER, A. (2011). Freezing of gait: moving forward on a mysterious clinical phenomenon. *The Lancet. Neurology*, 10(8), 734-744.
- OERTEL, W., DEUSCHL, G. & POEWE, W. (2011). *Parkinson-Syndrome und andere Bewegungsstörungen*. Stuttgart: Thieme.
- OLIVEIRA, M. A., RODRIGUES, A. M., CABALLERO, R. M., PETERSEN, R. D. & SHIM, J. K. (2008). Strength and isometric torque control in individuals with Parkinson's disease. *Exp Brain Res*, 184(3), 445-450.
- PAASUKE, M., ERELIN, J., GAPEYEVA, H., JOOST, K., MOTTUS, K. & TABA, P. (2004). Leg-extension strength and chair-rise performance in elderly women with Parkinson's disease. *J Aging Phys Act*, 12(4), 511-524.
- PAASUKE, M., MOTTUS, K., ERELIN, J., GAPEYEVA, H. & TABA, P. (2002). Lower limb performance in older female patients with Parkinson's disease. *Aging Clin Exp Res*, 14(3), 185-191.
- PANG, M. Y. & MAK, M. K. (2012). Influence of contraction type, speed, and joint angle on ankle muscle weakness in Parkinson's disease: implications for rehabilitation. *Arch Phys Med Rehabil*, 93(12), 2352-2359.

- PARKINSON, J. (2002). An essay on the shaking palsy. *The Journal of neuropsychiatry and clinical neurosciences*, 14(2), 223-236. (Original veröffentlicht 1817).
- PEDERSEN, S. W. & OBERG, B. (1993). Dynamic strength in Parkinson's disease. Quantitative measurements following withdrawal of medication. *European neurology*, 33(2), 97-102.
- PEDERSEN, S. W., OBERG, B., LARSSON, L. E. & LINDVAL, B. (1997). Gait analysis, isokinetic muscle strength measurement in patients with Parkinson's disease. *Scand J Rehabil Med*, 29(2), 67-74.
- PETERSON, D. S., PLOTNIK, M., HAUSDORFF, J. M. & EARHART, G. M. (2012). Evidence for a relationship between bilateral coordination during complex gait tasks and freezing of gait in Parkinson's disease. *Parkinsonism Relat Disord*, 1022-1026.
- PICELLI, A., MELOTTI, C., ORIGANO, F., NERI, R., VERZE, E., GANDOLFI, M., et al. (2014). Robot-assisted gait training is not superior to balance training for improving postural instability in patients with mild to moderate Parkinson's disease: a single-blind randomized controlled trial. *Clinical rehabilitation*, 10.1016/j.parkreldis.2013.1002.1010.
- PLOTNIK, M., GILADI, N., BALASH, Y., PERETZ, C. & HAUSDORFF, J. M. (2005). Is freezing of gait in Parkinson's disease related to asymmetric motor function? *Ann Neurol*, 57(5), 656-663.
- PLOTNIK, M., GILADI, N. & HAUSDORFF, J. M. (2007). A new measure for quantifying the bilateral coordination of human gait: effects of aging and Parkinson's disease. *Experimental brain research*, 181(4), 561-570.
- PLOTNIK, M., GILADI, N. & HAUSDORFF, J. M. (2008). Bilateral coordination of walking and freezing of gait in Parkinson's disease. *Eur J Neurosci*, 27(8), 1999-2006.
- PLOTNIK, M., GILADI, N. & HAUSDORFF, J. M. (2012). Is freezing of gait in Parkinson's disease a result of multiple gait impairments? Implications for treatment. *Parkinson's disease*, 2012, 459321.
- PLOTNIK, M. & HAUSDORFF, J. M. (2008). The role of gait rhythmicity and bilateral coordination of stepping in the pathophysiology of freezing of gait in Parkinson's disease. *Movement Disorders*, 23(2), 444-450.
- PODSIADLO, D. & RICHARDSON, S. (1991). The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *Journal of the American Geriatrics Society*, 39(2), 142-148.
- POTTER-NERGER, M. & VOLKMANN, J. (2013). Deep brain stimulation for gait and postural symptoms in Parkinson's disease. *Movement disorders*, 28(11), 1609-1615.
- QUTUBUDDIN, A. A., PEGG, P. O., CIFU, D. X., BROWN, R., MCNAMEE, S. & CARNE, W. (2005). Validating the Berg Balance Scale for patients with Parkinson's disease: a key to rehabilitation evaluation. *Arch Phys Med Rehabil*, 86(4), 789-792.
- ROBICHAUD, J. A., PFANN, K. D., COMELLA, C. L., BRANDABUR, M. & CORCOS, D. M. (2004). Greater impairment of extension movements as compared to flexion movements in Parkinson's disease. *Exp Brain Res*, 156(2), 240-254.
- ROBICHAUD, J. A., PFANN, K. D., VAILLANCOURT, D. E., COMELLA, C. L. & CORCOS, D. M. (2005). Force control and disease severity in Parkinson's disease. *Movement Disorders*, 20(4), 441-450.
- ROBINSON, K., DENNISON, A., ROALF, D., NOORIGIAN, J., CIANCI, H., BUNTING-PERRY, L., et al. (2005). Falling risk factors in Parkinson's disease. *NeuroRehabilitation*, 20(3), 169-182.
- ROSE, D. J., LUCCHESI, N. & WIERSMA, L. D. (2006). Development of a multidimensional balance scale for use with functionally independent older adults. *Arch Phys Med Rehabil*, 87(11), 1478-1485.
- SCHAAFSMA, J. D., GILADI, N., BALASH, Y., BARTELS, A. L., GUREVICH, T. & HAUSDORFF, J. M. (2003). Gait dynamics in Parkinson's disease: relationship to Parkinsonian features, falls and response to levodopa. *J Neurol Sci*, 212(1-2), 47-53.
- SCHIEPPATI, M., HUGON, M., GRASSO, M., NARDONE, A. & GALANTE, M. (1994). The limits of equilibrium in young and elderly normal subjects and in parkinsonians. *Electroencephalogr Clin Neurophysiol*, 93(4), 286-298.
- SCHIEPPATI, M. & NARDONE, A. (1991). Free and supported stance in Parkinson's disease. The effect of posture and 'postural set' on leg muscle responses to perturbation, and its relation to the severity of the disease. *Brain*, 114 (Pt 3), 1227-1244.

- SCHILLING, B. K., PFEIFFER, R. F., LEDOUX, M. S., KARLAGE, R. E., BLOOMER, R. J. & FALVO, M. J. (2010). Effects of moderate-volume, high-load lower-body resistance training on strength and function in persons with Parkinson's disease: a pilot study. *Parkinson's disease*, 2010, 824734.
- SCHOTT, N. (2011). Erfassung der Gleichgewichtsfähigkeit bei selbstständig lebenden Erwachsenen. *Z Gerontol Geriatr*, 44(6), 417-428.
- SHARIFIFAR, S., CORONADO, R. A., ROMERO, S., AZARI, H. & THIGPEN, M. (2014). The effects of whole body vibration on mobility and balance in Parkinson disease: a systematic review. *Iranian journal of medical sciences*, 39(4), 318-326.
- SHEN, X. & MAK, M. K. (2014). Balance and Gait Training With Augmented Feedback Improves Balance Confidence in People With Parkinson's Disease: A Randomized Controlled Trial. *Neurorehabilitation and neural repair*, 28(6), 524-535.
- SHERRINGTON, C., WHITNEY, J. C., LORD, S. R., HERBERT, R. D., CUMMING, R. G. & CLOSE, J. C. (2008). Effective exercise for the prevention of falls: a systematic review and meta-analysis. *J Am Geriatr Soc*, 56(12), 2234-2243.
- SHUMWAY-COOK, A. & WOOLLACOTT, M. H. (2012). *Motor control: translating research into clinical practice* (4. überarbeitete Aufl.). Philadelphia: Lippincott Williams & Wilkins.
- SILVA, K. N., MIZUSAKI IMOTO, A., ALMEIDA, G. J., ATALLAH, A. N., PECCIN, M. S. & FERNANDES MOCA TREVISANI, V. (2010). Balance training (proprioceptive training) for patients with rheumatoid arthritis. *The Cochrane database of systematic reviews*, (5), CD007648.
- SMANIA, N., CORATO, E., TINAZZI, M., STANZANI, C., FIASCHI, A., GIRARDI, P., et al. (2010). Effect of balance training on postural instability in patients with idiopathic Parkinson's disease. *Neurorehabil Neural Repair*, 24(9), 826-834.
- SOFUWA, O., NIEUWBOER, A., DESLOOVERE, K., WILLEMS, A. M., CHAVRET, F. & JONKERS, I. (2005). Quantitative gait analysis in Parkinson's disease: comparison with a healthy control group. *Archives of physical medicine and rehabilitation*, 86(5), 1007-1013.
- SOH, S. E., MORRIS, M. E. & MCGINLEY, J. L. (2011). Determinants of health-related quality of life in Parkinson's disease: a systematic review. *Parkinsonism & related disorders*, 17(1), 1-9.
- STELMACH, G. E., TEASDALE, N., PHILLIPS, J. & WORRINGHAM, C. J. (1989). Force production characteristics in Parkinson's disease. *Exp Brain Res*, 76(1), 165-172.
- STELMACH, G. E. & WORRINGHAM, C. J. (1988). The preparation and production of isometric force in Parkinson's disease. *Neuropsychologia*, 26(1), 93-103.
- STOLZENBERG, N., BELAVY, D. L., RAWER, R. & FELSEBERG, D. (2013). Whole-body vibration versus proprioceptive training on postural control in post-menopausal osteopenic women. *Gait & Posture*, 38(3), 416-420.
- STYLIANOU, A. P., MCVHEY, M. A., LYONS, K. E., PAHWA, R. & LUCHIES, C. W. (2011). Postural sway in patients with mild to moderate Parkinson's disease. *Int J Neurosci*, 121(11), 614-621.
- TAN, D. M., MCGINLEY, J. L., DANOUDIS, M. E., IANSEK, R. & MORRIS, M. E. (2011). Freezing of gait and activity limitations in people with Parkinson's disease. *Archives of physical medicine and rehabilitation*, 92(7), 1159-1165.
- TOMLINSON, C. L., HERD, C. P., CLARKE, C. E., MEEK, C., PATEL, S., STOWE, R., et al. (2014). Physiotherapy for Parkinson's disease: a comparison of techniques. *The Cochrane database of systematic reviews*, 6, CD002815.
- VAILLANCOURT, D. E., PRODOEHL, J., STURMAN, M. M., BAKAY, R. A., METMAN, L. V. & CORCOS, D. M. (2006). Effects of deep brain stimulation and medication on strength, bradykinesia, and electromyographic patterns of the ankle joint in Parkinson's disease. *Movement Disorders*, 21(1), 50-58.
- VAN WEGEN, E. E., VAN EMMERIK, R. E., WAGENAAR, R. C. & ELLIS, T. (2001). Stability boundaries and lateral postural control in parkinson's disease. *Motor Control*, 5(3), 254-269.
- VERCRUYSSSE, S., GILAT, M., SHINE, J. M., HEREMANS, E., LEWIS, S. & NIEUWBOER, A. (2014). Freezing beyond gait in Parkinson's disease: a review of current neurobehavioral evidence. *Neuroscience and biobehavioral reviews*, 43, 213-227.
- VIITASALO, M. K., KAMPMAN, V., SOTANIEMI, K. A., LEPPAVUORI, S., MYLLYLÄ, V. V. & KORPELAINEN, J. T. (2002). Analysis of sway in Parkinson's disease using a new inclinometry-based method. *Movement Disorders*, 17(4), 663-669.

- VISSER, J. E., ALLUM, J. H., CARPENTER, M. G., ESSELINK, R. A., SPEELMAN, J. D., BORM, G. F., et al. (2008). Subthalamic nucleus stimulation and levodopa-resistant postural instability in Parkinson's disease. *J Neurol*, 255(2), 205-210.
- WINTER, D. A. (1995). Human balance and posture control during standing and walking. *Gait & Posture*, 3(4), 193-214.
- WOOD, B. H., BILCLOUGH, J. A., BOWRON, A. & WALKER, R. W. (2002). Incidence and prediction of falls in Parkinson's disease: a prospective multidisciplinary study. *J Neurol Neurosurg Psychiatry*, 72(6), 721-725.
- YANAGAWA, S., SHINDO, M. & YANAGISAWA, N. (1990). Muscular weakness in Parkinson's disease. *Adv Neurol*, 53, 259-269.
- YELNIK, A. & BONAN, I. (2008). Clinical tools for assessing balance disorders. *Clinical neurophysiology*, 38(6), 439-445.

Anhang

A Studie 1: „Comparing the Fullerton Advanced Balance scale with the Mini-BESTest and Berg Balance Scale to assess postural control in patients with Parkinson’s Disease”

B Studie 2: „Resistance Training versus Balance Training to improve postural control in patients with Parkinson’s Disease – a randomized controlled rater blinded trial”

C Studie 3: „Split-Belt Locomotion in Parkinson’s Disease Links Asymmetry, Dyscoordination and Sequence Effect”

Comparing the Fullerton Advanced Balance scale with the Mini-BESTest and Berg Balance Scale to assess postural control in patients with Parkinson's Disease

Christian Schlenstedt, M.A.^{1,2}, Stephanie Brombacher¹, Gesa Hartwigsen, PhD³,
Burkhard Weisser, MD², Bettina Möller, PhD¹, Günther Deuschl, PhD¹

¹ Department of Neurology, Christian-Albrechts-University, Kiel, Germany

² Department of Sport Science, Christian-Albrechts-University, Kiel, Germany

³ Department of Psychology, Christian-Albrechts-University, Kiel, Germany

Corresponding author:

Prof. Dr. Günther Deuschl
Universityhospital Schleswig-Holstein, Campus Kiel
Department of Neurology
Schittenhelmstr. 10
24105 Kiel, Germany
Phone: +49-431-597-8501
Fax: +49-431-597-8502
Email: g.deuschl@neurologie.uni-kiel.de

Abstract

Objective. To validate the Fullerton Advanced Balance (FAB) scale for patients with idiopathic Parkinson's Disease (PD) and to compare it with the Mini Balance Evaluation System Test (Mini-BESTest) and the Berg Balance Scale (BBS).

Design. Observational study to assess concurrent validity, test-retest (3 ± 1 days) and interrater (3 raters) reliability of the FAB scale in patients with PD and to compare the distribution of the scale with the Mini-BESTest and BBS. Spearman correlation coefficients were used to evaluate validity and intraclass correlation coefficients (ICC) were calculated to assess interrater and test-retest reliability.

Setting. University hospital in an urban community.

Participants. 85 patients with idiopathic PD (Hoehn & Yahr stage: 1-4).

Interventions. Not applicable.

Main Outcome Measures. FAB scale, Mini-BESTest, BBS, Timed-up-and-go-test, Unified Parkinson's Disease Rating Scale (UPDRS) and Visual Analogue Scale (VAS)

Results. Interrater and test-retest reliability was high for all scales ($ICCs \geq 0.95$). The FAB scale was highly correlated with the Mini-BESTest (Spearman's $\rho = 0.87$) and with the Timed-up-and-go item of the Mini-BESTest (Spearman's $\rho = 0.83$). In contrast to the BBS, the FAB scale and the Mini-BESTest had only minimal ceiling effects. The FAB scale demonstrated the most symmetric distribution when compared with the Mini-BESTest and the BBS (skewness: FAB scale: -0.54; Mini-BESTest: -1.07; BBS: -2.14).

Conclusions. The FAB scale is a valid and reliable tool to assess postural control in patients with PD. No ceiling effect was noted for the FAB scale. Although the items of the FAB scale are more detailed when compared to the Mini-BESTest, interrater- and test-retest reliability was excellent and the scale is a promising tool to detect small changes of the postural control system in individuals with PD.

List of abbreviations:

BBS: Berg Balance Scale; **FAB:** Fullerton Advanced Balance; **H&Y:** Hoehn and Yahr; **ICC:** intraclass correlation coefficient; **Mini-BESTest:** Mini Balance Evaluation System Test; **PD:** Parkinson's Disease; **TUG:** Timed-up-and-go-test; **UPDRS:** Unified Parkinson's Disease Rating Scale; **VAS:** visual analogue scale

Key words:

Postural Balance, Posture, Parkinson's Disease, Reliability and Validity

One of the most disabling symptoms of idiopathic Parkinson's Disease (PD) is postural instability. Specifically, balance disturbances are associated with impaired quality of life,¹ and the reported postural impairments usually worsen with disease progression.²⁻⁵ Postural instability has been identified as one of the independent risk factors for falls,⁶⁻⁸ with fall rates ranging from 39 to 68 % in patients with PD.^{9,10} In comparison with aged-matched healthy control subjects, patients with PD have smaller limits of stability¹¹⁻¹⁴ and show larger sway during quiet stance in medio-lateral direction.^{3,15,16} When perturbing the stance surface, individuals with PD use several slow steps to recover equilibrium^{17,18} and have excessive antagonistic activity.^{19,20} In comparison to healthy elderly subjects, patients with PD also present with impairments in the adaptation to different perturbation- and stance conditions.^{19,21,22} Patients' balance performance worsens while performing a secondary cognitive task.^{23,24}

The assessment of balance performance is mandatory for the initiation of effective therapy. Balance tests should be able to reflect various dimensions of postural instability, as mentioned above. Due to the complexity of postural control mechanisms, multidimensional clinical balance scales often describe the overall balance performance more accurately than simple tests or biomechanical measurements.²⁵ Additionally, clinical balance scales evaluate postural stability in a more functional way and are closer related to real life situations.²⁵ To improve patient care and initiate an appropriate treatment at early disease stages, it is mandatory that clinical balance scales are sensitive to small differences in balance performance. Additionally, clinical balance scales need to be sensitive to therapeutically induced changes, particularly when interpreting intervention effects of two competing therapies. The detailed assessment of postural control is an important aim, especially

when comparing exercise interventions, where effect sizes are usually relatively small.²⁶

One of the standard clinical measures to assess balance disturbances in healthy elderly people and patients with PD is the Berg Balance Scale (BBS).^{27,28} Previous studies demonstrated that this 14-item scale is a valid and reliable measure of postural control.^{28,29} However, the test has some limitations, such as the lack of assessing reactive postural control (e.g., response to a perturbation),²⁷ a low responsiveness,^{29,30} and a ceiling effect.^{29,31}

Recently, Franchignoni et al.³² introduced the 14-item Mini Balance Evaluation Systems Test (Mini-BESTest), a shorter version of the BESTest developed by Horak and colleagues.³³ Previous studies did not report any ceiling effects of the Mini-BESTest when assessing balance performance in patients with balance disorders due to neurologic diseases.^{29,31} The test is highly reliable³⁴ and includes the assessment of dynamic postural control.³² Each task of the Mini-BESTest is assessed with a 3-point ordinal scale and as neither ceiling- nor floor effects have been documented, the scaling of the items covers a large range and might be not able to detect small differences of balance performance.

The Fullerton Advanced Balance (FAB) scale was developed to assess postural control in higher functioning older adults. It consists of 10 items which require static and dynamic postural control, sensory reception and integration and feedforward/feedback postural control.³⁵ In contrast to the BBS, the FAB scale includes the assessment of dynamic postural control (e.g., reactive postural control to a perturbation and gait performance). Furthermore, the FAB scale incorporates a secondary task during walking. These features are known to reflect balance challenges during activities of daily living.³⁶ As the test was developed for higher

functioning older adults, ceiling effects as reported for the BBS might be avoided. One advantage to of the FAB scale relative to the Mini-BESTest and the BBS is the efficient test time. The 10-item FAB scale takes only 10-12 minutes to complete,^{33, 35} while the 14-item Mini-BESTest and the 14-item BBS require up to 10-15 and 20 minutes, respectively.^{37,27,30, 32}

Another potential advantage of the FAB scale is the more sophisticated scaling. In contrast to the 3-point ordinal scale of the Mini-BESTest, each task of the FAB scale has a 5-point ordinal scale. Hence, the scaling of the items of the FAB scale appears more detailed than the scaling of the Mini-BESTest. The FAB scale might thus be able to better detect small differences in balance performance and might be more sensitive to therapeutically induced changes than the Mini-BESTest. Due to the differentiated scale incorporated in the FAB scale, this test can potentially be less reliable than the Mini-BESTest. But if it proves reliable, the FAB scale will be a promising quick and easy to use tool that allows for a more detailed assessment of postural control in patients with PD.

The purpose of this study was to analyze the concurrent validity of the FAB scale for the assessment of postural control in individuals with PD. Moreover, we aimed to compare the interrater and test-retest reliability of the FAB scale with the BBS and the Mini-BESTest. We hypothesized that despite its differentiated scaling, the FAB scale proves as reliable as the Mini-BESTest. The third aim of our study was the comparison of the distributions of the three balance scales. We expected that in contrast to the BBS, ceiling effects could be avoided when using the FAB scale.

Methods

Participants

Eighty-five patients with idiopathic PD completed this study. All patients met the following inclusion criteria: (1) diagnosed with idiopathic PD by a neurologist specialized in movement disorders and with an Hoehn & Yahr (H&Y) stage 1-4 and (2) >40 years of age. Exclusion criteria were: (1) deep brain stimulation, (2) other diseases and conditions that could influence stance- and gait performance (e.g. peripheral neuropathy, orthopedic injuries); determined by clinical examination of a neurologist, (3) cognitive impairment; patients with cognitive impairments were excluded as they may not be able to follow the instructions of the performed tests; this was determined by a clinical examination by a neurologist and in ambiguous cases, patients were excluded, (4) any change of medication during 4 weeks prior to participation. The study protocol was approved by the local ethics committee and all patients gave written informed consent prior to participating.

Testing Procedure

All patients took their regular PD medication and were assessed in the ON state of their medication. Each subject underwent the same order of testing for the following tests: FAB scale, Mini-BESTest, BBS, Unified Parkinson's Disease Rating Scale (UPDRS), Timed-up-and-go-test (TUG),³⁸ visual analogue scale (VAS). Any item that was duplicated between different balance scales was performed only once and scored using criteria from each scale. The TUG therefore has not been performed separately, but item 14 of the Mini-BESTest was used. In order to let the patients

perform each test under the same physical conditions, a seated rest was proposed by the assessor several times. If the assessor had the impression that a patient suffered from fatigue, a seated rest was given. The assessment was administered by two trained examiners who were familiar with the balance scales and who had experience with patients with movement disorders. The number of falls during the past 6 months was documented for each patient by asking them the question: "How often have you fallen during the last 6 months?".⁹ A fall was defined as an event resulting in an individual unintentionally coming to rest on the ground, floor, or other lower level, not as the result of a major intrinsic event.^{9,39} We enquired carefully about the frequency of falls and participants were encouraged to have another person present to add detail or to confirm the accounts.

FAB scale: The FAB scale is a 10-item balance scale with a 5-point ordinal scale (0-4) for each item and a maximal score of 40 points (higher values indicate better performance).³⁵ The following equipment is required to perform the scale: a stopwatch to assess stance time under various conditions, a pencil and 12-inch (30,5 cm) ruler to measure forward limits of stability, a 6-inch high bench (height: 6 in (15,2 cm); length: 18 in (45,6 cm); width: 14 in (35,6 cm)) for a step task to evaluate dynamic postural control, masking tape to assess a forward jump, 2 balance pads^a for a stance on an unstable surface, a yardstick and a metronome to give a secondary task while walking. The German version of the FAB scale was used in this protocol.³⁷ Patient instructions were given according to the standardized test protocol.

Mini-BESTest: The Mini-BESTest is a 14-item scale with a 3-point grading (0-2) for each item and a maximal score of 28 points (higher values indicate better performance).³² The following equipment is required to perform the scale: a stopwatch to assess stance time under various conditions and to perform the TUG

item, 1 balance pad for the stance on an unstable surface, 10 degree incline ramp (at least 2 x 2 ft to stand on) to measure stance performance on an inclined surface, stair step (height: 6 in (15,2 cm)), 2 stacked shoe boxes for gait assessment with obstacles, chair without arm rest for a sit-to-stand test and for the TUG item, masking tape. Patient instructions were given according to the standardized test protocol.

BBS: The BBS is a 14-item balance scale with a 5-point grading (0-4) for each item and a maximal score of 56 points (higher values indicate better performance).⁴⁰ The following equipment is required to perform the scale: a stopwatch to assess stance and sit performance under various conditions, a ruler to measure forward limits of stability, 2 chairs (one with and the other without arm rest) for a sit-to-stand transfer task, a stepper. Patient instructions were given according to the standardized test protocol.

TUG: The TUG requires patients to stand up from a chair, walk 3 m, turn around, walk back to the chair and sit down again – timed using a stopwatch.^{38,41}

VAS: To assess the degree to which the patients experience balance disturbances in daily life a 10 cm visual analogue scale (0-10, 0=not at all, 10=very much) was used together with the question: (English translation) "How much do you suffer from balance disturbances in daily life?"

Reliability

Sample size calculation was performed for interrater and test-retest reliability based on an alpha level of 0.05, a power of 0.90, a minimal acceptable level of intraclass correlation coefficient (ICC) of 0.80 and a favored level of reliability of 0.90.⁴² A required sample size of 13 patients was calculated for interrater reliability with three

examiners and a required sample size of 17 patients was calculated for test-retest reliability with two examinations.

Interrater reliability of the FAB scale, Mini-BESTest and BBS was determined with a subgroup of patients (n=15) and three raters. All raters were trained examiners who had experience assessing balance with the three scales prior to this study. Two raters were sport scientists with master's degrees and one rater was a psychology student. All three raters had experiences with the treatment of patients with neurologic diseases especially with PD. The raters were familiar with analyzing movements and with the conduction of balance task with the required assistance. All raters scored each scale independently and each of the raters was blinded to the other scores. One of the raters (SB) administered the assessment.

To determine test-retest reliability over the two sessions 17 participants were assessed by the same rater a second time after 3 (± 1) days. One rater performed all test-retest assessments. The second testing was performed at the same time of day and the patients were advised to take their antiparkinsonian medication equally to the first day of assessment.

In order to assess a representative sample of patients of different disease stages, the subgroups of patients for interrater- and test-retest reliability were determined concerning their H&Y stage. Patients of all H&Y stages (except H&Y stage 5) were included in order to cover a broad spectrum of disease stages.

Internal consistency was analyzed only for the FAB scale.

Validity

Concurrent validity was assessed by correlating the FAB-scale with the Mini-BESTest and TUG, which are two valid tools for the assessment of postural control in patients with PD.^{34,43} As disease severity is associated with postural instability and falls,^{9,44} we additionally correlated the FAB scales with the UPDRS total score and the UPDRS motor score. Due to the ceiling effect of the BBS, we did not consider the BBS as an appropriate instrument to assess concurrent validity.

Distributions / Ceiling Effects

The distributions of the FAB-scale, Mini-BESTest and BBS were analyzed by descriptive data and displayed graphically by histograms, scatter plots and Bland-Altman plots.⁴⁵ For the Bland-Altman plots, the scales were transformed to 0 – 100%. Statistical tests were performed to compare the distributions of the three scales.

Statistical Analysis

For statistical analysis SPSS (version 19.0)^b was used. Two-way random single measure intraclass correlations (ICC (2,1)) were calculated to assess both interrater and test-retest reliability⁴⁶ and Cronbach's alpha was calculated for internal consistency.⁴⁷ Reliability was considered to be reasonable, if ICCs scored higher than 0.90.⁴⁸ For concurrent validity Spearman's rank correlation coefficient (Spearman's Rho) was assessed.

The skewness was assessed by calculating the 95% confidence intervals using the Bootstrap method (5000 bootstrap samples). To analyze whether the tests are normal distributed a one-sample Kolmogorov-Smirnov (K-S) Test was computed.

Unless otherwise indicated, the level of significance was set at $p < 0.05$.

Results

Patients

85 patients met the inclusion criteria, were tested and completed the study.

Table 1 shows the subject characteristics of all 85 patients. The subgroup of participants for the assessment of interrater reliability ($n=15$) had a mean (SD) H&Y stage of 2.7 (0.7) (range: 1.0–4.0), 7.8 (6.1) years of disease duration, a mean age of 73.1 (7.8) years and a total UPDRS score of 38.5 (17.9). The patients assessed for test-retest reliability ($n=17$) had a mean (SD) H&Y stage of 2.6 (0.7) (range: 1.0-4.0), 9.8 (4.9) years of disease duration, age of 62.9 (11.2) years and a UPDRS score of 38.1 (14.5). One patient was included for both subgroups.

On average, three rest periods about 2 min were given during the testing.

Reliability and validity

The FAB scale demonstrated a high interrater- and test-retest reliability with an ICC of 0.99 respectively. The Mini-BESTest and BBS also showed high reliability for interrater and test-retest reliability with ICCs ≥ 0.95 (Table 2). The descriptive statistics of the test- retest assessments are presented in Table 3. Cronbach's alpha was 0.90 for the FAB scale ($n=85$).

Table 4 shows the correlation (Spearman's rank correlation coefficient) with other balance assessment tools and with measures for disease severity. The correlation of the FAB scale with the Mini-BESTest and with the TUG-item of the Mini-BESTest was high (Spearman's rho 0.87 and 0.83 respectively). Smaller correlations (Spearman's rho ranging from -0.56 – 0.39) were found between the clinical balance scales and the VAS. The FAB scale correlated higher than the Mini-BESTest and the BBS with the UPDRS total score and with the UPDRS motor score.

Distributions / Ceiling effects

The distributions of scores from the FAB scale, Mini-BESTest and BBS are shown in Figure 1. Two patients reached the highest value of the FAB scale, one patient scored highest at the Mini-BESTest and 15 patients (17.6%) performed the BBS perfectly with a maximal score of 56 points. Among these 15 subjects, four had H&Y stages higher than 2.0, indicating having postural impairments and four of them reported at least one fall in the past 6 months. None of the participants with maximal values on the FAB scale and Mini-BESTest had H&Y stages higher than 2.0 and none of them had fallen in the prior 6 months.

The test scores were normally distributed for the FAB scale and for the Mini-BESTest, but not for the BBS (Table 5). All three scales were left-skewed: FAB scale: -0.54; Mini-BESTest: -1.07; BBS: -2.14.

For the FAB scale, patients' scores ranged from 7.5% - 100% (similar to the Mini-BESTest) whereas the BBS ranged only from 42.9% - 100% and 25% of the patients had scores higher than 54 points (Table 5).

Figure 2A depicts a Bland-Altman-Plot of the FAB scale and the BBS. It shows that on average patients are rated 26.9% higher with the BBS in comparison to the FAB scale. This bias is not linear and changing over the range of the two scales. At a higher level of the scales a break is visible and the differences are getting smaller and converge to zero, as the BBS does not differentiate patients with only small balance disturbances. In contrast, only minimal ceiling effects are detectable for the FAB scale and the Mini-BESTest. The two scales have a small bias (7.0%) and a good agreement (Figure 2B).

Discussion

This study analyzed the utility of the FAB scale to assess postural control in patients with PD and compared the scale with the Mini-BESTest and BBS. The FAB scale was highly correlated with the Mini-BESTest and the TUG which are established as valid tools for the assessment of balance disturbances in patients with PD.^{34,43} The FAB scale was also correlated with disease severity, which is associated with postural instability and falls.^{9,44} Therefore we take validity as granted.

We found a high interrater and test-retest reliability with $ICC \geq .95$ for all three scales. The FAB scale has a 5-point ordinal scale and is therefore grading closer than the Mini-BESTest with its 3-point ordinal scale. Despite its differentiated scaling, the FAB scale proves as reliable as the Mini-BESTest. The range of the FAB scale was high (3-40 points) indicating that nearly the whole range of each item was used for this population.

As previously reported^{29,31} we found a ceiling effect for the BBS, because 17.6% of the patients reached the maximum value of the scale. Four of them had postural impairments, measured by the H&Y scale and by fall reports. Patients who scored highest at the FAB scale and at the Mini-BESTest did not report any prior falls during the past 6 months and had scores lower than 2.5 on the H&Y scale. We therefore conclude that the FAB scale and the Mini-BESTest only have minimal ceiling effects.

The FAB scale is 4 items shorter than the Mini-BESTest and the BBS. It took us only about 10 min to perform the scale which is in agreement with other studies.^{35,49} To assess the FAB scale was about 3 min shorter than the Mini-BESTest and about 5 min. shorter than the BBS.

In contrast to the BBS, the FAB scale and the Mini-BESTest include the assessment of reactive postural control. This is important, as poor reactive postural control is associated with increased fall risk.⁵⁰ Furthermore, the FAB scale and the Mini-BESTest measure postural stability while performing a secondary task. It has been shown that patients with PD worsen in balance performance when focusing on a secondary task.²⁴ In contrast to healthy elderly subjects, patients with PD give more priority to the cognitive task, which can result in falls during daily living.²³ The FAB scale and the Mini-BESTest therefore reflect more dimensions of PD induced postural instability.

Due to the above mentioned reasons, clinicians should use the FAB scale when aiming to assess various dimensions of postural instability of patients with Parkinson's Disease. The FAB scale is quicker to assess in comparison to the Mini-BESTest. As the FAB scale is more differentiated but as reliable as the Mini-BESTest, the FAB scale might be more appropriate to assess small differences in balance performance to early adapt an adequate therapy.

The smaller correlation coefficients of the correlations between the balance scales and the visual analogue scale shows only small agreement between clinical balance assessment and subjective perception of the patients. It remains an open question whether patients may underestimate postural disturbances due to other serious symptoms, e.g. tremor, or if clinical balance scales fail to represent patients balance impairments from activities of daily living.

Study Limitations

This study has some limitations. As the tests were not administered in a randomized order, there might be an order effect associated with the testing protocol. For interrater reliability testing, only one rater administered the test while the other raters scored the performance concurrently. Although there are written explanations how to administer the tests, verbal and nonverbal differences among the examiners could influence the performance of the participant and may lead to a higher variability. For test-retest reliability the time interval of 3 (± 1) days was short and memory effects are possible for patients and examiners. However, long time periods for the assessment of test-retest reliability are crucial for this population as fluctuations of the patients' disease state have to be taken into account. Finally, the study and its findings are limited to individuals with idiopathic PD.

Conclusions

In summary, the FAB scale is a reliable and valid tool for the assessment of postural control in patients with PD. The items of the FAB scale are more closely graded than the items of the Mini-BESTest, but both scales showed equal reliability. In contrast to the BBS, it has only a minimal ceiling effect. In comparison to the Mini-BESTest and the BBS, the FAB scale is shorter and it takes less time to perform the test. The use of the FAB scale with its differentiated scaling seems to be a promising tool for the detection of small balance disturbances and minor intervention effects. Future research should analyze sensitivity to change and clinical relevance of the FAB scale in comparison to other clinical balance scales.

Acknowledgement

The project was funded by the Coppenrath-Stiftung, Geeste/Groß-Hesepe, Niedersachsen, Germany and Krumme-Stiftung, Eckernförde, Schleswig-Holstein, Germany.

References

1. Muslimovic D, Post B, Speelman JD, Schmand B, de Haan RJ. Determinants of disability and quality of life in mild to moderate Parkinson disease. *Neurology*. 2008;70:2241-2247.
2. Bloem BR, Hausdorff JM, Visser JE, Giladi N. Falls and freezing of gait in Parkinson's disease: a review of two interconnected, episodic phenomena. *Mov Disord*. 2004;19:871-884.
3. Viitasalo MK, Kampman V, Sotaniemi KA, Leppavuori S, Myllyla VV, Korpelainen JT. Analysis of sway in Parkinson's disease using a new inclinometry-based method. *Mov Disord*. 2002;17:663-669.
4. Blaszczyk JW, Orawiec R. Assessment of postural control in patients with Parkinson's disease: sway ratio analysis. *Hum Mov Sci*. 2011;30:396-404.
5. Matinelli M, Korpelainen JT, Korpelainen R, Sotaniemi KA, Virranniemi M, Myllyla VV. Postural sway and falls in Parkinson's disease: a regression approach. *Mov Disord*. 2007;22:1927-1935.
6. Latt MD, Lord SR, Morris JG, Fung VS. Clinical and physiological assessments for elucidating falls risk in Parkinson's disease. *Mov Disord*. 2009;24:1280-1289.
7. Robinson K, Dennison A, Roalf D, et al. Falling risk factors in Parkinson's disease. *NeuroRehabilitation*. 2005;20:169-182.
8. Kerr GK, Worringham CJ, Cole MH, Lacherez PF, Wood JM, Silburn PA. Predictors of future falls in Parkinson disease. *Neurology*. 2010;75:116-124.
9. Ashburn A, Stack E, Pickering RM, Ward CD. Predicting fallers in a community-based sample of people with Parkinson's disease. *Gerontology*. 2001;47:277-281.
10. Wood BH, Bilclough JA, Bowron A, Walker RW. Incidence and prediction of falls in Parkinson's disease: a prospective multidisciplinary study. *J Neurol Neurosurg Psychiatry*. 2002;72:721-725.
11. Schieppati M, Hugon M, Grasso M, Nardone A, Galante M. The limits of equilibrium in young and elderly normal subjects and in parkinsonians. *Electroencephalogr Clin Neurophysiol*. 1994;93:286-298.
12. Menant JC, Latt MD, Menz HB, Fung VS, Lord SR. Postural sway approaches center of mass stability limits in Parkinson's disease. *Mov Disord*. 2011;26:637-643.
13. van Wegen EE, van Emmerik RE, Wagenaar RC, Ellis T. Stability boundaries and lateral postural control in parkinson's disease. *Motor Control*. 2001;5:254-269.
14. Mancini M, Rocchi L, Horak FB, Chiari L. Effects of Parkinson's disease and levodopa on functional limits of stability. *Clin Biomech (Bristol, Avon)*. 2008;23:450-458.
15. Stylianou AP, McVey MA, Lyons KE, Pahwa R, Luchies CW. Postural sway in patients with mild to moderate Parkinson's disease. *Int J Neurosci*. 2011;121:614-621.
16. Blaszczyk JW, Orawiec R, Duda-Klodowska D, Opala G. Assessment of postural instability in patients with Parkinson's disease. *Exp Brain Res*. 2007;183:107-114.
17. Lee PY, Gadareh K, Naushahi MJ, Gresty M, Bronstein AM. Protective stepping response in Parkinsonian patients and the effect of vibrotactile feedback. *Movement disorders : official journal of the Movement Disorder Society*. 2013;28:482-489.

18. McVey MA, Amundsen S, Barnds A, et al. The effect of moderate Parkinson's disease on compensatory backwards stepping. *Gait & Posture*. 2013;38:800-805.
19. Horak FB, Nutt JG, Nashner LM. Postural inflexibility in parkinsonian subjects. *J Neurol Sci*. 1992;111:46-58.
20. Carpenter MG, Allum JH, Honegger F, Adkin AL, Bloem BR. Postural abnormalities to multidirectional stance perturbations in Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2004;75:1245-1254.
21. Dimitrova D, Nutt J, Horak FB. Abnormal force patterns for multidirectional postural responses in patients with Parkinson's disease. *Exp Brain Res*. 2004;156:183-195.
22. Dimitrova D, Horak FB, Nutt JG. Postural muscle responses to multidirectional translations in patients with Parkinson's disease. *J Neurophysiol*. 2004;91:489-501.
23. Bloem BR, Grimbergen YA, van Dijk JG, Munneke M. The "posture second" strategy: a review of wrong priorities in Parkinson's disease. *J Neurol Sci*. 2006;248:196-204.
24. Plotnik M, Giladi N, Dagan Y, Hausdorff JM. Postural instability and fall risk in Parkinson's disease: impaired dual tasking, pacing, and bilateral coordination of gait during the "ON" medication state. *Experimental brain research*. 2011;210:529-538.
25. Yelnik A, Bonan I. Clinical tools for assessing balance disorders. *Neurophysiologie clinique = Clinical neurophysiology*. 2008;38:439-445.
26. Dibble LE, Addison O, Papa E. The effects of exercise on balance in persons with Parkinson's disease: a systematic review across the disability spectrum. *J Neurol Phys Ther*. 2009;33:14-26.
27. Berg K. Measuring balance in the elderly: preliminary development of an instrument. *Physiotherapy Canada*. 1989;41:304-311.
28. Qutubuddin AA, Pegg PO, Cifu DX, Brown R, McNamee S, Carne W. Validating the Berg Balance Scale for patients with Parkinson's disease: a key to rehabilitation evaluation. *Arch Phys Med Rehabil*. 2005;86:789-792.
29. Godi M, Franchignoni F, Caligari M, Giordano A, Turcato AM, Nardone A. Comparison of reliability, validity, and responsiveness of the mini-BESTest and Berg Balance Scale in patients with balance disorders. *Physical therapy*. 2013;93:158-167.
30. Pardasaney PK, Latham NK, Jette AM, et al. Sensitivity to change and responsiveness of four balance measures for community-dwelling older adults. *Physical therapy*. 2012;92:388-397.
31. King LA, Priest KC, Salarian A, Pierce D, Horak FB. Comparing the Mini-BESTest with the Berg Balance Scale to Evaluate Balance Disorders in Parkinson's Disease. *Parkinsons Dis*. 2012;2012:375419.
32. Franchignoni F, Horak F, Godi M, Nardone A, Giordano A. Using psychometric techniques to improve the Balance Evaluation Systems Test: the mini-BESTest. *Journal of rehabilitation medicine : official journal of the UEMS European Board of Physical and Rehabilitation Medicine*. 2010;42:323-331.
33. Horak FB, Wrisley DM, Frank J. The Balance Evaluation Systems Test (BESTest) to differentiate balance deficits. *Physical therapy*. 2009;89:484-498.
34. Leddy AL, Crowner BE, Earhart GM. Utility of the Mini-BESTest, BESTest, and BESTest sections for balance assessments in individuals with Parkinson disease. *J Neurol Phys Ther*. 2011;35:90-97.
35. Rose DJ, Lucchese N, Wiersma LD. Development of a multidimensional balance scale for use with functionally independent older adults. *Arch Phys Med Rehabil*. 2006;87:1478-1485.

36. Horak FB. Postural orientation and equilibrium: what do we need to know about neural control of balance to prevent falls? *Age Ageing*. 2006;35 Suppl 2:ii7-ii11.
37. Schott N. [Assessment of balance in community dwelling older adults : Reliability and validity of the German version of the Fullerton Advanced Balance Scale]. *Z Gerontol Geriatr*. 2011;44:417-428.
38. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *Journal of the American Geriatrics Society*. 1991;39:142-148.
39. Duncan RP, Leddy AL, Cavanaugh JT, et al. Comparative Utility of the BESTest, Mini-BESTest, and Brief-BESTest for Predicting Falls in Individuals With Parkinson Disease: A Cohort Study. *Phys Ther*. 2012.
40. Berg K, Wood-Dauphinee S, Williams JI. The Balance Scale: reliability assessment with elderly residents and patients with an acute stroke. *Scandinavian journal of rehabilitation medicine*. 1995;27:27-36.
41. Mathias S, Nayak US, Isaacs B. Balance in elderly patients: the "get-up and go" test. *Archives of physical medicine and rehabilitation*. 1986;67:387-389.
42. Walter SD, Eliasziw M, Donner A. Sample size and optimal designs for reliability studies. *Statistics in medicine*. 1998;17:101-110.
43. Morris S, Morris ME, Iansek R. Reliability of measurements obtained with the Timed "Up & Go" test in people with Parkinson disease. *Physical therapy*. 2001;81:810-818.
44. Landers MR, Backlund A, Davenport J, Fortune J, Schuerman S, Altenburger P. Postural instability in idiopathic Parkinson's disease: discriminating fallers from nonfallers based on standardized clinical measures. *Journal of neurologic physical therapy : JNPT*. 2008;32:56-61.
45. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet*. 1986;1:307-310.
46. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. *Psychological bulletin*. 1979;86:420-428.
47. Bland JM, Altman DG. Cronbach's alpha. *BMJ*. 1997;314:572.
48. Portney LG, Watkins MP. *Foundations of clinical research. Applications to practice*. 3rd ed ed. Upper Saddle River, N.J: Pearson/Prentice Hall; 2009.
49. Hernandez D, Rose DJ. Predicting which older adults will or will not fall using the Fullerton Advanced Balance scale. *Arch Phys Med Rehabil*. 2008;89:2309-2315.
50. Munhoz RP, Teive HA. Pull test performance and correlation with falls risk in Parkinson's disease. *Arq Neuropsiquiatr*. 2014;0:0.

Suppliers

- a. Airex AG, Sins, Switzerland (info@airexag.ch)
- b. IBM SPSS Statistics, version 19.0, Armonk, USA

Table 1. Patient characteristics (n=85).

Characteristics	
Number of female subjects (%)	28 (33)
Age (years)	
Mean (SD)	67.2 (9.8)
Median	69
Range	40 - 82
Disease duration (years)	
Mean (SD)	8.7 (5.8)
Median	7
Range	1-23
H&Y stage	
Stage 1-4 (Mean (SD))	2.7 (0.7)
Stage 1 (no. of patients)	4
Stage 1,5 (no. of patients)	1
Stage 2 (no. of patients)	12
Stage 2,5 (no. of patients)	33
Stage 3 (no. of patients)	25
Stage 4 (no. of patients)	10
UPDRS	
Total score (Mean (SD))	40.1 (16.4)
Part II (Mean (SD))	12.4 (6.8)
Part III (Mean (SD))	22.0 (10.4)
BMI (Mean (SD))	26.0 (4.4)

Table 2. Interrater and test-retest reliability for the FAB scale, Mini-BESTest and BBS.

Type of reliability	Test	ICC (2,1)	95% CI*
Interrater reliability (n=15)	FAB scale	.99	.99-1.0
	Mini-BESTest	.99	.97-1.0
	BBS	.98	.96-.99
Test-retest reliability (n=17)	FAB scale	.99	.96-.99
	Mini-BESTest	.98	.94-.99
	BBS	.95	.87-.98

*CI=confidence interval.

Table 3. Descriptive statistics of test- and retest assessments (n=17).

	Test		Retest	
	Mean (SD)	Median	Mean (SD)	Median
FAB scale	29.4 (8.2)	30	29.4 (8.0)	31
Mini-BESTest	21.6 (5.9)	23	22.3 (5.8)	24
BBS	52.9 (4.2)	54	53.6 (3.7)	55

Table 4. Correlations (Spearman's Rho) between the FAB scale, Mini-BESTest, BBS, TUG, PIGD*, VAS, UPDRS total score and UPDRS motor score.

	FAB scale	Mini-BESTest	BBS	TUG	PIGD	VAS	UPDRS total score	UPDRS motor score
FAB scale	1.00 [†]	.87 [†]	.93 [†]	-.83 [†]	-.67 [†]	-.49 [†]	-.54 [†]	-.41 [†]
Mini-BESTest	.87 [†]	1.00 [†]	.85 [†]	-.76 [†]	-.66 [†]	-.45 [†]	-.46 [†]	-.34 [‡]
BBS	.93 [†]	.85 [†]	1.00 [†]	-.81 [†]	-.66 [†]	-.56 [†]	-.51 [†]	-.35 [‡]
TUG	-.83 [†]	-.76 [†]	-.81 [†]	1.00 [†]	.66 [†]	.43 [†]	.54 [†]	.38 [†]
PIGD	-.67 [†]	-.66 [†]	-.66 [†]	.66 [†]	1.00 [†]	.39 [‡]	.61 [†]	.56 [†]
VAS	-.49 [†]	-.45 [†]	-.56 [†]	.43 [†]	.39 [‡]	1.00 [†]	.47 [†]	.30 [‡]

*PIGD=Postural Instability and Gait Difficulty scale (sum of UPDRS items 27-30); [†]significant correlation: $p < 0.001$; [‡]significant correlation: $p < 0.01$.

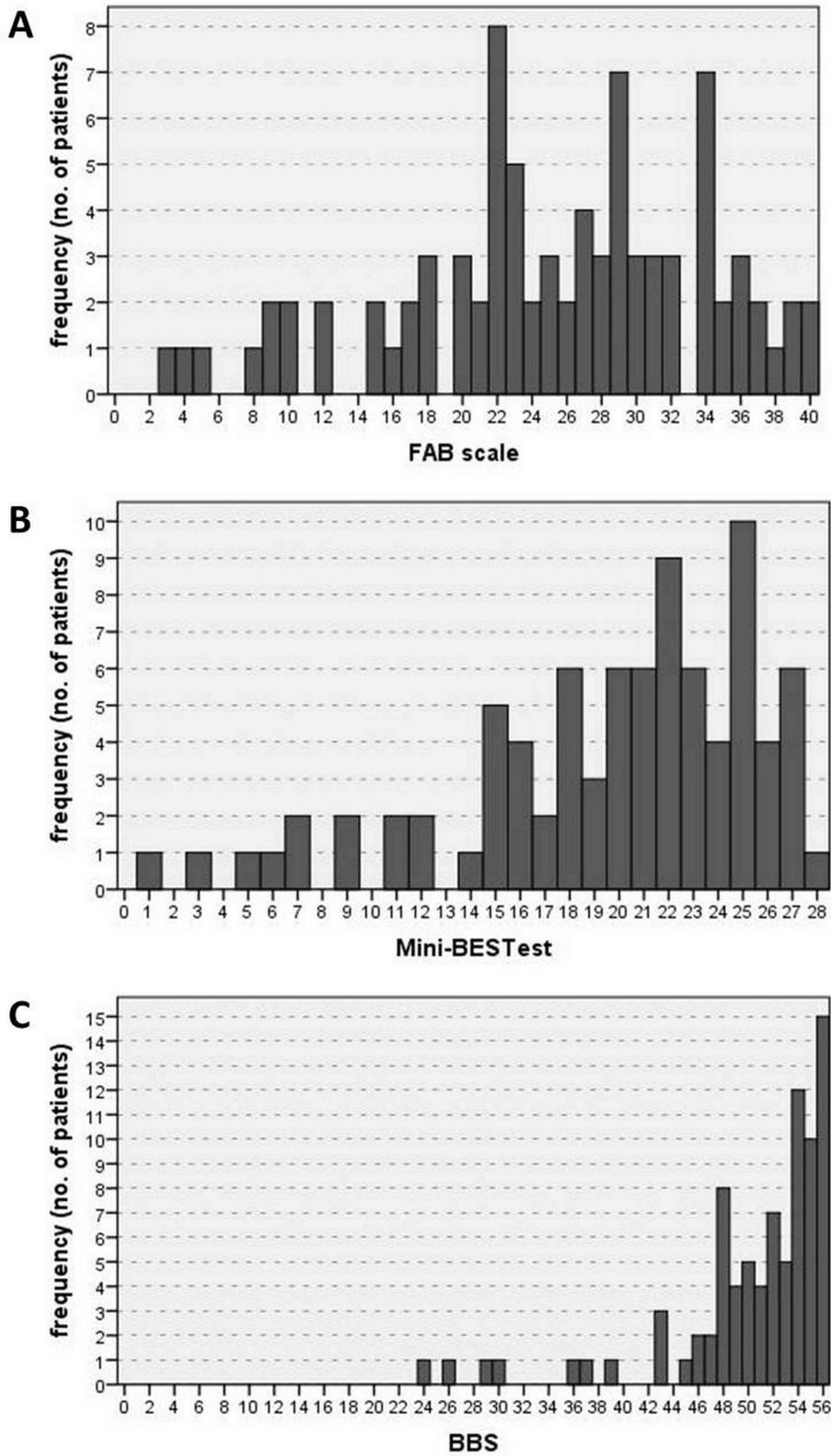


Figure 1. Distribution of the scores for A) FAB scale; B) Mini-BESTest; C) BBS.

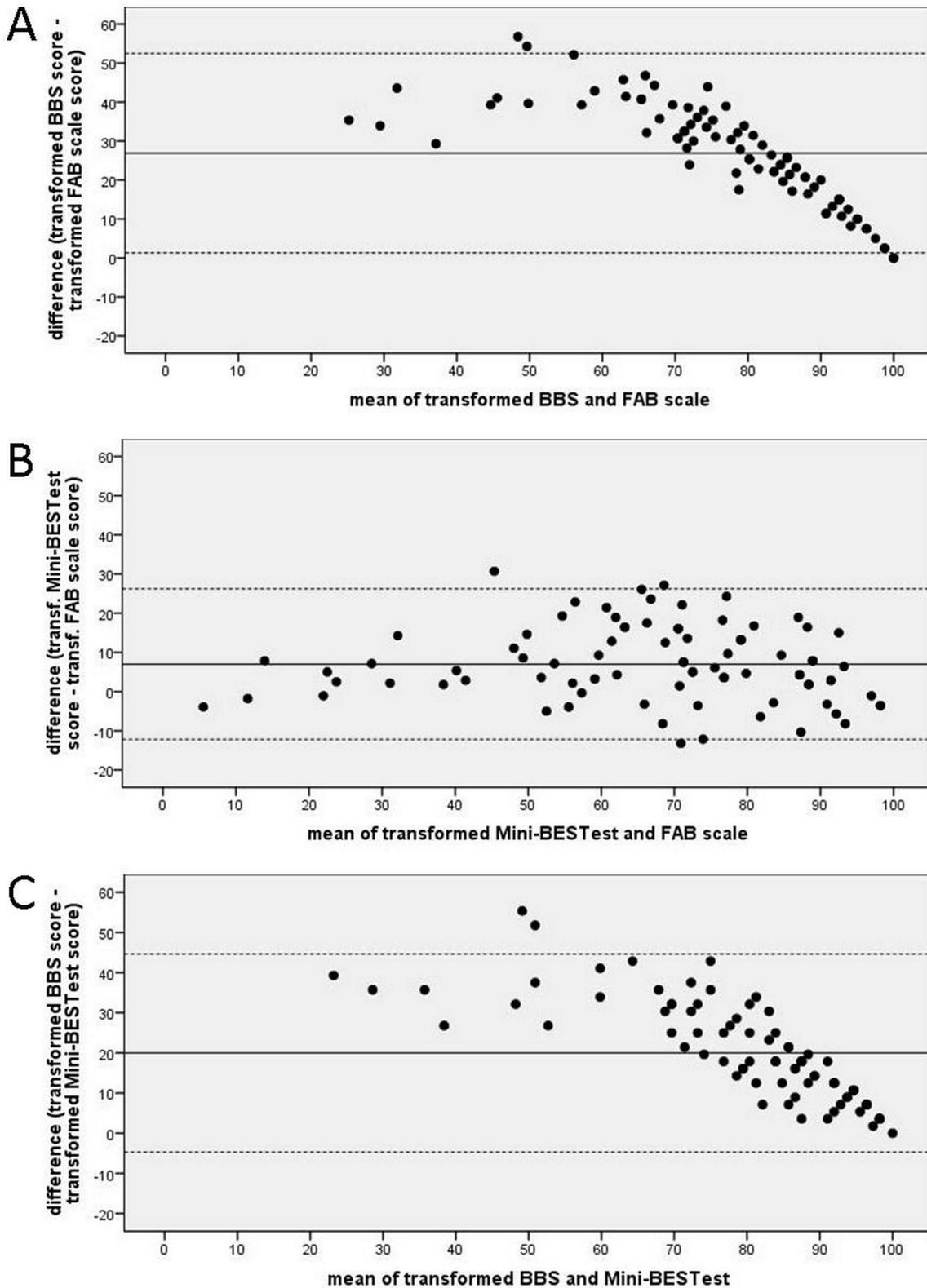


Figure 2. Bland-Altman-Plot of A) FAB scale and BBS; B) FAB scale and Mini-BESTest; C) Mini-BESTest and BBS; each balance scale was transformed to 0-100%; the line represents the mean difference (%) between the scales (bias); the dotted lines define the 95% limits of agreement (mean difference $\pm 1.96 \cdot SD$).

Resistance Training versus Balance Training to improve postural control in patients with Parkinson's Disease – a randomized controlled rater blinded trial

Christian Schlenstedt, M.A.^{1,2}, Steffen Paschen, MD¹, Annika Kruse, M.A.², Jan Raethjen, MD¹, Burkhard Weisser, MD², Günther Deuschl, PhD¹

¹ Department of Neurology, Christian-Albrechts-University, Kiel, Germany

² Department of Sport Science, Christian-Albrechts-University, Kiel, Germany

Word count text: 4041

Word count abstract: 246

No. of tables: 4

No. of figures: 2

No. of references: 41

Running title: Resistance- vs. Balance Training

Supplemental material online: Resistance- and Balance Training; Surface Perturbation; Gait Analysis; Strength Testing.

Corresponding author:

Prof. Dr. Günther Deuschl
Universityhospital Schleswig-Holstein, Campus Kiel
Department of Neurology
Schittenhelmstr. 10
24105 Kiel, Germany
Phone: +49-431-597-8501
Fax: +49-431-597-8502
Email: g.deuschl@neurologie.uni-kiel.de

Abstract

Background

Reduced muscle strength is an independent risk factor for falls and related to postural instability in patients with Parkinson's Disease (PD). The effect of resistance training (RT) to improve postural control still remains unclear.

Objective

To compare RT with balance training (BT) to improve postural control in patients with PD.

Methods

40 patients with idiopathic PD were randomly assigned into two training groups. Participants received either RT or BT twice a week for 7 weeks. The following assessments were performed at baseline, 8- and 12-weeks follow-up: primary outcome: Fullerton Advanced Balance (FAB) scale; secondary outcomes: center of mass analysis during surface perturbations, Timed-up-and-go-test (TUG), Unified Parkinson's Disease Rating Scale, Clinical Global Impression – Improvement (CGI-I), gait analysis, maximal isometric leg strength testing, Parkinson's Disease Questionnaire, Beck Depression Inventory. Clinical tests were videotaped and analysed by a second rater, blind to group allocation and assessment time.

Results

Patients from the RT-group, but not from the BT-group significantly improved on the FAB scale (+2.4 points) and in the TUG (-1.7 sec). No significant interaction was found between the two training types in any outcome parameter. Within the RT-group, improvements of the FAB scale were significantly correlated with improvements of rate of force development and stride time variability.

Conclusions

Postural control of patients with PD was improved by RT. RT might be more effective than BT to improve balance performance. The relationship between improvements of balance and rate of force development needs to be studied in further, larger trials.

List of abbreviations:

BDI: Beck Depression Inventory; **BT:** Balance Training; **CGI-I:** Clinical Global Impression – Improvement; **FAB:** Fullerton Advanced Balance; **ICC:** intraclass correlation coefficient; **LES:** less affected Parkinson's Disease side; **MES:** more affected Parkinson's Disease side; **MMSE:** Mini-Mental State Examination; **MVC:** maximal voluntary contraction; **PD:** Parkinson's Disease; **PDQ-39:** Parkinson's Disease Questionnaire; **PASE:** Physical Activity for the Elderly; **RFD:** rate of force development; **RT:** Resistance Training; **TUG:** Timed-up-and-go-test; **UPDRS:** Unified Parkinson's Disease Rating Scale.

Key words:

Resistance training, strength training, postural balance, physiotherapy, rehabilitation, Parkinson's Disease.

Introduction

Postural Instability is one of the major motor symptoms of patients with Parkinson's Disease (PD) and can hardly be improved by medication or Deep Brain Stimulation.¹⁻

⁴ Moderate evidence exists that exercise can improve balance performance.⁵⁻⁷ Smania et al. showed that balance training alone (BT) can be effective to improve postural control in patients with PD.⁸

Reduced muscle strength is one of the independent risk factors for falls in patients with PD⁹ and is associated with balance impairments.^{10,11} The effect of resistance training (RT) on postural control still remains unclear as only few studies exist, most of them not having the assessment of balance control as a primary outcome parameter and low sample sizes limit the informative value (for review see ^{12,13}). A recently published paper showed that postural stability can be improved by strength training.¹⁴ In order to create most effective exercises, studies often use multidimensional training programs.¹⁵⁻¹⁷ These physiotherapy techniques are difficult to compare and more specific trials are needed to give further information about which exercise program may be more effective and about the underlying processes leading to the results.^{5,18}

As compensatory mechanisms play an important role in PD and as there is a link between muscle strength and postural instability,^{10,11} we hypothesized that the improvement of strength facilitates the activation of strengthened balance related muscle-groups and thereby leads to enhanced postural control. A recently published study with healthy elderly emphasizes this idea, as the authors showed better improvement in postural control due to RT in comparison to classical balance training.¹⁹ The aim of the present study was to compare the effectiveness of RT with

BT to improve postural control in patients with PD and to describe the underlying mechanisms of the two training types.

Methods

Design

We designed a rater blinded randomized controlled trial to compare the effects of RT with the effects of BT for people with idiopathic PD. After baseline assessment patients were randomized into two groups, one received RT and the other BT twice a week over 7 weeks. 8-weeks follow-up assessment was performed during the week after completion of the trial and 12-weeks follow-up was conducted 4 weeks later. All clinical tests were carried out by a rater who was blind to the participant's group allocation. Clinical examination was videotaped and rated by a second rater, blind to subject's group allocation and assessment time.

Patients

Patients were included if they met the following inclusion criteria: (1) diagnosed with idiopathic Parkinson's Disease by a neurologist specializes in movement disorders as defined by the UK Brain Bank criteria,²⁰ (2) postural instable (Fullerton Advanced Balance (FAB) scale \leq 25 points), (3) ability to stand unaided and to walk with or without an assistive device and (4) able to follow exercise instructions (assessed during a pre-examination during which the FAB scale was performed (see below)). Exclusion criteria were: (1) deep brain stimulation, (2) other diseases that could influence stance- and gait performance (e.g. peripheral neuropathy, orthopedic injuries), (3) participation in a RT or BT (beside usual physical therapy) during the last

6 months, (4) participation in any other medical, behavioral or exercise treatment (additionally to the usual received therapeutic treatment) during the study period, (5) unstable medication and (6) cardiopulmonary/metabolic diseases that could interfere with the safe conduct of the training or testing protocol. Cognition was assessed with the Mini-Mental State Examination (MMSE). Cognitive impairments were no exclusion criteria as a representative sample of affected patients should be included. The study protocol was approved by the local ethics committee and all patients gave written informed consent prior to participating.

Screening and Randomization

To assess eligibility, all subjects were screened undergoing a pre-examination prior to inclusion in the study. The FAB scale was performed to determine the level of postural instability and to verify if patients are able to follow instructions. The patients who met the inclusion criteria were randomized in matched pairs for gender and level of postural instability (measured by the FAB scale in the pre-examination)) using computer generated random number sequences into the resistance- or balance training group in a ratio of 1:1. Participants were reassessed for baseline analysis at another day.

Intervention

Patients received 14 sessions (7 weeks, twice a week) of group exercise training with 4-5 patients per group. Each session lasted 60 minutes, 10 minutes warm-up followed by 50 minutes resistance- or balance training. Each session was guided by a movement disorders experienced sport scientist who had experience in neurological rehabilitation and with the help of a sport student. Participants were

instructed to follow their normal schedules for physical activity during the intervention period.

Resistance Training

RT was performed with the aim to improve muscle strength of the lower limbs. The trained muscle groups were hip flexors, extensors and abductors, knee flexors and extensors, ankle dorsiflexors and plantarflexors, as these are muscle groups primary involved in postural control mechanisms.^{10,11,21} As RT was performed with the primary aim to improve stability, movements were not controlled by machines but freely coordinated, in order to also enhance neuromuscular coordination. The subjects own weight, cuff weights and elasticated bands were used as resistance.²² Squats, knee extensions, toe/calf raises, hip abductions and other exercises were performed (for details about the exercise program see supplemental material online). In line with training recommendations based on previous studies (e.g. Hass et al.²³) participants completed three sets of 15 – 20 repetitions of each exercise. In an effort to keep training intensity high, once participants could complete more than 20 consecutive repetitions of an exercise, they were asked to increase the resistance to a point where they could only complete between 15 – 20 repetitions. Participants rested for 2 minutes between exercise sets.

Balance Training

BT involved stance- and gait tasks which require feedforward and feedback postural control.⁸ Feedforward postural control for example was trained by letting the patients lean forward, backward or sideward, thus letting them control their center of pressure inside the boundaries of their base of support. To practice feedback control one

exercise was to perturb the patients by shoulder pulls from the therapist. Training progression during the intervention period was reached by reducing or manipulating sensory information, necessary to obtain balance. Visual information for example was disturbed by closing the eyes or looking up to the ceiling. Proprioceptive feedback was manipulated by standing on different unstable surfaces instead of normal overground. Each exercise lasted for 45 sec and was performed 3 times, followed by a break of 2 minutes. (More details about the BT exercise program are available as supplemental material online.)

Outcome Measures

Primary outcome measure was the Fullerton Advanced Balance (FAB) scale.²⁴ The FAB scale is a validated clinical scale for the assessment of static and dynamic postural control, sensory reception/integration and feedforward/feedback postural control.^{25,26} The scale consists of 10 items, each with a 5-point ordinal scale (0-4) and a maximal score of 40 points (higher values indicate better performance). The test was carried out by an independent rater (blinded rating) who was blind to the participant's group allocation. Assessment was videotaped and rated by a second rater (blinded video rating), blind to subject's group allocation and assessment time.

The following tests were performed as secondary outcome measures:

Surface perturbations were performed in order to assess feedback- and feedforward postural control under standardized conditions. The patients were asked to maintain their balance without doing steps while standing on a movable platform which shifted unexpectedly towards anterior- or posterior direction (20cm with a velocity of 0.1m/s and an acceleration of 10m/s²). Participants were not aware neither when the platform would move nor in which direction the surface would change (for details see

supplementary material online). Center of mass (COM) displacement was analyzed by measuring the movement of body segments with an infrared movement analysis system (Qualisys, Gothenburg, Sweden) consisting of six infrared cameras (240 Hz sampling rate). 17 infrared light emitting diodes were placed on anatomic landmarks as described in detail elsewhere¹ and the COM was calculated as the weighted sum of all segments, as adapted from Winter et al.²⁷ According to Visser et al.¹ the vector length of three-dimensional COM displacement was calculated. In order to adapt to different biomechanical requirements due to different sizes of subjects, the vector length was normalized to COM height. The average normalized vector length over all backward- and forward pulls was calculated, respectively. The area under the curve of the normalized vector length from the beginning until 1 sec after the perturbation was defined as an instability outcome measure.¹ Trials during which subjects had to take steps were excluded and patients received two perturbations in each direction before starting the measurement in order to avoid recording first trial reactions.²⁸

The following tests were performed additionally: Timed-up-and-go-test (TUG),²⁹ Clinical Global Impression - Improvement (CGI-I),³⁰ Unified Parkinson's Disease Rating Scale (UPDRS)³¹ (assessed by a blinded rater and videotaped for a second rating by a person blind to group allocation and assessment time; for rigidity (item 22) the results of the first rater were used), Parkinson's Disease Questionnaire (PDQ-39),³² Beck Depression Inventory (BDI).³³

For gait analysis, patients' overground gait velocity was captured and afterwards participants walked 2 minutes on a motor-driven treadmill (Woodway, Weil am Rhein, Germany) meanwhile spatio-temporal parameters of gait were recorded by force transducers in the treadmill (Kistler, Winterthur, Switzerland). The following parameters were calculated: stride length, double support time, stride time variability,

bilateral coordination (Phase Coordination Index (PCI))³⁴ and gait asymmetry³⁵ (for details see supplementary material online).

Maximal isometric leg strength was measured on a custom designed leg press equipped with a force platform (Kistler, Winterthur, Switzerland) (1000Hz sampling rate). Maximal voluntary contraction (MVC) was assessed. Rate of force development (RFD) (defined as the slope of the force time curve ($\Delta\text{force}/\Delta\text{time}$)) was analyzed by calculating the peak RFD (maximal slope) and the average slope of the time interval 0-100ms after onset of muscle contraction. Testing was performed for both legs separately and results were analyzed according to the less- and more affected Parkinson's Disease side (less affected side (LES), more affected side (MES)) - defined by comparing the sums of the UPDRS items 20-26 for the left and right side separately.^{36,37} (For details of the strength testing procedure see supplementary material online)

Testing Procedure

As the testing protocol was long, assessments were performed on two separate days. Patients were tested in the medication ON-state (1 hour after the last intake of antiparkinsonian medication). Assessment time was documented for each patient and measurements at baseline, 8- and 12-weeks follow-up were performed at the same time of day for each patient.

Statistical Analysis

Power calculation was performed with G*Power (version 3.1.9)³⁸ and a sample size of 20 patients per group was found to be required to detect a between-group

difference of 2 points at the FAB scale from baseline to 8-weeks follow-up (power = 0.9, alpha = 0.05), allowing for a 10% drop-out rate.

Between-group differences in demographic and baseline variables were tested using the Mann-Whitney-U-Test. Within group differences from baseline to 8-weeks follow-up and baseline to 12-weeks follow-up were analysed with the Wilcoxon signed rank test.

To compare the effect of treatment between the two training groups, the differences between 8-weeks follow-up and baseline performance were computed for both groups and analysed with the Mann-Whitney-U-Test.

Chi-square tests were used to compare CGI-I between the groups.

Interrater reliability between the blinded rater and the blinded video rater were analysed by calculating two-way random single measure intraclass correlation coefficients (ICC (2,1)) in order to compare agreement between the results of the two raters.

To analyze the relationship between the magnitude of change in the different outcome parameters, Spearman's rank correlation coefficients (Spearman's Rho) were calculated and a linear regression analysis was performed.

Data were analyzed on a per-protocol basis. Participants were excluded if they missed more than two training sessions, if medication was changed or if any other injury which could influence stance- and gait performance occurred during the study period.

Statistical tests were performed with the use of SPSS software, version 19 (IBM). All statistical tests were two-sided and the α level for significance was set at $P < 0.05$. The Bonferroni correction was used in multiple comparisons.³⁹

Results

Flow of participants through the Trial

From September 2011 till August 2013 a total of 172 persons were screened for eligibility among 40 patients met the inclusion criteria and underwent randomization. Figure 1 shows the study design and flow of participants through the study. All patients were able to follow the instructions during the training sessions.

8 patients (20%; 3 RT; 5 BT) did not complete the training protocol. Within the RT group, one patient changed the antiparkinsonian medication, one patient received the diagnosis of not having idiopathic PD and one patient did not reach the minimum of training sessions due to health problems not related to the training. Among the BT group, one patient was injured by a fall not related to the training, one patient could not continue because his wife who drove him to the training fell ill, one patient was excluded as he started a second high intensity rehabilitation training and two patients did not complete the minimum of 12 training sessions due to health problems not related to the training.

Baseline data

The demographic characteristics of the participants are shown in Table 1. No significant differences were found in the demographic or baseline variables between the two training groups except for the outcome forward pull.

Agreement between the two blinded raters

The agreement between the blinded rater and the blinded video rater was high with ICCs >0.80 for baseline and 8-weeks follow-up for the FAB scale and UPDRS motor score. As the blinded video rater (the person who rated by videos) not only was blind to group allocation but also to assessment time, results are analysed and interpreted with priority to the blinded video rater.

Effect of intervention from baseline to 8-weeks follow-up

Table 2 shows the baseline- and 8-weeks follow-up-assessment data and their comparison for both groups separately and the p-values for the comparison of the effects between the two different intervention-groups.

The RT-group significantly improved from baseline to week 8 on average by 2.4 points on the FAB scale, whereas the score of the BT-group only increased on average by 0.3 points and that was statistically not significant (blinded video rating). The higher intervention effect of the RT-group did not differ significantly from the training effect of the BT-group ($p=0.143$).

No significant differences were found in the forward- and backward pull test when analysing the area under the curve of the normalized vector length of the COM displacement over the perturbation period. Figure 2 shows the average normalized

COM vector length during backward perturbations at baseline and 8-weeks follow-up for one patient. The percentage of trials during which the subjects made steps did not differ significantly from baseline to week 8 for the RT- and BT-group, respectively (RT: average nr. of trials with steps (SD): baseline: 1.3 (2.6), 8-weeks follow-up: 2.1 (2.9); BT: baseline: 1.8 (2.9), 8-weeks follow-up: 1.2 (2.1)).

The RT-group but not the BT-group performed the TUG significantly quicker at 8-weeks follow-up in comparison to baseline (on average -1.7sec, $p=0.038$) but the time x group interaction was statistically not significant ($p=0.116$).

Figure 2 shows the results of the CGI-I. 65% of the patients from the RT-group reported a clinical global improvement whereas only 40% of the participants from the BT-group indicated amelioration. However, the difference between both groups was not significant (Chi-square test, $p=0.162$).

In contrast to the RT-group, a significant improvement from baseline to week 8 was found for the BT-group at the UPDRS total score (on average -4.1 points, $p=0.033$) without any significant time x group interaction ($p=0.272$). No significant differences were found for the UPDRS motor score (blinded video rating).

No significant differences were found from baseline to week 8 and for interaction effects for all gait parameters.

The BT-group slightly improved the peak rate of force development of the less affected side from baseline to week 8, but this improvement was statistically not significant after Bonferroni-correction.

No significant differences were found for the PDQ-39 and the BDI.

Effect of intervention from baseline to 12-weeks follow-up

Table 3 shows the results from the subgroup of patients who passed the 12-weeks follow-up examination. At the FAB scale, training effects decreased to baseline level for the RT-group after one month without exercising. The BT-group even slightly worsened at Follow-Up in comparison to baseline (on average -0.8 points). Small improvements (-1.4 sec; 95% CI: -3.2; 0.4) remained at the TUG at 12-weeks follow-up for the RT-group (BT group: -0.8 sec; 95% CI: -3.5; 1.9). The differences within one group from baseline to week 12 and the comparison of changes between the two training groups were statistically not significant.

Correlation between different outcome parameters

When correlating the differences from baseline to week 8 of the FAB scale (Δ -FAB scale) with the magnitude of changes of the other test parameters, we found significant correlations between Δ -FAB scale and Δ -stride time variability (Spearman's Rho: -0.649, $p=0.009$) and Δ -RFD (LES) (Spearman's Rho: 0.643, $p=0.018$) within the RT-group (Table 4). A linear regression analysis showed that 71,6% (adjusted R^2) of the variance of Δ -FAB scale (as dependent variable) can be explained by Δ -stride time variability and Δ -RFD (LES) (as independent variables) and this model was statistically significant ($F=14.9$, $p=0.001$). Stride time variability and average RFD equally contributed to the model (stride time variability: Beta=0.517, $T=2.98$, $p=0.015$; RFD: Beta=-0.54, $T=-3.114$, $p=0.012$).

Within the BT-group significant correlations were found between Δ -FAB-scale and Δ -PCI (Spearman's Rho: -0.608, $p=0.047$) and Δ -BDI (Spearman's Rho: 0.718, $p=0.003$) (Table 4). With Δ -PCI and Δ -BDI as predictors for Δ -FAB-scale in the linear

regression analysis for the BT-group, the model failed to be significant ($F=2.191$, $p=0.174$).

No significant correlation was found when correlating the degree of cognitive impairment (measured by the MMSE) and Δ -FAB scale.

Discussion

No significant differences were found when comparing the effects of RT with the effects of BT to improve postural control in patients with PD. Within the RT group, patients significantly improved postural control, whereas participants from the BT group only slightly improved on the FAB scale but this amelioration was not significant. The fact, that the interaction effect between the two training groups was not significant, may be due to our small sample size. However, we conclude that there exists only a small difference between RT and BT with a given tendency that RT might be more effective to improve postural control in this population.

The higher training effects of the RT group in comparison to the BT group on the FAB scale is notable, as - in contrast to resistance training - the items of the FAB scale are closely related to the exercises of the balance training. All patients underwent an examination to assess eligibility before participating meanwhile the FAB scale was carried out the first time. At baseline the patients thus performed the scale the second time. This emphasizes to consider the improvement from baseline to week 8 due to training effects and not based on memory effects due to the repetition of the same test.

The RT-group improved to a higher extent than the BT-group (FAB scale, TUG and CGI-I) but this difference was statistically not significant with this sample size. It has

to be taken into account that patients only trained two times per week. Training frequency therefore was low and maybe not high enough to detect significant differences. As patients were in an advanced stage of disease (H&Y: 2.5-3.0) and all of them reported to have postural impairments, we considered this training frequency practical feasible as most of the patients were not able to come to the training sessions alone and probably may not be able to train more often. It also has to be announced that we compared two competing training types - interaction effects therefore remain small.

The relationship between the improvement in postural control and improvement in rate of force development of the less affected Parkinson's Disease site highlights the importance of strength with regard to balance performance. The ability to generate force in the early onset of muscle contraction seems to play an important role for postural control mechanisms. By contrast, the changes of overall motor and mobility performance (measured by the UPDRS and TUG) did not correlate with the improvements of balance. The fact that especially the RFD of the less- but not the more affected Parkinson's Disease site contributed to better balance performance is in accordance with a recent study showing that training the less affected side leads to higher improvements of gait performance in PD than standard exercise (Ricciardi et al., submitted). This raises the idea that strength training may be an effective compensatory strategy to enhance postural stability in this patient population.

Resistance training was not performed with exercise machines but subjects own weight, cuff weights and elasticated bands were used as resistance. This was done as we consider freely coordinated movements to be more effective in order to improve postural control. Besides, we wanted to perform a training type, which is – as balance training – easy and cost-effective to perform without the need of exercise

machines which are not always present in physical therapy. During freely coordinated resistance training an additional enhancement in sensorimotor integration is probable which is a key feature of balance training. This may be the reason for the higher improvements in postural control due to resistance training. On the other hand, improvements of strength, especially rate of force development, are also possible due to balance training as we see in our results and as described for healthy elderly.^{40,41}

Cognitive impairments were no exclusion criteria as we wanted to include a representative sample of affected patients. All patients were able to follow the instructions during the training sessions. As no relationship was found between the degree of cognitive impairment and magnitude of training effects, we do not consider a lack of cognition to have any influence on the results.

The following limitations have to be announced. The sample size is small and especially as the correlation- and regression analysis were performed with the RT- and BT-group separately, results have to be interpreted with caution. However, the blinded assessment gives reliability to our results. Second, we did not assess fall rates which would be of interest as strength- and balance performance are independent risk factors for falls. Furthermore, we did not measure how much the patients liked to participate in the training. Concerning long-term attendance it would be of interest to see if the patients would favor one of the training types.

Conclusions

This randomized controlled rater blinded trial shows that postural control of patients with PD was improved by resistance training. Tendencies are given, that resistance

training might be more effective than balance training and that the improvement of postural control might be related to improvements of rate of force development.

Acknowledgments

The project was funded by the Coppenrath-Stiftung, Geeste/Groß-Hesepe, Niedersachsen, Germany and Krumme-Stiftung, Eckernförde, Schleswig-Holstein, Germany.

References

1. Visser JE, Allum JH, Carpenter MG, et al. Subthalamic nucleus stimulation and levodopa-resistant postural instability in Parkinson's disease. *J Neurol*. 2008;255:205-210.
2. Bloem BR, Beckley DJ, van Dijk JG, Zwinderman AH, Remler MP, Roos RA. Influence of dopaminergic medication on automatic postural responses and balance impairment in Parkinson's disease. *Mov Disord*. 1996;11:509-521.
3. Potter-Nerger M, Volkmann J. Deep brain stimulation for gait and postural symptoms in Parkinson's disease. *Movement disorders : official journal of the Movement Disorder Society*. 2013;28:1609-1615.
4. Nantel J, McDonald JC, Bronte-Stewart H. Effect of medication and STN-DBS on postural control in subjects with Parkinson's disease. *Parkinsonism & related disorders*. 2012;18:285-289.
5. Dibble LE, Addison O, Papa E. The effects of exercise on balance in persons with Parkinson's disease: a systematic review across the disability spectrum. *J Neurol Phys Ther*. 2009;33:14-26.
6. Allen NE, Sherrington C, Suriyarachchi GD, Paul SS, Song J, Canning CG. Exercise and motor training in people with Parkinson's disease: a systematic review of participant characteristics, intervention delivery, retention rates, adherence, and adverse events in clinical trials. *Parkinsons Dis*. 2012;2012:854328.
7. Goodwin VA, Richards SH, Taylor RS, Taylor AH, Campbell JL. The effectiveness of exercise interventions for people with Parkinson's disease: a systematic review and meta-analysis. *Mov Disord*. 2008;23:631-640.
8. Smania N, Corato E, Tinazzi M, et al. Effect of balance training on postural instability in patients with idiopathic Parkinson's disease. *Neurorehabil Neural Repair*. 2010;24:826-834.
9. Latt MD, Lord SR, Morris JG, Fung VS. Clinical and physiological assessments for elucidating falls risk in Parkinson's disease. *Mov Disord*. 2009;24:1280-1289.
10. Nallegowda M, Singh U, Handa G, et al. Role of sensory input and muscle strength in maintenance of balance, gait, and posture in Parkinson's disease: a pilot study. *American journal of physical medicine & rehabilitation / Association of Academic Physiatrists*. 2004;83:898-908.
11. Nocera JR, Buckley T, Waddell D, Okun MS, Hass CJ. Knee extensor strength, dynamic stability, and functional ambulation: are they related in Parkinson's disease? *Arch Phys Med Rehabil*. 2010;91:589-595.

12. Briennesse LA, Emerson MN. Effects of resistance training for people with Parkinson's disease: a systematic review. *J Am Med Dir Assoc.* 2013;14:236-241.
13. Lima LO, Scianni A, Rodrigues-de-Paula F. Progressive resistance exercise improves strength and physical performance in people with mild to moderate Parkinson's disease: a systematic review. *J Physiother.* 2013;59:7-13.
14. Shen X, Mak MK. Balance and Gait Training With Augmented Feedback Improves Balance Confidence in People With Parkinson's Disease: A Randomized Controlled Trial. *Neurorehabilitation and neural repair.* 2014;28:524-535.
15. Hirsch MA, Toole T, Maitland CG, Rider RA. The effects of balance training and high-intensity resistance training on persons with idiopathic Parkinson's disease. *Arch Phys Med Rehabil.* 2003;84:1109-1117.
16. Gobbi LT, Oliveira-Ferreira MD, Caetano MJ, et al. Exercise programs improve mobility and balance in people with Parkinson's disease. *Parkinsonism Relat Disord.* 2009;15 Suppl 3:S49-52.
17. Toole T, Hirsch MA, Forkink A, Lehman DA, Maitland CG. The effects of a balance and strength training program on equilibrium in Parkinsonism: A preliminary study. *NeuroRehabilitation.* 2000;14:165-174.
18. Tomlinson CL, Herd CP, Clarke CE, et al. Physiotherapy for Parkinson's disease: a comparison of techniques. *The Cochrane database of systematic reviews.* 2014;6:CD002815.
19. Joshua AM, D'Souza V, Unnikrishnan B, et al. Effectiveness of progressive resistance strength training versus traditional balance exercise in improving balance among the elderly - a randomised controlled trial. *J Clin Diagn Res.* 2014;8:98-102.
20. Gelb DJ, Oliver E, Gilman S. Diagnostic criteria for Parkinson disease. *Archives of neurology.* 1999;56:33-39.
21. Allen NE, Sherrington C, Canning CG, Fung VS. Reduced muscle power is associated with slower walking velocity and falls in people with Parkinson's disease. *Parkinsonism Relat Disord.* 2010;16:261-264.
22. Martins WR, de Oliveira RJ, Carvalho RS, de Oliveira Damasceno V, da Silva VZ, Silva MS. Elastic resistance training to increase muscle strength in elderly: a systematic review with meta-analysis. *Archives of gerontology and geriatrics.* 2013;57:8-15.
23. Hass CJ, Buckley TA, Pitsikoulis C, Barthelemy EJ. Progressive resistance training improves gait initiation in individuals with Parkinson's disease. *Gait Posture.* 2012;35:669-673.
24. Rose DJ, Lucchese N, Wiersma LD. Development of a multidimensional balance scale for use with functionally independent older adults. *Arch Phys Med Rehabil.* 2006;87:1478-1485.

25. Schlenstedt C, Brombacher S, Hartwigsen G, Weisser B, Moller B, Deuschl G. Comparing the Fullerton Advanced Balance scale with the Mini-BESTest and Berg Balance Scale to assess postural control in patients with Parkinson's Disease. *Archives of physical medicine and rehabilitation*. 2014.
26. Schott N. [Assessment of balance in community dwelling older adults : Reliability and validity of the German version of the Fullerton Advanced Balance Scale]. *Z Gerontol Geriatr*. 2011;44:417-428.
27. Winter DA, Patla AE, Ishac M, Gage WH. Motor mechanisms of balance during quiet standing. *J Electromyogr Kinesiol*. 2003;13:49-56.
28. Oude Nijhuis LB, Allum JH, Valls-Sole J, Overeem S, Bloem BR. First trial postural reactions to unexpected balance disturbances: a comparison with the acoustic startle reaction. *Journal of neurophysiology*. 2010;104:2704-2712.
29. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *Journal of the American Geriatrics Society*. 1991;39:142-148.
30. Guy W. *ECDEU assessment manual for psychopharmacology*. Rockville, Md: U.S. Dept. of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute of Mental Health, Psychopharmacology Research Branch, Division of Extramural Research Programs; 1976.
31. Fahn S, Elton RL. Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden CD, Calne D, Goldstein M, eds. *Recent developments in Parkinson's disease*. Florham Park (NJ): MacMillan Health Care Information; 1987:153-163.
32. Jenkinson C, Fitzpatrick R, Peto V, Greenhall R, Hyman N. The Parkinson's Disease Questionnaire (PDQ-39): development and validation of a Parkinson's disease summary index score. *Age Ageing*. 1997;26:353-357.
33. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Archives of general psychiatry*. 1961;4:561-571.
34. Plotnik M, Giladi N, Hausdorff JM. A new measure for quantifying the bilateral coordination of human gait: effects of aging and Parkinson's disease. *Experimental brain research*. 2007;181:561-570.
35. Plotnik M, Giladi N, Balash Y, Peretz C, Hausdorff JM. Is freezing of gait in Parkinson's disease related to asymmetric motor function? *Ann Neurol*. 2005;57:656-663.
36. Geurts AC, Boonstra TA, Voermans NC, Diender MG, Weerdesteyn V, Bloem BR. Assessment of postural asymmetry in mild to moderate Parkinson's disease. *Gait & Posture*. 2011;33:143-145.

37. Plotnik M, Giladi N, Hausdorff JM. Bilateral coordination of walking and freezing of gait in Parkinson's disease. *Eur J Neurosci.* 2008;27:1999-2006.
38. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods.* 2007;39:175-191.
39. Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *Journal of the Royal Statistical Society. Series B (Methodological).* 1995;57:289-300.
40. Gruber M, Gollhofer A. Impact of sensorimotor training on the rate of force development and neural activation. *Eur J Appl Physiol.* 2004;92:98-105.
41. Gruber M, Gruber SB, Taube W, Schubert M, Beck SC, Gollhofer A. Differential effects of ballistic versus sensorimotor training on rate of force development and neural activation in humans. *J Strength Cond Res.* 2007;21:274-282.
42. Washburn RA, Smith KW, Jette AM, Janney CA. The Physical Activity Scale for the Elderly (PASE): development and evaluation. *J Clin Epidemiol.* 1993;46:153-162.

Figure Legend

Figure 1. Study design and flow of participants.

Figure 2. A: Results of the Clinical Global Impression – Improvement scale (CGI-I).

B: Average normalized center of mass (COM) vector length of one patient during backward perturbations at baseline and 8-weeks follow-up.

Table 1. Participant characteristics.

Variable	Resistance (n=17)	Balance (n=15)
Age (yr)	75.7 (5.5)	75.7 (7.2)
No. of female subjects	5 (29.4%)	6 (40%)
Duration of Disease (yr)	10.1 (6.0)	9.3 (7.9)
BMI (kg/m ²)	27.9 (5.5)	25.5 ±4.4
H&Y	2.8 (0.26)	2.7 (0.4)
H&Y (Range)	2.5-3.0	2.5-3.0
UPDRS total (ON)	40.2 (12.5)	37.7 (13.1)
UPDRS part II (ON)	13.4 (5.1)	11.1 (6.0)
UPDRS part III (ON)	21.5 (9.7)	21.2 (8.0)
FAB scale	21.0 (3.9)	22.4 (4.3)
MMSE	27.3 (3.6)	27.7 (3.0)
MMSE (Range)	17-30	20-30
PASE score	104.6 (87.3)	77.2 (63.1)
LEDD (mg/day)	817.4 (468.0)	674.7 (294.9)

Abbreviations: If not indicated differently, the values are either mean (SD) or number and percentage. BMI, Body-Mass-Index; H&Y, Hoehn & Yahr; UPDRS, Unified Parkinson's Disease Rating Scale; FAB, Fullerton Advanced Balance; MMSE, Mini-Mental State Examination; PASE, Physical Activity Scale for the Elderly⁴²; LEDD, levodopa equivalent daily dose.

Table 2. Comparison within- and between the two training groups from baseline to 8-weeks follow-up.

Variable	Group	Baseline	8-weeks follow-up	Mean change (95% CI) from baseline to 8-weeks follow-up	p-value (within group comparison)	p-value (between group comparison)
FAB scale [†]	RT	22.2 (4.8)	24.5 (5.4)	2.4 (0.1; 4.6)	0.04*	0.143
	BT	24.5 (4.6)	24.9 (5.3)	0.3 (-0.8; 1.5)	0.526	
Forward pull	RT	2270.3 (375.1)	2336.7 (274.0)	66.4 (-138.2; 270.9)	0.311	0.769
	BT	1807.4 (351.8)	1836.6 (360.9)	29.2 (-66.4; 124.9)	0.239	
Backward pull	RT	1882.3 (326.9)	1782.1 (373.4)	-100.2 (-311.5; 111.0)	0.286	0.332
	BT	1844.6 (411.4)	1917.4 (362.7)	72.8 (-261.4; 407.0)	0.657	
TUG (sec)	RT	11.2 (3.2)	9.5 (2.4)	-1.7 (-3.3; -0.1)	0.033*	0.139
	BT	9.2 (3.0)	9.0 (1.8)	-0.2 (-1.3; 0.9)	0.929	
UPDRS total score	RT	40.2 (12.5)	38.5 (12.3)	-1.7 (-5.1; 1.8)	0.347	0.272
	BT	37.7 (13.1)	33.6 (12.3)	-4.1 (-7.3; -0.9)	0.033*	
UPDRS motor score [‡]	RT	22.6 (8.8)	22.2 (8.9)	-0.4 (-2.0; 1.2)	0.568	0.911
	BT	20.3 (4.9)	19.4 (6.7)	-0.9 (-3.0; 1.1)	0.821	
gait velocity (cm/sec)	RT	104.3 (15.3)	106.1 (15.0)	1.8 (-5.2; 8.7)	0.619	0.692
	BT	106.9 (18.3)	106.8 (17.7)	-0.1 (-7.4; 7.4)	0.776	
stride length (cm)	RT	80.6 (13.0)	80.3 (11.7)	-0.4 (-4.5; 3.7)	0.865	0.097
	BT	88.8 (15.7)	91.5 (16.1)	2.7 (-0.4; 5.9)	0.131	
double support time (msec)	RT	156.6 (31.7)	156.3 (35.5)	-0.3 (-8.4; 7.8)	0.532	0.134
	BT	149.4 (24.9)	155.0 (32.1)	5.6 (-2.1; 13.3)	0.11	
stride time variability (%)	RT	3.8 (1.0)	3.7 (1.7)	-0.1 (-0.8; 0.6)	0.334	0.413
	BT	3.9 (1.8)	3.0 (0.8)	-0.9 (-2.0; 0.3)	0.182	
PCI (%)	RT	6.6 (1.5)	6.1 (1.8)	-0.5 (-1.1; 0.1)	0.061	0.077
	BT	6.1 (1.4)	6.9 (2.1)	0.8 (-0.7; 2.3)	0.286	
Asymmetry Index	RT	5.1 (4.1)	6.0 (4.3)	0.9 (-1.1; 0.1)	0.82	0.959
	BT	4.9 (3.7)	5.0 (5.3)	0.1 (-1.6; 1.8)	0.99	
leg strength (MVC), LES (N)	RT	393.8 (113.5)	416.9 (91.0)	23.0 (-15.5; 61.6)	0.279	0.458
	BT	416.5 (129.6)	408.8 (138.5)	-7.7 (-53.3; 37.8)	0.925	
leg strength (MVC), MES (N)	RT	401.8 (130.0)	399.8 (85.7)	-2.0 (-48.2; 44.2)	0.807	0.287
	BT	407.9 (134.4)	426.2 (131.6)	18.3 (-4.4; 41.1)	0.133	
peak RFD, LES (N/msec)	RT	1.5 (0.7)	1.6 (0.8)	0.1 (-0.4; 0.4)	0.753	0.223
	BT	1.6 (1.0)	1.8 (0.9)	0.3 (0.0; 0.5)	0.028**	
peak RFD, MES (N/msec)	RT	1.5 (1.0)	1.5 (0.7)	0.0 (-0.6; 0.5)	0.972	0.503
	BT	1.4 (0.7)	1.7 (0.9)	0.3 (-0.2; 0.8)	0.308	
RFD, LES (Interval 0-100ms) (N/msec)	RT	0.8 (0.6)	0.9 (0.6)	0.1 (-0.2; 0.5)	0.249	0.627
	BT	0.7 (0.5)	1.0 (0.6)	0.3 (0.0; 0.5)	0.056	
RFD, MES (Interval 0-100ms) (N/msec)	RT	0.8 (0.7)	0.9 (0.6)	0.1 (-0.3; 0.5)	0.600	0.939
	BT	0.9 (0.7)	0.9 (0.7)	0.0 (-0.4; 0.4)	0.507	
PDQ-39	RT	28.5 (12.7)	26.5 (12.0)	-2.0 (-4.5; 0.6)	0.123	0.174
	BT	28.5 (17.7)	30.2 (17.8)	1.7 (-3.5; 6.9)	0.499	
BDI	RT	9.9 (5.6)	8.4 (5.3)	-1.5 (-3.4; 0.3)	0.121	0.413
	BT	14.0 (9.1)	10.8 (5.9)	-3.2 (-6.7; 0.3)	0.073	

Abbreviations: Baseline- and 8-weeks follow-up values are mean (SD); CI, confidence interval; p -value of within-group comparison = p -value of Wilcoxon test; p -value of between-group comparison (interaction) = p -value of independent samples Mann-Whitney-U-Test; RT, resistance training (n=17); BT, balance training (n=15); FAB, Fullerton Advanced Balance; Forward/Backward Pull, value represents the area under the curve of the normalized vector length from 0 – 3 sec after the surface perturbation for forward and backward pull, respectively; TUG, Timed-up-and-go-test; UPDRS, Unified Parkinson's Disease Rating Scale; PCI, phase coordination index; MVC, maximal voluntary contraction; LES/MES, less/more affected Parkinson's Disease side; RFD, rate of force development (either peak or average RFD over the time interval 0-100ms after onset of muscle contraction); PDQ-39, Parkinson's Disease Questionnaire; BDI, Beck Depression Inventory; * significant different ($p < 0.05$); ** after Bonferroni-adjustment not significant; † blinded video rating; ‡ blinded video rating, without item 22 (rigidity).

Table 3. Comparison of baseline, 8- and 12-weeks follow-up.

Variable	Group	Baseline	8-weeks follow-up	12-weeks follow-up	Mean change (baseline to 12-weeks follow-up) (95% CI)
FAB scale [†]	RT	22.2 (5.3)	24.4 (5.7)	22.5 (5.1)	0.3 (-2.2; 2.8)
	BT	24.8 (4.2)	25.3 (4.4)	24.0 (4.6)	-0.8 (-2.6; 1.0)
TUG (sec)	RT	11.4 (3.6)	9.4 (2.5)	10.0 (2.1)	-1.4 (-3.2; 0.4)
	BT	9.2 (3.8)	9.0 (2.4)	8.4 (1.9)	-0.8 (-3.5; 1.9)
UPDRS total score	RT	40.7 (15.0)	40.7 (13.1)	39.4 (12.0)	-1.4 (-9.8; 7.1)
	BT	38.8 (14.7)	32.8 (13.5)	36.4 (15.9)	-2.5 (-9.0; 4.1)
UPDRS motor score [‡]	RT	23.7 (10.4)	23.4 (10.5)	22.5 (10.2)	-1.2 (-3.3; 0.9)
	BT	20.8 (4.1)	19.3 (6.6)	19.6 (5.5)	-1.3 (-3.4; 0.9)

Abbreviations: Values represent mean (SD); CI, confidence interval; RT, resistance training (n=14); BT, balance training (n=11); FAB, Fullerton Advanced Balance; TUG, Timed-up-and-go-test; UPDRS, Unified Parkinson's Disease Rating Scale; [†] blinded video rating; [‡] blinded video rating, without item 22 (rigidity).

Table 4. Correlation between the differences from baseline to 8-weeks follow-up of the FAB scale with the differences from baseline to 8-weeks follow-up of other outcomes.

	Resistance		Balance	
	Rho	p	Rho	p
Forward pull	-0.318	0.289	-0.366	0.241
Backward pull	-0.217	0.420	0.019	0.956
TUG	-0.097	0.754	0.230	0.497
UPDRS total score	-0.413	0.100	0.003	0.992
UPDRS motor score*	-0.397	0.115	0.030	0.915
gait velocity	0.148	0.572	0.058	0.837
stride length	0.319	0.246	-0.074	0.828
double support time	0.310	0.260	-0.357	0.281
stride time variability	-0.649	0.009	0.260	0.440
PCI	-0.152	0.587	-0.608	0.047
Asymmetry Index	0.215	0.441	-0.153	0.653
Leg Strength (MVC), LES	0.014	0.964	0.343	0.230
Leg Strength (MVC), MES	-0.510	0.075	-0.140	0.647
peak RFD, LES	0.114	0.712	-0.003	0.993
peak RFD, MES	0.263	0.385	-0.119	0.713
average RFD (Intervall 0-100ms), LES	0.643	0.018	0.276	0.340
average RFD (Intervall 0-100ms), MES	0.355	0.235	-0.174	0.569
PDQ-39	0.017	0.948	0.053	0.852
BDI	0.337	0.186	0.718	0.003

Abbreviations: Rho: Spearman's rank correlation coefficient; FAB, Fullerton Advanced Balance; Forward/Backward Pull, value represents the area under the curve of the normalized vector length from 0 – 3 sec after the surface perturbation for forward and backward pull, respectively; TUG, Timed-up-and-go-test; UPDRS, Unified Parkinson's Disease Rating Scale; PCI, phase coordination index; MVC, maximal voluntary contraction; LES/MES, less/more affected Parkinson's Disease side; RFD, rate of force development (either peak or average RFD over the time interval 0-100ms after onset of muscle contraction); PDQ-39, Parkinson's Disease Questionnaire; BDI, Beck Depression Inventory.

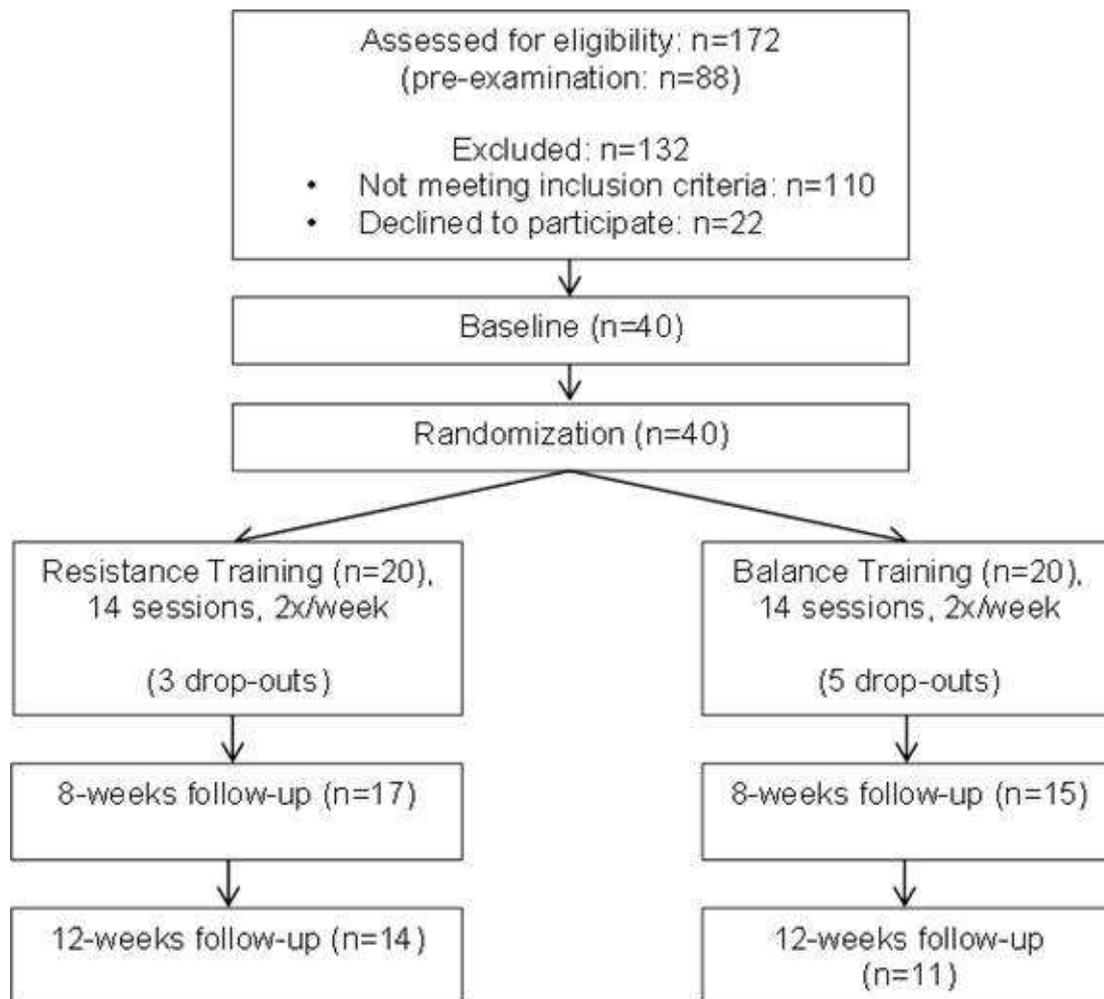


Figure 1. Study design and flow of participants.

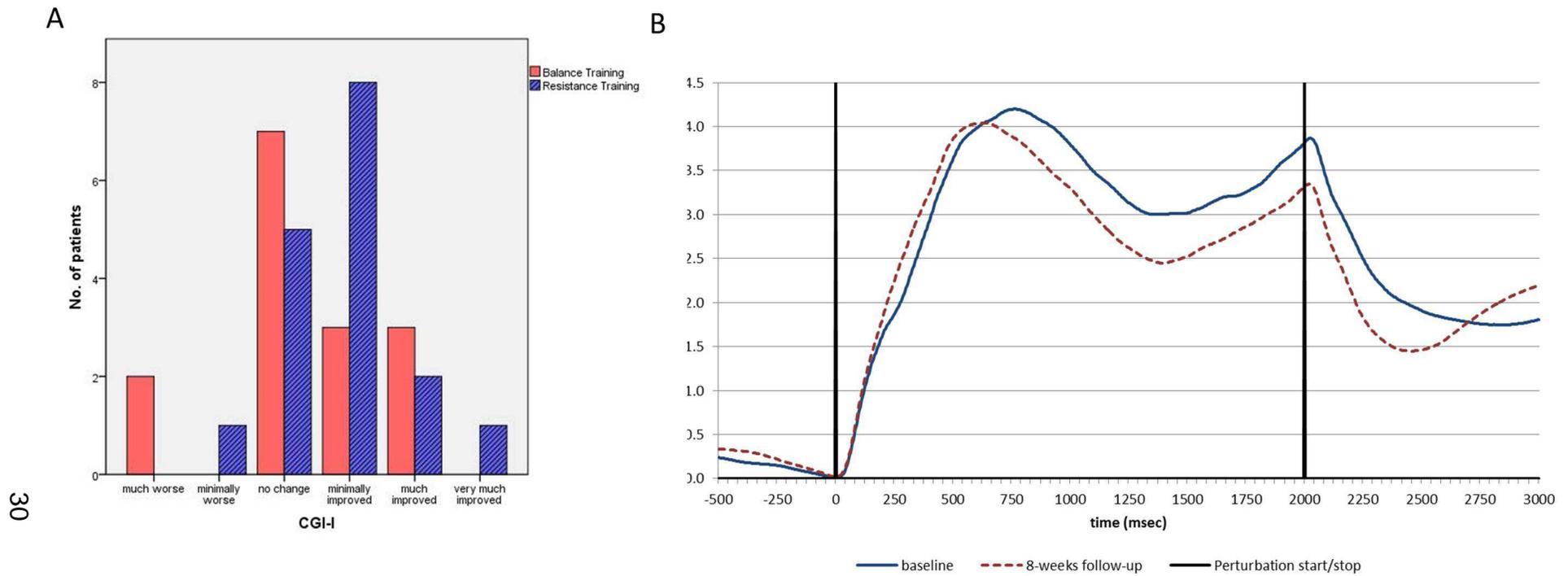


Figure 2. A: Results of the Clinical Global Impression – Improvement scale (CGI-I).

B: Average normalized center of mass (COM) vector length of one patient during backward perturbations at baseline and 8-weeks follow-up.

Supplemental material online

Resistance Training

Patients received 14 sessions (7 weeks, twice a week) of group exercise training with 4-5 patients per group. Each session lasted 60 minutes, 10 minutes warm-up followed by 50 minutes resistance training. In each session 4 of the following exercises were performed. Participants had to complete three sets of 15 – 20 repetitions of each exercise. In an effort to keep training intensity high, once participants could complete more than 20 consecutive repetitions of an exercise, participants were asked to increase the resistance to a point where they could only complete between 15 – 20 repetitions. Resistance was increased by cuff weights, elasticated bands or by the therapist who gave additional resistance. Participants rested for 2 minutes between exercise sets.

1. Squats



2. Knee extension (with cuff weight)



3. Calf raises



4. Toe raises (and hip flexion) (with elasticated band)

a)



b)

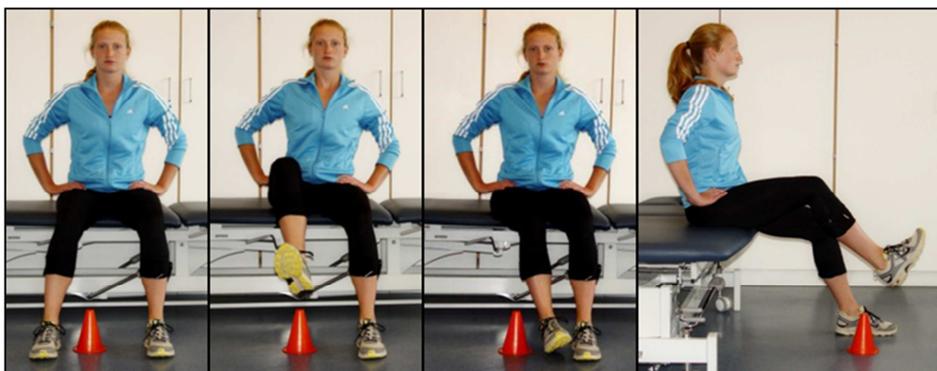


5. Hip flexion (with cuff weight)

a)



b)



6. Hip abduction



7. Ischiocrural muscles (with elasticated bands)



Balance Training

Patients received 14 sessions (7 weeks, twice a week) of group exercise training with 4-5 patients per group. Each session lasted 60 minutes, 10 minutes warm-up followed by 50 minutes balance training. Each exercise was hold for 45 sec and performed 3 times, followed by a break of 2 minutes. Training progression during the intervention period was reached by reducing or manipulating sensory information, necessary to obtain balance. Visual information for example was disturbed by closing the eyes or looking up to the ceiling. Proprioceptive feedback was manipulated by standing on different unstable surfaces instead of normal overground. Patient trained on normal overground during week 1-3 and on unstable surfaces during week 4-7.

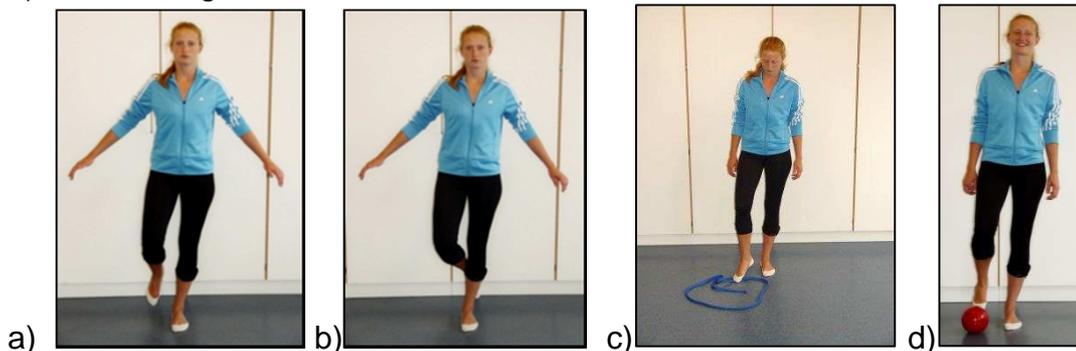
A) Stance on normal overground

1. Tandem stance

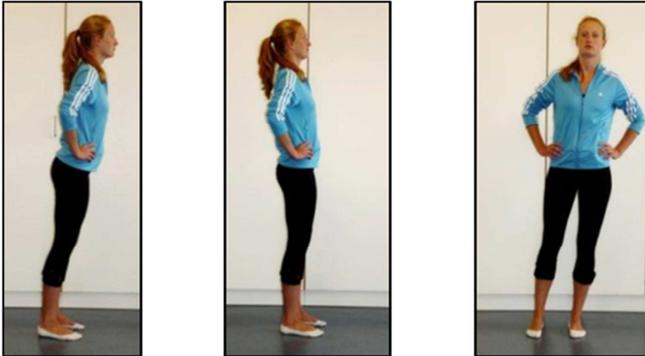


2. One leg stance:

- a) normal
- b) one foot clamped to the supporting leg
- c) the free leg has to move a rope in a circle
- d) the free leg has to move a ball in different directions



3. Limits of stability: leaning forward, backward or sideward



4. Shoulder pulls: participants were perturbed by shoulder pulls from the therapist

Variation / Training progression: In order to reach training progression, exercises 1-4 were performed with the following variations:

- Eyes open/closed
- Look to the side or up to the ceiling
- Participants had to hold a glass of water and focus on it

B) Stance on unstable surfaces

1.



2.



3.



Variation / Training progression: In order to reach training progression, exercises 1-3 were performed with the following variations:

- Eyes open/closed
- Look to the side or up to the ceiling
- Participants had to hold a glass of water and focus on it
- Participants were perturbed by shoulder pulls of the therapist

Surface Perturbation

Surface perturbations were performed in order to assess feedback- and feedforward postural control under standardized conditions. The patients were asked to maintain their balance without doing steps while standing on a movable platform which shifted unexpectedly towards anterior- or posterior direction. Participants were not aware neither when the platform would move nor in which direction the surface would change (for details see supplementary material online). 20 perturbations were conducted, 10 times in anterior direction (“backward pull”) and 10 times in posterior direction (“forward pull”). As in our experience the postural response to a perturbation depends on the previous perturbation type, all patients received the same randomized order of backward- and forward pulls at baseline and 8-weeks follow-up. The platform was moved 20 cm with a velocity of 0.1 m/s and an acceleration of 10 m/s². Patients’ balance therefore was perturbed two times - when the surface started to move and when the platform stopped. We used a relatively low velocity and long perturbation time in order to avoid the subjects doing steps and to let the patients anticipate the end of the perturbation. The first reaction when the platform started to move can be considered to be mostly feedback controlled. The reaction to the end of the perturbation was feedforward- and feedback controlled. Patients wore a safety harness (without weight assist) to avoid injuries due to falls.

Gait Analysis

Gait velocity of patients was measured during uninterrupted ground level walking. Subjects were requested to walk 5 times a distance of 5 m at a freely selected comfortable speed. Gait velocity was calculated as the mean of the 5 runs, recorded by light barriers placed at the beginning and at the end of the pathway. Afterwards,

patients were asked to walk 2 min. on a treadmill (length of 2.2 m and width of 0.7 m; Woodway, Weil am Rhein, Germany) with their overground gait velocity. Patients wore a safety harness without weight assist to avoid injuries due to falls. The treadmill comprised two separate belts, each with 4 force transducers (Kistler, Winterthur, Switzerland) (960Hz sampling rate). Contact times (heel strike, toe off) were measured by the force transducers to calculate the following spatio-temporal parameters:

- *Mean Stride length*: mean stride time (time from heel strike to heel strike) multiplied by belt speed (cm)¹
- *Double Support Time*: mean time (ms) both feet equally spend on the ground
- *Stride Time Variability*: coefficient of variation of stride time ($SD/mean \times 100$)
- *Phase Coordination Index (PCI)*: Bilateral coordination of gait was assessed by examining the phase between the step timing of the left and right legs.^{2,3} In short, each stride defines one gait cycle and the time between the start of a gait cycle and the time point when the other leg's heel strike occurs, was used to determine the phase. Normalizing the step time with respect to the stride time and scaling by 360° , defined the phase of the i -th stride (φ_i ; denoted in degrees). The PCI is a metric that combines the accuracy and consistency of stepping phases generation. The level of accuracy, i.e., how close are the series of generated phases to the value 180° , was assessed by the mean value of the series of absolute differences, $\varphi_i - 180^\circ$, denoted a measure of temporal accuracy as φ_ABS :

$$\varphi_ABS = |\varphi_i - 180^\circ|$$

The degree of consistency of the stepping phase generation was calculated by the coefficient of variation of φ , denoted as φ_{CV} and given as a percent. Therefore, assuming that $P\varphi_{ABS}=100*(\varphi_{ABS}/180)$, PCI was defined according to the following equation:

$$PCI = \varphi_{CV} + P\varphi_{ABS}$$

Thus, PCI is the sum of two relative values, each given as a percentile. Lower PCI values reflect a more consistent and more accurate phase generation and related to different health conditions, with higher values indicating more impaired bilateral coordination of gait.^{2,4}

- *Asymmetry Index (AI)*: $|\ln(SSWT/LSWT)|$, where SSWT and LSWT are the short and long swing time, respectively⁵

Strength Testing

A warm-up period of 5 minutes on a bicycle ergometer at 40-70W was mandatory for each subject before strength testing. Maximal isometric leg strength was measured on a custom designed leg press equipped with a force platform (Kistler, Winterthur, Switzerland) (1000Hz sampling rate). The subjects were positioned with the hip, knee and ankle angles adjusted at 90°. The position of each subject was documented that it was identical under the baseline-, 8- and 12-weeks follow-up conditions. The subjects were allowed to stabilize their upper body by holding on to handles attached to the leg press. Two submaximal isometric contractions were allowed to get accustomed to the testing procedure. Thereafter, each subject performed three leg press exercises with each leg separately with maximal voluntary effort. Subjects were carefully instructed to contract “as fast and forcefully as possible” and to hold the

maximal contraction for 3 sec. A 2 minutes rest was given between the trials of one leg and a 5 minutes rest was given between the 3 trials of the left/right leg. Maximal voluntary contraction (MVC) was defined as the highest value of the 3 attempts, for each leg respectively. As described elsewhere the trial with the highest MVC was analyzed during later offline analysis.⁶ The force signal was filtered by a digital fourth order recursive Butterworth low-pass filter, using a cutoff frequency of 50 Hz. The onset of muscle contraction was defined as the time at which the force curve exceeded baseline force by 15 N.⁷ Peak rate of force development (RFD) was defined as the maximal slope of the force time curve ($\Delta\text{force}/\Delta\text{time}$). Additionally, submaximal RFD-values were calculated as mean slope of the force-time curve (dF/dt) over time intervals of 0–100, 0-200, 0-300 and 0-500ms relative to the onset of force.⁶⁻⁸

MVC and RFD were analyzed for the more- and less-affected Parkinson's Disease side separately – defined by comparing the sums of the UPDRS items 20-26 for the left and right side separately.^{2,9}

References

1. Hoogkamer W, Bruijn SM, Duysens J. Stride length asymmetry in split-belt locomotion. *Gait & Posture*. 2014;39:652-654.
2. Plotnik M, Giladi N, Hausdorff JM. Bilateral coordination of walking and freezing of gait in Parkinson's disease. *Eur J Neurosci*. 2008;27:1999-2006.
3. Plotnik M, Giladi N, Hausdorff JM. A new measure for quantifying the bilateral coordination of human gait: effects of aging and Parkinson's disease. *Experimental brain research*. 2007;181:561-570.
4. Plotnik M, Hausdorff JM. The role of gait rhythmicity and bilateral coordination of stepping in the pathophysiology of freezing of gait in Parkinson's disease. *Mov Disord*. 2008;23 Suppl 2:S444-450.
5. Plotnik M, Giladi N, Balash Y, Peretz C, Hausdorff JM. Is freezing of gait in Parkinson's disease related to asymmetric motor function? *Ann Neurol*. 2005;57:656-663.
6. Gruber M, Gollhofer A. Impact of sensorimotor training on the rate of force development and neural activation. *Eur J Appl Physiol*. 2004;92:98-105.
7. Maffioletti NA, Bizzini M, Widler K, Munzinger U. Asymmetry in quadriceps rate of force development as a functional outcome measure in TKA. *Clinical orthopaedics and related research*. 2010;468:191-198.
8. Aagaard P, Simonsen EB, Andersen JL, Magnusson P, Dyhre-Poulsen P. Increased rate of force development and neural drive of human skeletal muscle following resistance training. *J Appl Physiol*. 2002;93:1318-1326.
9. Geurts AC, Boonstra TA, Voermans NC, Diender MG, Weerdesteyn V, Bloem BR. Assessment of postural asymmetry in mild to moderate Parkinson's disease. *Gait & Posture*. 2011;33:143-145.

Split-Belt Locomotion in Parkinson's Disease Links Asymmetry, Dyscoordination and Sequence Effect

Alfonso Fasano*, MD, PhD^{1,2}, Christian Schlenstedt*¹, Jan Herzog, MD, PhD¹; Meir Plotnik, PhD^{3,4,5}, Franziska E.M. Rose, MD¹, Jens Volkmann, MD, PhD^{1,6} and
Günther Deuschl, MD, PhD¹

* These authors equally contributed to the manuscript

¹ Department of Neurology, Christian-Albrechts-University, Kiel, Germany

² Morton and Gloria Shulman Movement Disorders Clinic and the Edmond J. Safra Program in Parkinson's Disease, Toronto Western Hospital and Division of Neurology, University of Toronto, Toronto, Ontario, Canada

³ Advanced Technologies Center, Department of Neurological Rehabilitation – Rehabilitation Hospital, Sheba Medical Center, Tel Hashomer, Israel

⁴ Department of Physiology and Pharmacology, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

⁵ Gonda Brain Research Center, Bar Ilan University, Ramat Gan, Israel

⁶ Department of Neurology, University of Würzburg, Germany

Supplemental material: Subjects, Testing paradigm, Gait analysis, Statistical analysis, Supplemental Tables 1-3

Corresponding author:
Prof. Dr. Günther Deuschl
Universityhospital Schleswig-Holstein, Campus Kiel
Department of Neurology
Schittenhelmstr. 10
24105 Kiel, Germany
Phone: +49-431-597-8509
Fax: +49-431-597-8502
Email: g.deuschl@neurologie.uni-kiel.de

Highlights

- Bilateral coordination, asymmetry of gait and sequence effect were studied during different split-belt conditions in patients with Parkinson's Disease.
- Both defective amplitude generation leading to sequence effect and bilateral coordination of lower limbs during gait are modulated by step length asymmetry possibly resulting from the same maladaptive motor behaviour.
- The after effect of split-belt gait with reduced velocity of the leg with the longer step length showed improved bilateral coordination, symmetry and sequence effect.
- Split-belt treadmill might be a useful therapeutic tool to modulate parkinsonian gait.

Abstract

Background. The pathophysiology of parkinsonian gait and particularly freezing of gait is not fully understood. Several hypotheses on potential motor deficits underlying the phenomenon were raised. Here we study the interplay between defective automaticity leading to the progressive reduction of the step length during walking (i.e. sequence effect) and impairment in bilateral coordination of lower limbs while walking.

Methods. We investigated the spatiotemporal properties, the phenomenon of sequence effect and the inter-limb symmetry and temporal coordination of gait during different split-belt conditions in 20 patients with advanced Parkinson's disease and different severities of freezing. Split-belt treadmill is an attractive tool to modulate the symmetry of motor performance because it provides a controlled means to simulate limping-like, straight-ahead gait at controlled speeds.

Results. Patients were found to be able to adapt to split-belt walking by inducing rapid changes of inter-limb temporal coordination; however, after prolonged split-belt walking the step length was differently modulated according to the reduction of the best or worst leg velocity. More importantly, we found that in spite of an improvement of spatial symmetry, the "best side reduction" led to a worsening of coordination and an increased sequence effect, significantly correlated with the severity of freezing; by contrast, in spite of a worsened spatial symmetry, the "worst side reduction" improved inter-limbs coordination and reduced the sequence effect.

Conclusions. These findings support the hypothesis that the irregularity of inter-limb coordination and defective amplitude generation leading to sequence effect might be

coupled and result from the same maladaptive motor behavior.

Table of abbreviations:

BSR: Best side reduction, **CV:** Coefficient of variation, **FOG:** Freezing of Gait, **PCI:** Phase coordination index, **TB:** tied-belt, **WSR:** Worst side reduction, φ : phase, φ_{ABS} : Mean value of the absolute differences between the phase and 180°, φ_{CV} : Coefficient of variation of φ measuring the inter-cycle variability.

Key words: Asymmetry; Freezing; Gait, Limb Coordination; Parkinson's Disease; Rehabilitation; Split-belt; Therapy

Introduction

A typical symptom of Parkinson's disease (PD) is a short-stepped, shuffling gait with slow walking velocity and cadence within the normal range (for a review see[1]). Gait is also complicated by the occurrence of freezing of gait (FOG), a gait disorder in which patients are unable to generate effective stepping[2]. The pathophysiology of parkinsonian gait (and FOG in particular) is not yet fully understood[3]. Beside other hypothesis (for a review see [2]) two main hypotheses on motor deficits related to FOG are currently explored 1) hypokinesia coupled with the lack of automaticity, thus leading to the progressive reduction of the step length during walking (i.e. sequence effect[4, 5]) or 2) by the impairment of gait cycle timing (e.g.,rhythmicity[6], symmetry[7]) in particular bilateral coordination of lower limbs[8]. Plotnik et al. [9], discussed the possibility that seemingly independent gait features may have mutual interactions which, during certain circumstances, jointly drive the predisposed locomotion system into a FOG episode. The used data presented by Chee et al. [5] to anecdotally demonstrate the feasibility of this idea, showing that step length shortening is interweaved with growing step length asymmetry

Split-belt treadmill has been used to investigate the neural coupling mechanisms underlying the inter-limb coordination during gait in either normal[10-13] or pathological[14-19] human subjects. When the legs are forced to walk at 2 different speeds, both rapid (reactive, feedback adjustment) and longer-duration (adaptive, feed-forward adjustment) changes to the gait pattern take place in healthy adult humans[10, 11, 15, 20].

So far, split-belt walking has received little attention in PD patients. In 1994, Dietz

and colleagues[10] published the first study but they mainly focused on muscle activity patterns. Only recently two studies investigated the effects of split-belt paradigm on kinematic features of parkinsonian gait but without focusing on the impact on baseline asymmetry[18] or without analyzing the effect of split walking on bilateral coordination and rhythmicity[19]. Another recent study addressed the impact of dopaminergic medication on the ability to adapt when gait was modulated by split-belt conditions[21].

The main aim of the present study was to explore how the experimental manipulation of gait symmetry during different split-belt conditions would have affected the major contributors of parkinsonian gait and particularly inter-limb symmetry, coordination and sequence effect. We therefore hypothesized that due to the asymmetry of the disease, patients would adapt differently when reducing the velocity of the leg with the longer versus shorter step length. We also anticipated to find a relationship between the different gait parameters playing a role in FOG pathophysiology.

Methods

Subjects

Twenty consecutive advanced PD patients (age: 60.5 ± 8.8 , disease duration: 12.2 ± 5.7 years, Hoehn & Yahr stage 2-3) participated in this study. Six patients did not report any FOG and they did not differ from patients with FOG in terms of the principal clinico-demographic data. See supplemental material online for details.

Testing paradigm

All subjects were assessed during the medication OFF condition, at least 12 hours after intake of the last anti-parkinsonian medication[22]. During different testing periods, subjects walked on a split-belt treadmill with the two belts either moving at the same speed ('tied' configuration) or different speeds ('split-belt' configuration). Based on the step length during the first testing condition, patients were categorized as having left or right "best" leg, i.e. the leg that generated longer step length values was defined as "best". During the tied configuration, treadmill belt speeds were adjusted exactly to the subject's individual gait velocity measured during ground level walking. In the split-belt configuration, one treadmill belt was set at a speed 25% slower than the other belt. The velocity was decreased rather than increased in order to avoid overload, as patients were assessed in the OFF medication condition. The following conditions were studied: TIED-BELT (TB) for 5 minutes; SPLIT-BELT – WORST SIDE REDUCTION (WSR) for 10 minutes; SPLIT-BELT – BEST SIDE REDUCTION (BSR) for 10 minutes. TB condition was performed before and after each split-belt condition. In order to assess the so-called "after-effect", patients' gait was re-examined in a second TB condition (TB2-WSR and TB2-BSR when following WSR and BSR, respectively) (Figure 1A). The order of WSR and BSR was randomized between patients.

Gait analysis

In addition to the standard gait parameters, spatial gait symmetry (best leg step length/worst step length ratio) and bilateral coordination of gait [phase coordination index (PCI)[23]] were assessed. In keeping with a previous study[5], the progressive

reduction in step-to-step amplitude (sequence effect) was measured by a linear regression slope computed by plotting consecutive stride time intervals against stride number (Figure 1B). See supplemental material online for additional methods.

Results

Based on the step length at baseline (TB1), patients were categorized as having left or right best leg (10 patients in each group).

No patients had FOG episodes during the assessments and all patients were able to walk on the treadmill without using the handrails. The seated rest of 15 min between the two trials was sufficient to avoid fatigue and none of the patient reported the need for additional rests.

Inter-limbs comparisons

During TB1-BSR, the step length of the best leg was significantly greater than the worst leg (Figure 2B). No other inter-limbs differences of gait variables emerged during TB1 conditions.

Effect of early WSR and BSR conditions

Early in adaptation, the best and worst leg had a significantly lower double support time than the contralateral limb during early-BSR and -WSR conditions, respectively (Table 1). Although stride times were equivalent for all periods, the percent time of the other gait phases were significantly different between the two limbs (Table 1, Figure 2A).

Effect of late WSR and BSR conditions

In the late adaptation phase, the percent time of the swing and stance phases continued to be significantly different across lower limbs during BSR (Figure 2A). During late-WSR the step length of the best leg was significantly higher than the worst leg (Figure 2B).

Effect of after WSR and BSR conditions

Mean velocity during TB2 conditions was 0.45 ± 0.03 m/sec, the same of TB1. In the early post-adaptation period following the BSR condition, there were no significant differences across lower limbs (Figure 2B).

Comparisons across conditions

Effects on temporal parameters

Repeated measures ANOVA detected a significant effect of the factor “condition” for the gait variables double support time for the best and worst leg ($F=4.0$, $p<0.001$ and $F=2.9$, $p=0.007$, respectively). As for the percent time of gait phases a significant effect was found for all the variables taken into account: stance phase (best leg: $F=7.6$, $p<0.001$; worst leg: $F=3.45$, $p=0.002$), swing phase (best leg: $F=7.6$, $p<0.001$; worst leg: $F=3.45$, $p=0.002$), and double support time (best leg: $F=6.0$, $p<0.001$; worst leg: $F=4.3$, $p<0.001$). Figure 2A and Table 1 show the post-hoc comparisons.

Effects on spatial parameters

Repeated measures ANOVA detected a significant effect of the factor “condition” for the gait variables step length of the best and worst leg ($F=4.5$, $p<0.001$; $F=3.2$,

$p=0.004$, respectively). On post-hoc tests, the step length of the worst leg resulted significantly higher in the after-BSR condition than TB1-BSR, whereas during the late-WSR it was significantly shorter than TB1-WSR and TB2-WSR (Figure 2B). The step length of the best leg was significantly longer during late-WSR than TB1-WSR (Figure 2B). No other significant effects on the standard gait parameters were found (Table 1).

Effects on asymmetry, variability, coordination and sequence effect

As expected, the changes of temporal and spatial properties of gait produced a significant effect on symmetry ratio, the measure of gait asymmetry (repeated measures ANOVA: $F=27.7$, $p=0.001$). On post-hoc test, the symmetry ratio during early-BSR and TB2-BSR was significantly lower (i.e. improved) than TB1-BSR; by contrast, it was significantly greater (i.e. worse) during late-WSR than all the other WSR conditions (Figure 2C).

As for the other variables measuring coordination and automaticity of gait, repeated measures ANOVA detected a significant effect of the factor “condition” for the gait variables PCI ($F=12.6$, $p<0.001$) and CV of stride time ($F=3.7$, $p<0.001$ and $F=3.5$, $p=0.002$, for best and worst leg, respectively). On post-hoc analyses, PCI during TB2-BSR was significantly reduced (i.e. improved) when compared to all the other BSR conditions (Figure 2C). Moreover, PCI during early- and after-WSR was significantly higher (i.e. worsened) than TB1-WSR and late-WSR (Figure 2C). Finally, the CV of stride time was significantly increased (i.e. worsened) in the TB2-WSR for both legs as compared with early and late WSR (Table 1).

The different experimental conditions had a significant effect on the number of

sequences ($F=2.7$, $p=0.03$) and regression slope beta ($F=2.7$, $p=0.03$). On post-hoc analyses, the number of sequences during after-BSR was significantly reduced than TB1-BSR and late-BSR; the regression slope was greater during late-BSR than TB1-BSR (Figure 3A). Figure 3B shows the regression slopes for an individual subject: the sequence effect worsens during late-BSR and improves (disappearing) during late-WSR condition (see video supplemental online).

Correlation analysis

ANCOVA analysis including the principal gait parameters as independent variables found that they accounted for 72.5% of beta regression variability ($F=18.5$, $p=0.001$). Univariate analysis disclosed that the major contributors were those related to variability (CV of swing phase: -0.21 ± 0.09 , $p=0.025$) and coordination (PCI: -0.46 ± 0.10 , $p<0.001$) (Supplemental Table 2).

At baseline, the FOG-questionnaire negatively correlated with stride and step length ($\rho=-0.624$, $p=0.003$ for both). When correlating the FOG-Q and the magnitude of change between late-BSR and the respective baseline (TB1-BSR), a significant positive correlation was found with the cadence ($\rho=0.663$, $p=0.001$) whereas the FOG-Q negatively correlated with stride and step length ($\rho=-0.679$, $p=0.001$ for both), thus meaning that the more severe the FOG was, the more the patients increased cadence and reduced spatial parameters of gait during late-BSR. No significant correlation was found between late-WSR and the respective baseline (TB1-WSR) (Supplemental Table 3).

Discussion

Our experimental protocol showed that PD patients are able to adapt to split-belt walking by inducing rapid changes of inter-limb temporal coordination without changing the total gait cycle for each lower limb; however, the adaptation phase drove different changes of the step length, according to the reduction of the best or worst leg velocity. More importantly, in spite of an improvement of spatial symmetry, BSR led to a worsening of coordination and an increased sequence effect whereas the opposite was found during the WSR. Notably, the detrimental effects of BSR were significantly associated with the severity of FOG. Finally, the after-effect induced by split-belt was translated into an improvement of sequence effect, coordination and symmetry after BSR. While the study does not directly address FOG episodes, or its subtypes (e.g., turning FOG, start hesitation), the interplay between two motor deficits disposing FOG has been dissected.

Early reaction to split-belt walking

In keeping with the first split-belt study in PD[10], we confirmed that PD patients can rapidly adapt to split-belt walking. In their recent study, Roemmich et al.[19] analyzed PD patients in the ON medication state and only used one split-belt paradigm, which was close to our BSR condition (the belt under the more affected leg was sped up to the fast speed while the belt under the contralateral leg remained at the slow speed) and found similar results for the early adaptation. However, we expanded this notion by showing that in our PD sample this was not observed during the WSR condition. Notably, in our sample and in keeping with Roemmich et al.[19], these immediate reactions were no longer detectable during the split-belt adaptation. Such differences

probably rely on the more profound effects undergone by step length (see below).

Gait adaptation to split-belt walking

In our PD sample the inter-limb coordination (i.e. PCI) slowly adapted and improved in both BSR and WSR in comparison with the respective early split-belt phases. However, PCI was further improved during the late-WSR in comparison with the baseline (TB1), in spite of a marked asymmetry of spatial measures of gait. A recent study investigated the stride time variability and inter-limbs coordination in 14 PD patients while walking on a split-belt treadmill at fixed speeds and found no change of PCI across study condition[18]. In contrast with our protocol, this study did not take into account the laterality of impairment at baseline and the different epochs of split-belt walking (early vs. late): these differences probably account for the different results in our study. In contrast with young healthy subjects[10, 20, 24], we observed a different modulation of step length depending on the reduction of the best or worst leg velocity. The detrimental effect of BSR on step length significantly correlated with the severity of FOG, which was also associated with an increase of cadence, in keeping with the well-known compensatory mechanism exerted by the latter[1]. More interestingly, our study found that during the late-WSR the worst leg showed a further decrease of step length whereas the best leg reached values of step lengths higher than baseline. Therefore, late-WSR unmasked the compensation normally operated by the best leg, which reduced its propulsion in order to adapt to the worst leg, thus keeping the inter-limb asymmetry to the minimum extent guarantying the fastest gait velocity at the lowest energy consumption,[12] as already found in other diseases with asymmetric motor performance (e.g. chronic hemiparesis)[17][25].

Symmetry, coordination and sequence effect

The experimental WSR condition accommodated the lower limbs asymmetry at baseline and accordingly the inter-limb coordination was markedly improved in spite of an increased spatial asymmetry. The opposite pattern was found when the best leg was forced to reduce its velocity (i.e. BSR).

So far, we are not aware of data demonstrating the existence of the sequence effect in freezers whilst turning. However, we suggest that the present results, can implicitly point to this option. Because of the separate functions for the inner and outer leg during turning, turning movements and split-belt walking are related to similar mechanisms[26]. This is relevant because clinical experience suggests that turning triggers FOG especially when the inner leg is the best one (i.e. the worst leg has to promote body propulsion)[7]. The observation that late-BSR led to a marked increase of the sequence effect supports the pathogenic link between asymmetry and sequence effect. Specifically, it is conceivable that when the inter-limb coordination is poor the best leg reduces its step length thus starting a vicious cycle that can end up with a new sequence or – if a given step length threshold is reached – a FOG episode. In keeping with the step length threshold hypothesis, we found that step length reduction induced by BSR was positively correlated with the severity of FOG. In addition, the experiment of Chee et al.[5] found that FOG episodes would present more frequently when artificially reducing patient's step length. Our protocol expands these notions by showing that sequence effects and inter-limbs coordination pathologically interact, as also demonstrated by the occurrence of an experimentally-induced sequence effect in patients not displaying it at baseline (Figure 3B). An independent post-hoc analysis of step length asymmetry based on the data reported

by Chee et al.[5] found a strong inverse relationship between step length and the level of asymmetry seen in the preceding stride (Spearman's $\rho=-0.76$, $p=0.005$): relatively increased values of asymmetry tend to precede relatively smaller step lengths in the next stride[9]. Our data supports this finding and sustains the idea that more than one gait feature may be deteriorating in PD. Chee et al.[5] discussed the lower background step length as a factor for the sequence. We also believe that FOG and step length scaling are associated, as we found a significant correlation between the severity of FOG and baseline step length as well as its changes during late-BSR. However, no significant contribution of step length in our correlation analysis was found. We therefore conclude that lower background step-length might still represent an important pathophysiological mechanism, but gait variability and poor gait coordination are main determinants of the sequence effect.

Insights for the treatment of parkinsonian gait

In our PD sample the after-effect induced by split-belt was translated into an improvement of symmetry, coordination and sequence effect after BSR, while the opposite pattern was found after WSR. Since locomotor adaptation on a split-belt treadmill has been found to improve walking symmetry in chronic hemiparesis[15, 27], the present study provides pilot data to support the use of split-belt training for the rehabilitation of PD patients. Interestingly, while our patients were assessed in the OFF state, a recent study found the after-effect induced by split-belt locomotion is further enhanced under the effects of dopaminergic medication[21]. Overall, these results might support the use of split-belt walking for rehabilitation of parkinsonian gait, especially if performed under medication. Potential long-term effects should be addressed by future studies.

Study limitations and conclusions

Our experimental protocol has a number of limitations to be acknowledged. Treadmill walking is not fully comparable to overground walking because the treadmill is pacing the gait, thus reducing its variability. This limitation mainly applies to the possible rehabilitative effect of split-belt treadmill during TB2, which was not the principal aim of the present study. In addition, in contrast with normal overground turns, inter-limbs load distribution and visual flow do not change during split-belt treadmill walking[26]. Second, no control group was exposed to the same experimental paradigm. However study's aim was not to compare patients with healthy subjects (extensively done by others[10, 18, 19]) but to investigate the impact of extrinsic manipulation of gait symmetry on specific features of parkinsonian gait. Likewise, we did not perform a between-group analysis comparing patients with and without FOG not only because of the small sample of the second subgroup but also in light of the supposed continuum between patients displaying different levels of gait impairment; to this end, a correlation analysis with FOG severity is a stronger argument in favor of causal mechanisms.

In conclusion, our findings probe the possibility that the sequence effect results from a maladaptive compensative strategy, thus reinforcing the idea that step scaling and gait coordination are coupled. Though a number of different and apparently competing theories have been formulated to explain PD-related gait impairment, it has been speculated that they may not necessarily be exclusive[3] and that mechanisms of two or more gait abnormalities may interact with each other and deteriorate synergistically under the effects of specific triggers[9].

Acknowledgments

A.F. was partially funded by NEURECA onlus – Milan. C.S. was funded by the Coppenrath-Stiftung and Krumme-Stiftung – Germany. The study was supported by the German BMBF (Kompetenznetz Parkinson)

Documentation of Author Roles

1. Research project: A. Conception, B. Organization, C. Execution;
2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique;

A.F. 1A, 1B, 1C, 2A, 2B,3A

C.S. 1C, 2C, 3A, 3B

J.H. 1B, 1C, 3B

M.P. 2C, 3C

F.E.M.R. 1B, 1C

J.V. 2C, 3C

G.D. 1A, 2C, 3B

References

- [1] Fasano A, Bloem BR. Gait disorders. *Continuum (Minneap Minn)*. 2013;19:1344-82.
- [2] Nieuwboer A, Giladi N. Characterizing freezing of gait in Parkinson's disease: models of an episodic phenomenon. *Mov Disord*. 2013;28:1509-19.
- [3] Nutt JG, Bloem BR, Giladi N, Hallett M, Horak FB, Nieuwboer A. Freezing of gait: moving forward on a mysterious clinical phenomenon. *Lancet Neurol*. 2011;10:734-44.
- [4] Iansek R, Huxham F, McGinley J. The sequence effect and gait festination in Parkinson disease: contributors to freezing of gait? *Mov Disord*. 2006;21:1419-24.
- [5] Chee R, Murphy A, Danoudis M, Georgiou-Karistianis N, Iansek R. Gait freezing in Parkinson's disease and the stride length sequence effect interaction. *Brain*. 2009;132:2151-60.
- [6] Hausdorff JM, Schaafsma JD, Balash Y, Bartels AL, Gurevich T, Giladi N. Impaired regulation of stride variability in Parkinson's disease subjects with freezing of gait. *Exp Brain Res*. 2003;149:187-94.
- [7] Plotnik M, Giladi N, Balash Y, Peretz C, Hausdorff JM. Is freezing of gait in Parkinson's disease related to asymmetric motor function? *Ann Neurol*. 2005;57:656-63.
- [8] Plotnik M, Hausdorff JM. The role of gait rhythmicity and bilateral coordination of stepping in the pathophysiology of freezing of gait in Parkinson's disease. *Mov Disord*. 2008;23 Suppl 2:S444-50.
- [9] Plotnik M, Giladi N, Hausdorff JM. Is freezing of gait in Parkinson's disease a result of multiple gait impairments? Implications for treatment. *Parkinsons Dis*. 2012;2012:459321.
- [10] Dietz V, Zijlstra W, Duysens J. Human neuronal interlimb coordination during split-belt locomotion. *Exp Brain Res*. 1994;101:513-20.
- [11] Reisman DS, Block HJ, Bastian AJ. Interlimb coordination during locomotion: what can be adapted and stored? *J Neurophysiol*. 2005;94:2403-15.
- [12] Finley JM, Bastian AJ, Gottschall JS. Learning to be economical: the energy cost of walking tracks motor adaptation. *J Physiol*. 2013;591:1081-95.
- [13] Saito M, Hyodo M, Masakado Y, Tomita Y, Ushiba J. Age-related differences in cognitive function for interlimb coordination during split-belt walking: a pilot study. *Somatosens Mot Res*. 2013;30:56-63.
- [14] Dietz V, Zijlstra W, Prokop T, Berger W. Leg muscle activation during gait in Parkinson's disease: adaptation and interlimb coordination. *Electroencephalogr Clin Neurophysiol*. 1995;97:408-15.
- [15] Reisman DS, Wityk R, Silver K, Bastian AJ. Locomotor adaptation on a split-belt treadmill can improve walking symmetry post-stroke. *Brain*. 2007;130:1861-72.
- [16] Choi JT, Vining EP, Reisman DS, Bastian AJ. Walking flexibility after hemispherectomy: split-belt treadmill adaptation and feedback control. *Brain*.

2009;132:722-33.

[17] Raja B, Neptune RR, Kautz SA. Coordination of the non-paretic leg during hemiparetic gait: expected and novel compensatory patterns. *Clin Biomech (Bristol, Avon)*. 2012;27:1023-30.

[18] Nanhoe-Mahabier W, Snijders AH, Delval A, Weerdesteyn V, Duysens J, Overeem S, et al. Split-belt locomotion in Parkinson's disease with and without freezing of gait. *Neuroscience*. 2013;236:110-6.

[19] Roemmich RT, Nocera JR, Stegemoller EL, Hassan A, Okun MS, Hass CJ. Locomotor adaptation and locomotor adaptive learning in Parkinson's disease and normal aging. *Clin Neurophysiol*. 2013.

[20] Morton SM, Bastian AJ. Cerebellar contributions to locomotor adaptations during splitbelt treadmill walking. *J Neurosci*. 2006;26:9107-16.

[21] Roemmich RT, Hack N, Akbar U, Hass CJ. Effects of dopaminergic therapy on locomotor adaptation and adaptive learning in persons with Parkinson's disease. *Behav Brain Res*. 2014;268:31-9.

[22] Defer GL, Widner H, Marie RM, Remy P, Levivier M. Core assessment program for surgical interventional therapies in Parkinson's disease (CAPSIT-PD). *Mov Disord*. 1999;14:572-84.

[23] Plotnik M, Giladi N, Hausdorff JM. A new measure for quantifying the bilateral coordination of human gait: effects of aging and Parkinson's disease. *Exp Brain Res*. 2007;181:561-70.

[24] Reisman DS, Bastian AJ, Morton SM. Neurophysiologic and rehabilitation insights from the split-belt and other locomotor adaptation paradigms. *Phys Ther*. 2010;90:187-95.

[25] Balasubramanian CK, Bowden MG, Neptune RR, Kautz SA. Relationship between step length asymmetry and walking performance in subjects with chronic hemiparesis. *Arch Phys Med Rehabil*. 2007;88:43-9.

[26] Courtine G, Schieppati M. Human walking along a curved path. II. Gait features and EMG patterns. *Eur J Neurosci*. 2003;18:191-205.

[27] Reisman DS, McLean H, Keller J, Danks KA, Bastian AJ. Repeated split-belt treadmill training improves poststroke step length asymmetry. *Neurorehabil Neural Repair*. 2013;27:460-8.

Table 1. Gait variables of PD sample across the different experimental conditions. Significant differences between best and worst leg are bold-typed.

	BSR				WSR				
	Baseline (TB1)	Early-split	Late-split	After (TB2)	Baseline (TB1)	Early-split	Late-split	After (TB2)	
Velocity (m/sec)	0.45±0.03	0.34±0.02/ 0.45±0.03	0.34±0.02/ 0.45±0.03	0.45±0.03	0.45±0.03	0.34±0.02/ 0.45±0.03	0.34±0.02/ 0.45±0.03	0.45±0.03	
Stride length (cm)	66.0±3.7	60.6±3.6	60.6±4.5	70.3±4.1	64.0±3.7	60.1±3.3	64.4±3.7	72.8±4.4	
Step mean (cm)	33.1±1.8	33.2±1.8	33.0±2.3	35.2±2.1	32.0±1.9	32.3±1.7	35.1±2.0	36.1±2.1	
Cadence (steps/min)	136.7±12.6	119.7±3.9	130.0±7.5	118.5±4.2	124.1±4.1	119.3±3.0	116.0±4.3	116.1±3.7	
Step width (mm)	106.3±10.2	124.3±10.2	102.2±11.2	125.1±10.0	119.4±10.0	128.0±10.3	100.8±12.4	123.3±11.4	
Step height (mm)	Best leg	244.4±12.9	210.7±14.9	216.3±15.5	248.3±13.5	243.2±12.9	253.8±12.3	252.7±12.7	242.4±14.2
	Worst leg	260.5±9.7	256.8±10.1	256.6±11.2	253.0±12.0	248.9±10.7	220.7±10.9	238.6±11.4	259.2±11.4
Stride time (msec)	Best vs. Worst								
	Best leg	1015.9±33.7	1032.3±28.7	982.8±50.8	1058.8±28.7	987.5±29.6	1015.5±23.5	1062.1±38.7	1081.9±29.4
	Worst leg	1020.2±34.8	1033.7±28.7	982.3±50.7	1057.8±28.6	987.7±29.9	1017.0±23.3	1061.3±38.5	1077.0±27.7
Stance phase (msec)	Best vs. Worst								
	Best leg	616.3±21.7	656.1±18.5	610.9±32.7	653.8±17.5	605.5±21.1	619.1±16.7	637.5±24.5	674.0±18.8
	Worst leg	614.9±23.8	628.1±19.5	578.2±32.7	645.4±18.7	600.7±21.4	643.9±19.6	653.7±27.0	658.5±18.4
Swing phase (msec)	Best vs. Worst								
	Best leg	399.6±12.4	376.2±12.1	371.8±18.4	405.1±12.9	382.0±10.0	396.4±8.4	424.6±14.6	407.9±12.5
	Worst leg	405.4±13.3	405.6±12.2	404.1±19.5	412.4±15.7	386.9±11.2	373.2±9.7	407.6±14.5	418.5±12.3
Double support time (msec)	Best vs. Worst								
	Best leg	101.9±5.8	109.0±4.5	97.0±8.6	133.2±9.4	113.4±7.9	144.8±10.6	114.8±8.1	117.5±6.3
	Worst leg	114.1±9.8	142.2±9.7	110.0±8.0	109.5±5.7	105.1±7.4	103.3±6.6	114.7±7.1	130.2±7.5
Hip ROM (°)	Best vs. Worst		0.002				0.002		
	Best leg	14.5±1.2	15.9±0.9	13.1±0.7	13.9±1.2	14.5±0.7	15.9±1.4	16.1±0.7	15.1±0.9
	Worst leg	11.4±1.4	14.5±1.4	12.9±1.2	13.2±1.7	14.1±0.9	14.5±0.9	14.4±0.8	15.9±1.0
knee ROM (°)	Best vs. Worst								
	Best leg	29.3±2.7	24.6±2.6	27.6±2.3	26.1±2.3	29.4±2.4	28.5±2.4	29.4±2.4	26.3±2.6
	Worst leg	33.0±2.3	32.2±2.4	28.4±3.5	29.1±3.1	32.5±2.4	28.7±2.4	28.8±2.5	31.3±2.3
Ankle ROM (°)	Best vs. Worst								
	Best leg	22.8±0.9	21.0±1.3	20.4±1.0	23.0±1.4	21.2±0.9	22.3±1.4	23.0±0.8	22.2±1.2
	Worst leg	24.1±1.3	22.7±1.7	24.0±1.2	23.0±1.7	22.9±1.6	20.8±1.6	21.9±1.6	23.5±1.5
Foot angle (°)	Best vs. Worst								
	Best leg	23.1±0.8	22.8±0.7	23.0±0.9	22.2±0.9	23.2±0.9	22.6±0.8	23.8±0.8	23.7±0.9
	Worst leg	21.3±0.8	21.6±0.8	22.3±0.8	22.7±1.0	21.2±0.5	21.9±0.7	21.5±0.7	22.5±0.7
CV stride time	Best vs. Worst								
	Best leg	3.3±0.5	2.0±0.1	5.3±1.5	6.7±3.0	4.9±1.4	2.0±0.1	2.2±0.2	11.9±3.3 ^a
	Worst leg	2.8±0.2	2.3±0.1	5.6±1.5	7.0±3.2	5.1±1.5	2.1±0.1	2.2±0.2	11.3±3.0 ^a
CV swing phase	Best vs. Worst								
	Best leg	6.6±1.1	4.8±0.3	5.9±0.5	5.0±0.3	6.5±1.0	4.4±0.3	5.1±0.4	5.5±0.6
	Worst leg	6.4±0.3	5.8±0.6	6.8±0.8	6.1±0.6	7.2±1.1	5.7±0.5	5.4±0.5	6.6±1.1
	Best vs. Worst								

All subjects had an asymmetric gait pattern during the TB conditions (symmetry ratio: 1.34±0.07 and 1.15±0.03 for TB1-BSR and TB1-WSR, respectively, not significantly different). Abbreviation: ^a: significantly different than early-WSR (p<0.001) and late-WSR (p<0.001)

Figure Legends

Figure 1. Experimental paradigm and analysis of the sequence effect. A: Belts represented in a different color run at a slower velocity than baseline “tied-belt” (TB). Two sequences of conditions were assessed: a) TB1 – WSR – TB2 and b) TB1 – BSR – TB2; the order of a) and b) was randomized between patients. During WSR the belt corresponding to the leg with the shortest step length (i.e. the worst leg) ran at a slower velocity than the contralateral; During BSR the belt corresponding to the leg with the longest step length (i.e. the best leg) ran at a slower velocity than the contralateral. There was a seated rest break of 15 min between a) and b) while the patients were asked to stand without moving for about 2 minutes between TB1, WSR/BSR and TB2. Vertical black arrows at the bottom indicate the time periods in which gait analysis was performed: baseline evaluation was performed at the end of TB1 in order to get the patients accustomed to treadmill locomotion; during the split-belts conditions, recordings were performed at the beginning and after 10 minutes to be sure to capture the modifications induced by the condition (“early” split-belt and “late” split-belt, respectively); recording was performed again at the beginning of TB2 to capture the after-effect induced by split locomotion. In the example presented by the figure, the subject’s leg with the shortest step length is the left one (i.e. worst leg).

B: The progressive reduction in stride-to-stride amplitude (sequence effect) was measured by a linear regression slope computed by plotting consecutive stride time intervals (a^n and b^n for right and left limb, respectively) against stride number. Ankle marker was used as reference. One or more regression slopes were calculated for each walking trial, representing either a decrease or an increase in inter-strides time interval. The occurrence of a sequence effect was determined when at least three

consecutive strides presented a progressive reduction of inter-strides time lag. In the example shown in the figure there are two sequences with comparable slopes.

Figure 2. Effects of split-belt paradigm on gait parameters. Trial patterns (i.e., BSR, WSR) and within trail sequences are indicated in the bottom of panel C.

A: Effects of split-belt paradigm on temporal parameters of the gait cycle generated by both legs. Stance time percentage is complemented (to "100%") by swing time percentage, while double support percentage overlaps the stance depiction. Inter-limbs comparisons: **a:** $p=0.001$; **b:** $p<0.001$. Inter-conditions comparisons: **c:** the percentage of swing and stance phases were respectively shorter and longer during early-BSR than TB1-BSR ($p<0.001$ for both comparisons) and after-BSR ($p=0.002$ for both comparisons); **d:** as for the best leg, the percentage of double limb support during TB2-BSR was significantly higher than TB1-BSR ($p=0.002$) and late-BSR ($p<0.001$); **e:** the percentage of double limb support during early-WSR was significantly higher than TB1-WSR ($p=0.001$), late-WSR ($p<0.001$) and after-WSR ($p<0.001$); **f:** the percentage of swing and stance phases were respectively longer and shorter during TB2-WSR than late-WSR ($p<0.001$ for both comparisons).

B: Effects of split-belt paradigm on spatial parameters of the gait cycle **a:** $p=0.002$; **b:** $p=0.001$; **c:** $p<0.001$.

C: Effects of split-belt paradigm on measures of spatial asymmetry (fast/slow step length, i.e. SR) and inter-limb coordination (PCI): **a:** significantly different than TB1 ($p<0.001$); **b:** significantly different than TB1-BSR ($p=0.001$), early-BSR ($p<0.001$) and late-BSR ($p=0.001$); **c:** significantly different than TB1-WSR ($p<0.001$); **d:** significantly different than TB1-WSR, early-WSR and after-WSR ($p<0.001$ for all comparisons); **e:** significantly different than early-WSR and after-WSR ($p<0.001$ for

both comparisons).

Figure 3. The effects of the spilt-belt paradigm on the number of sequences and regression slope beta. A: the number of sequences during after-BSR was significantly reduced than TB1-BSR (**a:** $p=0.01$) and late-BSR (**b:** $p=0.002$); the regression slope was greater during late-BSR than TB1-BSR (**c:** $p=0.02$). **B:** the regression slopes for an individual subject with worst side on the right: the sequence effect worsens during late-BSR and improves (disappearing) during late-WSR condition (see also video supplemental online).

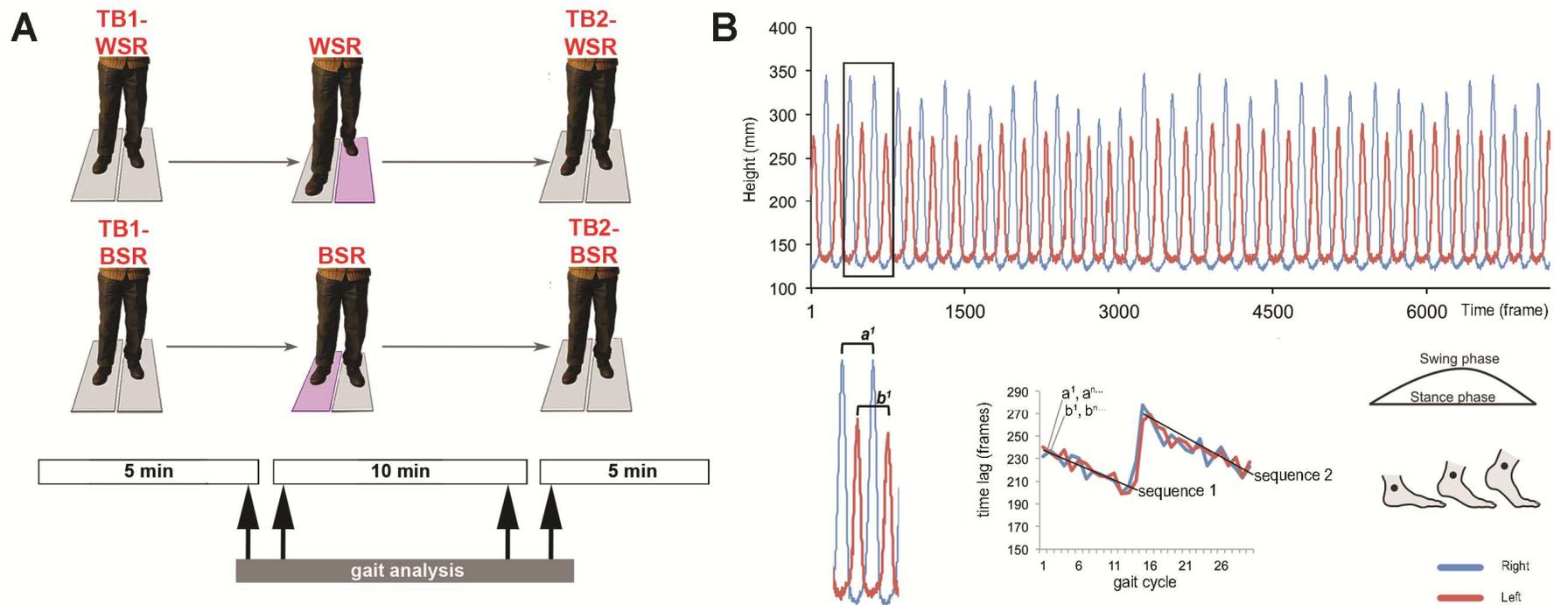


Figure 1. Experimental paradigm and analysis of the sequence effect.

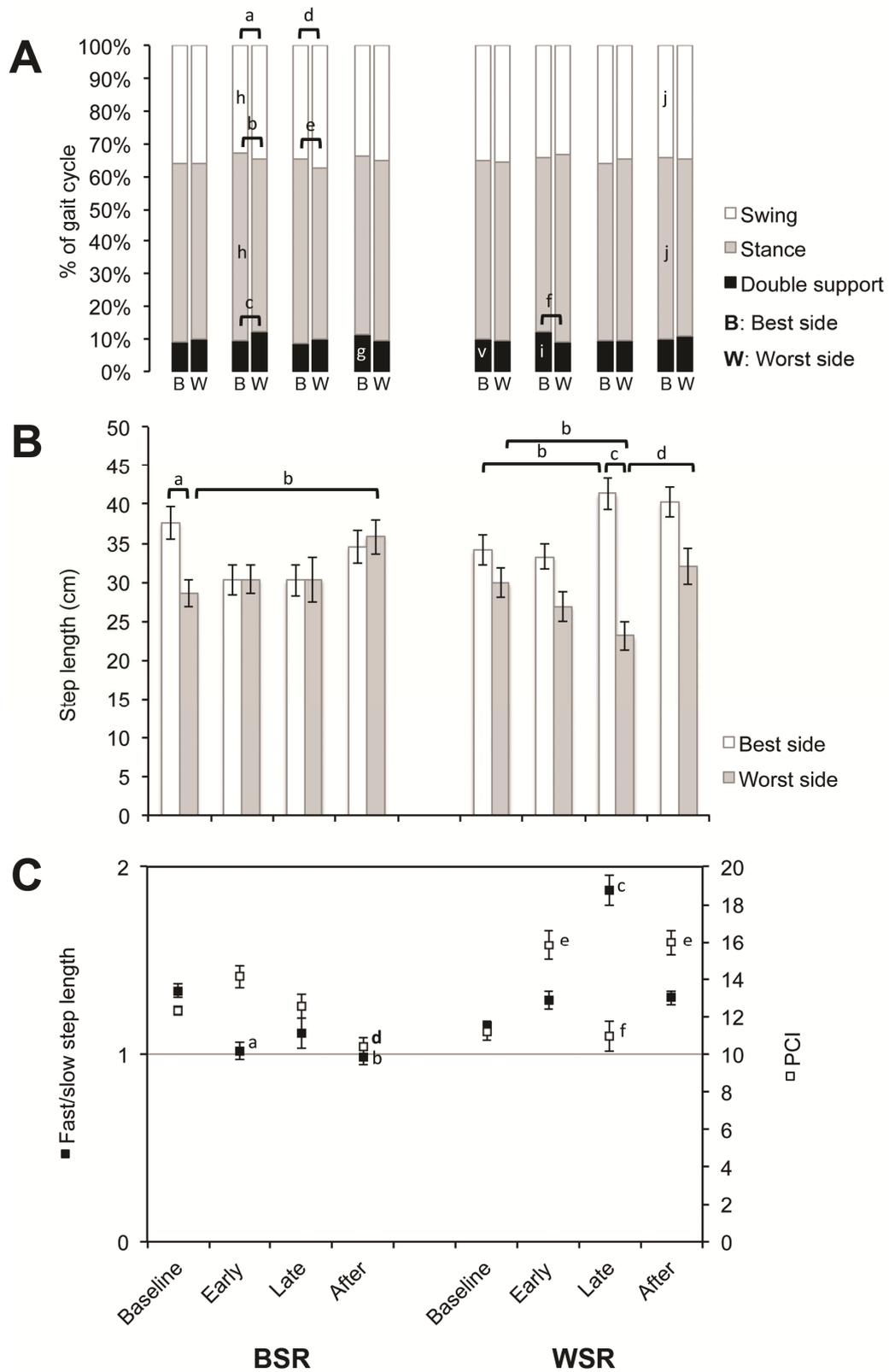


Figure 2. Effects of split-belt paradigm on gait parameters.

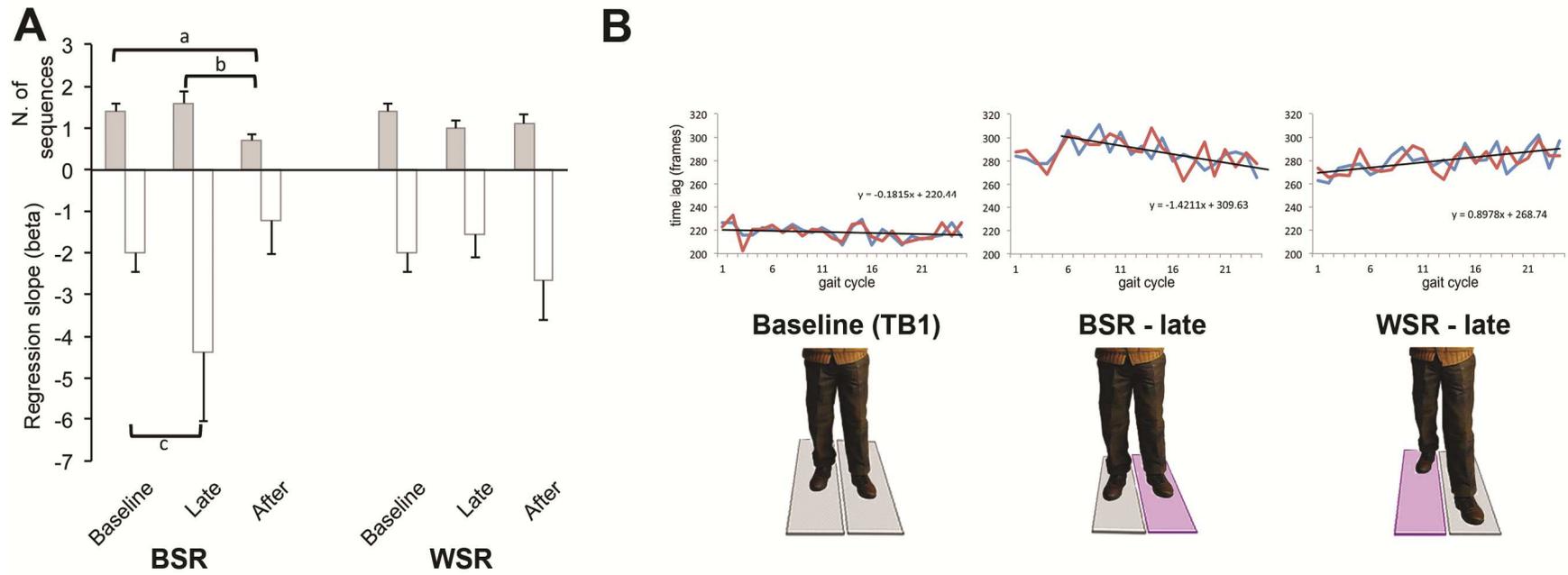


Figure 3. The effects of the split-belt paradigm on the number of sequences and regression slope beta.

Supplemental Material

Subjects

Twenty consecutive PD patients (age: 60.5 ± 8.8 , disease duration: 12.2 ± 5.7 years, Hoehn & Yahr stage: II-III) followed-up at the Department of Neurology, Kiel, Germany, participated in this study. Inclusion criteria were: diagnosis of PD as defined by the UK Brain Bank criteria [1], a stable clinical response to medications for at least 6 months, the ability to walk on a motor-driven treadmill, no orthopaedic or systemic disease interfering with gait performance other than PD, absence of dementia (score of the Mini-Mental State Examination above 27/30). Each patient was interviewed by using the freezing of gait questionnaire (FOG-Q)[2] and assessed with the motor section of the Unified Parkinson's Disease Rating Scale[3] OFF and ON medication (Table 1). All the patients were on treatment with levodopa and dopamine agonist with good response (mean improvement of $54.4 \pm 18.2\%$ at the levodopa challenge).

Patients were considered to have FOG if they scored at least 2 points at the third question of the FOG-Q ("Do you feel that your feet get glued to the floor while walking, making a turn or when trying to initiate walking (freezing)?")[2]. Six patients did not present FOG. In patients with FOG, FOG-Q ranged from 5 to 14. No significant differences in demographic and clinical data (except for FOG-Q) were detected in these two groups of patients (Table 1).

The study protocol was approved by the local ethical committee and patients consented to contribute to a study assessing their gait. However, in order to avoid

any kind of influence on motivation or expectation, patients did not receive any detail about the theoretical background of the study. However, patients were generally able to recognize when the one of the belt's velocity was reduced.

Testing paradigm

All subjects were assessed in a single morning session during the medication OFF condition, at least 12 hours after intake of the last anti-parkinsonian medication [4]. Before treadmill walking, gait velocity of patients was measured during uninterrupted ground level walking. Subjects were requested to walk a distance of 11 m at a freely selected comfortable speed. Gait velocity was calculated as the mean of two runs. Afterwards, patients were asked to walk on a treadmill (length of 2.2 m and width of 0.7 m; Woodway, Weil am Rhein, Germany) comprised of two separate belts, each with its own motor, that permitted the speed of each belt (i.e. each leg) to be controlled independently. During different testing periods, subjects walked on the treadmill with the two belts either moving at the same speed ('tied' configuration) or different speeds ('split-belt' configuration). Based on the step length during the first testing condition (i.e., TB1, see below), patients were categorized as having left or right "best" leg, i.e. the leg that generated longer step length values was defined as "best". During the tied configuration, treadmill belt speeds were adjusted exactly to the subject's individual gait velocity measured during ground level walking. In the split-belt configuration, one treadmill belt was set at a speed 25% slower than the other belt.

The following conditions were studied (Figure 1A): TIED-BELT (TB) for 5 minutes;

SPLIT-BELT – WORST SIDE REDUCTION (WSR): the belt corresponding to the leg with the shortest step length (i.e. the worst leg) running at a slower velocity than the contralateral for 10 minutes; SPLIT-BELT – BEST SIDE REDUCTION (BSR): the belt corresponding to the leg with the longer step length (i.e. the best leg) running at a slower velocity than the contralateral for 10 minutes. TB condition was performed before and after each split-belt condition. Therefore, two sequences of conditions were assessed: a) TB1 – WSR – TB2 and b) TB1 – BSR – TB2; the order of a) and b) was pseudorandomized between patients. In order to assess the so-called “after-effect”, patients’ gait was re-examined in a second TB condition (TB2-WSR and TB2-BSR when following WSR and BSR, respectively). There was a seated rest break of 15 min between a) and b) while the patients were asked to stand without moving for about 2 minutes between TB1, WSR/BSR and TB2.

In keeping with previous studies [5], prior to data collection, subjects were not given any practice in the split-belt configuration, though they were told that the two belts would move at two different speeds at some point during the testing. During testing, subjects were alerted when the treadmill was going to start, but were not instructed about belt speeds or coupling. Belt speeds were never changed while the belts were moving. Subjects were instructed to look straight ahead and refrain from looking down at the belts while walking so that they could not use visual information to determine belt speeds. An examiner stood by to monitor compliance with this instruction. Despite they did not receive any detail about the belts’ configuration, patients were generally able to recognize when the one of the belt’s velocity was reduced. No patients had FOG episodes during the assessments.

Gait analysis

For quantitative off-line analysis, gait was recorded while the patients were walking on the treadmill by an infrared movement analysis system (Qualisys, Gothenburg, Sweden) consisting of six infrared cameras (240 Hz sampling rate) and video processors connected to a computer. Seven infrared light-reflective spherical markers (1.8 cm diameter) were attached to the following points of each leg: anterior superior iliac spine, major trochanter, lateral thigh, knee joint, lateral malleolus, calcaneus, fifth metatarsal bone. Baseline evaluation was performed at the end of TB1 in order to get the patients accustomed to treadmill locomotion. During the split-belts conditions, recordings were performed twice: at the beginning and after 10 minutes to be sure to capture the modifications induced by the condition (“early” split-belt and “late” split-belt, respectively). Recording was performed again at the beginning of TB2 to capture the after-effect induced by split locomotion (Figure 1A). The duration of each recorded segment was 30 s.

Using a self-developed software [6] that combines the spatial data from the markers and the information about treadmill's belts' speed, we calculated the following standard spatiotemporal gait variables: stride- and step length, cadence, step width, step height, gait cycle time; duration of stance-, swing- and double limb support phase (also expressed as percentage of the gait cycle time), and the ratio between single support/double support time as an index of dynamic stability. The kinematic of lower limb joints excursion [expressed as range of motion – ROM (°)] and foot angle [6, 7] were also assessed. The symmetry of gait was spatially measured by means of the symmetry ratio (SR), corresponding to the best leg step length/worst step length ratio.

The coefficients of variation (CV) was calculated as a measure of variability of the temporal parameters swing phase duration and gait cycle time according to the formula: $(SD/mean) \times 100$ [8].

Bilateral coordination of gait was assessed using a previously described measure, i.e., the phase coordination index (PCI) [9]. Briefly, the stride time, the time between two consecutive heel strikes of the same leg, and the swing time, the time one foot is in the air, were determined using off-line computerized analysis (MATLAB 7.0, The Mathworks Inc., Natick, MA). Bilateral coordination of gait was assessed by examining the phase between the step timing of the left and right legs. In short, each stride defines one gait cycle and the time between the start of a gait cycle and the time point when the other leg's heel-strike occurs, was used to determine the phase. Normalizing the step time with respect to the stride time and scaling by 360° , defined the phase of the i -th stride (φ_i ; denoted in degrees). The PCI is a metric that combines the accuracy and consistency of stepping phases generation. The level of accuracy, i.e., how close are the series of generated phases to the value 180° , was assessed by the mean value of the series of absolute differences, $\varphi_i - 180^\circ$, denoted a measure of temporal accuracy as φ_ABS :

$$\varphi_ABS = |\varphi_i - 180^\circ|$$

The degree of consistency of the stepping phase generation was calculated by the coefficient of variation of φ , denoted as φ_CV and given as a percent. Therefore, assuming that $P\varphi_ABS = 100 * (\varphi_ABS / 180)$, PCI was defined according to the following equation:

$$PCI = \varphi_CV + P\varphi_ABS$$

Thus, PCI is the sum of two relative values, each given as a percentile. For the conditions characterized by rapidly adaptive changes (early BSR and early WSR) or transient after effect (TB2-BSR and TB2-WSR) the first 10 strides were taken into account. Lower PCI values reflect a more consistent and more accurate phase generation and related to different health conditions, with higher values indicating more impaired bilateral coordination of gait [10-12].

Finally, in keeping with a previous study [13], the progressive reduction in step-to-step amplitude (sequence effect) was measured by a linear regression slope computed by plotting consecutive stride time intervals against stride number. One or more regression slopes were calculated for each walking trial, representing either a decrease or an increase in inter-strides time interval. The occurrence of a sequence effect was determined when at least three consecutive strides presented a progressive reduction of inter-strides time lag (Figure 1B). Plots were visually analyzed by two independent observers (AF and CS) and a full agreement was reached for the number and regression slope beta of sequence effects in each individual. These analyses were not conducted in the early split-belt conditions in order to limit the number of indexes under analysis.

Statistical analysis

Repeated measures one-way analysis of variance (ANOVA) was employed to explore the effects of the experimental conditions on all the gait variables taken into account. In case of a significant effect of the condition factor on the dependent variables, post-hoc comparisons were calculated by means of the Fisher's LSD test. ANCOVA was used for correlation analyses, by considering the beta of the

regression slopes as dependent variables, other gait indexes as continuous independent variables and the experimental conditions as categorical independent variable. The inter-limbs comparison of gait variables during each experimental condition was performed by using t-test for independent variables. A separate analysis was conducted to compare patients with and without FOG. Given the small sample of patients without FOG, a Spearman test was run to correlate the FOG-Q and the magnitude of changes induced by BSR and WSR on respective gait indexes at baseline.

Values were expressed as mean \pm standard error of the mean (except for clinical and demographic data which were expressed as mean \pm SD). Statistica 7.0 (StatSoft, Tulsa, OK) software was used for all statistical analyses. All tests were two-sided with a level of significance set at $P < 0.05$. The Bonferroni correction was used for the multiple comparisons of post-hoc analyses.

References

- [1] Gelb DJ, Oliver E, Gilman S. Diagnostic criteria for Parkinson disease. *Arch Neurol.* 1999;56:33-9.
- [2] Giladi N, Shabtai H, Simon ES, Biran S, Tal J, Korczyn AD. Construction of freezing of gait questionnaire for patients with Parkinsonism. *Parkinsonism Relat Disord.* 2000;6:165-70.
- [3] Fahn S, Elton R, Committee. MotUD. Recent developments in Parkinson's disease. Folorham Park, NJ: Macmillan Health Care Information; 1987.
- [4] Defer GL, Widner H, Marie RM, Remy P, Levivier M. Core assessment program for surgical interventional therapies in Parkinson's disease (CAPSIT-PD). *Mov Disord.* 1999;14:572-84.
- [5] Reisman DS, Wityk R, Silver K, Bastian AJ. Locomotor adaptation on a split-belt treadmill can improve walking symmetry post-stroke. *Brain.* 2007;130:1861-72.
- [6] Stolze H, Kuhtz-Buschbeck JP, Mondwurf C, Boczek-Funcke A, Johnk K, Deuschl G, et al. Gait analysis during treadmill and overground locomotion in children and adults. *Electroencephalogr Clin Neurophysiol.* 1997;105:490-7.
- [7] Stolze H, Klebe S, Poepping M, Lorenz D, Herzog J, Hamel W, et al. Effects of bilateral subthalamic nucleus stimulation on parkinsonian gait. *Neurology.* 2001;57:144-6.
- [8] Hausdorff JM, Edelberg HK, Mitchell SL, Goldberger AL, Wei JY. Increased gait unsteadiness in community-dwelling elderly fallers. *Arch Phys Med Rehabil.* 1997;78:278-83.
- [9] Plotnik M, Giladi N, Hausdorff JM. A new measure for quantifying the bilateral coordination of human gait: effects of aging and Parkinson's disease. *Exp Brain Res.* 2007;181:561-70.
- [10] Meijer R, Plotnik M, Zwaafink EG, van Lummel RC, Ainsworth E, Martina JD, et al. Markedly impaired bilateral coordination of gait in post-stroke patients: Is this deficit distinct from asymmetry? A cohort study. *J Neuroeng Rehabil.* 2011;8:23.
- [11] Plotnik M, Giladi N, Hausdorff JM. Bilateral coordination of walking and freezing of gait in Parkinson's disease. *Eur J Neurosci.* 2008;27:1999-2006.
- [12] Fasano A, Herzog J, Seifert E, Stolze H, Falk D, Reese R, et al. Modulation of gait coordination by subthalamic stimulation improves freezing of gait. *Mov Disord.* 2011;26:844-51.
- [13] Chee R, Murphy A, Danoudis M, Georgiou-Karistianis N, Iansek R. Gait freezing in Parkinson's disease and the stride length sequence effect interaction. *Brain.* 2009;132:2151-60.

Table 1. Participants characteristics.

Variable	Total (n=20)	Non-FOG (n=6)	FOG (n=14)
Age (yr)	60.5 ± 8.8	58.3 ± 10.9	61.4 ± 7.7
Disease duration (yr)	12.2 ± 5.7	12.7 ± 6.0	12.0 ± 5.6
BMI (kg/m ²)	25.9 ± 4.12	24.0 ± 1.0	26.7 ± 4.7
UPDRS Part III (OFF)	31.5 ± 7.7	31.7 ± 5.2	31.4 ± 8.5
UPDRS Part III (ON)	15.1 ± 8.3	14.7 ± 1.4	15.3 ± 9.7
Levodopa responsiveness (%)	54.4 ± 17.7	52.4 ± 10.0	55.2 ± 20.4
LEDD (mg/day)	746.8 ± 387.5	762.0 ± 415.6	740.3 ± 376.0
FOG-Q	6.0 ± 4.9	0.0 ± 0.0*	8.6 ± 3.1*

Abbreviations: *: statistically significant different (p<0.001); BMI: body mass index; UPDRS: Unified Parkinson's Disease Rating Scale; LEDD: levodopa equivalent daily dose; GFAQ: Gait and Fall Questionnaire; FOGQ: Freezing of Gait Questionnaire.²

Table 2. Univariate results of the principal gait variables on the dependent variable beta of the regression slope (ANCOVA with experimental conditions ad categorical independent variable).

	beta	t	p
Cadence	-0.02±0.01	-1.28	0.203
Stride length	-0.12±0.24	-0.51	0.613
Step length*	0.31±0.49	0.62	0.536
Symmetry ratio	0.06±1.45	0.04	0.966
CV – swing phase*	-0.21±0.09	-2.28	0.025
CV – stride time*	0.03±0.03	1.10	0.274
PCI	-0.46±0.10	4.46	<0.001

Abbreviations: *: values averaged for best and worst leg, CV: coefficient of variation, PCI: phase coordination index.

Table 3. Results of the correlation (Spearman) between the FOG-Q and baseline gait parameters and the magnitude of changes induced by BSR and WSR. Statistically significant correlation (surviving Bonferroni's correction) are bold-typed.

	Baseline		$\Delta_{BSR - TB1-BSR}$		$\Delta_{WSR - TB1-WSR}$	
	ρ	p	ρ	p	ρ	p
Velocity	-0.55	0.012				
Cadence	0.191	0.419	0.663	0.001	0.321	0.168
Stride length	-0.624	0.003	-0.679	0.001	0.13	0.586
Step length*	-0.624	0.003	-0.679	0.001	-0.123	0.604
Symmetry ratio	0.358	0.121	0.364	0.114	0.432	0.057
CV – swing phase*	-0.006	0.979	-0.037	0.877	0.531	0.016
CV – stride time*	0.019	0.938	0.025	0.918	0.111	0.641
PCI	0.204	0.389	-0.031	0.897	0.062	0.796
No. of sequences	-0.007	0.978	-0.05	0.833	0.353	0.127
beta	-0.123	0.604	-0.173	0.466	-0.191	0.419

Abbreviations: *: values averaged for best and worst leg; CV: coefficient of variation; PCI: phase coordination index; ρ : Spearman's rank correlation coefficient (Rho).

Erklärung

Hiermit erkläre ich an Eides statt, dass die vorliegende Abhandlung nach Inhalt und Form meine eigene Arbeit ist.

Kiel, den

.....

(Christian Schlenstedt)

Lebenslauf

Christian Schlenstedt

geb. am 11.11.1983 in Melle

deutsche Staatsangehörigkeit

Ausbildung

- 05/2003 Abitur, Gymnasium Melle
- 10/2003 – 09/2004 Studium: Mathematik und Französisch (Lehramt an Gymnasien)
an der Universität Osnabrück
- 10/2004 – 11/2009 Studium: Sport, Mathematik, Französisch (Nebenfach) an der
Albert-Ludwigs-Universität Freiburg; Abschluss: Magister und
1. Staatsexamen (Lehramt an Gymnasien)

Beruflicher Werdegang

- 07/2006 – 09/2007 Hilfswissenschaftlicher Mitarbeiter am Institut für Sport und
Sportwissenschaft Freiburg; Arbeitsgruppe Gymlab
- 01/2008 Vierwöchiges Praktikum im BewegungsanalySELabor der
Universitätsklinik Brest (Frankreich)
- 03/2010 – 05/2010 Praktikum in der motorischen Arbeitsgruppe des Sportinstituts
A Coruna (Spanien) zum Thema „Laufbandtraining bei Patienten
mit Morbus Parkinson“
- seit 01/2011 Wissenschaftlicher Mitarbeiter der Klinik für Neurologie,
Universitätsklinikum Schleswig-Holstein, Campus Kiel
- seit 01/2011 Promotion im Promotionsfach Sportwissenschaft an der
Christian-Albrechts-Universität zu Kiel