Aus der Klinik für Neurologie mit Experimenteller Neurologie
der Medizinischen Fakultät Charité – Universitätsmedizin Berlin

DISSERTATION

Nicht-motorische Symptome bei Patienten mit neudiagnostiziertem Morbus Parkinson und Restless-Legs-Syndrom

zur Erlangung des akademischen Grades
Doctor medicinae (Dr. med.)

vorgelegt der Medizinischen Fakultät
Charité – Universitätsmedizin Berlin

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Datum der Promotion: 04. Juni 2021

Inhaltsverzeichnis

Verzeichnis wiederkehrender Abkürzungen

BDI	Beck Depression Inventory
CED	Chronisch-entzündliche Darmerkrankung
ESS	Epworth Sleepiness Scale
FSS	Fatigue Severity Scale
IRLS	International RLS Severity Scale
mTCNS	modified Toronto Clinical Neuropathy Score
PD	Parkinson’s Disease - Morbus Parkinson
PQSI	Pittsburgh Sleep Quality Index
RLS	Restless-Legs-Syndrom
STAI	State Trait Anxiety Inventory
UPDRS	Unified Parkinson’s Disease Rating Scale

Abstrakt

Einleitung: Die Bewegungsstörungen Morbus Parkinson (PD) und Restless-Legs-Syndrom (RLS) verursachen neben motorischen Defiziten oft multiple nicht-motorische Symptome. Deren Ausprägung wurde bislang zumeist bei fortgeschrittener Erkrankung unter laufender medikamentöser Therapie untersucht. Thema dieser Arbeit war die Erforschung der Aspekte somatosensorische Symptome, implizites Lernen, Depression, Ängstlichkeit und Schlafstörungen zum Zeitpunkt der Erstdiagnose der jeweiligen Bewegungsstörung sowie deren Einfluss auf die Lebensqualität der betroffenen Patienten.

Methodik: Untersucht wurden Patienten mit neu diagnostiziertem (de novo) PD und RLS bei chronisch-entzündlicher Darmerkrankung (CED) ohne bis dato erfolgte spezifische Therapie sowie jeweils altersgematchte Kontrollprobanden. Erfasst wurden nicht-motorische Symptome in Anamnesegesprächen, körperlichen Untersuchungen und durch strukturierte Fragebögen. Somatosensorische Defizite wurden zudem durch die elektro-neurographische Darstellung motorischer und sensibler peripherer Nerven untersucht. Die Veränderung impliziten Lernens wurde in einer Go-/NoGo-Verhaltensaufgabe unter der Bedingung der Handlungsinitiierung und -unterdrückung erfasst; hierbei wurden Reaktions-zeiten und Fehlerquoten mit und ohne Einfluss einer peroralen Levodopa-Gabe gemessen.

Ergebnisse: Die De-novo-PD-Patienten wiesen signifikant häufiger somatosensorische Symptome als die Kontrollprobanden auf. Die Diagnose PD wurde als prädiktiver Faktor für somatosensorische Defizite identifiziert. Die einmalige Levodopa-Gabe beeinflusste zudem das implizite Lernverhalten. Neu diagnostizierte PD-Patienten zeigten nach Medikation keinen Anstieg der Fehlerrate als Ausdruck einer nicht gelernten Stimuluskopplung im Vergleich zu unmedizierten und Kontrollprobanden, wenn eine Handlung unterdrückt werden musste. Bei CED-Patienten mit De-novo-RLS traten eine reduzierte Schlafdauer und -latenz sowie Fatigue signifikant häufiger auf als bei jenen CED-Patienten ohne RLS. Die Schwere der Ausprägung dieser Symptome korrelierte mit einer Zunahme depressiver und ängstlicher Stimmung. Alle Patientengruppen mit nicht-motorischen Symptomen gaben eine signifikant verringerte gesundheitsbezogene Lebensqualität an.

Fazit: Bereits zum Zeitpunkt der Erstdiagnose von PD und RLS sind nicht-motorische Beschwerden nachweisbar. Zudem wurde gezeigt, dass nicht-motorische Symptome wie beeinträchtigtes implizites Lernen erst durch die medikamentöse Therapie auftreten können. Da nicht-motorische Defizite die Lebensqualität der Patienten beeinträchtigen, sollten diese im Rahmen des klinischen Beschwerdebilds ausführlich erfasst sowie der Einfluss der medikamentösen Therapie berücksichtigt werden.

Abstract

Introduction: Movement disorders Parkinson's Disease (PD) and Restless Legs Syndrome (RLS) do cause characteristic motor deficits, but also a variety of non motor symptoms. Former studies focused on these symptoms in advanced stages of these movement disorder, mostly under running medication. In our work, we observed the aspects somatosensory symptoms, implicit learning, anxiety, sleeping disorders and depression within de novo diagnosed patients and these symptoms' influence on their quality of life.

Methods: De novo diagnosed patients with PD and RLS with chronic inflammatory bowel disease (CIBD) as well as age-matched controls were part of these studies. We recorded non motor symptoms by structured anamnesis, physical examination and specific questionnaires. Somatosensory deficits were additionally examined by electroneurography of motor and sensitive peripheral nerves. Implicit learning was investigated in a visual Go/ NoGo task in which participants had either to initiate or to inhibit an action; we measured reaction time and error rates, in particular in the PD group with and without substitution of oral levodopa.

Results: De novo PD patients showed significantly more somatosensory symptoms than the age-matched controls. The single intake of levodopa modulated implicit learning. Medicated de novo PD patients showed no rising error rate within inhibition of an action as seen for medication-naive patients and controls, which was understood as a lack of learning coupled stimuli. The CIBD patients with de novo RLS suffered significantly more from reduced sleeping time and latency as well as fatigue than those without RLS. The severity of RLS correlated with worse symptoms of depression and anxiety. All groups of patients with non motor symptoms reported a significantly lower health related quality of life than controls.

Take home points: Already at the time of diagnosis of movement disorders PD and RLS, several non motor symptoms can be detected. Furthermore, medical therapy can cause non motor symptoms as shown in case of implicit learning. Because non motor symptoms impair patients' quality of life, examiners should be aware of them including the influence of Levodopa medication on behavior.

Einführung

Sowohl der Morbus Parkinson (Parkinson's Disease – PD) als auch das Restless-Legs-Syndrom (RLS) zählen zu den Bewegungsstörungen. Das 1817 von James Parkinson erstbeschriebene Parkinson-Syndrom ist durch Akinesie, Rigidität, Tremor, Dystonien und Gangstörungen gekennzeichnet[1]. Das 1945 von Karl-Axel Ekbom erstmalig so bezeichnete RLS äußert sich durch einen vor allem nächtlich auftretenden unkontrollierbaren Bewegungsdrang der Beine, häufig begleitet von Parästhesien wie Kribbeln oder Schmerz, der durch körperliche Bewegung gelindert wird[2].

Beiden Bewegungsstörungen ist gemeinsam, dass in jüngeren Jahren nicht die Beschreibung der motorischen Charakteristika, sondern die Erforschung der nicht-motorischen Beschwerden im Fokus der Wissenschaft lag; so wurden in verschiedenen Studien Symptome wie Schmerz, Verlust von Riech- oder Sehfähigkeit, Störungen des vestibulären, propriozeptiven oder kinästhetischen Systems, Schlafstörungen, Depression oder kognitive Defizite systematisch untersucht [3-6].

Beiden Erkrankungen wird eine Störung des dopaminergen Transmittersystems im zentralen Nervensystem als Ursache zugeschrieben[7,8], sodass die Substitution mit Levodopa ein etablierter Teil des Therapieregimes beider Erkrankungen ist [9, 10].

Die vorangegangenen Studien untersuchten nicht-motorische Symptome zumeist bei bereits diagnostizierten und behandelten Patienten mit PD oder RLS. In der vorliegenden Arbeit wurden die Untersuchungen ausschließlich mit Patienten direkt nach Erstdiagnose der jeweiligen Bewegungsstörung durchgeführt, die im Vorfeld keinerlei dopaminerge Therapie erhalten hatten.

Untersucht wurden im Speziellen drei Aspekte der nicht-motorischen Symptomatik:

- Studie A: somatosensorische Symptome bei Patienten mit Morbus Parkinson und einer altersgematchten gesunden Kontrollgruppe,
- Studie B: implizites Lernen bei Patienten mit Morbus Parkinson vor und nach erstmaliger Gabe von Levodopa sowie einer altersgematchten gesunden Kontrollgruppe sowie
- Studie C: Schlafstörungen, Fatigue, kognitive Einschränkungen und Depression bei Patienten mit chronisch-entzündlicher Darmerkrankung mit und ohne Restless-Legs-Syndrom.

Des Weiteren wurden Assessments der daraus resultierenden gesundheitsbezogenen Lebensqualität durchgeführt.
Die Hypothese, dass bereits zum Zeitpunkt der Diagnose der Bewegungsstörungen PD und RLS nicht-motorische Symptome vorhanden sind und diese die Lebensqualität der Betroffenen schon nachhaltig beeinträchtigen, bildete die Grundlage für die Studien. Durch diese Erkenntnisse soll die Relevanz bereits bestehender nicht-motorischer Defizite bei beginnendem Krankheitsbild dieser Bewegungsstörungen unterstrichen und der Blick auf die vielfältige Symptomatik geschärft werden.

Die einzelnen Teilergebnisse dieser Dissertation wurden jeweils separat publiziert:

Studie A
Schindlbeck KA*, **Mehl A***, Geffe S, Benik S, Tütüncü S, Klostermann F, Marzinzik F. Somatosensory symptoms in unmedicated de novo patients with idiopathic Parkinson's disease. J Neural Transm. 2016;123(3):211–217. doi:10.1007/s00702-015-1459-4.
*** geteilte Erstautorenschaft**

Studie B
Geffe S, Schindlbeck KA, **Mehl A**, Jende J, Klostermann F, Marzinzik F. The single intake of levodopa modulates implicit learning in drug naive, de novo patients with idiopathic Parkinson's disease. J Neural Transm. 2016;123(6):601–610. doi:10.1007/s00702-016-1557-y.

Studie C
Schindlbeck KA, Becker J, Berger F, **Mehl A**, Rewitzer C, Geffe S, Koch P, Preiß J, Siegmund B, Maul J, Marzinzik F. Impact of restless legs syndrome in patients with inflammatory bowel disease on sleep, fatigue and quality of life. Int J Colorectal Dis 2017;32(1):125–130. doi:10.1007/s00384-016-2681-8.

Die Texte dieser Studien dienten als Grundlage bei der Verfassung dieser kumulativen Dissertation.

Methodik

Studienteilnehmer

Die Patienten wurden aus den Hochschulambulanzen der Kliniken für Neurologie und Gastroenterologie am Campus Benjamin Franklin der Charité – Universitätsmedizin Berlin rekrutiert. In den Studien A und B waren dies Patienten aus der Sprechstunde für Bewegungsstörungen unter Leitung von Prof. Dr. Fabian Klostermann sowie der allgemein-neurologischen Station unter der Leitung von Priv.-Doz. Dr. Frank Marzinzik, in Studie C aus der Sprechstunde für chronisch-entzündliche Darmerkrankungen (CED) unter Leitung von Dr. Joachim Maul. Notwendiges Einschlusskriterium war die Diagnose der Bewegungsstörung (PD oder RLS) sowie die Medikamentennaivität bezüglich einer Behandlung derselben. Weitere neurologische oder psychiatrische Diagnosen galten als Ausschlusskriterium.

Die Kontrollgruppen bestanden in den Studien A und B aus Angehörigen der Patienten und externen Freiwilligen, in Studie C aus Patienten mit CED. Voraussetzung zur Teilnahme der Kontrollprobanden war, dass sie nicht unter neurologischen oder psychiatrischen Erkrankungen litten.

Die Studienprotokolle wurden durch die Ethikkommission der Charité – Universitäts-medizin Berlin genehmigt, die Probanden dokumentierten nach umfangreicher Aufklärung schriftlich ihr Einverständnis zur Teilnahme.

Untersuchungen

Auf Grundlage einer ausführlichen Anamnese und neurologischen körperlichen Untersuchung der Patienten erfolgte durch erfahrene Spezialisten die Erstdiagnose der jeweiligen Bewegungsstörung. Die PD-Diagnose wurde entsprechend der United Kingdom Brain Bank Criteria[11] (UKBBC) gestellt und nach Hoehn-und-Yahr-Stadien[12] eingestuft. Bei allen Patienten war eine Verbesserung der motorischen Defizite um 30 Prozent nach einmaliger Einnahme von 250 mg Levodopa/62,5 mg Benserazid gefordert, gemessen mithilfe der Unified Parkinson's Disease Rating Scale (UPDRS) Teil III. Das RLS wurde nach den Kriterien der International RLS Study Group[13] diagnostiziert und anhand der International RLS Severity Scale (IRLS)[14] in Schweregrade der Symptomatik eingeteilt.

Das Vorkommen nicht-motorischer Symptome wurde in allen drei Studien mithilfe strukturierter und validierter Anamnese- und Testbögen erhoben, deren Anwendung im Einzelnen in Tabelle 1 zusammengefasst ist.

Test	**Inhalt**	**Studie A**	**Studie B**	**Studie C**
Nonmotor Symptom Questionnaire (NMSQuest)[15]	gastrointestinale, emotionale, vegetative Symptome	X		
Mini Mental State Examination (MMSE)[16]	Allgemeine kognitive Funktion	X	X	X
Beck Depression Inventory (BDI)[17]	depressive Symptomatik	X	X	X
Short-Form-36 Health Survey (SF-36)[18]	Gesundheitsassoziierte Lebensqualität	X		
Fatigue Severity Scale (FSS)[19]	Fatigue-Syndrom		X	X
Pittsburgh Sleep Quality Index (PSQI)[20]	Schlafstörungen			X
Epworth Sleepiness Scale (ESS)[21]	Tagesmüdigkeit			X
European Quality of Life 5 Dimensions (EQ-5D)[22]	Gesundheitsassoziierte Lebensqualität			X
d2-Test[23]	Selektive Aufmerksamkeit			X
Trail Making Test A/B (TMT-A/B)[24]	exekutive / geteilte Aufmerksamkeit			X
State Trait Anxiety Inventory (STAI)[25]	Ängstlichkeit			X

Tabelle 1 – Übersicht aller angewandten strukturierten Fragebögen in den drei Studien, mit Kreuz (X) sind die verwendeten Fragebögen gekennzeichnet.

Zudem fanden die folgenden jeweils studienspezifischen Untersuchungen statt.

Studie A

Für die Untersuchung somatosensorischer Defizite wurde der „modified Toronto Clinical Neuropathy Score“[26] (mTCNS) angewandt, ein Assessmentbogen zur Detektion leichter bis mäßiggradiger neuropathischer Symptome, ursprünglich bei diabetischer Genese. Somatosensorische Defizite wurden bei Bestehen mindestens eines der fünf untersuchten Symptome (Fußschmerzen, Taubheit, Kribbelparästhesien, Schwäche, Gangstörung) als vorhanden definiert. Weiterhin wurden unter standardisierten Umgebungsbedingungen umfangreiche elektrophysiologische Analysen durch einen erfahrenen Untersucher durchgeführt, in denen die Amplituden und Nervenleitgeschwindigkeiten von Arm- und Beinnerven der Probanden neurographisch erfasst wurden. Untersucht wurden im Einzelnen die Nervi medianus, ulnaris, peroneus und tibialis hinsichtlich der motorischen Reizleitung und des muskulären Antwortpotenzials sowie die Nervi medianus, ulnaris und suralis hinsichtlich der sensorischen Reizleitung und des nervalen Antwortpotenzials.

Studie B

In dieser experimentellen Studie wurden den Probanden im Rahmen eines Go-/NoGo-Paradigmas vier verschiedene Symbole in pseudorandomisierter Reihenfolge einzeln auf einem Computermonitor präsentiert. Es wurden zu Beginn ein Ziel-Symbol und drei Nicht-Ziel-Symbole festgelegt. Diese erschienen in zwei aufeinanderfolgenden Durchläufen jeweils 800 Mal nacheinander. Im ersten Durchlauf war es die Aufgabe, auf das Ziel-Symbol mit einem Tastendruck zu antworten (Go-Aufgabe), beim zweiten Mal sollte bei allen Symbolen außer dem Ziel-Symbol gedrückt und die Antwort auf das Ziel-Symbol unterdrückt werden (NoGo-Aufgabe). Erfasst wurden die Reaktionszeit des Tastendrucks sowie die Fehler. Die Präsentation der beiden Aufgaben (Go- und NoGo-Aufgabe) erfolgte ebenfalls in pseudorandomisierter Reihenfolge.

Im ersten Abschnitt erschien direkt vor dem Ziel-Symbol immer dasselbe Nicht-Ziel-Symbol (Kopplungs- bzw. Konditionierungsbedingung, 120 Reize), anschließend wurde diese Kopplung aufgehoben (Dekonditionierungsbedingung, 40 Reize). Den Probanden wurde dieser Ablauf nicht mitgeteilt. Die Phasen wurden insgesamt fünfmal wiederholt. Um Ermüdungseinflüssen vorzubeugen, wurden zusätzlich nach jeweils 200 Reizen zeitlich selbstbestimmte Pausen eingefügt, die nicht mit dem Wechsel zwischen den Bedingungen zusammenfielen. In früheren Studien[27] wurde gezeigt, dass sich die

Reaktionszeiten verlängerten und die Fehlerquote stieg, wenn der Kopplungsvorteil während der Dekonditionierungsbedingung wegfiel. Dieser Effekt wurde als Ausdruck des impliziten Lernprozesses verstanden, der von den Probanden nicht bewusst wahrgenommen oder verbalisiert wurde.
Das Go-/NoGo-Paradigma wurde mit der Kontrollgruppe einmalig, mit den PD-Patienten sowohl medikamentennaiv (OFF) sowie 60 Minuten nach erstmaliger Einnahme von 250 mg Levodopa/62,5 mg Benserazid (ON) durchgeführt. Die Reihenfolge der ON- und OFF-Prüfungen war pseudorandomisiert.

Studie C

Neben den in Tabelle 1 aufgeführten Fragebögen zur Untersuchung nicht-motorischer Symptome wurden der Harvey Bradshaw Index[28] bei Morbus-Chron-Patienten und der Partial Mayo Score[29] bei Colitis-ulcerosa-Patienten zur Ermittlung des Aktivitätsgrads der CED angewandt. Darüber hinaus erfolgten bei CED-Patienten Blutanalysen zum Ausschluss sekundärer Genese der nicht-motorischen Symptome infolge von Eisen- oder Vitamin-B12-Mangel-Syndromen.

Analyse

Für die statistische Auswertung der Daten wurde das Statistical Package for Social Sciences (SPSS-Version 19 bzw. 22) verwendet. Mittelwerte, Mediane und Standardabweichungen wurden bestimmt. Die demographischen und klinischen Daten der Patienten wurden mit denen der Kontrollgruppen durch nichtparametrische Tests verglichen. Die Verteilung der Geschlechter, der somatosensorischen Symptome (Studie A) und Krankheitsaktivitäten der CED (Studie C) innerhalb der Gruppen wurde mittels Chi-Quadrat-Test berechnet. Die Untersuchung demographischer, sozialer und klinischer Einflussfaktoren als Ursache der somatosensorischen Symptome (Studie A) wurde mittels einer multivariaten logistischen Regressionsanalyse durchgeführt. Für die Analyse der spezifischen Testergebnisse aus Studie B (Reaktionslatenz, Korrektheit der Ausführung im Go- und NoGo-Paradigma) wurden Varianzanalysen (ANOVA) ausgeführt. Für Details sei hier auf die Originalpublikationen verwiesen. Die weiteren Gruppenvergleiche wurden mithilfe des Mann-Whitney-U-Tests untersucht. Alle Tests wurden zweiseitig durchgeführt, die Signifikanzgrenze wurde in allen Studien bei $p<.05$ definiert.

Ergebnisse

Studie A

Es wurden 39 Patienten mit Erstdiagnose PD und mittlerem Hoehn-und-Yahr-Stadium von 2,1 (± 0,6) sowie 32 altersgematchte Kontrollprobanden in die Studie eingeschlossen. PD-Patienten gaben anamnestisch wesentlich häufiger somatosensorische Symptome an als die altersgematchten gesunden Kontrollprobanden (66,7 % vs. 31,2 %; p=.003), insbesondere Kribbelparästhesien, Taubheitsgefühl und Schmerzen der unteren Extremitäten. Die klinische Untersuchung ergab ebenfalls deutlich häufiger somatosensorische Defizite bei den Patienten als bei den Kontrollen (79,1% vs. 46,9%; p=.001). Die durchschnittliche Punktzahl im mTCNS der PD-Patienten war im Vergleich zu den Kontrollen erhöht (p<.001).

Die elektroneurographische Untersuchung der sensiblen und motorischen Extremitätennerven ergab zwischen PD-Patienten und Kontrollen keine signifikanten Unterschiede, weder in Amplituden noch in Nervenleitgeschwindigkeiten. Jedoch zeigte sich bei den Kontrollen mit somatosensorischen Symptomen eine signifikante Erniedrigung der sensiblen Amplituden der Nervi medianus (p<.001) und suralis (p=.001) gegenüber den Kontrollen ohne Symptome. In der PD-Gruppe gab es eine solche Übereinstimmung von Symptomen und elektroneurographischem Befund nicht.

Die multivariate logistische Regression ergab als prädiktive Faktoren für somatosensorische Symptome die Diagnose PD (p=.017; Odd's Ratio [OR] 3.66; Konfidenzintervall [CI] 1.265-10.607) und die Amplitudenreduktion des Nervus suralis (p=.005; OR 1.20; CI 1.06-1.35).

Somatosensorische Symptome führten bei PD-Patienten zu einer signifikant niedrigeren gesundheitsassoziierten Lebensqualität in den Bereichen soziale und körperliche Funktionen (p=.035 / p=.02).

Studie B

Es wurden 22 Patienten mit Erstdiagnose PD und mittlerem Hoehn-und-Yahr-Stadium 2,1 (± 0,6) sowie 23 altersgematchte Kontrollprobanden in die Studie eingeschlossen, die sich in Bildungsgrad und Händigkeit nicht unterschieden. Die PD-Patienten wiesen im BDI signifikant häufiger depressive Symptome als die Kontrollen auf (p<.001).

Im Go-Paradigma zeigten sich bei allen Teilnehmern in gleichem Maße verlängerte Reaktionszeiten in der Dekonditionierungsbedingung gegenüber der Konditionierungs-

bedingung (p<.001). Die Fehlerraten zwischen diesen Bedingungen waren für alle Teilnehmer nicht unterschiedlich (p>.4).

Im NoGo-Paradigma sahen wir bei den Kontrollen sowie den PD-Patienten im OFF eine Zunahme der Fehlerrate nach Wegfall der Kopplung von Ziel- und Nicht-Zielreiz (Dekonditionierungsbedingung) im Vergleich zur Konditionierungsbedingung (p<.001). Nach einmaliger Einnahme von Levodopa (ON) ließ sich dieser Effekt bei denselben PD-Patienten allerdings nicht mehr nachweisen. Für diese Gruppe zeigte sich keine Änderung der Fehlerrate zwischen der Dekonditionierungs- und Konditionierungsbedingung (p>.06)

Studie C

Es wurden 22 CED-Patienten mit klinisch relevanter Erstdiagnose RLS (IRLS ≥ 11) und 21 Kontroll-CED-Patienten ohne RLS in die Studie eingeschlossen. In den klinischen Parametern Krankheitsaktivität und -dauer der CED sowie Immunsuppression bestanden keine wesentlichen Abweichungen zwischen den Gruppen (p=.75).

Die CED-Patienten mit RLS gaben signifikant stärkere Beschwerden als die Kontrollprobanden in jenen Tests an, die Schlafprobleme und Fatiguesymptome erfragten (PQSI, FSS). Diese hatten gegenüber den CED-Patienten ohne RLS eine verlängerte Schlaflatenz (p=.031), kürzere Schlafdauer (p=.016) und stärkere Fatigue-Symptomatik (p=.016). Diese Beschwerden korrelierten zudem mit der im ILRS erfassten Ausprägung der RLS-Symptome (PSQI: r=.55, p=.013; FSS: r=.52, p=.016). Letzteres zeigte sich auch im ESS bezüglich der Tagesmüdigkeit (r=.5, p=.022).

Zusätzlich korrelierte die Ausprägung der im STAI-S/T (r=.65/.67, p=.003/.001) und BDI (r=.65, p=.001) erfassten Ängstlichkeits- und Depressionssymptome mit der Stärke der RLS-Beschwerden. CED-Patienten mit RLS-Symptomen gaben zudem eine niedrigere gesundheitsassoziierte Lebensqualität an als jene ohne RLS (p=.005) an.

Daneben lag die Dauer der RLS-Symptome bis zum Zeitpunkt der Diagnose des RLS bei 4,6 ± 3,9 Jahren (1-10 Jahre). Die Schwere der RLS-Symptomatik korrelierte nicht mit der Krankheitsdauer oder -aktivität der CED.

Diskussion

Alle drei Studien untersuchten nicht-motorische Symptome bei Patienten mit neu-diagnostiziertem und unbehandeltem PD oder RLS im Vergleich zu Kontrollgruppen.

Studie A

In der neurologischen Untersuchung waren bei vier von fünf neudiagnostizierten und Levodopa-naiven PD-Patienten Zeichen einer somatosensorischen Störung apparent. Dies kam auch in den Anamnesefragebögen zu entsprechenden Beschwerden zum Ausdruck. Hier gaben zwei von drei Patienten klinisch relevante somatosensorische Symptome an. In der multivariaten logistischen Regression wurde die Diagnose PD selbst als prädiktiver Faktor für somatosensorische Symptome ermittelt.

Als ursächlich für somatosensorische Defizite wurden in der Vergangenheit diverse zentral-nervale Mechanismen diskutiert: Störungen zentraler dopaminerger und nicht-dopaminerger Systeme wurden unter anderem in Bezug auf Schmerz, Sensibilität und propriozeptive Integration mit den Beschwerden in Verbindung gebracht[7,30,31]. Auch peripher-nervale Erklärungen wurden in Studien untersucht: So korrelierten auch Irregularitäten in peripheren Hautnervenfasern von PD-Patienten mit und ohne Medikation mit somatosensorischen Dysfunktionen[32]. Letzteres ließ sich in unserer Studie nicht sicher nachvollziehen, es fanden sich keine Abweichungen der elektroneurographischen Parameter zu den gleichaltrigen Kontrollprobanden. Da hier methodisch bedingt nur die mittleren und großen Nervenfasern charakterisiert werden, könnten Veränderungen der dünnen, nicht-myelinisierten Nerven (sogenannte „small fibre“) entgangen sein. Eine veränderte Funktion dieser dünnen Nervenfasern ließe sich in zukünftigen Studien durch weitere detaillierte Untersuchungen näher untersuchen.

Zusammenfassend sollten Defizite in der Somatosensorik nicht lediglich als additives Syndrom oder Komorbidität, sondern als immanenter nicht-motorischer Bestandteil des PD verstanden werden. Die in unserer Studie bestätigte Reduktion der gesundheits-bezogenen Lebensqualität - insbesondere gegenüber PD-Patienten mit ebenfalls motorischen Einschränkungen, aber ohne somatosensorische Symptome - unterstreicht die hohe Relevanz dieser Beschwerden für die betroffenen Patienten.

Studie B

Die Untersuchung von implizitem Lernverhalten therapienaiver PD-Patienten erfolgte durch die Erhebung von Leistungsparametern in einem visuellen Go-/NoGo-Paradigma, das die Initiierung oder die Unterdrückung einer Handlung erforderte.

Während sich sowohl für therapienaive PD-Patienten als auch für gesunde Kontrollprobanden ein ähnliches implizites Lernverhalten wie in Voruntersuchungen[27] nachweisen ließ, zeigten dieselben PD-Patienten nach der einmaligen Einnahme von Levodopa kein Lernverhalten, wenn eine Handlung unterdrückt werden sollte. Für die Handlungsinitiierung ließ sich kein solcher Gruppenunterschied finden, anders als in Vorstudien, die PD-Patienten im fortgeschrittenen Stadium und mit mehrjähriger dopaminerger Therapie untersucht hatten. Der beeinträchtigende Effekt der Levodopa-Einnahme auf das implizite Lernen scheint daher bei De-novo-PD-Patienten auf die Handlungsunterdrückung begrenzt zu sein.

Ein möglicher Grund könnte in der Komplexität der Aufgabenstruktur vermutet werden. Während die Handlungsinitiierung ein überwiegend abwartendes Verhalten mit exekutiver Antwort nur auf einen von vier Stimuli hin verlangte, beinhaltete die Aufgabe zur Handlungsunterdrückung dauerhaft aktive Antworten, die nur bei einem der vier Stimuli inhibiert wurde. Dass in der Handlungsinitiierung in allen Gruppen nach Wegfall der Kopplung zwar ein Anstieg der Reaktionszeiten, aber nicht der Fehlerrate zu verzeichnen war, kann als Kompensationsmechanismus im Sinne eines „Speed-Accuracy-Tradeoffs“[33] verstanden werden, bei dem eine Aufrechterhaltung der Genauigkeit durch eine reduzierte Reaktionsgeschwindigkeit erreicht wird. Über diese Kompensation können bei leichteren Aufgaben wie der Handlungsinitiierung offenbar auch de-novo-PD-Patienten nach Levodopa-Gabe noch adäquat verfügen, während dies in der schwereren Aufgabe der Handlungsinhibition nicht mehr ausreichend ist.

Dieser das Lernverhalten modulierende Effekt von Dopamin ist kompatibel mit der in der Literatur beschriebenen „Overdose-Hypothese“, nach der die dopaminerge Therapie eines PD zwar primär die motorischen Defizite lindert, aber in der Folge kognitive Funktionen durch ein „zu hohes“ Angebot an Dopamin limitiert[34-36]. Als Grundlage hierfür wird das geringer ausgeprägte dopaminerge Defizit im mesokortikalen gegenüber dem primär durch PD betroffenen nigrostriatalen System, insbesondere zu Beginn der Erkrankung[37,38], diskutiert. Der Beginn einer dopaminergen Substitution kann dann in den noch nicht dopamin-defizitären kognitiven Systemen zu

einer Überstimulation führen und dadurch deren Funktion beeinträchtigen. Anzunehmen ist, dass initial noch funktionierende mesokortikale Kompensationsmechanismen[39] angesichts der dopaminergen Überstimulation in der komplexeren Struktur der Inhibitionsaufgabe nicht mehr adäquat greifen und so implizites Erlernen komplexerer motorischer Aufgabenstellungen zunehmend eingeschränkt ist.
Zusätzlich zu den krankheitsimmanenten motorischen und nicht-motorischen Aspekten des PD verschlechtert die dopaminerge Therapie implizites Lernverhalten.

Studie C

Diese Untersuchung ergab den Nachweis vermehrter Schlafstörungen und Fatigue-Symptome bei Patienten, die sowohl unter einer CED als auch unter RLS litten im Vergleich zu Patienten ohne RLS. Die Qualität des Schlafes war insbesondere durch eine verlängerte Schlaflatenz sowie eine verkürzte Schlafdauer beeinträchtigt. Zudem korrelierten Ängstlichkeit und Depression mit der Stärke der RLS-Beschwerden.
In Voruntersuchungen wurden bei CED-Patienten erhöhte Prävalenzen von Stimmungs- und Angststörungen, Fatigue und reduzierter Schlafqualität gegenüber gesunden Menschen nachgewiesen[40,41]. Auch das RLS war in Studien mit Schlafstörungen, Depression und Angststörungen assoziiert[4,5,42]. Unsere Studie zeigte erstmals, dass die Kombination beider Erkrankungen eine nochmalige Verstärkung der Symptome bewirkt. Die CED-Patienten mit RLS wiesen eine deutlich verringerte Schlafqualität sowie mehr Fatigue-Symptome als die CED-Patienten ohne RLS auf. Im Schnitt wurde durch die Patienten mit beiden Erkrankungen eine schlechtere gesundheitsassoziierte Lebensqualität angegeben.
Hinsichtlich kognitiver oder neuropsychiatrischer Defizite wurden in unserer Studie erwartungsgemäß keine Unterschiede zur Kontrollgruppe festgestellt. Nur wenige Studien untersuchten bislang nicht-motorische Störungen bei RLS-Patienten in Verbindung mit zentral-nervalen Mechanismen. Es wurden jedoch Assoziationen zwischen Schlaflosigkeit und neuropsychologisch sowie bildgebend nachgewiesenen funktionellen Störungen im präfrontalen Kortex nachgewiesen[43]. Bei RLS-Patienten korrelierten gleichartige Störungen mit Defiziten in der Ausführung kognitiver Aufgaben[44].
Beachtenswert ist der Fakt, dass zwischen dem Auftreten erster Symptome der RLS und dem Zeitpunkt der ärztlich gestellten Diagnose oft mehrere Jahre (bis zu zehn

Jahre) vergehen. Trotz regelmäßiger Kontrolluntersuchungen im Verlauf der CED liegt faktisch eine Unterdiagnostizierung des Syndroms und somit eine unnötige, da vermeidbare Reduktion der Lebensqualität der Patienten vor. Neurologische Untersuchungen werden bislang, anders als in unserer Studie, nicht standardisiert als Teil der Diagnostik und Therapie von CED vorgenommen. Die frühzeitige Einbindung neurologischer Fachkompetenz in einem interdisziplinären Behandlungsteam wird empfohlen, ebenso die Erweiterung der klinischen Forschung zur Weiterentwicklung des Verständnisses der ursächlichen Mechanismen der nicht-motorischen Defizite.

Fazit

Alle Studien verdeutlichen die Komplexität an Symptomen bei PD und RLS, die weit über die motorische Symptomatik hinausgehen. Neu ist die Erkenntnis, dass bei Patienten mit diesen Bewegungsstörungen im Vergleich zu gesunden Probanden gleichen Alters verschiedene Aspekte wie die Somatosensorik oder die Schlafqualität bereits zum Zeitpunkt der Diagnosestellung deutlich eingeschränkt sein können. Ebenso können durch die Einleitung einer Therapie mit Levodopa – auch schon probatorisch im Rahmen der diagnostischen Untersuchungen – ab der ersten Gabe wesentliche Änderungen in grundlegenden integralen Funktionen des ZNS herbeigeführt werden, wie dies anhand des defizitären impliziten Lernens gezeigt wurde. Die klinische Relevanz dieser Störungen lässt sich anhand einer signifikant verminderten gesundheitsbezogenen Lebensqualität dieser Patienten nachweisen.

Aufgabe der erstdiagnostizierenden und -behandelnden Ärzte muss daher sein, neben den zur Diagnose von PD und RLS führenden motorischen Kardinalsymptomen sorgfältig alle weiteren somatischen, kognitiven und psychischen Funktionen zu begutachten und somit das Beschwerdebild und den Leidensdruck des Patienten individuell zu erfassen. Häufig werden diese zusätzlichen Defizite von den Patienten nicht erwähnt, da sie nicht mit der Bewegungsstörung in Zusammenhang gebracht werden, was in der Folge zu jahrelang unbeachteten Symptomen führen kann.

Hinzu kommt die Notwendigkeit, das Therapieschema auf den Einzelfall abgestimmt und unter Berücksichtigung aller dadurch auftretenden zusätzlichen Einschränkungen und Nebenwirkungen auszuwählen und anzupassen. Nur durch ein multimodales Verständnis der Erkrankung kann gewährleistet werden, dass die Therapie individuell angepasst und dadurch im Idealfall die Lebensqualität der Patienten verbessert wird.

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Eidesstattliche Versicherung

Ich, Arne Mehl, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema „Nicht-motorische Symptome bei Patienten mit neudiagnostiziertem Morbus Parkinson und Restless-Legs-Syndrom“ selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren beruhen, sind als solche in korrekter Zitierung (siehe „Uniform Requirements for Manuscripts (URM)“ des ICMJE - www.icmje.org) kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Tabellen) entsprechen den URM (s. o.) und werden von mir verantwortet.

Meine Anteile an den ausgewählten Publikationen entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem Betreuer angegeben sind. Sämtliche Publikationen, die aus dieser Dissertation hervorgegangen sind und bei denen ich Autor bin, entsprechen den URM (s. o.) und werden von mir verantwortet.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§§ 156, 161 des Strafgesetzbuches) sind mir bekannt und bewusst.

_____ _____

Datum Unterschrift

Anteilserklärung an den ausgewählten Publikationen

Arne Mehl hatte an den Publikationen den im Folgenden genannten Anteil:

Publikation 1 (Studie A)

Schindlbeck KA*, **Mehl A***, Geffe S, Benik S, Tütüncü S, Klostermann F, Marzinzik F. Somatosensory symptoms in unmedicated de novo patients with idiopathic Parkinson's disease. J Neural Transm. 2016;123(3):211–217.

*** geteilte Erstautorenschaft**

Konzeptionelle Entwicklung

Arne Mehl war aktiv an der konzeptionellen Erarbeitung der Studie mit einer eigenständigen Literaturrecherche zum Thema beteiligt. Darauf aufbauend wirkte er an der Auswahl der Untersuchungsmethoden und an der Planung des strukturierten Ablaufs der Untersuchungen (klinische Untersuchungen, Fragebögen, Elektrophysiologie) mit. Er beschäftigte sich mit der Frage zur standarisierten klinischen Erfassung von sensorischen Beschwerden und der Lebensqualität. Durch seine Anregungen wurden der modified Toronto Clinical Neuropathy Score (ursprünglich für Patienten mit diabetischer Neuropathie entwickelt) sowie der Short-Form-36 Health Survey für die Studie ausgewählt.

Rekrutierung und Durchführung der Untersuchungen

Arne Mehl rekrutierte selbstständig die Studienteilnehmer. Zudem war er an der Verfassung des Ethikantrags beteiligt. Er führte im Wechsel mit Katharina Schindlbeck eigenständig die Anamnesegespräche und körperlichen Untersuchungen durch: klinisch-neurologische Untersuchungen mit Fokus auf sensomotorische Defizite und extrapyramidale Motorik; standardisierte krankheitsspezifische Untersuchungen in Bezug auf somatosensorische Defizite (mTCNS - modified Toronto Clinical Neuropathy Score), motorische Beeinträchtigungen (UPDRS - Unified Parkinson's Disease Rating Scale) und Demenzhinweise (MMSE - Mini Mental State Examination). Zudem bereitete er die Teilnehmer auf die elektrophysiologische Untersuchung durch Katharina Schindlbeck vor.

Datenverarbeitung und statistische Auswertung der Ergebnisse

Durch Arne Mehl erfolgte eigenständig die Digitalisierung und Anonymisierung der Rohdaten und deren Vorbereitung zur statistischen Auswertung. Er wertete gemeinsam mit Katharina Schindlbeck unter der Supervision von Frank Marzinzik die Ergebnisse der Laboruntersuchungen und der Fragebögen aus und interpretierte diese (z. B. durch Anwendung von Cut-Off-Werten, Evaluierung des Normbereiches).

Die erste statistische Analyse der demographischen und klinischen Daten sowie der elektrophysiologischen Untersuchungen wurde nach einer Beratung am Institut für Biometrie und Klinische Epidemiologie (Dipl.-Math. Andrea Stroux) selbstständig durch Arne Mehl vorgenommen. So führte er Chi-Quadrat-Tests durch, um das Auftreten somatosensorischer Symptome, die Geschlechterverteilung, die Lateralisierung der Symptome und die Hoehn-und-Yahr-Stadien zwischen den Gruppen zu vergleichen. Weiterhin führte Arne Mehl unter der Supervision von Katharina Schindlbeck die multivariate logistische Analyse durch, um den Einfluss klinischer Faktoren wie Alter, Bildung und Vorhandensein eines PD auf die Ausbildung somatosensorischer Symptome zu untersuchen.

Verfassung des Manuskriptes und Veröffentlichung

Arne Mehl und Katharina Schindlbeck teilten sich die Literaturrecherche – Arne Mehl befasste sich dabei mit den Themen Lebensqualität, Erfassung von Aktivität der dünnen, nicht-myelinisierten Nerven sowie peripher-nervale Störungen als Ursache somatosensorischer Störungen – und interpretierten die Ergebnisse der Studie im Kontext der aktuellen Literatur. Anschließend erfolgte durch Arne Mehl und Katharina Schindlbeck gemeinsam die Verfassung der ersten Version des Manuskripts. Arne Mehl formulierte die erste Version der Ergebnisse der demographischen und klinischen Untersuchungen inklusive Erstellung der Tabellen 1 und 2. Hierbei erwiesen sich die im modified Toronto Clinical Neuropathy Score erfassten Daten als eine wichtige Grundlage für die Charakterisierung der klinischen Beschwerden und zudem als diskriminierender Parameter zwischen den beiden Untersuchungsgruppen. Zudem bildete die gesundheitsbezogene Lebensqualität der Patienten einen wesentlichen Punkt in der Arbeit und wurde in der selbstständigen Diskussion durch Arne Mehl aufgenommen.

Arne Mehl wirkte darüber hinaus bei der Revision, der Beantwortung der Fragen im Reviewprozess und der Anpassung des Manuskriptes aktiv mit.

Präsentation der Ergebnisse

Schindlbeck K, **Mehl A** et al: Presence of Neuropathy in unmedicated de novo patients with Morbus Parkinson‘; präsentiert auf dem Spotlight-Symposium des Kongresses der Deutschen Gesellschaft für Neurologie (DGN), München September 2014.

Zur Vorstellung der Ergebnisse der Studie verfassten Arne Mehl und Katharina Schindlbeck unter der Supervision von Frank Marzinzik einen Abstract, der zum jährlich stattfindenden Kongress der DGN eingereicht wurde. Dieser Abstract wurde speziell ausgewählt, um auf dem Spotlight-Symposium der DGN vorgestellt zu werden. Hierfür bereiteten Arne Mehl und Katharina Schindlbeck unter der Supervision von Frank Marzinzik eine Powerpoint-Präsentation mit den Studienergebnissen vor, die am Symposium von einem externen Experten vorgestellt wurden.

Publikation 2 (Studie B)

Geffe S, Schindlbeck KA, **Mehl A**, Jende J, Klostermann F, Marzinzik F. The single intake of levodopa modulates implicit learning in drug naive, de novo patients with idiopathic Parkinson‘s disease. J Neural Transm. 2016;123(6):601–610.

Konzeptionelle Entwicklung

Arne Mehl wirkte unter der Supervision von Frank Marzinzik an dem Konzept der Studie mit. So trug er durch selbstständiges Literaturstudium zur Auswahl der Untersuchungsmethoden bei und war an der Planung des strukturierten Ablaufs der Untersuchungen (klinische Untersuchungen, Fragebögen, Go/NoGo-Paradigma) aktiv beteiligt.

Rekrutierung und Durchführung der Untersuchungen

Arne Mehl rekrutierte selbstständig Studienteilnehmer in der allgemeinneurologischen Station und der Ambulanz für Bewegungsstörungen der Charité (Campus Benjamin Franklin). Zudem führte er eigenständig eine klinikinterne Anfrage zur Rekrutierung von Kontrollprobanden durch. Arne Mehl führte unter Supervision von Frank Marzinzik eigenständig Anamnesegespräche und körperliche Untersuchungen durch: klinisch-neurologische Untersuchung mit Fokus auf extrapyramidale Motorik; standardisierte

krankheitsspezifische Untersuchungen in Bezug auf motorische Beeinträchtigungen (UPDRS - Unified Parkinson's Disease Rating Scale) und Demenzhinweise (MMSE - Mini Mental State Examination). In Ausnahmefällen führte Arne Mehl in Vertretung für Sarah Geffe die Untersuchungen des Go/NoGo-Paradigmas sowie deren Vor- und Nachbereitungen unter der Supervision von Frank Marzinzik durch.

Datenverarbeitung und statistische Auswertung der Ergebnisse
Durch Arne Mehl erfolgte die Digitalisierung und Anonymisierung der Rohdaten und deren Vorbereitung zur statistischen Auswertung.

Verfassung des Manuskriptes und Veröffentlichung
Arne Mehl las vor Einreichung wiederholt das Manuskript und trug durch seine Anregungen und Korrektur zur essentiellen Verbesserung bei. Daneben wirkte er bei der Revision, der Beantwortung der Fragen im Reviewprozess und der Anpassung des Manuskriptes aktiv mit.

Publikation 3 (Studie C)
Schindlbeck K, Becker J, Berger F, **Mehl A**, Rewitzer C, Geffe S, Koch P, Preiß J, Siegmund B, Maul J, Marzinzik F. Impact of restless legs syndrome in patients with inflammatory bowel disease on sleep, fatigue and quality of life. Int J Colorectal Dis 2017;32(1):125–130.

Konzeptionelle Entwicklung
Arne Mehl wirkte an der Auswahl der Untersuchungsmethoden und an der Planung des strukturierten Ablaufs der Untersuchungen (klinische Untersuchung, Fragebögen) mit.

Rekrutierung und Durchführung der Untersuchungen
Arne Mehl rekrutierte selbstständig Studienteilnehmer (Kontrollprobanden). Er führte unter Supervision von Frank Marzinzik und Katharina Schindlbeck eigenständig Anamnesegespräche und körperliche Untersuchungen durch: klinisch-neurologische Untersuchung mit Fokus auf sensomotorische Defizite und extrapyramidale Motorik; Erfassung der der Ausprägung der Restless-Legs-Symptomatik durch den International

RLS Severity Scale (IRLS) und Schlafverhalten (Pittsburgh Sleep Quality Index (PSQI), Fatigue Severity Scale (FSS)). Unter der Supervision von Frank Marzinzik führte er in Vertretung von Katharina Schindlbeck mit den Studienteilnehmern auch eine neuropsychologische Testung (d2-Test, Trail Making Test A/B, Mini Mental State Examination, Beck's Depression Inventory (BDI)) selbstständig durch.

Datenverarbeitung und statistische Auswertung der Ergebnisse
Durch Arne Mehl erfolgte die Digitalisierung und Anonymisierung der Rohdaten und deren Vorbereitung zur statistischen Auswertung.

Verfassung des Manuskriptes und Veröffentlichung
Unter Berücksichtigung der Studienauswertung führte Arne Mehl zum Thema Schlafstörungen bei Restless-Legs-Patienten eine ergänzende Literaturrecherche durch. An der Verfassung der ersten Version des Manuskripts nahm er durch kritische Kommentierung und Korrekturlesen aktiv teil. Arne Mehl wirkte zudem bei der Revision und Anpassung des Manuskripts mit.

Präsentation der Ergebnisse:
Posterpräsentation auf dem 88. Kongress der Deutschen Gesellschaft für Neurologie (DGN): „Characterization of Restless Legs Syndrome in patients with Inflammatory Bowel Disease", Düsseldorf September 2015

Arne Mehl bereitete mit Frank Marzinzik und Katharina Schindlbeck eine Posterpräsentation zur Vorstellung der Ergebnisse vor und trug diese selbstständig auf dem Kongress der DGN am 24.09.2015 vor, an dem er als Stipendiat teilnahm.

Unterschrift, Datum und Stempel des betreuenden Hochschullehrers	Unterschrift des Doktoranden

J Neural Transm
DOI 10.1007/s00702-015-1459-4

Somatosensory symptoms in unmedicated de novo patients with idiopathic Parkinson's disease

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Received: 29 April 2015 / Accepted: 11 September 2015

Abstract Parkinson's disease (PD) is a neurodegenerative condition presenting with motor and non-motor symptoms including somatosensory disturbances. As neuropathic syndromes in advanced PD patients are supposed to be due to antiparkinsonian medication, we studied the presence of somatosensory symptoms and peripheral nerve function in drug naïve patients with PD as well as age-matched healthy controls. Somatosensory symptoms and signs were investigated in 39 de novo PD patients and 32 age-matched healthy controls using the modified Toronto Clinical Neuropathy Scale. To elucidate potential underlying mechanisms, peripheral nerve function was analyzed with sensory and motor neurography. About two thirds of de novo diagnosed levodopa naïve PD patients (66.7 %) reported somatosensory symptoms in comparison to one third of the control group (31.2 %) ($p = 0.003$). The presence of PD ($p = 0.017$) was a predictive factor for the occurrence of somatosensory symptoms among all participants. In contrast to the significantly higher frequency of somatosensory symptoms in patients with PD compared to controls, neurographically based peripheral nerve function did not differ between the groups. Our results indicate that somatosensory symptoms are a PD feature, which can be found when diagnosed first and independently of dopaminergic treatment. As the electrophysiologically determined peripheral nerve function was not different from that obtained in the control group, somatosensory symptoms are inherent in early PD and may be, at least partially, of central origin.

Keywords Parkinson's disease · Non-motor symptoms · Somatosensory syndrom · Neuropathic syndrom · De novo patients

Introduction

Parkinson's disease (PD) is a common neurodegenerative disorder that can cause a broad spectrum of motor and non-motor symptoms leading to significant disability. In addition to motor symptoms, patients may experience sensory disturbances like pain, visual impairment, olfactory loss, vestibular dysfunction, and proprioceptive or kinaesthetic dysfunction (Patel et al. 2014). In patients with PD, pain can be due to muscular rigidity or dystonic postures. Besides, central mechanisms like the dopaminergic system and the basal ganglia have been proposed to be part of the modulation and integration of sensory functions (Juri et al. 2010). A possible mechanism of central pain is discussed as a modified striatal selection of afferent input (Juri et al. 2010). However, somatosensory symptoms in PD might also occur due to peripheral mechanisms. Pathological changes in the enteric system, cardiac and pelvic plexus, and dorsal vagus ganglion (Comi et al. 2014) indicate peripheral nervous system impairment in PD. Furthermore, the occurrence of pathological α-synuclein in small nerve fibers and cutaneous fibers (Nolano et al. 2008; Donadio et al. 2014; Doppler et al. 2014) suggests that peripheral neuropathy (PN) is an intrinsic feature of PD (Comi et al. 2014). On the other hand, effects from the dopaminergic treatment have further been supposed to cause an increased frequency of predominantly sensory neuropathy in patients

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Published online: 21 September 2015

with idiopathic PD (Toth et al. 2010; Muller et al. 2013; Ceravolo et al. 2013; Rajabally and Martey 2011).

As previous studies investigated neuropathic syndromes in PD patients of mainly advanced stages, we focused on the presence of somatosensory aspects in early stages of the disease. Therefore, we analyzed somatosensory symptoms and the integrity of peripheral nerve function in patients with de novo and drug naÏve PD as well as age-matched healthy controls. We hypothesized that sensory symptoms would be already present in de novo PD patients mainly due to peripheral sensory neuropathy.

Methods

Sample

From January 2013 to October 2014, 44 de novo diagnosed and drug naÏve PD patients and 36 healthy subjects were recruited from patients and their relatives attending the outpatient clinic and ward of the Neurological Department of the Charité, Campus Benjamin Franklin. They gave written informed consent to the study protocol, which was approved by the ethic committee of the Charité.

Procedure

The diagnosis of PD was made by a movement disorder specialist based on the presence of bradykinesia and one of the following, muscular rigidity, rest tremor, and postural instability according to step 1 of the United Kingdom Brain Bank criteria (UKBBC) (Hughes et al. 1992). All patients and controls underwent a neurological examination, including the motor score of the UPDRS (part III). PD patients were staged according to Hoehn and Yahr (HY) (1967). Apart from the levodopa test, PD patients had no prior exposure to dopaminergic treatment. Potential non-motor symptoms were determined with the Nonmotor Symptom Questionnaire (NMSQuest), a 30-item questionnaire with screening questions for non-motor symptoms including pain and restless legs symptoms but missing further somatosensory symptoms (Storch et al. 2010). Other assessments included measures of global cognitive function (Mini-Mental State Examination, MMSE; Folstein et al. 1975), symptoms of depression (Beck Depression Inventory, BDI; Beck et al. 1961), and health-related quality of life (the Short-Form-36 Health Survey, SF-36; Bullinger 1995).

To assess somatosensory symptoms (pain, numbness, tingling, weakness, and ataxia) and signs (pinprick, temperature, light touch, vibration, and position sense) of the lower and upper limbs, we used the modified Toronto Clinical Neuropathy Score (mTCNS), a brief, easily administered semi-structured clinical interview and examination to assess sensory neuropathy (Bril et al. 2009). It was originally designed to assess diabetic neuropathy and is now used for neuropathy in general. The modified version of the TCNS, the mTCNS, was designed to investigate predominantly sensory neuropathy and shows a high validity for tracking mild to moderate sensimotor neuropathy to screen for neuropathic features in diabetic patients. The existence of somatosensory symptoms was defined as the presence of at least one of the five somatosensory symptoms investigated in the interview.

PD patients and controls underwent an electrophysiological assessment by a trained neurologist, including bilateral median, ulnar, peroneal and tibial motor plus bilateral median, and ulnar and sural sensory nerve conduction studies. Neurographically, compound motor action potentials after bilateral median, tibial, and peroneal nerve stimulation were recorded, respectively, from the musculus abductor pollicis, flexor hallucis brevis, and extensor digitorum brevis. Nerve conduction velocity was calculated from the latency difference of the potentials determined from proximal (median nerve: cubital fossa; tibial/peroneal nerve: mid/lateral popliteal fossa) versus distal stimulation position (median nerve: wrist; tibial/peroneal nerve: respective ankle points), referenced to the distance between the stimulation points per nerve. For sensory neurography, compound nerve action potentials were recorded from the end plantar index finger after median nerve stimulation at the wrist and from an area dorsal to the lateral malleolus after sural nerve stimulation about fourteen centimeters proximal to this site. All recordings were performed bilaterally with stick electrodes (3.5 cm cathode-to-anode distance) and a Medtronic Keypoint® system. To minimize the influence of the surrounding temperature on nerve conduction, the neurographic tests were principally performed at the end of the examination, after the patient had already been at a room temperature of 20 °C for at least 1 h.

To rule out causes of neuropathic syndromes, participants with a history of diabetes mellitus, chronic infectious diseases, metabolic diseases, cancer, chronic alcohol consumption, autoimmune disease, malnutrition, neurotoxic exposure, or a family history of neuropathy were excluded from both groups. Furthermore, controls had to be free of a neurological disorder. To assess potential risk factors and potential etiologies, we took blood samples from the patients with PD including fasting blood sugar, HbA1c, complete blood count, urea, creatinine, electrolytes, liver function test, thyroid-stimulating hormone, CRP, vitamin B12, serum folate, homocysteine, parathyroid hormone, p/c–ANCA (Anti-neutrophil cytoplasmatic antibodies), borrelia and hepatitis serology, antinuclear antibody,

rheumatoid factor, and serum protein electrophoresis with immunofixation.

Analysis

The Statistical Package for Social Sciences (SPSS Version 22) was used for data analysis. Means, medians, and standard deviations (SD) were determined. A multivariate logistic analysis was used to assess possible effects of demographic and clinical features on the occurrence of somatosensory symptoms, determined as the dependent variable. The demographic and somatosensory symptoms were compared between patients and controls with non-parametric tests. The Chi square test was used to compare frequencies of somatosensory symptoms and sex, lateralization, and Hoehn and Yahr stages between the groups. All other group comparisons were analyzed using Mann–Whitney *U* test. All tests are two-tailed, and the significance cut-off was $p < 0.05$.

Results

We screened 44 patients with de novo PD and 36 healthy controls for somatosensory symptoms and peripheral nerve affection. Five patients and four controls were excluded from further assessment because of a history of diabetes mellitus, cancer, chemotherapy, ongoing chronic infectious disease, or pathologic hematological findings indicating possible other etiologies of somatosensory symptoms. 39 patients with de novo PD with a mean Hoehn and Yahr stage of 2.1 (±0.6), disease duration of 1.75 years (±0.9) and 32 healthy controls were finally included. 19 of 39 patients (48.7 %) had left side of onset. PD patients and controls were comparable regarding demographic characteristics, whereas they showed significant differences regarding cognitive function, depressive symptoms, and health-related quality of life. Demographic and clinical characteristics are summarized in Table 1.

About two thirds of de novo diagnosed levodopa naÏve PD patients (66.7 %) reported somatosensory symptoms in comparison to one third of the control group (31.2 %; $p = 0.003$). The reported symptoms went along with a significantly higher rate of somatosensory deficits in the clinical examination among PD patients compared to controls (79.1 % versus 46.9 %; $p = 0.001$). The mean mTCNS was significantly higher in de novo diagnosed PD patients than in the control group ($p < 0.001$). The distribution of somatosensory symptoms and signs assessed with the mTCNS in PD patients and control subjects is shown in the box blot (see Fig. 1).

To investigate whether the reported somatosensory symptoms were due to peripheral sensory neuropathy, we analyzed limb nerve functions neurographically. The values from sensory ulnar, median, and sural nerves showed no significant differences between patients with PD and controls (see Table 2). Furthermore, motor amplitudes did not differ between the two groups. In addition, no difference was found with respect to nerve conduction velocity.

To delineate the influence of clinical factors as well as age and education on the expression of somatosensory symptoms, a multivariate logistic analysis over all patients was performed, which included the presence or absence of PD, sural nerve amplitudes, age, and education as independent variables. The presence of PD [$p = 0.017$; OR 3.66; 95 % confidence interval (CI) 1.265–10.607] and the

Table 1 Demographic and clinical data

	PD ($n = 39$)	CON ($n = 32$)	p value
Demographic characteristics			
Age (y)	66.4 (±12.3)	66.4 (±12.4)	≥0.867
Sex (f/m)	21/18	22/10	≥0.201
Education (y)	11.4 (±2.9)	11.7 (±3.5)	≥0.990
Clinical characteristics			
Disease duration (y)	1.75 (±0.9)		
Hoehn And Yahr stage	2.1 (±0.6)		
mUPDRS	27.4 (±9.8)	0.8 (±1.3)	≤0.001
MMSE	28.9 (±1.2)	29.5 (±0.9)	≤0.014
BDI	9.0 (±5.3)	2.9 (±3.5)	≤0.001
SF-36	52.4 (±14.2)	77.2 (±13.1)	≤0.001

Means and, in parentheses, standard deviations (SD) are given for age, number of years (y) of education, score on Hoehn and Yahr scale, disease duration in years, motor score on the Unified Parkinson's Disease Rating Scale Part III (mUPDRS), score of Mini–Mental State Examination (MMSE), score of Beck Depression Inventory (BDI), and Short-Form-36 Health Survey (SF-36)

CON healthy controls, *PD* patients with Parkinson's disease

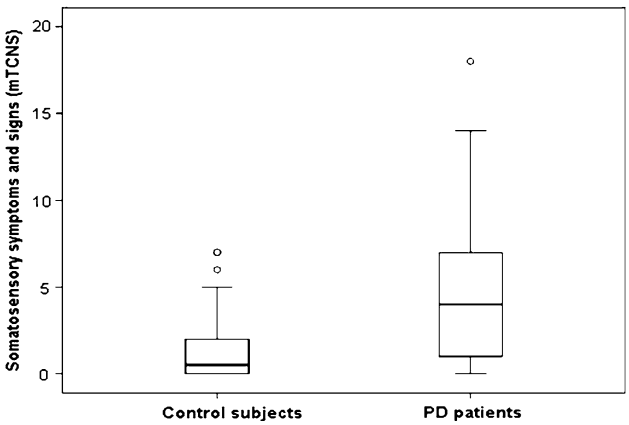

Fig. 1 The distribution of somatosensory symptoms and signs assessed with the mTCNS in PD patients and control subjects. The median mTCNS was significantly higher in PD patients compared to control subjects ($p < 0.001$)

Table 2 Characteristics of the clinical and electrophysiological examination

	PD ($n = 39$)	PD + SoSe ($n = 26$)	PD only ($n = 13$)	CON ($n = 32$)	CON + SoSe ($n = 10$)	CON only ($n = 22$)	p value
Clinical part							
mTCNS	5.0 (±4.5)	6.7 (±4.3)	1.5 (±1.9)	1.7 (±2.6)	4.5 (±3.0)	0.4 (±0.8)	≤0.001
Symptom score	2.0 (±2.0)	2.9 (±1.9)	0.0 (±0.0)	0.6 (±1.1)	2.0 (±1.2)	0.0 (±0.0)	≤0.003
Sensory test score	3.0 (±2.8)	3.8 (±2.8)	1.5 (±1.9)	1.1 (±0.7)	2.5 (±2.0)	0.4 (±0.8)	≤0.001
Electrophysiological part							
Sural nerve (μV)	8.5 (±4.8)	8.0 (±5.1)	9.5 (±4.3)	9.9 (±4.6)	6.1 (±3.7)	11.7 (±3.8)	≥0.250
Median sensory (μV)	24.6 (±12.7)	23.2 (±11.7)	27.3 (±14.8)	23.5 (±9.4)	15.4 (±5.3)	27.2 (±8.5)	≥0.917
Ulnar sensory (μV)	24.1 (±9.7)	23.5 (±8.6)	26.6 (±11.5)	23.9 (±10.5)	18.7 (±7.9)	26.2 (±10.8)	≥0.781

Means and, in parentheses, standard deviations are given for the total score on the modified Toronto Clinical Neuropathy Scale (mTCNS) as well as separated according to the symptom and sensory test score, and of the nerve action potential in μV for the bilateral sensory neurography after sural, median, and ulnar nerve stimulation. The results are presented for PD patient (PD) and healthy control (CON) divided into subgroups with (PD + SoSE/CON + SoSe) and without somatosensory symptoms (PD only/CON only). The statistical results refer to the comparisons between PD patients and healthy controls

reduction of sural nerve amplitudes ($p = 0.005$; OR = 1.20; 95 % CI 1.06–1.35) were predictive factors for the occurrence of somatosensory symptoms, whereas age ($p = 0.376$; OD = 1.09) and education ($p = 0.209$; OD = 1.03) had no influence.

In the control group, somatosensory symptoms including predominantly distal numbness or tingling of the lower limbs and weakness with unstable gait were present in one third of the participants. Subjects with somatosensory symptoms had significantly lower amplitudes of median ($p < 0.001$) and sural amplitudes of the sensory action potentials (SAP; $p = 0.001$) compared to those without them (see Table 2). Furthermore, controls with somatosensory symptoms showed significantly more neuropathic signs in the clinical examination ($p = 0.001$), were significantly older (75 versus 62.5 years; $p = 0.007$), and had lower education (9.6 versus 12.6 years; $p = 0.018$) compared to those without somatosensory symptoms. Compared to PD patients, sensory neuropathy determined by neurography was the main reason for somatosensory symptoms in control subjects.

In the PD group, subtle somatosensory symptoms and signs were frequent findings affecting the lower limbs and less often the arms. Most common symptoms were distal tingling (28 %), numbness (20 %), and pain (20 %). Clinical examination showed reduced vibration sense (54 %), temperature sensation (31 %), touch sensation (23 %), pinprick sensibility (21 %), and sense of position (23 %). Yet the PD patients showed no differences of SAP of median ($p = 0.263$), ulnar ($p = 0.331$), or sural ($p = 0.276$) nerves between the groups with regard to the presence of somatosensory symptoms.

Somatosensory disturbances in PD patients went along with a significantly poorer disease-related quality of life regarding social and physical function ($p = 0.035$; $p = 0.020$). Patients with and without somatosensory symptoms showed no significant differences regarding motor symptom severity (UPDRS part III; $p = 0.195$), HY stage ($p = 0.452$), disease duration ($p = 0.515$), or symptom lateralization ($p = 0.305$). Somatosensory symptoms were present in 25 % of the patients in HY stage 1.0 ($n = 4$), 66.7 % in HY stage 1.5 ($n = 6$), 76.9 % in HY stage 2.0 ($n = 13$), 72.7 % in HY stage 2.5 ($n = 11$), and 60 % in HY stage 3.0 ($n = 5$). Chi square test showed no association between increasing HY stages and the presence of somatosensory symptoms ($p = 0.403$). Furthermore, laboratory features (serum folate, $p = 0.478$; homocysteine, $p = 0.303$; vitamin B12, $p = 0.696$), cognitive function based on MMSE ($p = 0.897$), and depressive symptoms according to BDI ($p = 0.377$) showed no significant differences in PD patients with or without somatosensory symptoms.

Discussion

Somatosensory symptoms were present in two out of three de novo diagnosed and levodopa naïve PD patients and associated with a negative impact on health-related quality of life. As somatosensory symptoms due to neurographically assessed neuropathy affecting medium to large fibers were found in advanced PD patients, we hypothesized that they might be present, presumably less pronounced, in earlier stages of PD. However, in the present study, we could not identify neurographically based peripheral nerve damage exceeding the level in a cohort of healthy controls.

In a previous cohort study, mild somatosensory complaints assessed by interview were present in one third of the patients with early and untreated PD (Muller et al. 2011). However, our results showed higher frequencies of somatosensory complaints in about two thirds of de novo diagnosed PD patients

based on an interview considering different qualities of somatosensory function. Somatosensory disturbances can be heterogeneous as patients may experience symptoms including both positive and negative features like paresthesia, tingling, numbness, or pain. A little is known about the pathophysiology of somatosensory symptoms in patients with PD. The involvement of central dopaminergic and non-dopaminergic systems is one possible mechanism contributing to somatosensory abnormalities. Recent studies found abnormalities in sensory perception and proprioceptive integration (Snider et al. 1976; Seiss et al. 2003) and impaired discriminative sensory function (Lyoo et al. 2012) in patients with PD. In addition, abnormalities in nociceptive and mechanical thresholds have been reported in PD patients (Djaldetti et al. 2004; Zia et al. 2003). They are supposed to be due to altered central nociceptive processing and sensorimotor integration through the basal ganglia (Zia et al. 2003). Central pain is supposed to be due to pathological basal ganglia function in the form of a deranged striatal selection process of afferent inputs (Juri et al. 2010).

On the other hand, a possible involvement of the peripheral nervous system in PD is increasingly gaining attention. Several studies on genetic PD (Parkin, PINK1) showed altered somatosensory function analyzed with quantitative sensory testing (QST) in symptomatic and even asymptomatic mutation carriers (Gierthmuhlen et al. 2009, 2010). Neuropathological studies confirm the presence of lewy bodies in the peripheral nervous system like the enteric nervous system, dorsal vagus ganglion, submandibular gland, and cardiac sympathetic nerves (Del Tredici and Braak 2012; Beach et al. 2010; Cersosimo and Benarroch 2012). Besides, there is a growing evidence of the involvement of peripheral nerves as abnormalities of cutaneous fibers correlating with sensory dysfunction could be shown for both drug naïve and medicated PD patients (Nolano et al. 2008). Furthermore, pathological α-synuclein deposition was found in cutaneous sympathetic cholinergic fibers (Wang et al. 2013) and unmyelinated fibers of the dermis (Miki et al. 2010). Recent findings detected phosphorylated α-synuclein deposition correlating with small fiber neuropathy in PD patients compared to controls (Donadio et al. 2014; Doppler et al. 2014). Therefore, peripheral small fiber dysfunction might represent, in particular, a further cause of somatosensory symptoms along with central mechanisms in de novo PD patients.

Studies investigating neuropathic syndromes in drug naïve PD patients compared to an age-matched control group are lacking so far. In our study, the multivariate regression analysis confirmed that, in addition to the presence of PD, the reduction of sural nerve amplitudes was a predictive factor for somatosensory symptoms, while age and education had no influence. However, this was especially the case in controls with somatosensory symptoms showing significantly lower amplitudes of sensory nerves, whereas they showed no difference in PD patients. Our results indicate that somatosensory abnormalities in early stage and drug naÏve PD patients cannot be assessed by sensory neurography of medium to large fibers. However, small fiber function was not characterized, but somatosensory deficits in PD might be partially due to altered small fiber function.

The main limitation of this study is the relatively small sample size of both groups. Therefore, differential analysis of subgroups and disease stages was not possible. However, all the PD patients were diagnosed de novo, and the clinical and electrophysiological tests were assessed in detail. Other limitations of this study relate mainly methodical topics. As instruments to screen for somatosensory disturbances in patients with PD are lacking, the investigation of somatosensory symptoms could not be performed with an instrument developed or validated for PD patients. However, the Nonmotor Symptom Questionnaire (NMSQuest) is screening for somatosensory non-motor symptoms including pain and restless legs symptoms (Storch et al. 2010) but missing further somatosensory symptoms. Hence we used the mTCNS, a semi-structured clinical interview and examination to assess symptoms and signs of sensory disturbances. To identify peripheral causes of somatosensory disturbances, we used sensory neurography analyzing medium to large fibers, whereas pathologies in small fibers could not be detected. The investigation of small fiber function is based on the clinical examination only, and more detailed examinations like skin biopsy or QST are lacking.

Our results indicate that somatosensory disturbances can be found significantly more frequent in de novo PD patients compared to a control group. The occurrence of these symptoms seems not to be associated with severity of motor symptoms indicating that somatosensory symptoms represent an independent non-motor symptom in PD patients. However, as we were not able to identify neurographically based peripheral nerve damage exceeding the level in a cohort of healthy controls, our results emphasize that there are other mechanisms beyond peripheral neuropathy of medium to large fibers. Further studies, using quantitative somatosensory testing and methods investigating central function, are needed to discover whether small fiber function or impairments in central pathways or both contribute to the development of somatosensory syndromes in PD. Altogether, our findings point out that somatosensory disturbances represent a common intrinsic non-motor feature in early stage PD independent of dopaminergic therapy with a negative impact on the health-related quality of life.

Compliance with ethical standards

Financial disclosures Fabian Klostermann received honoraria for advisory activities or lecturer from Archimedes, UCB, Ipsen, and Abbott, and holds grants from the German Research Foundation (Kl 1276/4 and Kl 1276/5).

Conflict of interest None of the authors have any conflict of interest with respect to the present work.

Ethical approval All procedures performed in studies involving human participants were in accordance with ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendment or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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J Neural Transm (2016) 123:601–610
DOI 10.1007/s00702-016-1557-y

The single intake of levodopa modulates implicit learning in drug naïve, de novo patients with idiopathic Parkinson's disease

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Received: 23 February 2016 / Accepted: 12 April 2016 / Published online: 23 April 2016

Abstract Although dopamine is known to aggravate implicit learning, the exact impact on behaviour when feedback is unavailable remains unclear. Previous studies revealed that non-rewarded learning habits are affected in long-term dopaminergic treated patients with Parkinson's disease (PD). We studied the influence of a onetime levodopa intake on implicit learning in de novo, untreated PD patients. De novo PD patients ($n = 22$) before and after the single intake of levodopa and control subjects ($n = 23$) took part in a Go/NoGo paradigm. One stimulus was defined as target, which was first consistently preceded by one of three non-target stimuli (conditioning). This coupling was dissolved thereafter (deconditioning). In the 'Go version' subjects were asked to respond to the target by pressing a key, whereas in the 'NoGo version' response had to be inhibited. PD patients and controls ($n = 14$/$n = 19$) with an initial learning effect due to the target were included for further statistical analysis. Within the subgroup incorrect responses upon NoGo stimuli increased during the deconditioning phase. In contrast, the same patients failed to show any change after receiving 200 mg of levodopa. During the Go version, no change of the overall error rate between conditioning and deconditioning was detectable over all groups. Learning behaviour in untreated PD patients and healthy controls was indistinguishable. In contrast, the same patients varied in their implicit learning after one-time intake of levodopa, when actions had to be inhibited. Hence, the single intake of levodopa appears to modulate implicit learning behaviour in de novo PD patients.

Keywords Parkinson's disease · Non-motor smyptoms · Implicit learninig · de novo diagnose · Dopamine · Go/NoGo paradigm

Introduction

Parkinson's disease (PD) is a common neurodegenerative disorder that can cause a broad spectrum of motor and non-motor symptoms leading to significant disabilities. In addition to motor symptoms, patients have difficulties in initiating movements as well as controlling actions. These impairments are caused by cognitive disturbances, including executive control dysfunction and impaired procedural learning skills (Alonso-Prieto et al. 2003; Owen 2004; Saint-Cyr et al. 1988).

Implicit or procedural learning is characterized by the learning of relationships between events that occur sequentially in time, without the participant's intention to learn or the ability to consciously perceive of what has been learned (Reber 1989, 2013; Reber and Millward 1968). Different paradigms have been established in order to investigate implicit learning. Depending on the paradigm this leads to a change in reaction times and error rates over the course of the task (Destrebecqz and Cleeremans 2001; Hsiao and Reber 2001; Seger 1994). One of the most intensely investigated implicit learning paradigms is the serial reaction time task (SRTT), where learning is mediated through faster reaction times, when subjects respond

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to a fixed reoccurring sequence versus a random sequence (Ferraro et al. 1993; Jackson et al. 1995; Nissen and Bullemer 1987; Smith et al. 2001; Westwater et al. 1998). In this task learning is only tested in action initiation, whereas other tasks are able to capture procedural learning in initiating as well as inhibiting motor responses (Marzinzik et al. 2011).

A decisive amount of procedural learning and memory function seems to lie in the basal ganglia and the midbrain dopamine system (Knowlton et al. 1996; Saint-Cyr et al. 1988). The dysfunctional learning behaviour within PD patients can already be observed in the early stage of the disease, when the loss of dopamine is mainly limited to the striatum (Foerde and Shohamy 2011). Thus, impaired habit learning effects should improve after the substitution of the missing dopamine. However, procedural learning appears to be one of the most frequent cognitive functions that aggravate due to dopamine substitution therapy (Cools 2006; Cools et al. 2001; Foerde and Shohamy 2011; Macdonald and Monchi 2011).

In our preliminary work, we were able to reveal that the availability of dopamine influences implicit, non-rewarded learning habits in PD patients that underwent long-term dopaminergic treatment (Marzinzik et al. 2011). Patients off medication performed similar to controls, whereas the performance of both these groups strongly differed from the performance of patients on medication. In unmedicated PD patients and in controls errors to target only rose during the NoGo task, while in medicated patients errors increased due to response omissions to target cues within the Go version. This modulation suggests that in advanced PD patients dopamine supports habit conditioning under the task demand of response initiation, but dampens it when inhibition is required.

These findings raise the question if the delineated effects already occur (i) in drug naïve, de novo PD patients and may therefore be, (ii) independent of the long-term anti-parkinsonian medication. We hypothesized that implicit learning behaviour between healthy controls and de novo patients is indistinguishable, whereas the same patients after a single levodopa intake vary in their implicit learning patterns for both, initiating and inhibiting an action.

Methods

Participants

Twenty-two de novo diagnosed and drug naïve PD patients were recruited from the outpatient Clinic for Neurological Movement Disorders and the ward of the Neurological Department of the Charité, Campus Benjamin Franklin. Twenty-three healthy controls participated in this study recruited by an advertisement published on the hospital board. All participants gave written informed consent to the study protocol, which was approved by the ethic committee of the Charité.

Procedure

The diagnosis of PD was made by a movement disorder specialist based on the presence of bradykinesia in addition to one of the following: muscular rigidity, rest tremor and postural instability according to step 1 of the United Kingdom Brain Bank criteria (UKBBC; Hughes et al. 1992). All patients and controls underwent a neurological examination, including the motor score of the Unified Parkinson's Disease Rating Scale (UPDRS, part III). PD patients were staged according to Hoehn and Yahr (HY; Hoehn and Yahr 1967). Apart from the levodopa-test PD patients had no prior exposure to dopaminergic treatment. Other assessments included measures of global cognitive function due to Mini-Mental State Examination, MMSE (Folstein et al. 1975). Fatigue and symptoms of depression were determined with the Fatigue Severity Scale (FSS; Hagell et al. 2006) and Beck Depression Inventory (BDI; Beck et al. 1961). All participants' primary language was German and their vision was normal or corrected-to-normal. All participants were right-handed individuals assessed by the Edinburgh Handedness Inventory (Oldfield et al. 1971). Exclusion criteria were the presence of a psychiatric or neurological disease apart from PD in the PD group, current or severe traumatic head injuries, less than 24 points in the MMSE (Fillenbaum et al. 1990) and the intake of drugs with central mechanisms of action. In particular, none of the participants stated the current intake of anti-convulsants, anxiolytics, sedatives or antidepressants.

Go/NoGo paradigm

PD patients and healthy controls were engaged in two tasks, demanding selective reactions to visually presented target and non-target signals. Whereas controls only participated once in the trial, PD patients were engaged twice in randomized order. Half of the patients first took part before the levodopa-test and the other half started about 45–60 min after the intake of 250 mg Levodopa/62.5 mg Benserazid, once the motor effects occurred. Effects were measured by the implementation of the UPDRS III. For the second testing, patients were engaged after an interval of 48 h.

Participants sat in a darkened room within a distance of 1.5 m in front of a 17' computer screen with their right index finger comfortably positioned over a push-button on the right hand armrest. All stimuli appeared within an omnipresent 6 × 6 cm frame in the middle of the screen. In the Go version of the task, participants had to respond to

a predefined target signal by a right-finger button press, whereas responses should not be given to any of the other signals. In contrast to this, in the NoGo version the right-finger button press had to be performed upon any non-target signal, meaning, only upon the target signal this response had to be withheld.

In both the Go and NoGo task version four equiprobable visual stimuli occurred, including one target and three non-targets. Over blocks of 120 signals (conditioning) the target signal was consistently preceded by the same non-target signal (in the following labelled precue). After each conditioning phase, this coupling was dissolved; i.e. the former precue did no longer precede the target cue for a block of 40 signals (deconditioning). Every 160 signals (conditioning plus deconditioning) a new conditioning phase with another precue but constant target began. Five alternating conditioning/deconditioning phases were run overall containing 800 presentations. For further information see Marzinzik et al. (2011). Note that participants were not supposed to become aware of the alternating task structure. To this end, pauses of 1 min were taken every 200 trials. Hence, conditioning and deconditioning phases never appeared at the same point in time with respect to the breaks in order to avoid conscious perception of the task rules and trend effects from reduced vigilance or attention. Under the basic idea that performance declines during the deconditioning phase, implicit learning was detected through a deceleration of reaction times and the increase of error rates after decoupling. Within deconditioning, the previously learnt pattern did no longer lead to any benefit for participants.

Statistical analysis

The Statistical Package for Social Sciences (SPSS Version 22) was used for data analysis. Means, medians and standard deviations (SD) were determined. Demographic data and clinical score values were compared between patients (on versus off levodopa) and controls with non-parametric tests. The Chi square test was used for comparing the gender distribution between the groups. All other group comparisons were analyzed using Mann–Whitney *U* test.

For the analysis of response latencies (accepted within a range of 150–900 ms after Go stimuli and non-targets in the NoGo version) and accuracy of task performance, three-and four-way ANOVAs were run with respect to reaction times and error rates to target and non-target, respectively, if the data met criteria for parametric testing due to Kolmogorov–Smirnow and Levene testing. For the analysis of the target performance, *Group* was included as three-level test factor (control subjects/patients off levodopa/patients on levodopa), *Learning Phase* as a test factor with four levels, specified as equally long segments of performance throughout each block of conditioning and subsequent deconditioning (performance over stimulus 1–40/41–80/81–120/121–160, the latter segment being the deconditioning phase) and *Iteration* as a test factor with five levels (five alternating conditioning and deconditioning phases were run). Beside, with respect to statistical analysis of the non-targets a further test factor *Non-Target-Type* with two levels (precues/neutrals) was included. While the precues were predefined as the non-targets preceding the target whilst conditioning, the neutrals did not have any relation to the target during any of the versions. In case of sphericity violations, Huynh–Feldt corrections were performed. Post-hoc comparisons were run as Newman–Keuls tests.

For further analysis we included only those PD patients without dopaminergic medication ($n = 14$) as well as control subjects ($n = 19$), who showed an increase in the error rate during the deconditioning phase compared to conditioning phase defined by two standard deviations upon the target signals in the NoGo version. This can be defined as an initial learning effect. This subgroup is hereafter defined as Learning Group. No changes were detectable in the learning behaviour of the participants when adopting this strategy for the Go version of the task.

The rationale behind treating results from the same PD patients on versus off levodopa as stemming from different groups was that we aimed at the broadest possible analysis of medication-dependent modulation of normal task performance, together with a comprehensive assessment of putative interactions of the test factors. Importantly, this statistical approach is particularly conservative, since it minimises the risk of erroneously assuming differences between treated and untreated PD patients as the statistical assumption of data variance is larger for cohorts with distinct than with identical subjects. The treatment of within-subject as between-subject information overestimates data analogousness. In the debriefing procedure held as a standardized oral interrogation after the trial, none of the participants could report on any coupling of signals or on the alternation of task sequences, which supports the fact that the structure of the task remained hidden.

Results

Demographic and clinical data

The groups did not differ in age, education and handedness. While no differences were found between patients and control subjects related to demographic and cognitive characteristics, participants showed more depressive symptoms than control subjects regarding to BDI score ($p < .001$). Within the UPDRS III, we revealed an expected statistical distinction between patients and controls

($p < .001$) as well as between patients on and off levodopa ($p < .001$). Demographic and clinical characteristics are summarized in Table 1.

Go/NoGo paradigm

As for the NoGo version the statistical analysis of errors to target stimuli revealed *Learning Phase* to be a main factor [($F(3, 192) = 14.55$; $p < .001$)] among all participants. Post-hoc tests demonstrated that the significance of the main factor *Learning Phase* was due to the fact that over the course of the task all subjects showed an increase in the error rate during deconditioning phase compared to conditioning phase ($p < .001$), which can be regarded as a learning effect. No group differences could be proved: *Group* [($F(2, 64) = 0.52$; $p > .6$)]; *Learning Phase X Group* [($F(6, 192) = 1.18$; $p > .3$)]. In the Go version, the statistical analysis of omissions to target stimuli revealed *Learning Phase* to be a main factor [($F(3, 192) = 7.97$; $p < .001$)] for all participants. Post-hoc tests demonstrated no differences between deconditioning and conditioning phase for all participants ($p > .9$) but a significant rise within errors over the course of conditioning (L2/L3; $p > .001$). Group differences could be proved: *Group* [($F(2, 64) = 3.33$; $p < .04$)]. Post-hoc tests revealed that controls made significantly less errors due to the target than PD patients after levodopa intake. No interactions with learning phase were provable: *Learning Phase* × *Group* [($F(6, 192) = 1.01$; $p > .4$)]. In the following, we present the statistical results for NoGo and Go version of the paradigm by including the Learning Group. Results of statistical analysis for all participants as well as for the Learning Group are summarized in Tables 2 and 3.

NoGo version

Accuracy

In the NoGo version, the main factor *Learning Phase* [($F(3, 132) = 22.96$; $p < .001$)] was modified by the interaction *Group* × *Learning Phase* [($F(6, 132) = 2.58$; $p < .021$)]. Dissecting this two-way interaction revealed that only for control subjects and patients off levodopa *Learning Phase* is a main factor [($F(3, 54) = 12.78$; $p < .001$/($F(3, 39) = 20.05$; $p < .001$)], whereas patients on levodopa showed no differences in relation to the *Learning Phase* [($F(3, 39) = 2.78$; $p > .06$)]. Post-hoc tests demonstrated that for control subjects and patients off levodopa erroneous target reactions significantly increased during deconditioning compared to conditioning phase ($p < .001$/$p < .001$; see Fig. 1).

Evaluating the error rate of non-targets, neutrals as well as precue, we can demonstrate *Group* [($F(2, 44) = 9.31$; $p < .001$)] as a main factor modified by the interaction *Group* × *Learning Phase* × *Non-Target-Type* [($F(6, 132) = 2.45$; $p < .03$)]. Dissecting this three-way interaction demonstrated that over the course of the task errors within the control group appeared considerably less than in patients on ($p < .001$) and off levodopa ($p < .001$). No group differences occurred between PD patients on and off levodopa ($p > .7$). We did not find any differences between conditioning and deconditioning phase: *Learning Phase* [($F(3,132) = 0.74$; $p > .5$)].

Table 1 Demographic and clinical data of all participants

	PD ($n = 22$) Off/On	CON ($n = 23$)	p value
Demographic characteristics			
Age (y)	66.4 (±14.4)	67 (±10.3)	≥.426
Education (y)	14.2 (±2.3)	14.5 (±3.2)	≥.156
Clinical characteristics			
Disease duration (y)	2.2 (±2.2)		
Hoehn and Yahr stage	2.1 (±0.6)		
mUPDRS	29.5 (±0.6)/20.6 (±8.4)	0.7 (±1.5)	≤.001
MMSE	29.2 (±1.1)	29.4 (±0.9)	≥.395
BDI	8.4 (±5.3)	3.8 (±3.7)	≤.005
PANDA	22.3 (±4.2)	26.1 (±3.4)	≤.002
FSS	34.7 (±14.5)	27 (±13.7)	≥.162

Means and, in parentheses, standard deviations (SD) are given for age, number of years (y) of education, score on Hoehn and Yahr scale, years of disease duration based on an interview, motor score on the Unified Parkinson's Disease Rating Scale Part III (mUPDRS), score of Mini-Mental State Examination (MMSE), score of Beck Depression Inventory (BDI), score of Parkinson Neuropsychometric Dementia Assessment (PANDA) and Fatigue Severity Scale (FSS)

CON healthy controls, *PD* patients with Parkinson's disease, *Off* patients before levodopa intake, *On* the same patients after levodopa intake

Table 2 Statistical results for the NoGo version

	All participants			Learning Group		
	df	*F* value	*p* value	*df*	*F* value	*p* value
Accuracy target stimulus						
Learning Phase	*3.192*	*14.55*	*<.001*	*3.132*	*22.96*	*<.001*
Group	2.64	0.52	>.6	2.44	0.34	>.7
Group × Learning Phase	6.192	1.18	>.3	*6.132*	*2.58*	*<.021*
Accuracy non-target stimulus						
Learning Phase	3.192	0.19	>.9	3.132	0.74	>.5
Group	*2.64*	*7.09*	*<.002*	*2.44*	*9.31*	*<.001*
Group × Learning Phase	6.192	0.65	>.6	6.132	0.58	>.7
Reaction time non-target stimulus						
Learning Phase	*3.192*	*28.27*	*<.001*	*3.132*	*20.37*	*<.001*
Group	2.64	3.43	<.04	2.44	2.10	>.1
Group × Learning Phase	6.192	1.02	>.4	6.132	0.81	>.5

ANOVA results for all participants and the Learning Group with regard to the accuracy for the target and non-target stimulus as well as the reaction time for the non-target stimulus. Degrees of freedom (*df*), *F* value and *p* value are shown for the main factors *Learning Phase* and *Group* as well as for the interaction *Group* × *Learning Phase*

Significant results are shown in italics, $p < .05$

Table 3 Statistical results for the Go version

	All participants			Learning Group		
	df	*F* value	*p* value	*df*	*F* value	*p* value
Accuracy target stimulus						
Learning Phase	*3.192*	*7.97*	*<.001*	*3.132*	*5.49*	*<.008*
Group	*2.64*	*3.33*	*<.04*	*2.44*	*3.53*	*<.017*
Group × Learning Phase	6.192	1.01	>.4	6.132	0.53	>.7
Accuracy non-target stimulus						
Learning Phase	3.192	0.78	>.5	3.132	0.74	>.5
Group	2.64	0.7	>.4	2.44	0.5	>.6
Group × Learning Phase	6.192	0.46	>.8	6.132	0.87	>.5
Reaction time target stimulus						
Learning Phase	*3.192*	*64.81*	*<.001*	*3.132*	*50.27*	*<.001*
Group	2.64	2.64	<.05	2.44	1.37	>.2
Group × Learning Phase	6.192	0.53	>.7	6.132	1.05	>.3

ANOVA results for all participants and the Learning Group with regard to the accuracy for the target and non-target stimulus as well as the reaction time for the target stimulus. Degrees of freedom (*df*), *F* value and *p* value are shown for the main factors *Learning Phase* and *Group* as well as for the interaction *Group* × *Learning Phase*

Significant results are shown in italics, $p < .05$

Reaction time

The reaction times were only detectable for non-targets demanding a motor response. For both, neutrals as well as precue stimuli, a significant change within reaction times was to be demonstrated among the three groups for *Learning Phase* [$(F(3, 132) = 20.37; p < .001)$]. Post-hoc tests indicated that subjects showed prolonged reaction times in the deconditioning phase as opposed to conditioning phase ($p < .001$; see Fig. 2). Besides, *Non-Target-Type* [$(F(1, 44) = 11.02; p < .02)$] was main factor modified by the Interaction *Learning Phase* × *Non-Target-Type* [$(F(3, 132) = 8.36; p < .001)$]. Dissecting this two-way interaction *Learning Phase* still revealed as a main factor for neutrals [$(F(3, 132) = 4.18; p < .007)$] and precues [$(F(3, 132) = 23.82; p < .001)$], highlighting an

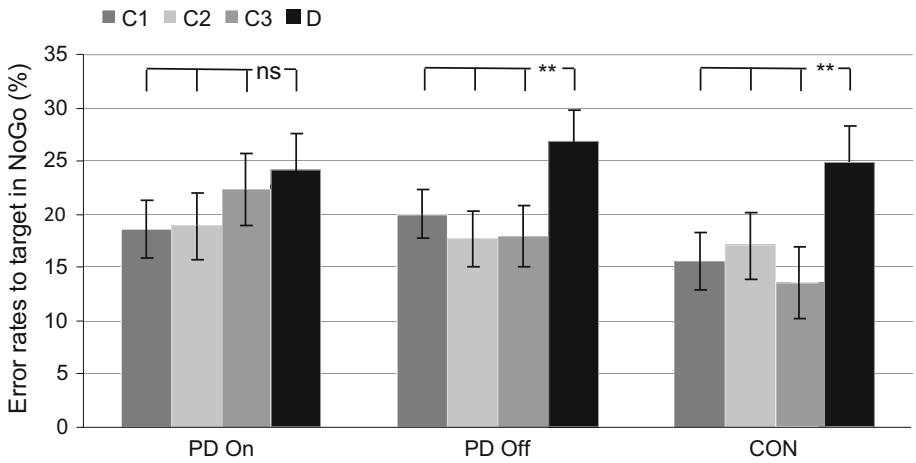

Fig. 1 Error rates in percent (%) to targets for NoGo version during conditioning and deconditioning phase of the Learning Group. Error rates are displayed per group over blocks of 40 presentations, exemplified by the responses to targets in the NoGo version. Since conditioning–deconditioning sequences comprised 120 presentations during conditioning followed by 40 presentations during deconditioning, block 1–3 (*C1*, *C2*, *C3*) reflect performance during conditioning, whereas block 4 (*D*) equates to deconditioning phase. The *error bars* indicate the standard error of the mean. *ns* not significant, $^{**}p < .01$

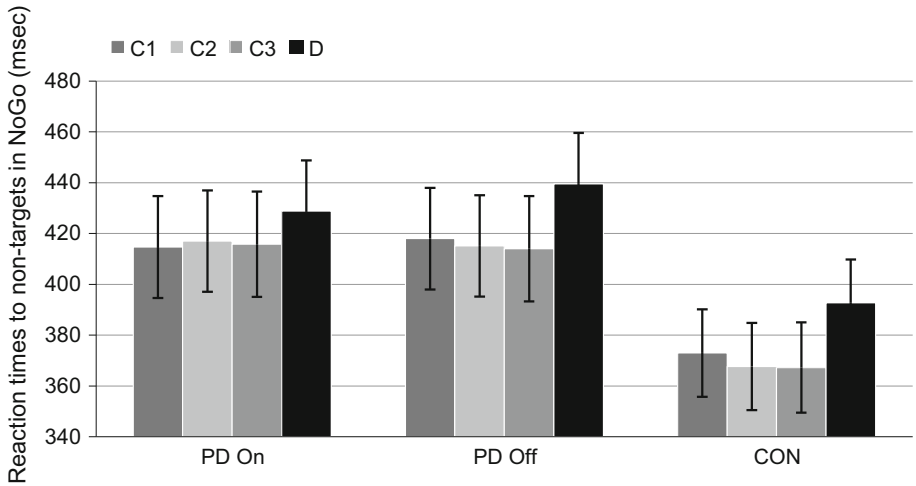

Fig. 2 Reaction times of responses in milliseconds (ms) during conditioning and deconditioning phase of the Learning Group. Average reaction times are displayed per group over blocks of 40 presentations, exemplified by the responses to non-targets in the NoGo version. Since conditioning–deconditioning phases comprised 120 presentations during conditioning followed by 40 presentations during deconditioning, block 1–3 (*C1*, *C2*, *C3*) reflect performance during conditioning phase, whereas block 4 (*D*) equates to deconditioning. The *error bars* indicate the standard error of the mean. Although all subjects (PD on, PD off, controls) showed prolonged reaction times in the deconditioning phase as opposed to conditioning phase (main factor *Learning Phase*), the presented interaction *Group* × *Learning Phase* was not significant

overall rise within reaction times during deconditioning compared to conditioning phase ($p < .001$) by Newmann–Keuls post hoc analysis. Besides, all participants reacted faster to the precue than they did in addition to the neutral stimuli ($p < .037$) verified for the second and third part of the conditioning phase ($p < .001/p < .002$). This difference between both non-target-types was trend level for the deconditioning phase ($p > .05$). Group differences could not be proved: *Group* [$(F(2, 44) = 2.10; p > .1)$]. Group × Learning Phase [$(F(6, 132) = 0.8; p > .5)$].

Go version

Accuracy

Although in the Go version *Learning Phase* was disclosed as a main factor [$(F(3, 132) = 5.49; p < .008)$], post hoc tests demonstrated no differences between deconditioning and conditioning phase for participants ($p > .15$). Group differences could be proved: *Group* [$(F(2, 44) = 3.53; p < .017)$]. Post-hocs revealed, that these distinctions were

due to the fact that the error rate of the controls was significantly lower than for PD patients before ($p < .03$) and after taking levodopa ($p < .01$). We revealed no differences between patients on and off levodopa ($p > .4$) in their error behaviour. No interactions were notable in regard to *Learning Phase*: *Group* × *Learning Phase* [($F(6, 132) = 0.53$; $p > .7$)].

No significant changes in the overall error rate were found for non-target stimuli: *Learning Phase* [($F(3, 132) = 0.74$; $p > .5$)]. No group differences or interactions could be proved: *Group* [(F (2, 44) = 0.5; $p > .6$)] and *Group* × *Learning Phase* [($F(6, 132) = 0.87$; $p > .5$)].

Reaction time

While pressing the target cue, target stimuli revealed *Learning Phase* to be the main factor [($F = (3, 132) = 50.27$; $p < 0.001$)]. Post-hoc tests indicated that all subjects showed prolonged reaction times in the deconditioning phase as opposed to the conditioning phase ($p < .001$; see Fig. 3). No significant group differences were obtainable: *Group* [($F(2, 44) = 1.37$; $p > .2$)]. No significant interaction was detectable: *Group* × *Learning Phase* [($F = (6, 132) = 1.05$; $p > .3$)].

Because PD patients had to participate twice (unmedicated/medicated), the order was randomized. For both versions, there were no statistical differences detectable comparing PD off followed by PD on vs PD off before PD on regarding error rates and reaction times.

Discussion

In this trial we investigated the influence of a single dopamine intake on implicit learning in de novo PD patients. Task performance of PD patients off levodopa and healthy controls was indistinguishable. By contrast, patients on levodopa varied in their implicit learning behaviour if a selective inhibition of an action was demanded. For initiating an action, no differences were detectable amongst the three groups.

As for the NoGo version both learning groups, healthy control subjects as well as unmedicated patients, showed a significant rise in errors of commission during deconditioning versus conditioning phase. As opposed to this, the same patients after the intake of dopamine did not show this behaviour any longer, emphasizing the group-specific distinctions upon the target. For non-targets, although representing 75 % of the stimuli, we were not able to detect an increase in the error rate. Additionally, during deconditioning all participants showed an increase in reaction times for non-target stimuli, indicating an unspecific effect concerning group interactions. As for the Go version no rise within the error rate was verifiable for targets as well as for non-targets during deconditioning. An increase in reaction times of target responses was measurable amongst all groups.

We hypothesized that patients after onetime levodopa intake are affected in their implicit learning behaviour versus drug-naïve patients having no restrictions. This

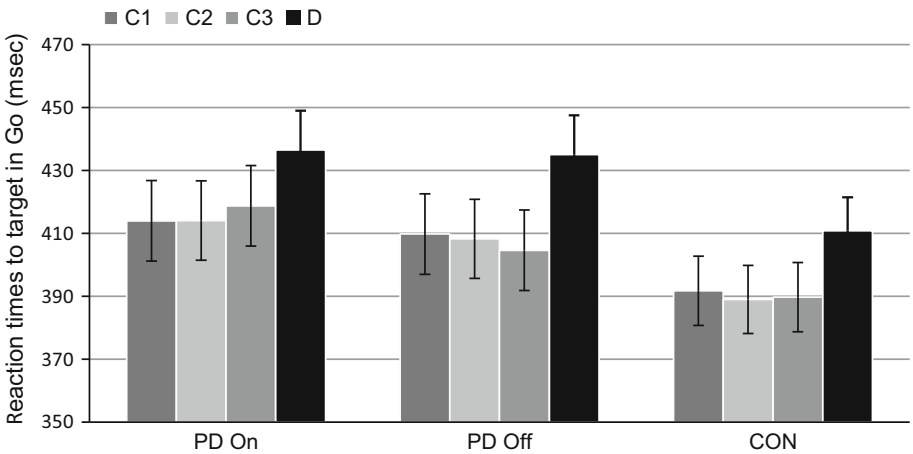

Fig. 3 Reaction times of responses in milliseconds (ms) during conditioning and deconditioning phase of the Learning Group. Average reaction times are displayed per group over blocks of 40 presentations, exemplified by the responses to targets in the Go version. Since conditioning-deconditioning phases comprised 120 presentations during conditioning followed by 40 presentations during deconditioning, block 1–3 (*C1*, *C2*, *C3*) reflect performance during conditioning phase, whereas block 4 (*D*) equates to deconditioning. The *error bars* indicate the standard error of the mean. Although all subjects (PD on, PD off, controls) showed prolonged reaction times in the deconditioning phase as opposed to conditioning phase (main factor *Learning Phase*), the presented interaction *Group* × *Learning Phase* was not significant

statement only applies for inhibiting an action. While we detected an expected rise within reaction times upon the target for the Go version, no group differences were found. The same applies for the accuracy upon target and non-targets during the Go version. As opposed to this, over the course of the NoGo version, unmedicated patients and controls could not maintain their error behaviour due to the target by only increasing their reaction times. Within the medicated group, the error rate remained stable over the course, indicating an inability for this group to unconsciously learn the structure of the task initially. However, evaluating reaction times due to the non-targets, a significant rise was also notable over all three groups during the deconditioning phase. Comprisingly, for both versions more capabilities were used during deconditioning. The substantially higher error rate within the NoGo version also indicates a potential coherence between the severity level and the deconditioning phase: internalized behavioural tendencies cannot be controlled adequately when a high cognitive effort is required in order to solve the given task (NoGo). However, when a lower cognitive effort is required, cognitive resources can still be mobilized properly (Go) among all participants.

Dopamine is known to aggravate procedural learning (Cools 2006; Cools et al. 2001; Gotham et al. 1988; Macdonald and Monchi 2011; Swainson et al. 2000). Nevertheless, the exact impact of dopaminergic medication on adaption learning is still unclear. Some studies reported deficits in medicated (Contreras-Vidal and Buch 2003) as well as in non-medicated patients (Krebs et al. 2001; Messier et al. 2007), while others found normal movement adaption in medicated patients (Marinelli et al. 2009). Within medicated PD patients, as previously shown in various forms of learning (Cools et al. 2001; Feigin et al. 2003; Graef et al. 2010; Swainson et al. 2000), we were able to find a medication-associated impairment. Functions performed by brain areas innervated through the ventral tegmentum are especially worsened due to dopamine substitution therapy, particularly in earlier stages of the disease (Cools 2006; Macdonald and Monchi 2011). In healthy controls, the administration of dopamine has also worsened their associative and reversal learning behaviour (Breitenstein et al. 2006; Mehta et al. 2001). The delineated inconsistency between the medication status and performance of our patients is consistent with Gotham's overdose theory (Gotham et al. 1988). Due to the substitution, dopamine levels are successfully restored in the dorsal striatum but at the same time lead to an overstimulation of ventral structures. Consequentially, medicated patients perform better on tasks that require structures, which are more affected but perform poorly on those less affected. Evidence for these results comes from several studies (Cools et al. 2001; Mehta et al. 2001). This effect may also explain that only two-thirds of our non-medicated patients showed an initial learning effect before but not after levodopa intake, measured by their error performances upon the target. Here, dopaminergic medication may have overstimulated certain areas, thereby inducing adaptation deficits, while in PD patients with a greater dopaminergic loss under stimulation produced similar deficits.

In our previous work (Marzinzik et al. 2011) we were able to demonstrate that PD patients off medication as well as healthy controls show a decrease of action control if a selective response inhibition is required. For patients on levodopa no behavioural changes occurred. The missing rise within the error rate in medicated patients seems to be consistent to earlier studies, where dopaminergic stimulation has a negative effect on inhibition learning (Cools et al. 2007; Frank et al. 2004). Therefore, the absent increase of errors can be understood as a correlation due to diminished learning of the task pattern, which normally takes place during conditioning. Whereas long-term dopaminergic treated patients on medication also showed a decrease of action control when an initiatory answer had to be made, we did not find a group-specificity due to the initiation of action control.

As for the Go version, the amount of overall errors due to target and non-target omissions was trivial. An explanation might be that compensation mechanisms still remain intact in de novo PD patients depending on the complexity of the task. Gamble et al. (2014) used a Triplets Learning Task (TLT) in order to evaluate implicit sequence learning in PD. They demonstrated that hippocampal dependent implicit sequence learning remains intact in PD patients, while striatal dependent learning is impaired. Thus, sequencing deficits in PD are likely due to striatal impairments, while other brain regions such as the hippocampus might be able to partly compensate for striatal decline. Transferred to our findings, these results underline the assumptions, that de novo PD patients with short symptom duration are still able to compensate dopaminergic changes due to efficient hippocampal performances when the initiation of action control is claimed. By contrast, in later stages hippocampal performances also diminish and are therefore unable to compensate the progressive striatal impairment for both, initiation and inhibition.

The overall missing increase within the error rate at a coincidental rise in reaction times within action initiation is compatible with the assumptions of so called sequential-sample models. This hypothesis implies that within decision conflicts between two options of an action, evidence will be sequentially repeated based on the decision, until it is sufficiently in order to pick up one of the options (Ratcliff et al. 2004). Hereafter, describing a performance as being dependent on the reaction time due to answers, the amount of evidence leading to a decision determines the

accuracy as well as the time used in order to response. Among versions in which a high amount of evidence yet claims a fast decision, the rate of wrong behavioural decisions increases (Starns and Ratcliff 2010). Assigned to the rise of errors during NoGo task, an accurate performance on basis of increased reaction times was not maintainable for non-medicated patients and controls.

Our results must be interpreted in the light of several limitations. The number of included patients was small. Although we found a dopamine dependent learning effect, a larger sample size might be necessary in order to evaluate group differences more precisely, especially in this early stage of the disease where cognitive characteristics do not differ as compared to healthy controls. Different factors may have contributed to the lack of group differences. Both tasks were constructed fairly easily and our cohort of PD patients was only mildly affected in their motor performance due to the short duration of the disease. This may reflect that we did not find any group differences on omission to reaction times or error rates when including all participants. More pronounced differences are detected in later stages of the disease. The next step ought to include an enhancement of error rates for both versions by adapting the severity level in order to adjust them. Furthermore, we tested the control subjects only once. Notwithstanding, our patients were tested in a randomised order. A more precise comparison between patients and controls would have been possible had we tested controls twice.

In conclusion, learning behaviour of untreated, de novo PD and healthy controls was indistinguishable. Contrarily, the same patients on medication differed, when actions had to be inhibited. This indicates that the single intake of dopamine modulates implicit learning abilities. Cognitive dysfunctions are an undisputed non-motor symptom in PD patients that worsens quality of life. Despite the fact that dopaminergic therapy is mostly dosed due to motor symptoms, it is increasingly understood that some cognitive dysfunctions arise due to the dopamine substitution. Clarifying the specific cognitive functions that are improved versus those that are impaired by dopaminergic medication can enhance treatment in patients, allowing clinicians to consider cognitive as well as motor complains in their therapy decisions.

Acknowledgments Fabian Klostermann received honoraria for advisory activities or lecturer from Archimedes, UCB, Ipsen and Abbott, and holds grants from the German Research Foundation (Kl 1276/4 and Kl 1276/5). We thank Nadine Danielle Richter for her competent comments and linguistic support.

Compliance with ethical standards

Conflict of interest None of the authors have any conflict of interest with respect to the present work.

Ethical approval All procedures performed in studies involving human participants were in accordance with ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendment or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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Int J Colorectal Dis
DOI 10.1007/s00384-016-2681-8

ORIGINAL ARTICLE

Impact of restless legs syndrome in patients with inflammatory bowel disease on sleep, fatigue, and quality of life

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Accepted: 11 October 2016

Abstract
Purpose Inflammatory bowel disease has been associated with neurological symptoms including restless legs syndrome. Here, we investigated the impact of restless legs syndrome in patients with inflammatory bowel disease on sleep, fatigue, mood, cognition, and quality of life.
Methods Two groups of inflammatory bowel disease patients, with and without restless legs syndrome, were prospectively evaluated for sleep disorders, fatigue, daytime sleepiness, depression, anxiety, and health-related quality of life. Furthermore, global cognitive function, executive function, attention, and concentration were assessed in both groups. Disease activity and duration of inflammatory bowel disease as well as current medication were assessed by interview. Inflammatory bowel disease patients with and without restless legs syndrome were matched for age, education, severity, and duration of their inflammatory bowel disease.
Results Patients with inflammatory bowel disease and clinically relevant restless leg syndrome suffered significantly more frequent from sleep disturbances including sleep latency and duration, more fatigue, and worse health-related quality of life as compared to inflammatory bowel disease patients without restless legs syndrome. Affect and cognitive function including cognitive flexibility, attention, and concentration showed no significant differences among groups, indicating to be not related to restless legs syndrome.
Conclusions Sleep disorders including longer sleep latency, shorter sleep duration, and fatigue are characteristic symptoms of restless legs syndrome in inflammatory bowel disease patients, resulting in worse health-related quality of life. Therefore, clinicians treating patients with inflammatory bowel disease should be alert for restless legs syndrome.

Keywords Inflammatory bowel disease · Restless legs syndrome · Quality of life

Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are immune-mediated inflammatory bowel diseases (IBDs) affecting the gastrointestinal tract. Extraintestinal manifestations (EIMs) are seen in up to 40 % of the patients with IBD [1, 2]. EIM may range from rheumatic, ophthalmologic, dermatologic, hematologic, and neurological symptoms and are more frequent in patients with CD than UC [3]. Neurological symptoms seen in IBD include neuropathy, fatigue, and restless legs syndrome (RLS). Furthermore, IBD patients often exhibit anemia, malnutrition, and micronutrient deficiencies [4, 5]. Iron or vitamin deficiencies as well as immune mechanisms can be associated with possible neurological manifestations including the peripheral as well as the central nervous system [6, 7]. However, neurological symptoms can also be present in the absence of deficiency syndromes.

RLS is a circadian and somatosensory disorder with the key feature being an urge to move the legs and any accompanying unpleasant sensations that begin or worsen during periods of rest or inactivity [8, 9]. Deficiency syndromes and in

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Published online: 18 October 2016

particular iron deficiency are known as a secondary cause of this syndrome. Yet, iron deficiency appears neither necessary nor sufficient to cause RLS [10]. The prevalence in Europe is about 5–15 % [11], and population-based and clinical studies have shown associations with sleep disorders, depression, anxiety, and cognitive deficits [12–16].

As IBD is a chronic inflammatory disease with phases of remission and relapse, we were interested whether symptoms of RLS represent a clinically relevant phenomenon or whether these symptoms are secondary with regard to the gastrointestinal symptom burden. Hence, this interdisciplinary study aims to investigate the clinical impact of RLS in patients with IBD. We hypothesized that RLS in patients with IBD is associated with sleeping disturbances, affective symptoms, cognitive dysfunction, and entailing poorer health-related quality of life.

Materials and methods

Study design

Between February 2014 and February 2015, patients with confirmed IBD were prospectively screened for symptoms of RLS by gastroenterologists in the outpatient clinic of the Department of Medicine (Gastroenterology, Infectious Diseases, Rheumatology) of Charité, Universitätsmedizin Berlin, Campus Benjamin Franklin. IBD patients were consecutively seen by an expert for movement disorders (Department of Neurology, Charité, Universitätsmedizin Berlin) to either confirm or exclude the diagnosis. To characterize the clinical phenotype of RLS in patients with IBD, we compared patients with IBD and RLS to those without RLS. All patients gave written informed consent to the study protocol, which was approved by the ethics committee of Charité, Universitätsmedizin Berlin.

Assessments

Inclusion criteria were (1) confirmed diagnosis of IBD, either Crohn's disease or ulcerative colitis; (2) de novo diagnosed restless leg syndrome; (3) absence of/no prior dopaminergic treatment; and (4) normal global cognitive function (Mini-Mental State Examination (MMSE) >27). IBD patients with psychiatric disorders or neurological symptoms apart from RLS were excluded. All participants underwent assessment of medical history and clinical neurological examination to identify potential "RLS mimics" like neuropathy. We performed detailed evaluation of somatosensory symptoms including numbness, tingling, pain, weakness, and ataxia. All patients were examined for potential somatosensory signs including pinprick, temperature, light touch, vibration, and position sense of lower and upper limbs. In case of abnormalities, patients were examined with electrophysiological assessment to exclude neuropathy.

RLS was diagnosed based on the following consensus diagnostic criteria for restless legs syndrome/Willis-Ekbom disease by the International RLS Study Group [9]: (1) an urge to move the legs, (2) the urge to move the legs and any accompanying unpleasant sensations begin or worsen during periods of rest or inactivity such as lying down or sitting, (3) the urge to move the legs and any accompanying unpleasant sensations are partially or totally relieved by movement, (4) the urge to move the legs and any accompanying unpleasant sensations during rest or inactivity only occur or are worse in the evening or night than during the day, and (5) the occurrence of the above features is not solely accounted for symptoms primary to another medical or a behavioral condition. The severity of RLS symptoms was assessed by the International RLS Severity Scale (IRLS) [17]. Accordingly, the IRLS allows the graduation in mild (1–10), moderate (11–20), severe (21–30), and very severe (31–40) symptoms.

To assess potential secondary causes for RLS, we took blood samples from all patients with RLS including iron, transferrin, ferritin, creatinine, urea, hemoglobin, folic acid, methylmalonic acid, and thyroid-stimulating hormone. Disease activity for CD patients was measured by using the Harvey Bradshaw Index (HBI) that is based on the patient's recall of average CD activity within the last days [18]. For UC patients, the Partial Mayo Score (PMS), a simplified 9-point version of the Mayo Score using the patient's ratings of stool frequency and bleeding components, was applied to define disease activity [19]. Potential sleep disorders were assessed with the Pittsburgh Sleep Quality Index (PSQI) [20]. Daytime sleepiness and symptoms of fatigue were rated by using the Epworth Sleepiness Scale (ESS)[21] and the Fatigue Severity Scale (FSS)[22]. To investigate symptoms of depression and anxiety, we used the Beck Depression Inventory (BDI)[23] and the State Trait Anxiety Scale (STAI) [21]. Health-related quality of life was measured by the European Quality of Life–5 Dimensions (EQ-5D) [22]. Furthermore, global cognitive function was assessed with the MMSE [23]. The d2 test, a paper-and-pencil-letter cancelation test, served to investigate attention and concentration capacities [24]. This test measures the selective attention by computing the concentration performance score as the number of correctly proposed items minus the number of errors of commission. Executive function was assessed by the Trail-Making Test (TMT) A and B [25]. The TMT-A measures simple graphomotor speed (consecutive numbers have to be connected) and the TMT-B (alternating numbers and letters have to be sequenced) studies divided attention.

Table 1 Demographic and clinical characteristics of IBD

	IBD with RLS (n = 22)	IBD without RLS (n = 21)	p value
Age (years)	50.3 (±15.3)	44.5 (±11.1)	0.170
Sex (men:women)	3:19	9:12	0.033[a]
Education (years)	12.4 (±3.1)	14.1 (±4.1)	0.111
IBD (CD:UC)	17:5	13:8	0.273
Disease duration (years)	13.8 (±10.5)	11.6 (±7.3)	0.734
HBI	4.2 (±3.8)	2.3 (±3.1)	0.310[a]
PMS	0.3 (±0.5)	1.1 (±1.7)	0.630[a]

Groups of patients with inflammatory bowel disease (IBD) with and without restless legs syndrome (RLS) were compared. Means and, in parentheses, standard deviations (SDs) are given for age, number of years of education, the Harvey Bradshaw Index (HBI) for patients with Crohn's disease (CD), and the Partial Mayo Score (PMS) for patients with ulcerative colitis (UC). p value based on Mann-Whitney U test for the different domains

[a] chi-squared test was used for sex, HBI and PMS

Analysis

The Statistical Package for Social Sciences (SPSS version 19) was used for data analysis. Means and standard deviations (SDs) were determined. The demographic and clinical symptoms were compared between IBD patients with and without RLS with non-parametric tests. The chi-squared test was used to compare frequencies of sex, disease activities, and relationship of CD and UC in the different groups. All other group comparisons were analyzed using Mann-Whitney U test. Correlations between the severity of RLS symptoms and other clinical parameters were assessed by the Spearman's correlation coefficient. All tests are two tailed and the significance cutoff was $p < 0.05$.

Results

IBD with concurrent RLS and a clinically relevant symptom severity according to an IRLS score ≥11 were found in 22 cases. In this group, the mean symptom duration of RLS was 4.6 ± 3.9 years with a minimum of 1 year and a maximum of 10-year symptom duration. The mean disease duration of the IBD was 11 ± 9.6 years. Secondary causes of RLS were found in 36.4 % (n = 8). Periodic limb movements during wakefulness were seen in 22.7 % and periodic limb movements during sleep in 4.5 % of the patients. Positive family history of RLS was reported in 31.8 %. Most of the patients with IBD and RLS were under current immunosuppression (63.6 %, n = 14).

The severity of RLS symptoms correlated with higher scores in the PSQI, indicating sleep problems (r = 0.55, p = 0.013). Symptom severity based on the IRLS correlated with more symptoms of daytime sleepiness according to ESS (r = 0.5, p = 0.022) and symptoms of fatigue measured by the FSS (r = 0.52, p = 0.016). Furthermore, moderate correlations of RLS symptom severity were seen with symptoms of depression based on BDI (r = 0.65, p = 0.001) and symptoms of anxiety according to the STAI-S (r = 0.65, p = 0.003) and STAI-T (r = 0.67, p = 0.001).

To characterize the clinical impact of RLS in patients with IBD, we compared IBD patients with at least moderate symptoms of RLS (n = 22) and without RLS (n = 21). Therefore, the groups were matched regarding age, education, relation of

Table 2 Results from the Pittsburgh Sleep Quality Index (PSQI)

PSQI score	IBD with RLS (n = 22)	IBD without RLS (n = 21)	p value
PSQI total score	8.6 (±5.8)	5.0 (±3.9)	0.049
Subjective sleep quality	1.5 (±1)	2.0 (±5)	0.074
Sleep latency	1.6 (±1.1)	0.85 (±0.9)	0.031
Sleep duration	1.2 (±1.1)	0.45 (±0.9)	0.016
Habitual sleep efficiency	1.4 (±1.3)	0.75 (±0.9)	0.122
Sleep disturbances	1.4 (±0.7)	1.15 (±0.5)	0.289
Use of sleep medication	0.2 (±0.5)	0.1 (±0.3)	0.779
Daytime dysfunction	1.4 (±0.9)	0.8 (±0.6)	0.056

Groups of patients with inflammatory bowel disease (IBD) with and without restless legs syndrome (RLS) were compared: Means and, in parentheses, standard deviations (SDs) are given for the Pittsburgh Sleep Quality Index (PSQI) and the seven subcategories of this questionnaire; p value based on Mann-Whitney U test for the different domains

Table 3 Characterization of quality of life and neuropsychiatric features

	IBD with RLS (n = 22)	IBD without RLS (n = 21)	p value
FSS	39.5 (±13.2)	29.1 (±11.7)	0.016
ESS	9.2 (±4.3)	6.8 (±4.1)	0.086
EQ-5D	80.0 (±17.2)	93.3 (±9.1)	0.005
BDI	9.6 (±7.9)	6.7 (±6.8)	0.227
STAI-S	38.0 (±11.6)	34.6 (±12.3)	0.204
STAI-T	39.2 (±11.9)	34.9 (±11.5)	0.178
MMSE	28.8 (±1.7)	29.3 (±1.1)	0.599

Groups of patients with inflammatory bowel disease (IBD) with and without restless legs syndrome (RLS) were compared: Means and, in parentheses, standard deviations (SDs) are given for the Fatigue Severity Scale (FSS), Epworth Sleepiness Scale (ESS), European Quality of Life–5 Dimensions (EQ-5D), Beck Depression Inventory (BDI), State Trait Anxiety Scale State and Trait (STAI-S/-T), and Mini-Mental State Examination (MMSE); p value based on Mann-Whitney U test for the different domains

CD and UC, disease activity, and disease duration. The groups differed with regard to sex; altogether, both groups showed a surplus of women. See Table 1 for further demographic and clinical characteristics.

Clinical characteristics like disease duration, disease activity, and immunosuppression of IBD patients with and without RLS did not differ significantly between the two groups. The disease activity of the IBD based on the HBI/PMS showed mainly mild expression and did not differ between the groups. Both IBD groups, with and without RLS, did not show significant differences in the use of immunosuppression (63.6 vs. 61.9 %, $p = 0.75$). Current oral cortisone therapy (<10 mg/d) was found in only one patient of each group. Furthermore, the severity of RLS symptoms did not correlate with disease activity (HBI $r = 0.2$, $p = 0.43$; PMS $r = 0.3$, $p = 0.54$) or the disease duration ($r = -0.2$, $p = 0.32$) of the IBD.

IBD patients with RLS had significantly more sleep problems according to the PSQI total score compared to those without RLS (8.6 ± 5.8 vs. 5 ± 3.9, $p = 0.059$). Furthermore, sleep latency was significantly longer in patients with RLS (PSQI component 2; 1.55 ± 1.1 vs. 0.85 ± 0.99, $p = 0.031$), and they had significantly shorter sleep duration (PSQI component 3; 1.18 ± 1.1 vs. 0.45 ± 0.89, $p = 0.016$) compared to those without RLS. Daytime dysfunction was more prominent in RLS patients compared to IBD patients without RLS (1.35 ± 0.9 vs. 0.8 ± 0.6, $p = 0.056$). For further details on the PSQI results, see Table 2.

Fatigue symptoms assessed by the FSS were significantly more frequent in patients with RLS (FSS sum score 39.5 ± 13.2 vs. 29.1 ± 11.7, $p = 0.016$) compared to those without RLS, whereas daytime sleepiness did not differ between the groups. IBD patients with RLS estimated health-related quality of life significantly worse than IBD patients without RLS (80 ± 17.2 vs. 93.3 ± 9.1, $p = 0.005$). They reported more impairment in usual daily life activities (1.5 ± 0.5 vs. 1.1 ± 0.2, $p = 0.003$) and significantly more pain and discomfort (1.8 ± 0.5 vs. 1.4 ± 0.6, $p = 0.037$) compared to IBD patients without RLS. Clinical features are summarized in Table 3.

All patients were screened for symptoms of depression or anxiety using questionnaires. IBD patients did not differ significantly regarding affective symptoms or symptoms of anxiety. Furthermore, global cognitive function based on MMSE, as well as executive function and cognitive flexibility based on the TMT-A and TMT-B, showed no differences among IBD patients with or without RLS. The d2 test, evaluating attention and concentration, showed no significant differences among the two groups.

Discussion

IBD patients with RLS had lower quality of sleep, reported more symptoms of fatigue compared to those patients without RLS, whereas no group differences were found for depression, anxiety, or cognitive deficits. Health-related quality of life was significantly worse in patients with IBD and RLS compared to those without RLS. Hence, clinicians should be alert for intermittent neurological symptoms in patients with IBD and consult a neurologist.

Patients with IBD are known for higher rates of neuropsychiatric disorders including mood disorders, anxiety disorders, fatigue, and poor sleep quality [26–29]. Sleep disruption leading to poor sleep quality in patients with IBD is common. Next to nighttime disruption due to diarrhea and abdominal pain, there is evidence that circulating inflammatory markers are associated with sleep disruption [29, 26]. Furthermore, fatigue is seen in up to 48 % in patients with IBD and correlates with the disease activity [28]. Compared to healthy controls, higher rates for depression and anxiety are seen in patients with IBD. Population-based and clinical studies have shown that RLS is associated with sleep disorders, depression, and symptoms of anxiety [12, 13, 30], indicating common comorbidities within IBD and RLS patients. Hence, in our cohort, we compared IBD patients with and without RLS in order to point out the clinical impact of RLS in these patients. Among patients with IBD, those with RLS had significantly more sleeping problems including longer sleep latency and shorter sleep duration. Furthermore, RLS was associated with significantly more symptoms of fatigue. In contrast, groups did not differ in mood disorders or symptoms of anxiety, indicating not to be related with RLS in patients with IBD. RLS was further associated with poorer health-related quality of life including significantly more pain and discomfort and impairment in daily life activities.

The association of cognitive dysfunction and RLS is controversially discussed in the literature. A population based cross-sectional study found similar cognitive function in patients with RLS compared to those without [31]. However, other studies report that RLS patients show characteristic deficits in cognitive tasks depending on prefrontal cortex (PFC) function [14]. Neuropsychological and imaging studies identified that cognitive tasks depending on PFC function are particularly sensitive to sleep loss [32]. Although we found sleep disturbances, we were not able to find significant differences regarding cognitive function among IBD patients with and without RLS.

Neurological diseases like peripheral neuropathy and fatigue represent comorbid disorders in patients with IBD. Little is known about potential mechanisms resulting in these diseases. Immune mechanisms as well as deficiencies are putative causes of neuropathy in IBD. Moreover, in patients with IBD, fatigue correlates with disease activity [28]. However, in our cohort, no evidence was found for a correlation between disease activity or duration and RLS symptoms. In addition, secondary causes were seen in about the same amount as in RLS without IBD [33]. Therefore, RLS seems to be rather independent of disease activity. Further studies with greater cohorts should focus on potential mechanisms. Interestingly, the mean time from symptom onset to the final diagnosis of RLS in the course of our study was 4 years with a maximum of 10 years. Hence, despite regular follow-ups in the course of a chronic disease, the syndrome seems to be rather underdiagnosed.

Our results have to be seen in the light of several limitations. The overall sample size was small. However, it has to be considered that we prospectively included patients diagnosed de novo with RLS in the absence of prior therapy. Further, groups differed regarding sex, as the surplus of women was greater in the group of IBD and RLS compared to IBD patients without RLS. Nevertheless, the groups were matched regarding age, education, relation of CD and UC, disease activity, and disease duration. As IBD is a chronic disease that occurs in acute episodes and changes between remission and relapse, it is of great importance to investigate comparable groups.

Conclusion

Sleep problems with longer sleep latency, shorter sleep duration, and fatigue are characteristic symptoms of RLS in IBD patients resulting in worse health-related quality of life. As the diagnosis of RLS in IBD patients can last up to 10 years, clinicians should be alert for RLS in patients with IBD. Correct diagnosis of RLS in IBD patients can potentially increase the quality of life in chronically ill patients.

Compliance with ethical standards

Funding None.

Conference presentation Congress of the German Society of Neurology (DGN), 09/2015, Düsseldorf Germany.

Conflict of interest BS served as consultant for Abbvie, Falk, Janssen, Hospira, Merck, MSD, Mundipharma, and Takeda and received lecture fees from Abbvie, Falk, Ferring, Hospira, MSD, and Takeda. JP has received consulting fees from MSD and Takeda and well as lecture fees from Abbvie, Pfizer, Vifor, Falk, MSD, and Takeda. JM has received consulting fees from MSD and lecture fees and travel accommodations from Abbvie, Falk Foundation, Janssen, MSD, Mundipharma, and Takeda. All remaining authors report no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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Lebenslauf

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

Komplette Publikationsliste

1.

Schindlbeck KA*, **Mehl A***, Geffe S, Benik S, Tütüncü S, Klostermann F, Marzinzik F. Somatosensory symptoms in unmedicated de novo patients with idiopathic Parkinson's disease. J Neural Transm. 2016;123(3):211–217. doi:10.1007/s00702-015-1459-4.

*** geteilte Erstautorenschaft**

Impact Factor: 2.776

1.1

Schindlbeck KA, **Mehl A** et al: Presence of Neuropathy in unmedicated de novo patients with Morbus Parkinson'; Abstrakt, präsentiert auf dem Spotlight-Symposium des Kongresses der Deutschen Gesellschaft für Neurologie (DGN), München September 2014.

2.

Geffe S, Schindlbeck KA, **Mehl A**, Jende J, Klostermann F, Marzinzik F. The single intake of levodopa modulates implicit learning in drug naive, de novo patients with idiopathic Parkinson's disease. J Neural Transm. 2016;123(6):601–610. doi:10.1007/s00702-016-1557-y.

Impact Factor: 2.776

3.

Schindlbeck KA, Becker J, Berger F, **Mehl A**, Rewitzer C, Geffe S, Koch P, Preiß J, Siegmund B, Maul J, Marzinzik F. Impact of restless legs syndrome in patients with inflammatory bowel disease on sleep, fatigue and quality of life. Int J Colorectal Dis 2017;32(1):125–130. doi:10.1007/s00384-016-2681-8.

Impact Factor: 2.533

3.1

Schindlbeck KA, **Mehl A** et al: „Characterization of Restless Legs Syndrome in patients with Inflammatory Bowel Disease", Poster, präsentiert auf dem 88. Kongress der Deutschen Gesellschaft für Neurologie (DGN), Düsseldorf September 2015.

Danksagung

Mein herzlichster Dank geht an alle, die mich bei der Arbeit an meiner Promotion mit Rat und Tat unterstützt haben.

Zu allererst danke ich meinem Doktorvater PD Dr. med. Frank Marzinzik, der mir immer ein großartiger Mentor, Lehrer und Vorbild als Arzt und Wissenschaftler ist und meine Arbeit unermüdlich und mit großer Hingabe begleitet, kritisch hinterfragt und mit zahllosen Ideen bereichert.

Gleichwohl größter Dank gilt Dr. med. Katharina Schindlbeck, durch deren persönliche Betreuung und unentwegten Einsatz viele Dinge erst möglich wurden und deren Anregungen mir immer von allerhöchstem Wert sind.

Die Studien entstanden in der Arbeitsgruppe Motorik und Kognition, deren Leiter Prof. Dr. med. Fabian Klostermann ist. Ihm und seinen Mitarbeitern möchte ich herzlich danken. Ein besonderer Dank geht ebenfalls an Sarah Geffe für die immer sehr angenehme Zusammenarbeit.

Für die fortwährende Unterstützung während meines Studiums, der Doktorarbeit und des Arztwerdens sowie in allen Lebenslagen darüber hinaus gilt mein unendlicher Dank meinen Eltern Birgit und Lars, meiner Schwester Inga, meiner Oma Christel und meinem Partner Andrés.