Aus der Neurologischen Klinik und Poliklinik
Klinik der Universität München
Direktor: Prof. Dr. med. Günter U. Höglinger

Die Gangstörung bei Patienten mit orthostatischem Tremor – Manifestation, Modulation und Strategien zur Therapie

The gait disorder in patients with orthostatic tremor – Manifestation, modulation, and strategies for therapy

Dissertation
zum Erwerb des Doktorgrades der Medizin
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Ken Maximilian Möhwald
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Die vorliegende Dissertation wurde nach § 4 a der Promotionsordnung für die Medizinische Fakultät der Ludwig-Maximilians-Universität München als kumulative Dissertation gestaltet.

Meinem verstorbenen Vater und meiner Mutter gewidmet

“Auch eine Reise von tausend Meilen beginnt mit einem ersten Schritt.“

- Laotse

Inhaltsverzeichnis

Abkürzungsverzeichnis

Abkürzung	Bedeutung
ABC	Activities-specific Balance Confidence Scale
AP	anterior-posterior
BoS	Spurbreite („base of support")
CV	Variabilitätskoeffizient („coefficient of variation")
Dsupp	Doppelstandphase („double support phase")
DTC	kognitiver Dual Task („cognitive dual task")
DTM	motorischer Dual Task („motoric dual task")
EC	Augenschluss („eyes closed")
EMG	Elektromyographie
FES-I	Falls Efficacy Scale-International
HR	Kopfreklination („head reclination")
ML	medio-lateral
MS	maximale Ganggeschwindigkeit („maximal walking speed")
MTV	Muskelsehnenvibration („muscle tendon vibration")
OT	orthostatischer Tremor
PS	selbstgewählte Geschwindigkeit („preferred walking speed")
SCS	Rückenmarkstimulation ("spinal cord stimulation")
SLength	Schrittlänge ("stride length")
SS	langsames Gehen („slow walking speed")
STime	Schrittdauer („stride time")
Swing	Schwungphase („swing phase")
VIM	Nucleus ventralis intermedius

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1 Einleitung

Hintergrund und Gegenstand der Dissertation

Der primäre orthostatische Tremor ist eine seltene neurologische Erkrankung, die durch einen hochfrequenten Muskeltremor (13-18 Hz) der unteren Extremitäten gekennzeichnet ist[1]. Die Erkrankung wurde 1970 beschrieben als Störung, die lediglich während des Stehens auftritt[2]. Der Begriff orthostatischer Tremor (OT), stellenweise auch als Syndrom der zittrigen Beine („shaky legs syndrome“) bezeichnet, wurde 1984 erstmalig geprägt[3]. Der hochfrequente Tremor, der zu einem Unsicherheitsgefühl der Patienten führt, ist beim Stehen vorhanden. Die Symptome verschwinden zumeist im Liegen oder Sitzen. Bei anfänglich wenigen klinischen Auffälligkeiten zeigt sich ein palpierbarer, selten sichtbarer Tremor meist der Beine. Die typische Tremorfrequenz von 13-18 Hz ist ableitbar mittels Elektromyographie (EMG)[1].

Da es sich beim orthostatischen Tremor um eine seltene Erkrankung handelt, liegen keine großen systematischen epidemiologischen Studien vor. Das mittlere Manifestationsalter liegt nach dem 50. Lebensjahr und es scheinen mehr Frauen als Männer betroffen zu sein (64-77%)[4,5]. Die Diagnosestellung erfolgt oft verzögert mit einer mittleren Dauer von 7,2 Jahren (0-44 Jahre) nach Symptombeginn[5].

Im Verlauf kommt es zu einer Ausbreitung der Symptome auf Körperstamm und auf die oberen Extremitäten als Zeichen einer chronisch progredienten Erkrankung[4,6]. Die Tremorfrequenz bleibt im Krankheitsprogress meist unverändert, jedoch kommt es im Verlauf zu einer signifikanten Zunahme der posturalen Unsicherheit und Körperschwankungen[7]. Stürze kommen bei etwa einem Viertel der Patienten vor[5].

Aufgrund der Seltenheit der Erkrankung fehlt bislang Evidenz aus größeren klinischen Studien zu wirksamen medikamentösen Therapieoptionen. Die meisten Berichte stützen sich auf Fallberichte und Fallserien. Hier zeigen sich die besten Effekte für Clonazepam 0,5-6 mg/Tag und Gabapentin 300-2400 mg/Tag[5,8]. Bei diesen und weiteren Substanzen scheint es jedoch im

Verlauf zu einem Wirkverlust und somit zu einer Pharmakoresistenz zu kommen. Andere Substanzen sind beim Großteil der Patienten ineffektiv. Bei therapierefraktären Patienten bestehen operative, neuromodulatorische Therapieansätze mittels tiefer Hirnstimulation im Bereich des Nucleus ventralis intermedius (VIM) des Thalamus[9-12] oder durch eine Rückenmarkstimulation (chronic spinal cord stimulation, SCS)[13-15].

Die Ätiologie und Pathophysiologie des Tremors waren lange Zeit unklar und sind nach wie vor Gegenstand wissenschaftlicher Diskussion[5,8]. Aufgrund der starken Kohärenz hochfrequenter Aktivierungen zwischen den unterschiedlichen Muskelgruppen wird ein zentraler Oszillator als Ursprung der Symptomatik vermutet. Zuletzt ließ sich im Rahmen mehrerer bildgebender Studien ein oszillatorisches Tremornetzwerk nachweisen, basierend auf erhöhten bilateralen ponto-zerebellär-thalamo-kortikalen Aktivitätsmustern[16,17]. Interessanterweise persistierte die gezeigte Netzwerkaktivität auch während der nicht-symptomatischen Perioden, z.B. im Liegen.

Auf Grundlage dieser Beobachtungen werden im Rahmen dieser Dissertation folgende weiterführende Fragestellungen behandelt:

a) Lässt sich während des Gehens ein relevanter Muskeltremor der unteren Extremität nachweisen? Wenn ja, wie ist dessen Aktivität und Frequenz moduliert?
b) Welche Konsequenzen hat der OT auf die unterschiedlichen Qualitäten des Gehens im Hinblick auf Tempo, Schwungverhalten, Stabilität und posturale Kontrolle?
c) Wie ist der Einfluss eines propriozeptiven, peripheren Vibrationsstimulus auf Tremoreigenschaften im Sitzen und Stehen?

Die vorliegende Dissertation fasst Forschungsergebnisse aus mehreren Studien zum Thema primärer OT zusammen. Zum einen werden die Pathophysiologie und noch nicht beschriebene Symptomausprägungen der Erkrankung näher untersucht, zum anderen wird eine neue, nicht-invasive Stimulationsmethode für die zum Teil schwer zu behandelnde Erkrankung diskutiert.

Die erste Publikation untersuchte den OT auf einem drucksensitiven Laufband während unterschiedlicher Stand- und Gangphasen. Der Tremor wurde dabei über eine Oberflächen-EMG-Messung abgeleitet[18]. Ziel war es, die Veränderung des Tremors bei der Transition vom Stehen zum Gehen zu untersuchen, da hierbei typischerweise eine subjektive Linderung der Beschwerden angegeben wird. Dafür wurden sowohl die Tremorfrequenz/-stärke in Abhängigkeit der Bewegungsaktivität untersucht als auch das spatiotemporale Gangmuster von Patienten mit OT charakterisiert.

Die zweite Studie beleuchtete die Gangstörung beim orthostatischen Tremor durch eine multimodale, klinisch-apparative Ganguntersuchung mit Analyse von spatiotemporalen Gangparametern in sieben verschiedenen Gangkonditionen im Vergleich zu einer altersgleichen gesunden Kontrollgruppe[19]. Hierbei lag der Fokus auf Veränderungen des Gangmusters unter verschiedenen Gangkonditionen, die als Hinweis für entsprechende sensomotorische oder kognitive Defizite dienen können.

Abschließend wurde in der dritten Studie der Effekt einer propriozeptiven Muskelsehnenstimulation (MTV) auf den Tremor und die Gleichgewichtskontrolle analysiert[20]. Patienten wurden im Stehen und Liegen mit und ohne MTV untersucht. Die Ergebnisse wurden im Kontext einer potentiellen, nicht-invasiven Therapieoption diskutiert.

Publikation I, Ko-Autorenschaft, Eigenanteil: Datenerhebung und -aufarbeitung (20%), statistische Analyse (20%), Interpretation der Ergebnisse (25%), Manuskript (20%)

Publikation II, Erstautorenschaft, Eigenanteil: Konzept und Design (30%), Datenerhebung und -aufarbeitung (50%), statistische Analyse (50%), Interpretation der Ergebnisse (60%), Manuskript (70%)

Publikation III, Ko-Autorenschaft, Eigenanteil: Datenerhebung und -aufarbeitung (20%), Interpretation der Ergebnisse (20%), Manuskript (20%)

Die Modulation des orthostatischen Tremors beim Gehen

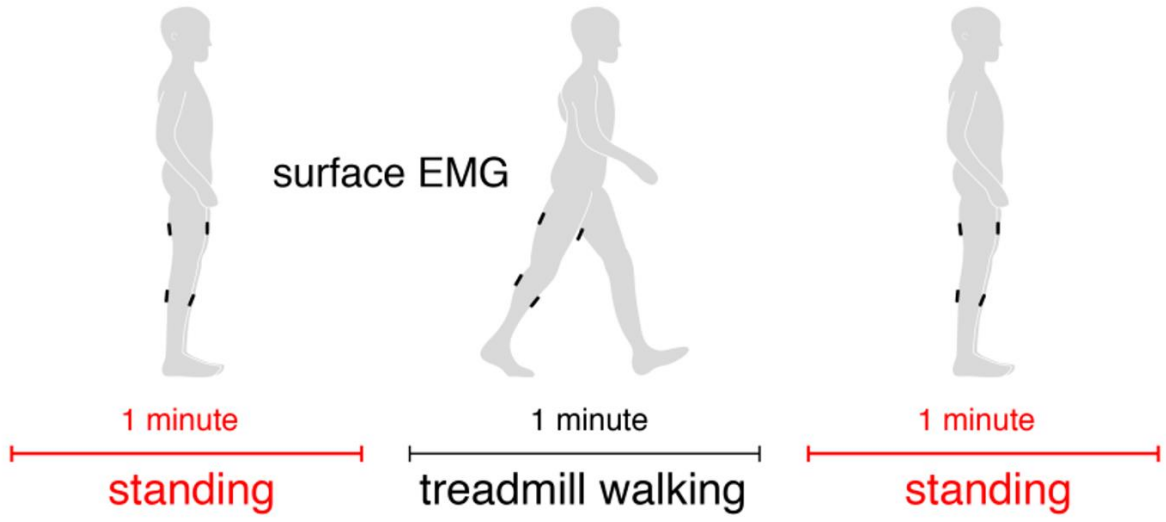

Abbildung 1: Übersicht der Methodik der Laufbanduntersuchung
Patienten wurden instruiert für je eine Minute zu stehen, zu gehen und erneut zu stehen, während über Oberflächenelektroden an vier Muskeln der orthostatische Tremor mittels EMG abgeleitet wurde. Die Phasenabhängigkeit und spatiotemporale Gangparameter wurden mit Hilfe eines drucksensitiven Laufbands untersucht.

In dieser Studie wurden neun Patienten mit primärem orthostatischem Tremor und neun gesunde Kontrollen untersucht. Die Diagnose des orthostatischen Tremors wurde durch die klinische Präsentation und Messung des hochfrequenten Tremors mittels EMG bestätigt. Auf

einem drucksensitiven Laufband (Zebris®, Isny, Deutschland; h/p/cosmos®, Nussdorf-Traunstein, Deutschland) wurden Patienten instruiert für je eine Minute zu stehen, unter langsamer oder mittlerer Geschwindigkeit zu gehen und erneut zu stehen. Während der Untersuchung wurde kontinuierlich die Tremoraktivität mit Hilfe einer Oberflächen-EMG-Messung an vier verschiedenen Muskeln des dominanten Beins überwacht. Zudem wurden mit Hilfe der Laufbandmessung spatiotemporale Gangparameter zur Charakterisierung des Gangmusters erhoben (siehe Abbildung 1).

In der Patientengruppe wurde während des Stehens ein hochfrequenter Tremor in allen Muskelgruppen abgeleitet (mittlere Frequenz 15,29±0,17 Hz, mittlere Kohärenz 0,75±0,02), der mit dem Gefühl einer posturalen Unsicherheit einherging. Die Patienten berichteten über einen Rückgang der Symptome beim Gehen, wohingegen der Tremor persistierte mit einer Verlagerung hin zu höheren Frequenzen (16,34±0,25 Hz; $p<0,001$, siehe Abbildung 2). Die Tremorintensität zeigte sich phasenabhängig moduliert und war vor allem in den Standphasen präsent, jedoch nahezu vollständig rückläufig während der Schwungphasen des Gehens ($p<0,001$, siehe Abbildung 3). Die Tremorintensität korrelierte zudem mit der Bodenreaktionskraft, die beim Gehen durch die Patienten ausgeübt wurde ($p<0,001$). Diese Effekte waren in beiden Ganggeschwindigkeiten und allen Muskelgruppen zu beobachten. Weiterhin waren bei den Patienten sowohl die Spurbreite ($p=0,019$) als auch die Schrittzyklusfluktuationen ($p=0,002$) während des Gehens im Vergleich zur Kontrollgruppe erhöht.

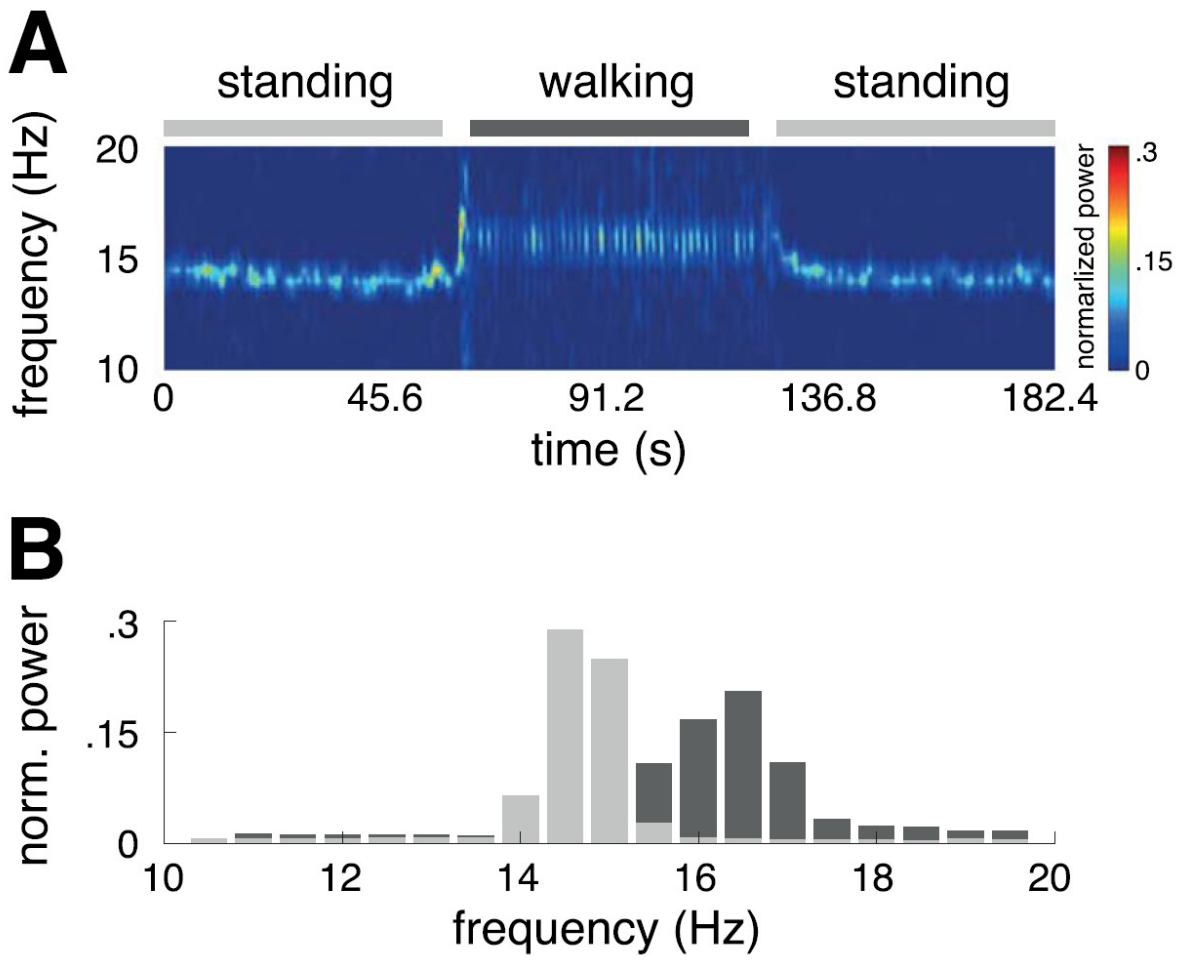

Abbildung 2: Vergleich der Aktivität des orthostatischen Tremors während des Stehens und Gehens[18]
Der Tremor persistiert nach Ganginitiation mit unmittelbarer Verlagerung der Tremorfrequenz zu höheren Frequenzbereichen. Nach Terminierung der Gangaktivität kehrt der Tremor zur Ausgangsfrequenz zurück. Creative Commons Attribution 4.0 International (CC BY 4.0), https://creativecommons.org/licenses/by/4.0/.

Eine analoge Modulation der Tremorfrequenz während Willkürbewegungen wurde bereits bei anderen zentralen Tremorformen im Zusammenhang mit Parkinsonerkrankungen oder dem essentiellen Tremor beschrieben. Diese Modulation wurde als Hinweis auf eine nicht-lineare Interaktion zwischen dem Tremoroszillator und den rhythmisch-motorischen Signalen der Willkürbewegung gedeutet[21]. Entsprechend kann die Tremorveränderung beim OT bedingt sein durch eine Interferenz des Tremors mit a) einer propriozeptiv-afferenten Rückkopplung, b) einer spinalen oder c) einer supraspinalen Lokomotoraktivität. Die ersten beiden Möglichkeiten sind unwahrscheinlich, da in anderen Studien weder eine periphere

Nervenstimulation noch eine Rückenmarkstimulation zu einer Veränderung des OT-Rhythmus führte[13,22,23]. Es gibt jedoch Evidenzen, die die letzte Möglichkeit stützen: (1) eine elektrische Stimulation über der posterioren Fossa führte in früheren Untersuchungen zu einer Rücksetzung des Tremors[23]; (2) supraspinale Lokomotionsareale decken sich zum großen Teil mit dem ponto-zerebello-thalamo-kortikalen Netzwerk des OT[16,17,24]; (3) zerebelläre Lokomotionsareale weisen eine Schrittmacheraktivität auf[25,26]. Auf Grundlage dieser Beobachtungen wird die Tremormodulation während des Gehens am wahrscheinlichsten durch eine nicht-lineare Interferenz zwischen der Tremoraktivität und den oszillatorischen, supraspinalen Lokomotorarealen verursacht.

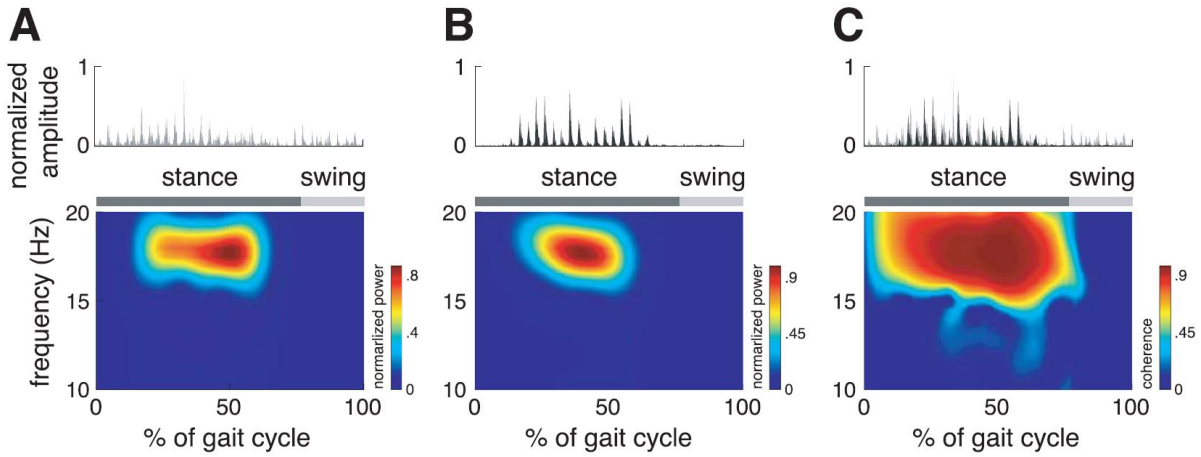

Abbildung 3: Phasenabhängige Modulation der Tremorfrequenz innerhalb des Gangzyklus[18]
EMG-Aufnahmen und korrespondierende Zeit-Frequenz-Repräsentationen der Tremorintensität in (A) Musculus gastrocnemius, (B) Musculus vastus medialis und (C) Kohärenz dieser zwei Muskeln. Die Tremoraktivität ist phasenabhängig, insbesondere während der Standphasen vorhanden und regredient während der Schwungphasen des Schrittzyklus. Creative Commons Attribution 4.0 International (CC BY 4.0), https://creativecommons.org/licenses/by/4.0/.

Die Tremorintensität zeigte sich phasenabhängig moduliert während des Gangzyklus und war unterschiedlich stark ausgeprägt in Abhängigkeit der Belastungsstärke der Muskeln. Diese Beobachtungen deuten zusammen mit vorhergehenden Studienergebnissen darauf hin, dass die periphere Manifestation des Tremormusters durch spinale Interneuron-Verschaltungen moduliert wird[27,28]. Die beobachteten Gangveränderungen bei Patienten mit OT werden im Nachfolgenden näher beleuchtet.

Die Gangstörung bei Patienten mit orthostatischem Tremor

Im Rahmen dieser Studie wurden 18 Patienten mit primärem OT (mittleres Alter 70,5±5,9 Jahre, 10 Frauen) und 18 altersgleiche, gesunde Probanden untersucht. Alle Patienten führten eine standardisierte, klinisch-apparative Ganganalyse auf einer drucksensitiven Gangmatte durch (GAITRite®, CIR Systems, Franklin, NJ, USA). Die Patienten gingen unter sieben verschiedenen sensomotorischen und kognitiven Gangbedingungen: Gehen mit selbstgewählter, langsamer und maximaler Geschwindigkeit, Gehen unter Kopfreklination sowie Augenschluss und während eines kognitiven und motorischen „Dual Tasks". Folgende spatiotemporale Gangparameter wurden erhoben: mittlere Ganggeschwindigkeit (cm/s), Schrittlänge (cm), Schrittdauer (s), Anteil der Doppelstandphasen (%), Schwungphasen (%), Spurbreite (cm) sowie mehrere Variabilitätsmarker für Schrittlänge, Schrittdauer und Spurbreite gemessen anhand des Variabilitätskoeffizenten („coefficient of variation", CV). Es erfolgte zudem eine standardisierte klinisch-neurologische Untersuchung mit Erhebung von weiteren klinischen Scores wie dem „Activities-specific Balance Confidence Scale" (ABC) und dem „Falls Efficacy Scale-International" (FES-I) sowie einer ausführlichen Sturzanamnese.

Eine Übersicht der Gangveränderungen über verschiedene Gangkonditionen hinweg ist in Abbildung 4 und 5 präsentiert. Die Patienten mit OT zeigten bereits während der selbstgewählten Ganggeschwindigkeit eine deutliche Gangstörung mit vergrößerter Spurbreite ($p=0,018$) und erhöhter Gangvariabilität ($p=0,010$). Die Ganggeschwindigkeit war moderat reduziert ($p=0,026$) mit einer verkürzten Schrittlänge ($p=0,001$) und verlängerten Doppelstandphasen ($p=0,001$). Die Gangveränderungen verschlechterten sich während des langsamen Gehens ($p=0,001$), unter Augenschluss sowie während des kognitiven Dual Tasks ($p<0,001$). Eine Verbesserung zeigte sich jedoch bei schnelleren Ganggeschwindigkeiten.

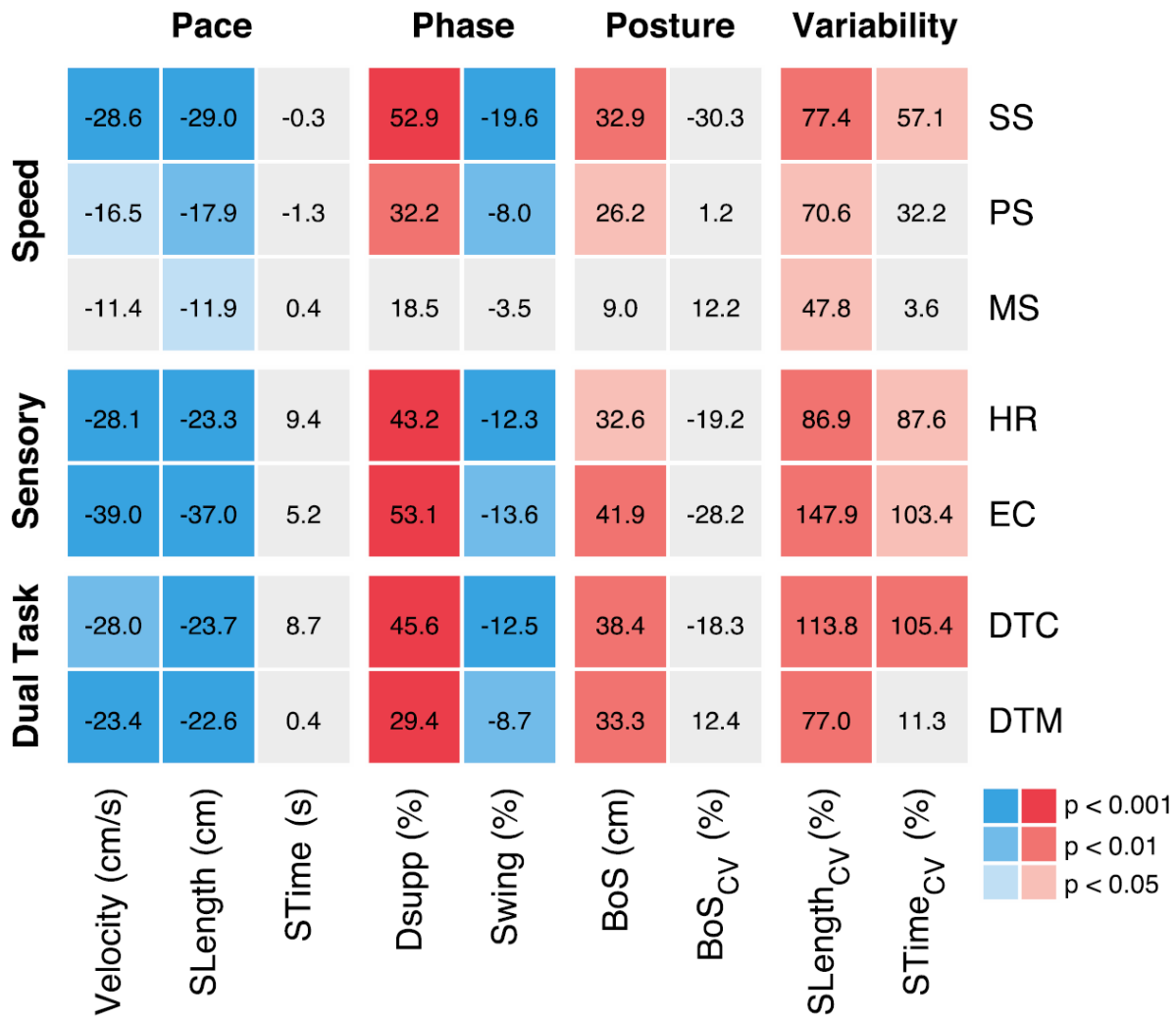

Abbildung 4: Übersicht der spatiotemporalen Gangparameter und Gangeinschränkungen bei Patienten mit orthostatischem Tremor[19]

Das Gangmuster von Patienten mit orthostatischem Tremor ist im Vergleich zu gesunden Probanden bei verschiedenen Geschwindigkeiten sowie bei sensorischen und Dual Task-Konditionen dargestellt (Reihen). Spatiotemporale Gangparameter wurden gruppiert in vier funktionelle Gangdomänen: Tempo („Pace“), Phase („Phase“), Haltung („Posture“) und Variabilität („Variability“). Die Nummer in jeder Kachel repräsentiert die mittlere prozentuale Abweichung der Gangleistung der Patienten im Vergleich zu den gesunden Kontrollen. Farblich markiert sind die signifikanten Abweichungen der Werte nach oben (rot) oder unten (blau) im Vergleich zur gesunden Kontrollgruppe, je dunkler die Farbe, desto signifikanter ist die Abweichung. Creative Commons Attribution 4.0 International (CC BY 4.0), https://creativecommons.org/licenses/by/4.0/. *Abkürzungen: SLength Schrittlänge, STime Schrittdauer, Dsupp Anteil der Doppelstandphasen, Swing Anteil der Schwungphasen, BoS Spurbreite, CV Variabilitätskoeffizient, SS langsames Gehen, PS selbstgewählte Geschwindigkeit, MS maximale Ganggeschwindigkeit, HR Kopfreklination, EC Augenschluss, DTC kognitiver Dual Task, DTM motorischer Dual Task.*

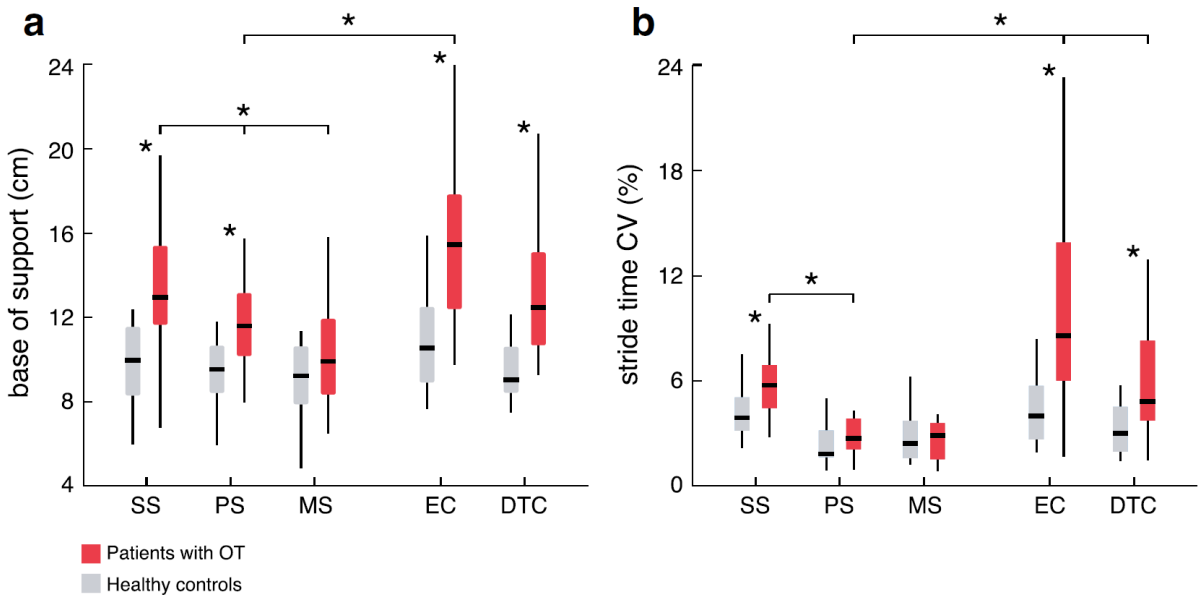

Abbildung 5: Veränderung das Gangmusters bei verschiedenen Gangkonditionen[19]
Veränderung der (a) Spurbreite und (b) Schrittzyklusvariabilität sind abgebildet für Patienten mit orthostatischem Tremor (rot) und gesunde Probanden (grau) in Abhängigkeit der Ganggeschwindigkeit (SS, PS, MS) und während des Gehens unter Augenschluss (EC) sowie beim kognitiven Dual Task (DTC). Die Markierung mit * entspricht einem signifikanten Unterschied ($p<0,05$). Creative Commons Attribution 4.0 International (CC BY 4.0), https://creativecommons.org/licenses/by/4.0/. *Abkürzungen: CV Variabilitätskoeffizient, SS langsame Geschwindigkeit, PS selbstgewählte Geschwindigkeit, MS maximale Geschwindigkeit, EC Augenschluss, DTC kognitiver Dual Task.*

Die Verlangsamung der Ganggeschwindigkeit, die vergrößerte Spurbreite sowie erhöhte Schrittvariabilität sind allesamt Indikatoren einer gestörten dynamischen Stabilität mit einem erhöhten Risiko für Stürze[27,29,30]. Passend dazu gab auch ein Drittel der Patienten ein Sturzereignis während der letzten 6 Monate an. Das breitbasige Gangmuster sowie die erhöhten Gangfluktuationen finden sich häufig im Rahmen von Gangstörungen bei sensorisch- oder zerebellär-ataktischen Syndromen[31-33]. Analoge klinische Beobachtungen wurden in einer kürzlich veröffentlichten Arbeit zum OT berichtet[34]. Die klinischen Zeichen für eine zerebelläre Beeinträchtigung in unserer Patientenkohorte deckten sich mit vorherigen Berichten[17,35]. Zudem wurde der OT bereits in früheren Studien immer wieder mit zerebellären Defiziten in Verbindung gebracht[36-38]. Alternativ könnte auch eine Störung der propriozeptiven Wahrnehmung der unteren Extremität verantwortlich sein für die Gangveränderung. Diese Vermutung wird durch klinische Zeichen für ein propriozeptives Defizit (Pallhypästhesie,

auffälliger Romberg-Test) sowie durch die beobachtete Verbesserung des Gangmusters bei schnelleren Ganggeschwindigkeiten unterstützt[32,39]. Eine Verbesserung der Gangstörung bei schnellem Gehen ist jedoch nicht spezifisch für ein peripher-sensorisches Defizit, sondern lässt sich auch im Zusammenhang mit zentralen Gangstörungen (wie z.B. beim Downbeat-Nystagmus-Syndrom mit einer gestörten zentral-vestibulären Integration) beobachten[40,41]. Schließlich deutet die Verschlechterung im kognitiven Dual Task auf mögliche motorisch-kognitive Verarbeitungsdefizite hin, passend zu den gestörten funktionellen fronto-zerebellären Defiziten beim orthostatischen Tremor[42,43].

Zusammenfassend lassen sich die Gangveränderungen beim orthostatischen Tremor im Rahmen einer komplexen Netzwerkdysfunktion mit Beteiligung sensomotorischer, zerebellärer und fronto-kortikaler Kontrollzentren erklären[17].

Reduktion der Symptome durch propriozeptive Muskelsehnenstimulation

In dieser Studie wurde der Effekt einer bilateralen, kontinuierlichen, niedrigschwelligen Muskelsehnenvibration (MTV) mit 50 Hz an der Sehne des Musculus soleus auf die Symptome bei neun Patienten mit OT untersucht. Die Patienten durchliefen vier Untersuchungsbedingungen: Stehen mit und ohne MTV, Liegen mit und ohne MTV. Der Tremor wurde mittels Oberflächen-EMG abgeleitet und die Körperschwankungen („Body Sway“) während des Stehens mittels Posturographie aufgezeichnet.

Während des Stehens war ein kohärenter, hochfrequenter Tremor in allen Beinmuskeln und in den Körperschwankungen entlang der z-Achse festzustellen (mittlere Frequenz 15,1 Hz, Spannweite 13,5-17,5 Hz), der im Liegen sistierte ($p<0,001$). Mittels MTV im Stehen zeigte sich keine Veränderung der Tremorfrequenz, jedoch eine Reduktion der Tremorintensität in allen Muskeln von durchschnittlich 32,5 ± 7,1% ($p<0,001$) mit moderat reduzierter Tremorkohärenz (Reduktion 5,6±1,7%, $p<0,001$, siehe Abbildung 6). Weiterhin kam es zu

einer Reduktion der Körperschwankungen in der Posturographie (mittlere Reduktion 37,2±6,8%, p=0,032). Bei 44,4% der Patienten kam es zu einer subjektiven Verbesserung der Symptome und Standunsicherheit, kein Patient gab eine Verschlechterung durch die MTV an. Im Liegen führte die MTV zu keiner Veränderung der Muskelaktivität.

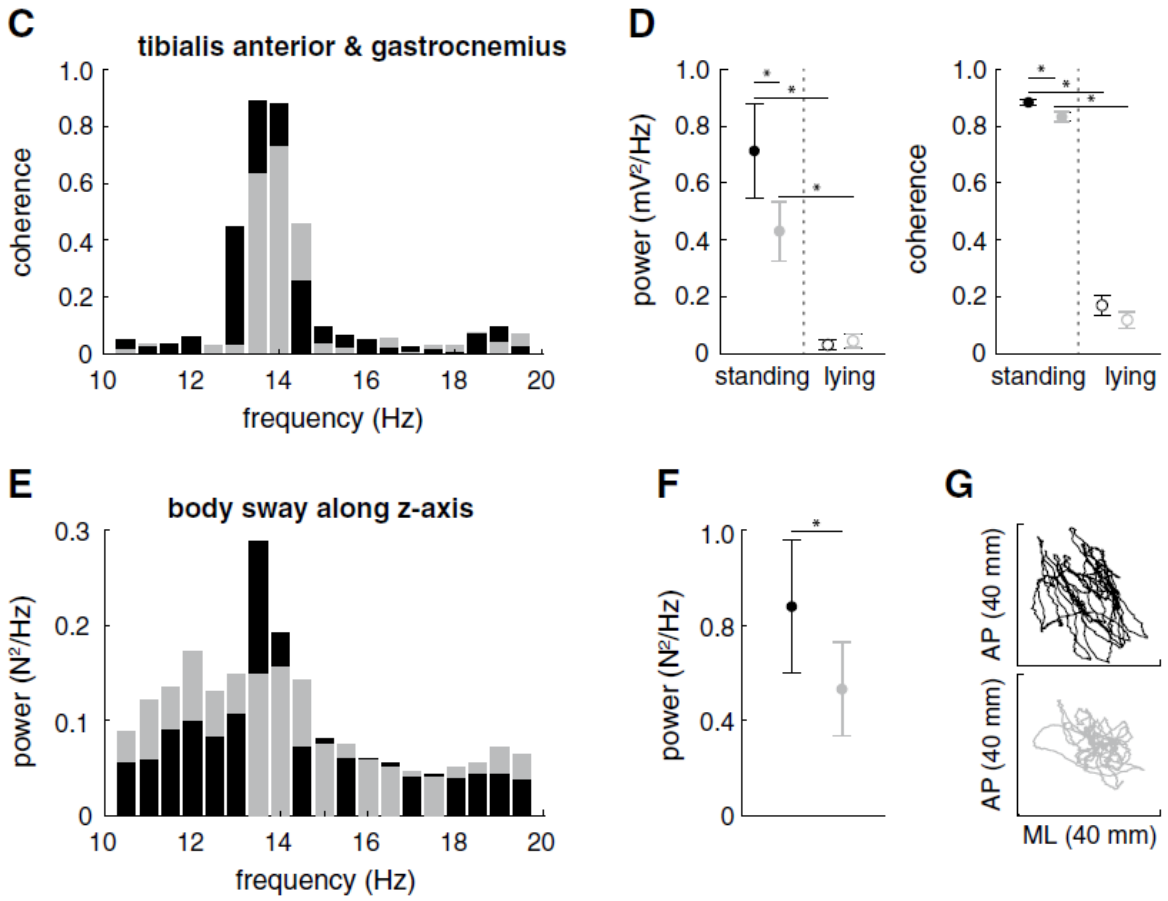

Abbildung 6: Effekt der propriozeptiven Muskelsehnenstimulation (MTV) beim orthostatischen Tremor auf die Tremorcharakteristika und Körperschwankungen mit Abbildung der Powerspektren[20]

(C) Kohärenz und Frequenzen in den Musculus tibialis anterior- und Musculus gastrocnemius-Muskelgruppen während des Stehens ohne (schwarz) und mit MTV (grau). (D) Gruppeneffekte der MTV auf die Tremorintensität und inter-muskuläre Kohärenz beim Stehen und Liegen. (E) Powerspektren der Körperschwankungen in der z-Achse beim Stehen ohne (schwarz) und mit MTV (grau). (F) Gruppeneffekt der MTV auf Körperschwankungen. (G) Exemplarische Körperschwankungstrajektorien ohne und mit MTV in den anterior-posterior (AP) und medio-lateral (ML)-Ebenen. Eine Markierung mit * entspricht einem signifikanten Unterschied (p<0,05).

Passend zu zuvor berichteten Untersuchungen einer peripheren Stimulation beim orthostatischen Tremor kam es zu keiner Veränderung der Tremorfrequenz[22,23], jedoch zu einer objektiven wie subjektiven Verbesserung der Tremorintensität und Körperschwankungen, wohingegen es bei gesunden betagten Personen bei peripheren Vibrationsreizen zu einer Verschlechterung der posturalen Kontrolle kommen kann[44]. Sowohl Golgi-Sehnenorgane mittels Nervenfasern der Klasse Ib als auch Muskelspindelafferenzen können durch MTV-Stimulation moduliert werden[23,45], sodass dieser direkte Einfluss die periphere Tremormanifestation beeinflussen könnte. Des Weiteren gibt es Hinweise, dass nach Initiation des Tremors die periphere, propriozeptive Rückkopplung zunehmend mit der Tremorfrequenz synchronisiert wird[16,46]. Dieser Effekt könnte die physiologischen, peripheren Rückkopplungsmechanismen außer Kraft setzen und die Kokontraktion der Haltungsmuskulatur erhöhen, was zu einem Teufelskreis mit stetig zunehmender subjektiver und objektiver Standunsicherheit führen würde[46]. Die kontinuierliche MTV könnte einen Bestandteil des Mechanismus unterbrechen und somit zu einer Symptomlinderung führen – ähnlich wie die Verbesserung der Symptome bei Ganginitiation[18,22].

Bei vielen Patienten mit orthostatischem Tremor sind die medikamentösen Therapieoptionen limitiert[4,8], alternative operative Behandlungsoptionen mittels tiefer Hirn- oder Rückenmarkstimulation zeigen erste vielversprechende Ergebnisse[15,47], müssen jedoch in weiteren klinisch-kontrollierten Studien mit größerer Fallzahl untersucht werden. Die Modulation des Tremors durch einen Muskelsehnenstimulus könnte somit eine weitere nicht-invasive Therapieoption für diese Erkrankung darstellen.

2 Zusammenfassung

Der primäre orthostatische Tremor ist eine seltene Erkrankung, die einen hochfrequenten Tremor von 13-18 Hz der unteren Extremität beim Stehen aufweist mit einer Symptomlinderung beim Sitzen, Gehen oder Hinlegen. Der Erkrankung liegt ein pathologisches, ponto-zerebello-thalamo-kortikales Tremornetzwerk zugrunde, das auch im Liegen weiter aktiviert bleibt. Im Zusammenhang mit dieser Erkrankung befasst sich diese Dissertation mit folgenden Fragestellungen:

1) Wie verändert sich der Tremor bei der Transition vom Stehen zum Gehen?

2) Gibt es eine objektivierbare Gangstörung trotz subjektiver Symptomregredienz beim Gehen?

3) Kann der Tremor durch propriozeptive Reize moduliert und gegebenenfalls gelindert werden?

In einer klinischen Untersuchung mittels eines drucksensitiven Laufbands und Oberflächen-Elektromyographie konnte gezeigt werden, dass der Tremor während des Gehens persistiert mit einer zwischenzeitlichen Verlagerung der Tremorfrequenz in höhere Frequenzbereiche. Die Tremorintensität zeigte sich zudem abhängig vom Gangzyklus und der muskulären Belastung während des Gehens. Diese Beobachtungen legen nahe, dass es zu einer Interaktion zwischen dem orthostatischen Tremor und oszillatorischen, supraspinalen Lokomotionsarealen kommt und dass die periphere Manifestation des Tremors durch spinale Interneuron-Verschaltungen moduliert wird.

Mittels einer multimodalen, klinisch-apparativen Ganguntersuchung wurden spatiotemporale Gangparameter bei Patienten mit orthostatischem Tremor erhoben, die mit einer altersgleichen, gesunden Kohorte verglichen wurde. Patienten mit orthostatischem Tremor zeigten ein

breitbasiges Gangmuster mit erhöhter Gangvariabilität. Das Gangmuster verschlechterte sich beim langsamen Gehen und unter Augenschluss passend zu einer ataktischen Gangstörung mit sensorischen- und/oder zerebellären Defiziten. Eine weitere Aggravation in der kognitiven Dual Task-Bedingung offenbarte zudem motorisch-kognitive Defizite der Patienten. Somit scheint beim orthostatischen Tremor eine komplexe Netzwerkerkrankung mit einer spezifischen spino-zerebello-frontokortikalen Gangstörung vorzuliegen.

Schließlich wurde in Folge einer kontinuierlichen Muskelsehnenvibrationsstimulation der unteren Extremitäten bei Patienten mit orthostatischem Tremor eine Reduktion der Tremorintensität und Körperschwankungen beobachtet. Bei bislang limitierten medikamentösen und invasiven Behandlungsmöglichkeiten bietet diese Beobachtung Hoffnung auf eine neue, nicht-invasive Therapieoption für Patienten mit orthostatischem Tremor.

Summary

Primary orthostatic tremor is a rare disorder with high-frequency (13-18 Hz) leg muscle contractions during standing with relief of symptoms while sitting, walking, and lying. Recent studies found a specific ponto-cerebello-thalamo-cortical tremor network with persisting activity during lying. The aim of this dissertation was to answer following questions:

1) How does the tremor change in response to the transition from standing to walking?

2) Is orthostatic tremor associated with a specific gait disorder despite patients' sensation of symptom relief while walking?

3) Can the tremor be modulated through a non-invasive proprioceptive stimulation?

In a first study, we examined the tremor of patients with orthostatic tremor during standing and walking conditions on a pressure-sensitive treadmill by means of surface electromyography of different leg muscles. We found that the tremor persisted during walking. Directly after gait initiation, the tremor frequency was shifted towards higher frequencies, but returned to the initial frequency after gait termination. While walking, the tremor was modulated in dependence of the gait cycle and individual exerted muscle forces. These observations point to a non-linear interference between the tremor and the oscillatory activity in supraspinal locomotor areas; furthermore, they indicate that the peripheral manifestation of the tremor is likely modulated by spinal interneuron connections.

In a second study, we performed a multi-conditional, instrument-based gait assessment in patients with orthostatic tremor and age-matched healthy controls. Patients showed a broad-based walking pattern with increased gait variability with aggravation during slow walking

modes and while walking with eyes closed. These gait alterations resemble an ataxic gait disorder indicative of sensory and/or cerebellar deficits. In addition, patients' walking performance deteriorated during a cognitive dual task paradigm pointing to a motor-cognitive dysfunction. Overall, the gait impairment in orthostatic tremor manifests in a specific spino-cerebello-frontocortical gait disorder.

In a third study, we examined the effects of a proprioceptive leg muscle stimulation via muscle tendon vibration in patients with orthostatic tremor. We found that this stimulation yielded a reduction of tremor intensity and postural sway. In the light of currently limited pharmacological and invasive treatment options for orthostatic tremor, the observations of this study might pave the way for a new, non-invasive treatment option for patients.

3 Publikationen

Fundstellen

Publikation I

Walking in orthostatic tremor modulates tremor features and is characterized by impaired gait stability

Max Wuehr, Cornelia Schlick, **Ken Möhwald**, Roman Schniepp

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Publikation II

The gait disorder in primary orthostatic tremor

Ken Möhwald, Max Wuehr, Fabian Schenkel, Katharina Feil, Michael Strupp, Roman Schniepp

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Publikation III

Proprioceptive muscle tendon stimulation reduces symptoms in primary orthostatic tremor

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zusätzliche relevante Publikationen

Gait ataxia in humans: vestibular and cerebellar control of dynamic stability

Roman Schniepp, **Ken Möhwald**, Max Wuehr.

Journal of Neurology 264.1 (2017): 87-92.

Mustererkennung in der Analyse von Gangstörungen.

Ken Möhwald, Max Wuehr, Roman Schniepp

Journal: NeuroTransmitter 5 (2017): 40-49.

Key gait findings for diagnosing three syndromic categories of dynamic instability in patients with balance disorders

Roman Schniepp, **Ken Möhwald**, Max Wuehr.

Journal of Neurology 267.1 (2020): 301-308.

Kongress- und Fortbildungsbeiträge zum Thema:

91. Kongress der Deutschen Gesellschaft für Neurologie, Neurowoche | Berlin, 2018

Vortrag: Modulation der sensorischen Rückkopplung als Therapieansatz beim orthostatischen Tremor - **Ken Möhwald**

Open Stage: Neuroscience – Tremorerkrankungen: von der Pathophysiologie zur Therapie

62. Wissenschaftliche Jahrestagung der Deutschen Gesellschaft für Klinische Neurophysiologie und Funktionelle Bildgebung (DGKN) | Berlin, 2018

Vorsitz Symposium: Orthostatischer Tremor – Neues zur Pathophysiologie, Symptomatik und Neuromodulation - **K. Möhwald** (München), M. Muthuraman (Mainz)

Vortrag: Der orthostatische Tremor – wichtige Aspekte für die klinische Praxis - **K. Möhwald**

Poster: Gait disturbance in patients with orthostatic tremor - **K. Möhwald**, M. Wuehr, K. Feil, F. Schenkel, C. Schlick, K. Jahn, M. Dieterich, T. Brandt, R. Schniepp

World Congress der International Society of Posture & Gait Research (ISPGR) | Fort Lauderdale, Florida, USA, 2017

Vortrag: Gait disturbance in patients with orthostatic tremor assessed by sensory-motor and cognitive gait analysis **- K. Möhwald**

Vertigo 21 - Periphere, zentrale und funktionelle Schwindelsyndrome: Grundlagen und Aktuelles | Fortbildung des Deutsches Schwindel- und Gleichgewichtszentrums (DSGZ) und der Neurologischen Klinik und HNO-Klinik, Klinikum der Universität München, Campus Großhadern | München, 2017

Vortrag: Videoquiz 3 zum orthostatischen Tremor - **Ken Möhwald**

Third International Master Class of the German Center for Vertigo and Balance Disorders and the European Dizzynet, Diagnosis and treatment of peripheral, central and functional vestibular disorders | University Hospital Munich | München, 2017

Vortrag: Videoquiz 1 zum orthostatischen Tremor - **Ken Möhwald**

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Urheberrechtslizenzen

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Publikation III

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Proprioceptive muscle tendon stimulation reduces symptoms in primary orthostatic tremor

Max Wuehr, Cornelia Schlick, Ken Möhwald, Roman Schniepp, Copyright 2018

SCIENTIFIC REPORTS

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Walking in orthostatic tremor modulates tremor features and is characterized by impaired gait stability

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M. Wuehr[1], C. Schlick[1], K. Möhwald[1,2] & R. Schniepp[1,2]

Primary orthostatic tremor (OT) is characterized by high-frequency lower-limb muscle contractions and a disabling sense of unsteadiness while standing. Patients consistently report a relief of symptoms when starting to ambulate. Here, we systematically examined and linked tremor and gait characteristics in patients with OT. Tremor and gait features were examined in nine OT patients and controls on a pressure-sensitive treadmill for one minute of walking framed by two one-minute periods of standing. Tremor characteristics were assessed by time-frequency analysis of surface EMG-recordings from four leg muscles. High-frequency tremor during standing (15.29 ± 0.17 Hz) persisted while walking but was consistently reset to higher frequencies (16.34 ± 0.25 Hz; $p < 0.001$). Tremor intensity was phase-dependently modulated, being predominantly observable during stance phases ($p < 0.001$). Tremor intensity scaled with the force applied during stepping ($p < 0.001$) and was linked to specific gait alterations, i.e., wide base walking ($p = 0.019$) and increased stride-to-stride fluctuations ($p = 0.002$). OT during walking persists but is reset to higher frequencies, indicating the involvement of supraspinal locomotor centers in the generation of OT rhythm. Tremor intensity is modulated during the gait cycle, pointing at specific pathways mediating the peripheral manifestation of OT. Finally, OT during walking is linked to gait alterations resembling a cerebellar and/or sensory ataxic gait disorder.

Primary orthostatic tremor (OT) is a unique clinical syndrome of unknown prevalence, characterized by a high-frequency pattern of coherent muscle contractions (13–18 Hz) in the lower limbs and trunk while standing[1–3]. The tremor is associated to the patient's intense sense of unsteadiness and dizziness. The exact pathophysiological mechanisms underlying primary OT remain unresolved. However, a central oscillatory ponto-cerebello-thalamo-cortical network has recently been identified in patients with OT[4,5].

Sitting or lying in OT typically lead to a complete relief of tremor activity and accompanying symptoms. During walking, most patients do not experience problems and report a profound relief of unsteadiness. However, patients in more advanced stages of the disease may face difficulties with tandem walking, walking slowly, or climbing stairs[6]. Furthermore, anecdotal reports in single patients with OT indicate that tremor activity may persist during walking[3,7,8]. However, it is hitherto unknown whether the ongoing tremor activity during ambulation is akin to that of standing or may exhibit specific changes with respect to frequency, intensity or coherence. It is further unclear whether OT during walking is linked to a specific gait disorder as observed in other types of tremor such as essential tremor[9]. Finally, it has to be resolved, why despite continuation of OT during walking, most patients consistently experience a substantial relief of subjective unsteadiness associated with activity.

To elucidate these questions, the present study systematically investigated the tremor activity and walking behavior of patients with OT. Tremor characteristics such as frequency, intensity, and coherence were evaluated by EMG-recordings during stance-walk and walk-stance transitions as well as for continuous steady-state walking. These findings were then linked to the walking performance of patients by simultaneous recordings of their spatiotemporal gait patterns.

[1]German Center for Vertigo and Balance Disorders, University Hospital, LMU Munich, Munich, Germany. [2]Department of Neurology, University Hospital, LMU Munich, Munich, Germany. Correspondence and requests for materials should be addressed to M.W. (email: Max.Wuehr@med.uni-muenchen.de)

Patient	Sex	Age (years)	Tremor frequency (Hz)	Duration (years)	Medication	Neurological findings
1	m	62	14.5	1	no	1, 4
2	f	55	14	5	Gabapentin 1200 mg/d	1
3	m	75	17.5	10	no	1, 2, 4
4	m	75	14	14	Clonazepam 1 mg/d	1, 2, 3, 4
5	f	56	17	5	no	1
6	f	75	16.5	6	no	1, 2, 3, 4
7	f	66	14	13	no	1, 2, 4
8	m	75	13.5	4	Gabapentin 600 mg/d	1, 4
9	m	76	15	3	Levodopa/Benserazid 300/75 mg/d	1

Table 1. Patient characteristics including neurological findings and medication. f = female; m = male; neurological findings: 1 = postural instability, 2 = dysmetria, dysdiadochokinesia or intention tremor upper limbs (uni- or bilateral), 3 = dysmetria lower limbs (uni- or bilateral), 4 = diminished ankle reflexes and/or reduced vibration sense.

Methods

Standard protocol approvals, registrations, and patients consent. The study protocol has been approved by the Ethics Committee of the University of Munich and was registered (DRKS00012907). All procedures were in accordance with the Helsinki declaration and patients gave their written informed consent.

Subjects. Nine patients with primary OT (mean age 68.3 ± 8.7 years, four females) and nine healthy controls (mean age 66.2 ± 4.8 years, four females) participated in the study (detailed patient characteristics are presented in Table 1). Definite diagnosis of OT was made by surface EMG-recording exhibiting a coherent tremor between homologous leg muscles within a frequency range of 13–18 Hz. Patients underwent a standardized neurological examination to exclude additional signs indicative of a secondary OT (i.e., hypokinesia, rigidity, dystonia, failure of gait initiation).

Procedures. Walking performance of patients and controls was examined for 60 s at slow (0.42 m/s) and medium (0.84 m/s) gait speed on a pressure-sensitive treadmill (Zebris®, Isny, Germany; h/p/cosmos®, Nussdorf-Traunstein, Germany; 1.6 m long with a sampling rate of 100 Hz) in a randomized order[10]. Both walking trials were preceded and followed by 60 s periods of standing. Acceleration and deceleration periods to reach continuous walking speed or rest position had a duration of 1.2 s for slow and 2.0 s for fast speed, resulting in a total trial duration of 182.4 s and 184.0 s respectively. Each trial was started after an initial 15 s period of standing, i.e., when the high-frequency pattern of leg muscle contractions became visible in all patients.

Surface EMG activity during standing and walking in patients and controls was recorded with Ag/AgCl electrodes simultaneously from the tibialis anterior, gastrocnemius, biceps femoris and vastus medialis muscles of the dominant leg side using a Zebris DAB-Bluetooth device (Zebris®, Isny, Germany) at 1000 Hz. EMG signals were amplified, bandpass-filtered at 10–100 Hz and full-wave rectified. To reduce the inter-individual variability of the EMG recordings, EMG signals were further normalized to the peak EMG from the respective muscle during the two walking trials[11].

Data analysis. Tremor intensity and coherence between every combination of recorded muscle pairs were analyzed in three steps: (1) The average tremor characteristics were analyzed for the two standing and the in-between walking periods separately by spectral analysis using finite fast Fourier transform with a block size set to 2 s resulting in a frequency resolution of 0.5 Hz[12]. Furthermore, the average EMG level (aEMG) for the stance and walk periods was obtained by dividing the integrated EMG signal by the respective period duration[13]. (2) The time-dependent tremor behavior for the whole trial duration was assessed by time-frequency spectral analysis using short-time Fourier transform with a window length of 2 s overlapping by 0.05 s resulting in a frequency resolution of 0.5 Hz[14]. Time-dependent estimates of tremor intensity were used to calculate the tremor onset latency, i.e., the time required for the tremor after walking to regain the average intensity of the initial stance period. (3) Short-time Fourier transform was further used to examine the phase-dependent tremor behavior during the gait cycle according to a previously described procedure[15]: First, EMG signals were cut into strides synchronized to the right heel strike. Subsequently, short-time Fourier transform was used to compute the time-dependent auto- and cross-spectra for each stride cycle. To account for stride-to-stride variability, single-cycle auto- and cross-spectra were resampled to the average stride duration of the walking trial. Finally, power spectrum and coherence estimates were obtained by averaging across all stride cycles. The peak tremor intensity and coherence were calculated for the stance and swing phase of the gait cycle.

Walking performance for each trial was assessed by calculating the following gait cycle parameters: The mean and the coefficient of variation (CV) of stride length, stride time, and base of support as well as the percentage of swing and double support duration with respect to the total stride duration. The average force applied during walking was further assessed by dividing the integrated vertical ground reaction force (vGRF) by the total walking period duration. The average vGRF was further normalized to the individual body weight (BW) and expressed in %BW[16].

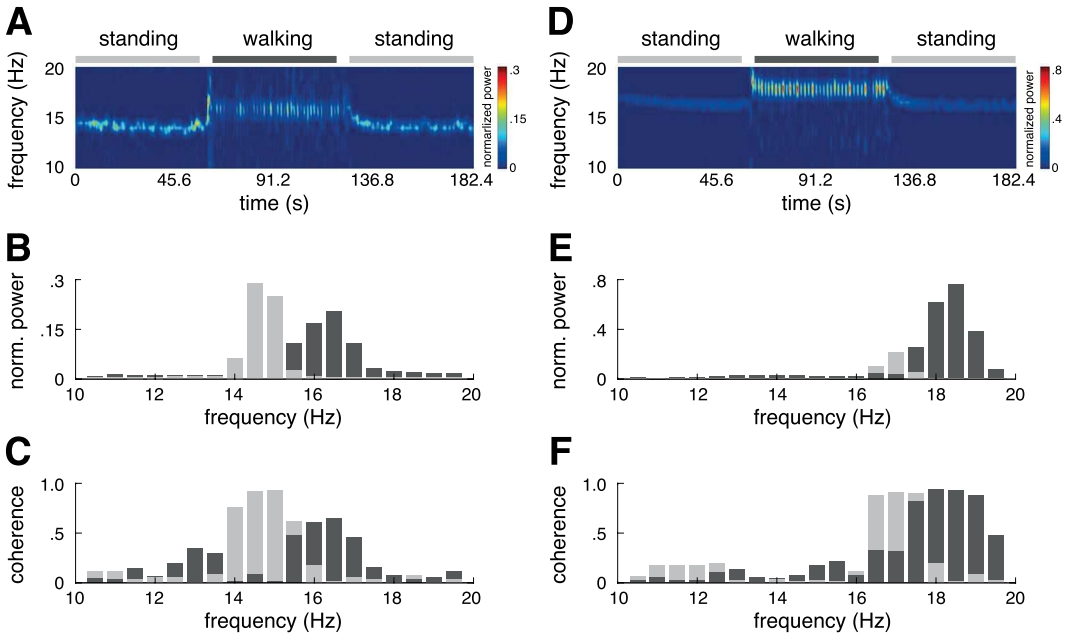

Figure 1. Comparison of orthostatic tremor activity during standing and walking. Exemplary time-frequency (upper panel) and frequency domain analysis (middle and lower panel) outcomes for two patients (left side: patient 1; right side: patient 5) (**A**,**D**). High-frequency contractions within the gastrocnemius are observable in both patients during the initial stance period. Tremor activity persist during walking but is shifted to a higher frequency range immediately after gait initiation. Tremor frequency returns to the default frequency right after gait termination (**B**,**E**). Changes in tremor intensity during walking show a high inter-individual variability, with an intensity reduction in patient 1 and a profound intensity increase in patient 5 (**C**,**F**). In contrast, tremor coherence (between gastrocnemius and vastus medialis) is only slightly affected by ambulation.

Statistical analysis. Data are reported as mean ± SEM. Activity effects on tremor frequency, intensity, and coherence were analyzed by repeated-measures analysis of covariance and Bonferroni post hoc analysis with group (OT vs. controls), gait speed (slow vs. medium), activity (standing vs. walking), and muscle type as factors and medication (yes vs. none) as covariate. Gait cycle phase effects on tremor intensity and coherence were analyzed correspondingly with gait speed, gait cycle phase (stance vs. swing period), and muscle type as factors and medication as covariate. Finally, alterations in gait performance were analyzed accordingly with group and gait speed as factors and medication as covariate. Pearson's correlations were performed to assess possible significant relations between on the one hand tremor characteristics during walking and on the other hand gait cycle parameters as well as vGRF and aEMG levels during walking. Results were considered significant at $p < 0.05$.

Results

During the initial standing period, all patients exhibited a coherent high-frequency tremor equally in all examined muscles (mean frequency: 15.29 ± 0.17, mean coherence: 0.75 ± 0.02, mean normalized power: 0.23 ± 0.03) and reported the concomitant symptoms of subjective unsteadiness and dizziness. In contrast, no control subject exhibited a coherent high-frequency tremor during standing or walking in the respective muscles ($p < 0.001$). While walking, all patients reported a relief of symptoms. However, EMG spectral analysis revealed that the tremor persisted during walking but was consistently reset to an even higher frequency (mean frequency: 16.34 ± 0.25; $p < 0.001$). This effect was equally found for both gait speeds and in all examined muscles. The reset tremor during walking was characterized by a decreased but still high inter-muscular coherence (mean coherence: 0.56 ± 0.03; $p < 0.001$) (Fig. 1). Changes in tremor intensity during walking showed a high inter-individual variability with an increase in intensity in four patients and a decrease in intensity in the remaining five patients (Fig. 2A).

Correlation analysis revealed that the tremor intensity during gait was highly associated to the patients' mode of walking, in particular the level of force production and muscle contraction during stepping (vGRF: $\rho = 0.295$, $p = 0.018$; aEMG: $\rho = 0.677$, $p < 0.001$; Fig. 2B). In turn, higher tremor intensities during walking had a negative impact on walking stability in terms of increased spatiotemporal gait variability (stride length CV: $\rho = 0.389$, $p = 0.002$; stride time CV: $\rho = 0.357$, $p = 0.004$; Fig. 2C) and a broadened walking base (base of support: $\rho = 0.292$, $p = 0.019$). This finding was also reflected in the comparison between gait patterns of patients with OT vs. healthy controls (Fig. 3). Patients walked with an increased spatiotemporal gait variability (stride length CV: $p = 0.009$; stride time CV: $p = 0.003$), which was only observable during slow walking and disappeared at faster locomotion. Furthermore, all analyzed gait parameter except base of support CV showed a clear speed dependency for both patients and healthy controls (swing percentage: $p < 0.001$; double support percentage: $p < 0.001$; stride length: $p < 0.001$; stride length CV: $p < 0.001$; stride time: $p < 0.001$; stride time CV: $p = 0.010$; base of support: $p = 0.006$).

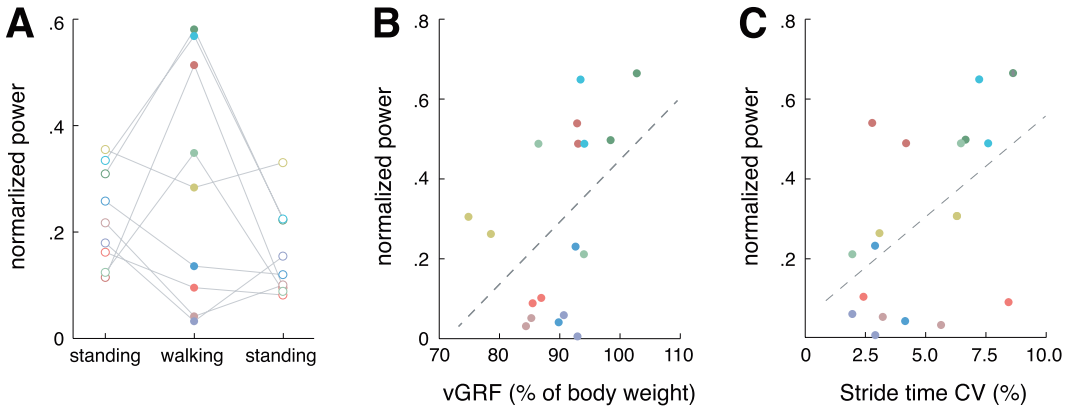

Figure 2. Relation of tremor intensity during walking to gait characteristics. (**A**) Changes in tremor intensity (average of the slow and fast walking trial) during walking compared to standing show a high inter-individual variability. (**B**) On the one hand, tremor intensity is associated to the force and muscle contraction levels applied during stepping. (**C**) On the other hand, high intensity of tremor activity during walking is accompanied by specific gait alterations, namely increased stride time and length variability and a broadened base of support. *vGRF = vertical ground reaction force*; *CV = coefficient of variation*.

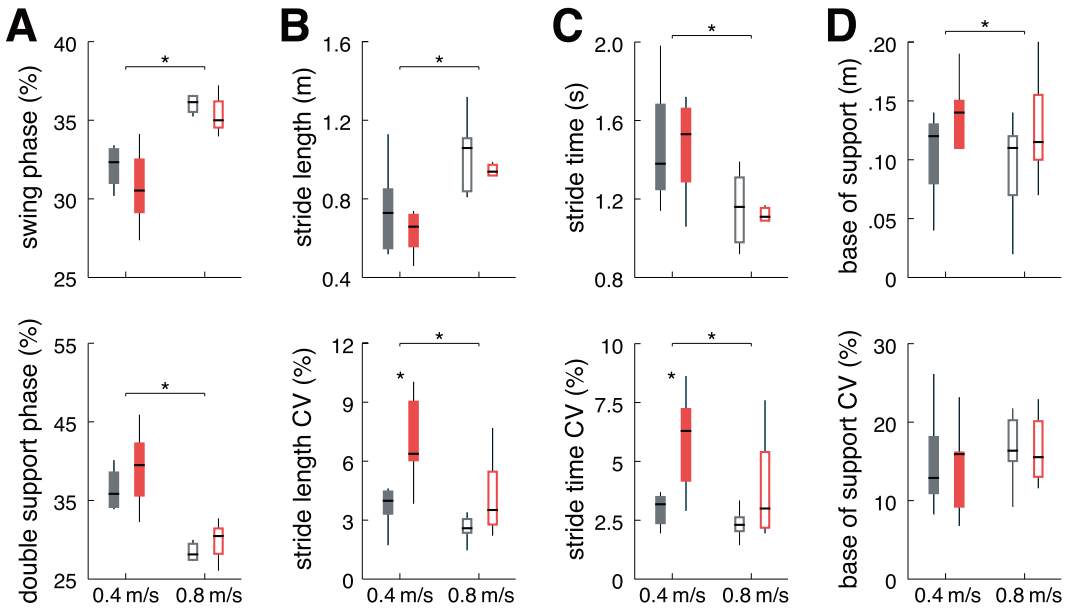

Figure 3. Walking characteristics of patients compared to healthy controls. Gait parameters of patients with OT (red) and healthy controls (gray) at slow (filled boxes) and medium walking speed (open boxes). (**A**) Gait cycle phase parameters, i.e., percentage of swing and double support phase. (**B**) Mean and variability magnitude of stride length. (**C**) Mean and variability magnitude of stride time. (**D**) Mean and variability magnitude of base of support. *Indicates a significant difference. *CV = coefficient of variation*.

Time-dependent tremor analysis within the gait cycle, revealed a persistent but phase-modulated pattern of high-frequency muscles contractions. Accordingly, tremor was predominantly observable during the stance phase (mean peak normalized power: 0.28 ± 0.04; mean peak coherence: 0.70 ± 0.02) but almost completely absent during the swing phase of walking (mean peak normalized power: 0.07 ± 0.01; mean peak coherence: 0.25 ± 0.02; $p < 0.001$). This effect was equal for both gait speeds and all examined muscles (Fig. 4).

After the walk-stance transition, the coherent tremor was found to be reset to the initially lower frequency (mean frequency: 15.35 ± 0.17 Hz, mean coherence 0.71 ± 0.02). However, the tremor showed a variable latency to reach the mean intensity level of the initial standing period (mean onset latency: 3.7 ± 0.9 s, range 0.1–37.9 s), resulting in a slightly decreased average intensity of the second stance period (mean normalized power: 0.16 ± 0.03). This effect was again equal for both gait speeds and all examined muscles. All of the observed effects were independent of the status of medication of patients.

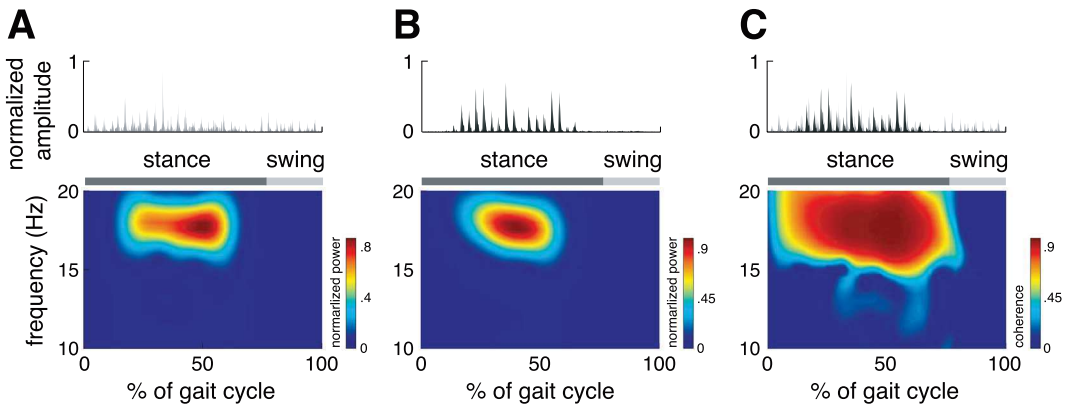

Figure 4. Phase-dependent modulation of tremor frequency within the gait cycle. Rectified EMG-traces and corresponding time-frequency representations (in dependence on the gait cycle phase) of tremor intensity in (**A**) the gastrocnemius and (**B**) the vastus medialis as well as of (**C**) tremor coherence between the two muscles. Tremor activity is phase-dependently modulated during the gait cycle being predominantly present during the stance phase and almost absent during the swing phase of the stride cycle.

Discussion

In the present study, we studied tremor activity during stance-walk transitions and continuous walking as well as gait performance in patients with OT. The main three findings were: (1) coherent high-frequency tremor bursts persist during walking but are shifted to a higher frequency range; (2) tremor intensity during walking is phase-dependently modulated and scales with the leg force levels applied during stepping; (3) intense tremor activity during walking is associated to specific gait alterations. In the following, these observations will be discussed with respect to their implications for the pathomechanism and the gait disorder in OT.

Although all patients consistently reported a relief of unsteadiness when starting to ambulate, tremor activity was found to persist while walking in accordance to previous reports[7,8]. The high inter-muscular coherence of tremor bursts during ambulation indicates that the tremor pattern is still governed by a supraspinal oscillatory source. However, immediately after gait initiation, the frequency of coherent muscle contractions was consistently shifted to a higher frequency range (average increase of 1.2 ± 0.1 Hz) compared to tremor frequency while standing. Tremor frequency shifts of similar order have been observed in other central tremor forms as Parkinson's disease or essential tremor in the presence of rhythmically paced voluntary limb movements[14]. In these cases, it was assumed that the modulation in tremor frequency might result from a nonlinear interaction between the tremor oscillator and the rhythmically paced motor commands. Accordingly, the tremor resetting during walking in OT could result from an interference of the default tremor pattern with either proprioceptive afferent feedback, spinal or supraspinal locomotor commands. The first two possibilities seem unlikely, as both peripheral nerve stimulation as well as spinal cord stimulation were found to not influence OT rhythm[7,17–19]. There is however evidence in favor of the third alternative in that OT frequency was found to be transiently reset by electrical stimulation over the posterior fossa[17]. Supraspinal locomotor areas in the cerebellum, thalamus, and motor cortex have a profound overlap with the ponto-cerebello-thalamo-cortical tremor network that was recently described in OT[4,5,20]. In particular cerebellar locomotor areas are known to exhibit oscillatory pacemaker activity for speed regulation during walking[21,22]. An interference of rhythmic activity in these areas with the default tremor activity appears therefore most likely to underlie the observed frequency modulation during walking in patients with OT.

Changes in tremor intensity during walking compared to standing showed a high inter-individual variability and proportionally scaled with leg muscle contraction intensity and the effective force levels applied during walking. Furthermore, tremor intensity during walking was intra-individually modulated in dependence on the gait cycle, being most prominent during the stance phase (i.e., in the presence of muscle contractions under load) and almost absent during the swing phase, when the leg was lifted off the floor. Taken together, these observations indicate that the central oscillatory pattern that appears to be active during symptomatic (i.e., standing) as well as non-symptomatic states (i.e., lying)[4] only manifests peripherally in muscles being contracted under load, i.e., during activation of Golgi tendon organ (GTO) afferents that directly project to Ib interneurons[23]. This in turn would suggest that the peripheral manifestation of OT does not occur via a direct projection of central oscillatory sources to spinal motoneurons, but is rather mediated via spinal interneurons that signal the loading state of respective muscles[17].

Intense OT activity during walking was further associated with specific gait alterations, namely a broadened base of support and high spatiotemporal gait fluctuations that were pathologically increased in particular during slow walking when compared to healthy controls. Both of these gait alterations are linked to an impaired regulation of dynamic gait stability and indicate an increased risk of falling[24–28]. Moreover, these gait impairments resemble the phenotype of either a cerebellar or a sensory ataxic gait, which are both characterized by a staggering wide based gait pattern especially at slow walking modes[27,29,30]. Signs for mild cerebellar motor abnormalities and a reduced vibration sense of the feet were frequently observed in our patients, in accordance to former studies[4,31]. Furthermore, previous evidence supports both either a cerebellar or a peripheral sensory deficit underlying the gait disorder in OT. On the one hand, recent studies suggest OT to be a cerebellar pathology indicated by changes

in cerebellar grey matter volume and alterations in the functional connectivity between the cerebellum and the supplementary motor area that both correlated with tremor and clinical severity in patients with OT[32–34]. There is further evidence for alterations in the connectivity of fronto-cerebellar circuits in OT that are linked to deficits of specific neuropsychological functions observed in patients[35,36]. Moreover, repetitive transcranial magnetic stimulation of the cerebellum was demonstrated to reduce tremor severity and associated changes in functional brain connectivity of patients with OT[32]. On the other hand, Fung *et al*. provided evidence for an impairment of peripheral sensory feedback underlying the symptoms emergence in OT[13]. Accordingly, it was suggested that during prolonged standing in OT, proprioceptive feedback from the periphery becomes increasingly synchronized at the tremor frequency. This tremor-locking of proprioceptive afferents would disrupt normal peripheral feedback regulation of posture and give rise to an increased co-contraction of anti-gravity musculature leading to a vicious cycle of escalating subjective and objective postural unsteadiness[13,19]. This assumption was further supported by a positive Romberg's sign, i.e., an aggravated balance disequilibrium in patients with OT while standing with eyes closed[13]. Thus, disturbed peripheral feedback during walking might hinder patients with OT to adequately adjust their stride-to-stride pattern for unintended irregularities[37,38], leading to the observed staggering wide base gait pattern. However, proprioceptive feedback available during repetitive tremor-free episodes (i.e., swing phases), might be sufficient to continuously update dynamic limb positions during walking and prevent patients with OT from becoming subjectively unsteady while ambulating.

As most studies on OT, the present findings are limited by the relatively small sample size due to the rarity of the disease. Moreover, walking on treadmill cannot be directly compared to overground walking performance. Previous studies however, demonstrated that in particular the magnitude of spatiotemporal gait fluctuations during treadmill vs. overground walking is comparable in healthy subjects and patients with neurological gait disorders[30,39]. Future studies on a larger sample size of patients with OT including the assessment of overground walking performance are required to confirm the findings of this study.

In conclusion, OT during walking was found to persist while resetting of tremor frequency indicates a non-linear interference between the default OT rhythm with oscillatory supraspinal locomotor activity. OT intensity was shown to be phase-dependently modulated during the gait cycle and linked to the loading state of respective muscles. Thus, peripheral manifestation of OT seems to be mediated via spinal interneurons signaling muscle loading. Finally, OT during ambulation was linked to specific gait alterations that suggest an underlying cerebellar and/or peripheral sensory deficit.

Data Availability

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

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Author Contributions

All of the authors have taken part in the preparation of this manuscript, have reviewed the results, and have approved the final version of this manuscript. M.W., C.S. and R.S. conceptualized and designed the study. M.W., C.S., K.M. and R.S. collected, analyzed, and interpreted the data. M.W. and R.S. wrote the paper.

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ORIGINAL COMMUNICATION

The gait disorder in primary orthostatic tremor

Ken Möhwald[1,2] · Max Wuehr[1] · Fabian Schenkel[1] · Katharina Feil[1,2] · Michael Strupp[1,2] · Roman Schniepp[1,2]

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Abstract

Objective To uncover possible impairments of walking and dynamic postural stability in patients with primary orthostatic tremor (OT).

Methods Spatiotemporal gait characteristics were quantified in 18 patients with primary OT (mean age 70.5 ± 5.9 years, 10 females) and 18 age-matched healthy controls. One-third of patients reported disease-related fall events. Walking performance was assessed on a pressure-sensitive carpet under seven conditions: walking at preferred, slow, and maximal speed, with head reclination or eyes closed, and while performing a cognitive or motor dual-task paradigm.

Results Patients exhibited a significant gait impairment characterized by a broadened base of support ($p = 0.018$) with increased spatiotemporal gait variability ($p = 0.010$). Walking speed was moderately reduced ($p = 0.026$) with shortened stride length ($p = 0.001$) and increased periods of double support ($p = 0.001$). Gait dysfunction became more pronounced during slow walking ($p < 0.001$); this was not present during fast walking. Walking with eyes closed aggravated gait disability as did walking during cognitive dual task ($p < 0.001$).

Conclusion OT is associated with a specific gait disorder with a staggering wide-based walking pattern indicative of a sensory and/or a cerebellar ataxic gait. The aggravation of gait instability during visual withdrawal and the normalization of walking with faster speeds further suggest a proprioceptive or vestibulo-cerebellar deficit as the primary source of gait disturbance in OT. In addition, the gait decline during cognitive dual task may imply cognitive processing deficits. In the end, OT is presumably a complex network disorder resulting in a specific spino-cerebello-frontocortical gait disorder that goes beyond mere tremor networks.

Keywords Orthostatic tremor · Gait disorder · Walking stability · Gait ataxia

Introduction

Primary orthostatic tremor (OT) is a rare neurological disease, characterized by a high-frequency tremor with a typical 13–18 Hz pattern affecting the leg and trunk musculature [1]. The tremor, which is associated with the patient's feeling of unsteadiness and dizziness, predominantly occurs during standing and vanishes in most patients while sitting or lying [2, 3]. Postural impairments in OT are, thus, primarily associated with static postural control. It is less clear whether and how OT affects dynamic postural control during walking. While most patients report a relief of symptoms when starting to ambulate, tremor activity has been recently shown to persist even during walking [4]. Ongoing high-frequency tremor activity might interfere with both central as well as peripheral feedback control of gait in OT patients. First, the pathological central oscillatory network activity that has been associated to OT encompasses supraspinal locomotor regions in the cerebellum, thalamus and motor cortex [5]. Second, high-frequency tremor bursts in the legs were shown to considerably impair afferent proprioceptive signaling in patients with OT [6]. It is, thus, conceivable, that OT is associated with a specific gait disorder as known in other types of tremor, such as essential tremor [7]. Our previous analyses depicted gait anomalies with broad-based walking and increased gait fluctuations resembling a cerebellar or sensory ataxic gait impairment [4]. However, gait performance was assessed in a highly controlled setting

✉ Ken Möhwald
Ken.Moehwald@med.uni-muenchen.de

[1] German Center for Vertigo and Balance Disorders, University Hospital, LMU Munich, Munich, Germany

[2] Department of Neurology, University Hospital, LMU Munich, Marchioninistr. 15, 81377 Munich, Germany

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of treadmill walking considering only a limited set of gait conditions.

Therefore, the aim of the study was to comprehensively characterize the gait abnormalities associated to OT by means of a quantitative examination of gait performance in patients with OT compared to healthy controls utilizing a standardized multiple condition gait assessment.

Methods

Ethics approval and patients' consent

The study procedures have been approved by the Ethics Committee of the University of Munich. All procedures were in accordance with the Declaration of Helsinki and all patients gave their written informed consent.

Participants and clinical assessment

Eighteen patients with primary OT (mean age 70.5 ± 5.9 years, 10 females) with typical symptoms and high-frequency tremor as well as 18 age-matched healthy controls (mean age 71.2 ± 6.3 years, 10 females) participated in the study. The patient cohort was derived from a previous study from our medical center focusing on the course of disease and postural imbalance assessed by posturographic measurements [8]. The average disease duration of OT was 14.0 ± 7.0 years. Detailed patient characteristics are presented in Table 1. All patients underwent a standardized neurological, neuro-ophthalmological, and neuro-otological examination. In addition to the neurological evaluation, this included assessment of eyesight and eye movements (smooth pursuit, spontaneous, gaze-evoked and head-shaking nystagmus, impaired visual fixation, among others), a head impulse test and examination of the subjective visual vertical (SVV). A cerebellar ocular motor disorder was defined by the presence of one of the following findings: gaze-evoked nystagmus (left, right, both horizontally) or downbeat nystagmus, rebound nystagmus, impaired visual fixation suppression of the VOR [9]. Pallesthesia was assessed using a C64/128 Hz tuning fork. Reduced vibration sense was defined as pallesthesia $\leq 4/8$. Romberg's test was considered positive, when patients showed signs of imbalance with considerable staggering after eye closure or if they were unable to perform the task. All patients completed the Activities-specific Balance Confidence Scale (ABC, ranging from 0 to 100%, > 80 high level of physical function; 50–80 moderate level of physical function; < 50 low level of physical function) and the Falls Efficacy Scale—International (FES-I, total score range from 16, i.e., no concern about falling, to 64, i.e., severe concern about falling) and were screened for fall events within the last 6 months.

Procedures and variables

All patients underwent the Functional Gait Assessment (FGA), a 10-item clinical gait performance evaluation (overall score ranging from 0 to 30, with 30 being the best possible score). Quantitative assessment of walking ability of patients and healthy controls was performed on a 6.7 m long pressure-sensitive gait carpet (GAITRite®, CIR Systems, Franklin, NJ, USA) with a sampling frequency of 120 Hz. Each participant completed a comprehensive gait assessment protocol comprising seven different speed, sensory, and dual-task walking conditions: walking (1) at preferred speed, (2) slow speed, (3) maximal speed, (4) with head reclination, (5) with eyes closed, (6) during cognitive dual task (calculatory serial 7 task), and (7) during motor dual task (carrying a tray). For each condition, a total of four trials were recorded. Walking performance and stability for each recording were characterized by the following spatiotemporal gait parameters: mean walking velocity (cm/s), stride length (cm), stride time (cm), percentage of double support phase (%), percentage of swing phase (%), base of support (cm) as well as the stride-to-stride variability of stride length, stride time, and base of support. Stride-to-stride variability was determined using the coefficient of variation (CV).

Statistical analysis

Descriptive statistics are reported as mean ± SD. Differences in walking performance of patients and controls were analyzed using a repeated-measures analysis of variance and Bonferroni post hoc analysis with group (patients vs. healthy controls) and walking condition as factors. Possible associations between clinical findings, fall status, and the average walking performance of patients across conditions (gait parameters as described above) were examined by a point-biserial Pearson's correlation. Results were considered significant at $p < 0.05$.

Availability of data and material

Anonymized datasets are available upon reasonable request to qualified researchers.

Results

Patient characteristics

Clinically, all patients showed a saccadic smooth pursuit and clinical signs for a mild cerebellar ocular motor impairment were found in two-thirds of patients.

Table 1 Patient characteristics including neurological findings and medication

Patient	Gender	Age (years)	Tremor frequency (Hz)	Duration (years)	Tremor treatment	Cerebellar signs	Further neurological findings	ABC	FES-I	FGA	Falls
1	f	54	17.0	7	Baclofen 30 mg/day	3	1, 6, 7	33	39	18[a]	No
2	f	73	16.5	26	Primidone 125 mg/day	1	1, 5, 6	22	42	19	Yes
3	m	77	17.5	23		1, 2, 3	1, 5, 6, horizontal periodic alternating nystagmus	43	43	20	No
4	m	72	13.5	23		3	1, 2, 4, 5, 6	15	51	15[a]	No
5	f	62	16.0	15		2, 3	1, 5, 6, 7	49	40	17[a]	Yes
6[c]	m	72	14.5	16	Clonazepam 0.5 mg/day	1, 2, 3	1, 2, 5, 6	53	28	18	Yes
7	f	72	17.0	8	Gabapentin 1200 mg/day + Primidone 375 mg/day	1, 2, 3	1, 2, 4, 5, 6	7	57	[b]	Yes
8	f	63	14.0	15	Pregabalin 150 mg/day	1, 2	1, 4, 5, 7	59	21	25	No
9	f	69	15.0	19	Gabapentin 300 mg/day	1, 2, 3	1, 4, 5, 6, head tremor	37	37	16[a]	No
10	m	72	17.0	10		2	1, 4, 5	87	25	26	No
11[c]	f	78	14.0	18	Gabapentin 900 mg/day	1, 2, 3	1, 2, 5, 6	62	46	[b]	Yes
12	f	72	16.0	20		2	1, 5, 6, pronation forearm holding test	24	48	18	No
13	m	77	14.5	18	Gabapentin 2000 mg/day	1, 2	1, 2, 5, 6	75	28	12[a]	No
14	m	73	11.5	8		2, 3	1, 5, 6, muscle atrophy of lower limb (right > left)	65	28	19	No
15	m	71	13.0	1		1, 2, 3, 4	1, 2, 5, 6, 7	24	24	20	No
16	f	72	11.0	5	Propranolol 120 mg/day	1, 4	1, 6, pronation forearm holding test	58	30	17	Yes
17	m	73	14.0	11		1, 2, 3	1, 2 (right), 3, 4, 5, 6	28	49	9[a]	No
18	f	67	15.5	9	Clonazepam 0.3 mg/day	1, 2	1, 2, 4, 5, 6, drooping mouth on right side	81	25	[b]	No

Cerebellar signs: 1 = cerebellar ocular motor disorder, 2 = upper limb dysmetria, dysdiadochokinesia or intention tremor (uni- or bilateral), 3 = lower limb dysmetria (uni- or bilateral), 4 = dysarthria

further neurological findings: 1 = saccadic smooth pursuit, 2 = pathological head impulse test (bilateral, if unilateral, left or right side indicated), 3 = rigidity, 4 = postural tremor, 5 = impaired ankle reflexes and/or reduced vibration sense, 6 = positive Romberg's sign, 7 = deviation of the subjective visual vertical (SVV)

ABC: Activities-specific Balance Confidence Scale (ranging from 0 to 100%, > 80 high level of physical function; 50–80 moderate level of physical function; < 50 low level of physical function); FES-I: Falls Efficacy Scale-International (total score range from 16, i.e., no concern about falling, to 64, i.e., severe concern about falling); FGA: Functional Gait Assessment (ranging from 0 to 30, with 30 being the best possible score)

f female, *m* male

[a]FGA score below the age-referenced norm [10]

[b]FGA testing aborted due to permanent instability

[c]Siblings

Eighty-nine percent of OT patients showed postural instabilities indicated by a positive Romberg's test as well as a reduced vibration sense or impaired reflexes of the legs. 61% of OT patients presented with a lower limb dysmetria and 44% showed a uni- or bilateral pathological head impulse test. All patients reported considerable impairments in physical function and daily activity (mean ABC score: 45.7 ± 23.4) and a moderate to severe concern about the risk to fall (mean FES-I score: 36.7 ± 10.9). Fall events within the last 6 months were reported by one-third of patients.

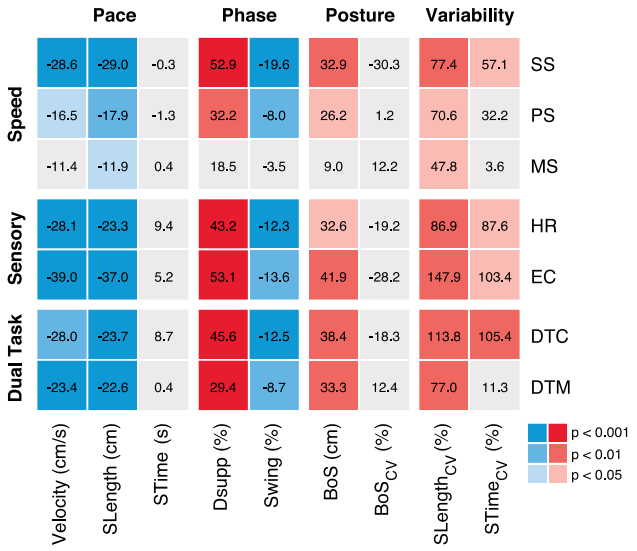

Fig. 1 Overview of walking impairments in patients with orthostatic tremor. Comparison of walking performance in patients with orthostatic tremor vs. healthy controls across different speed, sensory, and dual-task conditions (rows) and with respect to different gait parameters (columns, grouped by four functional gait domains: pace, phase, posture, and variability). Numbers within each tile represent the mean percentage difference of patients' walking performance compared to healthy controls. *SLength* stride length, *STime* stride time, *Dsupp* percentage of double support phase, *Swing* percentage of swing phase, *BoS* base of support, *CV* coefficient of variation, *SS* slow walking speed, *PS* preferred walking speed, *MS* maximal walking speed, *HR* head reclination, *EC* eyes closed, *DTC* cognitive dual task, *DTM* motor dual task

Gait performance and quantitative gait analysis

Functional impairments of gait during clinical assessment (FGA) were found in 50% of patients. Three patients were not able to perform the FGA due to permanent instability and six patients yielded a score below the age-referenced norm [10]. An overview on gait impairments of patients during quantitative gait assessment is presented in Fig. 1.

During preferred walking, patients exhibited a broadened base of support ($p = 0.018$) with increased spatiotemporal gait variability ($p = 0.010$). Walking speed was moderately reduced ($p = 0.026$) with shortened stride lengths ($p = 0.001$) and increased periods of double support ($p = 0.001$). Gait impairments became considerably pronounced during slow walking but mainly disappeared during fast walking ($p < 0.001$). Withdrawal of visual feedback aggravated walking disability as did walking during cognitive dual task ($p < 0.001$, Fig. 2).

Walking impairments in patients were associated with clinical signs for a cerebellar ocular motor disorder (stride time $r = -0.56$, $p = 0.015$; cadence $r = 0.51$, $p = 0.033$) and lower limb dysmetria (stride time CV $r = 0.66$, $p < 0.01$; velocity $r = -0.57$, $p = 0.013$; stride length $r = -0.49$, $p = 0.04$). Patients with a positive Romberg's test showed increased gait fluctuations (stride time CV $r = 0.47$, $p = 0.05$). Furthermore, patients who had fallen within the recent past were found to walk at slower speeds ($r = -0.51$, $p = 0.030$).

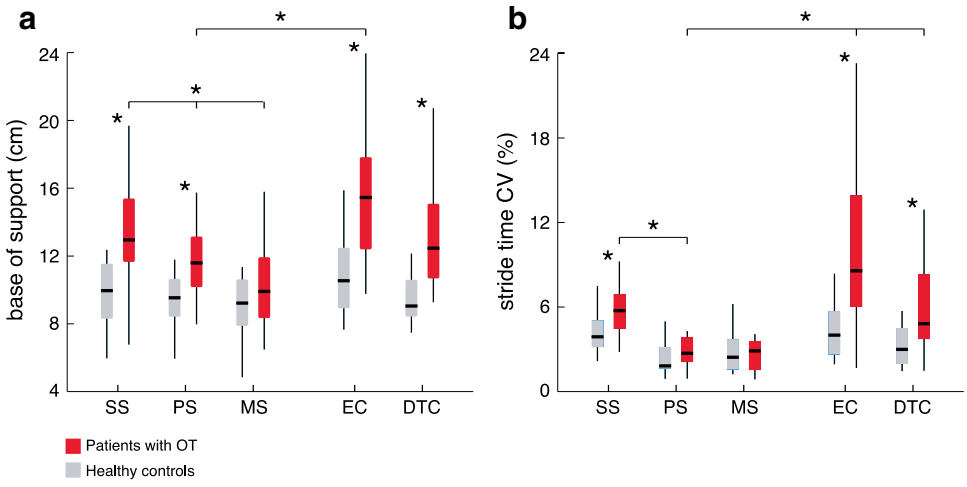

Fig. 2 Modulation of gait characteristics across different walking conditions. Alterations in **a** base of support and **b** stride time CV in patients with OT (red) and healthy controls (grey) in dependence on the walking speed (SS, PS, MS) as well as during walking with EC or DTC. *Significant difference. *CV* coefficient of variation, *SS* slow walking speed, *PS* preferred walking speed, *MS* maximal walking speed, *EC* eyes closed, *DTC* cognitive dual task

Discussion

Considerable impairments of walking in patients with OT were apparent in clinical and quantitative assessment of gait. Instrumented gait analysis in these patients revealed a general slowdown of walking with specific pathological alterations, such as an increased base of support and increased spatiotemporal gait variability. Both aspects indicate a deficient regulation of dynamic postural stability and have been associated with an increased risk of falling [11–13]. These findings were reflected in the patients' reports on limited physical activity and moderate to severe concerns about the risk to fall. Furthermore, one-third of patients did experience an actual fall within the past 6 months. Clinical examination in OT is, therefore, recommended to include a comprehensive examination of gait and physical function to identify those patients with a high risk for falling.

The staggering wide-based mode of walking in patients with OT is representative of the phenotype of a cerebellar or sensory ataxic gait disorder [14, 15]. Similar gait alterations have been reported in a recent publication [16]. Signs in our patients for cerebellar impairment coincide with previous reports [5, 17]. Additionally, recently it was hypothesized, that OT might primarily reflect a cerebellar pathology with altered functional connectivity between the cerebellum and supplemental motor areas as well as marked changes in cerebellar grey matter volume, which both correlated with clinical as well as tremor severity in patients [18–20]. In accordance to this hypothesis, application of a repetitive transcranial stimulation over the cerebellum led to a reduction of tremor severity and functional connectivity of these areas [18].

On the other hand, gait impairments in OT could also reflect deficits of proprioceptive sensing in the lower limbs, indicated by the frequent presentation of pallhypesthesia and a positive Romberg's sign in our patients and the considerable aggravation of their gait instability during withdrawal of visual feedback. Accordingly, signaling by proprioceptive afferents has been suggested to become disrupted by the high-frequency tremor bursts within lower limb muscles [6] that persist in particular during the stance phases of walking [4].

Even though cerebellar and sensory ataxic gait disorders are both characterized by a broadened base of support and increased gait fluctuation during slow walking modes compared to self-selected walking [14, 21–23], a proprioceptive deficit as the primary source for gait impairments in OT is further supported by the observed normalization of walking with faster speeds at which gait regulation is known to become increasingly independent from sensory feedback cues [15, 24].

However, the gait disorder in patients with downbeat nystagmus syndrome—a disorder linked to dysfunction of specific vestibulo-cerebellar regions [25]—has been shown to closely resemble sensory ataxic walking impairments with a gait unsteadiness restricted to slow walking modes [26]. Thus, the prevalent finding of impaired cerebellar ocular motor function as well as related impairments in static postural control in our patients may also point to a specific vestibulo-cerebellar dysfunction underlying the gait disorder in OT (as signs of a midline cerebellar dysfunction).

Finally, we observed noticeable walking difficulties of patients with OT while performing a cognitive dual task. This supports recent evidence in cognitive processing deficits in OT that have been suggested to reflect an impaired functional frontocerebellar connectivity [27, 28]. The gait decline during dual-task walking is also observed in other neurological diseases with neurocognitive deficits, such as idiopathic normal pressure hydrocephalus [29–31].

In the end, the results of our study question the concept of OT as a primary tremor disorder and instead suggest a complex network disorder with a characteristic spino-cerebello-frontocortical gait disorder. Hence, the gait impairment in OT might directly reflect the pathological ponto-cerebello-thalamo-cortical dysfunction, which was previously described by a whole brain ^{18}F-fluorodeoxyglucose-positron emission tomography analysis [5].

Limitations

This study has several limitations. First, the OT patient cohort consisted of only 18 patients from one medical center. However, this sample size is similar to many previously published studies due to the rarity of disease with a low prevalence [5, 18, 32]. Second, while clinical signs for impaired ankle reflexes and/or pallhypesthesia were prevalent in our cohort, patients did not report further typical symptoms for a peripheral neuropathy, such as paresthesia, burning or tingling pain or progressive pareses. Within the context of the current study, we were not able to determine whether the reduced proprioceptive function is independent from or directly caused by OT. In favor of the latter option, it has been suggested that during prolonged standing in patients with OT, proprioceptive feedback from the periphery becomes increasingly synchronized at the tremor frequency [6]. This tremor-locking of proprioceptive afferents could disrupt normal peripheral feedback regulation of posture and give rise to an increased co-contraction of anti-gravity musculature leading to a vicious circle of escalating subjective and objective postural unsteadiness. This hypothesis has been further supported by the recently shown beneficial effects of a proprioceptive muscle tendon stimulation on tremor intensity and body sway in patients with OT [33]. However, further studies that particularly examine

nerve conduction speed in OT patients in the presence and absence of tremor are necessary to conclusively decide on the origin of the prevalent proprioceptive dysfunction in these patients.

Conclusion

Overall, patients with primary orthostatic tremor showed a gait disorder with broadened based of support and increased gait variability resembling a sensory or cerebellar ataxic gait. Gait performance declined during walking with eyes closed and improved during faster walking compared to healthy subjects indicating that proprioceptive deficits and/or a specific dysfunction within the vestibulo-cerebellum contribute to the gait impairment in OT. Furthermore, gait performance declined during cognitive dual task, which implies the presence of additional frontal processing deficits in patients with OT. These findings suggest that OT represents a complex network disorder associated to a specific spino-cerebello-frontocortical gait disorder that goes beyond mere tremor networks.

Author contributions KM, MW and RS designed the study, collected, analyzed, and interpreted the data as well as drafted the manuscript. FS collected and retrieved patient data. KF and MS conceptualized the study, recruited patients, and reviewed the manuscript. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflicts of interest K. Möhwald, M. Wuehr, F. Schenkel, K. Feil and R. Schniepp report no disclosures or conflicts of interest. M. Strupp is Joint Chief Editor of the Journal of Neurology, Editor in Chief of Frontiers of Neuro-otology and Section Editor of F1000. He has received speaker's honoraria from Abbott, Actelion, Auris Medical, Bayer, Biogen, Eisai, Grünenthal, GSK, Henning Pharma, Interacoustics, Merck, MSD, Otometrics, Pierre-Fabre, TEVA, and UCB. He is a shareholder of IntraBio. He acts as a consultant for Abbott, Actelion, AurisMedical, Heel, IntraBio and Sensorion.

Ethics approval The study procedures have been approved by the Ethics Committee of the University of Munich. All procedures were in accordance with the Declaration of Helsinki and all patients gave their written informed consent.

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ORIGINAL COMMUNICATION

Proprioceptive muscle tendon stimulation reduces symptoms in primary orthostatic tremor

M. Wuehr[1] · C. Schlick[1] · K. Möhwald[1,2] · R. Schniepp[1,2]

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Abstract

Introduction Primary orthostatic tremor (OT) is characterized by high-frequency lower limb muscle contractions and a disabling sense of unsteadiness while standing. To date, therapeutic options for OT are limited. Here, we examined the effects of proprioceptive leg muscle stimulation via muscle tendon vibration (MTV) on tremor and balance control in patients with primary OT.

Methods Tremor in nine patients with primary OT was examined during four conditions: standing (1), standing with MTV on the bilateral soleus muscles (2), lying (3), and lying with MTV (4). Tremor characteristics were assessed by frequency domain analysis of surface EMG recordings from four leg muscles. Body sway was analyzed using posturographic recordings.

Results During standing, all patients showed a coherent high-frequency tremor in leg muscles and body sway that was absent during lying ($p < 0.001$). MTV during standing did not reset tremor frequency, but resulted in a decreased tremor intensity ($p < 0.001$; mean reduction: $32.5 \pm 7.1\%$) and body sway ($p = 0.032$; mean reduction: $37.2 \pm 6.8\%$). MTV did not affect muscle activity during lying. Four patients further reported a noticeable relief from unsteadiness during stimulation.

Conclusion Proprioceptive stimulation did not reset tremor frequency consistent with the presumed central origin of OT. However, continuous MTV influenced the emergence of OT symptoms resulting in reduced tremor intensity, improved posture, and a relief from unsteadiness in half of the examined patients. These findings indicate that MTV either directly interferes with the peripheral manifestation of the central oscillatory pattern or prevents proprioceptive afferent feedback from becoming extensively synchronized at the tremor frequency.

Keywords Orthostatic tremor · Muscle tendon vibration · Proprioception · Tremor · Body sway · Unsteadiness

Introduction

Primary orthostatic tremor (OT) is a rare condition of unknown prevalence, characterized by a high-frequency pattern of coherent muscle contractions (13–18 Hz) in the lower limbs and trunk while standing [1]. The tremor is linked to the main presenting symptom of subjective unsteadiness and dizziness during standing that typically relieves during sitting and lying or when patients start to ambulate.

The pathophysiological mechanisms underlying primary OT are not completely understood. However, the strong coherence between high-frequency activations of widely separated muscles suggests that the latter are a peripheral manifestation of a central oscillator. Correspondingly, a central oscillatory ponto-cerebello-thalamo-cortical network has recently been identified in patients with OT [2, 3]. This network appears to be active during symptomatic (i.e., standing) as well as non-symptomatic states (i.e., lying). During standing, isometric muscle contraction is believed to entrain the central oscillatory pattern in the respective anti-gravity muscles. Continuous tremor in anti-gravity muscles is in turn thought to negatively interfere with proprioceptive afferent feedback required for adequate balance regulation with the result of subjective unsteadiness and objectively impaired stance performance. Both phenomena typically develop over seconds in patients with OT while standing [4].

✉ M. Wuehr
Max.Wuehr@med.uni-muenchen.de

[1] German Center for Vertigo and Balance Disorders, University Hospital, LMU Munich, Marchioninistrasse 15, 81377 Munich, Germany

[2] Department of Neurology, University Hospital, LMU Munich, Munich, Germany

The aim of this study was to examine whether the course of symptoms emergence in patients with OT during standing might be positively influenced by a continuous proprioceptive stimulation of afflicted muscles. We, therefore, tested the effects of a continuous low-intensity muscle tendon vibration (MTV) on the bilateral soleus muscles on tremor frequency and intensity as well as balance performance and subjective unsteadiness in patients with OT.

Methods

Standard protocol approvals, registrations, and patients consent

The study protocol has been approved by the Ethics Committee of the University of Munich and was registered (DRKS00012907). All procedures were in accordance with the Helsinki declaration and patients gave their written informed consent.

Subjects

Nine patients with primary OT participated in the study (patient characteristics are presented in Table 1). Definite diagnosis was made by surface EMG-recording exhibiting a coherent tremor between homologous leg muscles within a frequency range of 13–18 Hz. Patients underwent a standardized neurological examination to exclude additional signs indicative of a secondary OT (i.e., hypokinesia, rigidity, dystonia, and failure of gait initiation). Age-associated signs of a reduced vibration sense of the feet were frequently observed. However, none of the patients presented with a clinically manifest peripheral neuropathy.

Procedures

Tremor intensity and postural performance (only stance conditions) were evaluated during four conditions (each 60 s duration): standing vs. standing with MTV and lying supine vs. lying with MTV. Recordings during MTV conditions were started 30 s after stimulation onset. After the recordings patients were asked whether they felt any noticeable change in subjective unsteadiness during MTV stimulation.

Muscle tendon vibration was applied bilaterally with two cylindrical vibrators (8.8 cm × 3.2 cm, 180 g) containing a small DC motor (Buehler, type 1.13.055.221, Germany), that were attached on the soleus muscle tendon by elastic bands. Stimulation consisted in a continuous moderate vibration (50 Hz, 1 mm) [5]. Surface EMG activity was recorded with Ag/AgCl electrodes simultaneously from the tibialis anterior, gastrocnemius, biceps femoris, and vastus medialis muscles of the dominant leg side using a Zebris DAB-Bluetooth device (Zebris Medical, Germany) at 1000 Hz. EMG signals were amplified, bandpass-filtered at 10–100 Hz, and full-wave rectified. Body sway was recorded on pressure-sensitive posturographic platform FDM-T (Zebris Medical, Germany) at 100 Hz.

Data analysis

Tremor intensity and coherence between every combination of recorded muscle pairs were analyzed by spectral analysis using finite fast Fourier transformation with a block size set to 2 s resulting in a frequency resolution of 0.5 Hz [6]. Body sway was analyzed by spectral analysis on the time series along z-axis of the posturographic measurements (N) and by calculating the mean position (mm), sway area (mm^2), path

Table 1 Patient characteristics including neurological findings and medication

Patient	Sex	Age (years)	Tremor frequency (Hz)	Duration (years)	Medication	Neurological findings
1	m	62	14.5	1	No	1, 4
2	f	55	14	5	Gabapentin 1200 mg/day	1
3	m	75	17.5	10	No	1, 2, 4
4	m	75	14	14	Clonazepam 1 mg/day	1, 2, 3, 4
5	f	56	17	5	No	1
6	f	75	16.5	6	No	1, 2, 3, 4
7	f	66	14	13	No	1, 2, 4
8	m	75	13.5	4	Gabapentin 600 mg/day	1, 4
9	m	76	15	3	Levodopa/benserazid 300/75 mg/day	1

Neurological findings: 1 = postural instability, 2 = dysmetria, dysdiadochokinesia or intention tremor upper limbs (uni- or bilateral), 3 = dysmetria lower limbs (uni- or bilateral), and 4 = diminished ankle reflexes and/or reduced vibration sense

f female, *m* male

(mm), and root mean square (RMS, mm) of the recorded center-of-pressure (CoP) trajectories [2].

Statistical analysis

Data are reported as mean ± SEM. MTV effects on tremor intensity and coherence were analyzed by repeated-measures analysis of variance and Bonferroni post hoc analysis with condition (standing vs. lying), stimulation (MTV vs. no MTV), and muscle type as factors. Because posturographic measures were not normally distributed, MTV effects on body sway were analyzed using a Wilcoxon matched-pairs signed-rank test. Results were considered significant at $p < 0.05$.

Results

During upright standing, all patients showed a coherent high-frequency tremor in all examined leg muscles and in *z*-axis body sway (mean tremor frequency: 15.1 Hz; range 13.5–17.5 Hz) that was absent during lying ($p < 0.001$). MTV did not reset tremor frequency but effectively reduced tremor intensity equally in all muscles by in average 32.5 ± 7.1% ($p < 0.001$). This was accompanied by a moderately reduced inter-muscular tremor coherence (mean reduction: 5.6 ± 1.7%, $p < 0.001$) (Fig. 1a–d). MTV effects on posture resulted in reduced high-frequency body sway along *z*-axis (mean reduction: 37.2 ± 6.8%; $p = 0.032$)

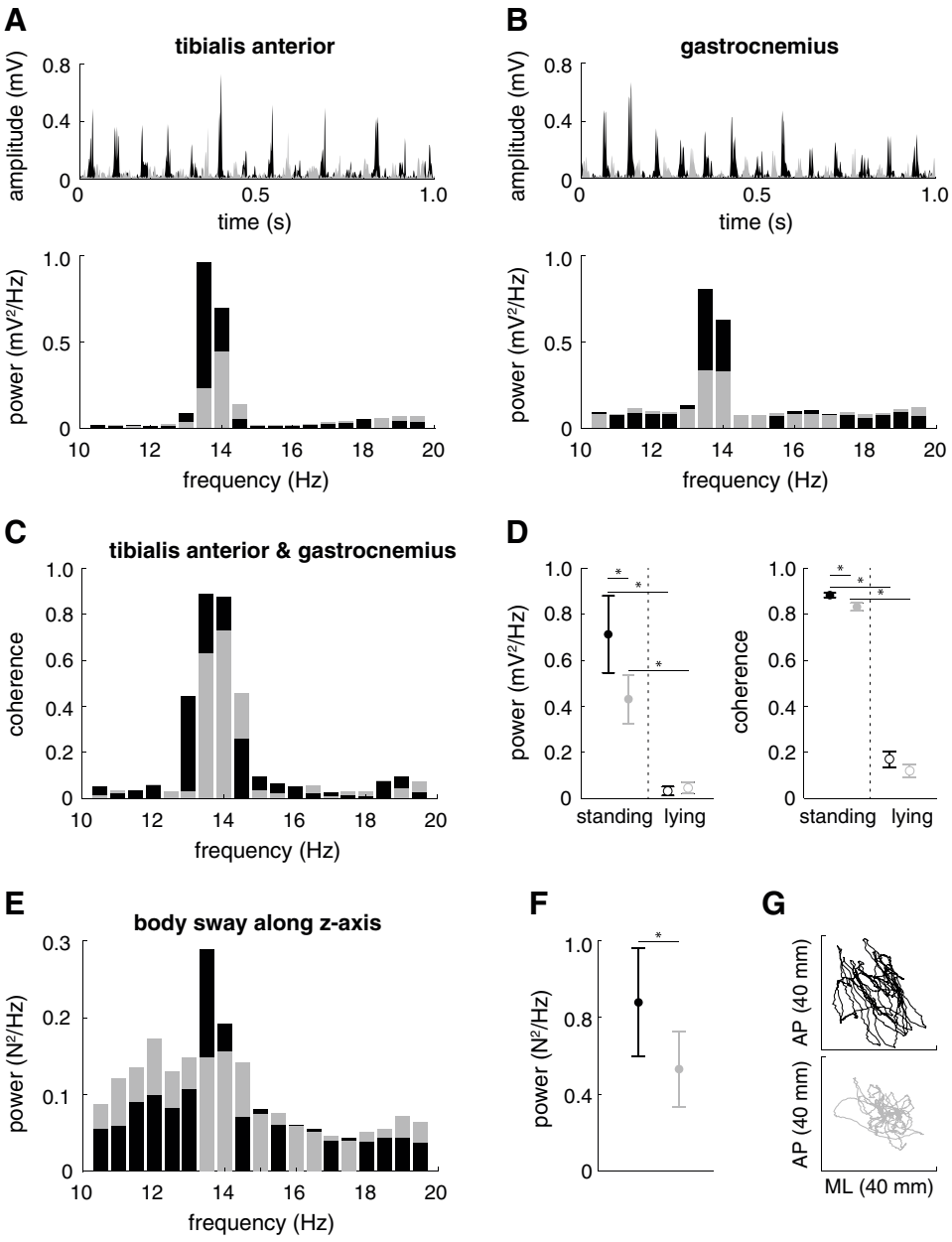

Fig. 1 Effects of proprioceptive stimulation on tremor characteristics and body sway. Rectified EMG traces and power spectra of the tibialis anterior (**a**) and gastrocnemius muscle (**b**) as well as coherence between both muscles (**c**) during normal standing (black) and standing with muscle tendon vibration (MTV) on the bilateral soleus muscle (gray). **d** Group effects of MTV on tremor intensity and inter-muscular coherence during standing as well as during lying. **e** Representative power spectrum of body sway along *z*-axis during normal standing (black) and standing with muscle tendon vibration (MTV) on the bilateral soleus muscle (gray). **f** Group effects of MTV on high-frequency body sway. **g** Corresponding center-of-pressure trajectories in anterior–posterior (AP) and medio-lateral plane (ML). Asterisk indicates a significant difference

and moderately improved balance indicated by smaller outcomes for area (mean reduction: 30.8 ± 10.0%; $p = 0.011$) and RMS (mean reduction: 10.6 ± 5.3%; $p = 0.038$) of body sway (Fig. 1e–g). Finally, we observed a moderate backward shift of the mean CoP position (− 24.2 ± 16.2 mm, $p = 0.015$) in response to the illusionary forward body tilt, which is known to be provoked by MTV on the soleus muscles [5, 7]. Four patients reported a subjectively felt improvement of unsteadiness during MTV and no patient indicated increase of unsteadiness due to stimulation. The presence of reduced vibration sense did not correlate with MTV effects on tremor intensity or posture.

Discussion

The present findings indicate that continuous low-intensity modulation of proprioceptive feedback has a positive moderating influence on the course of symptoms emergence in patients with OT while standing. In consistence with the previous examinations on the influence of peripheral stimulation in OT [1, 8], continuous MTV did not reset tremor frequency and only showed minor effects on inter-muscular tremor coherence underpinning the presumed central origin of OT. However, the observed reduction of tremor intensity indicates that continuous proprioceptive stimulation may mitigate the peripheral manifestation of the centrally generated oscillatory pattern during standing. In line with this, we further found that MTV induced improvements in body balance and subjective unsteadiness of patients with OT, whereas, in the healthy elderly vibratory leg muscle stimulation rather tends to destabilize posture [9].

OT could manifest peripherally via a direct projection of central oscillatory sources to spinal motoneurons. However, the observation that motoneurons can be activated voluntarily without exhibiting the tremor pattern (e.g., lifting one leg from the floor), while tremor burst persist in homologous muscles of the other limb, makes a direct connection unlikely [1]. The central oscillatory pattern could alternatively be relayed via spinal interneurons, since tremor bursts occur during muscle contraction under load, i.e., during activation of Golgi tendon organ (GTO) afferents that directly project to Ib interneurons [8]. GTO afferents as well as muscle spindle afferents are known to be strongly modulated by MTV applied on muscles under load [10], which would give a plausible site of action for a direct influence of MTV on peripheral tremor manifestation.

Alternatively, MTV might have a more indirect deescalating influence on symptoms emergence in OT. Accordingly, it has been suggested that after tremor onset while standing, proprioceptive feedback from the periphery becomes increasingly synchronized at the tremor frequency [3, 4]. This tremor-locking of proprioceptive afferents would disrupt normal peripheral feedback regulation of posture and give rise to an increased co-contraction of anti-gravity musculature leading to a vicious cycle of escalating subjective and objective postural unsteadiness [4]. The continuous engagement of proprioceptive afferents via MTV could to some extend prevent the tremor-locking of peripheral feedback and thereby deescalate the symptoms occurrence in OT. In this regard, the mode of action of MTV could be similar to that of continuous lower limb movements during gait that consistently relieve clinical symptoms in patients with OT, although the high-frequency leg tremor persists during ambulation [1].

Many patients with OT insufficiently respond to currently available pharmacological treatment options [11, 12]. Alternative interventions such as deep brain stimulation of the thalamus [13, 14] or spinal cord stimulation [15] showed positive effects in single patients that, however, need to be confirmed in future controlled clinical trials. In this respect, the present findings may open new avenues for a non-invasive therapeutic intervention via low-intensity modulation of proprioceptive feedback in patients with OT.

Author contributions Conceived and designed the study: MW, CS, and RS. Performed the study: MW, CS, KM, and RS. Performed statistical analysis: MW. Wrote the paper: MW. Critical revision of the manuscript: CS, KM, and RS.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no competing interests.

Ethical standard All experimental procedures were approved by the appropriate Ethics Committee.

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