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Effects of physiotherapy and home-based training in parkinsonian syndromes: protocol for a randomised controlled trial (MobilityAPP)

Cecilia Raccagni ,[1,2] Victoria Sidoroff,[2] Anisoara Paraschiv-Ionescu,[3] Nils Roth,[4] Gudrun Schönherr,[2] Björn Eskofier,[5] Heiko Gassner,[6] Felix Kluge,[7] Francesco Teatini,[1] Klaus Seppi,[2] Georg Goebel,[2] David H Benninger,[8] Kamiar Aminian ,[3] Jochen Klucken ,[9,10,11,12] Gregor Wenning[2]

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For numbered affiliations see end of article.

Correspondence to
Jochen Klucken; jochen.klucken@uni.lu and Dr Kamiar Aminian; kamiar.aminian@epfl.ch

ABSTRACT

Introduction Gait and mobility impairment are pivotal signs of parkinsonism, and they are particularly severe in atypical parkinsonian disorders including multiple system atrophy (MSA) and progressive supranuclear palsy (PSP). A pilot study demonstrated a significant improvement of gait in patients with MSA of parkinsonian type (MSA-P) after physiotherapy and matching home-based exercise, as reflected by sensor-based gait parameters. In this study, we aim to investigate whether a gait-focused physiotherapy (GPT) and matching home-based exercise lead to a greater improvement of gait performance compared with a standard physiotherapy/home-based exercise programme (standard physiotherapy, SPT).

Methods and analysis This protocol was deployed to evaluate the effects of a GPT versus an active control undergoing SPT and matching home-based exercise with regard to laboratory gait parameters, physical activity measures and clinical scales in patients with Parkinson's disease (PD), MSA-P and PSP. The primary outcomes of the trial are sensor-based laboratory gait parameters, while the secondary outcome measures comprise real-world derived parameters, clinical rating scales and patient questionnaires. We aim to enrol 48 patients per disease group into this double-blind, randomised-controlled trial. The study starts with a 1 week wearable sensor-based monitoring of physical activity. After randomisation, patients undergo a 2 week daily inpatient physiotherapy, followed by 5 week matching unsupervised home-based training. A 1 week physical activity monitoring is repeated during the last week of intervention.

Ethics and dissemination This study, registered as 'Mobility in Atypical Parkinsonism: a Trial of Physiotherapy (Mobility_APP)' at clinicaltrials.gov (NCT04608604), received ethics approval by local committees of the involved centres. The patient's recruitment takes place at the Movement Disorders Units of Innsbruck (Austria), Erlangen (Germany), Lausanne (Switzerland), Luxembourg (Luxembourg) and Bolzano (Italy). The data resulting from this project will be submitted to peer-reviewed journals, presented at international congresses and made publicly available at the end of the trial.

Trial registration number NCT04608604.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The multicentric study design enables the enlargement of the patients' cohort and therefore increases validity of the data especially for atypical parkinsonian disorders, where small sample size is often a limitation.
⇒ Patients are likely to benefit from a tailored, high-quality physiotherapy programme where they also have the opportunity to learn exercise and training to be performed at home.
⇒ The planned study population to be recruited is high, considering the rarity of the diseases and the fact that they must be able to walk to participate in the study. This could represent a challenge but the multicentric design will help to overcome it.

INTRODUCTION

Gait impairment and reduced mobility are typical symptoms of patients with advanced Parkinson's disease (PD) and atypical parkinsonian disorders (APD), including multiple system atrophy (MSA) and progressive supranuclear palsy (PSP). These features develop earlier and are more pronounced in APD,[1] where associated autonomic symptoms such as orthostatic hypotension (in MSA)[2] and frontal lobe dysfunction (in PSP)[3] exacerbate the impaired balance, increase risk of falls and reduce independence at activities of daily living.[4] The emergence of gait impairment represents a pivotal motor milestone in the natural history of parkinsonian syndromes indicating a transition to sustained disability and reduced quality of life. Impaired physical activity (PA) and sedentary behaviour are associated with reduced walking bouts and increased time spent in sitting or lying posture.[5] Therefore a vicious cycle begins, which is linked to higher mortality rate also in normal elderly people.[6 7] In contrast,

increased activity levels are the bedrock of independence, delay onset of decline and lower fall risk.[8 9] For gait impairment in PD and ADP, non-pharmacological interventions are increasingly recognised as complementary treatment options.[10] Up to now, a bundle of exercise-based interventions has been studied for PD and the scientific evidence for their efficacy is growing.[10–13] A few small-sized studies examined efficacy of diverse physiotherapy (PT) strategies in classical PSP-Richardson syndrome (PSP-RS) patients to improve balance, gait and gaze control,[14–16] therefore providing preliminary evidence to support the use of PT rehabilitation programmes in these patients. However, thus far, there is no controlled study that addressed PT in MSA with predominant parkinsonian features (MSA-P) patients, suggesting an unmet need.

In a pilot study, we investigated the feasibility, safety and impact of a gait-focused PT programme in MSA-P patients using sensor-based gait parameters as primary outcome measure.[17] The intervention was divided into a 5 day course of inpatient individual PT, followed by a 5 week unsupervised home-based training. The results showed a significant improvement of gait function after the intervention, as reflected by the increase of gait speed and stride length, which reached its maximum after the inpatient PT and tended to worsen after the home-based training programme. This fact suggests that the inpatient PT was more effective due to higher motivation levels and the relatively short although intense intervention. Importantly, the intervention was feasible and safe without falls or adverse events. Patient's retention rates were high (90%).

While PT and diverse exercise-based strategies are recommended for PD patients, the efficacy and feasibility of PT, as well as the duration, type, intensity, frequency, inpatient versus home-based of the exercise-based treatments for APD patients remain poorly explored. The effects of different forms of PTs on motor symptoms, well-being and sensor-derived outcome measures of APD patients have not yet been investigated. To the best of our knowledge, this is the first study to evaluate PT in MSA-P patients in a randomised-controlled trial.

In this paper, we illustrate the protocol of the 'Mobility_APP' study, that aims to examine the effects on mobility, gait parameters, well-being, motor and non-motor symptoms of a combined inpatient and home-based gait-focused exercise programme (GPT) among APD and PD patients. Results will be compared with an active control group, undergoing a matched inpatient and home-based exercise programme (here stated as 'standard physiotherapy' = SPT), with some differences regarding the addressed mobility exercise tasks.

Objectives

The primary objective of the trial is to examine the effects of GPT on gait as reflected by sensor-based gait analysis in laboratory in patients with APD, compared with SPT. The secondary objective is to explore the effects of GPT with regard to clinical rating scales, patient questionnaires and home-based mobility parameters in patients with APD, compared with SPT.

We hypothesise that GPT compared with SPT will be associated with greater improvements in the adopted outcome measures.

METHODS

The recruitment of patients will take place in five sites at the Movement Disorder Units (MDUs) of Innsbruck, Austria (MUI), Erlangen, Germany (UKER), Lausanne, Switzerland (CHUV), Luxembourg (CHL), and Bolzano, Italy.

Patient involvement

The feasibility pilot study[17] was granted by the patient's organisation MSA Coalition, which therefore was directly involved in the design of this research. Based on preliminary findings, we wrote this protocol, which has some changes based on feedback from patients and physical therapists. The data will be shared with patient's organisations (MSA Coalition, MSA trust), MSA and PSP clinical consortia.

Participants and sample size estimation

To be eligible for this study, participants must have diagnosis of probable or possible MSA-P according to revised Gilman criteria,[18] probable or possible PSP-RS or PSP-P according to the MDS-PSP criteria[19] or PD, according to MDS-PD diagnostic criteria.[20] Exclusion criteria are listed in Box 1.

We performed a sample size estimation based on a previous pilot study investigating the effects of a similar PT programme in patients with APD and PD.[17] To this aim, we stratified repeated measures analysis of variance for the PD and the APD groups. As primary outcome gait velocity and stride length were evaluated. Based on our preliminary study[17] data, we expect an effect size of d=0.53. An estimated sample size of at least 45 patients per disease group would be necessary to detect significant

Box 1 Exclusion criteria of the study participants

Exclusion criteria

Comorbidities that influence the clinical presentation of parkinsonian symptoms (as judged by the enrolling investigator).

Participation in other clinical trials that might influence the impact of the trial intervention (as judged by the enrolling investigator).

H&Y staging score>3.[35]

Change of antiparkinsonian and antiorthostatic hypotension medication 4 weeks prior to the interventional trial.

Secondary cause of autonomic failure or parkinsonism (eg, diabetic autonomic neuropathy, bladder surgery, drug-induced or vascular parkinsonism, etc).

Dementia according to DSM-V.[36]

Current or ongoing physiotherapy in the past 2 weeks before randomisation.

DSM-V, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.

within-group differences per gait parameter after the inpatient PT, and therefore, to reach a sufficient power. With respect to an expected 5% drop-out rate and additional comparisons between the groups, we intend to randomise 144 patients: 48 patients with MSA-P, 48 patients with PSP and 48 patients with PD.

Recruitment and randomisation

Screening of subjects will be performed during daily routine and based on patient's registries. Screened subjects will be contacted via telephone, mail or post. After 1 week of home monitoring, the patients will be randomly assigned to either GPT or SPT with a 1:1 allocation as per a computer-generated randomisation schedule stratified by diagnosis (PD, MSA and PSP) using permuted blocks of random sizes. The patients, as well as the investigator performing the baseline and follow-up visits, are unaware of the allocation possibilities, and they will also be blinded until the end of the study. In the consentment (uploaded), patients will be informed on the two different interventions. The randomisation list will be kept confidential and will be unblinded only in case of serious adverse events or withdrawal. The allocation number will be placed into sealed separate envelopes and only the physiotherapists will be concealed about it. The patients are requested not to inform or discuss the treatment details with the study investigator at follow-up visits.

Interventions

Patients are randomised to either GPT (intervention) or SPT (control). The frequency, duration and structure of GPT and SPT are the same, but the tasks are different. In both groups, patients receive daily inpatient PT sessions for 10 days, consisting of a 60 min-training programme. After 10 days, patients receive a standardised exercise programme for the following 5 weeks intervention period at home ('home-based training'), which contains the same tasks performed in the hospital. During the home-based training phase, patients are asked to perform these exercises for at most 60 min daily without supervision of a physiotherapist (caregiver is allowed). Every patient gets a non-structured telephone call from the physiotherapist once per week, interviewing patients about any issues with the training programme, adverse events, falls, compliance or questions.

Gait-focused physiotherapy (GPT)

The programme consists of 20 tasks, which are grouped into the domains of strength, transfers, posture/mobility, balance and gait. Among these 20 possible tasks, 8–12 are chosen by the physiotherapist, based on the individual needs of the patient. Similarly, the number of repetitions, variations and cues are tailored to each patient and marked on an extra printout for each task and set together to an individual folder. Patients undergo the GPT for 10 days with supervision, after that they receive the aforementioned home-based training.

Standard physiotherapy (SPT)

SPT is based on the European physiotherapy guidelines for PD and consists in total 20 tasks, selected from the groups of stretching, flexibility, transfers, strength and gait/balance.[21] Compared with GPT, a maximum of two tasks are chosen to improve gait or balance. Similar to GPT, each patient receives a tailored programme with 8–12 exercises, where number of repetitions, variations and cues are individualised. After 10 days, patients receive the home-based training, which contains the same exercises, to be performed at home.

Experimental protocol

The study is proposed to be conducted in a parallel-group, double-blinded, randomised-controlled fashion. Three types of assessment are included. First, Clinical Rating Scales (CRS) and questionnaires to objectify the patients clinical state and to assess quality of life are conducted (for a detailed overview, see table 1). Second, Instrumented Gait Analysis (IGA) measuring the gait performance of the patients by means of two wearable sensors (GaitLab, Portabiles Healthcare Technology GmbH, Erlangen, Germany), attached to the shoe instep position, collecting spatiotemporal gait features (eg, gait velocity, stride length, step cadence, etc), while the patients are undergoing standardised gait tests at clinics (@Clinics—supervised IGA) or at home (@Home—unsupervised IGA). Third, a home-based physical activity monitoring (PAM) is performed under real-life conditions in the first and last weeks using the same wearable sensors attached on the feet. CRS and IGA are performed at baseline (visit 0=V0), randomisation (visit 1=V1), 2 weeks after randomisation (visit 2=V2), 4 weeks after recruitment (visit 3=V3) and at the end of the intervention (visit 4=V4). PAM is performed prior to randomisation and in the last week of intervention. The study flowchart is represented by figure 1. Table 2 summarises the schedule of enrolment, interventions and assessments.

Instrumented gait analysis (IGA) at clinics and at home

Each wearable sensor includes an inertial measurement unit (IMU) recording 3D acceleration and 3D angular velocity with a sampling rate of 100 Hz. The gait kinematics are analysed through existing validated machine learning algorithms that provide objective metric data for the clinical rating of motor signs.[14–16 22] Although in-clinic tests can only provide a snapshot insight into a patient's mobility, they ensure a high reliability and comparability due to their supervised and standardised nature. Patients are instructed to perform the following gait tasks:

- 2×10 m self-determined preferred gait speed
- 2×10 m self-determined fast speed
- 2×10 m self-determined slow speed
- 2 min walking test at self-determined preferred gait speed

Table 1 Schedule of enrolment, interventions and assessments

Visit plan	V0, week −1 screening	V1, week 1 randomisation	V2 week 2±2 days	V3 week 4±2 days	V-PAM* week 7±2 days	V4 week 8±2 days
Provision of study information and written, informed consent	X					
Inclusion and exclusion criteria	X	X				
Demography, disease history	X					
Physiotherapy history	X					
Neurological examination	X	X	X	X		X
Concomitant medications use	X	X	X	X		X
MDS-UPDRS†	X	X	X	X		X
UMSARS†,‡	X	X	X	X		X
PSP-RS†,§	X	X	X	X		X
Hoehn and Yahr stage	X					X
Montreal Cognitive Assessment (MoCA)	X					X
Frontal Assessment Battery (FAB)	X					X
Orthostatic standing test¶	X	X[4]	X[4]	X[4]		X
Orthostatic Hypotension Questionnaire (OHQ)		X	X	X		X
History of falls**	X	X[5]	X[5]	X[5]		X[5]
International Physical Activity Questionnaire (IPAQ)		X	X	X		X
Freezing of Gait-Questionnaire (FOG-Q)		X	X	X		X
Parkinson's Disease Questionnaire (PDQ-8)		X				X
Clinical Global Impression of Severity (CGI-S)	X					X
Clinical Global Impression of Change (CGI-C)			X	X		X
Patient Global Impression of Severity (PGI-S)	X					X
Patient Global Impression of Change (PGI-C)			X	X		X
System Usability Scale (SUS)		X				X
Berg Balance Scale (BBS)		X	X	X		X
IGA at clinics††	X	X	X	X		X
Adverse events/severe adverse events reporting		X	X	X		X

Continued

Table 1 Continued

Visit plan	V0, week −1 screening	V1, week 1 randomisation	V2 week 2±2 days	V3 week 4±2 days	V-PAM* week 7±2 days	V4 week 8±2 days
PAM analysis‡‡	X				X	
Daily inpatient physiotherapy§§		X				
Daily home-based training¶¶			X			
Weekly phone call***			X			

*Patients living far away will receive the PAM system by certified delivery post.
†Clinical scores must be performed at the beginning of each visit. For screening: should be assessed after informed consent and checking inclusion and exclusion criteria.
‡Only for MSA-P patients.
§Only for PSP patients.
¶Orthostatic standing test needs to be done at screening, if there is no evidence for orthostatic hypotension, this has to be repeated only at V4.
**At V0, patients will be asked about falls in the last 12 months, at V1, V2, V3 and V4, patients will be asked about falls since last visit.
††Will be performed at the end of each visit.
‡‡Patients will be taught to use PAM system for 1 week at the beginning (V0 to V1) and at the end (V-PAM to V4) of the study. PAM will be returned at next visit.
§§From V1 to V2, patients receive inpatient physiotherapy for 60 min. Therapy should take place every day for 14 days excluding weekends.
¶¶From V2 to V4, patients have to train by themselves at home on a daily base. An exercise programme will be provided by the physiotherapist.
***Will be performed by a physiotherapist to check training compliance and adapt exercises where necessary.
IGA, Instrumented Gait Analysis; MDS-UPDRS, Movement Disorder Society-unified Parkinson's disease rating scale; MSA-P, multiple system atrophy with predominant parkinsonian feature; PAM, physical activity monitoring; PSP-RS, progressive supranuclear palsy Richardson syndrome; UMSARS, Unified Multiple System Atrophy Rating Scale.

- Test Timed Up and Go (TUG) Test
- 1×10 m tandem gait

This test battery has been previously validated in a pilot study.[17 2324] As an additional point of reference and to bridge the gap between supervised in-clinic tests and unsupervised continuous real-world monitoring, patients are asked to perform the same gait tasks they performed in-clinic, but unsupervised (similar to reference[25]). Therefore, patients are asked to annotate the timepoints when they would perform those gait-test in a hand-written diary. The timepoint is chosen by the patients in the indicated time slots, respectively, in the morning (between 08:00 and 10:00), the noon (12:00–14:00) and the evening (16:00–18:00). This timepoint can be later used to identify the individual tests within the continuous real-world data. The at-home tests are then analysed with the aforementioned algorithmic pipeline, providing the same outcome measures as the in-clinic recorded data.

Physical activity monitoring (PAM) at home

During each recording week, patients are asked to wear the wearable sensors every day from the time they wake up in the morning until the evening before bedtime. During this period, patients perform the activities of their daily lives while wearing the sensors. During the day, sensor recordings are stored on the sensors internal memory and transmitted via Bluetooth Low Energy to a smart device, for example, a smartphone at the end of each day for analysis (figure 2). The PAM will provide different dimensions of mobility such as walking bouts, the type of activity, its intensity, duration, frequency and dynamics or pattern using validated algorithms.[26]

Outcome measures

Using specific algorithms, various mobility and gait parameters can be derived from the sensor data afterwards. Objective outcomes based on IGA and PAM and clinical outcome measures based on CRS are listed in tables 2 and 3, respectively.

Data management

Anonymised/pseudonymised sensor data and clinical outcome measures will be shared via secure data servers according to the European data protection laws for analysis with the technical sites/partners. Results of the CRS, IGA and PAM are again provided to all clinical partners.

Data analysis plan

Mobility outcomes in terms of PA features and gait parameters will be derived from the wearable sensor data recorded @Clinics and @Home. These include supervised gait tests during the in-clinic visits, unsupervised gait tests performed by the patient at home as well as real-world gait from daily living activities.

According to the recording environment, specific analysis pipelines will be applied which will be based on previously validated algorithms as summarised as follows.

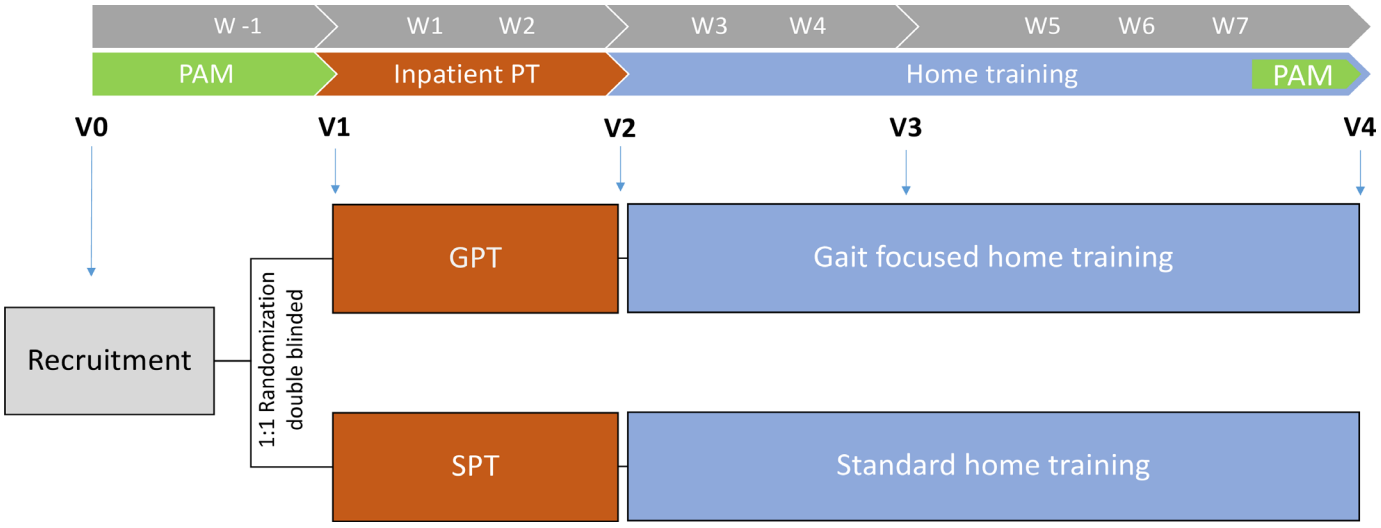

Figure 1 Study flow chart. GPT, gait-focused physiotherapy; IGA, instrumented gait analysis; PAM, physical activity monitoring; PT, physiotherapy; SPT, standard physiotherapy; V, visit; W, week.

Processing of gait test

While the @Clinic gait tests are annotated directly by the supervising clinical expert, the @Home gait tests are annotated retrospectively within the continuous home-monitoring data with the help of the available patient diaries, similar to reference.[25]

For each scenario of gait tests (@Clinic and @Home), spatio-temporal gait parameters are estimated for each stride from the raw foot-worn IMU data (3D acceleration and 3D angular velocity).

Therefore, first individual strides are identified by state-of-the-art stride segmentation algorithms like subsequent dynamic time warping[27] or pretrained hidden Markov models.[28] Next, relevant gait events like initial contact (IC) (usually heel-strike) and terminal contact (TC) (usually toe-off) are extracted to assess temporal parameters.[29]

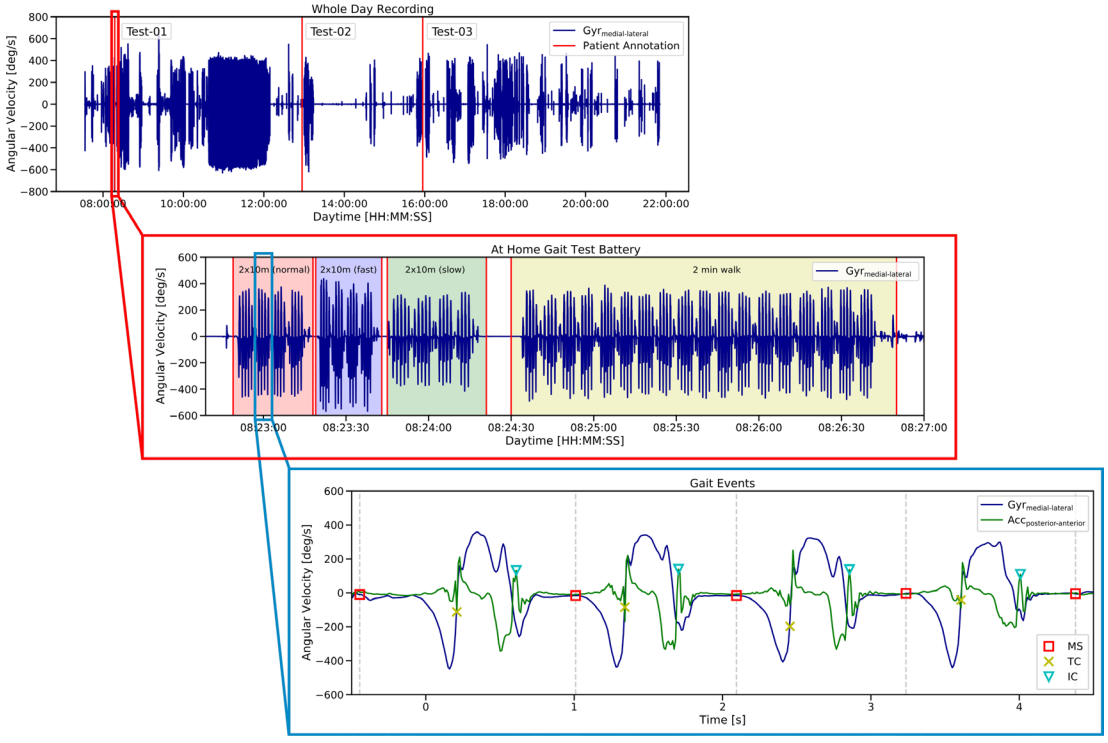

Figure 2 The upper plot shows an example of raw IMU data of one whole day recording using the PAM system. Patients were instructed to perform a battery of standardised gait test three times per day (morning, noon and evening) at home. The middle plot shows an example of an annotated test battery, including a 20 m walking test in normal, fast and slow speeds and a 2 min walk. The bottom plot illustrates a zoomed in view on the raw medio-lateral gyroscope data and corresponding gait event like initial contact (IC), terminal contact (TC) and mid-stance (MS). IMU, inertial measurement unit; PAM, physical activity monitoring.

Table 2 Sensor-derived outcome measures to be estimated for all included patients (MSA and PSP)

Evaluation	Objective outcomes
IGA primary outcomes	1. Temporal parameters: stride time, stance time, swing time and stance time ratio 2. Spatio parameters: stride length, gait speed, pitch angle at toe off and heel strike 3. Gait variability: interstride variability of spatio-temporal parameters 4. asymmetry: differences between left and right foot spatio-temporal parameters
PAM secondary outcomes	Real-world mobility parameters: 1. Type and amount: number of strides/steps per day, number of walking bouts, per cent of time spent walking and sedentary and activity distribution ratio (walking time vs sedentary time) 2. Duration of bouts: statistical distribution of walking and sedentary bouts (eg, typical duration and maximal duration) 3. Intensity: walking speed, cadence and stride length 4. Movement quality: gait asymmetry, stride variability, ability to manage the turning (gait parameters during detected turnings) and smoothness and freezing of gait pattern 5. Pattern: profiles of activity parameters over the course of the day (eg, hourly fluctuation of bout duration, number of steps and peaks activity levels), within and between days variability of PA parameters and temporal clustering of long walking bouts 6. Complexity of PA pattern quantified according to variations in type, intensity, duration and temporal dynamics of activity pattern (eg, breaking sedentary time)

IGA, Instrumented Gait Analysis; MSA, multiple system atrophy; PA, physical activity; PAM, physical activity monitoring ; PSP, progressive supranuclear palsy.

Furthermore, spatial parameters are derived from the reconstructed foot trajectory using a validated drift and gravity corrected double-integration approach.[29] After the reconstruction of individual stride parameters, the mean values as well as inter-stride variability (eg, SD and coefficient of variation) can be calculated to quantify gait performance within each individual test. An example of the analysed IMU data of standardised gait tests performed at home is shown in figure 1.

Processing of real-world physical activity (PA) data

The raw data (acceleration and angular velocity signals recorded by the feet-worn IMU devices) will be first checked for quality and validity by applying state-of-the-art algorithms for detection of outliers and sensor non-wearing during the monitoring protocol.[30] Daily recorded data will be considered valid for subsequent analysis (PA parameter extraction) based on the amount of missing values and the possibility to apply bias-free data imputation techniques.[31] Real-world PA parameters will be extracted from the raw data using validated algorithms for walking bouts detection,[32] gait analysis,[33] quantification of the distribution of walking bouts durations[34] and characterisation of dynamic complexity of PA pattern.[26 34]

Statistics

Numerical variables will be described with means and SD, and categorical variables by percentages. Group differences will be assessed by means of statistical tests

Table 3 Clinical outcome measures

Cohort	Clinical outcomes
All secondary outcomes	► Demography, disease history, health status, physiotherapy history, concomitant medications use ► Neurological examination ► History of falls ► Hoehn and Yahr scale[35] ► Motor and non-motor impairment of all, MSA and PSP patients will be assessed by the Movement Disorder Society (MDS)-sponsored a 'Task Force for Rating Scales in Parkinson's disease' (MDS-UPDRS)[37] ► Montreal Cognitive Assessment[38] ► Orthostatic Stress Test (OST)[39] ► International Physical Activity Questionnaire (IPAQ)[40] ► 8-item Parkinson's disease questionnaire (PDQ-8)[41] ► Frontal Assessment Battery (FAB)[42] ► The Freezing of Gait questionnaire (FOGQ)[43] ► The Berg Balance Scale (BBS)[44] ► The Global Impression of severity and change/improvement scales, clinical and patient based[45] ► The System Usability Scale[46]
MSA secondary outcome	► The Unified Multiple System Atrophy Rating Scale (UMSARS)[47]
PSP secondary outcome	► The Progressive Supranuclear Palsy Rating Scale (PSPRS)[48]

MSA, multiple system atrophy; PSP, progressive supranuclear palsy.

to determine/quantify the effects of interventions. First, the difference of baseline (V0, V1, W-1) and follow-up (V2, V4, V4, W7) outcomes (CRS, IGA and PAM) will be assessed for each individual. Second, the test of normality distribution will be performed for difference values, then we will compare the mean or median difference of outcomes between GPT and SPT groups, using a two-tailed t-test (normal distribution) or non-parametric Wilcoxon-Mann-Whitney rank sum test (non-normal distribution). For the outcome measures estimated at more than two visits (eg, baseline and all follow-up visits), we will use a mixed-effect ANOVA model, using training and visit as fixed factors, subject as a random factor and baseline values as covariates.

Author affiliations
[1]Department of Neurology, Provincial Hospital of Bolzano (SABES-ASDAA), Lehrkrankenhaus der Paracelsus Medizinischen Privatuniversität, Bolzano, Italy
[2]Department of Neurology, Medical University of Innsbruck, Innsbruck, Austria
[3]Ecole Polytechnique Federale de Lausanne, Lausanne, Switzerland
[4]Artificial Intelligence in Biomedical Engineering, FAU, Erlangen, Germany
[5]Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany
[6]Department of Molecular Neurology, Erlangen University Hospital, Erlangen, Germany
[7]Machine Learning and Data Analytics Lab, Department of Computer Science, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany
[8]Service de Neurologie, Département des Neurosciences Cliniques, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland
[9]Department of Molecular Neurology, Friedrich-Alexander University Erlangen, Nürnberg, Germany
[10]Luxembourg Centre for Systems Biomedicine (LCSB), University of Luxembourg, Esch-sur-Alzette, Luxembourg
[11]Digital Medicine - Dep. of Precision Health, Luxembourg Institute of Health, Strassen, Luxembourg
[12]Digital Medicine, Centre Hospitalier de Luxembourg, Luxembourg, Luxembourg

X Felix Kluge @kluger_felix

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Consent obtained directly from patient(s).

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ORCID iDs
Cecilia Raccagni http://orcid.org/0000-0002-6857-2860
Kamiar Aminian http://orcid.org/0000-0002-6582-5375
Jochen Klucken http://orcid.org/0000-0001-6645-9437

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