

Gait analysis in PSP and NPH

Dual-task conditions make the difference

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Abstract

Objective

To test whether quantitative gait analysis of gait under single- and dual-task conditions can be used for a differential diagnosis of progressive supranuclear palsy (PSP) and idiopathic normal-pressure hydrocephalus (iNPH).

Methods

In this cross-sectional study, temporal and spatial gait parameters were analyzed in 38 patients with PSP (Neurological Disorders and Stroke and Society for Progressive Supranuclear Palsy diagnostic criteria), 27 patients with iNPH (international iNPH guidelines), and 38 healthy controls. A pressure-sensitive carpet was used to examine gait under 5 conditions: single task (preferred, slow, and maximal speed), cognitive dual task (walking with serial 7 subtractions), and motor dual task (walking while carrying a tray).

Results

The main results were as follows. First, both patients with PSP and those with iNPH exhibited significant gait dysfunction, which was worse in patients with iNPH with a more broad-based gait ($p < 0.001$). Second, stride time variability was increased in both patient groups, more pronounced in PSP ($p = 0.009$). Third, cognitive dual task led to a greater reduction of gait velocity in PSP (PSP 34.4% vs iNPH 16.9%, $p = 0.002$). Motor dual task revealed a dissociation of gait performance: patients with PSP considerably worsened, but patients with iNPH tended to improve.

Conclusion

Patients with PSP seem to be more sensitive to dual-task perturbations than patients with iNPH. An increased step width and anisotropy of the effect of dual-task conditions (cognitive vs motor) seem to be good diagnostic tools for iNPH.

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Glossary

CERAD = Consortium to Establish a Registry for Alzheimer's Disease; CV = coefficient of variation; HS = healthy controls; iNPH = idiopathic normal-pressure hydrocephalus; PD = Parkinson disease; PSP = progressive supranuclear palsy.

Progressive supranuclear palsy (PSP) and idiopathic normal-pressure hydrocephalus (iNPH) have in common that they are clinically characterized by gait dysfunction, postural instability with retropulsion, and cognitive impairment. Moreover, they seem to share common pathophysiologic mechanisms, with dysfunction of the frontal lobe–basal ganglia and thalamo-mesencephalic loops.^{1–6}

There are accepted diagnostic criteria for PSP and iNPH. However, autopsy studies have demonstrated that the differential diagnosis of both disorders during lifetime might be difficult, not just early in the course of the disease.^{7–9}

The 2 disorders have certain differences in gait. Gait in PSP is characterized by the tendency to swing the legs forward and turn around abruptly without appropriate control.^{3,10} In contrast, gait in iNPH is broad based, the feet appear glued to the ground, and arm swing is exaggerated in at least some cases.^{3,11} While patients with PSP fall more frequently than patients with iNPH, the falls in both disorders are most likely related to motor and cognitive impairments.¹² Gait performance under dual-task conditions critically depends on intact frontal lobe–basal ganglia locomotion loops.¹³ So far, gait performance during cognitive and motor dual tasks has not been specifically addressed in studies of PSP, and quantitative gait parameters of PSP and iNPH have not been compared despite their clinical similarities.

The aims of the present study were to directly compare gait performance in patients with PSP and those with iNPH under single- and dual-task conditions, to test whether quantitative gait analysis can be used for a differential diagnosis of PSP and iNPH, and to stimulate the scientific discussion on the underlying pathophysiology of gait disorders in PSP and iNPH.

Methods

Participants

Thirty-eight patients with PSP and 27 patients with iNPH, diagnosed at the Department of Neurology, Ludwig-Maximilians University Munich, were recruited for this prospective cross-sectional study. The diagnosis of PSP was based on the criteria of the National Institute for Neurological Disorders and Stroke and Society for Progressive Supranuclear Palsy.¹⁴ The diagnosis of iNPH was based on the international iNPH guidelines.² Patients with iNPH were evaluated before CSF drainage. Each patient with PSP was age and sex matched to a healthy control (HS) with no history of neurologic or orthopedic problems that could affect gait and postural control. All participants underwent a complete

neurologic and neuro-ophthalmologic examination. The complete CERAD-Plus (Consortium to Establish a Registry for Alzheimer's Disease) neuropsychological test battery and tonic (mean time iNPH 346 ± 87 milliseconds) and phasic alertness (mean time iNPH 329 ± 82 milliseconds) were measured in the patients with iNPH. The Mini-Mental State Examination and Frontal Assessment Battery (mean PSP 13.9 ± 2.3) were performed in the patients with PSP. Participants were not explicitly matched according to those measures. Additional technical diagnostic procedures were performed (e.g., electrophysiologic examination, MRI of the spinal cord, and vestibular testing) to exclude differential diagnoses and neurologic comorbidities relevant for gait and cognitive function. All participating patients were able to walk at least 10 m without a walking aid.

Standard protocol approvals, registrations, and patient consents

The study was performed in accordance with the 1964 Declaration of Helsinki and was approved by the local ethics committee. Written informed consent was obtained from all participants.

Clinical assessment

The PSP Rating Scale was assessed at the time of examination.¹⁵ Every patient included in this study performed the Functional Gait Assessment in addition to the gait analysis.¹⁶ This score did not differ between the 2 patient groups (PSP 18.5 ± 4.0 vs iNPH 18.8 ± 3.7 , $p = 0.68$), and an interindividual comparison showed a good match. Thus, the differences in gait performance could not be explained by differences in the severity of the gait disorder in general. An evaluation of falls within the last 6 months was made for each patient.¹⁷ The midbrain diameter and the Evan index (maximal width of frontal horns/maximal width of inner skull) were quantitatively measured by MRI. The Fazekas scale was used to quantify the amount of white matter T2-hyperintense lesions.¹⁸ To exclude patients with a differential diagnosis or comorbidities, only patients scoring <2 on the Fazekas scale were included.

Gait assessment

Gait was analyzed with a computer-based, 6.7-m-long pressure-sensitive carpet system (GAITRite, CIR System, Havertown, PA) with a sampling rate of 120 Hz. Relevant temporal and spatial gait cycle parameters were recorded. The gait analysis involved a protocol of 5 different conditions: 3 single-task conditions (preferred, slow, and maximal speed), 1 cognitive dual-task condition (serial 7 subtractions from 100), and 1 motor dual-task condition (carrying a tray). Each condition was tested twice. To ensure steady-state

locomotion, every walk was started 1.5 m in front of the carpet and continued for 1.5 m behind it. The use of assistive walking aids was not allowed. Patients were always safeguarded by a researcher walking alongside. For the single-task conditions, the instructions were as follows: to walk with preferred velocity, slowly, and as fast as possible, but without running, and still safely. As dual-task conditions, the patients walked at their preferred speed while simultaneously counting backward or carrying a tray. No prioritization of any task was required. The researcher continuously motivated the participant to keep on calculating and walking to avoid any prioritization.

Statistical analysis

The primary outcome measures were velocity (centimeters per second), cadence (steps per minute), step width (centimeters), stride length (centimeters), and coefficient of variation (CV)¹⁹ of stride time, stride length, and step width.

$$CV(\%) = \frac{SD \text{ of parameter} \times 100}{\text{mean of parameter}}$$

The CV of stride length represents the variability in the anterior-posterior plane. The CV of step width represents the variability in the mediolateral plane.

Dual-task costs express the effect of divided attention and were presented as the percentage of the difference between single task and dual task.¹¹ Dual-task costs were calculated for all primary outcome measures.

Dual task cost(%)

$$= \frac{\text{parameter under dual task} - \text{parameter under single task}}{\text{parameter under single task}} \times 100$$

Statistical analyses were performed with SPSS (Statistical Package for Social Sciences, version 23, SPSS, Inc, Chicago, IL). For categorical data, absolute (number) and relative (percent) frequencies were determined and compared by use of the χ^2 test. Continuous data were presented as mean values with the corresponding SDs. The Kolmogorov-Smirnov test was used to ascertain whether data were normally distributed. Paired and unpaired t tests were used to compare normally distributed data. The effects of the dependent variable were analyzed with a 1-way analysis of variance. To address the question of the added value of dual-task testing in the differential diagnosis of PSP and iNPH, we performed discriminant analysis using gait parameters as independent variables and the patient groups (HS, PSP, iNPH) as dependent variables. The gait parameters of the 3 gait conditions (single task, cognitive dual task, motor dual task) were used separately and in combination to build a predictive model for group membership. The results were considered significant at $p < 0.05$.

Results

Patient characteristics

Mean age and sex distribution did not significantly differ between the 3 groups (table 1). First and leading symptoms of patients with PSP were generalized bradykinesia,

Table 1 Single-task gait parameters in HS and patients with PSP and iNPH

	HS (n = 38), mean (SD)	PSP (n = 38), mean (SD)	iNPH (n = 27), mean (SD)	p Value		
				HS vs PSP	HS vs iNPH	PSP vs iNPH
Female sex, n (%)	18 (47)	18 (47)	6 (22)	0.82	0.056	0.056
Age, y	68.9 (7.6)	69.0 (6.3)	72.0 (8.1)	0.95	0.12	0.11
Preferred speed						
Velocity, cm/s	111.6 (22.5)	82.3 (24.0)	63.9 (15.9)	<0.001	<0.001	0.001
Cadence, steps/min	108.5 (12.5)	98.3 (17.9)	98.3 (13.3)	<0.001	<0.001	0.99
Stride length, cm	122.9 (15.2)	99.0 (17.6)	78.3 (16.3)	<0.001	<0.001	<0.001
Step width, cm	9.3 (3.2)	10.2 (5.5)	16.0 (3.3)	0.41	<0.001	<0.001
CV of stride time, %	2.4 (1.0)	5.5 (3.7)	3.8 (1.2)	<0.001	<0.001	0.009
CV of stride length, %	2.9 (1.4)	5.2 (3.3)	6.8 (3.6)	<0.001	<0.001	0.063
CV of step width, %	23.4 (10.6)	10.2 (67.8)	12.8 (5.2)	0.24	<0.001	0.84
Slow speed						
Velocity, cm/s	59.9 (21.7)	42.6 (16.0)	35.9 (8.9)	<0.001	<0.001	0.055
Maximal speed						
Velocity, cm/s	159.7 (25.3)	125.9 (28.8)	106.9 (21.4)	0.001	0.001	0.005

Abbreviations: CV = coefficient of variability; HS = healthy controls; iNPH = idiopathic normal-pressure hydrocephalus; PSP = progressive supranuclear palsy.

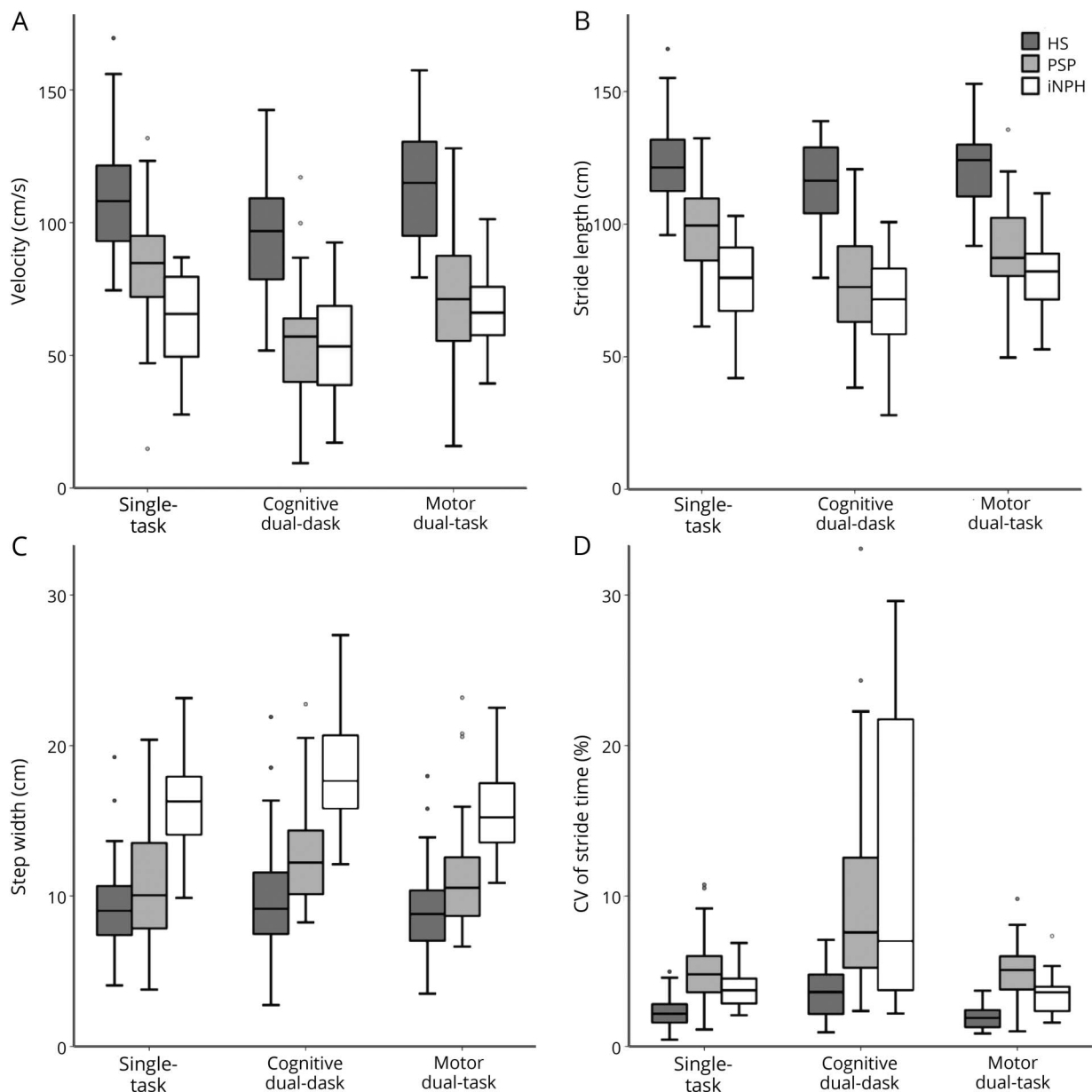
gait disturbance with falls, and supranuclear vertical gaze palsy (PSP Rating Scale score 31.1 ± 8.9). MRI scans of the brain showed relevant midbrain atrophy (mean midbrain diameter 15 ± 2 mm). The leading symptoms of patients with iNPH were gait dysfunction with slow, broad-based, and small-stepped gait, as well as cognitive deficits. The Evans index, an established parameter of ventricular enlargement,² was increased by 0.40 ± 0.05 in the iNPH group. The duration of symptoms was longer in the PSP

group (PSP 42.1 ± 27.5 vs iNPH 23.4 ± 19.9 months, $p = 0.009$). The rate of falls within the past 6 months was higher in the patients with PSP (PSP 100% vs iNPH 56%, $p < 0.001$).

Single-task condition

Compared to HS, both patients with PSP and those with iNPH had a significantly inferior gait performance (table 1). Compared with patients with PSP, the gait of patients with

Figure 1 Medians, 25% and 75% percentiles, and minimal and maximal values for single- and dual-task gait parameters in HS and patients with PSP and iNPH



The gait of patients with iNPH was characterized by a (A) lower velocity ($p = 0.001$) and (B) stride length ($p < 0.001$) than in patients with PSP. The main differences were (C) a more broad-based gait in iNPH ($p < 0.001$) and (D) a higher CV of stride time in patients with PSP than in those with iNPH ($p = 0.009$). Under the cognitive dual-task condition (serial 7 subtractions from 100), gait velocity was clearly more reduced in patients with PSP, while the reduction in patients with iNPH was comparable to that in HS (velocity reductions: PSP 34.4%, iNPH 16.9%, HS 14.8%). Under the motor dual-task condition (carrying a tray), velocity decreased in PSP by 10.3%; in contrast, velocity increased by 7.0% in patients with iNPH. CV = coefficient of variation; HS = healthy controls; iNPH = idiopathic normal-pressure hydrocephalus; PSP = progressive supranuclear palsy.

iNPH was characterized by a lower velocity ($p = 0.001$) and shorter stride length ($p < 0.001$). The main differences were a more broad-based gait in iNPH ($p < 0.001$) and a higher CV of stride time in PSP ($p = 0.009$) (figure 1).

When expressed as a function of gait velocity, the CV of stride time was highest for slow velocity and lowest for maximal velocity in both patient groups (figure 2). In patients with PSP, the CV of stride length increased at the time when the CV of step width decreased (Spearman rank correlation coefficient = -0.338). This correlation was not seen in patients with iNPH or HS.

Cognitive dual-task condition

As a general index of cognitive functioning, the Mini-Mental State Examination was compared between both groups (mean score: PSP 27.3 ± 3.1 vs iNPH 23.4 ± 3.3 , $p = 0.001$). The phonemic verbal fluency was compared between both groups to determine frontal-executive functioning (mean number: PSP 9.7 ± 4.5 vs iNPH 9.1 ± 4.0 words, $p = 0.661$). Cognitive dual task led to a significant impairment of gait in all 3 groups. Patients with PSP were significantly more sensitive to dual-task perturbation than patients with iNPH (table 2). Especially gait velocity was clearly more reduced in patients with PSP, while the reduction in patients with iNPH was comparable to that in HS (figure 1).

Motor dual-task condition

Motor dual task led to a significant decrease of gait velocity and stride length in patients with PSP, but to a lesser extent than cognitive dual task (table 2). These effects were also significant compared to those in HS and patients with iNPH. Surprisingly, the gait performance of patients with iNPH tended to even improve in the motor dual task ($p = 0.17$). For example, while the most relevant parameter, gait velocity, decreased in patients with PSP, it increased in patients with iNPH (figure 1).

Discriminant analysis

The gait parameters from the single-task condition were found to be able to classify patients into the 3 groups (PSP, iNPH, HS) with an accuracy of 76.7% (Wilks' $\lambda = 0.298$, $p < 0.001$). For the cognitive dual task, the accuracy was 77.7% (Wilks' $\lambda = 0.292$, $p < 0.001$), and for the motor dual task, the accuracy was 76.7% (Wilks' $\lambda = 0.290$, $p < 0.001$). When the gait parameters of all 3 conditions were combined, 90.3% of the patients were correctly classified (Wilks' $\lambda = 0.130$, $p < 0.001$).

The accuracy for the differential diagnosis of only PSP and iNPH (without HS) in the single task was 81.5% (Wilks' $\lambda = 0.559$, $p < 0.001$), in the cognitive dual task was 83.1% (Wilks' $\lambda = 0.557$, $p < 0.001$), in the motor dual-task was 86.2%

Figure 2 Stride time variability depends on gait velocity

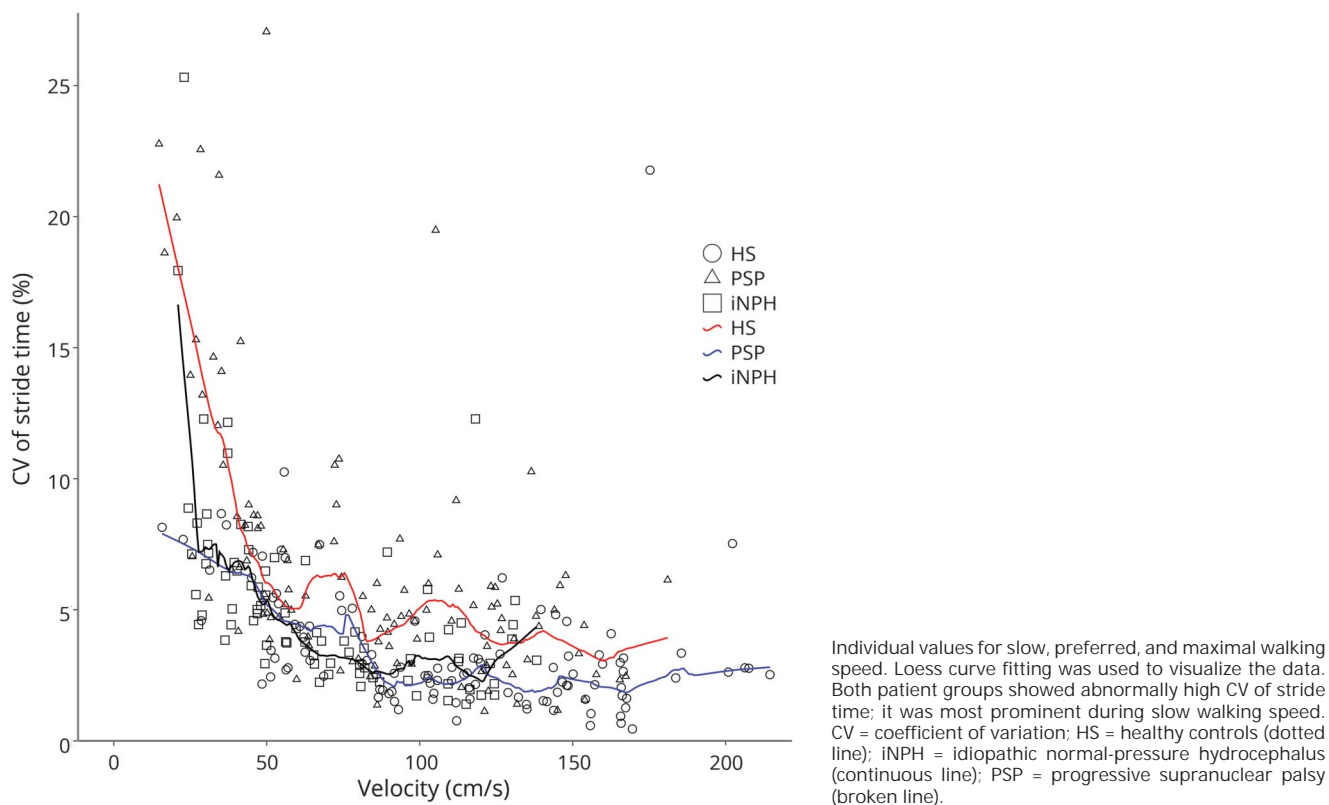


Table 2 Dual-task costs in HS and patients with PSP and iNPH

	HS (n = 38), mean (SD)	PSP (n = 38), mean (SD)	iNPH (n = 27), mean (SD)	p Value		
				HS vs PSP	HS vs iNPH	PSP vs iNPH
Cognitive dual-task cost						
Velocity, %	-14.8 (14.8) ^a	-34.4 (19.0) ^a	-16.9 (25.4) ^a	<0.001	0.70	0.002
Cadence, %	-9.0 (10.3) ^a	-17.6 (13.9) ^a	-5.1 (12.7) ^a	0.003	0.18	<0.001
Stride length, %	-7.0 (9.2) ^a	-22.0 (13.1) ^a	-13.6 (17.0) ^a	<0.001	0.075	0.028
Step width, %	7.4 (25) ^a	19.6 (50.5) ^a	15.9 (17.3) ^a	0.19	0.13	0.72
CV of stride time, %	100.6 (157.8) ^a	182.7 (282.9) ^a	251.0 (292.6) ^a	0.20	0.020	0.26
CV of stride length, %	43.2 (85.0) ^a	138.5 (200.0) ^a	110.1 (138.2) ^a	0.008	0.031	0.53
CV of step width, %	3.1 (57.4)	-52.5 (202.8)	-14.1 (33.5) ^a	0.11	0.16	0.34
Motor dual-task cost						
Velocity, %	4.0 (15.1)	-10.3 (15.3) ^a	7.0 (18.1)	<0.001	0.50	<0.001
Cadence, %	4.6 (8.2) ^a	-1.7 (9.6)	3.2 (8.2)	0.003	0.50	0.036
Stride length, %	-0.8 (7.4)	-8.8 (10.7) ^a	2.9 (13.6)	<0.001	0.16	<0.001
Step width, %	-0.0003 (16.9)	2.8 (46.4)	-0.37 (10.7)	0.73	0.92	0.69
CV of stride time, %	34.0 (198.8)	22.3 (80.4)	-6.0 (31.9)	0.74	0.92	0.056
CV of stride length, %	-3.9 (57.0) ^a	24.3 (104.6)	20.8 (47.7)	0.15	0.071	0.87
CV of step width, %	8.1 (54.4)	20.1 (158.5)	0.3 (42.9)	0.66	0.54	0.53

Abbreviations: CV = coefficient of variability; HS = healthy controls; iNPH = idiopathic normal-pressure hydrocephalus; PSP = progressive supranuclear palsy.
^aSignificantly different from the single-task condition within group.

(Wilks λ = 0.510, $p < 0.001$), and in the combination of all 3 conditions was 96.9% (Wilks λ = 0.264, $p < 0.001$).

Discussion

The main findings of this study can be summarized as follows: compared with patients with PSP, the gait of patients with iNPH was slower and more broad based; gait variability was higher in patients with PSP; and patients with PSP were more sensitive to dual-task perturbation. Under motor dual task, patients with iNPH tended to even improve.

Our patient groups showed a few typical gait changes regarding the gait parameters. The gait of patients with iNPH was slower and more broad based than that of patients with PSP, although the symptoms of patients with iNPH were of shorter duration. Similar results were reported by 2 previous studies that compared gait parameters in patients with iNPH and patients with Parkinson disease (PD).^{20,21} The slower gait speed in iNPH might reflect a more specific impairment of the cerebral locomotion network compared to that in PSP or PD. The anatomic correlate might be the medial septum neurons in the frontal lobe, which animal studies have shown mediate locomotion speed.^{22,23} This area is often affected by periventricular gliosis in iNPH. An alternative interpretation

might be that the course of disease progression in iNPH is steeper. However, our data and that of other studies^{20,21} cannot really differentiate disease progression or a longer asymptomatic phase. The broad-based gait in iNPH has been shown in the past to be a very promising parameter for differential diagnosis with PD.²¹ The PSP data on step width are controversial.^{10,24} HS also exhibit an iNPH-like gait pattern, but only in situations associated with fear of falls.³ One might assume that patients with iNPH value stability over efficiency. Gait variability as a marker for fall risk was higher in patients with PSP.²⁵⁻²⁷ This correlates well with clinical observations that the risk of falls increases in both iNPH and PSP, but more so in PSP. We found that the variability of stride duration decreased with increased walking speed in both patient groups. This effect was more pronounced in PSP. This might be due to an upregulation of the so-called direct locomotion pathway in PSP to compensate for the malfunctioning of the indirect locomotion pathways, as discussed elsewhere.⁴

In the discriminant analysis, the single task alone already yielded good accuracy in the differential diagnosis of PSP, iNPH, and HS. Nevertheless, the addition of the dual-task conditions led to a considerable increase of accuracy (13.6%). The results of the discriminant analysis demonstrate that quantitative gait analysis can be used for a differential diagnosis of PSP and iNPH.

Moreover, it is worthwhile to perform dual-task testing in addition to single-task testing. An earlier study of patients with PSP found that a cognitive dual-task condition could be used to discriminate patients according to their fall risk.¹³ We showed that a cognitive dual-task increases variability in the anterior-posterior plane and decreases gait velocity in PSP and iNPH, more pronounced in patients with PSP. One might consider this to be a poor effect, given the already slow gait velocity at baseline in patients with iNPH. However, when specifically instructed to walk slowly, patients with iNPH demonstrated that they were capable of further reducing their velocity (slow speed velocity 35.9 cm/s, cognitive dual-task velocity 53.0 cm/s, motor dual-task velocity 66.9 cm/s). That patients with PSP are more sensitive to dual-task perturbation at first seems to be exactly the opposite of what is initially expected because the gait of patients with PSP is considered subcortical and hypokinetic, while that of patients with iNPH is a frontal gait type.²⁰ In this study, participants were not matched for their cognitive function, but the phonemic verbal fluency, an index of frontal-executive functioning, did not show any difference between the 2 patient groups.^{28,29} Thus, their different performance during the cognitive dual task is not explained by differences in cognitive impairment. The inferior performance of patients with PSP therefore might indicate that more cortical, especially prefrontal, control is already necessary for single-task gait so that their capacities for additional recruitment are saturated. They also might have a reduced capacity per se for cortical and prefrontal recruitment.³⁰ The results in the discriminant analysis showed that the motor dual task was the most exact condition for differentiating PSP and iNPH. The gait performance of patients with iNPH and those with PSP showed a surprising dissociation during this condition. As expected, gait in patients with PSP worsened during motor dual task (although not as much as during cognitive dual task). In contrast, patients with iNPH tended to even improve. One interpretation might be that the motor dual task was not challenging enough for the iNPH group. In future studies, it would be interesting to increase the task complexity (i.e., by adding a glass filled with water) to test whether the improvement trend observed here becomes significant. However, because the patients with PSP already had major difficulties with this motor dual task, an increase in task complexity was not possible in our study. We hypothesize that dual-task situations result in increased activity of the prefrontal cortex, which partly compensates for the loss of callosal interhemispheric connections in iNPH. Because the motor dual task was the last condition tested in all the patients, a learning effect cannot be excluded. However, this seems rather unlikely because a tendency to improve was not observed in the PSP group or in other cohorts tested with the same paradigm in the past.^{11,19,31} Together, these interactions support the view that cognition and locomotion share common prefrontal areas and that the improvement of cognitive functions plays an essential role in the rehabilitation of gait disorders and vice versa.³⁰ There was a correlation, with the CV of stride length increasing at the time when the CV of step width decreased, in patients with PSP that was not seen in patients with iNPH or in HS. Mediolateral and anterior-posterior gait aspects in PSP thus

seem to be closely connected with each other.^{24,32} Interesting questions for future physical therapy studies are the mediolateral gait aspects of PSP and whether balance training in PSP and iNPH should focus on slow speed.

Our study has certain limitations. The most important one is the absence of a histopathologic diagnosis. This is a limitation of every study that relies on a clinical diagnosis. Because we were aware of this problem, we included only typical clinical cases that were examined and characterized in detail. A second unavoidable limitation of studies that compare different diseases is the definition of symptom load. We tried to solve this problem by determining the Functional Gait Assessment. We did not explicitly pose the question of whether the patients prioritized 1 task (calculation task vs walking task) because we did not examine the single-task calculation while the patient was seated.

The new and clinically relevant findings reported in this study are that patients with PSP are more sensitive to dual-task perturbations than patients with iNPH. The increased step width and anisotropy of the effect of dual-task conditions (cognitive vs motor) appear to be good diagnostic criteria for iNPH. The high rate of correct classification in the discriminant analysis reflects the high quality of our data and shows that quantitative gait analysis allows a differential diagnosis of PSP and iNPH.

Author contributions

Charlotte Selge: drafting/revising the manuscript, study concept and design, acquisition of data, analysis and interpretation of data, statistical analysis. Florian Schoeberl: drafting/revising the manuscript, analysis and interpretation of data. Andreas Zwergal: drafting/revising the manuscript, study concept and design. Georg Nuebling: drafting/revising the manuscript. Thomas Brandt and Marianne Dieterich: drafting/revising the manuscript, analysis and interpretation of data. Roman Schniepp: drafting/revising the manuscript, acquisition of data. Klaus Jahn: drafting/revising the manuscript, study concept and design, analysis and interpretation of data, study supervision.

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Disclosure

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