

RESEARCH ARTICLE

Type of exercise may influence postural adaptations in chemotherapy-induced peripheral neuropathy

Sarah Waibel^{1,2} , Anja Wehrle^{3,4}, Jana Müller^{2,5} , Hartmut Bertz² & Christoph Maurer¹¹Department of Neurology and Neuroscience, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany²Department of Medicine I, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany³Department of Sport and Sport Science, University of Freiburg, Freiburg, Germany⁴Institute for Exercise and Occupational Medicine, Faculty of Medicine, Medical Center, University of Freiburg, Freiburg, Germany⁵Working Group Exercise Oncology, Department of Medical Oncology, National Center for Tumor Diseases (NCT) and Heidelberg University Hospital, Heidelberg, Germany

Correspondence

Christoph Maurer, Department of Neurology and Neuroscience, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Breisacher Straße 64, 79106 Freiburg, Germany. Tel: +49 761 270 50010, Fax: +49 761 270 52300; E-mail: christoph.maurer@uniklinik-freiburg.de

Received: 17 September 2020; Revised: 15 June 2021; Accepted: 15 June 2021

Annals of Clinical and Translational Neurology 2021; 8(8): 1680–1694

doi: 10.1002/acn3.51426

Abstract

Objective: Traditional posturography measurements characterize postural instability in patients with chemotherapy-induced peripheral neuropathy (CIPN), while underlying postural control mechanisms remain unclear. Taking a model-based approach can yield insights into these mechanisms. This study's aim was to characterize the modifications in postural control of CIPN patients associated with exercise in relation to the postural behavior of healthy control participants (hCON) via an exploratory approach. **Methods:** Thirty-one CIPN patients were randomly assigned to two interventions (balance plus moderate endurance training vs. moderate endurance training only) and exercised twice per week over 12 weeks. Baseline data were compared to 36 matched hCONs. We recorded spontaneous sway and postural reactions to platform tilts using Optotrak and a Kistler force platform pre- and post-intervention. Data interpretation relied on a model-based parameter identification procedure. **Results:** Spontaneous sway amplitudes were larger and postural reactions smaller, with a relative phase advance, in our pre-intervention patients than the hCONs. Post-intervention, spontaneous sway, and postural reactions were reduced and the sensory-motor ratio larger in both groups, while the postural reaction timing differed between groups. **Interpretation:** The abnormally small postural reactions in CIPN patients before the intervention can be interpreted as the consequence of abnormally strong velocity control—a strategy modification that may serve as a prediction mechanism to compensate for the lack of timely and accurate proprioceptive signals. While both groups reduced postural sway and showed an adapted sensory-motor ratio post-intervention, the interventions seemed to trigger different velocity control strategies. This study emphasizes the need for taking a more differentiated perspective on intervention effects. **Trial registration:** German Clinical Trials Register (DRKS) number: DRKS00005419, prospectively registered on November 19, 2013.

Introduction

Specific chemotherapy agents damage the peripheral nerves leading to chemotherapy-induced peripheral neuropathy (CIPN) that impairs sensory perception primarily.¹ A disabling consequence of CIPN is postural instability, a topic drawing increasing attention in the

literature.^{2–11} The term CIPN-associated postural instability refers to impaired balance performance,^{3,5,11–13} poorer gait abilities,^{2,5} and increased fall risk^{2,4,8–10} compared to persons without CIPN. These functional symptoms can persist after the completion of chemotherapy.¹⁴

CIPN is associated with preferential damage to the myelinated primary afferent sensory nerve fibers^{15,16} that

also carry somatosensory information essential for adequate posture control.^{17,18} Applying the sensory organization test (SOT), Monfort et al.¹¹ confirmed the assumption that poor balance performance in CIPN is related to the impaired interpretation of somatosensory information. In line with their study, we detected abnormally low use of proprioceptive cues in CIPN patients potentially interfering with effective posture control by evaluating perturbed stance and applying a model-based analysis strategy in a pilot approach.¹⁹ Then, we compared the postural behavior of eight CIPN patients to healthy control participants before and after 12 weeks of intervention (endurance, balance, and strength training). Furthermore, in a cross-sectional study including H-reflex assessment, we observed an altered spinal reflex circuitry also associated with postural instability in CIPN patients.¹² Those findings point to interrelated CIPN-induced afferent dysfunction and postural instability.

Despite CIPN-related neuronal impairments, specific exercises might have the potential to improve the balance performance of CIPN patients.^{20–23} In general, balance exercises are a key interventional component to counteract stance- or gait disturbances that limit daily activities and raise the risk of falling.^{24–29} Balance training can induce neuromuscular adaptations that can improve postural control mechanisms.^{27,30} There is far too little known about underlying postural control mechanisms in conjunction with CIPN. Deeper understanding thereof would facilitate effective treatment strategies to manage postural instability in CIPN, since the evidence level is still insufficient.^{31,32} Only our aforementioned pilot study has so far identified relevant parameters responsible for postural adaptations in CIPN after exercising. There, we additionally implemented a balance-based exercise intervention that induced a sensory shift toward the postural behavior of healthy control participants by up-weighting proprioception despite CIPN.¹⁹ This pilot approach had certain limitations (e.g., no patient control group, small sample size, multimodal intervention),¹⁹ but it nevertheless formed the basis for the present study.

The present randomized controlled trial included cancer survivors suffering from CIPN after completing chemotherapy. All patients engaged in moderate endurance training, that is, cycling training, while half of the patient group additionally performed balance training, assuming that the addition of balance training would lead to better balance performance. The results of this primary endpoint were published elsewhere verifying our hypothesis.³³ Now, we present a subgroup analysis where we aimed to identify underlying mechanisms responsible for CIPN patients' modifications in postural behavior taking an exploratory approach. We, therefore, recorded spontaneous sway and postural reactions to platform tilts, and

applied an established postural control model^{34–36} (i) to detect differences in physiological principles leading to different postural behaviors of CIPN patients and healthy control participants and (ii) to explain the effects of both interventions on patients' postural behavior.

Materials and methods

Patients and study design

This model-based analysis uses data from patients who had been enrolled in a randomized controlled trial (RCT) published elsewhere.³³ In this RCT, 50 cancer survivors reporting CIPN symptoms after having completed anti-tumor treatment were randomly allocated to two intervention groups: patients (PAT) performed either balance training additionally to moderate endurance training (PAT_{E+B}) or only moderate endurance training (PAT_E). For further inclusion- and exclusion criteria, see 33.

Our subgroup analysis contains 42 CIPN patients who additionally underwent specific postural control assessments analyzed via a model-based approach. Eleven participants were omitted for the following reasons: Post-randomization data were unavailable on five of these patients (time conflict, further therapy indication, orthopedic problem). One additional patient was excluded due to a recruiting mistake, four patients failed to achieve $\geq 70\%$ training compliance, and one data set was unassessable. We thus describe our postural control analysis of 31 patients.

Postural behavior at baseline was compared to a group of 36 healthy control participants (hCONs) matching in sex, age, weight, and height (Table 1). The hCONs' exclusion criteria were a history of cancer diagnosis or symptoms of peripheral neuropathy, or any type of balance or gait disorder.

Patients underwent assessments of posture control twice (before and after 12 weeks of the supervised exercise intervention), while the hCONs underwent this assessment only once.

Moreover, patients took functional performance tests and a cardiopulmonary exercise test (CPET) on a stationary bicycle pre- and post-intervention in order to rule out any cardiovascular risks during exercise and to determine the load for the endurance exercise.³³

This study was approved by the Ethics Committee of the University of Freiburg, prospectively registered in the German Clinical Trials Register (DRKS00005419), and conducted according to the Declaration of Helsinki. Each patient had to sign written informed consent prior to inclusion.

Interventions

The one-on-one training sessions took place twice per week over 12 weeks in the division of Sports Oncology in the Clinic of Internal Medicine I. Both groups underwent

Table 1. Participants' characteristics.

	Patients			Patients All N = 31	hCON N = 36	p
	PAT _{E+B} n = 16	PAT _E n = 15	p			
Sex m:f N (%)	3 (19) : 13 (81)	6 (40) : 9 (60)		9 (29) : 22 (71)	17 (47) : 19 (53)	
Age*	67 (44–82)	60 (46–75)	0.041	64 (44–82)	70 (36–80)	0.9
Body height (cm)*	168 (148–182)	170 (148–190)	0.446	168 (148–190)	169 (151–190)	0.597
Body Mass (kg)*	72 (42–112)	72 (54–106)	0.83	72 (42–112)	69 (48–96)	0.955
Diagnosis N (%)						
Colorectal cancer	3 (19)	9 (60)		12 (39)		
Breast cancer	8 (50)	3 (20)		11 (36)		
Gynecological cancer [†]	1 (6)	1 (7)		2 (7)		
Upper gastrointestinal cancer	1 (6)	1 (7)		2 (7)		
Non-Hodgkin's lymphoma	3 (19)	1 (7)		4 (13)		
Therapies N (%)						
Surgery	15 (94)	15 (100)		30 (97)		
Radiation	8 (50)	3 (20)		11 (36)		
HCT	1 (6)	1 (7)		2 (7)		
Chemotherapy	16 (100)	15 (100)		31 (100)		
N cycles*	6 (2–16)	6 (2–16)	0.861	6 (2–16)		
N neurotoxic agents*	2 (1–4)	1 (1–4)	0.066	2 (1–4)		
Therapy-free weeks*	13 (1–167)	18 (3–98)	0.984	15 (1–167)		
CIPN symptoms N (%)						
Reduced vibration sense [#]	13 (81)	9 (60)		22 (71)		
Reduced joint position sense [†]	5 (31)	4 (27)		9 (29)		
Reduced temperature sensation [‡]	9 (56)	7 (47)		16 (52)		
Reduced pain sensation [‡]	2 (13)	1 (7)		3 (10)		
Loss of reflexes ATR / PTR	11 (69) / 2 (13)	10 (67) / 2 (13)		21 (68) / 4 (13)		
Compliance (%) *	92 (71–100)	100 (71–100)	0.118	92 (71–100)		

p-values <0.05 are marked in bold; * median (range); [†] other than breast; [#] measured on the first metacarpophalangeal joint, value < 5 (scale 0–8); [†] measured on the second toe, ≥ 3 failures out of 10 trials in random order; [‡] measured on arch, ≥ 3 failures out of 10 trials in random order. Abbreviations: ATR, Achilles tendon reflex; hCON, healthy control participants; HCT, hematopoietic cell transplantation; PAT_E, CIPN patients performing only endurance training; PAT_{E+B}, CIPN patients performing endurance plus balance training; PTR, patellar tendon reflex.

endurance training lasting up to 30 min of moderate intensity below the individual anaerobic threshold on a stationary bicycle. Half of the patient group (PAT_{E+B}) also did an additional 30 min of balance training (+balance). Balance exercise sessions included three to eight exercises with three repetitions each à 20–30s involving progressively increasing exercise difficulty by reducing the support surface and visual input, adding motor/cognitive tasks, and inducing instability. For both groups, we monitored exercise intensity by the perceived exertion rating scale ³⁷ aiming to achieve an adequate intensity level (meaning an exertion of “somewhat hard” to “hard”) by individually adapting the exercises accordingly.

Assessments of CIPN symptoms

Vibration sense was determined on the first metacarpophalangeal joint and knuckle via Rydel–Seiffer tuning fork. Furthermore, we used the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-CIPN20 questionnaire to estimate CIPN severity, see 33.

Functional performance tests

Functional performance tests were conducted on a force plate (Leonardo Mechanograph® GRFP, Novotec Medical GmbH, Pforzheim, Germany). For balance assessments, we recorded the duration (max. 30s) patients were able to stand on one leg on a stable and instable surface (foam), respectively. To evaluate the lower body's muscle power, patients performed a maximum counter-movement jump to measure the jumping height (cm) and maximum power output during take-off (P_{max}).³³

Data were analyzed using Leonardo Mechanography Research-Software (Novotec Medical GmbH, Pforzheim, Germany).

Assessment of postural control behavior

Postural control assessments, that is, *spontaneous sway* and *perturbed stance* were measured with a custom-built motion platform under two *visual conditions*, with eyes open and with eyes closed.^{38,39} Each trial lasted one

minute. The participants were told to stand upright on the platform in comfortable shoes. Stance width was predetermined within a marked area. For safety reasons, participants had to hold two ropes hanging from the ceiling in crossed-arms position so that they could not perceive a somatosensory spatial orientation signal.^{35,40}

Data analysis was conducted offline with custom-made software programmed in MATLAB® (The MathWorks Inc., Natick, MA, USA).

Spontaneous sway was measured on the non-moving platform. The center of pressure (COP) sway path was detected with a force-transducing platform (Kistler platform type 9286, Winterthur, Switzerland). From the COP excursions over time in anterior–posterior and mediolateral *sway directions*, we calculated the root mean square (RMS) around the mean COP position. After differentiating the time series, we calculated mean velocity (MV). In addition, the center frequency (CF) was extracted from the power spectrum.^{41,42}

Perturbed stance was measured on a moving platform to differentiate sensory contributions in reaction to external disturbances. We analyzed rotational tilts in the sagittal plane with the tilt axis passing through the participant's ankle joints, as the stimulus profile followed a pseudorandom stimulus (PRTS, pseudorandom ternary sequence³⁴) with two peak angular displacements (*stimulus amplitude*: 0.5° and 1° peak-to-peak). Data were analyzed at 11 *stimulus frequencies* (0.05, 0.15, 0.3, 0.4, 0.55, 0.7, 0.9, 1.1, 1.35, 1.75, and 2.2Hz).

Excursions of the lower (hip movement, determined by the angle of the leg segment with respect to the earth vertical) and upper (shoulder movement, determined by the angle of the head-and-trunk segment with respect to the earth vertical) *body segments* and of the platform in space were measured using an optoelectronic motion-measuring device (Optotrak 3020, Waterloo, Canada). Each marker consisted of three light-emitting diodes (LED) fixed to a rigid triangle. The triangles were fixed on the participant's hips and shoulders. Optotrak® and Kistler® output signals as well as the stimulus signals were sampled at 100Hz using an analog-digital converter. We recorded all data with software programmed in LabVIEW® (National Instruments, Austin, Texas, USA).

To analyze postural reactions in relation to platform stimuli, we calculated *transfer functions* from stimulus-response data via a discrete Fourier transform. Fourier coefficients of stimulus and response time series were used to determine *GAIN* and *PHASE* regarding stimulus frequencies. *GAIN* represents the size of the postural reaction as a function of stimulus size (platform angle), while *PHASE* is related to the relative timing between the postural reaction and stimulus⁴⁰.

Parameter identification of postural control assessment

Transfer functions derived from Fourier transforms served as the experimental data basis for model simulations using a specific version of an established postural control model^{34,36,39,43–45} with active time-delayed proportional, derivative, and integral feedback as well as passive stiffness and damping to extract basic constituents of postural control (Fig. 1). The physical part of the model is a single inverted pendulum model with corrective torque applied at the ankle joint. The model used here includes a negative feedback loop that relates the body's excursion detected by visual, vestibular, and proprioceptive sensors to a corrective torque via a neural controller. The neural controller represents the relation between a sensory error, that is, the difference between the current and desired position on the one hand, and the strength of the motor output, that is, torque, on the other hand. With the help of an automated optimization tool (fmincon, MATLAB®, The MathWorks Inc.) which minimized the difference between experimental and simulated GAIN and PHASE curves, we estimated the neural controller's parameters with proportional (*Kp*), derivative (*Kd*), and integral (*Ki*) contributions (PDI-controller), representing the ratio between sensory input and motor output. Moreover, we derived time delay (*Td*), proprioceptive sensory weight (*Wp*), and passive elasticity (*Bpas*) and dampening (*Dpas*) due to the biomechanical characteristics of muscles and tendons. We fitted model simulations to experimental transfer functions under different stimulus amplitudes (0.5° and 1°) and visual conditions (eyes open/closed).

Data analysis

Statistical analysis was performed using Microsoft Excel and statistic program (JMP®, SAS Institute Inc., Cary, NC, USA). The sample size is derived from the underlying RCT, for which we had calculated the sample size based on the primary outcome. Details have been published.³³ The comparison between patients at baseline and hCONs was conducted via regression model (least square fit): for spontaneous sway analysis, the parameters RMS, MV, and CF were each considered a dependent variable; for perturbed stance analysis, GAIN and PHASE; and for model-based analysis, the parameters *Kp*, *Kd*, *Ki*, *Td*, *Wp*, *Bpas*, and *Dpas*. Each analysis included group allocation as the primary independent variable. To analyze the intervention effect, group differences were subjected to multivariate analysis of variance (MANOVA) including aforementioned variables, CIPN symptoms, and functional performance

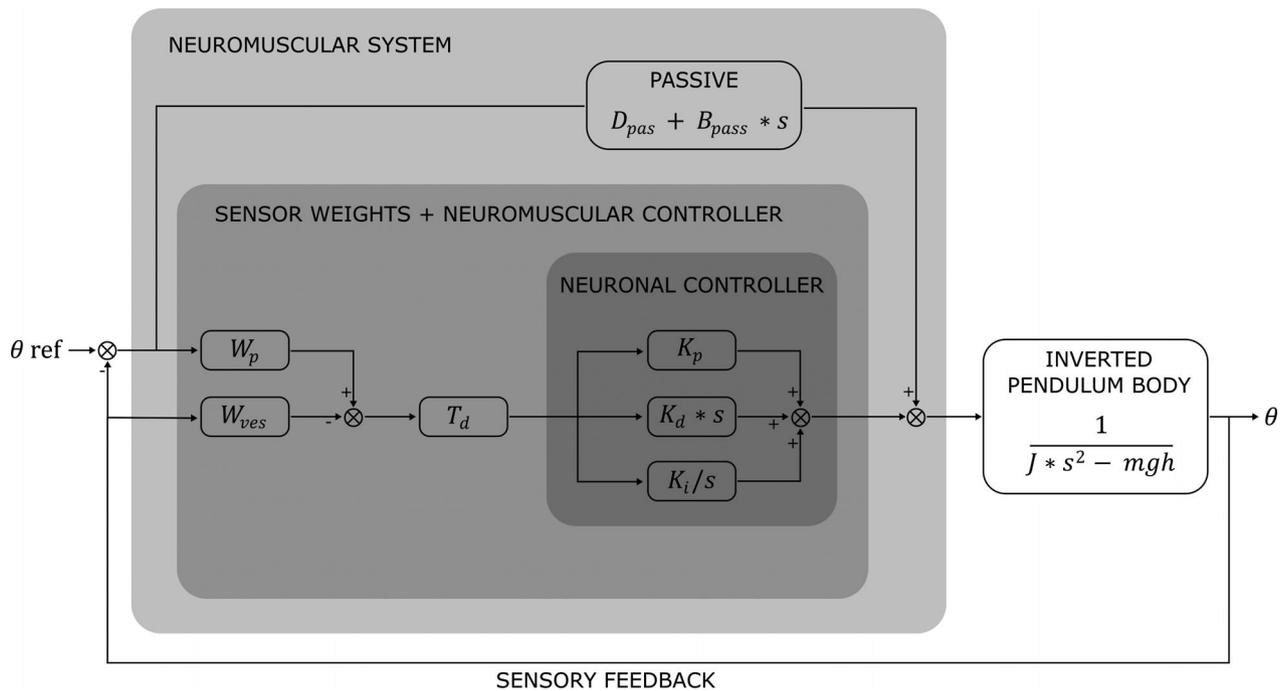


Figure 1. Schematic representation of the human postural control. The figure shows the modified postural control model used to identify parameters substantially involved in posture control via an optimization procedure where differences between experimental data and model simulations were minimized. The human body is represented by an inverted pendulum with the mass concentrated at the center of mass of the body (J , moment of inertia of the body; mgh , body mass*gravitational constant*height of the center of mass from the ankle joint; s , Laplace transform variable). Body movement (θ , body sway angle), as a response to an external stimulus (θ_{ref}) and to the sensory feedback, is regulated by the neuromuscular system including passive components (D_{pas} , passive damping factor, B_{pass} , passive stiffness factor;), sensory weighting factors (W_p , proprioceptive sensory weight; W_{ves} , vestibular sensory weight), a time delay (T_d), and a neural controller (K_p , proportional gain (stiffness factor); K_d , derivative gain (dampening factor); K_i , integral gain).

parameters as dependent variable each, time as the repeated measures variable and group allocation as independent variable.

If the primary analysis revealed a significant group difference, we conducted a sensitivity analysis as follows: For spontaneous sway analysis, visual condition and sway direction were applied as within-subjects' factors. For perturbed stance, stimulus frequency, visual condition, body segment, and rotational amplitude were applied as within-subjects' factors; for model-based analysis, visual condition and rotational amplitude were applied as within-subjects' factors. The level of statistical significance was set to $p = 0.05$. Results of our primary analysis are presented in Tables 2–6. The sensitivity analyses are described in the results' section and selectively illustrated in Figures 2–4.

Results

Comparing patients and hCONs revealed similar characteristics, while the comparative patients' groups, PAT_{E+B}

and PAT_E , differed significantly in age. To control for the potential influence of age on the interaction of specific parameters with time, we correlated change over time ($T1-T0$) with age for those parameters, where we detected a significant time effect between patients' groups.

Spontaneous sway

Patients' postural sway was more pronounced than the hCONs' ($F = 12.02$; $p = 0.001$; Table 2). This difference did not depend on visual condition ($F = 0.40$; $p = 0.526$) or sway direction ($F = 0.89$; $p = 0.345$). Neither did patients' and hCONs' MV ($F = 3.18$; $p = 0.076$) and CF ($F = 0.02$; $p = 0.898$) differ (Table 2). Longitudinally, patients' RMS changed significantly during the intervention time ($p = 0.014$; Table 2). This time effect is mainly based on a significant RMS reduction with eyes closed (-0.07 cm, 95% CI -0.01 to -0.13 cm) and in an anterior–posterior direction (-0.09 cm, 95% CI -0.02 to -0.16 cm), but does not depend on the intervention type (Fig. 2). In contrast, time did not affect MV and CF.

Table 2. Spontaneous sway.

	hCON	All patients	<i>p</i>	Group	Patients	Change after	Therapy-	Therapy-effect
	N = 36	at baseline						
	Mean (95% CI)	Mean (95% CI)			Mean (95% CI)	T1-T0	<i>p</i>	<i>p</i>
						Mean (95% CI)		
RMS (cm)	0.50 (0.46 to 0.53)	0.59 (0.55 to 0.63)	0.001	E + B	0.59 (0.54 to 0.65)	-0.03 (0.01 to -0.07)	0.014	0.392
				E	0.58 (0.52 to 0.64)	-0.07 (0.00 to -0.13)		
MV (cm/s)	0.99 (0.88 to 1.11)	1.15 (1.02 to 1.27)	0.076	E + B	1.23 (1.03 to 1.44)	-0.04 (0.05 to -0.13)	0.738	0.667
				E	1.07 (0.86 to 1.27)	0.01 (0.17 to -0.16)		
CF (Hz)	0.64 (0.61 to 0.67)	0.65 (0.61 to 0.68)	0.898	E + B	0.65 (0.60 to 0.69)	-0.01 (0.02 to -0.04)	0.554	0.846
				E	0.65 (0.60 to 0.69)	-0.01 (0.04 to -0.05)		

* indicates a significant change to T0; *p*-values <0.05 are marked in bold.

Abbreviations: CF, center frequency; CI, confidence interval; E, CIPN patients performing only endurance training; E + B, CIPN patients performing endurance plus balance training; hCON, healthy control participants; MV, mean velocity; PAT, patients; RMS, root means square.

Table 3. Perturbed stance.

	hCON	All patients	<i>p</i>	PAT	Patients	Change after	Therapy-	Therapy-effect
	N = 36	at baseline						
	Mean (95% CI)	Mean (95% CI)		Group	Mean (95% CI)	T1-T0	<i>p</i>	<i>p</i>
						Mean (95% CI)		
Mean GAIN	2.11 (2.10 to 2.16)	1.78 (1.76 to 1.82)	<0.001	E + B	1.85 (1.81 to 1.90)	-0.06 (-0.02 to -0.10)*	0.001	0.537
				E	1.71 (1.68 to 1.77)	-0.04 (0.01 to -0.09)		
Mean PHASE (°)	-128.22 (-130.2 to -125.4)	-116.58 (-118.9 to -113.8)	<0.001	E + B	-111.03 (-115.5 to -106.6)	-13.52 (-7.7 to -19.3)*	0.495	<0.001
				E	-121.78 (-126.3 to -117.2)	10.35 (17.3 to 3.4)*		

* indicates a significant change to T0; *p*-values <0.05 are marked in bold.

Abbreviations: E, CIPN patients performing only endurance training; E + B, CIPN patients performing endurance plus balance training; hCON, healthy control participants; PAT, patients.

Perturbed stance

Patients' GAIN was significantly smaller than that of hCONs ($F = 116.22$; $p < 0.001$; Table 3). In addition, group designation interacted significantly with frequency ($F = 7.33$; $p < 0.001$): at mid-range frequencies, hCONs exhibited a more pronounced GAIN than patients, in contrast to low or high frequencies (Fig. 3A–D). Group designation interacted significantly with visual condition ($F = 11.00$; $p = 0.001$) and body segment ($F = 27.01$; $p < 0.001$): Patients revealed a smaller GAIN with eyes open and closed (Fig. 3A–D), and hip and shoulder movement compared to hCONs (Fig. 3E,F). Differences between groups were more pronounced with eyes closed

(Fig. 3B,D) and at shoulder movement (Fig. 3E, upper body). Furthermore, group designation interacted with rotational amplitude ($F = 4.29$; $p = 0.038$): patients showed a smaller GAIN at 0.5° and 1° rotational amplitudes; patients' GAIN at 0.5° was comparable to hCONs' GAIN at 1° .

Longitudinally, patients' GAIN changed significantly over the intervention time (Table 3). This time effect interacted significantly with body segment ($F = 9.66$; $p = 0.002$) and frequency ($F = 2.42$; $p = 0.007$) and is mainly attributable to a GAIN reduction at the shoulder segment (Fig 3 E, upper body) and at mid-range frequencies (Figs 3 A–D), but it does not depend on the intervention type.

Table 4. Model parameters.

	hCON N = 36 Mean (95% CI)	All patients at baseline N = 31 Mean (95% CI)	<i>p</i>	PAT Group	Patients at baseline Mean (95% CI)	Change after interventions T1-T0 Mean (95% CI)	Therapy-effect (between groups) <i>p</i>
Ki (s ⁻¹ .rad ⁻¹)	76.15 (74.09 to 78.20)	73.00 (70.79 to 75.22)	0.041	E + B	70.86 (67.67 to 74.05)	0.69 (4.77 to -3.40)	0.738
				E	75.28 (71.99 to 78.58)	0.29 (4.55 to -3.98)	(0.892)
Kp (rad ⁻¹)	989.4 (949.3 to 1029.5)	936.2 (893.0 to 979.4)	0.077	E + B	943.1 (882.7 to 1003.5)	65.6 (108.4 to 22.7)*	<0.001
				E	928.9 (866.0 to 991.3)	85.8 (150.3 to 21.3)*	(0.600)
Kd (s.rad ⁻¹)	267.0 (257.4 to 276.7)	286.3 (275.9 to 296.7)	0.008	E + B	291.4 (276.5 to 306.4)	0.90 (13.39 to -11.58)	0.750
				E	282.8 (265.4 to 296.2)	-4.66 (15.71 to -25.04)	(0.637)
Wp (%)	71.93 (69.15 to 74.71)	70.87 (67.87 to 73.86)	0.610	E + B	72.08 (67.65 to 76.51)	-0.04 (0.00 to -0.08)*	0.022
				E	69.57 (65.00 to 74.15)	-0.03 (0.02 to -0.08)	(0.782)
Td (msec)	171 (165 to 177)	176 (171 to 182)	0.229	E + B	178 (170 to 186)	-8.1 (0.3 to -16.5)	0.011
				E	175 (167 to 183)	-10.5 (1.1 to -22.1)	(0.738)
Ppas (rad ⁻¹)	86.01 (83.73 to 88.29)	85.08 (82.62 to 87.53)	0.583	E + B	82.72 (79.47 to 85.97)	2.81 (6.06 to -0.44)	0.178
				E	87.59 (84.23 to 90.95)	1.23 (6.31 to -3.85)	(0.596)
Dpas (s.rad ⁻¹)	57.71 (56.32 to 59.10)	57.08 (55.58 to 58.58)	0.547	E + B	57.09 (54.79 to 59.39)	0.94 (3.68 to -1.79)	0.624
				E	57.07 (54.70 to 59.45)	0.16 (3.69 to -3.37)	(0.727)

* indicates a significant change to T0; *p*-values <0.05 are marked in bold.

Abbreviations: CI, confidence interval; Dpas, passive damping factor; E, CIPN patients performing only endurance training; E + B, CIPN patients performing endurance plus balance training; hCON, healthy control participants; Ki, integral gain of the neural controller; Kp, proportional gain (stiffness factor), Kd, derivative gain (dampening factor); PAT, patients; Ppas, passive stiffness factor; Td, feedback time delay; Wp, proprioceptive sensory weight.

Patients displayed less PHASE lag than the hCONs (F = 41.40; *p* <0.001; Table 3). Moreover, group designation interacted significantly with rotational amplitude (F = 32.69; *p* <0.001). Groups' PHASE behaviors differed between rotational amplitudes: patients revealed a smaller PHASE lag at 0.5° than hCONs (Fig. 4A,B), while PHASE behavior at 1° was approximately the same across groups (Fig. 4C,D). Differences in groups' PHASE behavior did not depend on visual condition, body segment or frequency.

The intervention type interacted significantly with time longitudinally (F = 27.21; *p* <0.001; Table 3). This time effect between intervention groups interacted significantly with visual condition (F = 12.05; *p* = 0.001), rotational amplitude (F = 12.55; *p* <0.001), and body segment (F = 4.64; *p* = 0.031). Thus, the time effect is mainly attributable to changes with eyes open (interaction: F = 33.70; *p* < 0.001) and at 0.5° rotational amplitude (interaction: F = 21.42; *p* = 0.001) (Fig 4 A), and to an

increase in PHASE lag at the hip segment for PAT_{E+B} (F = 4.49; *p* = 0.034; Fig. 4F) and a reduced PHASE lag at the shoulder segment for PAT_{E+B} (F = 28.22; *p* < 0.001; Fig 4E, upper body). As there was no significant correlation between PHASE change over time (T1-T0) and age (*r* = 0.0262, *p* = 0.173), we did not adjust our PHASE analysis for age.

The following results are derived from the model-based approach described above, and present the relevant parameter differences between groups.

Between patients and hCONs, we observed a significant group difference for the integral (Ki) (F = 4.21; *p* = 0.041) and derivative (Kd) (F = 7.11; *p* = 0.008) parts of the neural controller, while the proportional (Kp) part did not differ (Table 4). Group designation concerning Ki and Kd did not interact with visual condition or rotational amplitude. The sensory weighting factor Wp, indicating the proportion of proprioceptive versus

Table 5. CIPN symptoms.

	Group	Patients at baseline	Change after interventions	Therapy-effect <i>p</i>	Therapy-effect between groups <i>p</i>
		N = 31 Mean (95% CI)	T1-T0 Mean (95% CI)		
Vibration sense (scale 0 – 8)					
First metacarpophalangeal joint	PAT _{E+B}	1.9 (0.6 to 3.2)	1.1 (0.1 to 2.1)*	0.016	0.840
	PAT _E	4.4 (3.0 to 5.7)	0.7 (–0.4 to 1.7)		
Knuckle	PAT _{E+B}	3.7 (2.6 to 4.7)	0.1 (–0.8 to 1.0)	0.306	0.133
	PAT _E	5.0 (3.9 to 6.1)	0.7 (–0.3 to 1.6)		
EORTC-QLQ CIPN20 [#]					
Sum score	PAT _{E+B}	37 (25 to 48)	–6 (6 to –18)	0.024	0.469
	PAT _E	32 (20 to 43)	–11 (–2 to –21)*		
Sensory score	PAT _{E+B}	42 (29 to 54)	–3 (10 to –15)	0.038	0.164
	PAT _E	40 (27 to 53)	–14 (–3 to –24)*		
Motor score	PAT _{E+B}	33 (21 to 46)	–7 (7 to –21)	0.048	0.857
	PAT _E	23 (11 to 35)	–8 (–1 to –16)*		
Autonomic score	PAT _{E+B}	20 (7 to 33)	–8 (2 to –18)	0.021	0.590
	PAT _E	23 (10 to 37)	–13 (3 to –29)		
Upper extremity score	PAT _{E+B}	35 (19 to 50)	–4 (10 to –18)	0.109	0.535
	PAT _E	29 (13 to 44)	–8 (–1 to –17)*		
Lower extremity score	PAT _{E+B}	46 (31 to 60)	–8 (7 to –23)	0.018	0.483
	PAT _E	38 (24 to 53)	–14 (–2 to –27)*		

* indicates a significant change to T0; *p*-values <0.05 are marked in bold; [#] scoring from 0 (no symptoms) to 100 (severe symptoms).

Abbreviations: CI, confidence interval; CIPN20, module of the EORTC-QLQ (European Organization for Research and Treatment of Cancer Quality of Life) questionnaire; *p*, *p*-value; PAT_E, CIPN patients performing only endurance training; PAT_{E+B}, CIPN patients performing endurance plus balance training; T0, pre-intervention (baseline); T1, post-intervention.

vestibular and visual cues, the time delay between stimulus and response (Td), passive muscle stiffness (Bpas), and dampening (Dpas) did not differ significantly between patients and hCONs (Table 4).

Longitudinally speaking, patients' Kp increased significantly ($F = 15.45$, $p < 0.001$), while Wp ($F = 5.38$, $p = 0.022$) and Td ($F = 6.66$, $p = 0.011$) lessened with time (Table 4). These time effects did not interact with intervention type, visual condition, or rotational amplitude. Further model parameters were unaffected by time.

CIPN symptoms and functional performance

After the interventions, patients' vibration sense, subjective CIPN symptoms (Table 5), and functional performance outcomes were altered significantly (Table 6). Patients' vibration sense measured at the first metacarpophalangeal joint increased significantly over time ($F = 6.49$, $p = 0.016$), but did not interact with intervention type. Vibration sense measured at the knuckle remained stable ($F = 1.09$, $p = 0.306$). Accordingly, patients reported alleviated symptoms measured via EORTC-QLQ CIPN20 questionnaire leading to a significant reduction in sum- ($F = 5.79$, $p = 0.024$), sensory- ($F = 4.79$, $p = 0.038$), motor- ($F = 4.33$, $p = 0.048$), autonomic- ($F = 6.04$, $p = 0.021$), and lower extremity scores ($F = 6.45$, $p = 0.018$), which did not interact with

intervention type. Only the upper extremity score ($F = 2.75$, $p = 0.109$) was unaffected by time. Furthermore, patients improved their functional performance significantly: they prolonged their durations standing on one leg—on stable ($F = 4.36$, $p = 0.046$) and instable ($F = 26.14$, $p < 0.001$) surfaces—and raised their jump height ($F = 5.50$, $p = 0.028$). We also detected an interaction between the intervention type and duration of standing on one leg on an instable surface at T1 ($F = 20.87$, $p < 0.001$), a finding that relies on greater improvement in the PAT_{E+B} compared to PAT_E. As we noted a significant correlation between the change over time regarding the duration of standing on one leg on an instable surface (T1-T0) and age ($r = 0.5680$, $p = 0.003$), we adjusted our analysis for age. Adjusted for age, we found no time effect on the duration of standing on one leg on an instable surface ($F = 1.67$, $p = 0.209$).

Discussion

CIPN is unfortunately highly prevalent among cancer survivors⁴⁶ and the evidence is growing showing that CIPN patients benefit from exercising through alleviated symptoms^{23,47–52} and improved functional performance.^{21–23,48,51} Functional impairments and postural instability due to CIPN carry relevant health risks for affected patients.^{2,4,5,10} While there are many reports about CIPN-

Table 6. CIPN symptoms and functional performance.

Functional tests	Group	Patients at	Change after	Therapy-effect	Therapy-effect between groups
		baseline N = 31	interventions T1-T0		
		Mean (95% CI)	Mean (95% CI)	<i>p</i>	<i>p</i>
One leg stance (s)	PAT _{E+B}	24 (21 to 28)	3 (1 to 6)*	0.046	0.065
	PAT _E	30 (26 to 34)	0.0 (−3 to 3)		
One leg stance (s) on an instable surface	PAT _{E+B}	14 (8 to 19)	12 (8 to 15)*	<0.001	<0.001
	PAT _E	26 (20 to 32)	1 (−3 to 5)		
Jump height (cm)	PAT _{E+B}	23 (17 to 29)	1.3 (−0.8 to 3.4)	0.028	0.729
	PAT _E	31 (25 to 37)	1.8 (−0.4 to 4.0)		
Jump P _{max} (watt/kg)	PAT _{E+B}	25 (20 to 30)	0.0 (−1.2 to 1.3)	0.110	0.347
	PAT _E	31 (26 to 37)	1.6 (0.2 to 2.9)*		

* indicates a significant change to T0; *p*-values <0.05 are marked in bold.

Abbreviations: CI, confidence interval; *p*, *p*-value; PAT_E, CIPN patients performing only endurance training; PAT_{E+B}, CIPN patients performing endurance plus balance training; P_{max}, maximum power output (during take-off); T0, pre-intervention (baseline); T1, post-intervention.

induced postural instability,^{3,5,12,13,21,53} the underlying postural control mechanisms have barely been described^{3,11,19,53}—in particular when it comes to characterizing different exercise effects.¹⁹ The aim of the present exploratory study was, therefore, to quantify the exercise effect based on the set of abnormalities derived from comparing the quiet and perturbed stance of patients to healthy control participants via a model-based analysis. Interestingly, both intervention groups experienced alleviated CIPN-related impairments and exhibited alterations in their postural behavior.

Spontaneous sway

In line with previous CIPN studies,^{3,11,13,53} we identified greater postural sway in CIPN patients than in healthy participants. Our patients' larger sway did not depend on visual conditions or sway directions (anterior-posterior vs. mediolateral)—in contrast to, for example, Monfort et al.¹¹ or Mueller et al.¹³ who reported a preponderance with eyes closed. In an earlier pilot study, we replicated their finding of large postural sway with closed eyes.¹⁹ We are assuming that this study's patients were less severely affected by CIPN than those in our earlier pilot study, which may have contributed to this difference. In general, we are still assuming that this amplified postural sway is related to a CIPN-induced proprioceptive deficit,^{17,54–56} for example, due to more proprioceptive noise. Functionally speaking, larger postural sway seems to correlate with an increased fall risk.⁵⁷

Perturbed stance

Analyzing patients' body reactions to external perturbations enables us to deduce various adjustments in

physiological mechanisms such as the weighting of sensory information, the effort to correct for positional deviations of the body away from the desired position (sensorimotor feedback loop gain), or the duration of sensorimotor time.³⁴ In fact, we applied data on perturbed stance in this paper to evaluate postural reactions and to estimate parameters of a single inverted pendulum model including the neural controller.

Following this framework, reduced proprioceptive cues would imply a stronger spatial orientation rather than one relative to the platform. As a consequence, platform movements would yield smaller body excursions in CIPN patients than in healthy control participants, quantifiable by smaller GAIN.¹⁹ Indeed, patients exhibited a significantly smaller GAIN across both visual conditions than healthy participants. However, as we show below, the results of our model-based simulation imply another main strategy in the patient cohort studied here. GAIN differences were especially pronounced with eyes closed. While healthy participants demonstrated a significant GAIN increase from eyes open to eyes closed, the patients' GAIN increase was weaker. This group difference might be a consequence of either weighing visual orientation signals differently,¹⁹ or may be caused by other strategies discussed in the models' section below.

PHASE behavior relates to the relative timing of body reactions with respect to the platform stimulus. Since a decelerated nerve conduction velocity is an attribute of CIPN-induced nerve damage, one might expect that CIPN patients would display a relatively larger PHASE lag. Surprisingly, our patients' PHASE lag was less pronounced compared to healthy participants. We assume that a certain strategy triggers this relative PHASE advance. More specifically, we speculate that patients shift

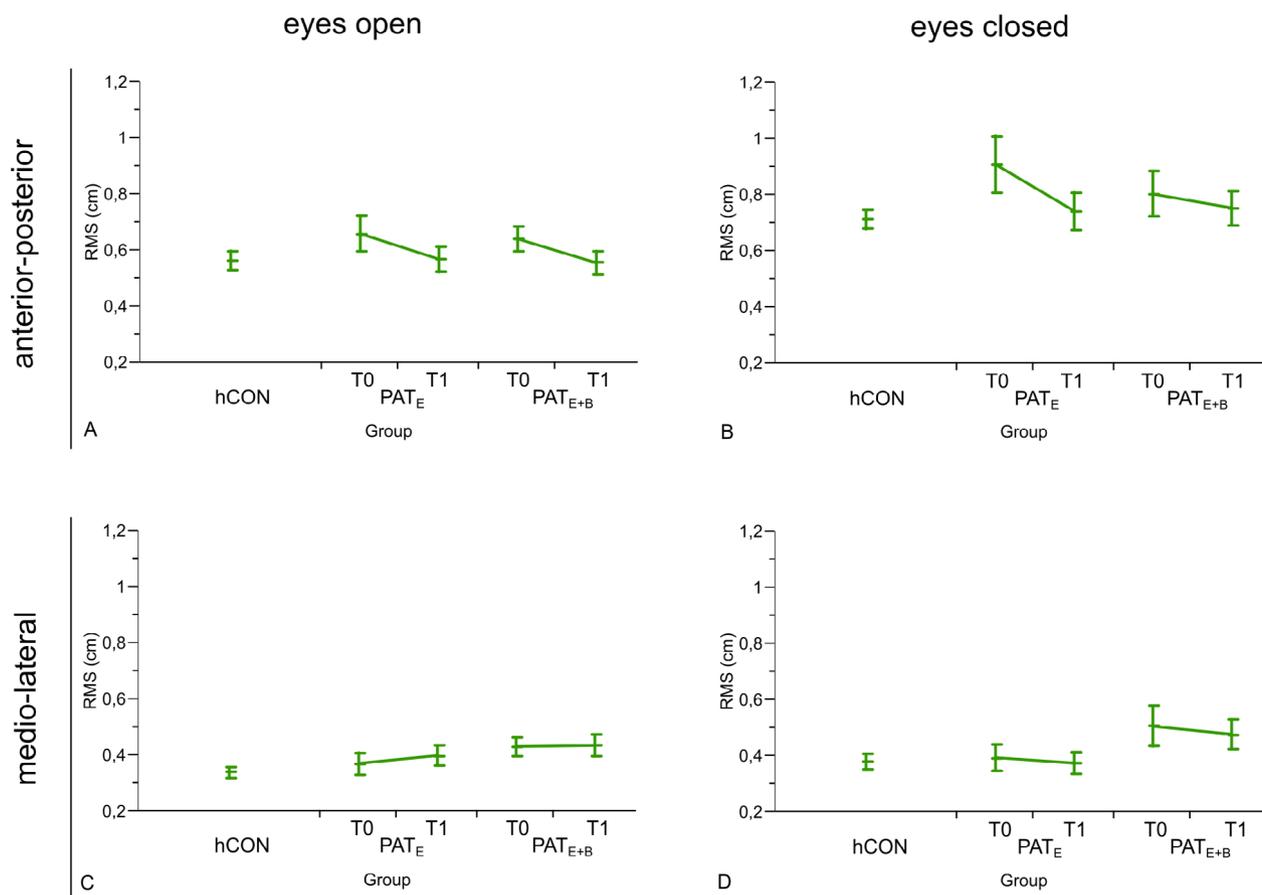


Figure 2. Spontaneous sway. The figure shows root means square (RMS) results of spontaneous sway measures as a function of the visual condition and sway direction. Mean and standard error of center of pressure (COP) RMS (cm) in anterior–posterior (A, B) and mediolateral (C, D) direction for eyes open (A, C) and eyes closed (B, D) condition in healthy control participants (hCON), CIPN patients before (PAT T0) and after (PAT T1) intervention. PAT_E, endurance exercise only; PAT_{E+B}, endurance exercise + balance exercise.

to controlling velocity away from controlling their position, which may function as a prediction mechanism.

Model-based parameter identification

To address patients' GAIN- and PHASE behavior, we fitted participants' data via a simple feedback system based on the single inverted pendulum mentioned above.^{36,44,58,59} Our CIPN patients showed a significantly lower integral part of the neuronal controller (K_i) and a significantly larger velocity part (K_d). We interpret this as a shift in the feedback gain toward velocity control in CIPN patients. This shift leads to the relative PHASE advance of CIPN patients compared to healthy control participants.

Interestingly, the model-based parameter identification procedure proved unable to identify a different use of proprioceptive cues represented by the sensory weighting

factor W_p , unlike in our pilot study.¹⁹ Comparing this study's patient group with our pilot study.

reveals differences in CIPN severity: those patients who participated in the present study were less severely affected by CIPN, probably because of less exposure to neurotoxins. The more severe neurotoxic impact on afferent pathways in the pilot study's patients may be reflected by their especially low use of proprioceptive cues, that is, W_p . We speculate that the present patients' afferent impairments have not yet significantly influenced their sensory weighting, rather, they have induced a mechanism that triggers velocity control as outlined above.

In line with our pilot study, parameters related to passive muscle and tendon behavior (passive stiffness and dampening, B_{pas} and D_{pas}) did not differ between patients and healthy control participants. These findings might further support the assumption that patients' different postural behavior might be a central mechanism—

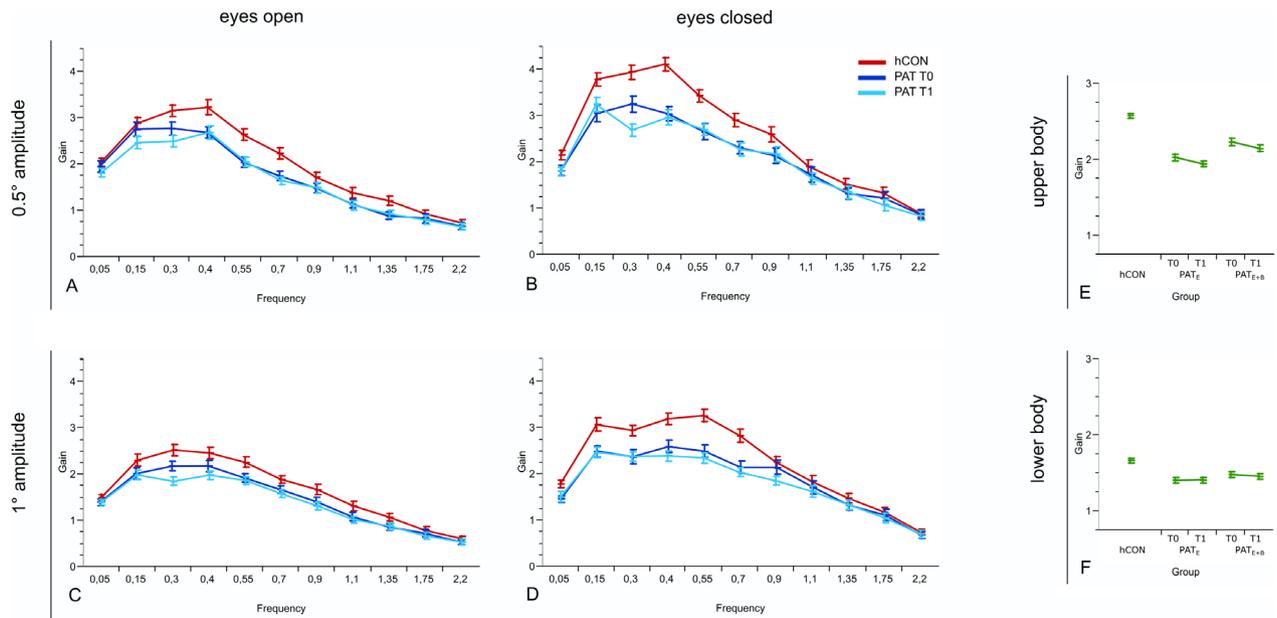


Figure 3. Transfer function: GAIN behavior. A–D show GAIN results as a function of frequency, visual condition, and rotational amplitude. Mean and standard error of GAIN as the function of frequency at 0.5° (A, B) and 1° (C, D) sway amplitude for eyes open (A, C) and eyes closed (B, D) condition in healthy control participants (hCon), patients before (Pat T0) and after (Pat T1) intervention. E and F show the mean GAIN across all frequencies, sway amplitude, and visual condition as a function of body segments. Mean and standard error of GAIN for upper body (E, shoulder movement) and lower body (F, hip movement) in healthy control participants (hCON), CIPN patients before (PAT T0) and after (PAT T1) intervention. PAT_E, endurance exercise only; PAT_{E+B}, endurance exercise + balance exercise.

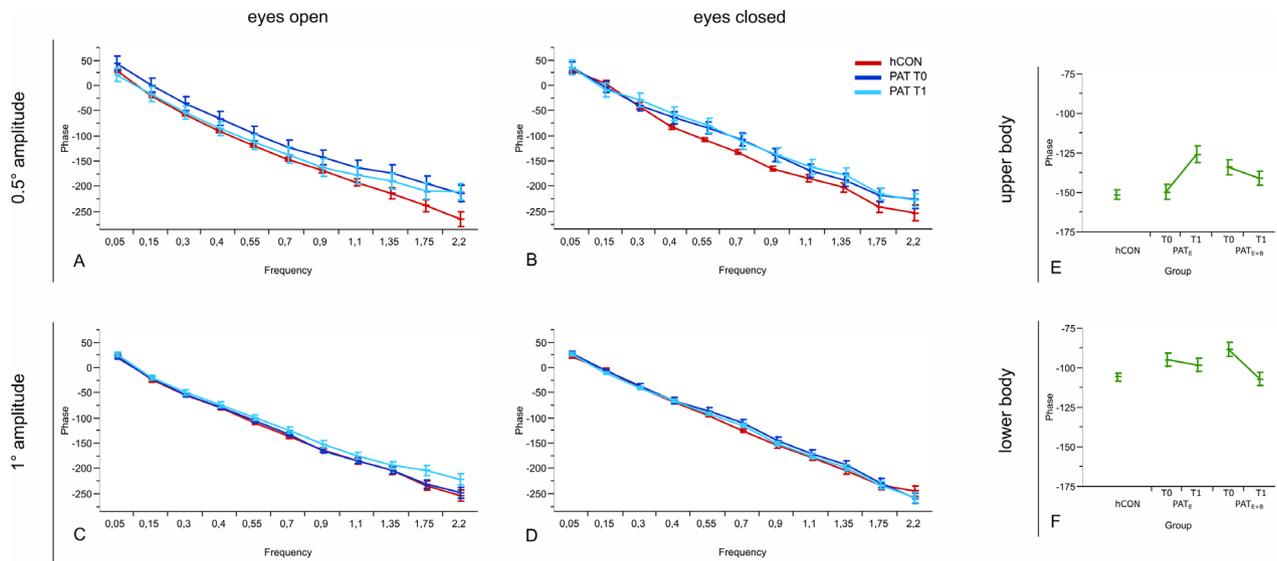


Figure 4. Transfer function: PHASE behavior. A–D show PHASE results as a function of frequency, visual condition, and rotational amplitude. Mean and standard error of PHASE as the function of frequency at 0.5° (A, B) and 1° (C, D) sway amplitude for eyes open (A, C) and eyes closed (B, D) condition in healthy control participants (hCon), patients before (Pat T0) and after (Pat T1) intervention. E and F show the mean PHASE across all frequencies, sway amplitude, and visual condition as a function of body segments. Mean and standard error of PHASE for upper body (E, shoulder movement) and lower body (F, hip movement) in healthy control (hCON), CIPN patients before (PAT T0) and after (PAT T1) intervention. PAT_E, endurance exercise only; PAT_{E+B}, endurance exercise + balance exercise.

rather than a result of CIPN-induced alterations on muscle- or tendon structures.

Intervention effect

Concerning spontaneous sway, both intervention groups reduced their postural sway slightly—mainly with eyes closed and in an anterior–posterior direction. Our spontaneous sway results may tend to concur with other CIPN-studies reporting reduced postural sway after an exercise intervention.^{21,51} However, Schwenk et al.²¹ reported a sway reduction with eyes open and in the mediolateral direction, and McCrary et al.⁵¹ also detected only an eyes-open effect on postural sway.

After the intervention time, both groups had changed their reaction to the external perturbation. Based on our pilot study's findings,¹⁹ one could speculate that patients after balance training would shift their postural behavior to resemble that of healthy participants more strongly. However, that was not the case. Instead, our patients' post-intervention GAIN continued to diminish compared to pre-intervention, a finding mainly relying on their GAIN reduction on the shoulder segment (upper body). The post-intervention decrease in proprioceptive sensory weight W_p may explain these GAIN findings: W_p results reflect the assumption that patients after interventions tend to integrate space cues even more strongly—a finding more pronounced in the balance-training group (PAT_{E+B}). We assume that CIPN patients optimize their individual postural control strategy when trying to respond to an impaired proprioceptive signal. However, we cannot conclusively clarify whether these effects are due to the intervention type or the natural recovery process, as our study lacks comparison to a non-intervention group. We had initially expected that moderate endurance training would not provoke postural adaptations (unlike additional balance training). Interestingly, PHASE effects contrasted across groups, which led us to suppose that our interventions might have triggered different postural strategies. The balance training group (PAT_{E+B}) increased their PHASE lag, meaning a shift toward the postural behavior of healthy participants. In contrast, the PAT_E (endurance training only) reduced their PHASE lag even more. The PHASE effect of PAT_E depends mainly on changes in upper body movements, while PAT_{E+B} changes lower body movements. Since both intervention groups differed in age, we cannot completely rule out the possibility that PHASE effects are at least partially age-related. However, to control for the age effect, we tested for any correlation between the PHASE change over time ($T1-T0$) and age across both groups, which was not significant. We, therefore, speculate that balance training could have induced more efficient muscular activation that may have moderated our patients' aforementioned prediction

strategy. Endurance training may also have increased muscular capacity and thus allowed them to intensify their proactive muscular activity, represented by the increase in the PHASE advance after training. Functional tests can highlight patients' stronger capacity after an intervention, that is, when they jump higher.

Both of our groups revealed a positive impact on time delay (T_d) and a larger sensory-motor ratio (K_p) of the feedback loop with both parameters corrected toward healthy participants' values. Additionally, patients subjectively reported having perceived alleviated symptoms (CIPN20) after the intervention time.³³ The present subgroup analysis revealed a greater improvement in PAT_E compared to PAT_{E+B} .

Conclusion

Our CIPN patients displayed larger postural sway associated with postural instability as compared to matched healthy controls. Our external perturbation experiments revealed patients' small sensory-motor ratio together with stronger velocity control leading to a smaller GAIN and shorter PHASE lag. After the intervention time, postural behavior changed, but in somewhat different ways. Both groups increased their sensory-motor ratio toward the normal range and reduced their time delay between sensory input and motor output. However, the balance training group (PAT_{E+B}) corrected their PHASE behavior toward that of healthy participants, while the endurance training group only (PAT_E) seemed to intensify their proactive posture strategy represented by a relative PHASE advance with respect to the pre-intervention state. Thus, the behavior of PAT_{E+B} shifts closer to resembling the behavior of healthy control participants. Although we cannot conclusively clarify whether interventions are, indeed, responsible for these effects, we propose including at least one type of the exercises we tested here into an interventional strategy to alleviate further the functional impairments that CIPN patients suffer.

Acknowledgments

The article processing charge was funded by the German Research Foundation (DFG) and the University Freiburg, Germany, in the funding program Open Access Publishing. We thank all patients and control participants who participated in this study. We gratefully acknowledge the cooperation and training implementation of sports- and physiotherapists of the Sports Oncology division in the Department of Medicine I, Medical Center – University of Freiburg, especially Simon Schneider for study assistance and data processing. Open Access funding enabled and organized by Projekt DEAL.

Authors' Contributions

SK and CM drafted the manuscript, analyzed, and interpreted the data. SK and AW participated in the study design, in obtaining funding, and in collecting data. CM, HB, and JM participated in the study's conception. JM recruited patients and collected data. HB participated in obtaining funding. All authors provided comments and critical revisions. All authors read and approved the final manuscript.

Funding Information

This work was supported by a grant from Janssen-Cilag GmbH (grant number 26866138MMY4065). The funder neither played a role in the study design nor in data collection, analysis and interpretation, the writing process of the manuscript or the decision to submit for publication. C.M. and S.K. were partially funded by the European Union's Horizon 2020 research and innovation program under grant agreements No 779963 (EUROBENCH) and No 769574 (HOLOBALANCE).

Conflict of Interest

The authors have no conflict of interest to declare.

References

- Argyriou AA, Kyritsis AP, Makatsoris T, Kalofonos HP. Chemotherapy-induced peripheral neuropathy in adults: a comprehensive update of the literature. *Cancer Manag Res* 2014;6:135–147.
- Winters-Stone KM, Horak F, Jacobs PG, et al. Falls, functioning, and disability among women with persistent symptoms of chemotherapy-induced peripheral neuropathy. *J Clin Oncol* 2017;35(23):2604–2612.
- Herman HK, Monfort SM, Pan XJ, et al. Effect of chemotherapy-induced peripheral neuropathy on postural control in cancer survivors. *J Clin Oncol* 2017;35(5_suppl):128.
- Bao T, Basal C, Seluzicki C, et al. Long-term chemotherapy-induced peripheral neuropathy among breast cancer survivors: prevalence, risk factors, and fall risk. *Breast Cancer Res Treat* 2016;159(2):327–333.
- Monfort SM, Pan X, Patrick R, et al. Gait, balance, and patient-reported outcomes during taxane-based chemotherapy in early-stage breast cancer patients. *Breast Cancer Res Treat* 2017;164(1):69–77.
- Marshall TF, Zipp GP, Battaglia F, et al. Chemotherapy-induced-peripheral neuropathy, gait and fall risk in older adults following cancer treatment. *J Cancer Res Pract* 2017;4(4):134–138.
- Winters-Stone KM, Hilton C, Luoh S-W, et al. Comparison of physical function and falls among women with persistent symptoms of chemotherapy-induced peripheral neuropathy. *J Clin Oncol* 2016;34(3_suppl):130.
- Kolb NA, Smith AG, Singleton JR, et al. The association of chemotherapy-induced peripheral neuropathy symptoms and the risk of falling. *JAMA Neurol* 2016;73(7):860–866.
- Gewandter JS, Fan L, Magnuson A, et al. Falls and functional impairments in cancer survivors with chemotherapy-induced peripheral neuropathy (CIPN): a University of Rochester CCOP study. *Support Care Cancer* 2013;21(7):2059–2066.
- Toftagen C, Overcash J, Kip K. Falls in persons with chemotherapy-induced peripheral neuropathy. *Support Care Cancer* 2012;20(3):583–589.
- Monfort SM, Pan X, Loprinzi CL, et al. Impaired postural control and altered sensory organization during quiet stance following neurotoxic chemotherapy: a preliminary study. *Integr Cancer Ther* 2019;18:1534735419828823.
- Kneis S, Wehrle A, Freyler K, et al. Balance impairments and neuromuscular changes in breast cancer patients with chemotherapy-induced peripheral neuropathy. *Clin Neurophysiol* 2016;127(2):1481–1490.
- Müller J, Ringhof S, Vollmer M, et al. Out of balance – postural control in cancer patients before and after neurotoxic chemotherapy. *Gait Posture* 2020;77:156–163.
- Ibrahim EY, Ehrlich BE. Prevention of chemotherapy-induced peripheral neuropathy: a review of recent findings. *Crit Rev Oncol Hematol* 2020;145:102831.
- Cata JP, Weng HR, Lee BN, et al. Clinical and experimental findings in humans and animals with chemotherapy-induced peripheral neuropathy. *Minerva Anestesiol* 2006;72(3):151–169.
- Han Y, Smith MT. Pathobiology of cancer chemotherapy-induced peripheral neuropathy (CIPN). *Front Pharmacol* 2013;4:156.
- Horak FB, Hlavacka F. Somatosensory loss increases vestibulospinal sensitivity. *J Neurophysiol* 2001;86(2):575–585.
- Horak FB, Macpherson JM. Postural orientation and equilibrium. *Handbook of physiology* pp. 255–292. New York: Oxford University Press, 1996.
- Kneis S, Wehrle A, Dalin D, et al. A new approach to characterize postural deficits in chemotherapy-induced peripheral neuropathy and to analyze postural adaptations after an exercise intervention. *BMC Neurol* 2020;20(1):23.
- Camisuli S, Cavazzi E, Baldissarro E, Leandri M. Rehabilitation of balance disturbances due to chemotherapy-induced peripheral neuropathy: a pilot study. *Eur J Phys Rehabil Med* 2016;52(4):479–488.
- Schwenk M, Grewal GS, Holloway D, et al. Interactive sensor-based balance training in older cancer patients with chemotherapy-induced peripheral neuropathy: a

- randomized controlled trial. *Gerontology* 2016;62(5):553–563.
22. Vollmers PL, Mundhenke C, Maass N, et al. Evaluation of the effects of sensorimotor exercise on physical and psychological parameters in breast cancer patients undergoing neurotoxic chemotherapy. *J Cancer Res Clin Oncol* 2018;144(9):1785–1792.
 23. Zimmer P, Trebing S, Timmers-Trebing U, et al. Eight-week, multimodal exercise counteracts a progress of chemotherapy-induced peripheral neuropathy and improves balance and strength in metastasized colorectal cancer patients: a randomized controlled trial. *Support Care Cancer* 2018;26(2):615–624.
 24. Granacher U, Muehlbauer T, Zahner L, et al. Comparison of traditional and recent approaches in the promotion of balance and strength in older adults. *Sports Med. Auckl. NZ* 2011;41(5):377–400.
 25. Sherrington C, Tiedemann A, Fairhall N, et al. Exercise to prevent falls in older adults: an updated meta-analysis and best practice recommendations. *New South Wales Public Health Bull* 2011;22(3–4):78–83.
 26. Macera CA, Cavanaugh A, Bellettiere J. State of the art review: physical activity and older adults. *Am J Lifestyle Med* 2016;11(1):42–57.
 27. Zech A, Hübscher M, Vogt L, et al. Balance training for neuromuscular control and performance enhancement: a systematic review. *J Athl Train* 2010;45(4):392–403.
 28. Lesinski M, Hortobágyi T, Muehlbauer T, et al. Effects of balance training on balance performance in healthy older adults: a systematic review and meta-analysis. *Sports Med. Auckl. NZ* 2015;45(12):1721–1738.
 29. Granacher U, Muehlbauer T, Gruber M. A qualitative review of balance and strength performance in healthy older adults: impact for testing and training. *J Aging Res.* 2012;2012:708905.
 30. Taube W. Neurophysiological adaptations in response to balance training. *Dtsch Z Für Sportmed* 2012;2012(09):273–277.
 31. Schmitz KH, Campbell AM, Stuiver MM, et al. Exercise is medicine in oncology: engaging clinicians to help patients move through cancer. *CA Cancer J Clin* 2019;69(6):468–484.
 32. Campbell KL, Winters-Stone KM, Wiskemann J, et al. Exercise guidelines for cancer survivors: consensus statement from international multidisciplinary roundtable. *Med Sci Sports Exerc* 2019;51(11):2375–2390.
 33. Kneis S, Wehrle A, Müller J, et al. It's never too late - balance and endurance training improves functional performance, quality of life, and alleviates neuropathic symptoms in cancer survivors suffering from chemotherapy-induced peripheral neuropathy: results of a randomized controlled trial. *BMC Cancer* 2019;19(1):414.
 34. Peterka RJ. Sensorimotor integration in human postural control. *J Neurophysiol* 2002;88(3):1097–1118.
 35. van Kordelaar J, Pasma JH, Cenciari M, et al. The reliance on vestibular information during standing balance control decreases with severity of vestibular dysfunction. *Front Neurol* 2018;9:371.
 36. Engelhart D, Pasma JH, Schouten AC, et al. Impaired standing balance in elderly: a new engineering method helps to unravel causes and effects. *J Am Med Dir Assoc* 2014;15(3):227.e1–6.
 37. Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc* 1982;14(5):377–381.
 38. Maurer C, Mergner T, Peterka RJ. Multisensory control of human upright stance. *Exp Brain Res* 2006;171(2):231–250.
 39. Cnyrim C, Mergner T, Maurer C. Potential roles of force cues in human stance control. *Exp Brain Res* 2009;194(3):419–433.
 40. Wiesmeier IK, Dalin D, Wehrle A, et al. Balance training enhances vestibular function and reduces overactive proprioceptive feedback in elderly. *Front Aging Neurosci* 2017;9:273.
 41. Prieto TE, Myklebust JB, Hoffmann RG, et al. Measures of postural steadiness: differences between healthy young and elderly adults. *IEEE Trans Biomed Eng* 1996;43(9):956–966.
 42. Maurer C, Peterka RJ. A new interpretation of spontaneous sway measures based on a simple model of human postural control. *J Neurophysiol* 2005;93(1):189–200.
 43. van der Kooij H, Jacobs R, Koopman B, van der Helm F. An adaptive model of sensory integration in a dynamic environment applied to human stance control. *Biol Cybern* 2001;84(2):103–115.
 44. Mergner T, Maurer C, Peterka RJ. Sensory contributions to the control of stance: a posture control model. *Adv Exp Med Biol* 2002;508:147–152.
 45. Welch TDJ, Ting LH. A feedback model explains the differential scaling of human postural responses to perturbation acceleration and velocity. *J Neurophysiol* 2009;101(6):3294–3309.
 46. Seretny M, Currie GL, Sena ES, et al. Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: a systematic review and meta-analysis. *Pain* 2014;155(12):2461–2470.
 47. Streckmann F, Kneis S, Leifert JA, et al. Exercise program improves therapy-related side-effects and quality of life in lymphoma patients undergoing therapy. *Ann Oncol* 2014;25(2):493–499.
 48. Schönsteiner SS, Bauder Mißbach H, Benner A, et al. A randomized exploratory phase 2 study in patients with chemotherapy-related peripheral neuropathy evaluating whole-body vibration training as adjunct to an integrated program including massage, passive mobilization and physical exercises. *Exp Hematol Oncol* 2017;6:5.

49. Kleckner IR, Kamen C, Gewandter JS, et al. Effects of exercise during chemotherapy on chemotherapy-induced peripheral neuropathy: a multicenter, randomized controlled trial. *Support Care Cancer* 2018;26(4):1019–1028.
50. Dhawan S, Andrews R, Kumar L, et al. A randomized controlled trial to assess the effectiveness of muscle strengthening and balancing exercises on chemotherapy-induced peripheral neuropathic pain and quality of life among cancer patients. *Cancer Nurs* 2020;43(4):269–280.
51. McCrary JM, Goldstein D, Sandler CX, et al. Exercise-based rehabilitation for cancer survivors with chemotherapy-induced peripheral neuropathy. *Support Care Cancer Off J Multinatl Assoc Support Care Cancer* 2019;27(10):3849–3857.
52. Streckmann F, Lehmann HC, Balke M, et al. Sensorimotor training and whole-body vibration training have the potential to reduce motor and sensory symptoms of chemotherapy-induced peripheral neuropathy—a randomized controlled pilot trial. *Support Care Cancer* 2019;27(7):2471–2478.
53. Wampler MA, Topp KS, Miaskowski C, et al. Quantitative and clinical description of postural instability in women with breast cancer treated with taxane chemotherapy. *Arch Phys Med Rehabil* 2007;88(8):1002–1008.
54. Simoneau GG, Ulbrecht JS, Derr JA, Cavanagh PR. Role of somatosensory input in the control of human posture. *Gait Posture* 1995;3(3):115–122.
55. Simoneau GG, Ulbrecht JS, Derr JA, et al. Postural instability in patients with diabetic sensory neuropathy. *Diabetes Care* 1994;17(12):1411–1421.
56. Dickstein R, Shupert CL, Horak FB. Fingertip touch improves postural stability in patients with peripheral neuropathy. *Gait Posture* 2001;14(3):238–247.
57. Fino PC, Horak FB, El-Gohary M, et al. Postural sway, falls, and self-reported neuropathy in aging female cancer survivors. *Gait Posture* 2019;69:136–142.
58. Mergner T, Maurer C, Peterka RJ. A multisensory posture control model of human upright stance. *Prog Brain Res* 2003;142:189–201.
59. van der Kooij H, Peterka RJ. Non-linear stimulus-response behavior of the human stance control system is predicted by optimization of a system with sensory and motor noise. *J Comput Neurosci* 2011;30(3):759–778.