

Supplementary material

Supplementary table 1. Main clinical, neurophysiological and neuropathological characteristics of peripheral neuropathy assessment between Parkinson's disease patients with (PD-PNP) and without (PD-noPNP) peripheral neuropathy.

	PD-PNP (N=40)	PD-noPNP (N=59)	p
NIS-LL	3.7 (3)	1.4 (2)	<0.001***
mTCNS	3.4 (2)	1.3 (2)	<0.001***
Sural nerve SNAP amplitude (μ V)	12.5 (10)	16 (8)	0.011*
Sup. peroneal nerve SNAP amplitude (μ V)	11.8 (8)	14.5 (6)	0.028*
Peroneal nerve CMAP amplitude (mV)	4.5 (2)	5.2 (2)	0.126
Peroneal nerve CMAP velocity (m/s)	47.2 (9)	48.2 (4)	0.792
Peroneal nerve CMAP latency (ms)	3.5 (0.8)	3.4 (0.5)	0.091
QST \geq 97 th (N)	19	3	0.003*
IENFD proximal	11.4 (4)	11.5 (4)	0.88
IENFD distal	6.1 (3)	8.2 (3)	<0.001***

Values are expressed in mean (SD), except for QST value corresponding to subjects' number. CMAP: compound muscle action potential; IENFD: Intraepidermal nerve fiber density; mTCNS: modified Toronto Clinical Neuropathy Score; NIS-LL: Neuropathy Impairment Score for Lower Limbs; PD-PNP: Parkinson's disease patients with peripheral neuropathy; PD-noPNP: Parkinson's disease patients without peripheral neuropathy; QST: Quantitative Sensory Test; SNAP: sensory nerve action potential; Sup: superficial; *p<0.05; ***p<0.001

Supplementary table 2. Clinical and demographic characteristics of large and small fiber neuropathy groups.

	Large fiber neuropathy	Small fiber neuropathy	p
Sex	4F (33.3 %)	14F (50 %)	0.374
Age	69.5 (12)	65.3 (10)	0.118
PD onset (years)	59 (17)	59.8 (10)	0.558
Disease duration (years)	7.9 (7)	6.9 (5)	0.845
H&Y	2.5	2	0.284
LEDD (mg)	768.5 (333)	725.2 (386)	0.642
UPDRS III ON	15.3 (10)	15.1 (9)	0.964
UPDRS III OFF	24.9 (14)	24.1 (11)	0.988
NMSS	28.4 (18)	29.2 (23)	0.799
DRS	125.7 (14)	120.4 (16)	0.343
NIS-LL	4.6 (3)	3.2 (2)	0.188
mTCNS	3.5 (3)	3.2 (2)	0.642
Sural nerve SNAP amplitude (μ V)	3.4 (3)	16.4 (10)	<0.001***
Sup. peroneal nerve SNAP amplitude (μ V)	4.1 (3)	15.2 (7)	<0.001***
Peroneal nerve CMAP amplitude (mV)	3.5 (3)	4.9 (2)	0.033*
Peroneal nerve CMAP velocity (m/s)	43.4 (15)	48.8 (4)	0.188
Peroneal nerve CMAP latency (ms)	3.4 (1)	3.6 (0.5)	0.916
QST \geq 97 th (N)	5 (41.6 %)	14 (50 %)	0.889
IENFD proximal	9.7 (2)	12.2 (4)	0.079
IENFD distal	5.1 (2)	6.5 (3)	0.423

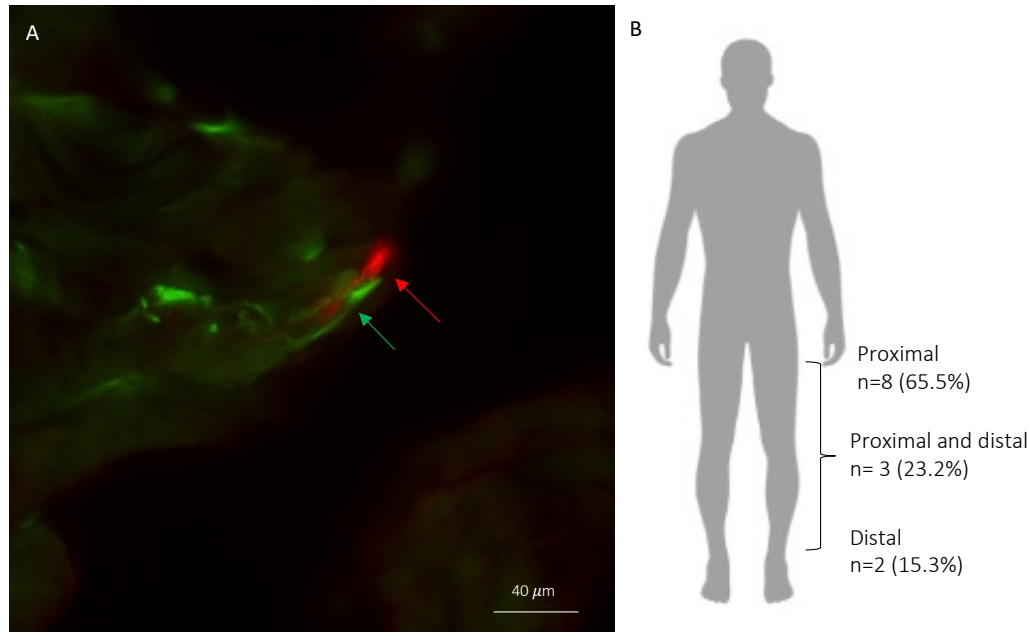
Values are expressed in mean (SD), except for QST value corresponding to subjects' number. CMAP: compound muscle action potential; DRS: dementia rating scale; H&Y: Hoehn and Yahr stage; IENFD: Intraepidermal nerve fiber density; LEDD: Levodopa Equivalent Daily Dose; mTCNS: modified Toronto Clinical Neuropathy Score; NIS-LL: Neuropathy Impairment Score for Lower Limbs; NMSS: Non-motor symptoms scale for Parkinson's disease; PD-PNP: Parkinson's disease patients with peripheral neuropathy; PD-noPNP: Parkinson's disease patients without peripheral neuropathy; QST: Quantitative Sensory Test; SNAP: sensory nerve action potential; Sup: superficial; UPDRS: Unified Parkinson's Disease Rating Scale. p<0.05; **p<0.01.

Supplementary table 3. Etiological classification and laboratory work-up for PD-PNP participants.

PD-PNP patients	PNP type	Etiology	Laboratorial findings
#1	Small FN	Undisclosed etiology	
#2	Small FN	Abnormal metabolic alterations	VB12=182.9 pg/L
#3	Small FN	Abnormal metabolic alterations	VB12=464.9 pg/L; MMA=560 nmol/L
#4	Small FN	Abnormal metabolic alterations	VB12=232.3 pg/L; MMA=498 nmol/L
#5	Small FN	Undisclosed etiology	
#6	Small FN	Undisclosed etiology	
#7	Small FN	Undisclosed etiology	
#8	Small FN	Abnormal metabolic alterations	VB6=267 nmol/L
#9	Small FN	Undisclosed etiology	
#10	Small FN	Undisclosed etiology	
#11	Small FN	Glucose dysmetabolism	DM
#12	Small FN	Glucose dysmetabolism	HbA1c=11.2%
#13	Small FN	Undisclosed etiology	
#14	Small FN	Abnormal metabolic alterations	VB12=490 pg/L; Hcy=12.6 umol/L
#15	Small FN	Undisclosed etiology	
#16	Small FN	Undisclosed etiology	
#17	Small FN	Glucose dysmetabolism	HbA1c=7.5%
#18	Small FN	Undisclosed etiology	
#19	Small FN	Abnormal metabolic alterations	VB12=297 pg/L; MMA=468 nmol/L
#20	Small FN	Glucose dysmetabolism and abnormal metabolic alterations	DM; VB12=245 pg/L; Hcy=15.5 umol/L; VB6=160 nmol/L
#21	Small FN	Glucose dysmetabolism	DM
#22	Small FN	Abnormal metabolic alterations	VB6=205 nmol/L
#23	Small FN	Glucose dysmetabolism and abnormal metabolic alterations	DM; VB12=485 pg/L; Hcy=12.7 umol/L
#24	Small FN	Undisclosed etiology	
#25	Small FN	Undisclosed etiology	
#26	Small FN	Glucose dysmetabolism and abnormal metabolic alterations	DM; VB12=483 pg/L; MMA=1221 nmol/L; Hcy=12.3 umol/L; VB6=135 nmol/L
#27	Small FN	Abnormal metabolic alterations	VB12=329 pg/L; Hcy=15.6 umol/L
#28	Small FN	Undisclosed etiology	
#29	Both	Glucose dysmetabolism	HbA1c=7.4%
#30	Both	Undisclosed etiology	
#31	Both	Undisclosed etiology	
#32	Both	Abnormal metabolic alterations	VB12=239 pg/L; Hcy=14.7 umol/L; VB6=138 nmol/L
#33	Both	Abnormal metabolic alterations	VB12=213 pg/L; MMA=784 nmol/L; Hcy=13.8 umol/L; VB6=396 nmol/L
#34	Both	Glucose dysmetabolism	DM
#35	Both	Glucose dysmetabolism and abnormal metabolic alterations	DM; VB12=179 pg/L; MMA=455 nmol/L; Hcy=13.3 umol/L
#36	Large FN	Undisclosed etiology	
#37	Large FN	Abnormal metabolic alterations	VB12=271 pg/L; MMA=801 nmol/L; Hcy=11.3 umol/L
#38	Large FN	Undisclosed etiology	
#39	Large FN	Undisclosed etiology	
#40	Large FN	Undisclosed etiology**	

DM= previously diagnosed Diabetes Mellitus; **HbA1c**= Hemoglobin A1c; **Hcy**= Homocysteine; **MMA**= Methylmalonic acid; **VB6**= vitamin B6; **VB12**= vitamin B12; ** due to incomplete investigation.

Supplementary Figure I. Phospho- α -synuclein staining and localization.



(A) Photomicrograph of skin biopsy of one PD participant double stained with anti-PGP9.5 (red) and anti-phospho- α -synuclein (green). Note colocalization phospho- α -synuclein (green arrows) in a nerve fiber (red arrows) of the subepidermal plexus. Images were acquired via motorized widefield fluorescence microscope at 40x/0.60 objective (Leica DMI6000, Leica Microsystems). **(B)** Phospho- α -synuclein localization (n, %).

Supplementary table 4. Estimated means and univariate analysis of variances of the main gait parameters during straight walking, circular walking and turns at OFF and ON medication states in Parkinson's disease patients with (PD-PNP) and without (PD-noPNP) peripheral neuropathy.

Straight walking							
Gait parameter	Medication state	PD group	Mean	Std. Error	95% Confidence Interval		Univariate test
					Lower	Upper Bound	
Stride length (m)	OFF	PD-noPNP	0.964	0.026	0.913	1.014	p=0.029*
		PD-PNP	0.878	0.029	0.819	0.936	
	ON	PD-noPNP	1.025	0.025	0.975	1.075	p=0.013*
		PD-PNP	0.929	0.028	0.873	0.986	
Gait speed (m/s)	OFF	PD-noPNP	0.922	0.023	0.877	0.967	p=0.005**
		PD-PNP	0.822	0.026	0.77	0.874	
	ON	PD-noPNP	0.993	0.022	0.949	1.037	p=0.006**
		PD-PNP	0.900	0.025	0.85	0.95	
Heel strike angle (deg)	OFF	PD-noPNP	11.411	0.654	10.112	12.709	p=0.826
		PD-PNP	11.192	0.751	9.701	12.682	
	ON	PD-noPNP	12.239	0.621	11.004	13.473	p=0.936
		PD-PNP	12.163	0.703	10.765	13.562	
Toe off angle (deg)	OFF	PD-noPNP	-54.865	1.099	-57.048	-52.683	p=0.002**
		PD-PNP	-49.633	1.261	-52.139	-47.127	
	ON	PD-noPNP	-57.932	0.997	-59.914	-55.949	p<0.001***
		PD-PNP	-51.914	1.129	-54.159	-49.668	
Circular walking							
Gait parameter	Medication state	PD group	Mean	Std. Error	95% Confidence Interval		Univariate test
					Lower	Upper Bound	
Stride length (m)	OFF	PD-noPNP	0.593	0.016	0.56	0.626	p=0.28
		PD-PNP	0.566	0.019	0.529	0.603	
	ON	PD-noPNP	0.679	0.02	0.638	0.719	p=0.116
		PD-PNP	0.63	0.023	0.585	0.676	
	OFF	PD-noPNP	0.561	0.02	0.521	0.601	p=0.019*

Gait speed (m/s)	ON	PD-PNP	0.489	0.023	0.444	0.534	p=0.057
		PD-noPNP	0.66	0.021	0.619	0.701	
		PD-PNP	0.6	0.023	0.553	0.646	
Heel strike angle (deg)	OFF	PD-noPNP	6.198	0.528	5.15	7.246	p=0.773
		PD-PNP	5.968	0.597	4.783	7.154	
	ON	PD-noPNP	7.295	0.45	6.401	8.188	p=0.341
Toe off angle (deg)	OFF	PD-noPNP	-38.717	1.168	-41.036	-36.397	p=0.007**
		PD-PNP	-33.852	1.321	-36.476	-31.229	
	ON	PD-noPNP	-43.685	1.054	-45.779	-41.591	p=0.001**
		PD-PNP	-38.464	1.184	-40.816	-36.112	
Peak angular velocity (deg/s)	OFF	PD-noPNP	58.27	1.921	54.456	62.084	p=0.002**
		PD-PNP	48.997	2.153	44.722	53.271	
	ON	PD-noPNP	59.85	1.726	56.42	63.279	p=0.01*
		PD-PNP	54.397	1.922	50.579	58.215	

Turns (TUG assessment)

Gait parameter	Medication state	PD group	Mean	Std. Error	95% Confidence Interval		Univariate test
					Lower	Upper Bound	
Duration of turns	OFF	PD-noPNP	3.161	0.118	2.926	3.396	p=0.007**
		PD-PNP	3.655	0.136	3.386	3.924	
	ON	PD-noPNP	3.049	0.098	2.854	3.244	p=0.042*
		PD-PNP	3.358	0.113	3.133	3.583	
Peak angular velocity (deg/s)	OFF	PD-noPNP	58.27	1.921	54.456	62.084	P=0.002**
		PD-PNP	48.997	2.153	44.722	53.271	
	ON	PD-noPNP	59.85	1.726	56.42	63.279	P=0.01*
		PD-PNP	54.397	1.922	50.579	58.215	

PD-PNP: Parkinson's disease patients with peripheral neuropathy; PD-noPNP: Parkinson's disease patients without peripheral neuropathy. Covariates appearing in the model are evaluated at the following values: Age = 67.13. * p<0.05; **p<0.01; ***p<0.001.

Supplementary table 5. Estimated means and univariate analysis of variances of balance parameters during closed eyes on the foam condition at OFF medication state in Parkinson's disease patients with (PD-PNP) and without (PD-noPNP) peripheral neuropathy.

Closed eyes static balance OFF	PD group	Mean	Std. Error	95% Confidence Interval		Univariate
				Lower Bound	Upper Bound	
Jerk AP (cm/s ³)	PD-noPNP	0.081	0.002	0.078	0.084	p=0.028*
	PD-PNP	0.084	0.002	0.08	0.088	
Jerk ML (cm/s ³)	PD-noPNP	1.131	0.044	1.044	1.219	p=0.001**
	PD-PNP	1.392	0.053	1.287	1.497	
Acceleration AP (cm/s ²)	PD-noPNP	3.115	0.278	2.558	3.672	p=0.03*
	PD-PNP	3.992	0.334	3.324	4.66	
Acceleration ML (cm/s ²)	PD-noPNP	0.086	0.001	0.083	0.088	p=0.297
	PD-PNP	0.088	0.002	0.084	0.091	
Velocity AP (cm/s)	PD-noPNP	1.518	0.057	1.403	1.632	p=0.034*
	PD-PNP	1.715	0.069	1.577	1.852	
Velocity ML (cm/s)	PD-noPNP	5.935	0.574	4.786	7.084	p=0.578
	PD-PNP	4.689	0.689	3.31	6.069	
Sway area (cm ² /s ⁴)	PD-noPNP	31.121	1.895	27.328	34.914	p<0.001***
	PD-PNP	43.69	2.274	39.138	48.242	

PD-PNP: Parkinson's disease patients with peripheral neuropathy; PD-noPNP: Parkinson's disease patients without peripheral neuropathy. Covariates appearing in the model are evaluated at the following values: Age = 67.13. * p<0.05; **p<0.01; ***p<0.001.

Supplementary table 6. Comparison of gait and balance parameters between Parkinson's disease patients with large and small fiber neuropathy (FN) groups and without peripheral neuropathy (PD-noPNP).

Straight walking								
Gait parameter	Medication state	PNP types		Mean Difference	Std. Error	Sig.	95% Confidence	
							Lower	Upper
Stride length (m)	OFF	PD-noPNP	Large FN	0.112	0.062	0.074	-0.011	0.235
		PD-noPNP	Small FN	0.067	0.046	0.148	-0.024	0.159
		Large FN	Small FN	-0.044	0.067	0.513	-0.178	0.09
Stride length (m)	ON	PD-noPNP	Large FN	0.117	0.055	0.037*	0.007	0.226
		PD-noPNP	Small FN	0.079	0.04	0.052	-0.001	0.16
		Large FN	Small FN	-0.037	0.06	0.535	-0.156	0.081
Gait speed (m/s)	OFF	PD-noPNP	Large FN	0.123	0.057	0.032*	0.011	0.236
		PD-noPNP	Small FN	0.086	0.042	0.046*	0.002	0.17
		Large FN	Small FN	-0.037	0.062	0.546	-0.16	0.085
Gait speed (m/s)	ON	PD-noPNP	Large FN	0.1	0.048	0.041*	0.004	0.196
		PD-noPNP	Small FN	0.092	0.035	0.011*	0.021	0.162
		Large FN	Small FN	-0.008	0.052	0.877	-0.112	0.096
Toe-off angle (deg)	OFF	PD-noPNP	Large FN	-8.686	2.438	0.001**	-13.53	-3.843
		PD-noPNP	Small FN	-3.596	1.851	0.055	-7.274	0.081
		Large FN	Small FN	5.09	2.659	0.059	-0.193	10.373
Toe-off angle (deg)	ON	PD-noPNP	Large FN	-9.383	2.311	<0.001***	-13.978	-4.788
		PD-noPNP	Small FN	-4.657	1.652	0.006**	-7.941	-1.373
		Large FN	Small FN	4.725	2.475	0.06	-0.196	9.647
Circular walking								
Stride length (m)	OFF	PD-noPNP	Large FN	0.015	0.036	0.682	-0.057	0.086
		PD-noPNP	Small FN	0.036	0.028	0.193	-0.019	0.091
		Large FN	Small FN	0.021	0.04	0.59	-0.057	0.1
Stride length (m)	ON	PD-noPNP	Large FN	0.037	0.046	0.416	-0.054	0.129
		PD-noPNP	Small FN	0.059	0.034	0.089	-0.009	0.127
		Large FN	Small FN	0.022	0.05	0.664	-0.077	0.12
Gait speed (m/s)	OFF	PD-noPNP	Large FN	0.062	0.044	0.167	-0.026	0.149
		PD-noPNP	Small FN	0.082	0.034	0.019*	0.014	0.149
		Large FN	Small FN	0.02	0.048	0.682	-0.076	0.116
Gait speed (m/s)	ON	PD-noPNP	Large FN	0.009	0.046	0.85	-0.083	0.1
		PD-noPNP	Small FN	0.084	0.035	0.017*	0.015	0.152
		Large FN	Small FN	0.075	0.05	0.135	-0.024	0.174
Toe-off angle (deg)	OFF	PD-noPNP	Large FN	-6.731	2.577	0.01*	-11.847	-1.615
		PD-noPNP	Small FN	-3.949	1.983	0.049*	-7.887	-0.011
		Large FN	Small FN	2.782	2.811	0.325	-2.8	8.364
Toe-off angle (deg)	ON	PD-noPNP	Large FN	-5.712	2.324	0.016*	-10.326	-1.099
		PD-noPNP	Small FN	-5.371	1.735	0.003**	-8.815	-1.927
		Large FN	Small FN	0.342	2.531	0.893	-4.683	5.366
Peak ang vel (deg/s)	OFF	PD-noPNP	Large FN	13.489	8.699	0.124	-3.783	30.761
		PD-noPNP	Small FN	14.545	6.688	0.032*	12.65	27.824
		Large FN	Small FN	1.056	9.489	0.912	-17.785	19.897
Peak ang vel (deg/s)	ON	PD-noPNP	Large FN	16.806	9.331	0.075	-1.722	35.334
		PD-noPNP	Small FN	16.121	6.973	0.023*	2.276	29.965
		Large FN	Small FN	-0.685	10.145	0.946	-20.829	19.458
Static balance with closed eyes on a foam								
Balance parameter	Medication state	PNP types		Mean Difference	Std. Error	Sig.	95% Confidence	
							Lower	Upper
Jerk AP (cm/s ³)	OFF	PD-noPNP	Large FN	-0.005	0.004	0.206	-0.013	0.003
		PD-noPNP	Small FN	-0.003	0.003	0.261	-0.008	0.002
		Large FN	Small FN	0.002	0.004	0.649	-0.006	0.01
Jerk ML (cm/s ³)	OFF	PD-noPNP	Large FN	-0.331	0.112	0.004**	-0.554	-0.107
		PD-noPNP	Small FN	-0.125	0.088	0.16	-0.299	0.05

		Large FN	Small FN	0.206	0.126	0.106	-0.045	0.458
Acc AP (cm/s ²)	OFF	PD-noPNP	Large FN	-0.398	0.617	0.521	-1.628	0.832
		PD-noPNP	Small FN	-0.959	0.492	0.055	-1.939	0.022
		Large FN	Small FN	-0.561	0.696	0.423	-1.948	0.827
Acc ML (cm/s ²)	OFF	PD-noPNP	Large FN	-0.008	0.003	0.005**	-0.013	-0.002
		PD-noPNP	Small FN	0	0.002	0.885	-0.004	0.004
		Large FN	Small FN	0.007	0.003	0.013*	0.002	0.013
Vel AP (cm/s)	OFF	PD-noPNP	Large FN	-0.285	0.15	0.062	-0.585	0.014
		PD-noPNP	Small FN	-0.094	0.109	0.387	-0.311	0.122
		Large FN	Small FN	0.191	0.165	0.25	-0.137	0.519
Vel ML (cm/s)	OFF	PD-noPNP	Large FN	0.093	1.217	0.94	-2.333	2.518
		PD-noPNP	Small FN	1.21	0.906	0.185	-0.594	3.015
		Large FN	Small FN	1.118	1.334	0.405	-1.541	3.777
Sway area (cm ² /s ⁴)	OFF	PD-noPNP	Large FN	-17.145	4.563	<0.001***	-26.258	-8.033
		PD-noPNP	Small FN	-8.854	3.281	0.009**	-15.407	-2.302
		Large FN	Small FN	8.291	5.003	0.102	-1.7	18.282

PD-PNP: Parkinson's disease patients with peripheral neuropathy; PD-noPNP: Parkinson's disease patients without peripheral neuropathy. * p<0.05; **p<0.01; ***p<0.001.