

Supplementary material to “Behavioural and neuroplastic effects of a double-blinded randomised controlled exercise trial in people with Parkinson’s disease”

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Supplementary Table 1. Correlation matrix of all behavioural and BDNF outcomes.																		
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
1. Mini-BESTest	1	0.47	0.52	-0.56	0.38	0.26	-0.37	-0.42	0.53	0.26	0.35	-0.17	-0.07	0.03	-0.4	0.45	-0.29	-0.18
2. Gait speed	0.47	1	0.89	-0.49	0.45	0.25	-0.29	-0.34	0.44	0.26	0.14	-0.08	-0.12	0.11	-0.22	0.37	-0.32	0.06
3. Step length	0.52	0.89	1	-0.5	0.49	0.25	-0.38	-0.39	0.47	0.22	0.14	-0.12	-0.12	0.12	-0.27	0.43	-0.34	-0.01
4. Walk-12	-0.56	-0.49	-0.5	1	-0.34	-0.25	0.39	0.63	-0.79	-0.21	-0.25	0.03	0.09	0.01	0.72	-0.73	0.69	0.48
5. Steps/day	0.38	0.45	0.49	-0.34	1	0.25	-0.23	-0.33	0.27	0	0.08	-0.13	-0.09	0.03	-0.24	0.23	-0.2	-0.04
6. Frändin-Grimby	0.26	0.25	0.25	-0.25	0.25	1	-0.11	-0.16	0.07	0.13	0.22	-0.11	0	-0.17	-0.11	0.25	-0.23	-0.05
7. MDS-UPDRS III	-0.37	-0.29	-0.38	0.39	-0.23	-0.11	1	0.82	-0.26	-0.21	-0.31	0.22	0.13	-0.23	0.2	-0.23	0.21	0.02
8. MDS-UPDRS total	-0.42	-0.34	-0.39	0.63	-0.33	-0.16	0.82	1	-0.51	-0.15	-0.24	0.2	0.22	-0.03	0.57	-0.5	0.54	0.38
9. ABC	0.53	0.44	0.47	-0.79	0.27	0.07	-0.26	-0.51	1	0.1	0.19	0.08	-0.16	-0.08	-0.65	0.63	-0.6	-0.45
10. MoCA	0.26	0.26	0.22	-0.21	0	0.13	-0.21	-0.15	0.1	1	0.56	-0.12	0.11	0	-0.07	0.08	-0.1	0.1
11. Executive function	0.35	0.14	0.14	-0.25	0.08	0.22	-0.31	-0.24	0.19	0.56	1	0.01	0.09	0.11	-0.14	0.13	-0.24	-0.1
12. proBDNF	-0.17	-0.08	-0.12	0.03	-0.13	-0.11	0.22	0.2	0.08	-0.12	0.01	1	-0.16	-0.04	0.06	-0.15	0.28	0.08
13. mBDNF	-0.07	-0.12	-0.12	0.09	-0.09	0	0.13	0.22	-0.16	0.11	0.09	-0.16	1	0.06	0.13	0.03	0.02	-0.04
14. Voice sound level	0.03	0.11	0.12	0.01	0.03	-0.17	-0.23	-0.03	-0.08	0	0.11	-0.04	0.06	1	0.04	0.01	0.11	0.01
15. PDQ-39	-0.4	-0.22	-0.27	0.72	-0.24	-0.11	0.2	0.57	-0.65	-0.07	-0.14	0.06	0.13	0.04	1	-0.65	0.66	0.74
16. EQ5D, VAS	0.45	0.37	0.43	-0.73	0.23	0.25	-0.23	-0.5	0.63	0.08	0.13	-0.15	0.03	0.01	-0.65	1	-0.65	-0.6
17. HADS depression	-0.29	-0.32	-0.34	0.69	-0.2	-0.23	0.21	0.54	-0.6	-0.1	-0.24	0.28	0.02	0.11	0.66	-0.65	1	0.65
18. HADS anxiety	-0.18	0.06	-0.01	0.48	-0.04	-0.05	0.02	0.38	-0.45	0.1	-0.1	0.08	-0.04	0.01	0.74	-0.6	0.65	1

All values are Pearson's correlation coefficients. The figures in the upper row correspond to the outcome name with the same figure presented in the left most column. Mini-BESTest = the Mini-Balance Evaluation Systems Test, Frändin-Grimby = the Frändin-Grimby scale, MDS-UPDRS = Movement Disorders Society - Unified Parkinson's Disease Rating Scale, MoCA = the Montreal Cognitive Assessment score ABC = the Activities-specific Balance Confidence Scale, proBDNF = precursor BDNF, mBDNF = mature BDNF, PDQ-39 = the Parkinson's Disease Questionnaire-39, EQ5D- VAS = the EuroQol 5 dimensions visual analogue scale, HADS = the Hospital Anxiety and Depression scale.

Supplementary Table 2. Credibility assessments and expectations of the two interventions.					
	HiBalance m (sd)	Active control m (sd)	t-value	p-value	adjusted p-value
How successful symptom alleviation	6.6 (1.4)	5.8 (1.1)	-3.1	0.0026	0.0070
Recommend to a friend	7.6 (1.2)	6.5 (1.3)	-3.9	0.00021	0.0021
How much better (%)	53.3 (23)	55.1 (20)	0.4	0.69	0.69
Challenging tasks	5.5 (1)	5 (1.6)	-1.6	0.11	0.14
Feels valuable to me	7.5 (1.2)	6.6 (1.6)	-3	0.0035	0.0070
Enhance my memory	5.3 (1.9)	5.9 (1.4)	1.7	0.094	0.14
Get to know my group members	5.9 (1.6)	6.3 (1.3)	1.2	0.22	0.25
Enhance my dual task ability	6 (1.4)	5.3 (1.7)	-2	0.046	0.077
Benefit	7.5 (1.2)	6.7 (1.3)	-3.1	0.0027	0.0070
Motivation	8.1 (1)	7.4 (1.2)	-3	0.0035	0.0070

Questionnaire answered at week 3 to 4 into the interventions. Range 1-9 for all questions but “How much better” where percentage was used. The questionnaire was inspired by Borkovec and Nau.¹⁵ P-values were adjusted using the false discovery rate with alpha = 0.05.

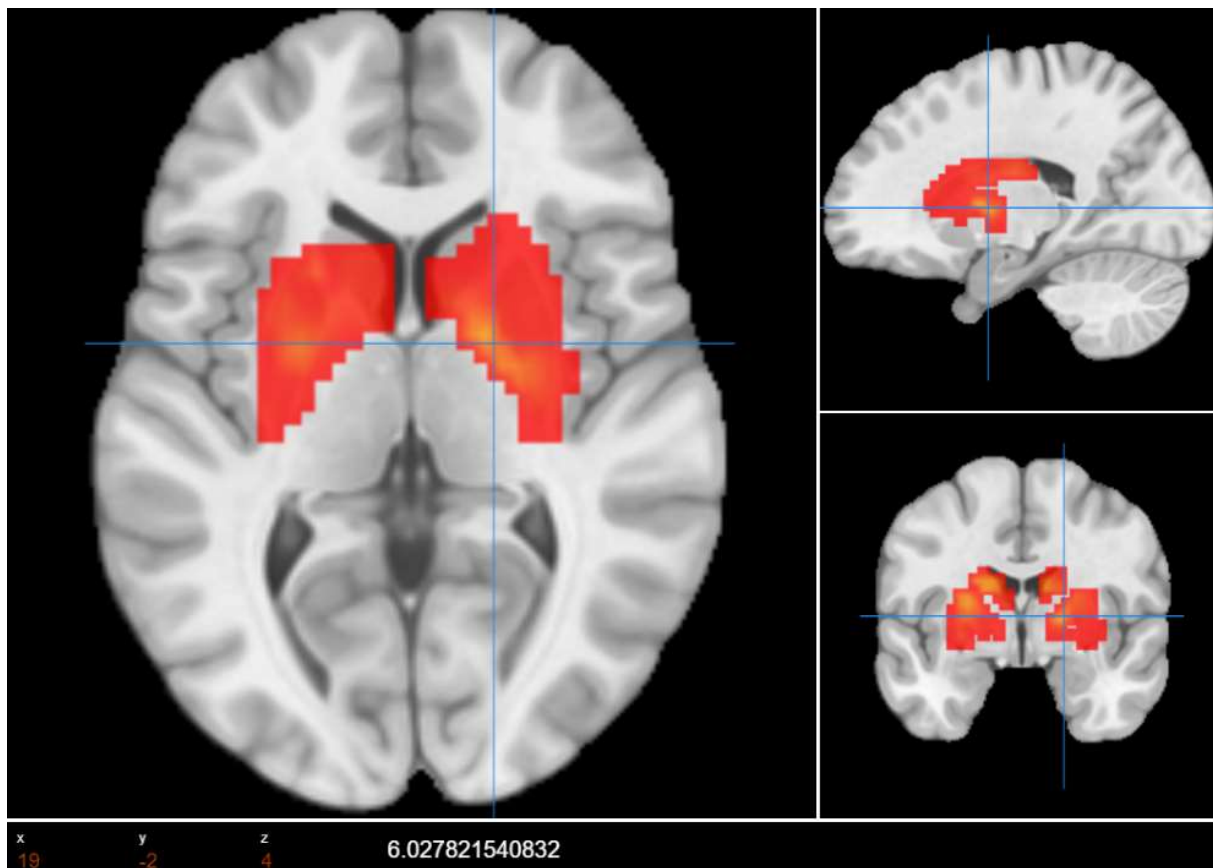
Supplementary Table 3. Blinding of the assessors at the post intervention assessments.						
	Knew before n (%)	Guessed before n (%)	Correct guess before n (%)	No guess n (%)	Guessed after n (%)	Not reported n (%)
Mini-BESTest	5 (6.8)	1 (1.4)	1 (1.4)	44 (59.5)	9 (12.2)	15 (20.3)
MDS-UPDRS	3 (4.1)	0 (0)	0 (0)	49 (66.2)	2 (2.7)	15 (20.3)
MRI	3 (4.6)	4 (6.2)	1 (1.5)	24 (36.9)	32 (49.2)	12 (18.5)
Speech, cognition	6 (9.2)	9 (13.8)	8 (12.3)	43 (66.2)	9 (13.8)	6 (9.2)
<p>All blinding scores were reported at the end of the assessment. Knew before = the assessor knew group allocation before the post assessment started, Guessed before = the assessor guessed group allocation based in information obtained before the post assessment started, Correct guess before = the assessor was right in the guessed group allocation based on information obtained before the post assessment started, No guess = the assessor had no guess on group allocation either before the start or at the end of the post assessment, Guessed after = the assessor obtained a guess on group allocation at the end of the post assessment, Not reported = missing blinding score. Mini-BESTest = the Mini-Balance Evaluation Systems Test, MDS-UPDRS = Movement Disorders Society - Unified Parkinson's Disease Rating Scale, MRI = magnetic resonance imaging.</p>						

Supplementary Table 4. Medication changes over the course of the intervention.				
	HiBalance group (n = 40)	Active control group (n = 35)	t-value	p-value
Number of participants who increased their medication during the intervention	5	6		
Increase mg, m (sd)	89.6 (23.3)	105.7 (35.4)	0.4	0.39
Number of participants who decreased their medication during the intervention	1	1		
Decrease mg (m)	-93.0	-49.5		
mg = milligram, m = mean, sd = standard deviation.				

Supplementary Table 5. Estimates of the MLM analyses based on the imputed data (by intention to treat).

		Group		Time		Group x Time		Intercept	
	reg	b (95% CI)	P	b (95% CI)	P	b (95% CI)	P	b (95% CI)	P
Mini-BESTest	lin.	-0.3 (-1.7, 1)	0.65	0.6 (-0.4, 1.6)	0.22	0.4 (-1, 1.9)	0.57	21 (20, 21.9)	< 0.0001
Gait speed	lin.	0.9 (-6.8, 8.5)	0.82	2.4 (-3.3, 8.1)	0.41	4.4 (-3.2, 12.1)	0.25	118.9 (113.5, 124.4)	< 0.0001
Step length	lin.	0.5 (-3, 4.1)	0.77	1.1 (-1.8, 4)	0.47	1.1 (-2.3, 4.5)	0.53	64.4 (61.9, 67)	< 0.0001
Walk 12	poiss.	0.2 (-0.2, 0.5)	0.31	0 (-0.2, 0.2)	0.89	-0.1 (-0.4, 0.1)	0.29	2.1 (1.9, 2.4)	< 0.0001
Steps/day	log lin.	-0.1 (-0.3, 0.2)	0.66	0 (-0.1, 0.2)	0.65	-0.1 (-0.4, 0.2)	0.47	8.5 (8.3, 8.7)	< 0.0001
Frändin -Grimby	binom.	-0.1 (-1.2, 1.1)	0.92	-0.5 (-1.6, 0.7)	0.43	0.9 (-0.8, 2.6)	0.30	-0.6 (-1.4, 0.3)	0.19
MDS-UPDRS III	lin.	-0.5 (-5.1, 4)	0.82	-1.9 (-5.5, 1.7)	0.30	-0.4 (-5.5, 4.6)	0.87	31.8 (28.5, 35)	< 0.0001
MDS-UPDRS Tot.	lin.	0.5 (-6.4, 7.5)	0.88	-3 (-8, 1.9)	0.28	-0.3 (-7.6, 6.9)	0.93	50.4 (45.5, 55.4)	< 0.0001
ABC	beta	-0.1 (-0.6, 0.4)	0.73	0.1 (-0.1, 0.3)	0.019	0.2 (-0.1, 0.4)	0.27	1.7 (1.3, 2.1)	< 0.0001
Executive function	lin.	1.3 (0.2, 2.4)	0.024	0.6 (-0.1, 1.4)	0.10	0.2 (-0.8, 1.1)	0.75	-0.7 (-1.5, 0.1)	0.090
mBDNF	lin.	196.3 (-3095.1, 3487.8)	0.91	-369.5 (-2409.5, 1670.6)	0.72	106.8 (-2752.6, 2966.3)	0.94	38071.9 (35714.7, 40429.1)	< 0.0001
Voice sound level	lin.	-0.5 (-2.1, 1.2)	0.58	2 (1.1, 2.9)	<0.0001	-2.1 (-3.4, -0.9)	0.0012	70.9 (69.7, 72)	< 0.0001
PDQ-39	poiss.	0.2 (-0.1, 0.6)	0.16	-0.2 (-0.4, 0.1)	0.16	-0.1 (-0.4, 0.2)	0.56	2.7 (2.4, 2.9)	< 0.0001
EQ5D VAS	beta	-0.4 (-0.9, 0)	0.044	0 (-0.2, 0.3)	0.037	0.2 (-0.1, 0.5)	0.26	1.3 (1, 1.7)	< 0.0001
HADS Depression	poiss.	0.1 (-0.3, 0.5)	0.59	0 (-0.3, 0.3)	0.95	-0.1 (-0.4, 0.3)	0.79	0.9 (0.7, 1.2)	< 0.0001
HADS Anxiety	poiss.	0.2 (-0.2, 0.5)	0.34	0.1 (-0.2, 0.4)	0.46	-0.1 (-0.5, 0.2)	0.38	1.1 (0.9, 1.4)	< 0.0001
proBDNF (pg/ml)	lin.	0.6 (-0.4, 1.6)	0.21	0.5 (-0.3, 1.3)	0.26	-0.3 (-1.3, 0.7)	0.54	5.1 (4.4, 5.9)	< 0.0001
ratioBDNF (pg/ml)	lin.	0.2 (-0.2, 0.5)	0.31	0.1 (-0.2, 0.4)	0.43	-0.1 (-0.5, 0.3)	0.51	-9.1 (-9.3, -8.8)	< 0.0001

The column reg. defines the type of multilevel model (mlm) used for the outcome; lin. = linear, log lin. = linear mlm on logged values, binom. = logistic, poiss. = poisson, beta = mlm based on beta regression. Mini-BESTest = the Mini-Balance Evaluation Systems Test, Frändin-Grimby = the Frändin-Grimby scale, MDS-UPDRS = Movement Disorders Society - Unified Parkinson's Disease Rating Scale, ABC = the Activities-specific Balance Confidence Scale, mBDNF = mature BDNF, PDQ-39 = the Parkinson's Disease Questionnaire-39, EQ5D- VAS = the EuroQol 5 dimensions visual analogue scale, HADS = the Hospital Anxiety and Depression scale, proBDNF = precursor BDNF, ratioBDNF = proBDNF/mBDNF.



Supplementary Figure 1: The f-values map of the striatum from the time by group interaction analysis. A more yellow colour indicates a higher f-value, range: 0 (deepest red) to 8.9 (brightest yellow). Contrast: sequence trial blocks/random trial blocks. An interactive whole brain f-values map from the time by group interaction analysis can be found here: <https://neurovault.org/collections/DORLUDYE/>

Supplementary Table 6. Difference score correlations within the groups between the behavioural outcomes and the fMRI data and mBDNF.

		Mini-BESTest			Gait speed			Executive function		
	group	rho	p	adj. p	rho	p	adj. p	rho	p	adj. p
Striatum	HiBalance	-0.06	0.75	0.97	-0.10	0.58	0.97	-0.09	0.64	0.97
	Active control	0.13	0.50	0.97	0.24	0.22	0.97	-0.03	0.89	0.97
Primary motor c.	HiBalance	0.02	0.91	0.97	0.06	0.75	0.97	0.21	0.26	0.97
	Active control	-0.11	0.57	0.97	0.19	0.34	0.97	0.03	0.87	0.97
Premotor c.	HiBalance	0.06	0.75	0.97	0.14	0.45	0.97	0.10	0.61	0.97
	Active control	0.04	0.83	0.97	0.26	0.18	0.97	0.00	0.99	0.99
Suppl. motor c.	HiBalance	0.03	0.87	0.97	0.05	0.77	0.97	-0.07	0.71	0.97
	Active control	-0.02	0.91	0.97	0.24	0.21	0.97	0.11	0.58	0.97
ACC	HiBalance	0.16	0.41	0.97	-0.2	0.28	0.97	-0.03	0.88	0.97
	Active control	-0.16	0.56	0.97	0.46	0.02	0.54	-0.15	0.47	0.97
DLPFC	HiBalance	0.18	0.33	0.97	-0.15	0.41	0.97	0.09	0.63	0.97
	Active control	0.07	0.71	0.97	0.29	0.14	0.97	-0.01	0.97	0.99
mBDNF	HiBalance	0.03	0.86	0.86	0.17	0.39	0.86	0.09	0.64	0.86
	Active control	0.05	0.83	0.86	-0.20	0.37	0.86	-0.07	0.76	0.86

rho = Spearman's rank order correlation coefficients. adj. p = false discovery rate adjusted p (alpha = 0.05). Primary motor c. = Primary motor cortex, Suppl. motor c. = Supplementary motor cortex, ACC = anterior cingulate cortex, DLPFC = dorsolateral prefrontal cortex, mBDNF = mature BDNF.

Supplementary Table 7. Comparison of the difference score correlations between the behavioural outcomes and brain activity and mBDNF, over the groups.

		Mini-BESTest			Gait speed			Executive function		
		z	p	adj. p	z	p	adj. p	z	p	adj. p
Striatum		0.72	0.47	0.71	1.29	0.20	0.59	0.21	0.83	0.83
Primary motor c.		0.49	0.63	0.84	0.48	0.63	0.84	0.65	0.51	0.84
Premotor c.		0.06	0.95	0.95	0.47	0.63	0.84	0.34	0.73	0.84
Suppl. Motor c.		0.20	0.85	0.91	0.72	0.47	0.84	0.65	0.51	0.84
DLPFC		0.40	0.69	0.84	1.67	0.10	0.72	0.36	0.72	0.84
ACC		0.99	0.32	0.84	2.70	0.010	0.10	0.43	0.66	0.84
mBDNF		0.05	0.96	1.0	1.25	1.0	1.0	0.53	0.59	1.0

z = estimates of the Fischer's Z significance tests. adj. p = false discovery rate adjusted p (alpha = 0.05). Primary motor c. = Primary motor cortex, Suppl. motor c. = Supplementary motor cortex, ACC = anterior cingulate cortex, DLPFC = dorsolateral prefrontal cortex, mBDNF = mature BDNF.

Supplementary Table 8. Estimates of the MLM analysis of the reaction time outcome of the serial reaction time task (motor learning task performed during fMRI).

Seq.		Group		Time		Seq. x Time x Group		Seq. x Group		Seq. x time		Group x time		Trial order		Intercept	
b (ci)	p	b (ci)	p	b (ci)	p	b (ci)	p	b (ci)	p	b (ci)	p	b (ci)	p	b (ci)	p	b (ci)	p
-0.01	0.020	-0.01	0.63	-0.03	< 0.0001	0	0.53	0.01	0.23	-0.01	0.00030	0.01	0.035	0	< 0.0001	0.63	< 0.0001
(-0, -0)		(-0, 0)		(0, 0)		(0, 0)		(-0, 0)		(-0, -0)		(0, 0)		(0, 0)		(0.6, 0.7)	

Seq. = type of block (hidden sequence or random trials), b = unstandardised estimates.

Supplementary Table 9. Estimates of the MLM per protocol analyses.

	reg	Group		Time		Group x Time		Intercept	
		b (95% CI)	P	b (95% CI)	P	b (95% CI)	P	b (95% CI)	P
Mini-BESTest	lin.	-0.3 (-1.8, 1.1)	0.68	0.4 (-0.4, 1.2)	0.30	0.5 (-0.6, 1.5)	0.37	21.4 (20.4, 22.5)	< 0.0001
Gait speed (m/sec)	lin.	0.002 (-0.08, 0.09)	0.95	0.01 (-0.03, 0.05)	0.58	0.05 (-0.002, 0.1)	0.061	1.2 (1.2, 1.3)	< 0.0001
Step length	lin.	0.6 (-3.4, 4.5)	0.78	0.6 (-0.9, 2.1)	0.45	1.3 (-0.8, 3.4)	0.22	65.6 (62.7, 68.5)	< 0.0001
Walk 12	poiss.	0.1 (-0.3, 0.5)	0.50	0 (-0.1, 0.2)	0.90	-0.1 (-0.3, 0.1)	0.27	2 (1.7, 2.3)	< 0.0001
Steps/day	log lin.	-0.1 (-0.4, 0.2)	0.64	0 (-0.1, 0.1)	0.63	-0.1 (-0.2, 0.1)	0.31	8.6 (8.4, 8.8)	< 0.0001
Frändin -Grimby	binom.	0 (-1.4, 1.3)	0.96	-0.6 (-1.9, 0.6)	0.30	1 (-0.6, 2.7)	0.23	-0.4 (-1.5, 0.6)	0.39
MDS-UPDRS III	lin.	1.2 (-4, 6.5)	0.64	-1.7 (-5.1, 1.8)	0.35	-0.9 (-5.7, 3.8)	0.70	30.4 (26.6, 34.2)	< 0.0001
MDS-UPDRS Tot.	lin.	2.2 (-5.8, 10.3)	0.59	-3.5 (-7.7, 0.7)	0.11	0 (-5.8, 5.8)	0.99	49.3 (43.4, 55.2)	< 0.0001
ABC	beta	-0.1 (-0.7, 0.5)	0.68	0 (-0.2, 0.3)	0.66	0.2 (-0.1, 0.4)	0.26	1.9 (1.5, 2.3)	< 0.0001
Executive functions	lin.	1.1 (-0.1, 2.3)	0.073	0.6 (0.2, 1.1)	0.011	0.2 (-0.5, 0.8)	0.62	-0.5 (-1.4, 0.4)	0.26
mBDNF	lin.	293.5 (-2779, 3366)	0.85	-276.5 (-2103.5, 1550.5)	0.77	238.3 (-2241.8, 2718.5)	0.85	36678.1 (34434.3, 38922)	< 0.0001
Voice int	lin.	-0.2 (-2, 1.6)	0.79	2 (1.1, 2.9)	0.0001	-2.2 (-3.5, -0.9)	0.0012	71 (69.7, 72.3)	< 0.0001
PDQ-39	log. lin.	0.2 (-0.2, 0.6)	0.29	-0.2 (-0.3, 0)	0.053	-0.1 (-0.3, 0.2)	0.58	2.7 (2.4, 3)	< 0.0001
EQ5D VAS	beta	-0.4 (-0.9, 0.1)	0.082	0 (-0.2, 0.3)	0.75	0.2 (-0.2, 0.5)	0.27	1.3 (1, 1.7)	< 0.0001
HADS dep.	poiss.	0 (-0.4, 0.5)	0.85	0 (-0.3, 0.2)	0.80	0 (-0.3, 0.4)	0.94	0.9 (0.6, 1.3)	< 0.0001
HADS anx.	poiss.	0.2 (-0.2, 0.6)	0.28	0 (-0.2, 0.3)	0.69	-0.1 (-0.4, 0.2)	0.47	1.1 (0.8, 1.4)	< 0.0001
proBDNF (pg/ml)	lin.	0.2 (-1, 1.4)	0.76	0.3 (0, 0.5)	0.054	-0.3 (-0.7, 0)	0.085	5.7 (4.8, 6.6)	< 0.0001
ratioBDNF (pg/ml)	lin.	0 (-1.2, 1.3)	0.95	0.2 (0, 0.5)	0.058	-0.3 (-0.6, 0)	0.10	-4.8 (-5.8, -3.9)	< 0.0001

The column reg. defines the type of multilevel model (mlm) used for the outcome; lin. = linear, log lin. = linear mlm on logged values, binom. = logistic, poiss. = poisson, beta = mlm based on beta regression. Mini-BESTest = the Mini-Balance Evaluation Systems Test, Frändin-Grimby = the Frändin-Grimby scale, MDS-UPDRS = Movement Disorders Society - Unified Parkinson's Disease Rating Scale, ABC = the Activities-specific Balance Confidence Scale, mBDNF = mature BDNF, PDQ-39 = the Parkinson's Disease Questionnaire-39, EQ5D- VAS = the EuroQol 5 dimensions visual analogue scale, HADS = the Hospital Anxiety and Depression scale, proBDNF = precursor BDNF, ratioBDNF = proBDNF/mBDNF.

Supplementary References

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