Supplementary Material

Effects of a Highly Challenging Balance Training Program on Motor Function and Brain Structure in Parkinson's Disease

Table of Contents

Supplementary Table 1. Motor and cognitive phenotypes in the participants with PD. 3

Supplementary Table 2. Linear mixed model for balance performance. 3

Supplementary Table 3. Linear mixed model for gait speed. 4

Supplementary Table 4. Coordinates of brain structure alterations. 5

Supplementary Table 5. Left Putamen community changes. 6

Supplementary Table 6. Results of structural covariance network analyses. Community changes before and after the intervention obtained with the Louvain algorithm. 8

Supplementary Table 7. Results of partial correlations of motor outcome with gray matter volume in the putamen corrected for total intracranial volume. 11

Supplementary Material 1. R scripts for the behavioral data analyses. 12

Statistics for longitudinal analysis of EXPANd 12

Read in the data for the summary table 12

Overview over the data 12

Summary table for the paper 14

Reading in data for the linear mixed model 16

Linear mixed model with random intercept for MiniBESTest 16

Linear mixed model with random intercept for gait speed 19

Linear mixed model outputs as tables 21

Packages and versions used for this script: 22

Repeated Measures Correlation 24

Reading in data 24

Subsetting the data 24

Correlation for repeated measures 24

Gait speed in A 24

Gait speed in B 26

Comparison of repeated measures correlation coefficients 26

Repeated Measures Correlation MiniBESTest 27

MiniBESTest in A 27

MiniBESTest in B 28

Packages and versions used for this script: 29

Putamen volume correlation with gait speed and MiniBESTest 30

Reading in data for motor variables and gray matter volume *30*
Subsetting the data *31*
Correlation A and B of post gait speed and post gray matter volume *31*
Revision: Partial Correlation for pre, post and delta values controlling for total intracranial volume *32*
Plots using the residuals of gait controlled for intracranial volume (TIV) in the post values *34*
Packages and versions used for this script: *35*
Supplementary Material 2. Preregistration protocol from aspredicted.org. 37

Supplementary Table 1. Motor and cognitive phenotypes in the participants with PD.

	HiBalance (N=34)	Active Control Group (N=31)	Total (N=65)
Motor Phenotype			
Indetermined	6	6	12
Postural instability/ gait dominant	21	16	37
Tremor dominant	6	5	11
Missing	1	4	5
Cognitive Phenotype			
Mild cognitive impairment	9	10	19
Non-mild cognitive impairment	25	21	46

Motor phenotype according to Stebbins et al. 2013, cognitive phenotype according to Litvan et al. 2012.

Supplementary Table 2. Linear mixed model for balance performance.

	Balance Performance (Mini-BESTest)					
Predictors	*Estimates*	*Std. Error*	*Std. Beta*	*CI*	*p*	*df*
(Intercept)	21.25	0.58	-0.03	20.09 – 22.41	<0.001	60.00
Group [Active Control Group]	0.32	0.84	0.06	-1.36 – 1.99	0.706	60.00
Time	0.87	0.45	0.13	-0.03 – 1.78	0.058	60.00
Group [Active Control Group] * Time	-0.21	0.65	-0.03	-1.51 – 1.09	0.750	60.00
Random Effects						
σ^2	3.28					
$\tau_{00\ ID}$	7.55					
N_{ID}	62					
Observations	124					
Marginal R^2	0.048					

CI, confidence interval; df, degrees of freedom; Std, standard

Supplementary Table 3. Linear mixed model for gait speed.

	Gait Speed, m/s					
Predictors	*Estimates*	*Std. Error*	*Std. Beta*	*CI*	*p*	*df*
(Intercept)	1.23	0.03	0.06	1.16 – 1.29	<0.001	62.00
Group [Active Control Group]	0.00	0.05	-0.13	-0.09 – 0.09	0.988	62.00
Time	0.06	0.02	0.15	0.01 – 0.10	0.010	62.00
Group [Active Control Group] * Time	-0.05	0.03	-0.13	-0.11 – 0.01	0.105	62.00
Random Effects						
σ^2	0.01					
$T_{00\ ID}$	0.03					
N_{ID}	64					
Observations	128					
Marginal R^2	0.015					

CI, confidence interval; df, degrees of freedom; Std, standard

Supplementary Table 4. Coordinates of brain structure alterations.

Cluster p (FWE)	Voxels	T	Z	Peak p (uncorrected)	x,y,z	Anatomical region
VBM Main effect of time, p<0.001, k=100						
0.331	420	24.04	4.35	<0.001	57 -15 -33	R inferior temporal gyrus
0.658	188	21.49	4.13	<0.001	10 -28 14	R thalamus
0.593	225	20.6	4.05	<0.001	-56 -69 -4	L middle temporal/ inferior occipital gyrus
0.25	511	20.04	3.99	<0.001	-27 -68 -32	L cerebellum exterior
0.585	230	19.4	3.93	<0.001	-58 -21 -34	L inferior temporal gyrus
0.671	181	18.27	3.82	<0.001	-9 -36 4	L thalamus
		13.76	3.33	<0.001	-10 -28 14	L thalamus
		13.72	3.32	<0.001	-3 -26 8	L thalamus
0.605	218	16.96	3.69	<0.001	18 -64 16	R precuneus / cuneus
0.819	102	16.44	3.63	<0.001	-40 -16 0	L posterior insula / transverse temporal gyrus
VBM Active Control Group$_{pre}$ > $_{post}$, p<0.001, k=100						
0.100	942	4.63	4.28	<0.001	-30 -68 -28	L cerebellum exterior
.0279	529	4.38	4.07	<0.001	-56 -69 -3	L middle temporal gyrus
0.787	112	4.33	4.03	<0.001	10 -28 14	R thalamus
0.550	264	4.31	4.02	<0.001	8 -8 54	R supplementary motor cortex
0.661	189	4.14	3.88	<0.001	-36 -94 -6	L inferior occipital gyrus
0.239	589	4.03	3.79	<0.001	18 -64 16	R precuneus/ cuneus
		3.43	3.27	<0.001	10 -74 26	R cuneus
0.578	244	4.03	3.78	<0.001	56 -15 -32	R inferior temporal gyrus
0.725	149	3.98	3.74	<0.001	27 -42 -3	R lingual gyrus/ hippocampus
0.772	121	3.84	3.63	<0.001	-68 -42 -8	L middle temporal gyrus
0.745	137	3.70	3.51	<0.001	-9 40 10	L anterior cingulate gyrus
0.803	102	3.50	3.34	<0.001	15 -88 32	R superior occipital gyrus
0.100	942	4.63	4.28	<0.001	-30 -68 -28	L cerebellum exterior

Anatomical regions were obtained with the neuromorhpometrics atlas probability in SPM12. FEW, family-wise error; L, left; R, right; VBM, voxel-based morphometry.

Supplementary Table 5. Left Putamen community changes.

HiBalance		
Stable Nodes	**Nodes Pre-intervention**	**Nodes Post-intervention**
lAcc	lAmy	lBst
rAcc	rAmy	rBst
rPut	lExtCbe	lCau
lBasCbr+FobBr	rExtCbe	rCau
rBasCbr+FobBr	lHip	lCbeWM
lPosIns	rHip	rCbeWM
rPosIns	rCbeLoCbe6-7	lCbrWM
lTem	lCbeLoCbe8-10	rCbrWM
lSCA	rCbeLoCbe8-10	lPal
rSCA	lAntIns	rPal
	rAntIns	lThaPro
	lEnt	rThaPro
	rEnt	lAntCinGy
	lFroOpe	lCenOpe
	rFroOpe	rInfTemGy
	lRecGy	lMidCinGy
	rRecGy	rMedPoCGy
	lInfTemGy	rSupMedFroGy
	rLatOrbGy	lParOpe
	lMedFroCbr	lSupMarGy
	rMedFroCbr	lSupTemGy
	lInfFroGy	
	rInfFroGy	
	rInfFroOrbGy	
	lParHipGy	
	rParHipGy	
	lPosOrbGy	
	rPosOrbGy	
	lPla	
	rPla	
	rTem	
	rSupTemGy	
	lTemPo	
	rTemPo	
	lInfFroAngGy	

No changes were found in the active control group. Structural covariance networks build from nodes of the gray matter volumes from the neuromorphometrics atlas. Edges build of Pearson correlations between every pair of nodes resulting in a representative adjacency matrix for each group. lAcc, Left Accumbens; rAcc, Right Accumbens; lAmy, Left Amygdala; rAmy, Right Amygdala; lBst, Left Brainstem; rBst, Right Brainstem; lCau, Left Caudate; rCau, Right Caudate; lExtCbe, Left Exterior Cerebellum; rExtCbe, Right Exterior Cerebellum; lCbeWM, Left Cerebellum White Matter; rCbeWM, Right Cerebellum

White Matter; lCbrWM, Left Cerebral White Matter; rCbrWM, Right Cerebral White Matter; lHip, Left Hippocampus; rHip, Right Hippocampus; lPal, Left Pallidum; rPal, Right Pallidum; lPut, Left Putamen; rPut, Right Putamen; lThaPro, Left Thalamus Proper; rThaPro, Right Thalamus Proper; rCbeLoCbe6-7, Right Cerebellar Lobule Cerebellar Vermal Lobules VI-VII; lCbeLoCbe8-10, Left Cerebellar Lobule Cerebellar Vermal Lobules VIII-X; rCbeLoCbe8-10, Right Cerebellar Lobule Cerebellar Vermal Lobules VIII-X; lBasCbr+FobBr, Left Basal Cerebrum and Forebrain Brain; rBasCbr+FobBr, Right Basal Cerebrum and Forebrain Brain; lAntCinGy, Left Anterior Cingulate Gyrus; lAntIns, Left Anterior Insula; rAntIns, Right Anterior Insula; lCenOpe, Left Central Operculum; lEnt, Left Entorhinal Area; rEnt, Right Entorhinal Area; lInfTemGy, Left Inferior Temporal Gyrus; rInfTemGy, Right Inferior Temporal Gyrus; lMidCinGy, Left Middle Cingulate Gyrus; lMedFroCbr, Left Medial Frontal Cerebrum; rMedFroCbr, Right Medial Frontal Cerebrum; rSupMedFroGy, Right Superior Medial Frontal Gyrus; lInfFroGy, Left Inferior Frontal Gyrus; rInfFroGy, Right Inferior Frontal Gyrus; rInfFroOrbGy, Right Inferior Frontal Orbital Gyrus; lParHipGy, Left Parahippocampus Gyrus; rParHipGy, Right Parahippocampus Gyrus; lPosOrbGy, Left Posterior Orbital Gyrus; rPosOrbGy, Right Posterior Orbital Gyrus; lPla, Left Planum Polare; rPla, Right Planum Polare; lTem, Left Temporal; rTem, Right Temporal; lSCA, Left Subcallosal Area; rSCA, Right Subcallosal Area; lSupMarGy, Left Supramarginal Gyrus; lSupTemGy, Left Superior Temporal Gyrus; rSupTemGy, Right Superior Temporal Gyrus; lTemPo, Left Temporal Pole; rTemPo, Right Temporal Pole; lInfFroAngGy, Left Inferior Frontal Angular Gyrus; rInfFroAngGy, Right Inferior Frontal Angular Gyrus.

Supplementary Table 6. Results of structural covariance network analyses. Community changes before and after the intervention obtained with the Louvain algorithm.

HiBalance							
Pre-intervention				Post-intervention			
Comm 1	**Comm 2**	**Comm 3**	**Comm 4**	**Comm 1**	**Comm 2**	**Comm 3**	**Comm 4**
lBst	lAcc	lAngGy	lCbeLoCbe1-5	lAcc	lExtCbe	lAmy	rAntCinGy
rBst	rAcc	rAngGy	rCbeLoCbe1-5	rAcc	rExtCbe	rAmy	lAntOrbGy
lCau	lAmy	lCal+Cbr	lAntCinGy	lBst	lCbeLoCbe1-5	lHip	rAntOrbGy
rCau	rAmy	rCal+Cbr	rAntCinGy	rBst	rCbeLoCbe1-5	rHip	lCal+Cbr
lCbeWM	lExtCbe	rCenOpe	lAntOrbGy	lCau	lCbeLoCbe6-7	lAntIns	rCal+Cbr
rCbeWM	rExtCbe	lCun	rAntOrbGy	rCau	rCbeLoCbe6-7	rAntIns	lCun
lCbrWM	lHip	rCun	lCenOpe	lCbeWM	lCbeLoCbe8-10	lAngGy	rCun
rCbrWM	rHip	lFroPo	rFroPo	rCbeWM	rCbeLoCbe8-10	rAngGy	lFroPo
lPal	lPut	lInfOccGy	lFusGy	lCbrWM	lMidOccGy	rCenOpe	rFroPo
rPal	rPut	rInfOccGy	rFusGy	rCbrWM	lPosCinGy	lEnt	lInfOccGy
lThaPro	rCbeLoCbe6-7	lLinGy	lLatOrbGy	lPal	rPosCinGy	rEnt	rInfOccGy
rThaPro	lCbeLoCbe8-10	rLinGy	lMidCinGy	rPal		lFroOpe	lLinGy
lCbeLoCbe6-7	rCbeLoCbe8-10	lMidOccGy	rMidCinGy	lPut		rFroOpe	rLinGy
rInfTemGy	lBasCbr+FobBr	rMidOccGy	lMidFroGy	rPut		lFusGy	lLatOrbGy
lSupMarGy	rBasCbr+FobBr	lMidTemGy	rMidFroGy	lThaPro		rFusGy	rMidCinGy
lSupTemGy	lAntIns	rMidTemGy	lMedOrbGy	rThaPro		lRecGy	lMidFroGy
	rAntIns	lOccPo	rMedOrbGy	lBasCbr+FobBr		rRecGy	rMidFroGy
	lEnt	rOccPo	lMedPoCGy	rBasCbr+FobBr		lInfTemGy	lMedOrbGy
	rEnt	lOccFusGy	rMedPoCGy	lAntCinGy		rLatOrbGy	rMedOrbGy
	lFroOpe	rOccFusGy	lMedPrcGy	lCenOpe		lMedFroCbr	lMedPoCGy
	rFroOpe	lPosCinGy	rMedPrcGy	rInfTemGy		rMedFroCbr	lMedPrcGy
	lRecGy	rPosCinGy	lSupMedFroGy	lMidCinGy		rMidOccGy	rMedPrcGy
	rRecGy	lPCu	rSupMedFroGy	rMedPoCGy		lMidTemGy	lSupMedFroGy
	lInfTemGy	rPCu	lInfFroOrbGy	rSupMedFroGy		rMidTemGy	lOccPo
	rLatOrbGy	lParOpe	lPoCGy	lPosIns		lInfFroGy	rOccPo
	lMedFroCbr	rParOpe	rPoCGy	rPosIns		rInfFroGy	lOccFusGy
	rMedFroCbr	lSupOccGy	lPrcGy	lParOpe		rInfFroOrbGy	rOccFusGy
	lInfFroGy	rSupOccGy	rPrcGy	lTem		lParHipGy	lInfFroOrbGy
	rInfFroGy	lSupParLo	lSupFroGy	lSCA		rParHipGy	lPCu
	rInfFroOrbGy	lTemTraGy	rSupFroGy	rSCA		lPosOrbGy	rPCu
	lParHipGy	rTemTraGy	lCbr+Mot	lSupMarGy		rPosOrbGy	rParOpe
	rParHipGy		rCbr+Mot	lSupTemGy		rPla	lPoCGy
	lPosIns		rSupMarGy			rTem	rPoCGy
	rPosIns		rSupParLo			rSupTemGy	lPla
	lPosOrbGy		rInfFroAngGy			lTemPo	lPrcGy
	rPosOrbGy					rTemPo	rPrcGy
	lPla					lInfFroAngGy	lSupFroGy
	rPla					rInfFroAngGy	rSupFroGy
	lTem						lCbr+Mot
	rTem						rCbr+Mot

	lSCA				rSupMarGy
	rSCA				lSupOccGy
	rSupTemGy				rSupOccGy
	lTemPo				lSupParLo
	rTemPo				rSupParLo
	lInfFroAngGy				lTemTraGy

Active Control Group

Pre-intervention			**Post-intervention**		
Comm1	**Comm 2**	**Comm 3**	**Comm1**	**Comm 2**	**Comm 3**
lAcc	lHip	lAmy	lAcc	lHip	lAmy
rAcc	rThaPro	rAmy	rAcc	rThaPro	rAmy
lBst	lAngGy	lExtCbe	lBst	lAngGy	lExtCbe
rBst	lCal+Cbr	rExtCbe	rBst	lCal+Cbr	rExtCbe
lCau	rCal+Cbr	rHip	lCau	rCal+Cbr	rHip
rCau	rCenOpe	lPal	rCau	rCenOpe	lPal
lCbeWM	lCun	rPal	lCbeWM	lCun	rPal
rCbeWM	rCun	lPut	rCbeWM	rCun	lPut
lCbrWM	rFroOpe	rPut	lCbrWM	rFroOpe	rPut
rCbrWM	lFusGy	lCbeLoCbe1-5	rCbrWM	lFusGy	lCbeLoCbe1-5
lThaPro	rFusGy	rCbeLoCbe1-5	lThaPro	rFusGy	rCbeLoCbe1-5
lBasCbr+FobBr	lRecGy	lCbeLoCbe6-7	lBasCbr+FobBr	lRecGy	lCbeLoCbe6-7
rBasCbr+FobBr	rRecGy	rCbeLoCbe6-7	rBasCbr+FobBr	rRecGy	rCbeLoCbe6-7
rAntCinGy	lInfOccGy	lCbeLoCbe8-10	rAntCinGy	lInfOccGy	lCbeLoCbe8-10
lAntIns	rInfOccGy	rCbeLoCbe8-10	lAntIns	rInfOccGy	rCbeLoCbe8-10
rAntIns	rInfTemGy	lAntCinGy	rAntIns	rInfTemGy	lAntCinGy
lAntOrbGy	lLinGy	lCenOpe	lAntOrbGy	lLinGy	lCenOpe
rAntOrbGy	rLinGy	lEnt	rAntOrbGy	rLinGy	lEnt
rAngGy	lMedFroCbr	rEnt	rAngGy	lMedFroCbr	rEnt
lFroPo	rMedFroCbr	lFroOpe	lFroPo	rMedFroCbr	lFroOpe
rFroPo	lMidOccGy	lInfTemGy	rFroPo	lMidOccGy	lInfTemGy
lLatOrbGy	rMidOccGy	lMidCinGy	lLatOrbGy	rMidOccGy	lMidCinGy
rLatOrbGy	lSupMedFroGy	rMidCinGy	rLatOrbGy	lSupMedFroGy	rMidCinGy
lMidFroGy	lMidTemGy	lMedPoCGy	lMidFroGy	lMidTemGy	lMedPoCGy
rMidFroGy	rMidTemGy	rMedPoCGy	rMidFroGy	rMidTemGy	rMedPoCGy
lMedOrbGy	lOccPo	lMedPrcGy	lMedOrbGy	lOccPo	lMedPrcGy
rMedOrbGy	rOccPo	rMedPrcGy	rMedOrbGy	rOccPo	rMedPrcGy
lInfFroGy	lOccFusGy	rSupMedFroGy	lInfFroGy	lOccFusGy	rSupMedFroGy
lInfFroOrbGy	rOccFusGy	rInfFroGy	lInfFroOrbGy	rOccFusGy	rInfFroGy
rPoCGy	lPosCinGy	rInfFroOrbGy	rPoCGy	lPosCinGy	rInfFroOrbGy
rPosOrbGy	rPosCinGy	lParHipGy	rPosOrbGy	rPosCinGy	lParHipGy
lSCA	lPCu	rParHipGy	lSCA	lPCu	rParHipGy
rSCA	rPCu	lPosIns	rSCA	rPCu	lPosIns
rSupMarGy	lParOpe	rPosIns	rSupMarGy	lParOpe	rPosIns
lInfFroAngGy	rParOpe	lPla	lInfFroAngGy	rParOpe	lPla
rInfFroAngGy	lPoCGy	lPrcGy	rInfFroAngGy	lPoCGy	lPrcGy
	lPosOrbGy	rPrcGy		lPosOrbGy	rPrcGy

rPla	lSupFroGy	rPla	lSupFroGy
lTem	rSupFroGy	lTem	rSupFroGy
rTem	lCbr+Mot	rTem	lCbr+Mot
lSupOccGy	rCbr+Mot	lSupOccGy	rCbr+Mot
rSupOccGy	lSupMarGy	rSupOccGy	lSupMarGy
lSupParLo	lSupTemGy	lSupParLo	lSupTemGy
rSupParLo	rSupTemGy	rSupParLo	rSupTemGy
lTemTraGy	lTemPo	lTemTraGy	lTemPo
rTemTraGy	rTemPo	rTemTraGy	rTemPo

Structural covariance networks build from nodes of the gray matter volumes from the neuromorphometrics atlas. Edges build of Pearson correlations between every pair of nodes resulting in a representative adjacency matrix for each group. Comm, community; lAcc, Left Accumbens; rAcc, Right Accumbens; lAmy, Left Amygdala; rAmy, Right Amygdala; lBst, Left Brainstem; rBst, Right Brainstem; lCau, Left Caudate; rCau, Right Caudate; lExtCbe, Left Exterior Cerebellum; rExtCbe, Right Exterior Cerebellum; lCbeWM, Left Cerebellum White Matter; rCbeWM, Right Cerebellum White Matter; lCbrWM, Left Cerebral White Matter; rCbrWM, Right Cerebral White Matter; lHip, Left Hippocampus; rHip, Right Hippocampus; lPal, Left Pallidum; rPal, Right Pallidum; lPut, Left Putamen; rPut, Right Putamen; lThaPro, Left Thalamus Proper; rThaPro, Right Thalamus Proper; lCbeLoCbe1-5, Left Cerebellar Lobule Cerebellar Vermal Lobules I-V; rCbeLoCbe1-5, Right Cerebellar Lobule Cerebellar Vermal Lobules I-V; lCbeLoCbe6-7, Left Cerebellar Lobule Cerebellar Vermal Lobules VI-VII; rCbeLoCbe6-7, Right Cerebellar Lobule Cerebellar Vermal Lobules VI-VII; lCbeLoCbe8-10, Left Cerebellar Lobule Cerebellar Vermal Lobules VIII-X; rCbeLoCbe8-10, Right Cerebellar Lobule Cerebellar Vermal Lobules VIII-X; lBasCbr+FobBr, Left Basal Cerebrum and Forebrain Brain; rBasCbr+FobBr, Right Basal Cerebrum and Forebrain Brain; lAntCinGy, Left Anterior Cingulate Gyrus; rAntCinGy, Right Anterior Cingulate Gyrus; lAntIns, Left Anterior Insula; rAntIns, Right Anterior Insula; lAntOrbGy, Left Anterior Orbital Gyrus; rAntOrbGy, Right Anterior Orbital Gyrus; lAngGy, Left Angular Gyrus; rAngGy, Right Angular Gyrus; lCal+Cbr, Left Calcarine and Cerebrum; rCal+Cbr, Right Calcarine and Cerebrum; lCenOpe, Left Central Operculum; rCenOpe, Right Central Operculum; lCun, Left Cuneus; rCun, Right Cuneus; lEnt, Left Entorhinal Area; rEnt, Right Entorhinal Area; lFroOpe, Left Frontal Operculum; rFroOpe, Right Frontal Operculum; lFroPo, Left Frontal Pole; rFroPo, Right Frontal Pole, lFusGy, Left Fusiform Gyrus; rFusGy, Right Fusiform Gyrus; lRecGy, Left Gyrus Rectus; rRecGy, Right Gyrus Rectus; lInfOccGy, Left Inferior Occipital Gyrus; rInfOccGy, Right Inferior Occipital Gyrus; lInfTemGy, Left Inferior Temporal Gyrus; rInfTemGy, Right Inferior Temporal Gyrus; lLinGy, Left Lingual Gyrus; rLinGy, Right Lingual Gyrus; lLatOrbGy, Left Lateral Orbital Gyrus; rLatOrbGy, Right Lateral Orbital Gyrus; lMidCinGy, Left Middle Cingulate Gyrus; rMidCinGy, Right Middle Cingulate Gyrus; lMedFroCbr, Left Medial Frontal Cerebrum; rMedFroCbr, Right Medial Frontal Cerebrum; lMidFroGy, Left Middle Frontal Gyrus; rMidFroGy, Right Middle Frontal Gyrus; lMidOccGy, Left Middle Occipital Gyrus; rMidOccGy, Right Middle Occipital Gyrus; lMedOrbGy, Left Medial Orbital Gyrus; rMedOrbGy, Right Medial Orbital Gyrus; lMedPoCGy, Left Medial Postcentral Gyrus; rMedPoCGy, Right Medial Postcentral Gyrus; lMedPrcGy, Left Medial Precentral Gyrus; rMedPrcGy, Right Medial Precentral Gyrus; lSupMedFroGy, Left Superior Medial Frontal Gyrus; rSupMedFroGy, Right Superior Medial Frontal Gyrus, lMidTemGy Left Middle Temporal Gyrus, rMidTemGy Right Middle Temporal Gyrus, lOccPo Left Occipital Pole, rOccPo Right Occipital Pole; lOccFusGy, Left Occipital Fusiform Gyrus; rOccFusGy, Right Occipital Fusiform Gyrus; lInfFroGy, Left Inferior Frontal Gyrus; rInfFroGy, Right Inferior Frontal Gyrus; lInfFroOrbGy, Left Inferior Frontal Orbital Gyrus; rInfFroOrbGy, Right Inferior Frontal Orbital Gyrus; lPosCinGy, Left Posterior Cingulate Gyrus; rPosCinGy, Right Posterior Cingulate Gyrus; lPCu, Left Precuneus; rPCu, Right Precuneus; lParHipGy, Left Parahippocampus Gyrus; rParHipGy, Right Parahippocampus Gyrus; lPosIns, Left Posterior Insula; rPosIns, Right Posterior Insula; lParOpe, Left Parietal Operculum; rParOpe, Right Parietal Operculum; lPoCGy, Left Postcentral Gyrus; rPoCGy, Right Postcentral Gyrus; lPosOrbGy, Left Posterior Orbital Gyrus; rPosOrbGy, Right Posterior Orbital Gyrus; lPla, Left Planum Polare; rPla, Right Planum Polare; lPrcGy, Left Precentral Gyrus; rPrcGy, Right Precentral Gyrus; lTem, Left Temporal; rTem, Right Temporal; lSCA, Left Subcallosal Area; rSCA, Right Subcallosal Area; lSupFroGy, Left Superior Frontal Gyrus; rSupFroGy, Right Superior Frontal Gyrus; lCbr+Mot, Left Cerebrum and Motor; rCbr+Mot, Right Cerebrum and Motor; lSupMarGy, Left Supramarginal Gyrus; rSupMarGy, Right Supramarginal Gyrus; lSupOccGy, Left Superior Occipital Gyrus; rSupOccGy, Right Superior Occipital Gyrus; lSupParLo, Left Superior Parietal Lobule; rSupParLo, Right Superior Parietal Lobule; lSupTemGy, Left Superior Temporal Gyrus; rSupTemGy, Right Superior Temporal Gyrus; lTemPo, Left Temporal Pole; rTemPo, Right Temporal Pole; lInfFroAngGy, Left Inferior Frontal Angular Gyrus; rInfFroAngGy, Right Inferior Frontal Angular Gyrus; lTemTraGy, Left Temporal Transverse Gyrus; rTemTraGy, Right Temporal Transverse Gyrus.

Supplementary Table 7. Results of partial correlations of motor outcome with gray matter volume in the putamen corrected for total intracranial volume.

Partial Correlation	***R***	**p**	***t***
HiBalance			
Gait speed pre	0.238426542	0.18880259	1.34469627
Gait speed post	0.392723312	*0.02619026**	2.33895347
Gait speed post-pre	0.057190318	0.75587633	0.31375780
MiniBESTest pre	-0.212411334	0.25129639	-1.17058233
MiniBESTest post	0.037688617	0.84047233	0.20310371
MiniBESTest post-pre	-0.188840137	0.30896262	-1.03556735
Active Control Group			
Gait speed pre	0.182419028	0.33463357	0.98174356
Gait speed post	-0.006437473	0.97306731	-0.03406461
Gait speed post-pre	-0.125616281	0.50834237	-0.67000607
MiniBESTest pre	-0.135438491	0.48360618	-0.71030396
MiniBESTest post	0.031191921	0.87238977	0.16215688
MiniBESTest post-pre	0.015089512	0.93807516	0.07841633

R, partial correlation coefficient; t, test statistic.

Supplementary Material 1. R scripts for the behavioral data analyses.

Statistics for longitudinal analysis of EXPANd

Dr. rer. nat. Franziska Albrecht

8/14/2020

Read in the data for the summary table

```
# as xlsx for tableby function
subjectx= read_excel(
  here("data", "demo_wide_copy.xlsx"))
```

Overview over the data

```
summary(subjectx)
```

```
##       ID                Group               Sex_M_0            Age        
##  Length:65          Length:65          Min.   :0.0000   Min.   :61.00  
##  Class :character   Class :character   1st Qu.:0.0000   1st Qu.:66.00  
##  Mode  :character   Mode  :character   Median :0.0000   Median :69.00  
##                                        Mean   :0.3846   Mean   :70.35  
##                                        3rd Qu.:1.0000   3rd Qu.:75.00  
##                                        Max.   :1.0000   Max.   :83.00  
##                                                                        
##       YrD             DD             MCI_1        NEW_MCI_1_Int_2  
##  Min.   :2002   Min.   : 0.000   Min.   :0.0000   Min.   :0.0000  
##  1st Qu.:2011   1st Qu.: 2.000   1st Qu.:0.0000   1st Qu.:0.0000  
##  Median :2015   Median : 4.000   Median :0.0000   Median :1.0000  
##  Mean   :2013   Mean   : 5.138   Mean   :0.2923   Mean   :0.7846  
##  3rd Qu.:2016   3rd Qu.: 8.000   3rd Qu.:1.0000   3rd Qu.:1.0000  
##  Max.   :2018   Max.   :16.000   Max.   :1.0000   Max.   :2.0000  
##                                                                   
##      LED_v1           Motor               HaY_v1          HaY_v2     
##  Min.   :   0.0   Length:65          Min.   :2.000   Min.   :2.000  
##  1st Qu.: 312.5   Class :character   1st Qu.:2.000   1st Qu.:2.000  
##  Median : 500.0   Mode  :character   Median :2.000   Median :2.000  
##  Mean   : 536.9                      Mean   :2.159   Mean   :2.203  
##  3rd Qu.: 710.0                      3rd Qu.:2.000   3rd Qu.:2.000  
##  Max.   :1324.0                      Max.   :3.000   Max.   :3.000
```

```
##  NA's   :3                          NA's   :2       NA's   :1
##   UPDRS.III_v1    UPDRS_Tot_v1     UPDRS.III_v2    UPDRS_Tot_v2
##  Min.   :10.00   Min.   : 22.00   Min.   : 6.00   Min.   :12.00
##  1st Qu.:22.50   1st Qu.: 36.50   1st Qu.:19.00   1st Qu.:33.00
##  Median :28.00   Median : 49.00   Median :29.00   Median :41.50
##  Mean   :29.87   Mean   : 49.67   Mean   :28.72   Mean   :46.70
##  3rd Qu.:36.50   3rd Qu.: 57.50   3rd Qu.:39.00   3rd Qu.:61.25
##  Max.   :70.00   Max.   :110.00   Max.   :48.00   Max.   :85.00
##  NA's   :2       NA's   :2        NA's   :1       NA's   :1
##   MOCA_Edu_v1    MOCA _Edu_1_upto_12yrs_v1  MOCA_Tot_v1     MiniBEST_v1
##  Min.   : 9.00   Min.   :0.0000            Min.   :21.00   Min.   :14.00
##  1st Qu.:13.75   1st Qu.:0.0000            1st Qu.:24.00   1st Qu.:19.00
##  Median :16.00   Median :0.0000            Median :26.00   Median :22.00
##  Mean   :15.30   Mean   :0.2069            Mean   :26.03   Mean   :21.32
##  3rd Qu.:17.00   3rd Qu.:0.0000            3rd Qu.:28.00   3rd Qu.:24.00
##  Max.   :22.00   Max.   :1.0000            Max.   :30.00   Max.   :27.00
##  NA's   :9       NA's   :7                 NA's   :2       NA's   :2
##   MiniBEST_v2    MiniBEST_v2-v1    MiniBest_Responder  Gang_Tot_v1
##  Min.   :11.00   Min.   :-7.0000   Min.   :0.0000     Min.   : 1.00
##  1st Qu.:20.00   1st Qu.:-1.0000   1st Qu.:0.0000     1st Qu.: 5.00
##  Median :22.00   Median : 1.0000   Median :1.0000     Median : 8.50
##  Mean   :22.08   Mean   : 0.7742   Mean   :0.5968     Mean   :10.84
##  3rd Qu.:24.25   3rd Qu.: 2.7500   3rd Qu.:1.0000     3rd Qu.:16.75
##  Max.   :27.00   Max.   : 8.0000   Max.   :1.0000     Max.   :36.00
##  NA's   :1       NA's   :3         NA's   :3          NA's   :3
##   Gang_Tot_v2    Gang_v2-v1_highscoreWorse proBDNF [pg/mL] Pre
##  Min.   : 1.00   Min.   :-14.0000          Min.   :   0.00
##  1st Qu.: 4.00   1st Qu.: -3.0000          1st Qu.:  32.54
##  Median : 8.00   Median :  0.0000          Median : 489.96
##  Mean   :10.70   Mean   : -0.1852          Mean   :1095.92
##  3rd Qu.:16.25   3rd Qu.:  1.0000          3rd Qu.:1209.10
##  Max.   :32.00   Max.   : 13.0000          Max.   :6241.69
##  NA's   :9       NA's   :11                NA's   :20
##  proBDNF [pg/mL] Post mBDNF [pg/mL] Pre mBDNF [pg/mL] Post  Velocity_VG1
##  Min.   :   1.08      Min.   :23372     Min.   :21687      Min.   : 76.8
##  1st Qu.:  83.41      1st Qu.:32949     1st Qu.:33128      1st Qu.:109.7
##  Median : 495.79      Median :37748     Median :36632      Median :124.5
##  Mean   :1097.32      Mean   :37715     Mean   :36480      Mean   :123.0
##  3rd Qu.:1149.54      3rd Qu.:42286     3rd Qu.:39647      3rd Qu.:137.8
##  Max.   :6398.91      Max.   :55756     Max.   :52889      Max.   :155.9
##  NA's   :23           NA's   :5         NA's   :6          NA's   :1
##   Mean_SL_VG1     Velocity_AS1    Mean_SL_AS1     Velocity_VG2
```

```
##  Min.   :41.85   Min.   : 58.8   Min.   :42.00   Min.   : 84.5
##  1st Qu.:61.50   1st Qu.:103.0   1st Qu.:58.56   1st Qu.:112.3
##  Median :66.00   Median :118.0   Median :62.51   Median :126.2
##  Mean   :66.39   Mean   :116.2   Mean   :63.71   Mean   :126.1
##  3rd Qu.:73.73   3rd Qu.:133.8   3rd Qu.:70.75   3rd Qu.:139.8
##  Max.   :83.64   Max.   :159.1   Max.   :85.99   Max.   :168.6
##  NA's   :1       NA's   :1       NA's   :1       NA's   :1
##   Mean_SL_VG2     Velocity_AS2    Mean_SL_AS2     Velo_Diff_VG
##  Min.   :48.23   Min.   : 70.3   Min.   :43.54   Min.   :-22.700
##  1st Qu.:62.33   1st Qu.:100.0   1st Qu.:60.22   1st Qu.: -5.225
##  Median :66.73   Median :118.5   Median :64.50   Median :  3.400
##  Mean   :67.47   Mean   :119.4   Mean   :64.95   Mean   :  3.145
##  3rd Qu.:73.07   3rd Qu.:139.1   3rd Qu.:71.13   3rd Qu.: 10.125
##  Max.   :86.08   Max.   :175.2   Max.   :85.60   Max.   : 37.300
##  NA's   :1       NA's   :1       NA's   :1       NA's   :1
##   Velo_VG_Resp    Velo_Diff_AS      Velo_AS_Resp      SL_Diff_VG
##  Min.   :0.000   Min.   :-26.800   Min.   :0.0000   Min.   :-8.839
##  1st Qu.:0.000   1st Qu.: -5.625   1st Qu.:0.0000   1st Qu.:-2.112
##  Median :1.000   Median :  2.050   Median :1.0000   Median : 1.220
##  Mean   :0.625   Mean   :  3.264   Mean   :0.5781   Mean   : 1.078
##  3rd Qu.:1.000   3rd Qu.: 11.775   3rd Qu.:1.0000   3rd Qu.: 3.934
##  Max.   :1.000   Max.   : 46.100   Max.   :1.0000   Max.   :15.738
##  NA's   :1       NA's   :1         NA's   :1        NA's   :1
##    SL_Diff_AS         TIV_v1         TIV_v2
##  Min.   :-9.255   Min.   :1193   Min.   :1215
##  1st Qu.:-0.883   1st Qu.:1405   1st Qu.:1401
##  Median : 1.268   Median :1545   Median :1535
##  Mean   : 1.238   Mean   :1524   Mean   :1521
##  3rd Qu.: 3.734   3rd Qu.:1604   3rd Qu.:1609
##  Max.   :13.320   Max.   :2058   Max.   :2073
##  NA's   :1
```

Summary table for the paper

ANOVA table split into the intervention groups

```
# create a lael for the table items

tablelabel <- list(Age="Age, yrs", Sex_M_0="Sex, 0 male", DD="Disease duration, yrs", LED_v1= "Levo
dopa equivalent dose", HaY_v1= "Hoehn&Yahr", UPDRS.III_v1= "MDS-UPDRS Scale III", UPDRS_Tot_v1= "MD
S-UPDRS Total score", MOCA_Tot_v1="MoCA Total score", MiniBEST_v1="MiniBesTest pre", MiniBEST_v2="M
iniBesTest post", Velocity_VG1= "Velocity pre", Velocity_VG2= "Velocity post")


# create a table object
```

```
table_one <- tableby(Group ~ Age + as.factor(Sex_M_0) + DD + LED_v1 + HaY_v1 + UPDRS.III_v1 + UPDRS
_Tot_v1 + MOCA_Tot_v1 + MiniBEST_v1+ MiniBEST_v2 + Velocity_VG1+ Velocity_VG2, data = subjectx)


# Show the table
summary(table_one, labelTranslations = tablelabel, digits=2,title = " Data")
```

```
##
## Table:  Data
##
## |                            |    A (N=34)     |    B (N=31)     |  Total (N=65)   | p value|
## |:---------------------------|:---------------:|:---------------:|:---------------:|-------:|
## |**Age, yrs**                |                 |                 |                 |   0.900|
## |   Mean (SD) |  70.26 (5.82)   |  70.45 (6.11)   |  70.35 (5.92)   |        |
## |   Range     |  61.00 - 83.00  |  61.00 - 82.00  |  61.00 - 83.00  |        |
## |**as.factor(Sex_M_0)**      |                 |                 |                 |   0.638|
## |   0         |   20 (58.8%)    |   20 (64.5%)    |   40 (61.5%)    |        |
## |   1         |   14 (41.2%)    |   11 (35.5%)    |   25 (38.5%)    |        |
## |**Disease duration, yrs**   |                 |                 |                 |   0.245|
## |   Mean (SD) |   5.71 (4.55)   |   4.52 (3.49)   |   5.14 (4.09)   |        |
## |   Range     |  0.00 - 16.00   |  1.00 - 15.00   |  0.00 - 16.00   |        |
## |**Levodopa equivalent dose**|                 |                 |                 |   0.072|
## |   N-Miss    |        2        |        1        |        3        |        |
## |   Mean (SD) | 610.50 (355.83) | 458.30 (293.26) | 536.85 (333.33) |        |
## |   Range     | 0.00 - 1324.00  | 0.00 - 1224.00  | 0.00 - 1324.00  |        |
## |**Hoehn&Yahr**              |                 |                 |                 |   0.401|
## |   N-Miss    |        1        |        1        |        2        |        |
## |   Mean (SD) |   2.12 (0.33)   |   2.20 (0.41)   |   2.16 (0.37)   |        |
## |   Range     |   2.00 - 3.00   |   2.00 - 3.00   |   2.00 - 3.00   |        |
## |**MDS-UPDRS Scale III**     |                 |                 |                 |   0.235|
## |   N-Miss    |        1        |        1        |        2        |        |
## |   Mean (SD) |  31.55 (12.91)  |  28.03 (10.00)  |  29.87 (11.66)  |        |
## |   Range     |  10.00 - 70.00  |  11.00 - 50.00  |  10.00 - 70.00  |        |
## |**MDS-UPDRS Total score**   |                 |                 |                 |   0.245|
## |   N-Miss    |        1        |        1        |        2        |        |
## |   Mean (SD) |  52.30 (20.79)  |  46.77 (16.06)  |  49.67 (18.75)  |        |
## |   Range     | 22.00 - 110.00  |  22.00 - 84.00  | 22.00 - 110.00  |        |
## |**MoCA Total score**        |                 |                 |                 |   0.768|
## |   N-Miss    |        1        |        1        |        2        |        |
## |   Mean (SD) |  26.12 (2.61)   |  25.93 (2.41)   |  26.03 (2.49)   |        |
## |   Range     |  21.00 - 30.00  |  22.00 - 30.00  |  21.00 - 30.00  |        |
## |**MiniBesTest pre**         |                 |                 |                 |   0.589|
## |   N-Miss    |        1        |        1        |        2        |        |
## |   Mean (SD) |  21.09 (3.70)   |  21.57 (3.19)   |  21.32 (3.45)   |        |
## |   Range     |  14.00 - 27.00  |  14.00 - 27.00  |  14.00 - 27.00  |        |
```

```
## |**MiniBesTest post**          |                 |                 |                 |   0.912|
## |&amp;nbsp;&amp;nbsp;&amp;nbsp;N-Miss      |        1        |        0        |        1        |        |
## |&amp;nbsp;&amp;nbsp;&amp;nbsp;Mean (SD)   |  22.12 (3.26)   |  22.03 (3.11)   |  22.08 (3.16)   |        |
## |&amp;nbsp;&amp;nbsp;&amp;nbsp;Range       |  11.00 - 27.00  |  14.00 - 26.00  |  11.00 - 27.00  |        |
## |**Velocity pre**              |                 |                 |                 |   0.988|
## |&amp;nbsp;&amp;nbsp;&amp;nbsp;N-Miss      |        1        |        0        |        1        |        |
## |&amp;nbsp;&amp;nbsp;&amp;nbsp;Mean (SD)   | 122.94 (18.04)  | 123.02 (20.42)  | 122.98 (19.07)  |        |
## |&amp;nbsp;&amp;nbsp;&amp;nbsp;Range       | 82.20 - 150.90  | 76.80 - 155.90  | 76.80 - 155.90  |        |
## |**Velocity post**             |                 |                 |                 |   0.292|
## |&amp;nbsp;&amp;nbsp;&amp;nbsp;N-Miss      |        1        |        0        |        1        |        |
## |&amp;nbsp;&amp;nbsp;&amp;nbsp;Mean (SD)   | 128.48 (15.64)  | 123.62 (20.78)  | 126.12 (18.32)  |        |
## |&amp;nbsp;&amp;nbsp;&amp;nbsp;Range       | 107.50 - 168.60 | 84.50 - 160.10  | 84.50 - 168.60  |        |
```

```
#Write a data frame to csv
tab1 <- as.data.frame(summary(table_one, labelTranslations = tablelabel, digits=2,title = " Data"))
write.csv(tab1, here("results", "test.csv"))
```

Reading in data for the linear mixed model

-demographic data in wide and long format

-gait speed data only in wide format

```
#for statistics data needs to be in long format, time points in rows
#read in gait data wide
gaitrite_wide= read.table(here("data", "gaitrite_wide.csv"), header = TRUE, sep = ";", quote = "\""
, dec = ",", fill = TRUE)
#demographic data for subjects in long format, full dataset, deleted all NA
subjects_long_filter= read.table(
  here("data", "demo_long_full.csv"), header = TRUE, sep = ";", quote = "\"", dec = ",", fill = TRU
E
  )
#demographic data for subjects in wide format
 subjects_wide= read.table(
  here("data", "demo_wide.csv"), header = TRUE, sep = ";", quote = "\"", dec = ",", fill = TRUE
  )
 #Gait parameters
 gaitrite_long=read.table(
  here("data", "gaitrite_long.csv"), header = TRUE, sep = ";", quote = "\"", dec = ",", fill = TRUE
  )
```

Linear mixed model with random intercept for MiniBESTest

```
#for longitudinal design no random slope for time when only two variables
MiniBnew <- lme(MiniBEST ~ Group * time, random = ~ 1 | ID, data = subjects_long_filter)
```

```
summary(MiniBnew)
```

```
## Linear mixed-effects model fit by REML
##  Data: subjects_long_filter
##        AIC      BIC    logLik
##   612.3309 629.0558 -300.1654
##
## Random effects:
##  Formula: ~1 | ID
##         (Intercept) Residual
## StdDev:    2.747827  1.81238
##
## Fixed effects: MiniBEST ~ Group * time
##                 Value Std.Error DF  t-value p-value
## (Intercept) 21.250000 0.5818955 60 36.51858  0.0000
## GroupB       0.316667 0.8365276 60  0.37855  0.7064
## time         0.875000 0.4530951 60  1.93116  0.0582
## GroupB:time -0.208333 0.6513652 60 -0.31984  0.7502
##  Correlation:
##             (Intr) GroupB time
## GroupB      -0.696
## time        -0.389  0.271
## GroupB:time  0.271 -0.389 -0.696
##
## Standardized Within-Group Residuals:
##         Min          Q1         Med          Q3         Max
## -2.54881147 -0.43699256  0.04552625  0.49178443  1.73725515
##
## Number of Observations: 124
## Number of Groups: 62
```

```
################## Controlling for...
MiniBAge <- lme(MiniBEST ~ Group * time+Age, random = ~ time | ID, data = subjects_long_filter)
summary(MiniBAge)
```

```
## Linear mixed-effects model fit by REML
##  Data: subjects_long_filter
##        AIC      BIC    logLik
##   615.1338 640.1459 -298.5669
##
## Random effects:
##  Formula: ~time | ID
##  Structure: General positive-definite, Log-Cholesky parametrization
##             StdDev   Corr
## (Intercept) 3.100229 (Intr)
```

```
## time        1.990845 -0.456
## Residual    1.141486
##
## Fixed effects: MiniBEST ~ Group * time + Age
##                Value Std.Error DF   t-value p-value
## (Intercept) 32.40419  4.522605 60  7.164940  0.0000
## GroupB       0.24319  0.840096 59  0.289485  0.7732
## time         0.87500  0.453095 60  1.931162  0.0582
## Age         -0.15815  0.063585 59 -2.487145  0.0157
## GroupB:time -0.20833  0.651365 60 -0.319841  0.7502
##  Correlation:
##             (Intr) GroupB time   Age
## GroupB      -0.125
## time        -0.063  0.338
## Age         -0.992  0.035  0.000
## GroupB:time  0.044 -0.486 -0.696  0.000
##
## Standardized Within-Group Residuals:
##          Min           Q1          Med           Q3          Max
## -1.915761935 -0.286398200  0.009927428  0.299843208  1.063399920
##
## Number of Observations: 124
## Number of Groups: 62
```

```
MiniBSex <- lme(MiniBEST ~ Group * time+Sex_M_0, random = ~ time | ID, data = subjects_long_filter)
summary(MiniBSex)
```

```
## Linear mixed-effects model fit by REML
##  Data: subjects_long_filter
##        AIC      BIC    logLik
##   613.6771 638.6892 -297.8386
##
## Random effects:
##  Formula: ~time | ID
##  Structure: General positive-definite, Log-Cholesky parametrization
##             StdDev   Corr
## (Intercept) 3.184235 (Intr)
## time        1.975267 -0.448
## Residual    1.154938
##
## Fixed effects: MiniBEST ~ Group * time + Sex_M_0
##                 Value Std.Error DF  t-value p-value
## (Intercept) 21.706180 0.6667290 60 32.55622  0.0000
## GroupB       0.306529 0.8608264 59  0.35609  0.7230
```

```
## time         0.875000 0.4530951 60  1.93116  0.0582
## Sex_M_0     -1.216479 0.7819706 59 -1.55566  0.1251
## GroupB:time -0.208333 0.6513652 60 -0.31984  0.7502
##  Correlation:
##             (Intr) GroupB time   Sx_M_0
## GroupB      -0.628
## time        -0.430  0.333
## Sex_M_0     -0.440  0.008  0.000
## GroupB:time  0.299 -0.479 -0.696  0.000
##
## Standardized Within-Group Residuals:
##         Min          Q1         Med          Q3         Max
## -1.83174032 -0.29914309  0.03856201  0.36645855  1.09312510
##
## Number of Observations: 124
## Number of Groups: 62
```

Linear mixed model with random intercept for gait speed

```
#transform gait speed into m/s  by dividing by 100 to convert from cm/s
#new column saved to new dataframe
gaitrite_long_ms <- transform(gaitrite_long, velocity_vg_ms=velocity_vg / 100)
VeloVGnewms <- lme(velocity_vg_ms ~ Group * time, random = ~ 1 | ID, data = gaitrite_long_ms)
summary(VeloVGnewms)
```

```
## Linear mixed-effects model fit by REML
##  Data: gaitrite_long_ms
##         AIC       BIC   logLik
##   -99.18084 -82.25915 55.59042
##
## Random effects:
##  Formula: ~1 | ID
##         (Intercept)   Residual
## StdDev:   0.1674209 0.08491476
##
## Fixed effects: velocity_vg_ms ~ Group * time
##                  Value  Std.Error DF  t-value p-value
## (Intercept)  1.2294242 0.03267855 62 37.62175  0.0000
## GroupB       0.0007371 0.04695392 62  0.01570  0.9875
## time         0.0553636 0.02090457 62  2.64840  0.0102
## GroupB:time -0.0493636 0.03003657 62 -1.64345  0.1054
##  Correlation:
##             (Intr) GroupB time
```

```
## GroupB      -0.696
## time        -0.320  0.223
## GroupB:time  0.223 -0.320 -0.696
##
## Standardized Within-Group Residuals:
##         Min          Q1         Med          Q3         Max
## -2.53498171 -0.47157178  0.03351003  0.51497417  1.78699888
##
## Number of Observations: 128
## Number of Groups: 64
```

```
##Controlling for...
VeloVGAge <- lme(velocity_vg_ms ~ Group * time+Age, random = ~ 1 | ID, data = gaitrite_long_ms)
summary(VeloVGAge)
```

```
## Linear mixed-effects model fit by REML
##  Data: gaitrite_long_ms
##         AIC       BIC   logLik
##   -97.25627 -77.57098 55.62814
##
## Random effects:
##  Formula: ~1 | ID
##         (Intercept)   Residual
## StdDev:   0.1548014 0.08491473
##
## Fixed effects: velocity_vg_ms ~ Group * time + Age
##                  Value  Std.Error DF   t-value p-value
## (Intercept)  2.0213528 0.25052835 62  8.068359  0.0000
## GroupB       0.0010448 0.04416207 61  0.023659  0.9812
## time         0.0553636 0.02090456 62  2.648400  0.0102
## Age         -0.0112451 0.00353054 61 -3.185094  0.0023
## GroupB:time -0.0493636 0.03003656 62 -1.643451  0.1054
##  Correlation:
##             (Intr) GroupB time   Age
## GroupB      -0.083
## time        -0.042  0.237
## Age         -0.992 -0.002  0.000
## GroupB:time  0.029 -0.340 -0.696  0.000
##
## Standardized Within-Group Residuals:
##         Min          Q1         Med          Q3         Max
## -2.51137528 -0.53046371  0.05352567  0.56301526  1.81060665
##
## Number of Observations: 128
```

```
## Number of Groups: 64
```

```
VeloVGSex <- lme(velocity_vg_ms ~ Group * time+Sex_M_0, random = ~ 1 | ID, data = gaitrite_long_ms)
summary(VeloVGSex)
```

```
## Linear mixed-effects model fit by REML
##  Data: gaitrite_long_ms
##         AIC       BIC   logLik
##   -94.64718 -74.96189 54.32359
##
## Random effects:
##  Formula: ~1 | ID
##         (Intercept)   Residual
## StdDev:   0.1662033 0.08491476
##
## Fixed effects: velocity_vg_ms ~ Group * time + Sex_M_0
##                  Value  Std.Error DF  t-value p-value
## (Intercept)  1.2536030 0.03713751 62 33.75571  0.0000
## GroupB      -0.0016628 0.04671665 61 -0.03559  0.9717
## time         0.0553636 0.02090457 62  2.64840  0.0102
## Sex_M_0     -0.0613769 0.04566528 61 -1.34406  0.1839
## GroupB:time -0.0493636 0.03003657 62 -1.64345  0.1054
##  Correlation:
##             (Intr) GroupB time   Sx_M_0
## GroupB      -0.627
## time        -0.281  0.224
## Sex_M_0     -0.484  0.038  0.000
## GroupB:time  0.196 -0.321 -0.696  0.000
##
## Standardized Within-Group Residuals:
##         Min          Q1         Med          Q3         Max
## -2.56945626 -0.48246606  0.01762987  0.53521045  1.75252434
##
## Number of Observations: 128
## Number of Groups: 64
```

Linear mixed model outputs as tables

```
# https://cran.r-project.org/web/packages/sjPlot/vignettes/tab_mixed.html
#for more settings and explanation:
#https://strengejacke.github.io/sjPlot/articles/tab_mixed.html
#MiniBESTest Model
tab_model(MiniBnew, show.df = TRUE, show.se = TRUE, show.std = TRUE)
```

	MiniBEST							
Predictors	*Estimates*	*std. Error*	*std. Beta*	*standardized std. Error*	*CI*	*standardized CI*	*p*	*df*
(Intercept)	21.25	0.58	-0.03	0.16	20.09 – 22.41	-0.36 – 0.30	**<0.001**	60.00
Group [B]	0.32	0.84	0.06	0.24	-1.36 – 1.99	-0.41 – 0.54	0.706	60.00
time	0.87	0.45	0.13	0.07	-0.03 – 1.78	-0.00 – 0.27	0.058	60.00
Group [B] * time	-0.21	0.65	-0.03	0.10	-1.51 – 1.09	-0.23 – 0.17	0.750	60.00
Random Effects								
σ^2	3.28							
$\tau_{00\ ID}$	7.55							
N_{ID}	62							
Observations	124							
Marginal R^2 / Conditional R^2	0.048 / NA							

```
#Gait speed single task Model with ms unit
tab_model(VeloVGnewms, show.df = TRUE,show.se = TRUE, show.std = TRUE)
```

	velocity_vg_ms							
Predictors	*Estimates*	*std. Error*	*std. Beta*	*standardized std. Error*	*CI*	*standardized CI*	*p*	*df*
(Intercept)	1.23	0.03	0.06	0.17	1.16 – 1.29	-0.27 – 0.39	**<0.001**	62.00
Group [B]	0.00	0.05	-0.13	0.24	-0.09 – 0.09	-0.60 – 0.35	0.988	62.00
time	0.06	0.02	0.15	0.06	0.01 – 0.10	0.04 – 0.26	**0.010**	62.00
Group [B] * time	-0.05	0.03	-0.13	0.08	-0.11 – 0.01	-0.29 – 0.03	0.105	62.00
Random Effects								
σ^2	0.01							
$\tau_{00\ ID}$	0.03							
ICC	0.80							
N_{ID}	64							
Observations	128							
Marginal R^2 / Conditional R^2	0.015 / 0.799							

Packages and versions used for this script:

```
sessionInfo()
```

```
## R version 4.0.2 (2020-06-22)
## Platform: x86_64-apple-darwin17.0 (64-bit)
## Running under: macOS Catalina 10.15.7
##
## Matrix products: default
## BLAS:   /Library/Frameworks/R.framework/Versions/4.0/Resources/lib/libRblas.dylib
## LAPACK: /Library/Frameworks/R.framework/Versions/4.0/Resources/lib/libRlapack.dylib
##
## locale:
## [1] en_US.UTF-8/en_US.UTF-8/en_US.UTF-8/C/en_US.UTF-8/en_US.UTF-8
##
## attached base packages:
## [1] stats     graphics  grDevices utils     datasets  methods   base
##
## other attached packages:
##  [1] sjstats_0.18.0  sjPlot_2.8.4    nlme_3.1-148    broom_0.7.8
##  [5] readxl_1.3.1    arsenal_3.5.0   forcats_0.5.1   stringr_1.4.0
##  [9] dplyr_1.0.7     purrr_0.3.4     readr_1.4.0     tidyr_1.1.3
## [13] tibble_3.1.2    ggplot2_3.3.5   tidyverse_1.3.1 here_1.0.1
## [17] knitr_1.29
##
## loaded via a namespace (and not attached):
##  [1] httr_1.4.2         jsonlite_1.7.2     splines_4.0.2      modelr_0.1.8
##  [5] assertthat_0.2.1   statmod_1.4.34     highr_0.8          cellranger_1.1.0
##  [9] yaml_2.2.1         bayestestR_0.7.2   pillar_1.6.1       backports_1.1.8
## [13] lattice_0.20-41    glue_1.4.1         digest_0.6.25      minqa_1.2.4
## [17] rvest_1.0.0        colorspace_1.4-1   Matrix_1.2-18      htmltools_0.5.0
## [21] pkgconfig_2.0.3    haven_2.3.1        xtable_1.8-4       mvtnorm_1.1-1
## [25] scales_1.1.1       lme4_1.1-23        emmeans_1.4.8      generics_0.0.2
## [29] sjlabelled_1.1.6   ellipsis_0.3.2     withr_2.4.2        cli_2.4.0
## [33] survival_3.1-12    magrittr_2.0.1     crayon_1.4.1       effectsize_0.3.2
## [37] estimability_1.3   evaluate_0.14      fs_1.5.0           fansi_0.4.1
## [41] MASS_7.3-51.6      xml2_1.3.2         tools_4.0.2        hms_1.1.0
## [45] lifecycle_1.0.0    munsell_0.5.0      reprex_2.0.0       ggeffects_0.15.1
## [49] compiler_4.0.2     rlang_0.4.10       nloptr_1.2.2.2     grid_4.0.2
## [53] parameters_0.8.2   rstudioapi_0.13    rmarkdown_2.3      boot_1.3-25
## [57] gtable_0.3.0       DBI_1.1.0          sjmisc_2.8.5       R6_2.4.1
## [61] lubridate_1.7.10   performance_0.4.8  utf8_1.1.4         rprojroot_2.0.2
## [65] insight_0.9.0      stringi_1.4.6      Rcpp_1.0.5         vctrs_0.3.8
## [69] dbplyr_2.1.1       tidyselect_1.1.0   xfun_0.16          coda_0.19-4
```

Repeated Measures Correlation

Dr. rer. nat. Franziska Albrecht

8/19/2020

Reading in data

```
# Gait speed
# #long format
ROI_long= read_excel(here("data", "ROIVelo_longI.xlsx"))
# #MiniBEST
# #long format
ROIMB_long= read_excel(here("data", "ROIMB_longI.xlsx"))
```

Subsetting the data

Split the file into the groups according to column 'Group' into group A and B.

```
#convert ID to factor from character
ROI_long$ID <- as.factor(ROI_long$ID)
class(ROI_long$ID)
## [1] "factor"
ROIMB_long$ID <- as.factor(ROIMB_long$ID)
class(ROIMB_long$ID)
## [1] "factor"
# split into A and B for gait speed
AROI_long=subset(ROI_long, ROI_long$Group == 'A')
BROI_long=subset(ROI_long, ROI_long$Group == 'B')


#split into A and B for MiniBEST
AROIMB_long=subset(ROIMB_long, ROIMB_long$Group == 'A')
BROIMB_long=subset(ROIMB_long, ROIMB_long$Group == 'B')
```

Correlation for repeated measures

Gait speed in A

```
pdf((here("results",file="rmcorrAvelo.pdf")))#to save the plot as pdf
## Warning: Arguments must be unnamed
#rmcorr:https://cran.r-project.org/web/packages/rmcorr/rmcorr.pdf
# example: 47 rows and three columns with subject, and two measures
#my.rmc <- rmcorr(participant = Subject, measure1 = PaCO2, measure2 = pH, dataset = bland1995)
#plot(my.rmc, overall = TRUE)
```

```r
#Set color for the graphs
pal <- colorRampPalette(glasbey(n = 32)) #color for plot

#gait speed in group A
velo.rmc <- rmcorr(participant = ID, measure1 = velocity_vg, measure2 = GMV, dataset = AROI_long)
velo.rmc
```

```
##
## Repeated measures correlation
##
## r
## 0.2584
##
## degrees of freedom
## 32
##
## p-value
## 0.140064
##
## 95% confidence interval
## -0.09923527 0.5569146
```

```r
#Get rmcorr coeff and p-value from rmcorr fct, round values
rmcorr.coeff.velo <- sprintf("%.3f", round(velo.rmc$r, 3)) #Round to three decimal places
p.velo <- sprintf("%.3f", round(velo.rmc$p, 3)) #Round to three decimal places

#plot
plot(velo.rmc,
     palette = pal,# palatte for color of graph
     ylim = c(0.3, 0.57),xlim = c(75, 170),# range axis
     ylab = "Gray Matter Volume", xlab = "Velocity",
     main= "Repeated Measures Correlation HiBalance", font.main =1,#to use plain font and not bold
     overall = TRUE,#overall regression line
     overall.col = "gray50" # color of the line
     )
        text(75,0.55, adj = 0, bquote(italic(R[rm])~"="~ .(rmcorr.coeff.velo)))   #pass the r coeff
icent
        text(75,0.53, adj = 0, bquote(italic('p')~"="~ .(p.velo)))#pass the p value

#########
        x <- data.frame("p" =p.velo)
        write.csv(x,file = "test.csv",row.names = TRUE,
            col.names = TRUE)
```

```
dev.off()
```

Gait speed in B

```
pdf((here("results",file="rmcorrBvelo.pdf")))#to save the plot as pdf
# Gait speed in B
veloB.rmc<- rmcorr(participant = ID, measure1 = velocity_vg, measure2 = GMV , dataset = BROI_long)
veloB.rmc
##
## Repeated measures correlation
##
## r
## -0.1436383
##
## degrees of freedom
## 30
##
## p-value
## 0.432868
##
## 95% confidence interval
## -0.4791141 0.228453
#Get rmcorr coeff and p-value from rmcorr fct, round values
rmcorr.coeff.veloB <- sprintf("%.3f", round(veloB.rmc$r, 3)) #Round to three decimal places
p.veloB <- sprintf("%.3f", round(veloB.rmc$p, 3)) #Round to three decimal places

#Plot
plot(veloB.rmc, #data
        palette = pal,# palatte for color of graph
     ylim = c(0.30, 0.57),xlim = c(75, 170),# range axis
     ylab = "Gray Matter Volume", xlab = "Velocity", #names axes
     main= "Repeated Measures Correlation HiCommunication",font.main=1,
     overall = TRUE,#overall regression line
     overall.col = "gray50"# color of the line
     )
#Add p and r
        text(75,0.55, adj = 0, bquote(italic(R[rm])~"="~ .(rmcorr.coeff.veloB)))   #pass the r coef
ficent))
        text(75,0.53, adj = 0, bquote(italic('p')~"="~ .(p.veloB)))


        dev.off()
```

Comparison of repeated measures correlation coefficients

```
#https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4383486/

#comparison can also be conducted based on the correlation coefficients and the group sizes using t
he function #cocor.indep.groups().


#RMCorr gait speed

cocor.indep.groups(r1.jk=+0.25, r2.hm=-0.14, n1=34, n2=31, alternative="two.sided", alpha=0.05, con
f.level=0.95, null.value=0)
```

```
##
##   Results of a comparison of two correlations based on independent groups
##
## Comparison between r1.jk = 0.25 and r2.hm = -0.14
## Difference: r1.jk - r2.hm = 0.39
## Group sizes: n1 = 34, n2 = 31
## Null hypothesis: r1.jk is equal to r2.hm
## Alternative hypothesis: r1.jk is not equal to r2.hm (two-sided)
## Alpha: 0.05
##
## fisher1925: Fisher's z (1925)
##   z = 1.5202, p-value = 0.1285
##   Null hypothesis retained
##
## zou2007: Zou's (2007) confidence interval
##   95% confidence interval for r1.jk - r2.hm: -0.1135 0.8316
##   Null hypothesis retained (Interval includes 0)
```

Repeated Measures Correlation MiniBESTest

MiniBESTest in A

```
pdf((here("results",file="rmcorrAMB.pdf")))#to save the plot as pdf

#MiniBEST in A

mbA.rmc <- rmcorr(participant = ID, measure1 = MiniBEST, measure2 = GMV , dataset = AROIMB_long)

mbA.rmc
```

```
##
## Repeated measures correlation
##
## r
## 0.04587888
##
## degrees of freedom
## 31
##
## p-value
```

```
## 0.7998624
##
## 95% confidence interval
## -0.3135587 0.3938168
#Get rmcorr coeff and p-value from rmcorr fct, round values
rmcorr.coeff.mbA <- sprintf("%.3f", round(mbA.rmc$r, 3)) #Round to three decimal places
p.mbA <- sprintf("%.3f", round(mbA.rmc$p, 3)) #Round to three decimal places

#plot
plot(mbA.rmc,
             palette = pal,# palatte for color of graph
     ylim = c(0.3, 0.57),xlim = c(10, 30),# range axis
     ylab = "Gray Matter Volume", xlab = "Mini-BESTest",
     main= "Repeated Measures Correlation HiBalance", font.main=1,
     overall = TRUE,#overall regression line
     overall.col = "gray50"# color of the line
     )
#Add p and r
        text(10,0.55, adj = 0, bquote(italic(R[rm])~"="~ .(rmcorr.coeff.mbA)))   #pass the r coeffi
cent))
        text(10,0.53, adj = 0, bquote(italic('p')~"="~ .(p.mbA)))
 dev.off()
```

MiniBESTest in B

```
pdf((here("results",file="rmcorrBMB.pdf")))#to save the plot as pdf
# #MiniBEST in B
mbB.rmc <- rmcorr(participant = ID, measure1 = MiniBEST, measure2 = GMV , dataset = BROIMB_long)
mbB.rmc
##
## Repeated measures correlation
##
## r
## -0.01020338
##
## degrees of freedom
## 29
##
## p-value
## 0.9565553
##
## 95% confidence interval
## -0.3753056 0.3576397
#Get rmcorr coeff and p-value from rmcorr fct, round values
```

```
rmcorr.coeff.mbB <- sprintf("%.3f", round(mbB.rmc$r, 3)) #Round to three decimal places
p.mbB <- sprintf("%.3f", round(mbB.rmc$p, 3)) #Round to three decimal places


#Plot
plot(mbB.rmc,
        palette = pal,# palatte for color of graph
        ylim = c(0.3, 0.57),xlim = c(10, 30),# range axis
     ylab = "Gray Matter Volume", xlab = "Mini-BESTest",
     main= "Repeated Measures Correlation HiCommunication", font.main=1,
     overall = TRUE,#overall regression line
     overall.col = "gray50"# color of the line
     )
#Add p and r
        text(10,0.55, adj = 0, bquote(italic(R[rm])~"="~ .(rmcorr.coeff.mbB)))   #pass the r coeffi
cent))
        text(10,0.53, adj = 0, bquote(italic('p')~"="~ .(p.mbB)))


        dev.off()
```

Packages and versions used for this script:

```
sessionInfo()
## R version 4.0.2 (2020-06-22)
## Platform: x86_64-apple-darwin17.0 (64-bit)
## Running under: macOS Catalina 10.15.7
##
## Matrix products: default
## BLAS:   /Library/Frameworks/R.framework/Versions/4.0/Resources/lib/libRblas.dylib
## LAPACK: /Library/Frameworks/R.framework/Versions/4.0/Resources/lib/libRlapack.dylib
##
## locale:
## [1] en_US.UTF-8/en_US.UTF-8/en_US.UTF-8/C/en_US.UTF-8/en_US.UTF-8
##
## attached base packages:
## [1] stats     graphics  grDevices utils     datasets  methods   base
##
## other attached packages:
##  [1] cocor_1.1-3     pals_1.6        readxl_1.3.1    rmcorr_0.4.0
##  [5] forcats_0.5.1   stringr_1.4.0   dplyr_1.0.7     purrr_0.3.4
##  [9] readr_1.4.0     tidyr_1.1.3     tibble_3.1.2    ggplot2_3.3.5
## [13] tidyverse_1.3.1 here_1.0.1      knitr_1.29
##
```

```
## loaded via a namespace (and not attached):
##  [1] Rcpp_1.0.5       lattice_0.20-41  lubridate_1.7.10 assertthat_0.2.1
##  [5] rprojroot_2.0.2  digest_0.6.25    psych_2.1.3      utf8_1.1.4
##  [9] R6_2.4.1         cellranger_1.1.0 backports_1.1.8  reprex_2.0.0
## [13] evaluate_0.14    httr_1.4.2       pillar_1.6.1     rlang_0.4.10
## [17] rstudioapi_0.13  rmarkdown_2.3    munsell_0.5.0    broom_0.7.8
## [21] compiler_4.0.2   modelr_0.1.8     xfun_0.16        pkgconfig_2.0.3
## [25] mnormt_2.0.1     tmvnsim_1.0-2    htmltools_0.5.0  tidyselect_1.1.0
## [29] fansi_0.4.1      crayon_1.4.1     dbplyr_2.1.1     withr_2.4.2
## [33] grid_4.0.2       nlme_3.1-148     jsonlite_1.7.2   gtable_0.3.0
## [37] lifecycle_1.0.0  DBI_1.1.0        magrittr_2.0.1   scales_1.1.1
## [41] cli_2.4.0        stringi_1.4.6    mapproj_1.2.7    fs_1.5.0
## [45] xml2_1.3.2       ellipsis_0.3.2   generics_0.0.2   vctrs_0.3.8
## [49] tools_4.0.2      dichromat_2.0-0  glue_1.4.1       maps_3.3.0
## [53] hms_1.1.0        parallel_4.0.2   yaml_2.2.1       colorspace_1.4-1
## [57] rvest_1.0.0      haven_2.3.1
```

Putamen volume correlation with gait speed and MiniBESTest

Dr. rer. nat. Franziska Albrecht

8/19/2020

This script is for analyzing the association between the putamen increase over time and motor variables. During the revision we added analyses of the active control group.

Reading in data for motor variables and gray matter volume

```
# gait speed

# Long format

ROI_long= read.table(here("data", "ROIA1smA2_long.csv"), header = TRUE, sep = ";", quote = "\"", de
c = ",", fill = TRUE)

#wide format includes differences pre and post

ROI_wide= read.table(here("data", "ROIVelo_wide.csv"), header = TRUE, sep = ";", quote = "\"", dec
= ",", fill = TRUE)


# MiniBESTest

# long format

ROIMB_long= read.table(here("data", "ROIMB_long.csv"), header = TRUE, sep = ";", quote = "\"", dec
= ",", fill = TRUE)

#wide format includes differences pre and post

ROIMB_wide= read.table(here("data", "ROIMB_wide.csv"), header = TRUE, sep = ";", quote = "\"", dec
= ",", fill = TRUE)
```

Subsetting the data

Split the file into the groups according to column ‘Group’ into group A and B.

```
# split into A and B using the long and wide format
# Velocity
AROI=subset(ROI_wide, ROI_wide$Group == 'A')
BROI=subset(ROI_wide, ROI_wide$Group == 'B')

AROI_long=subset(ROI_long, ROI_long$Group == 'A')
BROI_long=subset(ROI_long, ROI_long$Group == 'B')

#MiniBESTest
AROIMB_wide=subset(ROIMB_wide, ROIMB_wide$Group == 'A')
BROIMB_wide=subset(ROIMB_wide, ROIMB_wide$Group == 'B')

AROIMB_long=subset(ROIMB_long, ROIMB_long$Group == 'A')
BROIMB_long=subset(ROIMB_long, ROIMB_long$Group == 'B')
```

Correlation A and B of post gait speed and post gray matter volume

```
# test for normality of values
shapiro.test(AROI$GMV_1)
##
##  Shapiro-Wilk normality test
##
## data:  AROI$GMV_1
## W = 0.96235, p-value = 0.3007
shapiro.test(AROI$velocity_vg_1)
##
##  Shapiro-Wilk normality test
##
## data:  AROI$velocity_vg_1
## W = 0.93915, p-value = 0.06419
shapiro.test(AROIMB_wide$MiniBEST_1)
##
##  Shapiro-Wilk normality test
##
## data:  AROIMB_wide$MiniBEST_1
## W = 0.92249, p-value = 0.02429
```

```
# http://www.sthda.com/english/wiki/correlation-test-between-two-variables-in-r#compute-correlation-in-r

# parametric pearson

# example res2 <-cor.test(my_data$wt, my_data$mpg,  method = "spearman")


# A: correlation of post velocity and post gray matter volume

Apost<- cor.test(AROI$GMV_1, AROI$velocity_vg_1,  method = "pearson")# simple correlation with estimate of "r"

Apostsum <- summary(lm(AROI$GMV_1 ~ AROI$velocity_vg_1))# linear model to get r squared


# B: correlation of post velocity and post gray matter volume

Bpost<- cor.test(BROI$GMV_1, BROI$velocity_vg_1,  method = "pearson")

Bpostsum <- summary(lm(BROI$GMV_1 ~ BROI$velocity_vg_1))
```

Revision: Partial Correlation for pre, post and delta values controlling for total intracranial volume

```
#get intracranial volume (TIV) pre and post from the demographic data set

demo_wide<-read.xlsx(here("data", "demo_wide_copy.xlsx"))

Tiv_info<- demo_wide %>%

  dplyr::select(

    "ID",

    TIV_v1,

         TIV_v2)


# merge with the full dataset and redo subsetting into intervention groups

# Gait speed

# wide format includes differences pre and post

ROI_wide= read.table(here("data", "ROIVelo_wide.csv"), header = TRUE, sep = ";", quote = "\"", dec = ",", fill = TRUE)


# MiniBESTest

# wide format includes differences pre and post

ROIMB_wide= read.table(here("data", "ROIMB_wide.csv"), header = TRUE, sep = ";", quote = "\"", dec = ",", fill = TRUE)


#merge the data with the intracranial volume info

# and deselect the empty row of NP1015

ROI_wide<-ROI_wide%>%

  full_join(Tiv_info, by="ID")%>%

filter(ID!="NP1015")


ROIMB_wide<-ROIMB_wide%>%
```

```
  full_join(Tiv_info, by="ID")%>%
filter(ID!="NP1015")

# split into A and B using the wide format after merging with intracranial volume
# Gait speed
AROI=subset(ROI_wide, ROI_wide$Group == 'A')
BROI=subset(ROI_wide, ROI_wide$Group == 'B')

# MiniBESTest
AROIMB_wide=subset(ROIMB_wide, ROIMB_wide$Group == 'A')
BROIMB_wide=subset(ROIMB_wide, ROIMB_wide$Group == 'B')

# calculate intracranial volume delta  for the gait data set
AROI$TIV_D<-AROI$TIV_v2-AROI$TIV_v1
BROI$TIV_D<-BROI$TIV_v2-BROI$TIV_v1

# calculate gray matter delta for MiniBESTest dataset
AROIMB_wide$GMV_D <- AROIMB_wide$GMV_1-AROIMB_wide$GMV_0
BROIMB_wide$GMV_D <- BROIMB_wide$GMV_1-BROIMB_wide$GMV_0
AROIMB_wide$TIV_D<-AROIMB_wide$TIV_v2-AROIMB_wide$TIV_v1
BROIMB_wide$TIV_D<-BROIMB_wide$TIV_v2-BROIMB_wide$TIV_v1
#################

# partial correlation between x and y, controlling for z: pcor.test(x, y, z)
# Order: pre values gait speed and gray matter volume, post, delta, then pre post delta MiniBESTest
# first all A then all B
a<-pcor.test(AROI$GMV_0, AROI$velocity_vg_0, AROI$TIV_v1)
b<-pcor.test(AROI$GMV_1, AROI$velocity_vg_1, AROI$TIV_v2)
c<-pcor.test(AROI$GMV_D, AROI$velocity_vg_D, AROI$TIV_D)
d<-pcor.test(AROIMB_wide$GMV_0, AROIMB_wide$MiniBEST_0, AROIMB_wide$TIV_v1)
e<-pcor.test(AROIMB_wide$GMV_1, AROIMB_wide$MiniBEST_1, AROIMB_wide$TIV_v2)
f<-pcor.test(AROIMB_wide$GMV_D, AROIMB_wide$MiniBEST_D, AROIMB_wide$TIV_D)
g<-pcor.test(BROI$GMV_0, BROI$velocity_vg_0, BROI$TIV_v1)
h<-pcor.test(BROI$GMV_1, BROI$velocity_vg_1, BROI$TIV_v2)
i<-pcor.test(BROI$GMV_D, BROI$velocity_vg_D, BROI$TIV_D)
j<-pcor.test(BROIMB_wide$GMV_0, BROIMB_wide$MiniBEST_0, BROIMB_wide$TIV_v1)
k<-pcor.test(BROIMB_wide$GMV_1, BROIMB_wide$MiniBEST_1, BROIMB_wide$TIV_v2)
l<-pcor.test(BROIMB_wide$GMV_D, BROIMB_wide$MiniBEST_D, BROIMB_wide$TIV_D)

#merge all results in a table with partial correlation results
parcor_all<-a%>%
bind_rows(b,
```

```
c,
d,
e,
f,
g,
h,
i,
j,
k,
l)
```

Plots using the residuals of gait controlled for intracranial volume (TIV) in the post values

```
# obtain residuals for gait speed and gray matter volume
# A
AROI$velo_resid<-resid(lm(velocity_vg_1~TIV_v2,AROI))
AROI$GMV_resid<-resid(lm(GMV_1~TIV_v2,AROI))
# B
BROI$velo_resid<-resid(lm(velocity_vg_1~TIV_v2,BROI))
BROI$GMV_resid<-resid(lm(GMV_1~TIV_v2,BROI))
##################################################


#plot the post gait speed gray matter volume correlation
grDevices::pdf(here("results",file="parcorrApostgait.pdf"))#to save the plot as pdf
ggscatter(AROI, x="velo_resid", y="GMV_resid", #data
          ylab = "Gray Matter Volume Post Residuals", xlab = "Gait Speed Post Residuals", #labels p
lot
         main = "Partial Correlation HiBalance Post Training",
        color = "turquoise", shape = 16, size = 2, # Points color, shape and size
        ylim = c(-0.05, 0.06),xlim = c(-40, 40),# range axis
   add = "reg.line",  # Add regression line
   add.params = list(color = "gray50", fill = "lightgray"), # Customize reg. line
   conf.int = TRUE, # Add confidence interval
   cor.coef = TRUE,# Add correlation coefficient. see ?stat_cor
   cor.coef.coord = c(-40, 0.055), #position of R coefficient
   cor.coeff.args = list(method = "pearson", label.x = 3, label.sep = "\n")
   )
## `geom_smooth()` using formula 'y ~ x'
dev.off()
##################################################
# B
```

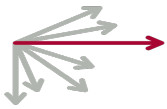
```
grDevices::pdf(here("results",file="parcorrBpostgait.pdf"))#to save the plot as pdf
ggscatter(BROI, x='velo_resid', y='GMV_resid', #data
          ylab = "Gray Matter Volume Post Residuals", xlab = "Gait Speed Post Residuals", #labels p
lot
         main = "Partial Correlation Active Control Group Post Training",
        color = "chocolate", shape = 16, size = 2, # Points color, shape and size
        ylim = c(-0.05, 0.06),xlim = c(-40, 40),# range axis
   add = "reg.line",  # Add regression line
   add.params = list(color = "gray50", fill = "lightgray"), # Customize reg. line
   conf.int = TRUE, # Add confidence interval
   cor.coef = TRUE,# Add correlation coefficient. see ?stat_cor
   cor.coef.coord = c(-40, 0.055), #position of R coefficient
   cor.coeff.args = list(method = "pearson", label.x = 3, label.sep = "\n")
   )
## `geom_smooth()` using formula 'y ~ x'
dev.off()
```

Packages and versions used for this script:

```
sessionInfo()
## R version 4.0.2 (2020-06-22)
## Platform: x86_64-apple-darwin17.0 (64-bit)
## Running under: macOS Catalina 10.15.7
##
## Matrix products: default
## BLAS:   /Library/Frameworks/R.framework/Versions/4.0/Resources/lib/libRblas.dylib
## LAPACK: /Library/Frameworks/R.framework/Versions/4.0/Resources/lib/libRlapack.dylib
##
## locale:
## [1] en_US.UTF-8/en_US.UTF-8/en_US.UTF-8/C/en_US.UTF-8/en_US.UTF-8
##
## attached base packages:
## [1] stats     graphics  grDevices utils     datasets  methods   base
##
## other attached packages:
##  [1] here_1.0.1      openxlsx_4.2.3  ppcor_1.1       MASS_7.3-51.6
##  [5] cocor_1.1-3     ggpubr_0.4.0    forcats_0.5.1   stringr_1.4.0
##  [9] dplyr_1.0.7     purrr_0.3.4     readr_1.4.0     tidyr_1.1.3
## [13] tibble_3.1.2    ggplot2_3.3.5   tidyverse_1.3.1 knitr_1.29
##
## loaded via a namespace (and not attached):
##  [1] httr_1.4.2        jsonlite_1.7.2    splines_4.0.2     carData_3.0-4
```

```
##  [5] modelr_0.1.8      assertthat_0.2.1  cellranger_1.1.0  yaml_2.2.1
##  [9] pillar_1.6.1      backports_1.1.8   lattice_0.20-41   glue_1.4.1
## [13] digest_0.6.25     ggsignif_0.6.0    rvest_1.0.0       colorspace_1.4-1
## [17] htmltools_0.5.0   Matrix_1.2-18     pkgconfig_2.0.3   broom_0.7.8
## [21] haven_2.3.1       scales_1.1.1      rio_0.5.16        mgcv_1.8-31
## [25] farver_2.0.3      generics_0.0.2    car_3.0-9         ellipsis_0.3.2
## [29] withr_2.4.2       cli_2.4.0         magrittr_2.0.1    crayon_1.4.1
## [33] readxl_1.3.1      evaluate_0.14     fs_1.5.0          fansi_0.4.1
## [37] nlme_3.1-148      rstatix_0.6.0     xml2_1.3.2        foreign_0.8-80
## [41] tools_4.0.2       data.table_1.13.0 hms_1.1.0         lifecycle_1.0.0
## [45] munsell_0.5.0     reprex_2.0.0      zip_2.1.0         compiler_4.0.2
## [49] rlang_0.4.10      grid_4.0.2        rstudioapi_0.13   labeling_0.3
## [53] rmarkdown_2.3     gtable_0.3.0      abind_1.4-5       DBI_1.1.0
## [57] curl_4.3          R6_2.4.1          lubridate_1.7.10  utf8_1.1.4
## [61] rprojroot_2.0.2   stringi_1.4.6     Rcpp_1.0.5        vctrs_0.3.8
## [65] dbplyr_2.1.1      tidyselect_1.1.0  xfun_0.16
```

Supplementary Material 2. Preregistration protocol from aspredicted.org.



ASPREDICTED

CREDIBILITY LAB

(http://credlab.wharton.upenn.edu)

You are logged in as: **franziska.albrecht@ki.se**

HOME (index.php) See List (see_list.php)

Change my AsPredicted email (update_email1.php) Log out (logout.php)

As Predicted: *"Effects of a highly challenging balance training on brain structure in PD"* (#43137)

Created: 06/18/2020 03:49 AM (PT)

Author(s)

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1) Have any data been collected for this study already?

It's complicated. We have already collected some data but explain in Question 8 why readers may consider this a valid pre-registration nevertheless.

2) What's the main question being asked or hypothesis being tested in thisstudy?

HYPOTHESES: We aim to investigate neuroplasticity effects associated with a highly challenging balance, gait, and cognitively demanding training (HiBalance) program in a cohort of people with

mild to moderate Parkinson's disease (PD). We hypothesize that after receiving this intensive training, participants with PD will show an increase of gray matter volume in motor and cognitive-related brain areas compared to an active control group, which underwent a speech and communication training (HiCommunication) program. Both group-based trainings had a similar setting, dose, and frequency (Franzén et al., 2019). Further, we hypothesize that improvements in variables measuring the efficacy of the training will be correlated with the gray matter volume increases. Finally, we will explore the impact of different cognitive and motor phenotypes on the response to intensive training and related brain changes in people with PD. BACKGROUND: PD is associated with motor deficits and brain circuit changes that have a detrimental impact on gait and balance. To this date, no cure has been found for PD, thus there is an urgent need to develop new therapies that can maintain and improve quality of life of people with PD. In particular, neuroplasticity through physical exercise could be used as a method to inhibit potential degenerative processes related to PD. Previous findings suggest that intensive, challenging, and cognitively demanding physical exercise can induce neuroplasticity in PD (Petzinger et al., 2013). We have also shown that a highly challenging balance training (HiBalance program) is associated with positive effects on gait and balance (Conradsson et al., 2015). Further, physical exercises can lead to better cognition in people with PD as demonstrated by a meta-analysis (da Silva et al., 2018). Recently, we demonstrated that our highly challenging, intense, and demanding training program also enhances cognition in people with PD, as measured by enhanced performance in a counting task during walking (Löfgren et al., 2019). Note that the HiBalance program incorporates elements that are cognitively demanding like dualtasking. Few studies have investigated neuroplastic effects of physical exercises targeting balance and gait deficits in people with PD as summarized by Johansson et al. (2020). In a study by Sehm et al. (2013), improved performance in a whole-body dynamic balancing training over a period of 6 weeks was associated with gray matter volume increases in 20 participants with mild-moderate PD. In a study by Colcombe et al. (2006), 59 healthy, but sedentary, participants between 60–79 years were enrolled in a 6-month randomized clinical trial to compare an aerobic training group with a toning/ stretching control group. The training group showed gray matter volume increases in comparison to the controls.

3) Describe the key dependent variable(s) specifying how they will be measured.

Magnetic resonance imaging (MRI) was applied before and after the interventions on a 3T Phillips Ingenia scanner. Structural, resting-state, and task-based functional MRI sequences were acquired. The structural 3D T1-weighted sequence had the following parameters: repetition/ echo time (TR/TE)=6.1/2.8 ms and voxel-size of 1x1x1mm. For the described project, we will only analyze structural MRI of participants before and after the interventions. Mini Balance Evaluation Systems Test (Mini-BESTest) assessed balance control pre- and post-training and is a validated scale for people with PD. The scale is the main outcome of the efficacy of the intervention (HiBalance program).

4) How many and which conditions will participants be assigned to?

Data was collected within the framework of a randomized controlled trial (Franzén et al., 2019). Main inclusion criteria for participants were mild-moderate disease stage of idiopathic Parkinson's disease, Hoehn&Yahr 2-3, age≥60 years, and a Montreal Cognitive Assessment score≥21. Participants were randomly assigned to either the physical exercise (HiBalance)

program or to an active control group (the HiCommunication program, addressing speech and communication). The interventions took place in small groups, two times a week with 1h sessions for over 10weeks. Additionally, 1h weekly home exercise program was also performed. The patients underwent a broad and detailed assessment of balance/gait, overall motor impairment, neuropsychological test battery, and speech/voice/communication as well as MRI before and after the interventions.

5) Specify exactly which analyses you will conduct to examine the main question/hypothesis.

Structural MRI data will be preprocessed by the longitudinal pipeline of CAT12 (C. Gaser & R. Dahnke, version 12.6) in SPM12 (version 7771). This longitudinal pipeline performs intra-subject analysis and is suitable for experiments with short distances between timepoints. Preprocessing comprises initial registration of each participants' image to the mean image of the participant by an inverse-consistent realignment. The mean image of the realigned images is estimated and spatial normalization on the segmented mean images is performed. Images will be modulated and smoothed with a 12mm kernel at full-width half-maximum (FWHM). First, a hypothesis-driven analysis using regions of interest (ROI) will be performed to compare patients before and after the interventions. The ROIs will be selected based on two studies investigating balance and aerobic exercise in people with PD and elderly participants (Sehm et al., 2013; Colcombe et al., 2006) and include the anterior precuneus, inferior parietal cortex, ventral premotor cortex, anterior cingulate cortex, middle/ superior temporal gyrus, supplementary motor area, and inferior frontal gyrus. ROIs based on the Neuromorphometrics atlas, will be extracted and analyzed with CAT12 in a flexible factorial design with the factors GROUP (HiBalance vs. HiCommunication) and TIME (pre-vs. post-intervention). We will further analyze the relationship between the extracted ROIs using graph theory analyses with BRAPH (Mijalkov et al., 2017; version 1.0.0). Furthermore, voxel-wise whole-brain regression analyses will be run on the variables of interest in separate full factorial models in SPM12 including as covariates the Mini-BESTest, mature BDNF levels, cognitive status, and motor phenotype. Exploratory whole-brain voxel-based and surface-based morphometry analyses will be carried out in SPM12 using a flexible factorial design with the factors GROUP (HiBalance vs. HiCommunication) and TIME (pre-vs. post-intervention). All statistical models will be corrected for age, gender, and total intracranial volume. The resulting statistical parametric maps will be corrected for multiple comparisons at a FWE $p<0.05$ cluster-level and uncorrected $p<0.001$ voxel-level.

6) Describe exactly how outliers will be defined and handled, and your precise rule(s) for excluding observations.

MRI data will be checked for quality by 'weighted overall image quality' and measures of 'sample homogeneity' in CAT12. Quality ratings below 'sufficient' will indicate which imaging data needs to be excluded. We do not exclude outliers regarding the behavioral variables. Only participants that did not drop-off during the randomized controlled trial and were able to perform both MRI sessions (pre-and post-intervention) will be included in the analyses.

7) How many observations will be collected or what will determine sample size? No need to justify decision, but be precise about exactly how the number will be determined.

The project is part of a randomized controlled trial and the study protocol has been published (Franzén et al., 2019). Here, a power calculation was done on pilot data. To achieve 82% power to detect the main outcome of the trial, 40 subjects per intervention would be enough. Accounting for dropouts and other exclusions (e.g., neuroimaging quality), the aim was to acquire a sample of 50 participants for each intervention group. The number of included participants for the behavioral measures was 96 participants and 20 participants dropped out of the intervention. Not all patients were eligible for MRI, thus data for 68 participants can be analyzed longitudinally.

8) Anything else you would like to pre-register? (e.g., secondary analyses, variables collected for exploratory purposes, unusual analyses planned?)

We argue that our preregistration is valid, even though, we collected data beforehand. Data was acquired within the framework of a randomized controlled trial (Franzén et al., 2019), which was registered at ClincalTrials.gov (NCT03213873). During the data collection of the trial, all actively involved persons assessors were blinded to the assignment of intervention groups. All authors remained blinded for preprocessing of the data. We did not investigate or run any analyzes on the data before this preregistration. Only authors performing the analyses will be unblinded for this study in two steps. First, for analyses, the group allocation will be revealed, assigning only group A and B to participants. Second, for discussing the results, the actual training program will be assigned to the groups.
EXPLORATORY VARIABLES: Brain-derived neurotrophic factor (BDNF), taken from blood serum pre- and post- the interventions, is another marker of plasticity and training impact. Pro and mature BDNF were analyzed using an ELISA commercial analyzing kit. In the analyses we will focus on mature BDNF. Movement Disorders Society Unified PD Rating Scale (MDS-UPDRS) characterizes disease-related symptoms and was assessed before and after the interventions. The motor scale (III) and total score will be used to describe the cohort and for correlation analyses. PD mild cognitive impairment (PD-MCI) status was calculated according to the criteria of Litvan et al. (2012). PD-MCI was assigned by applying the Level II certainty criteria using a threshold between 1-2 standard deviations below normative test data. Motor phenotypes of tremor dominant (TD) and postural instability/gait difficulty (PIGD) PD were assessed based on the criteria from Stebbins et al. (2013) using ratios of items of the MDS-UPDRS.

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